The Surgical Management of Parasitic Diseases

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To Polina and Suzy

George Tsoulfas

Preface

Parasitic diseases encompass a wide-reaching problem affecting a significant percentage of the global population. The etiology and the manifestations, as well as the treatment, are variable and highly dependent on regional differences. Their effect on the patients can be quite severe, especially when they lead to complications involving the gastrointestinal tract, in addition to multiple other systems. Surgery represents a key part of the therapy both for the disease, as well as for the complications.

This book is designed to present a comprehensive and state-of the-art approach to the diagnosis and surgical management of parasitic diseases involving different organ systems, with emphasis on the gastrointestinal tract. Sections will address the various etiologies, current diagnostic dilemmas and methods, as well as the key principles involved in their surgical management.

The introduction presents the overall epidemiology and classification of parasitic diseases. The first section focuses on different types of the most frequently encountered parasitic diseases of the gastrointestinal tract found in different parts of the world, with special attention given to the existing surgical debates regarding the use of minimally invasive procedures. The second section places special emphasis on hydatid disease. Hydatid liver disease, despite its limited numbers in the USA, is quite prevalent world-wide and especially in the Mediterranean basin. Part of the book will describe the current extent of hydatid disease; describe changes in its management including (but not limited to) the various surgical techniques having to do with more extensive or more limited techniques and also the use of minimally invasive surgery; and describe the most frequent complications and tips on how to avoid them. The third section discusses the surgical management of parasitic diseases affecting different organ systems, including the heart, the lungs, the brain, and the urinary system. The fourth section presents the surgical dilemmas encountered in special situations, such as pregnancy and the pediatric patient.

The different chapters are written by worldwide experts in the specific field who, apart from an overview of the problem and the surgical management, share with the reader their own wide-encompassing experience, including pre-operative evaluation, surgical management, and post-operative follow-up.

The importance of this resource lies in the fact that it affects a significant number of patients on a global scale and the distilled experience and wisdom of the authors that it provides will prove to be an asset to surgeons of all specialties dealing with

parasitic diseases. The fact that it includes the surgical management of non-gastrointestinal parasitic disease can potentially lead to an authoritative surgical textbook on this wide-ranging, global surgery topic, which is currently lacking and will be of interest to a wide variety of physicians and surgeons of different specialties.

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Part I

Epidemiology and Classification

Epidemiology of Parasitic Diseases

1

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Global Epidemiology of Parasitic Diseases

At least one in six persons worldwide is thought to be infected with a parasitic disease [1]. The global health burden of parasitic diseases is immense and is disproportionally concentrated in nations of economic and social disadvantage. This major health burden is reflected in the World Health Organization (WHO) list of "neglected tropical diseases" (NTDs) which is dominated by parasites [2], many of which require surgical treatment (Table 1.1). The worldwide impact of these diseases is described by the WHO:

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Table 1.1 WHO list of neglected tropical diseases

Parasitic	Non-parasitic
Protozoan:	**Mycobacterial/bacterial:**
Chagas disease	Buruli ulcer
Dengue and chikungunya	Leprosy
Trypanosomiasis	Mycetoma
Leishmaniasis	Yaws
Helminthic:	Trachoma
Guinea worm	**Viral:**
Echinococcosis	Dengue and chikungunya
Food-borne trematodiases	Rabies
Lymphatic filariasis	**Others:**
River blindness	Snake bite
Schistosomiasis	
Soil-transmitted helminthiasis	
Taeniasis	
Cysticercosis	
Ectoparasite:	
Scabies and other ectoparasites	

> Neglected tropical diseases cause immense human suffering and death. They pose a devastating obstacle to health and remain a serious impediment to poverty reduction and socio-economic development.

In fact, all surgically relevant parasitic diseases are listed by the WHO as NTDs. This textbook focuses on many of these neglected tropical diseases, particularly those major parasitic infections that are surgically relevant. These illnesses create a perpetual cycle of poverty through poor sanitation, education and living conditions. They predispose populations to infection, and the infection itself greatly reduces the productivity of those individuals within these communities. The only major parasitic disease with a worldwide burden that is *not* listed as a neglected tropical disease is malaria: all others are on this list.

Global Burden of Parasitic Diseases

The 2010 Global Burden of Disease Study estimated that neglected tropical diseases accounted for 26.06 million disability-adjusted life years (DALYs) worldwide [3]. For infections that are surgically relevant, DALYs attributable in 2015 to soil-transmitted helminths (i.e. ascariasis, trichuriasis, etc.) were 4.4 million, cysticercosis 1.8 million, onchocerciasis 1.1 million, food-borne trematodiasis 1.1 million and 0.6 million for echinococcosis [4]. The areas of highest endemicity for these illnesses include South America, Africa, Asia and the Middle East (Fig. 1.1 [4]).

The economic burden of these diseases is considerable and disproportionately affects the "bottom billion" of the world's population who are:

> … the poorest in the world; they are often subsistence farmers, who essentially live on no money and are stuck in a poverty trap of disease, conflict, and no education. [1]

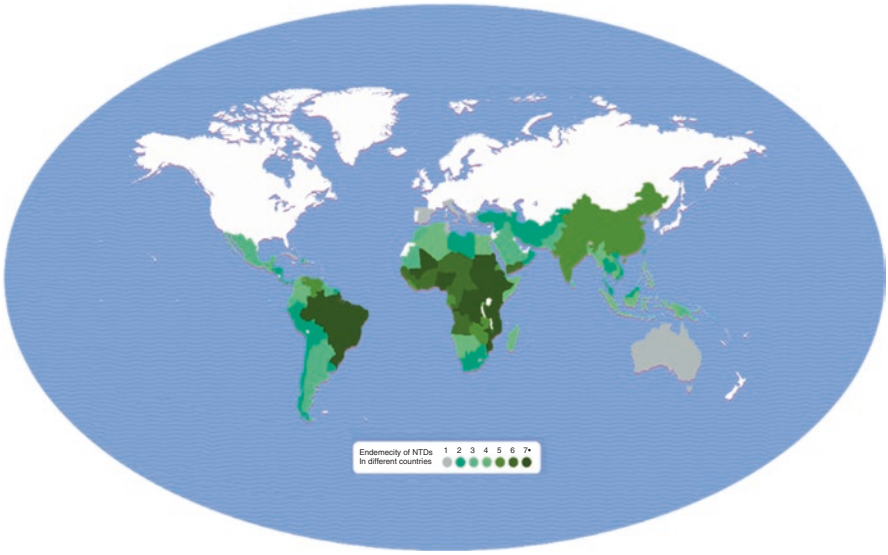

Fig. 1.1 Neglected tropical diseases. Prevalence of neglected tropical diseases (NTDs) by country. The burden of NTDs in different countries is expressed as number of NTDs increased (ranging from one to seven or more). (Modifed from Mitra and Mawson [4] and United to Combat. Burden map – Neglected Tropical Diseases [73])

The economic cost is not just reflected through sickness and limited productivity of the individual. For instance, hydatid disease, which affects livestock, is responsible for decreased milk yield and meat/carcass weight, decreased wool production and increased condemnation of meat products and offal [5]. Thus these neglected parasitic diseases exert a major toll medically, socially and economically.

Public Health and Research Directions

With respect to focus on major disease in developing countries, the WHO acknowledges there has been disproportionate spending and focus on the "big three" diseases of malaria, tuberculosis and HIV/AIDS when compared to other parasitic diseases [2].

The most comprehensive epidemiological and clinical programmes for addressing parasitic illnesses have been formulated by the WHO, including comprehensive surveillance, prevention and treatment programmes for the various diseases [6]. However on a global scale, healthcare spending and research is typically directed to "Western" illnesses, as the neglected diseases by definition pose little economic incentive for private investment. This predicament has been elegantly summarised in the example of the development of vaccines for tropical diseases:

> …the development of what Hotex and Ferris have referred to as anti-poverty vaccines, must be considered one of the major unachieved goals of modern immunology. The absence of a

> commercial market remains a serious disincentive for industry to take on this effort, but even when product development partnerships have existed to oversee vaccine development through to proper human trials, the goal of producing a highly effective vaccine has still not been met. [7]

From 2000 to 2014, 66 novel products entered phase I clinical trials intended to prevent or treat neglected tropical diseases (NTDs). This accounted for 1.65% of all 4006 phase I trials [8]. Despite still accounting for only a tiny fraction of overall spending, absolute spending on neglected diseases has increased in the last two decades with five medications reaching phase III trials between 2000 and 2013 [9]. Encouragingly, research funding into neglected illnesses reached an all-time high in 2017 of US$3.6 billion, led by the United States, the United Kingdom and European Union [10]. This funding is a combination of public funding and private philanthropy (most prominently from the Bill and Melinda Gates Foundation, which has a special interest in neglected tropical disease) in addition to small investments from private enterprise.

Types of Parasites

Parasitic organisms are generally categorised into helminthic or protozoan infections. Helminths are highly prevalent organisms that exist as free-living worms or parasites of animals or plants. These helminths have co-evolved with specific species; thus most are restricted to non-human hosts. Only a small fraction of these organisms cause human infection. Protozoa are single-celled eukaryotic organisms that can be free-living or parasitic. The majority of surgically relevant parasitic infections are of the helminthic variety; thus this epidemiological review focuses on these infections.

Global Burden of Disease from Helminthic Infections

The primary focus of this text is on helminthic infections: multicellular organisms with complex organ systems and life cycles that can involve humans at some stage. Major types of these organisms include the *tapeworms (cestodes)*, *flukes (trematodes)* and *roundworms (nematodes)*. As described below, it is likely billions of individuals harbour these organisms, with frank disease present only in a fraction in selected cases. Medical management with anthelmintic medications is the treatment for the majority of helminth-related disease; however surgery is a central treatment for some of these conditions.

The comprehensive WHO study on the impact of the 11 most important parasitic food-borne diseases (comprised of protozoan and helminthic infections) demonstrated the high impact of these diseases worldwide in DALYs and deaths (see Fig. 1.2) [11]. The total number of DALYs and deaths produced by the common cestodes, nematodes and trematodes (excluding schistosomiasis) were 7,064,277 and 58,029 deaths in 2015.

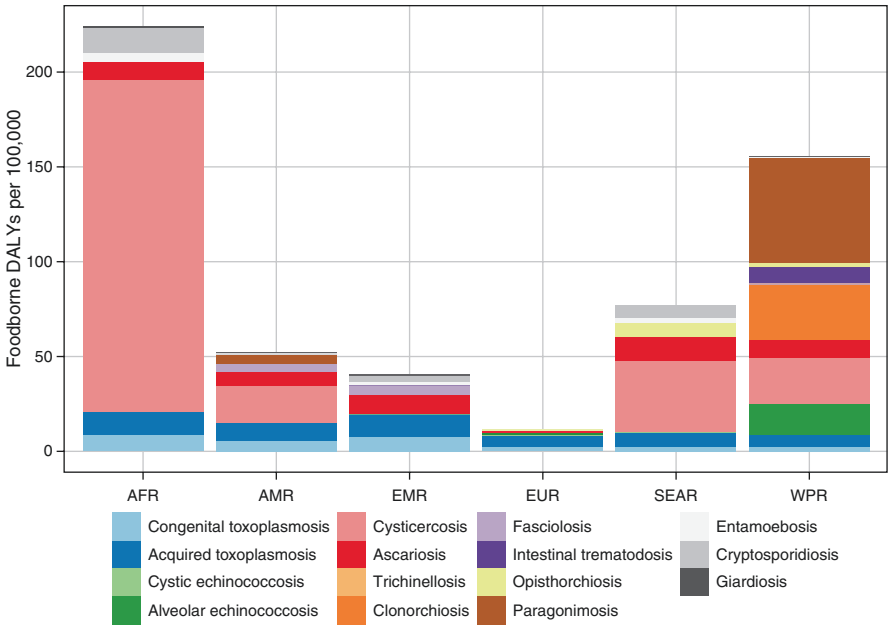

Fig. 1.2 DALYs associated with food-borne parasitic diseases [11]. Contribution of each parasite to foodborne disability-adjusted life years in regions: the relative contribution to the DALY incidence by each agent for each of the regions

Epidemiology of Cestodes

Tapeworms (cestodes) cause human disease in two ways. The classic type of infection is with an adult worm living within the gastrointestinal tract (e.g. the beef tapeworm *Taenia saginata* etc.). This type of infection is usually treated medically with anthelmintic medications and only comes to surgical attention in exceptional circumstances (e.g. bowel obstruction or migration into the biliary tract).

The second type of presentation is with larval-stage parasites present in various organ systems (i.e. when the human is the intermediate host). This type of infection often requires surgical management, and much of this text is devoted to this type of disease, in particular cystic echinococcosis (i.e. *hydatid disease*).

Echinococcosis: Epidemiological Aspects

Echinococcosis is an infection caused in humans by the larval stage of *Echinococcus granulosus* complex, *E. multilocularis* or *E. vogeli*. *E. granulosus* causes *cystic hydatid disease* in regions mainly where livestock is raised in association with dogs.

These parasites are found on all continents but with particularly high prevalence in China, Central Asia, the Middle East, the Mediterranean region, eastern Africa, Australia and parts of South America.

E. multilocularis causes *alveolar echinococcosis*, a condition with a long asymptomatic period (~10 years) which later presents as a malignant-like hepatic mass with epigastric pain and jaundice. This parasite is found in Alpine, sub-Arctic or Arctic regions, including Canada and the United States, central and northern Europe, China and Central Asia.

Cystic Echinococcosis

E. granulosus causes cystic echinococcosis, known as hydatid disease, when it affects the liver. The life cycle of this organism involves the dog, which is the definitive host (i.e. harbours the adult worms). The dogs excrete the eggs in their stool and are ingested through the faecal-oral route by the intermediate host (usually livestock such as sheep) where they migrate to various organ systems (e.g. the liver) to turn into cysts. Thus this disease is seen primarily in areas of livestock (e.g. sheep, goats, etc.). Humans are an accidental host.

Surgery is central to the treatment of this illness, and a large proportion of this text is devoted to the treatment of this condition; thus a large proportion of this chapter is devoted to this particular illness.

Echinococcosis: A Worldwide Snapshot

Numerous genetically distinct strains of *E. granulosus* have been well described in diverse geographic locations with predilections for different animals including sheep, horses, cows, pigs and other animals. It appears the common sheep strain (G1) is most frequently associated with human disease [12]. As predicted by their life cycle, rates of infection with *E. granulosus* are highest in regions with extensive sheep farming and presence of a large number of dogs [13, 14].

Cystic echinococcosis is a worldwide disease, however is concentrated mainly in regions of South America, the Middle East, eastern Mediterranean, some African regions, China and eastern Europe as demonstrated in the map produced by the WHO which highlights the regions with the highest prevalence (Fig. 1.3). The worldwide prevalence of cystic echinococcosis has fallen in recent decades [12]; however the WHO estimates that at least one million individuals are affected at any one time [15]. Prevalence levels of up to 5–10% of humans occur in parts of Argentina, Central Asia, China, East Africa and Peru. The prevalence of echinococcosis in livestock and dogs can vary from 20 to 95% in hyperendemic areas.

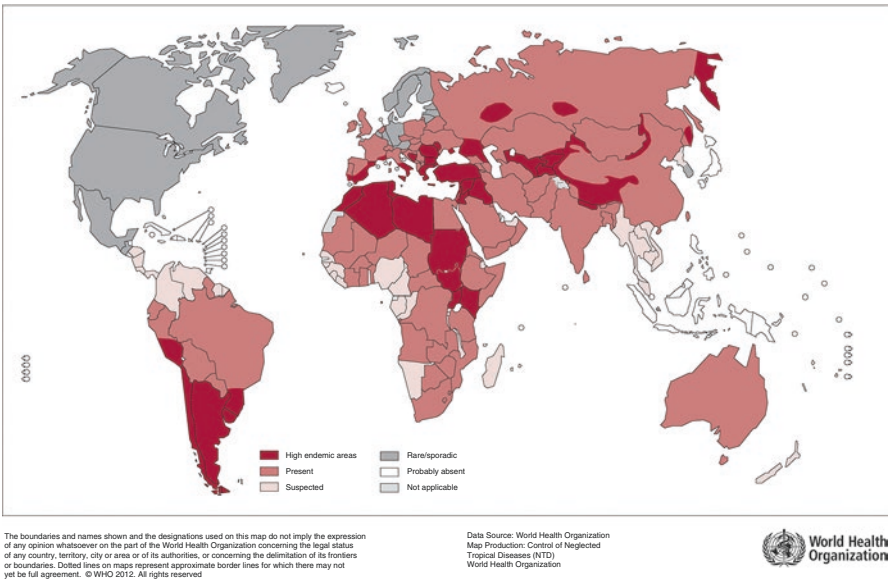

Fig. 1.3 WHO diagram of human echinococcosis [74]

Echinococcosis by Region

Western Developed Countries

Echinococcosis is rare in Western developed countries. The 2016 data from the Annual Epidemiological Report for the European Centre for Disease Prevention and Control found that 414 cases of *E. granulosus*, 104 cases of *E. multilocularis* and 257 unknown echinococcal species were diagnosed with a rate of 0.2 cases per 100,000. Data was available for 27 European Economic Area countries with the highest numbers of cases found in Bulgaria (35%), Germany (17%) and Spain (11%). One death was recorded [16].

The epidemiology of echinococcosis worldwide is well studied, but surprisingly little contemporary research exists for recent decades in North America. This is likely because echinococcosis is thought to be rare and (unlike Europe) is not a reportable disease. Recent epidemiological data from the contiguous United States is extremely lacking. In the United States and Canada, the "cervid" strain (G8) is found in Alaska, the northern United States and Canada. The common sheep strain (G1) is found in the Western United States [12]. There were 41 reported deaths from echinococcosis in the United States from 1990 to 2007 [17].

In Australia, the G1 strain is well established in native wallabies and kangaroos and has been disseminated by dingoes and wild dogs [12]. 80–100 cases are reported per year (0.4 per 100,000) with higher rates in rural farming and indigenous areas, especially where there is a high prevalence of dogs [18].

South America

Very high animal and human prevalence is observed in temperate regions in South America. This has been thought to be due to the practice of feeding dogs the uncooked viscera of home-butchered sheep [19]. The dogs can easily pass the tapeworm eggs to humans (e.g. playful contact with children).

The incidence of cases requiring surgery is as high as 127 per 100,000 in the Central Andes [20]. Asymptomatic hydatid disease is found in between 3% and 9.3% on imaging surveys in rural villages in the Peruvian highlands [21, 22]. Prevalence in livestock and dogs can be as high as 90% in some hyperendemic areas [23]. Surgical incidence can reach up to 20 cases per 100,000 in parts of Southern Chile [23].

Lower prevalence is reported overall in Uruguay, Brazil and Argentina, but these countries too have endemic regions in central Uruguay, Southern Brazil and several Patagonian provinces [24–26].

Approximately 5000 new cases are diagnosed each year in the endemic regions of Argentina, Chile, Peru, Uruguay and Southern Brazil combined, with approximately 880 deaths recorded in 6 years (2.9% fatality rate). The Regional Initiative for Control of Cystic Echinococcosis has been established by these five countries and has been partially successful in control programmes [27, 28].

E. granulosus is rare in Central America, Colombia, Ecuador and Venezuela [23].

China and Southeast Asia

Echinococcosis is highly endemic in the rural regions of Western China. It has been estimated that one million disability-adjusted life years (DALYs) were caused by both cystic and alveolar echinococcosis globally; however 0.4 million of these were attributable to Western China [29]. The prevalence of hydatid disease in some of these regions may be the highest in the world, with many regions with human prevalence over 5% and livestock prevalence approaching 100% [30].

Africa and the Middle East

Cystic echinococcosis is highly endemic among nomadic pastoral tribes of East Africa. It is common in dogs in all countries in sub-Saharan Africa, but is rare in agriculturally based communities [31]. In the more economically developed South Africa, incidence and prevalence is lower. Epidemiological data for South Africa

are incomplete; however it is thought approximately 130 cases per year are diagnosed [32].

Cystic echinococcosis has been reported in all countries in the Middle East and Arabic North Africa. It is highly prevalent in Iran, Turkey, Iraq, Morocco, Tunisia and Libya with various surveys indicating high prevalence in livestock (especially sheep) in these regions [33].

Echinococcosis: Costs

Cystic echinococcosis is thought to cost up to US$1.9 billion per year in adjusted economic losses for human illness and up to US$2.1 billion for livestock losses [5]. Approximately one million DALYs were calculated to be lost due to this infection.

As described in this text, hepatic interventions and surgery form the cornerstone of treatment for many aspects of hydatid disease. As expected, these interventions are expensive and pose difficulties for resource-poor countries. An Italian institution calculated the median cost of treatment for individuals treated with surgery was €11,033, with median operative time of 258 minutes per case [34]. Total median costs over 10 years in an Austrian study were €16,253, with most of the expenditure spent in the first year [35].

Public Health and Research Status

Echinococcosis is recognised as one of the WHO neglected tropical diseases. The findings of the most recent meeting of the WHO echinococcus working group in December 2016 have been published [36]. The report stated that diagnosis and management of this illness was based on expert opinion and case series as opposed to rigorous randomised controlled trials. Given the lack of economic investment in this disease from pharmaceutical companies, this was unlikely to change in the foreseeable future. Regional strategies were described to improve coordination of data collection and to better describe outcomes in light of the lack of rigorous clinical trials.

Eradication

Eradication strategies have focused on anthelmintic treatment of dogs, improvements in abattoir and farm practices (in particular hygiene and feeding of offal to dogs), education and testing. Highly successful eradication programmes have been undertaken on islands (for example New Zealand, Tasmania and the Falkland Islands) primarily through aggressive dog treatments; however continental approaches have been largely unsuccessful [37]. Various animal vaccines, first described in 1996, have been implemented with varying degrees of success [38].

E. multilocularis

Alveolar echinococcosis is restricted to the Northern Hemisphere, in particular in China, Russia and continental Europe and North America. Alveolar echinococcosis is highly endemic to Western China, and of 18,235 known annual cases diagnosed, approximately 16,629 (91%) are diagnosed in China [29].

Russia has a very large endemic region stretching from Eastern Europe to Siberia, with over 1100 cases per year reported from this part of the country [29]. Other foci exist within central Europe, Asia and worldwide; however the number of reported cases is several orders of magnitude lower per year when compared to China.

Nearly all cases of alveolar echinococcosis involve liver lesions. Complete radical resection is recommended and provides the best chance for cure [39]. Unresectable lesions condemn the patient to protracted anthelmintic medications, and liver transplant for this condition has been described [40]. The cost of these therapies is clearly substantial.

Cysticercosis

The pork tapeworm, *Taenia solium*, is noteable in that human disease is caused by both the adult forms residing within the intestine and surgically relevant disease from larval forms which occur in various tissues (i.e. cysticercosis).The pork tapeworm is found worldwide but is highly endemic in many developing areas including Mexico and South America, sub-Saharan Africa, China and India (see Fig. 1.4) [41]. Infection is generally found in subsistence farming communities in developing countries of Africa, Asia and Latin America, especially where pigs and cattle come into contact with human faeces [41].

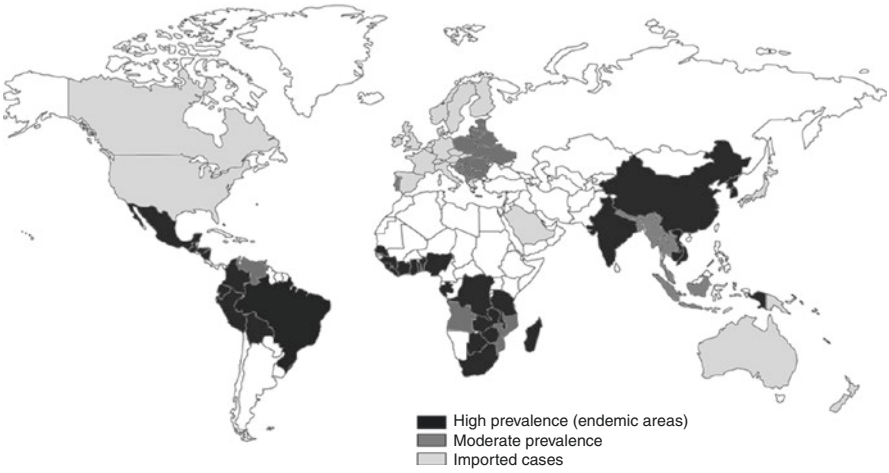

Fig. 1.4 World-wide distribution of cysticercosis [41]. World map showing countries where cysticercosis is endemic

The intestinal disease requires standard anthelmintic medications; however the larval disease in the central nervous system (known as *neurocysticercosis*) may require surgical resection, anti-seizure medications and shunting [42]. Neurocysticercosis is the most frequent preventable cause of epilepsy worldwide and accounts for up to 30% of epilepsy cases where the disease is endemic and is the most common helminthic infection of the central nervous system. An estimated 50 million people worldwide have neurocysticercosis, causing 50,000 deaths per year and up to 50% of late-onset epilepsy in developing countries [43].

Intestinal Cestodes

Intestinal cestode infection with adult worms is usually managed medically. The best known of these infections are the beef tapeworm (*Taenia saginata*), the dwarf tapeworm (*Hymenolepis nana*) and *Diphyllobothrium* species. Most of these worms occur worldwide however are over-represented in areas with poor sanitation and where undercooked meat is customary.

Nematodes

Infestations due to nematodes typically manifest in three broad ways: intestinal infestation with adult worms, tissue-penetrating disease or filarial disease.

Intestinal nematodes are thought to infect over one billion people worldwide [44], disproportionately affecting the developing world. Hundreds of helminth species exist that can infect humans; however only a fraction of these are prevalent enough to account for the majority of the burden of disease on a worldwide scale. These include the roundworm (*Ascaris lumbricoides*), hookworms (*Necator americanus*, *Ancylostoma duodenale*), *Strongyloides stercoralis*, whipworm (*Trichuris trichiura*) and the well-known pinworm (*Enterobius vermicularis*). The prevalence of infection for each of these worms is thought to be in the hundreds of millions [44]. Pinworm is common and well-known in Western countries; however the other worms predominantly affect the developing world.

Clinical Burden of Intestinal Nematode Disease

The true clinical impact of nematode infestation is difficult to quantify. Clinically evident disease is proportional to the degree of infestation, and it is thought that most infestations are asymptomatic. As the life cycle of almost all helminths requires replication outside the host (i.e. humans or other organism), the burden of infestation correlates to the intensity of exposure. Thus regions with poor faecal sanitation are usually associated with clinically apparent infection. Furthermore complicating disease burden estimates, there may be potential benefits of asymptomatic colonisation: the eosinophilic inflammatory response that nematodes and other helminths elicit is thought to be protective against allergic disease. Documented declining nematode infection rates have been inversely proportional

to a rise in atopic disease and improvement in sanitation and living standards as seen in many middle income countries that have seen rapid economic development [45].

Most infections with intestinal nematodes are asymptomatic or cause mild, non-specific symptoms. Frank surgical disease is seen when nematodes migrate into the biliary system or heavy infestation causes bowel obstruction. Seemingly asymptomatic infection has been shown to cause many deleterious effects, particularly in children through reduced cognitive function, anaemia and developmental delay. Attempts have been made to quantify the morbidity associated with intestinal nematodes. This is difficult due to non-specific clinical effects such as "cognitive deficit" which generates difficulties in calculation of disability weights and years of life with disability. These calculations are also based on epidemiological data in resource-poor countries, which may be inaccurate or incomplete [44].

Nevertheless, within these limitations, the 2001 Global Burden of Disease study estimated 58.1 million people suffered "high-intensity" *A. lumbricoides* infection, 26.6 million with high-intensity *T. trichiura* infection and 59.9 million with high-intensity hookworm infection. Only 3000 deaths were attributable to each species; however each was responsible for between 0.8 and 1.8 million DALYs. These DALYs were concentrated in Southeast Asia and sub-Saharan Africa. Much higher DALYs have been calculated in other studies (e.g. 39 million DALYs for *A. lumbricoides*) when disability weights are altered to include chronic low-level disease leading to anaemia, cognitive impairment, and other less morbid sequelae [44].

Tissue Nematodes

The next main class of diseases attributable to nematodes is those that cause invasive tissue infections. The most well-known of these is trichinellosis, caused by ingestion of undercooked trichinous meat (classically pork) in which parasites migrate to the host striated muscle. Other significant nematode tissue diseases include visceral and ocular larva migrans, cutaneous larva migrans and cerebral angiostrongyliasis.

Trichinellosis has been reported worldwide; however the prevalence is unknown. It is thought that there are significant under-reporting and asymptomatic cases. A literature review conducted through 1986 to 2009 revealed 65,818 cases of trichinellosis and 42 deaths reported from 41 countries [46]. Cases are concentrated in Europe, especially Romania, the former Soviet Union and Central Europe. Other places with high prevalence include China, Thailand, Mexico, Argentina and Bolivia. Trichinellosis is rare in the United States, with only 90 reported cases between 2008 and 2012 [47].

The seroprevalence of antibodies to *Toxocara* species (accounting for visceral and ocular larva migrans) has been estimated at 5% in the United States and is declining with time [48]. As seen in many parasitic diseases diagnosed in Western countries, these often occur in migrants or families of migrants, with many infections thought to be asymptomatic. Hookworm-related cutaneous larva migrans is endemic in resource-poor countries in the developing world but is also frequently seen in returning travellers from these regions [49].

Other Nematodes

Eight species of filarial nematodes infect approximately 120 million people worldwide [50]. These organisms reside in the lymphatic channels. The best known of these is *Wuchereria bancrofti*, which accounts for the majority of cases. As is common with helminthic infections, the spectrum of disease ranges from asymptomatic and minimally symptomatic (with subtle signs of haematuria, proteinuria etc.) to frank lymphatic disease and elephantiasis: 44 million people worldwide suffer the severe symptoms of lymphoedema and elephantiasis. In 2000, the WHO launched an ambitious programme to eliminate lymphatic filariasis by 2020, and more than 4.5 billion treatments have been provided in 59 countries with a reduction in the incidence of lymphatic filariasis by 59% in 2012 [51].

The filarial nematode *Onchocerca volvulus* causes "river blindness", another WHO neglected tropical disease, affecting at least 25 million individuals in 35 countries (99% in sub-Saharan Africa). Efforts to eliminate this illness have been problematic [52].

The Guinea worm (*Dracunculus medinensis*) is a nematode that deserves special epidemiological mention. This long nematode migrates from the stomach to the lower extremity where it forms a painful blister and ruptures, releasing larva-rich fluid for ingestion by the crustacean *Cyclops* to complete the life cycle. The worm can then be extracted surgically, or by winding it around a stick gradually. No medical treatment exists. Through dedicated eradication programmes, the number of reported cases has declined from 3.5 million in 1986 to only about 30 per year, making it a candidate for the first parasitic disease to be eradicated [53].

Epidemiology of Trematodes

As is a common theme for parasitic diseases, parasitic fluke infection is rare in developed high-income countries (with the exception of returned travellers or immigrants and South Korea). In contrast, there is substantial burden of disease in lower-income countries with at least 200 million infected by the "blood fluke" *Schistosoma*, which colonises blood vessels [54].

In 2015, the WHO estimated that at least 40 million people worldwide are affected by food-borne trematodes including liver flukes, lung flukes and intestinal flukes although some estimates are much higher [55]. These three types of flukes are known as the food-borne trematodoses, which are another WHO neglected tropical disease category.

A comprehensive 2012 systematic review revealed that the global burden of human food-borne trematodiasis was approximately 665,352 DALYs, with 7.9 million with severe sequelae and 7158 deaths, mostly from cholangiocarcinoma and cerebral infection [56].

Schistosomasis

The "blood fluke" schistosomiasis (*S. haematobium*, *S. mansoni*, etc.) is the most important fluke infection in humans. This organism (which uses the snail as the intermediate host) is acquired through penetration of the skin, usually bare feet,

in fresh-water contact. The worldwide burden of disease from this organism is second only to malaria. Schistosomiasis is generally treated medically; however it is surgically relevant as it is a major risk factor for the development of bladder cancers in regions where urogenital schistosomiasis is prevalent [57]. Given it is generally treated medically, it is not considered further here; however the contemporary epidemiological trends of this fluke have been described in multiple sources [58, 59].

Liver Flukes

The liver flukes are surgically relevant through their propensity to cause chronic biliary infestation and obstruction [60]. Bile duct obstruction is a common cause of cirrhosis in endemic regions. Gallstone formation and recurrent cholangitis also are seen, and the link between liver flukes and cholangiocarcinoma is well-known. The eggs from liver flukes arise from undercooked fish and are released into the duodenum and migrate into the biliary tree, where they can reside for many years and lead to chronic infection and inflammation. As expected, infection is concentrated in river regions where fishing is common, in particular where the tradition of eating undercooked or raw fish is widespread.

The Chinese or oriental fluke *Clonorchis* is endemic among fish-eating mammals in the Far East with approximately 35 million humans infected [61] (15 million in China alone [62]). Southern China and Manchuria regions are endemic with rates of prevalence between 10% and 85%. Despite significant declines in many parasitic diseases, *Clonorchis* and other liver fluke infections are significant problems in the highly developed South Korea, with up to 1.4 million infected. These cases are highly concentrated in traditional Korean fishing villages near rivers where the ancient practice of eating raw fish has been difficult to stop [63]. These regions have comparably a very high prevalence of cholangiocarcinoma (5.5 per 100,000).

Opisthorchiasis is thought to affect approximately 23 million individuals worldwide [61, 64]. Infection with *Opisthorchis* species is common in Southeast Asia, classically in the northern part of Thailand where the tradition of eating *koi pla*, a salad containing raw meat (Fig. 1.5), is widespread and the seroprevalence is estimated to be approximately 15.7% [65].In contrast, the urbanised part of Thailand was observed to have a very low seroprevalence. Specific regions and villages can have prevalence rates of up to 80%.

Similarly the flukes of the *Fasciola* zoonoses are acquired through consumption of certain aquatic plants. Fascioliasis affects between 2.4 and 17 million people worldwide [66].

Burden of disease estimates are difficult to quantify for liver flukes as is common for all helminthic infections, as a large proportion of infections are asymptomatic or minimally symptomatic. Flukes can occupy the biliary tree for decades and induce varying degrees of chronic inflammation and unexplainable lassitude, which can result in significant reductions in lifetime productivity.

The association of cholangiocarcinoma with liver fluke infection is well-known. For example, the incidence of liver fluke in Thailand is extremely high. The highest percentage of cholangiocarcinoma is seen in the northeast of the country, which

Fig. 1.5 [75] (**a**) Fluke-infected fish are plentiful in the local rivers such as the Chi River in Khon Kaen province, Thailand. (**b**) Local people catch the fish in nets and prepare the fish-based meals with local herbs, spices and condiments. (**c**) The finished dish of *koi pla* accompanied by rice and vegetables. This dish is a dietary staple of many northeastern Thai villagers and is a common source of infection with *O. viverrini*

correlates to the highest incidence of *O. viverrini* [67]. Similar observations are seen with *C. sinensis* in China and elsewhere [68].

Control strategies for liver fluke have been described. For example, in 2016, a multifaceted Thai strategy incorporating education, avoidance of uncooked meat and improved faecal sanitation practices saw significant reductions in infection rates for humans and animals [69].

Intestinal and Lung Flukes

Two species of flukes (*Fasciolopsis buski* in Southeast Asia and *Heterophyes heterophyes* in Egypt) cause intestinal infestations with adult worms, similar to the listed cestodes and nematodes. Epidemiological studies of these organisms are difficult for similar regions: many patients are asymptomatic or minimally symptomatic with non-specific symptoms. It is thought that the number infected worldwide is in the millions [70].

The lung fluke *Paragonimus westermani* is highly endemic to West Africa, Central and South America and Asia with at least several million people infected worldwide [71]. Adult encapsulated worms are found in the lungs of infected humans. In addition to medical therapy, some patients require operative resection.

Epidemiology of Protozoan Parasites

The worldwide burden of diseases from protozoan parasites such as malaria, leishmaniasis, Chagas disease and amoebiasis is highly significant. Malaria in particular poses the largest and most significant burden of disease for a parasitic organism. In most cases, these illnesses are not treated with surgery and are not surgically relevant, and for brevity, their epidemiological characteristics are not described here.

Amoebiasis is prototypical example of a protozoal infection that can cause liver abscess and colitis which can require operation. The interested reader is referred to contemporary reviews of the epidemiological status of amoebiasis [72]. The cases in which protozoan illnesses require surgery are discussed in Chap. 3.

References

1. Hotez PJ, Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. Lancet. 2009;373(9674):1570–5.
2. World Health Organization. Investing to overcome the global impact of neglected tropical diseases: WHO third report on neglected tropical diseases. Geneva: WHO; 2015.
3. Hotez PJ, Alvarado M, Basáñez M-G, Bolliger I, Bourne R, Boussinesq M, et al. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. PLoS Negl Trop Dis. 2014;8(7):e2865.
4. Mitra A, Mawson A. Neglected tropical diseases: epidemiology and global burden. Trop Med Infect Dis. 2017;2(3):36.
5. Budke CM, Deplazes P, Torgerson PR. Global socioeconomic impact of cystic echinococcosis. Emerg Infect Dis. 2006;12(2):296.
6. World Health Organization. Integrating neglected tropical diseases into global health and development: fourth WHO report on neglected tropical diseases. Geneva: World Health Organization; 2017.
7. Sacks DL. Vaccines against tropical parasitic diseases: a persisting answer to a persisting problem. Nat Immunol. 2014;15(5):403.
8. Jain N, Hwang T, Franklin JM, Kesselheim AS. Association of the priority review voucher with neglected tropical disease drug and vaccine development. JAMA. 2017;318(4):388–9.
9. Weng H-B, Chen H-X, Wang M-W. Innovation in neglected tropical disease drug discovery and development. Infect Dis Poverty. 2018;7(1):67.
10. Wise J. Spending on research into neglected disease reached record high in 2017. BMJ. 2019;364:l303.
11. Torgerson PR, Devleesschauwer B, Praet N, Speybroeck N, Willingham AL, Kasuga F, et al. World Health Organization estimates of the global and regional disease burden of 11 foodborne parasitic diseases, 2010: a data synthesis. PLoS Med. 2015;12(12):e1001920.
12. Grosso G, Gruttadauria S, Biondi A, Marventano S, Mistretta A. Worldwide epidemiology of liver hydatidosis including the Mediterranean area. World J Gastroenterol. 2012;18(13):1425.
13. Acosta-Jamett G, Weitzel T, Boufana B, Adones C, Bahamonde A, Abarca K, et al. Prevalence and risk factors for echinococcal infection in a rural area of northern Chile: a household-based cross-sectional study. PLoS Negl Trop Dis. 2014;8(8):e3090.
14. Yuan R, Wu H, Zeng H, Liu P, Xu Q, Gao L, et al. Prevalence of and risk factors for cystic echinococcosis among herding families in five provinces in western China: a cross-sectional study. Oncotarget. 2017;8(53):91568.
15. WHO (World Health Organization). Echinococcosis- Fact sheet 2017. Geneva, Switzerland: WHO; 2017. Available online: https://www.who.int/en/news-room/factsheets/detail/echinococcosis.
16. European Centre for Disease Prevention and Control (ECDC), 2010. Annual epidemiological report of communicable diseaes in Europe 2010. Stockholm, Sweden: ECDC. Available online: https://www.ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/1011_SUR_Annual_Epidemiological_Report_on_Communicable_Diseases_in_Europe.pdf.

17. Bristow BN, Lee S, Shafir S, Sorvillo F. Human echinococcosis mortality in the United States, 1990–2007. PLoS Negl Trop Dis. 2012;6(2):e1524.
18. Keong B, Wilkie B, Sutherland T, Fox A. Hepatic cystic echinococcosis in Australia: an update on diagnosis and management. ANZ J Surg. 2018;88(1–2):26–31.
19. Li J, Wu C, Wang H, Liu H, Vuitton DA, Wen H, et al. Boiling sheep liver or lung for 30 minutes is necessary and sufficient to kill Echinococcus granulosus protoscoleces in hydatid cysts. Parasite. 2014;21:64.
20. Moro PL, Budke CM, Schantz PM, Vasquez J, Santivanez SJ, Villavicencio J. Economic impact of cystic echinococcosis in Peru. PLoS Negl Trop Dis. 2011;5(5):e1179.
21. Tamarozzi F, Hou A, Morales ML, Giordani MT, Vilca F, Mozo K, et al. Prevalence and risk factors for human cystic echinococcosis in the Cusco region of the Peruvian highlands diagnosed using focused abdominal ultrasound. Am J Trop Med Hyg. 2017;96(6):1472–7.
22. Gavidia CM, Gonzalez AE, Zhang W, McManus DP, Lopera L, Ninaquispe B, et al. Diagnosis of cystic echinococcosis, central Peruvian highlands. Emerg Infect Dis. 2008;14(2):260.
23. Moro P, Schantz PM. Cystic echinococcosis in the Americas. Parasitol Int. 2006;55:S181–S6.
24. Irabedra P, Ferreira C, Sayes J, Elola S, Rodríguez M, Morel N, et al. Control programme for cystic echinococcosis in Uruguay. Mem Inst Oswaldo Cruz. 2016;111(6):372–7.
25. Larrieu E, Costa MT, Cantoni G, Labanchi JL, Bigatti R, Pérez A, et al. Control program of hydatid disease in the province of Río Negro, Argentina. 1980–1997. Boletin chileno de parasitologia. 2000;55(3/4):49–53.
26. de La Rue ML. Cystic echinococcosis in southern Brazil. Rev Inst Med Trop Sao Paulo. 2008;50(1):53–6.
27. Pavletic CF, Larrieu E, Guarnera EA, Casas N, Irabedra P, Ferreira C, et al. Cystic echinococcosis in South America: a call for action. Rev Panam Salud Publica. 2017;41:e42.
28. Larrieu E. Prevention and control of hydatidosis at local level: South American initiative for the control and surveillance of cystic Echinococcosis/Hydatidosis. PANAFTOSA Tech Manual. Washington D.C.: Pan American Health Organization; 2017;18:56. Available online: https://iris.paho.org/handle/10665.2/49043.
29. Torgerson PR, Keller K, Magnotta M, Ragland N. The global burden of alveolar echinococcosis. PLoS Negl Trop Dis. 2010;4(6):e722.
30. Zhenghuan W, Xiaoming W, Xiaoqing L. Echinococcosis in China, a review of the epidemiology of Echinococcus spp. EcoHealth. 2008;5(2):115–26.
31. Magambo J, Njoroge E, Zeyhle E. Epidemiology and control of echinococcosis in sub-Saharan Africa. Parasitol Int. 2006;55:S193–S5.
32. Wahlers K, Menezes CN, Wong M, Mogoye B, Frean J, Romig T, et al. Human cystic echinococcosis in South Africa. Acta Trop. 2011;120(3):179–84.
33. Sadjjadi SM. Present situation of echinococcosis in the Middle East and Arabic North Africa. Parasitol Int. 2006;55:S197–202.
34. Narra R, Maestri M, Budke CM, Tamarozzi F, Mariconti M, Nicoletti GJ, et al. Costs associated with surgically treated cases of abdominal cystic echinococcosis: a Single Center's experience from 2008 to 2014, Pavia, Italy. Am J Trop Med Hyg. 2016;95(2):405–9.
35. Lötsch F, Budke CM, Auer H, Kaczirek K, Waneck F, Lagler H, et al. Evaluation of direct costs associated with alveolar and cystic echinococcosis in Austria. PLoS Negl Trop Dis. 2019;13(1):e0007110.
36. Organization WH. Meeting of the WHO Informal Working Group on Echinococcosis (WHO-IWGE): WHO Headquarters, Geneva, 15–16 December 2016. World Health Organization; 2017.
37. Craig PS, McManus DP, Lightowlers MW, Chabalgoity JA, Garcia HH, Gavidia CM, et al. Prevention and control of cystic echinococcosis. Lancet Infect Dis. 2007;7(6):385–94.
38. Pourseif MM, Moghaddam G, Saeedi N, Barzegari A, Dehghani J, Omidi Y. Current status and future prospective of vaccine development against Echinococcus granulosus. Biologicals. 2018;51:1–11.
39. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. Bull World Health Organ. 1996;74(3):231–42.
40. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114(1):1–16.

41. Del Brutto OH. Neurocysticercosis: a review. Sci World J. 2012;2012:159821.
42. White AC, Coyle CM, Rajshekhar V, Singh G, Hauser WA, Mohanty A, et al. Diagnosis and treatment of neurocysticercosis: 2017 clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg. 2018;98(4):945–66.
43. Bouteille B. Epidemiology of cysticercosis and neurocysticercosis. Med Sante Trop. 2014;24(4):367–74.
44. Brooker S. Estimating the global distribution and disease burden of intestinal nematode infections: adding up the numbers–a review. Int J Parasitol. 2010;40(10):1137–44.
45. Smits HH, Everts B, Hartgers FC, Yazdanbakhsh M. Chronic helminth infections protect against allergic diseases by active regulatory processes. Curr Allergy Asthma Rep. 2010;10(1):3–12.
46. Murrell KD, Pozio E. Worldwide occurrence and impact of human trichinellosis, 1986–2009. Emerg Infect Dis. 2011;17(12):2194.
47. Wilson NO, Hall RL, Montgomery SP, Jones JL. Trichinellosis surveillance—United States, 2008–2012. Morb Mortal Wkly Rep Surveill Summ. 2015;64(1):1–8.
48. Liu EW, Chastain HM, Shin SH, Wiegand RE, Kruszon-Moran D, Handali S, et al. Seroprevalence of antibodies to Toxocara species in the United States and associated risk factors, 2011–2014. Clin Infect Dis. 2017;66(2):206–12.
49. Heukelbach J, Feldmeier H. Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans. Lancet Infect Dis. 2008;8(5):302–9.
50. Joshi PL. Epidemiology of Lymphatic Filariasis. In: Tyagi B. (eds) Lymphatic Filariasis. Singapore: Springer; 2018.
51. Ramaiah K, Ottesen EA. Progress and impact of 13 years of the global programme to eliminate lymphatic filariasis on reducing the burden of filarial disease. PLoS Negl Trop Dis. 2014;8(11):e3319.
52. Colebunders R, Basáñez M-G, Siling K, Post RJ, Rotsaert A, Mmbando B, et al. From river blindness control to elimination: bridge over troubled water. Infect Dis Poverty. 2018;7(1):21.
53. Molyneux D, Sankara DP. Guinea worm eradication: Progress and challenges—should we beware of the dog? PLoS Negl Trop Dis. 2017;11(4):e0005495.
54. King CH, Dickman K, Tisch DJ. Reassessment of the cost of chronic helmintic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet. 2005;365(9470):1561–9.
55. Organization WH. WHO estimates of the global burden of foodborne diseases: foodborne disease burden epidemiology reference group 2007–2015. Geneva: World Health Organization; 2015.
56. Fürst T, Keiser J, Utzinger J. Global burden of human food-borne trematodiasis: a systematic review and meta-analysis. Lancet Infect Dis. 2012;12(3):210–21.
57. Ishida K, Hsieh MH. Understanding urogenital schistosomiasis-related bladder cancer: an update. Front Med. 2018;5:223.
58. King CH, Galvani AP. Underestimation of the global burden of schistosomiasis. Lancet. 2018;391(10118):307–8.
59. McManus DP, Dunne DW, Sacko M, Utzinger J, Vennervald BJ, Zhou XN. Schistosomiasis. Nat Rev Dis Primers. 2018;4(1):13.
60. Harrington D, Lamberton PH, McGregor A. Human liver flukes. Lancet Gastroenterol Hepatol. 2017;2(9):680–9.
61. Keiser J, Utzinger J. Emerging foodborne trematodiasis. Emerg Infect Dis. 2005;11(10):1507.
62. Lai D-H, Hong X-K, Su B-X, Liang C, Hide G, Zhang X, et al. Current status of Clonorchis sinensis and clonorchiasis in China. Trans R Soc Trop Med Hyg. 2016;110(1):21–7.
63. Shin E-H, Guk S-M, Kim H-J, Lee S-H, Chai J-Y. Trends in parasitic diseases in the Republic of Korea. Trends Parasitol. 2008;24(3):143–50.
64. Andrews RH, Sithithaworn P, Petney TN. Opisthorchis viverrini: an underestimated parasite in world health. Trends Parasitol. 2008;24(11):497–501.
65. Kaewpitoon N, Kaewpitoon SJ, Pengsaa P. Opisthorchiasis in Thailand: review and current status. World J Gastroenterol. 2008;14(15):2297.

66. Mas-Coma S, Valero MA, Bargues MD. Chapter 2. Fasciola, lymnaeids and human fascioliasis, with a global overview on disease transmission, epidemiology, evolutionary genetics, molecular epidemiology and control. Adv Parasitol. 2009;69:41–146.
67. Kamsa-ard S, Kamsa-ard S, Luvira V, Suwanrungruang K, Vatanasapt P, Wiangnon S. Risk factors for cholangiocarcinoma in Thailand: a systematic review and meta-analysis. Asian Pacific J Cancer Prev. 2018;19(3):605.
68. Choi BI, Han JK, Hong ST, Lee KH. Clonorchiasis and cholangiocarcinoma: etiologic relationship and imaging diagnosis. Clin Microbiol Rev. 2004;17(3):540–52.
69. Sripa B, Echaubard P. Prospects and challenges towards sustainable liver fluke control. Trends Parasitol. 2017;33(10):799–812.
70. Chai J-Y. Intestinal flukes. In: Foeod-borne parasitic zoonoses. New York: Springer; 2007. p. 53–115.
71. Blair D, Agatsuma T, Wang W. Paragonimiasis. In: Food-borne parasitic zoonoses. New York: Springer; 2007. p. 117–50.
72. Shirley DT, Farr L, Watanabe K, Moonah S. A review of the global burden, new diagnostics, and current therapeutics for amebiasis. Open Forum Infect Dis. 2018;5(7):ofy161.
73. Disease UtC-NT. United to Combat Burden Map—Neglected tropical diseases. 2009. Available from: http://unitingtocombatntds.org/resource/burden-map-neglected-tropical-diseases.
74. Organization WH. Distribution of E. granulosus and cystic echinococcosis worldwide 2011. Available from: https://www.who.int/echinococcosis/Global_distribution_of_cystic_echinococcosis_2011.pdf?ua=1.
75. Sripa B, Kaewkes S, Sithithaworn P, Mairiang E, Laha T, Smout M, et al. Liver fluke induces cholangiocarcinoma. PLoS Med. 2007;4(7):e201.

Classification of Parasitic Diseases

2

Eirini Christaki

Classification

Parasites are primarily divided into ectoparasites/arthropods, which live on the surface of other organisms, such as lice or ticks, and (endo)parasites, which live within organisms. Parasites occur in nature in two major forms, namely, protozoa, which are single-cell eukaryotic organisms, and helminths, which are multicellular organisms. Helminths are otherwise called worms. Protozoa can be further divided based on their mode of reproduction and their means of movement into amebae/Sarcodina, flagellates/Mastigophora, sporozoans/Apicomplexa, and ciliates/Ciliophora. The first two belong to the same phylum. Helminths can be divided into flatworms and nematodes/roundworms. Flatworms are further subdivided into tapeworms/cestodes and flukes/trematodes [1–3]. Ectoparasites/arthropods will not be covered in this chapter. Common terms in parasitology and their respective definitions are shown in Table 2.1.

Diagnosis of Parasitic Diseases

Parasites most often are large enough and have a typical morphology, so diagnosis of parasitic diseases relies primarily on microscopy. However, antigen, antibody tests, as well as molecular methods are also used for the identification of parasites and disease diagnosis [1, 3].

A. *Microscopy* continues to be the mainstay for the detection and identification of most parasitic diseases. Microscopic examination can be performed either directly from the collected specimen or after concentration, and the use of specific staining (i.e., Giemsa, hematoxylin, trichrome stain) enhances sensitivity.

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Table 2.1 Commonly used terms in parasitology and their respective explanations

Term	Definition
Trophozoite	Motile, reproducing form
Cyst	Nonmotile, nonreproducing, usually surrounded by a thick membrane
Promastigotes	Flagellated forms
Amastigotes	Non-flagellated forms
Larva(e)	Immature form(s) (helminths)
Definite host	Sexual phase occurs
Intermediate host	Asexual phase occurs
Reservoir	Population of organisms in which the pathogen (naturally) lives
Obligate parasite	Needs the host to complete its life cycle
Facultative parasite	It can survive both as free-living organism and within the host

Determination of the morphologic characteristics of protozoa and adult forms of helminths, as well as specific features of eggs or larvae, allows the identification of each parasite. Specimens should be examined promptly, i.e., stool within 1 hour from collection. Since cysts are passed intermittently in the stools, at least three separate specimens should be examined.

B. *Antigen detection* is possible for *Entamoeba histolytica*, *Giardia lamblia*, *Plasmodium* spp., *Cryptosporidium* spp., and *Trichomonas vaginalis* with good sensitivity.

C. *Nucleic acid-based tests* are routinely used for *Trichomonas vaginalis* and *Plasmodium* spp. These tests may also be useful for the detection of parasites like *Trypanosoma* spp., *Toxoplasma gondii*, or *Leishmania* spp., when only few organisms may be present in a biologic sample. For the detection of other parasites, nucleic acid-based tests are available in reference laboratories.

D. *Serology* may be useful for diagnosis in non-endemic regions, as a large percent of the population may have a positive serology in endemic countries.

E. *Culture* is rarely possible for parasites, and if so, it is available usually only at reference laboratories. One exception is *Trichomonas vaginalis*, which can be cultured in commercially available media.

Protozoa

Taxonomic classification of protozoa has changed with the application of phylogenetic analysis, and some organisms formerly categorized as protozoa have been found to be genetically closer to fungi, for example, *Pneumocystis jirovecii* and *Microsporidia* [4, 5]. A clinically relevant classification of protozoa entails the separation according to the affected organ system and/or their mode of transmission (Table 2.2).

Amebae typically use pseudopodia and/or protoplasmic flow to move. The main representative organisms are *Entamoeba*, *Acanthamoeba*, and *Naegleria*. Flagellates are characterized by possessing one or more flagella(s), which is a structure resembling a whip and helps the parasite move. They also sometimes contain an undulating membrane (i.e., trypanosomes). Medically important organisms in this group

Table 2.2 Major protozoa, which cause disease in humans according to the site of infection

Site of infection	Protozoa	Mode of transmission
Intestinal protozoa	*Entamoeba histolytica*	Fecal-oral/ingestion of cysts
	Giardia lamblia	Fecal-oral/ingestion of cysts
	Cryptosporidium spp. (*Cryptosporidium hominis*, *Cryptosporidium parvum*)	Fecal-oral/ingestion of oocysts
	Cystoisospora species (*Cystoisospora belli*)	Fecal-oral/ingestion of oocysts
	Cyclospora species (Cyclospora cayetanensis)	Fecal-oral/ingestion of oocysts
	Balantidium coli	Fecal-oral
Urogenital Protozoa	*Trichomonas vaginalis*	Sexual transmission
Blood and tissue Protozoa	*Plasmodium* species	Female *Anopheles* mosquito
	Babesia species (*Babesia microti*)	Ticks, blood transfusion
	Toxoplasma gondii	Ingestion of parasites from undercooked meat, ingestion of oocysts after contact with cat feces, blood transfusion, transplacental
	Trypanosoma species *T. cruzi.* *T. brucei gambiense.* T. brucei gambiense.	Reduviid (kissing) bug, blood transfusion, transplacental Tsetse fly Tsetse fly
	Leishmania species *L. donovani* (visceral leishmaniasis). *L. tropica*, *L. major* (Old World cutaneous leishmaniasis). *L. mexicana* complex (New World cutaneous leishmaniasis). *L. aethiopica*, *L. Mexicana pifano* (disseminated cutaneous leishmaniasis). *L. braziliensis* complex (mucocutaneous leishmaniasis).	Sandfly
	Acanthamoeba	Exposure to contaminated water usually after swimming in freshwater lakes, hot springs, rivers, and swimming pools and/or eye trauma
	Naegleria	Inhalation of contaminated water usually after swimming in freshwater lakes, hot springs, rivers, and swimming pools
	Sarcocystis spp.	Food-borne (meat)

are (A) flagellates which involve the intestinal and genitourinary system, like *Giardia* and *Trichomonas*, respectively, and (B) flagellates which circulate in the blood and can invade tissues, like *Trypanosoma* and *Leishmania* [2, 6].

Sporozoa have a complex life cycle involving intermediate hosts, which is characterized by sexual and asexual reproductive phases. These parasites are almost always intracellular. Major organisms in this group are *Plasmodium*, *Babesia*, *Cryptosporidium*, *Cyclospora*, and *Toxoplasma*. Ciliates possess two types of nuclei in each cell, and they have cilia, organized in rows or patches. The only medically important human parasite of this group is *Balantidium coli*, a very big cell which can be found in the intestinal tract of infected individuals, though actual disease in humans is rare [2, 6].

A separate group, formerly categorized as Sporozoa, are Microsporidia. However, recent genomic analysis has demonstrated that these organisms are more closely related to fungi [5]. These diverse spore-forming organisms possess a characteristic polar filament (or polar tube), and they can infect a large variety of hosts. The main species causing human disease are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*, and they are opportunistic pathogens [2].

Amebae

Entamoeba

The life cycle of *Entamoeba histolytica* consists of two stages, the trophozoite and cyst stage. Cysts are acquired by ingestion of fecally contaminated food or water. Within the intestine, cysts differentiate to form trophozoites (ileum), which cause dysentery by invading the colonic mucosa (cecum and colon), and through which they can spread via the bloodstream to the liver, or less commonly to the lung and brain. Cysts and trophozoites are being passed with feces to the environment, where cysts can survive, whereas trophozoites are killed by exposure to air. Anal-oral transmission in men who have sex with men (MSM) has also been reported. Humans are the only host [4, 5].

Infection with *E. histolytica* is asymptomatic in 90% of cases. The clinical syndromes of amebiasis include acute intestinal amebiasis (amebic dysentery), chronic amebiasis, and liver abscess. Less commonly, a granulomatous lesion, called an ameboma, may be found in the cecum or retrosigmoid area and must be differentiated from colonic adenocarcinoma. Liver abscess can present with fever, right-upper-quadrant pain, weight loss, and hepatomegaly. Aspiration fluid from the abscess is thick, contains necrotic material, and has a characteristic brownish color, resembling anchovy paste [4, 5].

Diagnosis is made by microscopic examination of the stool for trophozoites or cysts. Stool is usually heme positive, and there is paucity of neutrophils. Trophozoites contain ingested red blood cells. Their nucleus has a characteristic appearance with small central nucleolus and fine chromatin granules at the border of the nuclear membrane. Cysts have small size and contain four nuclei, which is an important

diagnostic characteristic. Trophozoites are rare in liver abscess aspirates because they are usually present near the capsule. Cysts of *E. histolytica* and *E. dispar* are morphologically indistinguishable, but stool ELISA for Gal/GalNAc lectin can differentiate the two species, since it is only positive in *E. histolytica*. Antibodies against trophozoite antigens do not offer lifelong protection, and reinfection can occur. However, serologic tests can be used for the diagnosis of invasive amebic disease [1–4].

Free-living amebae* are *Acanthamoeba*, *Naegleria*, and *Balamuthia

The first two are found worldwide and have been isolated from fresh water lakes, taps, swimming pools, hot springs, as well as air conditioning and heating units. *Balamuthia* has been found in soil.

Naegleria causes meningoencephalitis following either aspiration of contaminated (with cysts or trophozoites) water or inhalation of contaminated dust. *Naegleria* invades the meninges via the nasal mucosa and cribriform plate. The presentation and findings resemble that of purulent bacterial meningitis, cranial nerve palsies are common, and progression can be rapid with an overall poor prognosis. Motile trophozoites in CSF wet mount confirm the diagnosis, while serology is not helpful [2, 4, 6].

Balamuthia mandrillaris also causes amebic meningoencephalitis with a usually subacute course but grave prognosis. Brain imaging yields hypodense space-occupying lesions, and CSF shows pleocytocis with a neutrophilic or monocytic predominance [2, 4, 6].

Acanthamoeba causes granulomatous amebic encephalitis and keratitis**.** Granulomatous amebic encephalitis occurs most commonly in immunosuppressed or debilitated patients and has a subacute course with headache, altered mental status, cranial nerve palsies, focal neurologic deficit, or ataxia. Diagnosis is made by detection of trophozoites or cysts in CSF or biopsy specimens, and prognosis is extremely poor. Keratitis by *Acanthamoeba* can occur via trauma and exposure to contaminated water or most commonly with the use of extended-wear contact lenses (while swimming or sub-optimally disinfected). *Acanthamoeba* cysts can be identified in corneal scrapings or biopsy specimens. Corneal invasion and abscess formation can lead to vision loss, and these infections are hard to treat [2, 4, 6].

Flagellates

Trypanosoma

The *Trypanosoma* subspecies which elicit disease in humans are (a) *Trypanosoma cruzi*, which is the cause of Chagas disease (American trypanosomiasis), (b) *Trypanosoma brucei gambiense*, and (c) *Trypanosoma brucei rhodesiese*. The last two are the etiologic agents of sleeping sickness (African trypanosomiasis).

T. cruzi is transmitted by the triatomine insects (*reduviid bugs*), which acquire the parasite after feeding from infected humans or animals. Parasites multiply in the insect's gut and are then released with bug feces onto the skin or mucosa of the host at the time of the insect bite. Transmission has also been reported with organ donation, blood transfusion, vertically from mother to child, as well as after laboratory accident exposure. Clinical disease can be divided into three entities, an acute self-limiting febrile illness, an indeterminate phase of asymptomatic Chagas disease (detectable antibodies and minimal, if any, parasitemia), and in few patients a clinical syndrome with gastrointestinal and cardiac involvement and serious prognosis. Megaesophagus can result in severe reflux and aspiration pneumonitis; megacolon presents with constipation and sometimes obstruction, volvulus, and sepsis; and cardiac disease includes rhythm disturbances, dilated cardiomyopathy, thromboembolism, and heart failure [7, 8]. Detection of parasites by microscopic examination of blood or of Giemsa-stained thin and thick blood smears as well as hemoculture or PCR can confirm the diagnosis of acute Chagas, whereas serology is the test of choice for the diagnosis of chronic Chagas disease [3, 7, 8].

T. brucei gambiense (West African) and the *T. brucei rhodesiense* (East African) are morphologically indistinguishable and are transmitted to humans via infected tsetse flies (*Glossina* genus). The parasites multiply in the insect's midgut and then migrate to the salivary gland from where they are released to inoculate the host's skin at the time of the blood meal. What is interesting about these trypanosomes is that they can evade immune response mechanisms for a long period by extensive antigenic variation of their surface glycoproteins [8, 9]. Human African trypanosomiasis or sleeping sickness initially presents as an acute febrile illness that can lead many years later to severe neurologic impairment and death, in untreated patients. Apart from having a different epidemiology, the clinical syndromes associated with the two subspecies are quite distinct. A painful chancre may appear at the inoculation site, and stage I disease is characterized by fever, lymphadenopathy, as well as generalized symptoms, hepatosplenomegaly, and tachycardia. Stage II disease involves the CNS and is more acute (<9 months) in East African trypanosomiasis, whereas in West African, it can occur after many months or years. Neurologic symptoms comprise of daytime somnolence, progressive indifference, loss of speech, extrapyramidal signs, ataxia, and progressive neurologic impairment. Diagnosis is made by detection of the parasites after microscopic examination of the blood, buffy coat, bone marrow, lymph node aspirate, chancre aspirate, or CSF. Serology has variable sensitivity and specificity [2, 8, 9].

Leishmania

Leishmania species are intracellular protozoa, transmitted by phlebotomine sandflies and cause different clinical syndromes according to the *Leishmania* species, the geographic location, and host response. *Leishmania* infect macrophages in the dermis, nasopharyngeal mucosa, and reticuloendothelial system resulting in

cutaneous, mucosal, and visceral leishmaniasis (kala-azar) respectively. Sandflies at the time of the blood meal regurgitate the promastigotes into the skin of the host, and these are phagocytosed by macrophages where they are transformed to amastigotes. When ingested by sandflies, amastigotes transform to promastigotes. The clinical course of the infection largely depends on the balance between T_H1 and T_H2 immune responses [2, 10, 11]. An extensive review of these syndromes is beyond the scope of this chapter. The major *Leishmania* species with their respective clinical syndromes are included in Table 2.2. Diagnosis relies on detection of the parasite by microscopic examination of bone marrow aspirates, dermal scrapings, impression smears of biopsy specimens, or other tissue specimens. Also, molecular methods have been developed for the detection and identification of *Leishmania* species [1, 3].

Giardia

Giardia lamblia causes giardiasis, which presents as diarrhea and is one of the most common parasitic diseases in developed and developing countries. Transmission occurs with ingestion of cysts (as low as ten) from fecally contaminated water or food. Trophozoites are released from cysts in the small intestine and attach to the epithelium, but they do not spread hematogenously. Cysts, which are excreted in stool, can survive in the environment, especially in cold fresh water, and they are killed by boiling or removed by water filtration. Most commonly, giardiasis causes epidemics in day-care centers, and episodic infections have been reported. Diarrhea is associated with abdominal pain, bloating, flatus, belching, and nausea and usually lasts more than 1 week, and chronic or intermittent symptoms are more frequently encountered than with other infectious causes [2, 12]. Diagnosis is made by detection of cysts or trophozoites in stool with microscopy or detection of parasite antigen in feces. Alternatively, parasites may be detected in duodenal fluid or biopsy of the small intestine. Giardia cysts contain four nuclei and are approximately 8–12 μm × 7–10 μm in size, whereas trophozoites are characteristically pear-shaped and flattened and contain two nuclei and four pairs of flagella [2, 3].

Trichomonas

Trichomonas vaginalis is transmitted with sexual contact and causes vaginitis in women and urethritis, epididymitis, or prostatitis in men. *T. vaginalis* is a motile, pear-shaped, 10 × 7 μm in size organism, with a central nucleus and four anterior flagella. It only exists as a trophozoite, which can be detected by microscopic examination of wet mount of vaginal fluid or prostatic secretions, albeit with moderate sensitivity. Alternatively, direct immunofluorescence staining, which has better sensitivity, can be used, or culture, which however is more time-consuming and usually not routinely available [12].

Sporozoa

Babesia

Babesiosis is a vector-borne disease transmitted by ticks, while the reservoir of Babesia species is wild and domestic animals. Most of the documented cases in the United States are due to *Babesia microti*, while in Europe the infection is rare, and the most commonly isolated *pathogen is Babesia divergens.* Transmission can occur also by blood transfusion in endemic areas. Infection in immunocompetent hosts is usually asymptomatic or self-limiting, but it can be life-threatening (hemolytic anemia, disseminated intravascular coagulation, multi-organ failure) in asplenic, immunocompromised, or elderly individuals. Diagnosis is made by the detection of ring forms or characteristic tetrads (resembling a Maltese cross) in thin blood smears. Other tests are the immunofluorescence antibody test (IgG) for *B. microti*, which however cannot differentiate past from active infection and PCR-based species-specific tests [2, 13].

Toxoplasma

Toxoplasma gondii is an intracellular parasite that infects mammals and birds. Its life cycle consists of two stages, the nonfeline and feline stage. During the nonfeline stage, cysts are ingested by the host, and after exposure to the acidic gastric secretions, sporozoites are released and infect the epithelial cells of the small intestine. There, they are transformed into tachyzoites which multiply within the cells, until these rupture, releasing more parasites which can reach other tissues via the bloodstream. Cyst forms containing bradyzoites (slowly replicating parasites) can persist in some organs like the brain and muscle. The feline stage takes place within the parasite's definite host, the cat. Ingestion of cysts is followed by the formation of gametes, whose fusion results in a zygote which is secreted in the feces in the form of unsporulated cyst (envelope only), which then transforms to sporulated oocyst or sporozoites after exposure to air. Transmission in humans is mainly through ingestion of oocysts from contaminated soil or bradyzoites (tissue cysts) from undercooked meat. Transmission also occurs transplacentally, and gestational age at the time of (primary) infection is critical in predicting the risk of transmission and the risk of congenital infection [2, 14].

In immunocompetent individuals, *T. gondii* most commonly causes an asymptomatic self-limiting disease. It can also manifest with lymphadenopathy, usually cervical, and generalized symptoms. Complications such as pneumonia, myocarditis, pericarditis, and meningoencephalitis or encephalopathy are rare. Immunocompromised individuals specifically patients with AIDS or lymphoproliferative disorders receiving chemotherapy can develop clinical toxoplasmosis, most commonly (more than 50%) with CNS involvement manifesting as meningoencephalitis or ring enhancing mass-like lesions. Ocular toxoplasmosis represents 35% of all chorioretinitis cases in the United States and Europe and is believed to result from congenital infection and to a much lesser extent from acquired infection [14, 15].

Diagnosis of toxoplasmosis can be made by detection of *T. gondii* tachyzoites in body fluids or lymph nodes. The isolation of cysts from tissues is not diagnostic of acute infection. However, more commonly, serology (IgG, IgM, IgA) is used for diagnosis, and molecular PCR-based techniques are also available for the detection of *T. gondii* in biologic samples. Imaging of the brain with CT, MRI, or CT/SPECT is necessary for the evaluation and diagnosis of CNS toxoplasmosis [3].

Cryptosporidium

The most common encountered *Cryptosporidium* species in human infections are *Cryptosporidium hominis* and *Cryptosporidium parvum*, which cause a self-limited diarrheal disease in immunocompetent individuals, while they can have a more severe and protracted course in immunocompromised patients, including those with AIDS. Transmission occurs via the fecal-oral route with the ingestion of oocysts, which release sporozoites that later form into merozoites, which infect epithelial cells. Infections can occur in travelers, day-care centers, and water recreational facilities [16–18]. Cysts are small (4–5 μm) and may not be easily detected in routine fecal preparations; therefore modified acid-fast stain or direct immunofluorescence stain and enzyme immunoassays may be needed for diagnosis [16].

Cystoisospora, Cyclospora

Isospora and *Cyclospora* also cause diarrheal disease after ingestion of oocysts. Similar to *Cryptosporidium*, patients with HIV/AIDS may have a more protracted course with weight loss, fatigue, and chronic diarrhea. Modified acid-fast stain may help in the diagnosis of *Isospora* large cycts (approximately 25 μm) and *Cyclospora* cycts (8–10 μm), although the latter stain variably but they can be seen under UV light microscopy.

Plasmodium

Plasmodium species are the etiologic agents of malaria, which is endemic in more than 100 countries worldwide. The five human *Plasmodium* species, namely, *Plasmodium falciparum*, *Plasmodium malaria*, *Plasmodium ovale*, *Plasmodium vivax*, and *Plasmodium knowlesi*, are transmitted by the bite of the female *Anopheles* spp. mosquito. At the time of the blood meal, infected mosquitos inoculate sporozoites, which travel via the bloodstream to the liver, where they replicate in hepatocytes (intrahepatic or proerythrocytic schizogony). Merozoites are released from the liver cells into the bloodstream and infect red blood cells (intraerythrocyte stage), where they transform into trophozoites and replicate every 48 to 72 hours. At the end of this stage, schizonts burst and release merozoites, which again infect other RBCs. After asexual reproduction, some of the parasites transform into distinct sexual forms, the gametes, which are ingested by mosquitoes upon their blood meal.

Female and male gametes form a zygote at the midgut of the insect, which matures into an ookinete and then an oocyst, which releases sporozoites who then migrate at the salivary gland. The periodic release of merozoites in the bloodstream causes periodic fever and chills, which is typical for malaria. Malaria presents with fever, chills or rigors, malaise, headache, muscle aches, arthralgias, abdominal pain, or discomfort, and patients have anemia and splenomegaly. Severe malaria, which is almost always caused by *P. falciparum*, may result in cerebral malaria, hypoglycemia, acidosis, renal failure, pulmonary edema, and liver dysfunction and can be complicated with septicemia [2, 19, 20]. An extensive review of these syndromes is beyond the scope of this chapter. Diagnosis is confirmed with microscopy of Giemsa-stained thin and thick peripheral blood smears, and Plasmodium species can be differentiated based on their morphology. Antigen-based diagnostic tests are also routinely used as well as molecular PCR-based methods [3].

Helminths

Helminths comprise of flatworms (Platyhelminthes) and roundworms (nematodes).

Flatworms (Platyhelminthes) are further divided into two classes: Cestoda (Digenea, tapeworms) and Trematoda (flukes) (Table 2.3).

Table 2.3 Major flatworm infections, which cause disease in humans, according to the site of infection

Site of infection	Flatworm	Mode of transmission
A. Cestodes (tapeworms).		
Intestinal tapeworms	*Taenia saginata* (beef tapeworm)	Ingestion of larvae in undercooked beef
	Taenia solium (pork tapeworm)	Ingestion of larvae in undercooked pork, ingestion of eggs (fecal-oral)
	Diphyllobothrium latum (fish tapeworm)	Ingestion of larvae in undercooked fish
	Hymenolepis nana (dwarf tapeworm)	Fecal-oral
Somatic/tissue tapeworms	*Echinococcus* spp. *Echinococccus granulosus* *Echinococcus multilocularis*	Ingestion of eggs
	Taenia solium (pork tapeworm)	Ingestion of larvae in undercooked pork, ingestion of eggs (fecal-oral)
B. Trematodes (flukes).		
Intestinal flukes	*Fasciolopsis buski*	Fecal-oral
	Heterophyes heterophyes	Fecal-oral
Liver flukes	*Fasciola hepatica*	Ingestion of cysts (watercress)
	Clonorchis sinensis	Ingestion of undercooked fish
Lung flukes	*Paragonimus* spp. (*Paragonimus westermani*)	Ingestion undercooked crayfish or crabs
Blood flukes	*Schistosoma* spp. *Schistosoma mansoni* *Schistosoma haematobium* *Schistosoma japonicum*	Skin penetration

Trematodes (Flukes)

Trematodes are parasitic species that affect a considerable number of people worldwide and cause significant morbidity and mortality. For clinical purposes, they can be divided into two large categories: intestinal and tissue flukes. Tissue flukes can be further divided into three categories: blood flukes, hepatic/biliary flukes, and lung flukes.

They have common morphological characteristics, including the shape of the body and the suckers.

Except schistosomes, all trematodes are hermaphroditic. Male and female schistosomes coexist in the same body. The life cycle of the trematodes includes an asexual part in the intermediate host, usually specific species of freshwater snails, and a sexual part in the definitive host, which is humans. The life cycle begins with the ingestion of the cercaria or through skin penetration (schistosomes). Cercaria are produced during the asexual stage in the snails. After ingestion, adult trematodes proceed to the sexual production of eggs which are excreted with feces, sputum, or urine, according to the type and the location of the fluke. Then the eggs infect the intermediate hosts, which are snails and some species of fish and crabs.

The most important pathogens of this category are *Schistosoma* species (blood flukes), *Clonorchis sinensis* (liver flukes), and *Paragonimus westermani* (lung flukes) [21].

Schistosoma Species (Blood Flukes)

Schistosomiasis is caused by five species of the genus *Schistosoma*. The most important ones are *S. mansoni* and *S. japonicum*, which affect the intestinal tract and the liver, and *S. haematobium,* which affects the urinary tract. As mentioned above, the free-swimming tailed cercariae of the parasite penetrate the skin in order to infect humans. As they enter the subcutaneous tissue, they leave their tail and transform into schistosomula. The schistosomulas migrate through the veins to the liver, where the parasite matures to the adult fluke which contains the male and the female attached to the same body. After the maturity (in about 6 weeks), the parasite migrates through the portal circulation to the vesical (*S. haematobium*) and the intestinal (mesenteric) veins. The adult flukes can reach up to 2 cm in length. Serologic. After mating, the parasites produce and deposit their eggs intravascularly. These penetrate the endothelium and reach the genitointestinal tissues, from where they are finally excreted into feces and urine [2, 22].

At the penetration site, a localized erythema or dermatitis can be observed. Acute infection (Katayama syndrome) is characterized by systematic symptoms like fever, headache, malaise, and cough. Diarrhea may be present, and hepatosplenomegaly, lymphadenopathy, and eosinophilia during the migration stage are common findings. In chronic schistosomiasis, patients can be asymptomatic. Cirrhosis may develop with portal hypertension, ascites, massive splenomegaly, esophageal varices, and hepatic failure. Urinary schistosomiasis is usually present with hematuria and dysuria. Chronic fibrotic changes can lead to hydroureter or hydronephrosis, chronic kidney disease, bacterial urinary tract infections, and bladder cancer. Diagnosis is established by the detection of the characteristic eggs in the stools or

urine or other infected tissues (rectum, bladder, and liver biopsy most commonly). Quantitative determination is important. More than 400 eggs per gram of feces or per 10 ml of urine suggests heavy infection with higher risk of complication. The *S. haematobium* egg is a large ovum with a terminal spine. *S. mansoni* eggs are large eggs with lateral spine. *S japonicum* eggs are smaller than *S. mansoni*'s eggs with a small spine. Serologic tests (ELISA) are available with high sensitivity and specificity but cannot distinguish the acute or chronic phase, so the diagnosis depends also on the clinical presentation and the history of exposure. Other diagnostic tests include the detection of circulating schistosome antigens in the blood and other body fluids (urine, CSF) [2, 22].

Liver/Biliary Flukes

Fasciolia hepatica

Fasciola hepatica and *Fasciola gigantica* are known as sheep liver flukes. Sheep and humans are infected by the ingestion of the parasite eggs usually through the consumption of aquatic plants such as watercress. After ingestion, metacercariae penetrate the intestinal wall and reach the liver and the biliary system, where the hermaphrodite flukes produce their eggs. Symptoms can occur during the acute phase of migration or the chronic infection. At the migration phase, fever, abdominal pain primarily at the right upper quadrant, hepatomegaly, eosinophilia, leukocytosis, and urticaria may occur. On the other hand, chronic infection is characterized by biliary obstruction, jaundice, cholangitis, and biliary cirrhosis. Diagnosis is made by the detection of the parasite ova in the stool examination. This may be difficult at the early stages of the disease in which high degree of suspicion is critical for the diagnosis. Imaging studies with CT scan may reveal hypodense migratory lesions. Serologic tests are useful with high sensitivity and specificity. Antigen detection methods are also used in veterinary medicine with high sensitivity and specificity, but more trials are needed in humans [3, 22, 23].

Clonorchis and *Opisthorchis* (Asian/Oriental Fluke)

Clonorchis sinensis, *Opisthorchis viverrini*, and *Opisthorchis felineus* are endemic in Asian countries. Humans are incidental hosts and are infected by eating raw or undercooked fish contaminated with the metacercariae of the parasite. The parasite excysts in the duodenum and migrates through the Vater's ampulla to the biliary tree. In the bile ducts, the parasite matures and can reach 1–2 cm in length. As it is a hermaphrodite parasite, it produces eggs, which are excreted with the bile to the feces and released in the environment, where they are ingested by freshwater snails (first intermediate host). The snails release the larvae that transform into cercariae which are eaten by the freshwater fish (second intermediate host). Infected individuals may be asymptomatic. Right upper quadrant pain may be present in the acute phase, especially during parasite migration, accompanied with fever, eosinophilia, and hepatomegaly. Cholangitis and biliary obstruction with jaundice also may occur. Chronic inflammation of the bile ducts causes hyperplasia and fibrosis, and the infection with *C. sinensis* has been related to cholangiocarcinoma. Diagnosis is

established with the detection of the characteristic eggs of the parasite in stool. In the acute phase, diagnosis may be difficult because eggs are detected in feces 3–4 weeks after infection. Serologic and molecular tests have been also been developed and are used to support the diagnosis [22, 24].

Lung Flukes

Paragonimiasis

The main representative in this category is *Paragonimus westermani*. The life cycle of *Paragonimus* includes two intermediate hosts as described in clonorchiasis. Humans are infected by the ingestion of raw or undercooked crayfish or crabs, which contain parasite metacercariae in their muscles and viscera. After ingestion, the eggs excyct in the duodenum and migrate through the peritoneum, the diaphragm, and the pleural cavity to the lungs. In the lungs, they mature in about 2 months, and they form cyst lesions. The eggs of the parasite pass to the environment by the sputum, or they are swallowed again and are excreted with the feces. The first intermediate hosts in the environment are snails, who release larvae, which are taken by crayfish and crabs. As seen in other migrating parasites, during the acute phase of migration, fever, urticaria, and eosinophilia may develop. When parasites encyst in the lungs, they can cause symptoms of pneumonia, productive cough, brownish sputum, bronchitis, bronchiectasis, chest pain, pleural effusion, lung abscess, and diarrhea. Extrapulmonary disease is rare but may occur, mainly in the CNS with symptoms of space-occupying lesion, such as headache, focal neurologic signs, and seizures. Diagnosis is made by the detection of the parasite's eggs in the sputum or stool. Serologic tests may be helpful especially in CNS infection or when stool examination is negative. Imaging studies may reveal lung infiltrates, bronchiectasis, abscess and nodular cavities with or without calcification, pleural effusion, and fibrosis [22, 25].

Intestinal Flukes (*Heterophyes heterophyes* and *Fasciolopsis buski*)

Humans are infected by eating raw plants (*F.buski*) and freshwater fish (*H. heterophyes*) which contain eggs of the parasite. After ingestion, the parasites mature in the small intestine and produce eggs that pass through the feces. Infection is usually asymptomatic. In heavy parasitosis, diarrhea and abdominal pain may occur. Eosinophilia may be seen in the blood count. Diagnosis is made by the detection of the parasite's ova in the stools [22].

Cestode Infections

Tapeworms (cestodes) consist of two parts: the scolex and the proglottids. The parasite uses the scolex (a rounded head) to attach to the small intestine mucosa. The mature proglottids produce the eggs (hermaphroditic) which are excreted in the feces in order to transmit to various hosts. The length of tapeworms varies, and it can reach several meters. It depends on the number of proglottids, which can count

more than 1000. The eggs are very similar morphologically among the different *Taenia* species. As a result, differences in the morphology of the scolex and the proglottids comprise the basis of the diagnosis and species identification.

Tapeworms are divided into two categories: intestinal tapeworms (non-invasive) and tissue (somatic, invasive) tapeworms. The four major tapeworms that cause non-invasive infections are *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm, the adult form), *Diphyllobothrium latum* (fish tapeworm) and *Hymenolepis nana* (dwarf tapeworm). *Taenia solium* can also cause invasive infection by the form of cysticercosis (larvae). Invasive tapeworm infection is caused by two major pathogens: *Taenia solium*, the cause of cysticercosis, and *Echinococcus* species, primary *Echinococcus granulosus* (hydatid disease) and secondary *Echinococcus multilocularis* [21].

Intestinal (Non-invasive) Cestodes

Taenia saginata (Beef Tapeworm)

T. saginata is transmitted to humans by ingesting raw or undercooked beef, which contains larvae of the parasite. Humans are the definitive host. The larvae attach to the small intestine and mature in the adult form that can reach 10 m in length, a process that can last for 2–3 months. Most of the patients are asymptomatic. Symptoms like abdominal pain or cramps, diarrhea, malaise, loss in appetite, and weight loss can occur. Usually patients notice the parasite in their feces, and as the proglottids are often motile, they can have perianal discomfort and pruritus. Diagnosis relies on the detection of the proglottids in the feces. The scolex has four suckers but no hooks that characterize *T. solium*. Also, *T. saginata* has 15–30 uterine branches in each gravid proglottid segment, in contrast to 7–12 in *T. solium*. Eggs are morphologically indistinguishable, and serologic tests are not helpful for the diagnosis [2, 26].

Taenia solium (Pork Tapeworm)

T. solium is transmitted to humans by eating raw or undercooked pork meat. The adult forms of the parasite cause taeniasis, and the clinical futures are similar to *T. saginata* infection. The larval forms can cause invasive infection, cysticercosis, which is discussed separately. The tapeworm can reach 3 m in length. Diagnosis is made similarly to *T. saginata*, and it depends on the detection of the parasite segments in the feces. The distinction between *T. solium* and *T. saginata* is made by the different characteristics of scolex and gravid proglottids as described above.

Diphyllobothrium latum (Fish Tapeworm)

Humans are infected by consuming raw or undercooked freshwater fish. Fish acquire the parasite by eating freshwater crustaceans containing embryos from the parasite eggs. The adult form is the longest tapeworm, and it can reach 20–25 meters in length .Maturation lasts from 3 to 5 weeks, and the parasite resides in the ileum. Clinically, most patients are asymptomatic, but non-specific gastrointestinal

symptoms may occur. Occasionally, intestinal obstruction may develop, and rarely cholangitis and cholesystitis may occur due to migration of the proglottids. The infection may also cause vitamin B12 deficiency by two mechanisms: (1) consumption of the vitamin from the parasite and (2) dissociation of the vitamin from the intrinsic factor, which results in vitamin malabsorption. Diagnosis relies on detection of characteristic eggs (oval shape, operculum) in the stool [2, 26].

Hymenolepis nana (Dwarf Tapeworm)

H. nana is the most common tapeworm infection. The parasite is transmitted between humans without requiring intermediate host. Infection follows the ingestion of food contaminated with human feces containing *H. nana* eggs. The egg is attached in the small intestine mucosa and matures to the adult form. The adult form can reach 2–5 cm length and is considered the smallest tapeworm that infects humans. It matures over 10–12 days. Then it releases fertilized eggs, which either can pass through the feces or can cause autoinfection by reattaching in the small intestinal wall. The clinical manifestations include non-specific gastrointestinal symptoms, although the infection is mostly asymptomatic, even with high numbers of parasites. Diagnosis is made with the detection of eggs in stool [26].

Tissue (Somatic, Invasive) Cestodes

Cysticercosis

Cysticercosis, as mentioned above, is caused by the larval forms of *T. solium*, the pork tapeworm. The infection occurs with the consumption of food or water contaminated with human feces, containing the eggs of the parasite. The consumption of raw or undercooked pork meet only causes taeniasis. Autoinfection may occur when a carrier host with tapeworm consumes contaminated food or water by his or her own feces containing the eggs of *T. solium*. The life cycle of the parasite begins when humans ingest raw or undercooked pork, which contains the larvae. The helminths mature in the small intestine producing many eggs daily by the gravid proglottids. Three to five proglottids are released daily in the feces, and each one produces up to 50,000 eggs, which can survive for several months in the environment. The intermediate host is the pig, which consumes food contaminated with human feces. Then the larvae mature in the intestine of the animal, penetrate the intestinal wall, intersperse to the tissues, and cause cysticerci. The parasite shows tropism for striated muscle tropism [26, 27].

Cysticerci can potentially affect any tissue and organ. Most commonly they infect the brain/CSF, the skeletal muscles, the skin and subcutaneous tissue, and the eye. Neurologic symptoms of hydrocephalus or increased intracranial pressure symptoms (confusion, headache, vomiting, blurred vision, dizziness, ataxia, hypertension, bradycardia, papilledema) and seizures are common. The presentation of these symptoms depends on the location and the expansion of the cysticerci. In the eye, the larvae can be visualized in the vitreous, and they can cause uveitis and retinitis. Subcutaneous nodules may develop that contain the parasites. In most of the

cases, the diagnosis is based on a combination of clinical manifestations, imaging, and serologic tests [27–29].

The absolute diagnostic criterion is the detection of the parasite in the tissues. This can be achieved in three ways: (a) histological detection of the parasite in biopsy material or surgically excised tissue, (b) visualization of the parasite by fundoscopy, and (c) neuroimaging with MRI or CT scan to detect the lesions containing the scolex. The lesions are cystic and may present with enhancement and nodular calcifications. They can reach 5–20 mm in diameter, and if they are located in the subarachnoid space or the ventricles, they can cause obstructive hydrocephalus. Another helpful examination is serological testing in the blood. Specific antibodies can be detected with ELISA. However some patients may not develop antibodies (single and calcificated lesions). Antigen detection methods have developed, but they are not widely available. Response to empiric therapy with albendazole or praziquantel is another useful criterion for the diagnosis. Diagnostic criteria of cysticercosis have been developed and can be found elsewhere [30, 31].

Echinococcus Species

The most important pathogen in this category is *Echinococcus granulosus* (dog tapeworm). Less common infections occur due to *Echinococcus multilocularis* (found in foxes). The definitive hosts are canines. Life cycle begins when eggs originating in the small intestine of dogs are excreted through feces in the environment. Ingestion of eggs by intermediate hosts, which include sheep, humans, cattle, goats, camels, and horses, is followed by the development of oncosphere embryos in the intestine and their migration primarily to the liver, but also the lungs, the brain, and the bones, where they develop into hydatid cysts. Skeletal muscles, kidneys, and spleen are alternative locations.

E. granulosus is a small tapeworm. The scolex is similar to *T. solium*, consisting of hooks and four suckers, with the difference that *E. granulosus* has only three proglottids, and it can reach 5 mm in length. In humans, the two most affected organs are the liver (65%) and the lungs (25%). Larvae develop into hydatid cysts. They are fluid-filled unilocular lesions with an external layer, a thick membrane of fibrous tissue, and an inner germinal layer. The inner layer contains scoleces, daughter cysts, and brood capsules which are germinating cystic structures that produce protoscolices (new larvae). *E. multilocularis* is generally a more aggressive pathogen, which causes multilocular cysts with local and distant spread [2, 26].

The cysts of *E. granulosus* develop slowly over the years. The signs and symptoms depend on the location and the size of the cyst. Infected individuals may commonly be asymptomatic until the cyst is enlarged and presents as a space-occupying lesion. Symptoms include abdominal pain and discomfort, mostly in the right upper quadrant, biliary obstruction and jaundice, cholangitis, cirrhosis, and portal hypertension. Pulmonary symptoms like chest pain, cough, bronchial obstruction, and dyspnea may occur with lung cysts. The cysts may be secondarily infected with bacteria and transform into abscesses. If the cyst is located in the brain, it can cause

headache and focal neurologic symptoms. Rupture of the cyst may cause dissemination of the parasites, which can form new cysts, severe allergic reaction, and anaphylactic shock. This may occur spontaneously or during the surgical removal of the cyst [26, 27, 32]. Hydatid cyst disease is extensively described in other chapters.

Imaging studies are essential for the diagnosis. Ultrasonography, MRI, and CT scan are the most common examinations performed for the evaluation of the cysts. Daughter cysts in a larger cyst are considered pathognomonic. Imaging usually reveals well-defined cysts with thick or thin walls. Mural calcification of the cyst may be seen which makes the cysts inactive. In the lungs, cysts present as solid masses with central necrosis and plaque-like calcifications. Serologic tests may be useful for the diagnosis, and they are up to 90% positive if liver cysts are present. Negative tests do not exclude the diagnosis. ELISA and immunoblotting techniques are used with sensitivity and specificity up to 80% [3, 26, 27, 33].

Nematodes (Roundworms)

Nematodes can be divided into intestinal nematodes, tissue nematodes, and nematodes whose larvae cause disease (larva migrans) (Table 2.4).

Table 2.4 Major roundworm infections, which cause disease in humans, according to the site of infection

Site of infection	Roundworm	Mode of transmission
Intestinal roundworms	*Ascaris lumbricoides* (roundworm of humans)	Fecal-oral
	Ancylostoma duodenale (Old World hookworm)	Skin penetration
	Necator americanus (New World hookworm)	Skin penetration
	Enterobius vermicularis (pinworm)	Fecal-oral
	Trichuris trichiura (whipworm)	Fecal-oral
	Strongyloides stercoralis	Skin penetration, autoinfection
	Anisakidae	Ingestion of uncooked saltwater fish
Tissue roundworms	*Trichinella spiralis*	Undercooked pork or wild game
	Wuchereria bancrofti	*Culex* mosquitoes
	Brugia malayi	*Mansonia*, *Anopheles* mosquitoes
	Loa loa	*Chrysops* (deerflies)
	Onchocerca volvulus	*Simulium* (blackflies)
	Dracunculus medinensis	Water
	Angiostrongylus cantonensis	Undercooked seafood, snails
Larva migrans syndromes	*Toxocara canis* and *Toxocara cati*	Oral/ingestion of eggs
	Ancylostoma braziliense	Skin penetration

Intestinal Nematodes

Infection with intestinal nematodes is very common worldwide, as more than one billion people are infected with one or more intestinal nematodes. However, these organisms are more common in resource-poor countries, where sanitation may be limited, and in immigrants and refugees from these countries. They have complex life cycles and vary in size from 1 mm to few centimeters. Intestinal roundworm infections may contribute to malnutrition. Clinical disease often requires prolonged stay in an endemic area, because in order to acquire a heavy burden of adult worms, one has to have repeated exposure to the infectious parasite forms [34]. Roundworm infections are commonly associated with parasitemia (Table 2.5).

Ascaris lumbricoides

Ascaris Lumbricoides reside in the small intestine and is the largest parasite in its group, reaching up to 40 cm in length. Transmission is via the fecal-oral route, when humans ingest eggs (residing in soil). Larvae hatch in the small intestine, invade through the mucosa, and migrate to the lungs (9–12 days after egg ingestion) where they ascend the bronchial tree, and then they are swallowed again reaching the small intestine and maturing into adult forms. Clinical manifestations include pulmonary and gastrointestinal symptoms. During lung migration, a nonproductive cough, chest discomfort, and fever may develop. Eosinophilia is common at early stages. Chest X-ray may show evidence of eosinophilic pneumonitis (Loffler's syndrome) with fleeting infiltrates. Symptoms from the intestinal tract, like abdominal pain or obstruction, usually occur with heavy parasite burden. Complications include intussusception, volvulus and perforation, cholecystitis, cholangitis, pancreatitis, or, rarely, liver abscess and should be included in the differential diagnosis of acute abdomen in endemic areas. Diagnosis is made by macroscopic detection of adult worms in feces or sputum and/or eggs in stool [2, 34, 35].

Table 2.5 Parasites most commonly associated with eosinophilia

Site of infection	Flatworm
Roundworms	*Ascaris lumbricoides*
	Ancylostoma spp.
	Trichinella spiralis
	Strongyloides stercoralis
	Wuchereria bancrofti, *Brugia* spp., *Lao loa*, *Onchocerca volvulus*
	Toxocara spp.
	Angiostrongylus cantonensis
	Gnathostoma spinigerum
Tapeworms/cestodes	*Echinococcus granulosus*
	Taenia solium
Flukes/Trematodes	*Schistosoma* spp.
	Clonorchis sinensis
	Fasciola hepatica
	Paragonimus spp.

Ancylostoma duodenale (Old World Hookworm), *Necator americanus* (New World Hookworm)

Ancylostoma duodenale (Old World hookworm) and *Necator americanus* (New World hookworm) cause hookworm disease when there is heavy parasite burden and/or prolonged duration of infection. Infection when combined with decreased iron uptake can result in iron deficiency anemia. However, most infections are asymptomatic. Adult worms attach to the small bowel mucosa (sucking blood) and produce eggs, which are excreted with feces. In the soil, larvae hatch and transform to the infective adult filariform worms. These penetrate the skin and reach the lung through the bloodstream, where they ascend the bronchial airways and are swallowed and descend to the small intestine. Symptoms are usually mild and include pruritic dermatitis, subcutaneous migration, pneumonitis, abdominal pain, and inflammatory diarrhea. Eosinophilia is usually present, and iron deficiency anemia as well as hypoproteinemia can develop, as mentioned above. Diagnosis is made by microscopic detection of hookworm eggs in stool samples [34, 35].

Enterobius vermicularis (Pinworm)

Infection with *Enterobius vermicularis* is very common in children worldwide. Transmission occurs with ingestion of parasite eggs, which then hatch in the small intestine and give rise to larvae that migrate to the colon after maturing into the adult forms. Male and female reproduce in the colon, and the female worm releases the eggs at the perianal skin area at night. After scratching the area, infectious embryonated eggs can cause re-infection through contamination of fingers and re-ingestion. Diagnosis is made using the clear cellulose acetate tape technique in order to recover eggs from the perianal area and examine them microscopically. Worms may also be seen in stool [2].

Trichuris trichiura (Whipworm)

Trichuris trichiura infection is more common in tropical areas and resource-poor countries. The life cycle is similar to that of *Enterobius vermicularis*. Most infections are asymptomatic; however it can cause diarrhea or rectal prolapse due to increased peristalsis in children with heavy parasite burden. The adult worm is whip-like, and eggs are barrel (or lemon)-shaped, and their detection confirms the diagnosis [2, 35].

Strongyloides stercoralis

Strongyloides stercoralis, as opposed to other helminths, has the ability to replicate within the human host; thus persistent infection can develop without repeated exposure to infective larvae from the environment. This is particularly important in immunocompromised patients who can present with disseminated disease due to these autoinfection cycles. Strongyloides is a facultative parasite and can survive in the soil as a free-living organism. Transmission occurs when filariform larvae from the soil penetrate the skin and reach the lungs via the bloodstream; there they ascend the airways, and they are swallowed and descend to the small intestine. The female worms reproduce in the intestinal mucosa by parthenogenesis, and eggs hatch

releasing larvae which migrate to the lumen and are excreted with feces. Rhabditiform larvae can also transform to infective forms that penetrate the mucosa or perianal skin and re-infect the host. Clinical symptoms are usually mild and include recurrent urticaria, a serpiginous eruption at the site of larva migration known as "larva currens," gastrointestinal symptoms, weight loss, colitis, and rarely bleeding or obstruction. Eosinophilia is present, and pulmonary symptoms are not frequent. Hyperinfection syndrome occurs more commonly in patients receiving glucocorticoids, and it can be life-threatening presenting as disseminated disease affecting many organs. Due to the disruption of enteric mucosal barrier, it is usually accompanied by Gram-negative bacteremia (also polymicrobial). Diagnosis is based on larvae detection in serial stool samples or if needed in duodenal aspirates or biopsy specimens. These are 250 μm in length and can be distinguished morphologically by hookworms due to their short buccal cavity. ELISA-based antibody tests are used for diagnosis, with good sensitivity for uncomplicated infections [35–38].

Tissue Roundworms

Trichinella spp.

Infection with *Trichinella* species (eight are recognized), most commonly *T. spiralis*, causes trichinellosis. Transmission occurs after ingestion of undercooked meat containing cysts, most usually pork but also other carnivores or wild game. Larvae excyst in the small intestine mucosa and mature into adult forms. Adult females produce eggs, and larvae are released via the bloodstream to different organs; however cysts develop in striated muscle cells, where they can remain viable for many years. When the parasite burden is high, diarrhea or other gastrointestinal symptoms can occur 1 week after infection. Low parasite burden infections are asymptomatic. During the second week, symptoms due to muscle invasion or larval migration may develop. The latter presents as hypersensitivity reaction with eosinophilia, rash, and fever, but also periorbital and facial edema as well as subconjuctival, retinal, and splinter hemorrhages are described. Complications include myocarditis, tachyarrhythmias, pneumonitis, and, less frequently, encephalitis. Muscle edema, myalgias, muscle weakness, and myositis symptoms reflect larval encystment, and affected areas are the extraocular muscles; muscles of the neck, face, and back; biceps; and diaphragm. Eosinophilia is very common and peaks between weeks 2 and 4 after infection; CPK is also elevated and clinical suspicion is important for diagnosis. Serologic tests can confirm the diagnosis; otherwise a muscle (1gr) biopsy may be needed for microscopic detection of cysts [2, 39, 40].

Wuchereria bancrofti, Brugia malayi, Loa loa, Onchocerca volvulus, Dracunculus medinensis

Filariasis affects more than 170 million people worldwide. Although eight filarial worms infect humans, five of them cause clinically important disease. These are *Wuchereria bancrofti*, *Brugia malayi*, *Loa loa*, *Onchocerca volvulus*, and *Dracunculus medinensis*. The filarial parasites are transmitted by mosquitos and

other arthropods. Their life cycle is complex and involves a larval stage within the insect and an adult worm phase, which is carried out in the lymphatics or subcutaneous tissues in humans. Adult worms produce microfilariae, which can either circulate in the bloodstream or penetrate the skin. Arthropods ingest microfilariae, which develop into infective larvae within the insect. Filariasis usually occurs after repeated exposure to the infectious forms of the parasite and typically manifests as chronic infection, especially in endemic areas. Nonetheless, the disease can have a more acute presentation in newly exposed individuals (non-natives) [34].

W. bancrofti and *B. malayi* cause lymphatic filariasis, which can lead to significant lymphatic obstruction due to inflammatory changes and eventually fibrosis of the lymphatics, triggered by the filarial adult worms. In extreme forms, lymphedema can evolve to elephantiasis of (usually lower) extremities. Diagnosis is based on detection of microfilariae in blood or other biologic specimens. Antigenic detection and PCR-based tests are also useful, if available [2, 3, 34].

Onchocerciasis is the cause of "river blindness," while *Loa loa* (African eye worm) causes loiasis and can manifest with episodic Calabar swellings (localized areas of angioedema) [2, 34].

Larva Migrans Syndromes

Toxocara canis (dog) and *Toxocara cati* (cat) cause visceral larva migrans. The definite host is the dog, and humans are accidental dead-end hosts. Diagnosis is made with the detection of larvae in tissue. The larvae can migrate in various organs, where they are encapsulated and die. However, granulomas can form around the dead larvae, and the mechanism is a delayed hypersensitivity response. Blindness is the most serious complication. Serologic tests can be useful, and eosinophilia and hypergammaglobulinemia are supportive of the diagnosis [2].

Ancylostoma braziliense (cat) and *Ancylostoma caninum* (dogs) cause cutaneous larva migrans. Larvae enter the human host via skin penetration, but they cannot complete their life cycle. As larvae migrate through the subcutaneous tissues, a creeping eruption occurs, which is intensely pruritic [2].

Angiostrongylus cantonensis, *Gnathostoma spinigerum*, and *Baylisascaris* can cause eosinophilic meningitis.

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References

1. Murray PR. The clinician and the microbiology laboratory. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
2. Brooks GF, Carroll KC, Butel JS, Morse SA, Mietzner TA. Chapter 46. Medical parasitology. In: Jawetz, Melnick, & Adelberg's medical microbiology, 26e. McGraw Hill; 2013.

3. Reed SL, Davis CE. Chapter e25 Laboratory diagnosis of parasitic infections. Harrison's Princ Intern Med. 18th ed. McGraw Hill; 2012.
4. Reed SL. Amebiasis and infection with free-living amebas. In: Kasper DL, Fauci AS, editors. Harrison's infectious diseases. McGraw Hill; 2010. p. 1070–1076.
5. Petri WA, Haque R. Entamoeba species, including amebic colitis and liver abscess. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
6. Koshy AA, Blackburn BG, Singh U. Free-living amebae. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
7. Kirchhoff L V. Trypanosoma species (American Trypanosomiasis, Chagas' disease): biology of trypanosomes. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
8. Kirchhoff L V. Trypanosomiasis. In: Kasper DL, Fauci AS, editors. Harrison's infectious diseases. McGraw Hill; 2010. p. 1111–1117.
9. Kirchhoff L V. Agents of African trypanosomiasis (sleeping sickness). In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 2014.
10. Herwaldt B. Leishmaniasis. In: Kasper DL, Fauci AS, editors. Harrison's infectious diseases. McGraw Hill; 2010.
11. Magill AJ. Leishmania species: visceral (kala-azar), cutaneous, and mucosal leishmaniasis. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
12. Weller PF. Protozoal intestinal infections and trichomoniasis. In: Kasper DL, Fauci AS, editors. Harrison's infectious diseases. McGraw Hill; 2010. p. 1127–1133.
13. Gelfand JA, Vannier EG. Babesia species. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
14. Contopoulos-Ioannidis D, Montoya JG. Toxoplasma gondii (Toxoplasmosis). In: Principles and practice of pediatric infectious siseases. 4th ed. Philadelphia: Elsevier/Saunders; 2012.
15. Kasper LH. Toxoplasma infections. In: Dennis L. Kasper ASF, editor. Harrison's infectious diseases. McGraw Hill; 2010. p. 1118–1126.
16. Checkley W, White AC, Jaganath D, Arrowood MJ, Chalmers RM, Chen XM, et al. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. Lancet Infect Dis. 2015;15(1):85–94. https://doi.org/10.1016/S1473-3099(14)70772-8.
17. Huang DB, White AC. An updated review on cryptosporidium and giardia. Gastroenterol Clin North Am. 2006;35(2):291–314.
18. White AC. Cryptosporidiosis (Cryptosporidium species). In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
19. Fairhurst RM, Wellems TE. Malaria (Plasmodium species). In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014.
20. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Seminar: malaria. Lancet. 2014;383(9918):723–35.
21. Maguire JH. Introduction to helminth Infections. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases: In; 2014.
22. Maguire JH. Trematodes (Schistosomes and liver, intestinal, and lung flukes). In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier; 2014; 12(6): p. 636–649.
23. Ashrafi K, Bargues MD, O'Neill S, Mas-Coma S. Fascioliasis: a worldwide parasitic disease of importance in travel medicine. Travel Med Infect Dis. 2014;12(6):636–49.
24. Qian MB, Utzinger J, Keiser J, Zhou XN. Clonorchiasis. In: The Lancet. 2016;387:800–10. Published Online August 21, 2015. https://dx.doi.org/10.1016/S0140-6736(15)60313-0.
25. Narain K, Agatsuma T, Blair D. Paragonimus. In: Molecular detection of foodborne pathogens. Florida: Taylor and Francis Group; 2010.
26. White AC, Peter F. Weller. Cestodes. In: Kasper DL, Fauci AS, editors. Harrison's infectious diseases. McGraw Hill; 2010.
27. Webb C, Cabada MM. Intestinal cestodes. Curr Opin Infect Dis. 2017.

28. Garcia HH, Nash TE, Del Brutto OH. Clinical symptoms, diagnosis, and treatment of neurocysticercosis. Lancet Neurol [Internet]. 2014;13(12):1202–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442214700948.
29. Craig P, Ito A. Intestinal cestodes. Curr Opin Infect Dis [Internet]. 2007;20(5):524–32. Available from: http://journals.lww.com/00001432-200710000-00014.
30. Del Brutto OH, Nash TE, White AC, Rajshekhar V, Wilkins PP, Singh G, et al. Revised diagnostic criteria for neurocysticercosis. J Neurol Sci [Internet]. 2017;372:202–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022510X16307481.
31. White AC, Coyle CM, Rajshekhar V, Singh G, Hauser WA, Mohanty A, et al. Diagnosis and Treatment of Neurocysticercosis: 2017 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg [Internet]. 2018;98(4):945–66. Available from: http://www.ajtmh.org/content/journals/10.4269/ajtmh.18-88751.
32. Agudelo Higuita NI, Brunetti E, McCloskey C. Cystic Echinococcosis. Kraft CS, editor. J Clin Microbiol [Internet]. 2016;54(3):518–23. Available from: https://jcm.asm.org/content/54/3/518.
33. Jenkins D. WHO/OIE manual on Echinococcosis in humans and animals: a public health problem of global concern. Int J Parasitol [Internet]. 2001;31(14):1717–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0020751901003186.
34. Maguire JH. Intestinal nematodes (roundworms). In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Saunders; 2014.
35. Weller PF, Nutman TB. Intestinal nematodes. In: Kasper DL, Fauci AS, editors. Harrison's infectious diseases. McGraw Hill; 2010. p. 1139–1145.
36. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis Infection. Clin Infect Dis [Internet]. 2001;33(7):1040–7. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/322707.
37. Iriemenam NC, Sanyaolu AO, Oyibo WA, Fagbenro-Beyioku AF. Strongyloides stercoralis and the immune response. Parasitol Int [Internet]. 2010;59(1):9–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1383576909001354.
38. Montes M, Sawhney C, Barros N. Strongyloides stercoralis: there but not seen. Curr Opin Infect Dis [Internet]. 2010;23(5):500–4. Available from: http://journals.lww.com/00001432-201010000-00017.
39. Kocięcka W. Trichinellosis: human disease, diagnosis and treatment. Vet Parasitol [Internet]. 2000;93(3–4):365–83. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0304401700003526.
40. Rostami A, Gamble HR, Dupouy-Camet J, Khazan H, Bruschi F. Meat sources of infection for outbreaks of human trichinellosis. Food Microbiol. 2017;64:65.

Part II

Parasitic Diseases of the Gastrointestinal Tract

3 The Role of Surgery in Treating Parasitic Diseases of the Gastrointestinal Tract from Protozoa

Ioannis A. Ziogas and George Tsoulfas

Introduction

Protozoa (from the Greek words *protos* [meaning first] and *zoon* [meaning animal]) constitute common inhabitants of the human gastrointestinal tract [1]. The majority of protozoa can easily change from their active feeding form (trophozoite) to the inactive and resistant form (cyst), which is also responsible for the process of transmission (Fig. 3.1). The most common route of transmission is fecal-oral, mostly through the consumption of undercooked meat or contaminated water [2]. In comparison to the majority of helminths, parasitic protozoa have the innate capacity to replicate within the host's corpus, which does explain not only their survivability but also the burden of disease they can cause from a single exposure [1]. Lumen-dwelling protozoa are subdivided into the following phyla based on their motility abilities: (a) Mastigophora (flagellates), (b) Sarcodina (amebae), (c) Sporozoa, and (d) Ciliophora (ciliates) [3].

Even though they mostly represent non-pathogenic commensals or cause just mild disease, protozoa may cause significant morbidity and mortality in certain occasions. The low socioeconomic status of developing countries along with the suboptimal conditions of hygiene renders it easier for intestinal protozoa to flourish with a consistently high incidence [2]. On the other hand, they have occasionally been accused of causing diarrheal or other enfeebling diseases, especially in the immunocompromised as well as in developed countries [4–7]. The better sanitary conditions of these countries lead to an ignorance against the severity of disease that enteric protozoa can engender [8]. Consequently, they are sometimes omitted from

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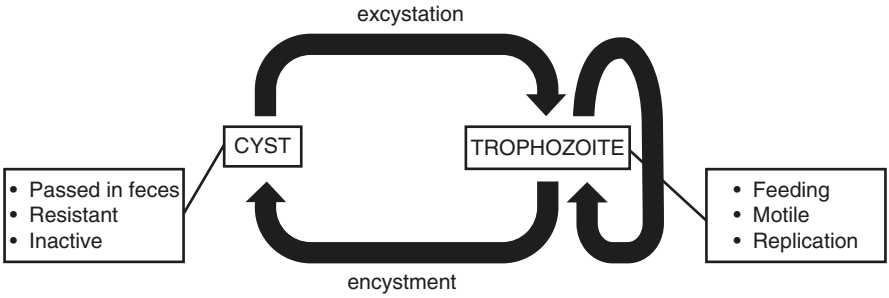

Fig. 3.1 Typical protozoal life cycle

Table 3.1 Common protozoan pathogens causing gastrointestinal infection that may require surgical intervention

1. Mastigophora (flagellates)
Giardia lamblia (or *G. duodenalis* or *G. intestinalis*)
Dientamoeba fragilis
Trypanosoma cruzi
2. Sarcodina (amebae)
Entamoeba histolytica
3. Sporozoa
Cryptosporidium parvum
Cyclospora cayetanensis
4. Ciliophora (ciliates)
Balantidium coli

the differential diagnosis, and thus severe complications may arise; under such circumstances, medical therapy is usually inadequate to eliminate the disease, and surgical intervention is inevitable.

This chapter aims to highlight the role of surgery against the protozoal disease of the gastrointestinal system through the discussion of the most common intestinal protozoa individually (Table 3.1).

Mastigophora (Flagellates)

Giardiasis

Giardia lamblia (also known as *G. duodenalis* or *G. intestinalis*) is a flagellate protozoon contributing to a significant number of epidemic or sporadic cases of diarrhea worldwide [9]. The first patient afflicted by giardiasis was described in 1681 by Van Leeuwenhoek [10], but the organism was rediscovered and named in 1859 by Lamb [11]. *G. lamblia* is subdivided into seven molecular types (A through G) with types A and B constituting the primary human pathogens [12]. Risk factors for giardiasis infection include poor hygiene conditions and lack of water treatment resources [9]; people are in particularly high risk during backpacking or recreational

water use activities or consuming water from surface wells [13]. Admittedly, giardiasis in one of the most common pathogens causing diarrheal disease in international travelers returning to the USA and Europe [14–16]. Although water-borne and food-borne are the main ways of transmission, little children attending day-care facilities are also at an increased risk (fecal-oral transmission), as well as men having sex with men (oral-anal contact) [13, 17]. Patients with cystic fibrosis, hypogammaglobulinemia, IgA deficiency, and decreased secretion of gastric acid constitute high-risk candidates for *G. lamblia* infection [13, 18, 19].

Giardiasis can be asymptomatic in 10–15% of the patients, but most of them typically present with acute giardiasis symptoms, such as diarrhea (95%), malaise (86%), foul-smelling fatty stools (75%), abdominal cramping (70%), nausea (70%), and bloating (50%) [13, 20]. The incubation period for diarrhea from *G. lamblia* is approximately 1–2 weeks, and the onset is indolent; disease duration lasts 2–4 weeks with treatment and 6 or more weeks without treatment, while giardiasis is generally considered self-limited. Chronic disease may either develop after acute symptoms when the disease does not resolve on its own or even without a previous acute illness and usually presents in one-third of the patients [21]. Symptoms that should raise concern for chronic disease include loose stools without diarrhea, steatorrhea, significant weight loss, malabsorption (hypoalbuminemia and vitamin deficiency), malaise, and depression. Differential diagnosis should include microbial diarrhea caused by *Salmonella* or *Campylobacter*, as well as celiac disease, tropical sprue, Whipple's disease, lactose intolerance, irritable bowel syndrome (IBS), and Crohn ileitis [13]. Definitive diagnosis is established via antigen detection immunoassays or nucleic acid amplification assays in stool samples and stool microscopy.

Antimicrobial agents and supportive care, i.e., fluid and electrolyte imbalance, are the mainstay of treatment for giardiasis. Treatment should be initiated as soon as the diagnosis is made, even in asymptomatic patients to preclude further transmission. Therapeutic agents commonly implemented are tinidazole and nitazoxanide, as well as metronidazole, albendazole or mebendazole, paromomycin, furazolidone, quinacrine, secnidazole, and ornidazole [13, 22, 23]. The only exception to prompt treatment includes pregnant and lactating women with mild symptoms that can retain their nutrition and hydration status; in these patients, treatment should be delayed at least until the second trimester in order to avoid any potential teratogenic effects of the drugs [24]. If the patient's condition necessitates treatment during the first trimester, paromomycin should be first-line, while during second and third trimester, multiple agents may be appropriate, such as paromomycin, tinidazole, metronidazole, or nitazoxanide [24]. In the case of resistance to treatment or relapse, medical therapy is still warranted [13, 25].

Surgical intervention may be required only under certain circumstances. Data suggest that *G. lamblia* may be the accused of causing cholecystitis [11], and thus, cholecystectomy should be performed. However, the diagnosis in these cases is mostly incidental during the histopathologic examination of the surgical specimen. *G. lamblia* is also one of the causes of nodular lymphoid hyperplasia of the gastrointestinal tract [26, 27]. Although treatment eradicates the symptoms caused by giardiasis in these cases [28], typically neither the number nor the size of the

nodules seems to regress [29], and due to the risk of malignant transformation, surgical resection may be the only therapeutic option [27, 30]. Even though infection from *G. lamblia* is managed medically in the vast majority of cases, the surgical community should be aware of this protozoal infection as surgical patients may also be part of the patient pool. Individual cases of giardiasis postoperatively after transplant surgery, Roux-en-Y gastric bypass, or other surgical operations involving manipulation of the gastrointestinal tract have been published in the literature to date [31, 32]. Notably, *G. lamblia* trophozoites have also been found in the fine-needle aspiration specimens of patients with pancreatic cancer, who apart from pancreatic resection may also require antimicrobial treatment [33, 34].

Dientamoeba fragilis

Dientamoeba fragilis is an ameboflagellate that causes infection of the gastrointestinal tract not via invasion, but rather via epithelial irritation [35]. Transmission occurs through the orofecal route, and *Dientamoeba* infections have higher prevalence in Australia [36], the USA [37], the Netherlands [38], and Oman [39]. Residing in rural areas and exposure to pets seem to be risk factors for *Dientamoeba* infections [40]. Notably, *Enterobius vermicularis* (the human pinworm) seems to assist *Dientamoeba* in terms of its transmission [41].

Although many infected patients remain asymptomatic, the most common manifestations are diarrhea, abdominal pain, anorexia, nausea, weight loss, and vomiting [42]. As *Dientamoeba* localizes in the colon, it can cause colitis; thus it should be included in the differential diagnosis of eosinophilic colitis [43], while the definitive diagnosis is made via stool microscopy or polymerase chain reaction (PCR) [44].

Asymptomatic individuals diagnosed with *Dientamoeba* in their stools do not require any form of treatment. However, patients with diarrhea or abdominal pain for more than 7 days diagnosed with *Dientamoeba* infection should be treated with either of the following agents: metronidazole, paromomycin, iodoquinol, doxycycline, or tetracycline [45–47]. All of them appear to be efficacious, while paromomycin has the shorter treatment course (7 days) and thus is suggested by some experts [35].

Data suggest that surgery may be required under particular circumstances in order to treat *Dientamoeba* infection or its complications. Indeed, multiple reports showed that *Dientamoeba* could lead to appendicitis, and hence, appendectomy is the mainstay of treatment on this occasion [48].

Trypanosoma cruzi

Trypanosoma cruzi is the cause of Chagas disease a zoonotic disease transmitted by hematophagous triatomine vectors (a type of reduviid bugs), particularly in North, Central, and South America; it usually manifests with cardiomyopathy and

gastrointestinal disease [49]. Other modes of transmission include blood transfusion, organ transplantation, and via contaminated water or food, while Chagas disease can also be transmitted congenitally [50].

T. cruzi infection can be distinguished in two phases, acute and chronic. Acute phase begins after 2 weeks of incubation and constitutes a 2- to 3-month period of nonspecific symptomatology, such as fever, lymphadenopathy, and hepatosplenomegaly [51]. Some patients develop chagoma (inflammation and swelling) at the site of inoculation, while inoculation through the conjunctiva manifests as the Romaña sign (unilateral swelling of both eyelids) [50]. Severe acute infection is seen in less than 1% of the patients, and it frequently manifests as pericardial effusion, acute myocarditis, or meningoencephalitis [52]. On the other hand, chronic disease develops over years or even decades and presents as Chagas cardiomyopathy, megaesophagus, esophageal carcinoma, or megacolon [52].

Anti-trypanosomal agents with proven efficacy include benznidazole and nifurtimox [49], but they are not adequate to prevent the progression of Chagas digestive disease [53, 54]. The goal in the management of megaesophagus is to ameliorate the resting pressure in the lower esophageal sphincter; hence stages I, II, and III are managed either with surgery (laparoscopic Heller's myotomy and fundoplication) or with pneumatic dilation (avoided in stage IV due to high risk of rupture). Stage IV disease may necessitate esophagectomy if laparoscopic Heller's myotomy is inadequate to obtain positive outcomes in terms of symptom improvement [55]. *T. cruzi* infection increases the risk of esophageal carcinoma, and if this devastating complication arises, esophagectomy may be required. Megacolon-induced constipation can initially be managed conservatively with high-fiber diet, laxatives, and fecal disimpactions. Indications for surgical intervention include severe constipation not amenable to conservative management or complications, such as sigmoid volvulus and stercoral ulcer; in such occasions, rectosigmoidectomy with retrocecal interpositioning or with end-to-side low colorectal anastomosis can be performed [56].

Sarcodina (Amebae)

Entamoeba histolytica (Amebiasis)

Entamoeba histolytica is the cause of intestinal or extraintestinal infection in around 50,000,000 patients per annum and the cause of death in approximately 100,000 people worldwide per year [57, 58]. Amebiasis was firstly described by Fedor Aleksandrovich Losch in 1875 [59]. Four *Entamoeba* species, namely, *E. histolytica*, *E. dispar*, *E. moshkovskii*, and *E. bangladeshi*, are responsible for intestinal amebiasis [60]. *E. dispar*, which is not pathogenic, is ten times more common than *E. histolytica*, which is pathogenic [57]. Although its occurrence has been described worldwide, developing countries exhibit higher prevalence rates due to poor socioeconomic conditions, and some of the areas with increased infection rates include, but are not limited to, India, Mexico, Africa, and Central and South America [61].

In developed countries, amebiasis is more commonly seen in immigrants, international travelers, and expatriates [57]; however, only 0.3% of the total number of international travelers with diarrheal disease are infected by *E. histolytica* [62]. Sexually active homosexuals and long-term institutionalized patients are also in particularly high risk of transmission [63], and the most common routes of transmission are orofecal and human-to-human transmission [57].

Most of the *Entamoeba* infections are asymptomatic, and *E. histolytica* is the most common pathogen (90%), as *E. dispar* and *E. moshkovskii* are usually nonpathogenic. The development of invasive disease is determined by the strain of *E. histolytica*, as well as by the age, immune condition, and genetic susceptibility of the patient [61]. Symptomatic intestinal amebiasis frequently develops over a period of 1–3 weeks with subacute onset of symptoms, which consist of mild diarrhea to life-threatening dysentery, abdominal pain, bloody diarrhea, or even the complications of amebiasis, such as amebic colitis, toxic megacolon (fulminant colitis), perforation of the gastrointestinal tract, intraabdominal abscess, amebic appendicitis, amebic granuloma, amebic stricture, and perianal amebiasis [57, 64]. In rare occasions, intestinal amebiasis can mimic inflammatory bowel disease (IBD) by causing a syndrome of chronic diarrheal disease, weight loss, and abdominal pain with no dysentery. Differential diagnosis should include bacteria diarrheal disease from *Escherichia coli*, *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium difficile*, or *Vibrio* species and IBD or ischemic bowel disease. Diagnosis is made via stool microscopy, colonoscopy with histological examination of the specimen, antigen detection, serology, or molecular identification.

In terms of treatment, *E. histolytica* infections should always be treated, even in asymptomatic patients, while there is no need for treating *E. dispar* [61]. There is no unanimous recommendation for treating *E. moshkovskii*, but treating symptomatic patients may be sound. A 7- to 10-day metronidazole (or tinidazole or nitazoxanide) course is the mainstay of treatment for invasive colitis followed by a luminal agent (paromomycin) for the elimination of intraluminal cysts [65]. In the case of bacterial superinfection or even amebic colitis, broad-spectrum antibiotics should be administered [66]. Broad-spectrum antibiotic therapy should also be initiated in patients with known or suspected peritonitis, bowel perforation, or intraabdominal abscesses, while most patients require surgical intervention as soon as possible [67]. For localized disease, partial colectomy with colostomy is advised over primary anastomosis, while extensive disease usually requires total colectomy. Amebic appendicitis is a rare complication that requires prompt management and taking the patient to the operating room for an appendectomy.

Extraintestinal amebiasis entails amebic liver abscess, as well as the involvement of other organs such as the heart, lungs, and brain [68]. Amebic liver abscess is usually seen in adult males between 40 and 50 years old [69–71] and is attributed to the ascending flow of amebae through the portal venous system [72]. It may take between 8 and 20 weeks to become symptomatic, and the most common clinical manifestations include 1–2 weeks of right upper quadrant abdominal pain along with high fever, sweating, cough, weight loss, and anorexia, while ultrasonography,

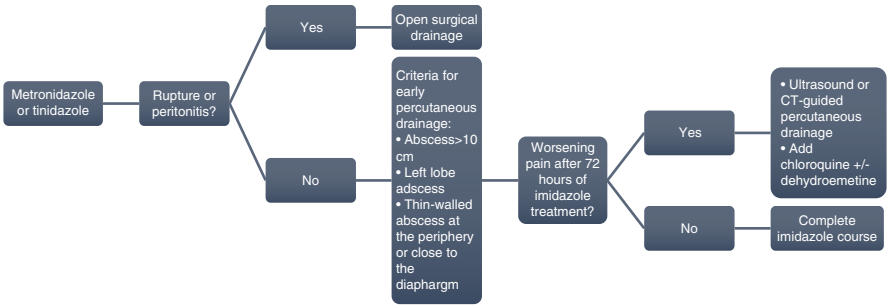

Fig. 3.2 Proposed algorithm on the management of amebic liver abscess

computed tomography scan, and magnetic resonance imaging are useful in guiding toward the diagnosis [57]. Most of these patients develop antibodies that can be detected via serologic testing, but the test may be negative in the first 7 days [73, 74]. Pyogenic liver abscess, echinococcal disease, and malignancy should be included in the differential diagnosis.

Treatment of amebic liver abscess consists similarly of a tissue agent (i.e., metronidazole, tinidazole) followed by a luminal agent, while the role of abscess drainage is when antibiotic therapy is inadequate [57]. Evidence suggests that there is no benefit with drainage following medical therapy in uncomplicated liver abscesses [75]. Clinicians should entertain the idea of abscess aspiration in the following occasions: size >10 cm in diameter, abscess in the left lobe (to prevent rupture into the pericardium), or abscess close to the serosal surface [57]. Another criterion that should be used for determining the appropriateness of drainage is if the patient is on medical therapy for 72 hours and, instead of improving, he or she is experiencing worsening pain [76]. Last but not least, there is no doubt that abscess rupture or peritonitis requires an immediate trip to the operating room. Figure 3.2 depicts a proposed algorithm regarding the management of amebic liver abscess [57].

Sporozoa

Cryptosporidium parvum (Cryptosporidiosis)

Cryptosporidium infection is linked to emerging diarrheal disease and biliary tract disease [77], while initial reports were published in 1975 [78]. *Cryptosporidium parvum* is the primary human pathogen and is separated into two distinct species, namely, *C. hominis* and *C. parvum* [79]. *C. hominis* is predominantly associated with infections in children attending day-care facilities and international travelers, while *C. parvum* infection arises more commonly in humans in close quarters with farm animals [80]. Transmission usually occurs through feces containing *Cryptosporidium* oocysts that have contaminated

drinking or swimming water, food, or residential surfaces, while human-to-human transmission is also possible [81, 82]. Its prevalence is higher in developing nations, but it poses a significant pathogen for both children and the elderly in developed countries [78].

Clinical manifestations depend on a great extent on the immunologic status of the patient. Indeed, immunocompromised individuals may suffer from a life-threatening disease course, while symptoms usually resolve within 7–14 days without treatment in immunocompetent patients [78]; however, asymptomatic patients may sometimes fall in either category [83, 84]. The most typical clinical presentation is secretory diarrhea after a 1-week incubation period accompanied by anorexia, abdominal pain, and fever. Significant volume depletion is associated with worse outcomes and increased mortality rates in the elderly [85]. Long-term effects of *C. parvum* infection have been studied even 1 year after the resolution of acute infection including diarrhea, abdominal, eye or joint pain, weight loss, and symptoms consistent with IBS [86]. Even though symptoms can help guide toward the diagnosis, it is usually established via stool microscopy (acid-fast staining), PCR, or enzyme immunoassays.

As cryptosporidiosis can lead to significant fluid loss, the most reasonable approach is to initiate treatment with an anti-diarrheal agent and in case of severe dehydration to start parenteral nutrition [87]. Aggressive nutritional support helps restore cellular immunity, while HIV/AIDS patients are benefited from early initiation of antiretroviral treatment [78]. Currently, nitazoxanide is the only Food and Drugs Administration approved therapy against cryptosporidiosis, and data from trials suggest that it can shorten disease duration and decrease parasite load [88–90]. If nitazoxanide is not well-tolerated or not available, paromomycin can be used as an alternative agent [91].

Under certain circumstances, surgery may be the next appropriate step in patients diagnosed with cryptosporidiosis. In particular, immunodeficient patients can present with biliary tract disease, such as acalculous cholecystitis, sclerosing cholangitis, and pancreatitis [92–94]. Patients with cryptosporidial acalculous cholecystitis will benefit from cholecystectomy, while endoscopic retrograde cholangiopancreatography (ERCP) with or without stent placement may be needed in case of sclerosing cholangitis. There is evidence suggesting that *Cryptosporidium* infection can mimic pancreatic cancer due to the invasion of the pancreatic ducts by the parasites, and according to a report, there has been a patient submitted to gastroduodenopancreatectomy for this reason [95]. Another report of a child treated at Memorial Sloan Kettering Cancer Center for acute myeloblastic leukemia and chronic functional constipation highlights the role of surgery in cryptosporidiosis [96]. This girl's condition was complicated by toxic megacolon and recurrent infection with *Cryptosporidium*, and thus the decision to proceed with a fully diverting, double-barreled ileostomy along with mucous fistula was inevitable. On the whole, the cryptosporidial infection can take place either in the gastrointestinal or in the pancreato-biliary tract; as a result, there is

great necessity to include it in the differential diagnosis of patients with diarrheal disease, to intervene promptly and take the patient to the operating room in case complications arise.

Cyclospora cayetanensis

Cyclospora cayetanensis is a coccidian food- and water-borne protozoon accused of causing diarrheal disease [97]. Its prevalence has been reported all over the world including Southeastern Asia, Central America, the USA, and Africa [98], while it is particularly prevalent among travelers and individuals diagnosed with HIV/AIDS [97, 99].

Many infected people do not exhibit any symptoms, while those who often do present with abdominal pain, watery diarrhea, anorexia, flatulence, fever, anorexia, nausea, and weight loss after a 1-week incubation period [97, 100–102]. Acalculous cholecystitis is another clinical manifestation attributed to *Cyclospora* infection [103]. Diagnosis is made via stool microscopy or PCR, while there no serologic test available to date [104].

A 7- to 10-day course of trimethoprim-sulfamethoxazole (TMP-SMX) is the gold standard of treatment for cyclosporiasis [105, 106]. Nitazoxanide is a decent alternative for patients with sulfa allergy [107], while ciprofloxacin can be used if TMP-SMX is not well-tolerated [108]. However, in the case of acalculous cholecystitis, surgeons need to act in a timely fashion and perform cholecystectomy [100].

Ciliophora (Ciliates)

Balantidium coli

Balantidiasis is caused by *Balantidium coli*, which is the largest protozoon and the sole ciliate afflicting humans [109, 110]. Transmission happens through the orofecal route, while balantidiasis is prevalent among countries in Southeast Asia, South America, and Western Pacific islands [35].

The three types of disease consist of asymptomatic excretion of cysts, acute colitis, and chronic balantidiasis [111, 112]. The spectrum of acute symptomatology includes watery or dysenteric diarrheal disease, nausea, anorexia, weight loss, vomiting, and abdominal pain [112]. Extraintestinal disease with involvement of the liver, lung, or appendix can also take place [35, 113]. Stool microscopy or histopathologic examination of endoscopic biopsy specimens can lead to the diagnosis [114].

Therapeutic agents include tetracycline, doxycycline, metronidazole, or iodoquinol [35]. However, surgical intervention may be required in case of appendiceal involvement (appendectomy) or fulminant dysentery complicated by bowel perforation and peritonitis.

Conclusion

Gastrointestinal infections constitute a significant health issue worldwide not only in developing but also in developed countries, and protozoa pose a significant human pathogen responsible for the enormous burden of disease. Despite the increased susceptibility of immunocompromised individuals, immunocompetent people can also be afflicted by pathogenic intestinal protozoa. In the vast majority of cases, patients present with diarrheal disease along with other symptoms of the gastrointestinal tract that can be managed with medical therapy. Sometimes disease progression may lead to devastating complications that can only be alleviated via surgical intervention. Consequently, both physicians and surgeons should be aware of the broad spectrum of symptomatology that protozoa can lead to in order to intervene promptly and obtain optimal outcomes with minimal morbidity for the patient. Undoubtedly, future research should focus on ways to belittle the burden of disease via prevention of disease transmission, improvement in the sanitary conditions, and development of more efficient and specific antiprotozoal agents.

References

1. Magill AJ. 88 – General principles. In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious disease [Internet]. 9th ed. London: W.B. Saunders; 2013. p. 655–658. Available from: http://www.sciencedirect.com/science/article/pii/B9781416043904000886.
2. Sarkari B, Hosseini G, Motazedian MH, Fararouei M, Moshfe A. Prevalence and risk factors of intestinal protozoan infections: a population-based study in rural areas of Boyer-Ahmad district, Southwestern Iran. BMC Infect Dis. 2016;16(1):703.
3. Centers for Disease Control and Prevention. About Parasites [Internet]. 2016 [cited 2019 May 7]. Available from: https://www.cdc.gov/parasites/about.html.
4. Stark D, Barratt JLN, van Hal S, Marriott D, Harkness J, Ellis JT. Clinical significance of enteric protozoa in the immunosuppressed human population. Clin Microbiol Rev. 2009;22(4):634–50.
5. Stensvold CR, Nielsen SD, Badsberg J-H, Engberg J, Friis-Moller N, Nielsen SS, et al. The prevalence and clinical significance of intestinal parasites in HIV-infected patients in Denmark. Scand J Infect Dis. 2011;43(2):129–35.
6. Kucerova Z, Sokolova OI, Demyanov AV, Kvac M, Sak B, Kvetonova D, et al. Microsporidiosis and cryptosporidiosis in HIV/AIDS patients in St. Petersburg, Russia: serological identification of microsporidia and Cryptosporidium parvum in sera samples from HIV/AIDS patients. AIDS Res Hum Retrovir. 2011;27(1):13–5.
7. Meusburger S, Reichart S, Kapfer S, Schableger K, Fretz R, Allerberger F. Outbreak of acute gastroenteritis of unknown etiology caused by contaminated drinking water in a rural village in Austria, August 2006. Wien Klin Wochenschr. 2007;119(23–24):717–21.
8. Fletcher SM, Stark D, Harkness J, Ellis J. Enteric protozoa in the developed world: a public health perspective. Clin Microbiol Rev. 2012;25(3):420–49.
9. Feng Y, Xiao L. Zoonotic potential and molecular epidemiology of Giardia species and giardiasis. Clin Microbiol Rev. 2011;24(1):110–40.
10. Adam RD. Biology of Giardia lamblia. Clin Microbiol Rev [Internet]. 2001;14(3):447–75. Available from: https://cmr.asm.org/content/14/3/447.
11. McGowan JM, Nussbaum CC, Burroughs EW. Cholecystitis due to Giardia Lamblia in a Left-sided Gallbladder. Ann Surg [Internet]. 1948;128(5). Available from: https://journals.

lww.com/annalsofsurgery/Fulltext/1948/11000/CHOLECYSTITIS_DUE_TO_GIARDIA_LAMBLIA_IN_A.26.aspx.
12. Cacciò SM, Ryan U. Molecular epidemiology of giardiasis. Mol Biochem Parasitol [Internet]. 2008;160(2):75–80. Available from: http://www.sciencedirect.com/science/article/pii/S0166685108000923.
13. Adam RD. 90 – Giardiasis. In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious disease [Internet]. 9th ed. London: W.B. Saunders; 2013. p. 668–672. Available from: http://www.sciencedirect.com/science/article/pii/B9781416043904000904.
14. Minetti C, Chalmers RM, Beeching NJ, Probert C, Lamden K. Giardiasis. BMJ. 2016;355:i5369.
15. Harvey K, Esposito DH, Han P, Kozarsky P, Freedman DO, Plier DA, et al. Surveillance for travel-related disease–GeoSentinel surveillance system, United States, 1997–2011. MMWR Surveill Summ. 2013;62:1–23.
16. Schlagenhauf P, Weld L, Goorhuis A, Gautret P, Weber R, von Sonnenburg F, et al. Travel-associated infection presenting in Europe (2008–12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. Lancet Infect Dis. 2015;15(1):55–64.
17. Adam EA, Yoder JS, Gould LH, Hlavsa MC, Gargano JW. Giardiasis outbreaks in the United States, 1971–2011. Epidemiol Infect. 2016;144(13):2790–801.
18. Oksenhendler E, Gérard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis [Internet]. 2008;46(10):1547–54. Available from: https://doi.org/10.1086/587669.
19. Roberts DM, Craft JC, Mather FJ, Davis SH, Wright JAJ. Prevalence of giardiasis in patients with cystic fibrosis. J Pediatr. 1988;112(4):555–9.
20. Hill DR. Giardia lamblia. In: Principles and practise of clinical parasitology [Internet]. Copyright © 2001 John Wiley & Sons, Ltd, USA; 2002. p. 219–41. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/0470842504.ch10.
21. Cantey PT, Roy S, Lee B, Cronquist A, Smith K, Liang J, et al. Study of nonoutbreak giardiasis: novel findings and implications for research. Am J Med. 2011;124(12):1175.e1–8.
22. Ozbilgin A, Ertan P, Yereli K, Tamay AT, Kurt O, Degerli K, et al. Giardiasis treatment in Turkish children with a single dose of ornidazole. Scand J Infect Dis. 2002;34(12):918–20.
23. Lalle M. Giardiasis in the post genomic era: treatment, drug resistance and novel therapeutic perspectives. Infect Disord Drug Targets. 2010;10(4):283–94.
24. Gardner TB, Hill DR. Treatment of giardiasis. Clin Microbiol Rev. 2001;14(1):114–28.
25. Abboud P, Lemee V, Gargala G, Brasseur P, Ballet JJ, Borsa-Lebas F, et al. Successful treatment of metronidazole- and albendazole-resistant giardiasis with nitazoxanide in a patient with acquired immunodeficiency syndrome. Clin Infect Dis. 2001;32(12):1792–4.
26. Baran B, Gulluoglu M, Akyuz F. Nodular lymphoid hyperplasia of duodenum caused by giardiasis. Clin Gastroenterol Hepatol. 2013;11(10):A22.
27. Albuquerque A. Nodular lymphoid hyperplasia in the gastrointestinal tract in adult patients: a review. World J Gastrointest Endosc. 2014;6(11):534–40.
28. Hermans PE, Huizenga KA, Hoffman HN, Brown ALJ, Markowitz H. Dysgammaglobulinemia associated with nodular lymphoid hyperplasia of the small intestine. Am J Med. 1966;40(1):78–89.
29. Luzi G, Zullo A, Iebba F, Rinaldi V, Sanchez Mete L, Muscaritoli M, et al. Duodenal pathology and clinical-immunological implications in common variable immunodeficiency patients. Am J Gastroenterol. 2003;98(1):118–21.
30. Rubio CA. Nonprotruding colorectal neoplasms: epidemiologic viewpoint. World J Surg. 2000;24(9):1098–103.
31. Genser L, Poitou-Bernert C, Brot-Laroche E. Asymptomatic Giardia intestinalis infection and Roux-en-Y gastric bypass. Surg Obes Relat Dis [Internet]. 2015;11(5):1182–3. Available from: http://www.sciencedirect.com/science/article/pii/S1550728915001641.

32. Mukku KK, Raju S, Yelanati R. Refractory giardiasis in renal transplantation: a case report. Vol. 20, Nephrology (Carlton, Vic.). Copyright © 2014 John Wiley & Sons, Ltd, USA. 2015. p. 44.
33. Mitchell CM, Bradford CM, Kapur U. Giardia lamblia trophozoites in an ultrasound-guided fine-needle aspiration of a pancreatic mucinous neoplasm. Diagn Cytopathol. 2011;39(5):352–3.
34. Furukawa M, Lee L, Ikegami T, Maeda T, Nishiyama K, Itaba S, et al. Giardiasis in the pancreas accompanied by pancreatic cancer. Vol. 40, Pancreas. Copyright © 2011 Lippincott Williams & Wilkins, USA. 2011. p. 168–169.
35. Garcia LS. 94 – Miscellaneous intestinal protozoa. In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious disease [Internet]. 9th ed. London: W.B. Saunders; 2013. p. 685–90. Available from: http://www.sciencedirect.com/science/article/pii/B9781416043904000941.
36. Stark D, Beebe N, Marriott D, Ellis J, Harkness J. Prospective study of the prevalence, genotyping, and clinical relevance of Dientamoeba fragilis infections in an Australian population. J Clin Microbiol. 2005;43(6):2718–23.
37. Kappus KD, Lundgren RGJ, Juranek DD, Roberts JM, Spencer HC. Intestinal parasitism in the United States: update on a continuing problem. Am J Trop Med Hyg. 1994;50(6):705–13.
38. van Gool T, Dankert J. 3 emerging protozoal infections in the Netherlands: Cyclospora, Dientamoeba, and Microspora infections. Ned Tijdschr Geneeskd. 1996;140(3):155–60.
39. Windsor JJ, Rafay AM, Shenoy AK, Johnson EH. Incidence of Dientamoeba fragilis in faecal samples submitted for routine microbiological analysis. Br J Biomed Sci. 1998;55(3):172–5.
40. Heusinkveld M, Mughini-Gras L, Pijnacker R, Vennema H, Scholts R, van Huisstede-Vlaanderen KW, et al. Potential causative agents of acute gastroenteritis in households with preschool children: prevalence, risk factors, clinical relevance and household transmission. Eur J Clin Microbiol Infect Dis. 2016;35(10):1691–700.
41. Butler WP. Dientamoeba fragilis An unusual intestinal pathogen. Dig Dis Sci [Internet]. 1996;41(9):1811–1813. Available from: https://doi.org/10.1007/BF02088750.
42. Girginkardesler N, Coskun S, Cuneyt Balcioglu I, Ertan P, Ok UZ. Dientamoeba fragilis, a neglected cause of diarrhea, successfully treated with secnidazole. Clin Microbiol Infect. 2003;9(2):110–3.
43. Cuffari C, Oligny L, Seidman EG. Dientamoeba fragilis masquerading as allergic colitis. J Pediatr Gastroenterol Nutr. 1998;26(1):16–20.
44. Johnson EH, Windsor JJ, Clark CG. Emerging from obscurity: biological, clinical, and diagnostic aspects of Dientamoeba fragilis. Clin Microbiol Rev. 2004;17(3):553–70, table of contents.
45. Nagata N, Marriott D, Harkness J, Ellis JT, Stark D. Current treatment options for Dientamoeba fragilis infections. Int J Parasitol Drugs Drug Resist. 2012;2:204–15.
46. Preiss U, Ockert G, Broemme S, Otto A. On the clinical importance of Dientamoeba fragilis infections in childhood. J Hyg Epidemiol Microbiol Immunol. 1991;35(1):27–34.
47. Preiss U, Ockert G, Bromme S, Otto A. Dientamoeba fragilis infection, a cause of gastrointestinal symptoms in childhood. Klin Padiatr. 1990;202(2):120–3.
48. Swerdlow MA, Burrows RB. Dientamoeba fragilis, an intestinal pathogen. J Am Med Assoc. 1955;158(3):176–8.
49. Bern C. Chagas' disease. N Engl J Med. 2015;373(5):456–66.
50. López-Vélez R, Norman FF, Bern C. 98 – American trypanosomiasis (Chagas disease). In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious disease [Internet]. 9th ed. London: W.B. Saunders; 2013. p. 725–38. Available from: http://www.sciencedirect.com/science/article/pii/B9781416043904000989.
51. Rassi AJ, Rassi A, Marin-Neto JA. Chagas disease. Lancet (London, England). 2010;375(9723):1388–402.
52. Bern C, Martin DL, Gilman RH. Acute and congenital Chagas disease. Adv Parasitol. 2011;75:19–47.

53. Bern C, Montgomery SP, Herwaldt BL, Rassi AJ, Marin-Neto JA, Dantas RO, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. JAMA. 2007;298(18):2171–81.
54. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. N Engl J Med. 2011;364(26):2527–34.
55. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. Am J Gastroenterol. 1998;93(6):884–9.
56. Cutait DE, Cutait R. Surgery of chagasic megacolon. World J Surg. 1991;15(2):188–97.
57. Houpt E, Hung C-C. 89 – Entamoeba histolytica (amebiasis). In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious disease [Internet]. 9th ed. London: W.B. Saunders; 2013. p. 659–67. Available from: http://www.sciencedirect.com/science/article/pii/B9781416043904000898.
58. Bercu TE, Petri WA, Behm JW. Amebic colitis: new insights into pathogenesis and treatment. Curr Gastroenterol Rep. 2007;9(5):429–33.
59. Ravdin JI. Amebiasis. Clin Infect Dis [Internet]. 1995;20(6):1453–64. Available from: http://www.jstor.org/stable/4458589.
60. Parija SC, Mandal J, Ponnambath DK. Laboratory methods of identification of Entamoeba histolytica and its differentiation from look-alike Entamoeba spp. Trop Parasitol. 2014;4(2):90–5.
61. Peterson KM, Singh U, Petri WA. Chapter 92 – Enteric amebiasis. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical infectious diseases: principles, pathogens and practice [Internet]. 3rd ed. Edinburgh: W.B. Saunders; 2011. p. 614–22. Available from: http://www.sciencedirect.com/science/article/pii/B9780702039355000926.
62. Weinke T, Friedrich-Janicke B, Hopp P, Janitschke K. Prevalence and clinical importance of Entamoeba histolytica in two high-risk groups: travelers returning from the tropics and male homosexuals. J Infect Dis. 1990;161(5):1029–31.
63. Salit IE, Khairnar K, Gough K, Pillai DR. A possible cluster of sexually transmitted Entamoeba histolytica: genetic analysis of a highly virulent strain. Clin Infect Dis. 2009;49(3):346–53.
64. Gonzales MLM, Dans LF, Sio-Aguilar J. Antiamoebic drugs for treating amoebic colitis. Cochrane Database Syst Rev. 2019;(1):CD006085.
65. Misra NP, Gupta RC. A comparison of a short course of single daily dosage therapy of tinidazole with metronidazole in intestinal amoebiasis. J Int Med Res. 1977;5(6):434–7.
66. Hesse AAJ, Nouri A, Hassan HS, Hashish AA. Parasitic infestations requiring surgical interventions. Semin Pediatr Surg. 2012;21(2):142–50.
67. Takahashi T, Gamboa-Dominguez A, Gomez-Mendez TJ, Remes JM, Rembis V, Martinez-Gonzalez D, et al. Fulminant amebic colitis: analysis of 55 cases. Dis Colon Rectum. 1997;40(11):1362–7.
68. Haque R, Huston CD, Hughes M, Houpt E, Petri WAJ. Amebiasis. N Engl J Med. 2003;348(16):1565–73.
69. Acuna-Soto R, Maguire JH, Wirth DF. Gender distribution in asymptomatic and invasive amebiasis. Am J Gastroenterol. 2000;95(5):1277–83.
70. Stanley SLJ. Amoebiasis. Lancet (London, England). 2003;361(9362):1025–34.
71. Pritt BS, Clark CG. Amebiasis. Mayo Clin Proc. 2008;83(10):1154–60.
72. Aikat BK, Bhusnurmath SR, Pal AK, Chhuttani PN, Datta DV. The pathology and pathogenesis of fatal hepatic amoebiasis–a study based on 79 autopsy cases. Trans R Soc Trop Med Hyg. 1979;73(2):188–92.
73. Adams EB, MacLeod IN. Invasive amebiasis. I. Amebic dysentery and its complications. Medicine (Baltimore). 1977;56(4):315–23.
74. Katzenstein D, Rickerson V, Braude A. New concepts of amebic liver abscess derived from hepatic imaging, serodiagnosis, and hepatic enzymes in 67 consecutive cases in San Diego. Medicine (Baltimore). 1982;61(4):237–46.
75. Chavez-Tapia NC, Hernandez-Calleros J, Tellez-Avila FI, Torre A, Uribe M. Image-guided percutaneous procedure plus metronidazole versus metronidazole alone for uncomplicated amoebic liver abscess. Cochrane Database Syst Rev. 2009;(1):CD004886.

76. vanSonnenberg E, Mueller PR, Schiffman HR, Ferrucci JTJ, Casola G, Simeone JF, et al. Intrahepatic amebic abscesses: indications for and results of percutaneous catheter drainage. Radiology. 1985;156(3):631–5.
77. Chen X-M, Keithly JS, Paya CV, LaRusso NF. Cryptosporidiosis. N Engl J Med. 2002;346(22):1723–31.
78. Xiao L, Griffiths JK. 91 – Cryptosporidiosis. In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious disease [Internet]. 9th ed. London: W.B. Saunders; 2013. p. 673–9. Available from: http://www.sciencedirect.com/science/article/pii/B9781416043904000916.
79. Peng MM, Xiao L, Freeman AR, Arrowood MJ, Escalante AA, Weltman AC, et al. Genetic polymorphism among Cryptosporidium parvum isolates: evidence of two distinct human transmission cycles. Emerg Infect Dis. 1997;3(4):567–73.
80. Davies AP, Chalmers RM. Cryptosporidiosis BMJ. 2009;339:b4168.
81. Cama VA, Ross JM, Crawford S, Kawai V, Chavez-Valdez R, Vargas D, et al. Differences in clinical manifestations among Cryptosporidium species and subtypes in HIV-infected persons. J Infect Dis. 2007;196(5):684–91.
82. Cama VA, Bern C, Roberts J, Cabrera L, Sterling CR, Ortega Y, et al. Cryptosporidium species and subtypes and clinical manifestations in children. Peru Emerg Infect Dis. 2008;14(10):1567–74.
83. Petersen C. Cryptosporidium and the food supply. Lancet (London, England). 1995;345(8958):1128–9.
84. Janoff EN, Limas C, Gebhard RL, Penley KA. Cryptosporidial carriage without symptoms in the acquired immunodeficiency syndrome (AIDS). Vol. 112, Annals of internal medicine. Copyright © 1990 American College of Physicians, USA. 1990. p. 75–76.
85. Mor SM, DeMaria AJ, Griffiths JK, Naumova EN. Cryptosporidiosis in the elderly population of the United States. Clin Infect Dis. 2009;48(6):698–705.
86. Stiff RE, Davies AP, Mason BW, Hutchings HA, Chalmers RM. Long-term health effects after resolution of acute Cryptosporidium parvum infection: a 1-year follow-up of outbreak-associated cases. J Med Microbiol. 2017;66(11):1607–11.
87. Rossignol J-F. Cryptosporidium and Giardia: treatment options and prospects for new drugs. Exp Parasitol. 2010;124(1):45–53.
88. Pantenburg B, Cabada MM, White ACJ. Treatment of cryptosporidiosis. In: Expert review of anti-infective therapy. Vol. 7. England; Copyright © 2009 Taylor & Francis, United Kingdom. 2009. p. 385–391.
89. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by Cryptosporidium parvum: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. J Infect Dis. 2001;184(1):103–6.
90. Rossignol J-F, Kabil SM, el-Gohary Y, Younis AM. Effect of nitazoxanide in diarrhea and enteritis caused by Cryptosporidium species. Clin Gastroenterol Hepatol. 2006;4(3):320–4.
91. White ACJ, Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind trial. J Infect Dis. 1994;170(2):419–24.
92. Vakil NB, Schwartz SM, Buggy BP, Brummitt CF, Kherellah M, Letzer DM, et al. Biliary cryptosporidiosis in HIV-infected people after the waterborne outbreak of cryptosporidiosis in Milwaukee. N Engl J Med. 1996;334(1):19–23.
93. Teare JP, Daly CA, Rodgers C, Padley SP, Coker RJ, Main J, et al. Pancreatic abnormalities and AIDS related sclerosing cholangitis. Sex Transm Infect. 1997;73(4):271–3.
94. Hashmey R, Smith NH, Cron S, Graviss EA, Chappell CL, White CA. Cryptosporidiosis in Houston, Texas a report of 95 cases. Medicine (Baltimore). 1997;76(2):118–39.
95. do Rosário de Souza L, Rodrigues MAM, Morceli J, Kemp R, Mendes RP. Cryptosporidiosis of the biliary tract mimicking pancreatic cancer in an AIDS patient. Rev Soc Bras Med Trop [Internet]. 2004;37:182–5. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0037-86822004000200015&nrm=iso.

96. Sidebotham EL, Sepkowitz K, Price AP, Steinherz PG, La Quaglia MP, Kayton ML. Eradication of cryptosporidium from a defunctionalized colon limb by refeeding stoma effluent. J Pediatr Surg [Internet]. 2010;45(1):e33–6. Available from: http://www.sciencedirect.com/science/article/pii/S002234680900921X.
97. Ortega YR, Sterling CR, Gilman RH, Cama VA, Diaz F. Cyclospora species–a new protozoan pathogen of humans. N Engl J Med. 1993;328(18):1308–12.
98. Shlim DR, Connor BA. 92 – Cyclosporiasis. In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious disease [Internet]. 9th ed. London: W.B. Saunders; 2013. p. 680–2. Available from: http://www.sciencedirect.com/science/article/pii/B9781416043904000928.
99. Chacin-Bonilla L. Epidemiology of Cyclospora cayetanensis: a review focusing in endemic areas. Acta Trop. 2010;115(3):181–93.
100. Ortega YR, Sanchez R. Update on cyclospora cayetanensis, a food-borne and waterborne parasite. Clin Microbiol Rev. 2010;23(1):218–34.
101. Hoge CW, Shlim DR, Rajah R, Triplett J, Shear M, Rabold JG, et al. Epidemiology of diarrhoeal illness associated with coccidian-like organism among travellers and foreign residents in Nepal. Lancet (London, England). 1993;341(8854):1175–9.
102. Fleming CA, Caron D, Gunn JE, Barry MA. A foodborne outbreak of Cyclospora cayetanensis at a wedding: clinical features and risk factors for illness. Arch Intern Med. 1998;158(10):1121–5.
103. Sifuentes-Osornio J, Porras-Cortes G, Bendall RP, Morales-Villarreal F, Reyes-Teran G, Ruiz-Palacios GM. Cyclospora cayetanensis infection in patients with and without AIDS: biliary disease as another clinical manifestation. Clin Infect Dis. 1995;21(5):1092–7.
104. Verweij JJ, Laeijendecker D, Brienen EAT, van Lieshout L, Polderman AM. Detection of Cyclospora cayetanensis in travellers returning from the tropics and subtropics using microscopy and real-time PCR. Int J Med Microbiol. 2003;293(2–3):199–202.
105. Hoge CW, Gaudio P, Echeverria P, Shlim DR, Rabold JG, Pandey P, et al. Placebo-controlled trial co-trimoxazole for cyclospora infections among travellers and foreign residents in Nepal. Lancet. 1995;345(8951):691–3.
106. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65(12):e45–80.
107. Diaz E, Mondragon J, Ramirez E, Bernal R. Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico. Am J Trop Med Hyg. 2003;68(4):384–5.
108. Verdier RI, Fitzgerald DW, Johnson WDJ, Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients. A randomized, controlled trial. Ann Intern Med. 2000;132(11):885–8.
109. Weiss LM, Keohane EM. The uncommon gastrointestinal protozoa: microsporidia, blastocystis, isospora, dientamoeba, and balantidium. Curr Clin Top Infect Dis. 1997;17:147–87.
110. Schuster FL, Ramirez-Avila L. Current world status of Balantidium coli. Clin Microbiol Rev. 2008;21(4):626–38.
111. Esteban JG, Aguirre C, Angles R, Ash LR, Mas-Coma S. Balantidiasis in Aymara children from the northern Bolivian Altiplano. Am J Trop Med Hyg. 1998;59(6):922–7.
112. Ferry T, Bouhour D, De Monbrison F, Laurent F, Dumouchel-Champagne H, Picot S, et al. Severe peritonitis due to Balantidium coli acquired in France. Eur J Clin Microbiol Infect Dis. 2004;23(5):393–5.
113. Ladas SD, Savva S, Frydas A, Kaloviduris A, Hatzioannou J, Raptis S. Invasive balantidiasis presented as chronic colitis and lung involvement. Dig Dis Sci. 1989;34(10):1621–3.
114. Castro J, Vazquez-Iglesias JL, Arnal-Monreal F. Dysentery caused by Balantidium coli–report of two cases. Endoscopy. 1983;15(4):272–4.

Surgical Treatment of Intestinal Cestodes

4

Samer Deeba

Introduction

Cestodes are parasites belonging to the genus *Helminthes* that infect the gastrointestinal tract of humans as the end-stage adult, or tapeworm, and have complex life cycles, involving one or more intermediate hosts with the larvae form better known as metacestodes. The tapeworm body has a head or scolex carrying the fixation hooks to cling onto the intestinal luminal mucosa, a neck, and several segments called proglottids carrying the reproductive organs or strobili. The attachment mechanism can be hooks on the scolex, suckers, or a combination of the former with bothria depending on the species. The proglottids appear from the neck and mature as they go distally with both male and female reproductive organs. Hence at the distal end of the tapeworm are the proglottids that have matured shedding eggs from the strobili and pass in the feces to the definitive host. The anatomical shape of the eggs, proglottids, and scolex in the tapeworm is usually sufficient to identify the genus and species in most cases. After the intermediate host ingests the above eggs, larvae are released and immediately invade the host tissues forming larval stages, called cysticerci, cysticercoids, and plerocercoids depending on the species at hand. Then when the final host, usually, humans, ingests the infected tissue of the intermediate host, the larva is released in the intestine of humans and grows to form the adult tapeworms.

Transmission varies among species. Eggs are usually ingested from poorly washed food, soil, or water contaminated with feces from the intermediate hosts. Larvae are ingested from raw or poorly cooked meat from the intermediate host animals with infective larval stage [1]. This chapter will tackle the five species of adult worms that infect the human gut and the medical treatment briefly with

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emphasis on the surgical presentation and management of these worms in the emergency setting, as surgery is usually needed only in the acute setting after a late complication of the above infection which went unnoticed and was not treated medically to begin with.

Taenia solium Taeniasis

The *T. solium* tapeworm is one of the long and large tapeworms to infect the human gut in its adult form reaching up to 4 m in length. The scolex is equipped with a four-sucker apparatus and two rows of hooks that cling to the intestinal mucosa. The mature gravid proglottids at the distal end produce eggs around 30 um in diameter that are shed with feces and then ingested by pigs in farms. The eggs deploy the oncosphere that invades the mucosal lining and travel hematogenously to distant organs like the muscle and central nervous system, where the cysticercus forms within the end tissues and remains dormant. The humans then ingest poorly cooked meat from the intermediate host, and the cysticerci will release the scolex to form a new tapeworm that grows into adult form to complete the life cycle. *T. solium* infection in humans is very common in the farmlands of the Americas, Africa, and Asia and less commonly in Europe and North America where it is usually found in immigrants from the former continents [2]. As the above cycle depicts, it is only logical to see that there is close association between the prevalence of free roaming pigs cysticercosis which are the intermediate hosts and countries with increased incidence of taeniasis in humans like studies have shown [3]. These infections sometimes go unnoticed until the passage of worms or parts of worms in feces. The diagnosis after the presentation is usually done with fecal examination. The examination includes simple microscopy and more complex molecular and serologic testing to differentiate between species of the genus and might progress for the new PCR methods [4, 5].

The primary line of treatment is praziquantel or niclosamide and is highly effective. Niclosamide has less side effects especially less headaches and seizure activity with patients that present with neurocysticercosis and hence is preferred when available. However, for patients with no neural system, involvement studies have shown the above use of praziquantel is safe and efficacious [6].

Taenia saginata/Asiatica

This tapeworm can reach up to 10 m in length with a scolex having four suckers but no hook rows unlike the *T. solium*. The proglottids are motile and disperse eggs away from human feces and hence are ingested by cattle off grass not feces as cattle are not known as coprophagic. After ingestion by bovine, the oncospheres are released into the mucosa and in turn invade mucosae of bovine and hematogenously spread to striated muscle commonly. The human ingestion of these infected muscles

of bovine species ends their life cycle as the humans are the definitive hosts and the cysticerci grow to the adult worm in the human gut [7].

Taenia asiatica is very similar anatomically to *T. saginata*, but the intermediate host is pig and not cattle, and its intermediate larval stage is spent in the muscle and liver of the former [8].

The treatment of the above when symptomatic is usually single and rarely multiple-dose praziquantel or niclosamide according to disease burden [9].

Hymenolepis nana

It has a short life span of average 4–6 weeks and is the shortest human tapeworm measuring up to 4 cm long. The adult tapeworm produces eggs that are highly contagious which n turn facilitates the easy spread in one household bt the fecal oral route. After ingestion the eggs release the oncosphere that infects the intestinal mucosa and form a metacestode called cysticercoid, and after incubation for 2–3 weeks, a new tapeworm emerges completing the cycle. It is the only tapeworm that can auto-infect the same host as the adult can shed eggs internally that in turn will invade the same individual host tissues before reaching outside.

H. nana is the most common tapeworm infection in human and can reach up to 30% in poor countries in Africa [10]. Humans with low socioeconomic status and live in crowded conditions, without access to proper sanitation, clean food, and treated water supply are at a high risk. The presenting symptoms are usually diarrhea, abdominal cramps, headache, and malaise in children, and we usually find anemia, loss of appetite, malnutrition, and weight loss in infected patients [11, 12].

Medical treatment is single-dose praziquantel at 25 mg/kg and is effective in over 95%, alternatively nitazoxanide for 3 days or niclosamide for 7 days can be administered with similar effective results [13].

Diphyllobothrium Species

Better known as broad or fish tapeworms and is the largest and can reach up to 25 m in length and is very diverse with up to 14 different species identified. The scolex has two bilateral grooves that attach to human intestinal mucosa, and the proglottids release their eggs that pass in human feces. The eggs need 3 weeks in the fresh water to form oncospheres. Oncospheres are ingested by freshwater crustaceans and form procercoid larvae [14]. The crustaceans are ingested by small freshwater fish where the procercoid larva migrates to deep muscle tissue and forms plerocercoid larva there. Predator fish like trout and pike eat the smaller fish, and once again the plerocercoid larva migrates to muscle tissue. The infection into humans is reintroduced when we ingest the larger fish meat that is raw or undercooked. The larva is released in the human gut and reached its adult tapeworm phase to complete the cycle. The wide acceptance of fresh raw fish cuisine-like sushi and ceviche and nigiri has helped in the growing incidence of fish tapeworm infections. The infection is

prevalent in areas where the above dishes are common like Northern Europe, Japan, China, Russia, and more recently in Middle East and South America such as Brazil and Peru and in Italy due to increased prevalence in freshwater lakes pike fish [15, 16].

Human infection is usually mild, and one out of five exhibits symptoms that present to medical personnel like abdominal pain, diarrhea, and pernicious anemia due to uptake of vitamin B12 by the worm. Visible parts and segments are seen in stool and lead to the diagnosis by morphologic examination along with observation of eggs and segments. Treatment is single-dose praziquantel or niclosamide.

Surgical Treatment

As we can see, the majority of these parasitic infections can be treated as they become symptomatic with a simple antiparasitic agent that is usually a one-off single-dose treatment. However, due to the lack of resources in underserviced areas or maybe due to patient neglect, these infections might be left unattended by medical personnel and might progress and present as a late presentation which is usually a complication of these parasites growing unhindered. These presentations are intestinal obstruction, intestinal perforation and fistulization, intestinal bleeding, and appendicitis. Intestinal obstruction occurs from the formation of parasitic balls or bezoars in the intestinal lumen as they grow and cluster together hindering motility in the gut and compromising intestinal lumen especially in the small intestine. Intestinal perforation occurs when the area of the lumen where the tapeworm has attached becomes too friable from the inflammatory reaction that pursues or from local ischemia due to the sucking effect of the tapeworm which causes the intestinal integrity to become compromised and hence perforate into the free abdomen or, on the other hand, perforate into an adjoining viscus or organ such as urinary bladder causing an internal fistula. Intestinal bleeding has the same etiology of the later, but the inflammatory reaction erodes into an intramural vessel resulting into a luminal bleed. All the above presentations are surgical emergencies rare in occurrence and require urgent surgical input. Appendicitis would occur if the tapeworm aggregate blocked the appendicular lumen and hence same pathogenesis of an appendicolith, but the inciting factor is a bezoar of tapeworms. These tapeworms might also complicate surgical operations causing leaks in anastomosis or appendicular stump blowouts.

Intestinal Obstruction

The pathogenesis of the obstruction is the compromise of the intestinal lumen and motility by a ball of interlocking tapeworms that become big enough to block the lumen, and the intestine will not be able to propagate that ball further especially if that ball gets stuck in tight areas of the terminal ileum and the ileocecal valve

Fig. 4.1 Tapeworm bezoar causing luminal obstruction [17]

(Fig. 4.1). The presentation is typical of any small bowel obstruction with obstipation of several days with abdominal pain and cramps, distention, nausea, vomiting, malnutrition, and dehydration. The presentation is usually acute in the emergency department setting, and diagnostic imaging is typically a CT scan showing findings of intestinal obstruction, and rarely it is diagnosed on the scan as a cause, but previous symptoms should alert the attending physician to the cause of the obstruction, like history of tapeworm infections or passage of segments of the worms or full worms in stools that were not treated for a long time [17, 18].

The CT scan findings are typical of small bowel obstruction with dilated bowel loops and fecal sign in the bowel lumen proximal to the obstruction and bowel deflation distal to the obstruction. The tapeworm mass is radiolucent, so it will not appear in the scan but might be read as a bezoar or fecaloma by the radiologist.

Usually patients will not settle with conservative treatment of intravenous hydration and nasogastric tube decompression as the obstruction is a mechanical obliteration of the lumen by the tapeworm ball and will require a laparotomy to deal with it. The diagnosis is seldom done until laparotomy where the surgeon will realize that there is a bezoar causing the obstruction and will identify the cause as tapeworms at the time of enterotomy to retrieve the bezoar or after enterectomy of the affected segment and then inspection of the surgical field.

An enterotomy and retrieval of the tapeworm bezoar are a feasible option if the intestine is deemed healthy and viable not affected by the ongoing process and then the enterotomy is closed by a two layer absorbable suture technique as shown in Fig. 4.1

However if the intestine is deemed nonviable, an enterectomy is warranted, and bowel continuity is achieved by an enteroenterostomy. Postoperative treatment by praziquantel is mandatory to eradicate the remaining tapeworm infestation.

Intestinal Perforation

The pathophysiology of perforation is very close to that of obstruction where the area with the tapeworm is adherent and suffers from an inflammatory reaction due to the suction effect of the scolex apparatus and at the same time due to diminished blood supply to the intestinal wall in that area attributed to the effect of the scolex suction. This with time can lead to tissue loss, and then when the inflammation erodes into the luminal wall, it causes a free perforation into the abdominal cavity.

The presentation is typically like any viscus perforation presentation. Patients present with severe abdominal pain are not resolving on pain medication and nausea, vomiting, and malnutrition. The presentation is typically an acute one to the emergency department. On exam the patients will be tender all over the abdominal quadrants with fever and leukocytosis. A CT scan will show air in the abdomen with the perforation site and abdominal-free fluid. This is an urgent presentation, and no time should be lost in taking the patient for an urgent laparotomy.

On laparotomy the bowel is run, and the perforation site is identified. The cause of the perforation is seldom found before the laparotomy and is diagnosed as tapeworm usually intraoperatively where the ball of tapeworms causing the perforation is palpated and delivered out of the intestine from the perforation site. The perforation is seldom sutured primarily as that area is usually inflamed and friable, so wedge resection enterectomy is performed with a stapled or hand sewn anastomosis to achieve bowel continuity. The site of the perforation is usually terminal ileum where the lumen of the bowel narrows down and rarely do we find it to be colonic as the lumen increases in the colon [19, 20].

On the other hand, this can be tackled laparoscopically also by experienced laparoscopic surgeon that will explore the abdomen laparoscopically and run the bowel identifying the perforation site that can be then withdrawn extracorporeal through a minilaparotomy and the repair or enterectomy done outside. This approach can help in shortening the recovery and hospital stay as all laparoscopic procedures do but should be performed by experienced surgeons as shown in Figs. 4.2 and 4.3.

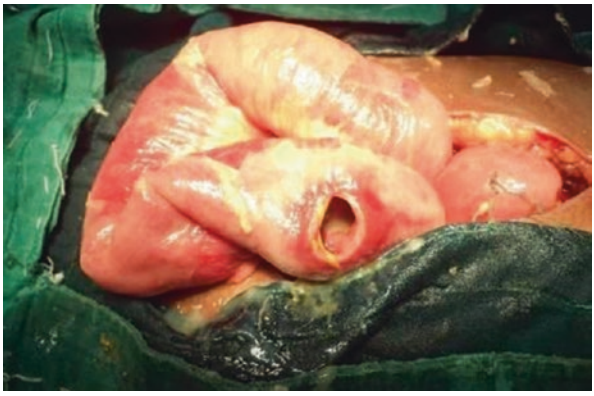

Fig. 4.2 Perforation from terminal ileum due to tapeworm infestation [19]

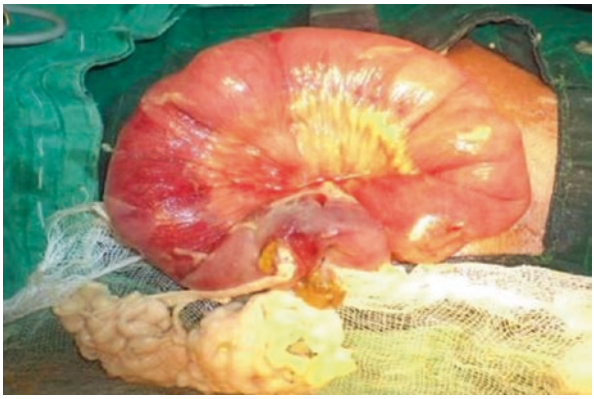

Fig. 4.3 Perforation and tapeworm extruding out from terminal ileum [19]

Intestinal Bleeding

This is another rare presentation to the emergency department, the pathophysiology of which is the same as above, basically an overwhelming inflammatory reaction due to the presence of the scolex adherent to bowel wall where this reaction erodes into a perforating arteriole that bleed freely into the lumen. The presentation is that of anemia and malaise with passage of melena stools, with a drop of hemoglobin to below 7 g/dl. The workup is usually futile in the classical means of OGD and colonoscopy that will show no pathology as the site is usually in the jejunal or ileal segments. Push enteroscopy can reveal the site of the bleed if the area in question is distal ileum. However the above along with CT angiography of the intestine rarely shows the site as the bleed is not sufficient enough to light up of angiography scanning. On the other hand, a more invasive SMA arteriography can show the site if bleeding is excessive enough. The best means of diagnosis are a capsule endoscopy that can reveal the presence of the tapeworms and the site of presence of excess intraluminal blood clots [21]. The usual treatment is medical when diagnosis is made with anti-helminthic medication with blood resuscitation and the bleed usually settles with that. However it is very rare that the bleed is causing hemodynamic instability; hence it needs intervention to control it. The less invasive method is through an interventional radiology technique where the SMA angiography reveals the site of active bleeding and then the corresponding terminal branches of the ileal arcade are embolized [22, 23].

If the above intervention does not settle and control the bleeding site and the patient becomes hemodynamically unstable or is requiring daily blood transfusion to keep the hemoglobin above 8 g/dl, then surgical exploration is warranted. The patient can be taken for an exploratory laparotomy and the bowel run where the bleeding site is identified with the presence of clots in the lumen that are evacuated through an enterotomy and that segment excised as in the above presentation. The tapeworm is usually identified and removed for the lumen by pulling it out. As in the previous presentation, the control of the bleed can be done

laparoscopically, and the bleeding bowel segment can be extruded to the outside by a minilaparotomy and the tapeworm removed and enterectomy done. Sometimes the bleeding site is one small area, and simple suturing to control it can be done through an enterotomy that can be closed later in two-layer technique. Seldom is the need for surgery as the above medical treatment or interventional approach usually suffice for control.

Helminthal Appendicitis

The above presentation is very rare and presents as a typical appendicitis to the emergency department. The pathophysiology of the disease is tapeworm infestation of the appendicular lumen and hence blocking of the flow through the lumen and obstruction of the appendix with a "tapeworm appendicolith." This leads to the cascade of events like a typical appendicitis progression. The patient presents with vague abdominal pain that localizes over a few hours to the right lower quadrant, with nausea and vomiting and loss of appetite. The radiologic conformation of appendicitis can be with CT scan showing marked dilation of the appendix more than 1 cm in diameter with all the inflammatory changes and the fat stranding that usually accompany appendicitis.

This is a surgical condition and necessitates an urgent appendectomy. This can be done through a McBurney open approach where the abdomen is entered in a muscle-splitting technique and the appendix and mesoappendix mobilized, freed, ligated, and cut. It is at that point that a tapeworm might spill into the field giving the surgeon the suspicion that this tapeworm is the cause of the appendicitis, but this is rarely seen. The above tapeworm will be seen on histopathologic examination of the specimen and hence the diagnosis [24, 25]. The appendectomy can be done laparoscopically with the same findings. A pneumoperitoneum is achieved through the umbilicus and two ports inserted in the lower quadrants; these are used to mobilize the appendix and mesoappendix and the base tied or stapled off, with the specimen retrieved in a retrieval bag. The laparoscopic approach carries lot less morbidity, and patients recover quicker as per all laparoscopic approach operations [26] as shown in Figs. 4.4 and 4.5.

Tapeworm infestation can also lead to Meckel's diverticulitis as has been expressed in a few case reports in the literature. The presentation is typical of a Meckel's diverticulitis with abdominal pain, fever, nausea, and vomiting. Preoperative workup reveals leukocytosis, and CT scan is suggestive of a Meckel's diverticulitis with surrounding fat stranding and sentinel loops. The treatment is usually a laparoscopic or open approach Meckel's diverticulectomy with a stapling device or a wedge resection of the small bowel if the base of the diverticulum is more than 2 cm in length. It is at the time of transection of the diverticulum when the surgeon realizes the infestation with tapeworms and diagnosies the cause. Postoperative treatment is mandatory with anti-helminthic medication to eradicate the infestation [27].

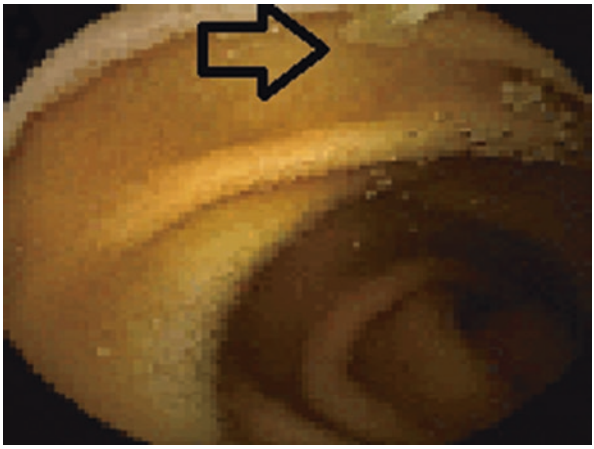

Fig. 4.4 Capsule endoscopy showing head of tapeworm [21]

Fig. 4.5 Capsule endoscopy showing body of tapeworm [21]

Tapeworm Complications

Intestinal taeniasis can also complicate surgical procedures especially when these procedures have suture or staple lines in the bowel. The tapeworms can migrate through a suture line or a staple line and perforate through it to cause a bowel content leak into the abdominal cavity necessitating urgent intervention by the surgeon. There have been reports in the literature for appendicular stump blowouts after appendectomy due to perforation by *T. saginata*, and patients represent a few days post appendectomy be it open or laparoscopic with a right iliac fossa abscess. Management of these is by percutaneous drainage, and usually the tapeworm finds its way out of the wound and is retrieved bedside. Medical treatment with anti-helminthic medication is warranted to eradicate other worms in the intestines. With this conservative management, the majority of these cases settle the abscess and heal the leak or fistula [28].

Other citations in the literature do report on leaks from bowel anastomosis post a colectomy. The leaks happened in the immediate postoperative period and not delayed and were dealt with within the same admission of the colectomy. A patient was complicated with a free leak into the abdominal cavity after a right hemicolectomy and leaked from the ileo-transverse anastomosis on the third-day post-op. Because of frank peritonitis and frank leak from the drain site, she was directly taken to exploration, and the cause of the leak was a *T. saginata* tapeworm perforating the anastomosis, the abdomen was washed, the anastomosis taken down, and an end ileostomy fashioned due to fecal soiling of the abdominal cavity [29]. Other leaks have been also reported post esophagectomy from the esophageal anastomosis and were treated conservatively with drainage and support [30].

These leaks and blowouts from the perforation from a cestode seldom require urgent laparotomy unless the leak is free into the abdominal cavity causing fecal peritonitis; otherwise they can be managed conservatively when they resent late causing a walled-off abscess. The abscess can be percutaneously drained, and the physician can be alerted to the cause from the passage of the worms from the draining catheter site or per anus from history of the patient. Treatment with anti-helminthic medication is sufficient to treat the cause, and these abscesses and fistulization usually settle conservatively as shown in Fig. 4.6.

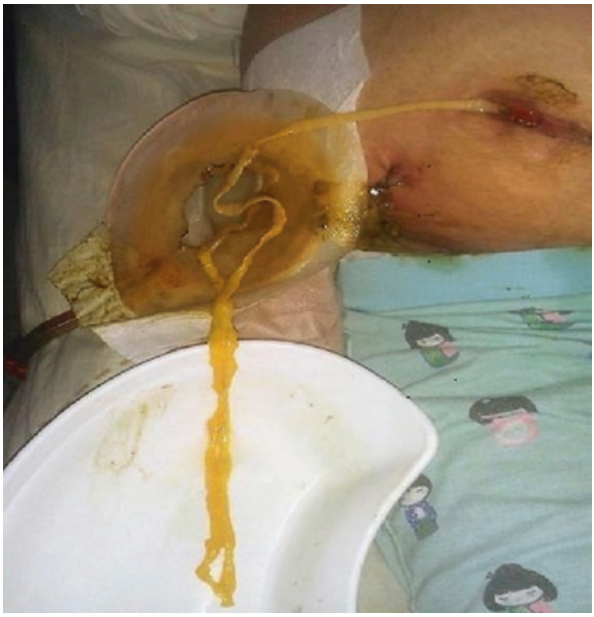

Fig. 4.6 Tapeworm withdrawn post appendectomy from appendectomy wound [28]

Summary

Surgical presentations from tapeworm infestation are rare presentations and seldom seen in the emergency setting. The diagnosis is usually delayed and upon surgical exploration when the surgeon usually sees the tapeworms in the surgical field. The treatment of these is usually the treatment of the complication arising from the unnoticed presence of the infestation, as per the basic surgical treatment principles. Medical therapy with anti-helminthic medication is the gold standard if these infestations are diagnosed before presentation as a surgical emergency. Prophylaxis is also mainstay, and avoiding uncooked meat of the intermediate host is of utmost importance especially in areas that are endemic.

References

1. Schantz PM. Tapeworms (cestodiasis). Gastroenterol Clin N Am. 1996;25(3):637–53.
2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388:1545–602.
3. O'Neal SE, Moyano LM, Ayvar V, et al. Geographic correlation between tapeworm carriers and heavily infected cysticercotic pigs. PLoS Negl Trop Dis. 2012;6:e1953.
4. Madinga J, Polman K, Kanobana K, et al. Epidemiology of polyparasitism with Taenia solium, schistosomes and soil-transmitted helminths in the co-endemic village of Malanga, Democratic Republic of Congo. Acta Trop. 2017;171:186–93.
5. Nkouawa A, Sako Y, Okamoto M, Ito A. Simple identification of human Taenia species by multiplex loop-mediated isothermal amplification in combination with dot enzyme-linked immunosorbent assay. Am J Trop Med Hyg. 2016;94:1318–23.
6. Braae UC, Magnussen P, Ndawi B, et al. Effect of repeated mass drug administration with praziquantel and track and treat of taeniosis cases on the prevalence of taeniosis in Taenia solium endemic rural communities of Tanzania. Acta Trop. 2017;165:246–51.
7. Rossi GA, de Simoni HA, Lopes WD, et al. Prevalence and geospatial distribution of bovine cysticercosis in the state of Mato Grosso, Brazil. Prev Vet Med. 2016;130:94–8.
8. Galán-Puchades MT, Fuentes MV. Updating Taenia asiatica in humans and pigs. Parasitol Res. 2016;115:4423–5. A review of the current knowledge on T. asiatica infection.
9. Tanowitz HB, Weiss LM, Wittner M. Diagnosis and treatment of intestinal helminths. I. Common intestinal cestodes. Gastroenterologist. 1993;1(4):265–73.
10. Abdel Hamid MM, Eljack IA, Osman MK, et al. The prevalence of Hymenolepis nana among preschool children of displacement communities in Khartoum state, Sudan: a cross-sectional study. Travel Med Infect Dis. 2015;13:172–7.
11. Willcocks B, McAuliffe GN, Baird RW. Dwarf tapeworm (Hymenolepis nana): characteristics in the Northern Territory 2002–2013. J Paediatr Child Health. 2015;51:982–7.
12. Khalil HM, el Shimi S, Sarwat MA, et al. Recent study of Hymenolepis nana infection in Egyptian children. J Egypt Soc Parasitol. 1991;21:293–300.
13. Chero JC, Saito M, Bustos JA, et al. Hymenolepis nana infection: symptoms and response to nitazoxanide in field conditions. Trans R Soc Trop Med Hyg. 2007;101:203–5.
14. Scholz T, Garcia HH, Kuchta R, Wicht B. Update on the human broad tapeworm (genus Diphyllobothrium), including clinical relevance. Clin Microbiol Rev. 2009;22:146–60.
15. Kuchta R, Serrano-Martínez ME, Scholz T. Pacific broad tapeworm Adenocephalus pacificus as a causative agent of globally reemerging Diphyllobothriosis. Emerg Infect Dis. 2015;21:1697–703.

16. Gustinelli A, Menconi V, Prearo M, et al. Prevalence of Diphyllobothrium latum (Cestoda: Diphyllobothriidae) plerocercoids in fish species from four Italian lakes and risk for the consumers. Int J Food Microbiol. 2016;235:109–12.
17. Atef M, Emna T. A rare cause of intestinal obstruction. J Clin Case Rep. 2015;5:9.
18. Karanikas ID, Sakellaridis TE, Alexiou CP, Siaperas PA, Fotopoulos AC, Antsaklis GI. Taenia saginata: a rare cause of bowel obstruction. Trans R Soc Trop Med Hyg. 2007;101(5):527–8. Epub 2006 Sep 12.
19. Kurane SB, Kurane BT. Ileal perforation peritonitis caused by T. Saginata: a case report. Int J Med Res Rev. 2013;1(3):138–41.
20. Demiriz M, Günhan O, Celasun B, Aydin E, Finci R. Colonic perforation caused by taeniasis. Trop Geogr Med. 1995;47:180–2.
21. Settesoldi A, Tozzi A, Tarantino O. Taeniasis: a possible cause of ileal bleeding. World J Clin Cases. 2017;5(12):432–6. https://doi.org/10.12998/wjcc.v5.i12.432.
22. Hongsakul K, Pakdeejit S, Tanutit P. Outcome and predictive factors of successful transarterial embolization for the treatment of acute gastrointestinal hemorrhage. Acta Radiol. 2014;55:186–94.
23. Navuluri R, Kang L, Patel J, Van Ha T. Acute lower gastrointestinal bleeding. Semin Interv Radiol. 2012;29:178–86.
24. Lejbkwicz F, Abel AB, Tsilman B, Cohen HI. Taenia infestation in the appendix: a report of two cases. J Med Microbiol. 2002;51:90–1.
25. Sartorelli AC, da Silva MG, Rodrigues MA, da Silva RJ. Appendiceal taeniasis presenting like acute appendicitis. Parasitol Res. 2005;97(2):171–2. Epub 2005 Jun 29.
26. Jaschinski T, Mosch C, Eikermann M, Neugebauer EA. Laparoscopic versus open appendectomy in patients with suspected appendicitis: a systematic review of meta-analyses of randomised controlled trials. BMC Gastroenterol. 2015;15:48. https://doi.org/10.1186/s12876-015-0277-3.
27. Chirdan LB, Yusufu LM, Ameh EA, Shehu SM. Meckel's diverticulitis due to *Taenia saginata:* case report. East Afr Med J. 2001;78:107–8.
28. Najih M, Laraqui H, Njoumi N, Mouhafid F, Moujahid M, Ehirchiou A, Zentar A. Taenia saginata: an unusual cause of post-appendectomy faecal fistula Mohammed Najih. Pan Afr Med J. 2016;25:200. https://doi.org/10.11604/pamj.2016.25.200.11003.
29. Sozutek A, Colak T, Dag A, Turkmenoglu O. Colonic anastomosis leakage related to taenia saginata infestation. Clinics (Sao Paulo). 2011;66(2):363–4.
30. Baleela RM, Hueassain MY, Ahmed ME. Anastomotic esophageal leak due to *Taenia saginata* following esophagectomy for esophageal cancer. Saudi Med J. 2006;27:241–3.

5 The Role of Surgery in Treating Parasitic Diseases of the Gastrointestinal Tract from Nematodes

Amanda Hamilton, Ashley Jenkin, Andrew Phillip Maurice, and Yik-Hong Ho

Introduction

Human parasitic nematode infection constitutes a major public health concern. This is particularly true in developing countries where lack of recognition and treatment can lead to various and occasionally serious life-threatening complications [1, 2]. The human enteric nematodes, also called roundworms, are tubular in structure and include *Ascaris lumbricoides*, the hookworms *Ancylostoma duodenale* and *Necator americanus*, *Strongyloides stercoralis* and *Trichuris trichiura*, also known as whipworm, and *Enterobius vermicularis* also called pinworm or threadworm [3]. Infection into the human host occurs by transmission of the worm eggs or larvae from which they begin their cycle of development. Transmission occurs by ingestion, penetration through the skin or rarely by inhalation and is specific for human host such that there is no animal reservoir. The larvae of some species can remain dormant in soil but potentially infectious for long periods of time. The key to long-term strategic control of enteric nematodes is interruption to transmission [1, 4]. There are major health initiatives currently in place to help educate endemic areas in prevention of enteric parasitic infection by way of hygiene, use of shoes, construction of sanitation and effective sewage systems, sterilisation of human excreta designed for use as fertiliser in some regions and regular community-based anti-helminth treatment [1].

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Taxonomy + Morphology

Nematodes belong to the kingdom Animalia, subkingdom Aschelmintha and phylum Nematoda. [5, 6] Nematodes are a very diverse species. There are estimated to be over 20,000 species, over 300 of which infect humans. There are six major nematode species that infect the human gastrointestinal tract. These species have evolved in morphology, physiology and reproductive structures, and have been found to invade more habitats than any other multicellular organism. They are divided into two major classes and several subclasses based on a defined set of characteristics. The first class is Rhabditea which is composed of mainly parasitic but also some free-living nematodes. Rhabditea gives rise to the hookworm, pinworm, *Ascaris lumbricoides* and *Strongyloides stercoralis*. The second class is Enoplea which give rise to the *Trichuris* species that come from the parasitic superfamily Dorylaimines which are found to have a buccal cavity with a toothlike spear for feeding activity.

Nematodes are eukaryote, multicellular organisms that are generally cylindrical, thin and elongated in structure [3, 6]. The majority of enteric nematodes are non-segmented and tapered at either end. For the most part, nematodes have a body plan which consists of a tube within a tube. The inner tube is a complete, basic alimentary tract. The inner tube and gonads are surrounded by another tube which is the outer, protective layer for the worm, i.e. the body wall. The body wall has a dorsal and ventral longitudinal muscle layer, an epidermis and a cuticle. The organism also consists of a developed nervous system that controls muscle function and allows chemosensation for movement. The outer cavity is fluid-filled which creates a pressure system within the worm for writhing movements. Most of the nematode worms are microscopic. An important exception is the female *Ascaris lumbricoides* which is approximately 30 cm long by 2–6 mm diameter. Within a species, the female tends to be generally larger in size than the male. To illustrate this, the adult *Trichuris* worm is slender anteriorly, shaped as a whip, and males are shorter with a coiled posterior.

The parasites body wall is made up of an outer cuticle which is non-cellular, a thin cellular hypodermis and a single layer of smooth muscle [3, 4, 6]. The outer cuticle in some nematodes has longitudinal ridges called alae, and some of the male species have a flap-like extension on the posterior end of the cuticle used to grasp the female nematode during copulation [6].

Specifically, the Rhabditida have chemically impermeable cuticles and a modified pharynx which has allowed them to develop more compact bodies likely from evolutionary pressures [6]. The Rhabditia subclass is characterised by their well-developed posterior sensory structures called phasmids which may function in modulation of chemorepulsion but have poorly developed amphids (olfactory sensation). The Enoplea class (i.e. *Trichiura*) have an amphid resembling a pocket. The Enopleans have a smoother appearance, possess a simple excretory system and lack phasmids. The *Trichiura* spp. are found primarily in the tropics, are pinkish-white in colour and have a narrow anterior oesophageal end with a thicker posterior end [3].

Life Cycle

There are six major stages to the parasitic nematode life cycle [4]. Of the six stages, there are four larval forms that occur followed by a pre-adult phase. Each larval stage is preceded by a moulting of the outer cuticle and is essential for development and growth of the organism. The first larval stage develops while in the egg, called L1 or rhabditiform larvae which are not infectious, but are able to feed. L2 is also referred to as rhabditiform, but, thereafter, the third and remaining stages are called the filariform larvae. The filariform larvae are infectious and unable to feed during this stage. Once transmitted into the human host, the worm is able to further develop, exiting the larval stage to become young adult worms. The young worm undergoes maturation to become an adult from which the female subsequently commences egg production. There are differences between stages for the different nematode species. Of note, the *Trichuris* spp. which comes from the Enoplea class, are infectious at L1 larval stage.

These nematode species are highly specific for the human host and rely on humans to complete their life cycle [5]. There are however some reports of animals becoming infected by the human enteric nematodes. For *Ascaris*, *Enterobius* and *Trichuris*, the eggs are transmitted by ingestion into the gastrointestinal tract, while for *Necator*, *Ancylostoma*, *Strongyloides* and *Trichinella*, the eggs embryonate in the soil and are ingested as larvae [1, 3]. Aside from *Enterobius* all the human nematode species require soil during their life cycle for development to become infectious. In endemic regions, *A. lumbricoides* and *T. trichiura* are often transmitted easily due to the larvae remaining infectious in dust and soil, and populations in endemic regions tend to walk around barefoot.

For *Ascaris lumbricoides*, the egg hatches in the small intestine predominantly the jejunum, and the larvae penetrate the blood vessels to be transported first to the liver and then the lungs where they move into the bronchial tree before being re-ingested [3, 6]. Eventually the parasite matures into an adult over 2 months. Migrating larvae can cause pneumonitis and eosinophilia associated with allergic reaction.

Similarly, *A. duodenale* can also be transmitted via ingestion. However, the hookworm is generally known for its penetration through the skin as a person walks on it. The hookworm often provokes a localised erythematous reaction at the skin known as ‘ground itch’ secondary to eosinophilic infiltration inducing high levels of IgE when the larvae penetrate the skin [3]. Once inside the human tissue, the invasive larvae migrate into the bloodstream to visit the lungs before ascending via the bronchial tree to be ingested and finally make their way into the gastrointestinal tract for maturation and reproduction.

Infective larvae of *Strongyloides stercoralis* are similar to hookworm in life cycle in that they move from contaminated soil by penetration of the skin and may cause localised pruritic reaction, with ‘ground itch’ at the entry point by induction of IgE and eosinophilia [3, 6]. The larvae are carried in the bloodstream to the lungs and ascend the bronchial tree before being ingested to enter the gastrointestinal tract, again causing potential pneumonitis. Once into the small intestine, the larvae attach

to the mucosal layer and mature into adult worms. The adult produces embryonated eggs which are shed and excreted into faeces; however, unlike other roundworms, some can hatch into larvae while in the intestine or perianal skin. Thus, the larvae can penetrate the perianal skin to directly re-enter the intestinal lumen within 30 days resulting in auto-reinfection which can lead to lifelong infections within the same human host.

Unlike the other roundworms which require migration through the tissues, when the eggs *Trichuris* are ingested by the human host, they hatch into larvae in the jejunum. The larvae mature into adults which migrate to the large intestine primarily to the caecum for reproduction. The adult *Trichuris* excretes eggs into the immediate environment, i.e. the faeces. These eggs can survive for several years in soil.

Similar to *Trichuris*, *Enterobius vermicularis* has a more simplistic life cycle which does not require migration through tissues. The *Enterobius vermicularis* eggs are ingested where they hatch into larvae in the small intestine, most commonly in the jejunum. Within a few weeks, the larvae have developed into mature worms which then make their way into the colon, particularly favouring the caecum. Most adult female worms migrate to the perianal area where they lay their eggs which contaminates the perianal skin, along with clothes, bed linen and fingernails.

Taken together, the life cycle of the six common human enteric nematodes is slightly different [3, 6]. The adult worm lives primarily in the human intestine and produces many eggs per day which are excreted into the local environment via the faeces [1, 3, 6]. For example, the female *Ascaris lumbricoides* can produce up to 240,000 eggs per day and survive in the intestine for approximately 1 year. The exception to this is *Strongyloides* which can also survive as an adult in the soil. Parasitic nematodes obtain their nutrition from cell and tissue secretions from the host. Reproduction of species is via sexual reproduction and interbreeding to produce fertile offspring. However, they are also known to use hermaphroditism and pseudogamy where the sperm stimulates the egg to develop into an embryo as opposed to the normal fertilization process.

Clinical Presentation

Over one billion people worldwide are thought to be infected with roundworm which contributes to approximately 20,000 deaths annually. Most deaths occur in endemic regions due to ineffective sanitation where children play in areas where soil is contaminated with human faeces [1]. Clinical presentation for *Ascaris lumbricoides* tends to correlate with worm load. A light worm load is generally asymptomatic, while heavy infestations can cause abdominal symptoms such as discomfort, diarrhoea, anorexia and malnutrition by impairing absorption of proteins, fats and carbohydrates. On occasion these worms can cause intestinal obstruction due to worm bolus or stimulation of sensory receptors of mucosa. They may also invade other organs causing extra-intestinal manifestations and may indeed emerge from other orifices such as the umbilicus, lacrimal glands, anus, mouth and nose (particularly with emesis). Worms have been known to

invade the appendix, biliary and pancreatic ducts after stimulation. They can perforate the intestine and enter different cavities including the peritoneum, respiratory tract, urethra, vagina, placenta and foetus (if present).

Clinical presentation for patients with the hookworm (*A. duodenale* and *N. americanus*) includes anorexia, abdominal discomfort, diarrhoea, fever, weight loss and anaemia due to blood loss [3]. Likewise for *Strongyloides*, abdominal symptoms include abdominal discomfort, particularly epigastric pain and mucoid diarrhoea due to inflammation and ulceration of the intestine. At both ends of the spectrum, some people remain asymptomatic of strongyloidiasis, while people with compromised immune systems are at risk of developing severe life-threatening haemorrhagic enteritis with disseminated infection leading to pulmonary haemorrhage, pneumonia, pyogenic meningitis and death. In addition, patients infected by hookworm or *S. stercoralis* may also present with localised erythematous reaction at the site of penetration through the skin. These roundworms can also cause pneumonitis, cough, dyspnoea and haemoptysis due to larval migration through the lungs.

Similarly, trichuriasis and enterobiasis are self-limiting and often carried asymptomatic if there is a light worm infestation. Otherwise patients with trichuriasis might complain of nausea, vomiting, abdominal pain, diarrhoea, anaemia and weight loss. The adult *Trichuris* worm can also cause tenesmus and rectal prolapse when in the rectum. In addition, stunted growth and finger clubbing can result from long-term infestation due to minor blood loss with anaemia and nutritional deficiencies due to intestinal mucosal inflammation. While enterobiasis manifests primarily as pruritus ani which is commonly seen in children, but on occasion, patients may complain of insomnia secondary to pruritus ani, along with abdominal pain and anorexia if worm infestation is large. Scratching can result in eczematous dermatitis and secondary bacterial infection. These worms can also cause appendicitis, and due to anatomical proximity of the anus to the vagina in females, females are also susceptible to genitourinary infection.

Diagnosis and Treatment

Infection is readily diagnosed by identifying eggs in the faeces of patients with active infestation [1, 7]. Concentration methods can be used during light infections of parasite, while heavy infestation rarely requires concentration of faeces. Examination of faecal specimen should occur within 30 minutes of passing specimen; otherwise the specimen should be preserved in 10% formalin [7]. Specimen can be concentrated using flotation such as zinc sulphate or Sheather's sugar so that the organisms ascend to the surface while the debris descends to the base. Sedimentation technique can be used, but this method is less effective than flotation as the eggs or cysts of parasites may collapse, and some parasitic eggs do not float making identification more difficult. Sedimentation uses concentration through a filter followed by the use of a lower specific gravity agent such as formalin-ethyl acetate to force the parasitic matter to descend to the base of specimen.

The only exception to the diagnostic testing above is *Enterobius vermicularis* which rarely identifies the egg in the faeces [7]. Instead Scotch tape can be used as a perianal swab. Scotch tape is placed onto the perianal region to obtain eggs. The Scotch tape can be placed onto this region in the morning prior to bathing or hygiene. The eggs can then be transferred from the Scotch tape onto a microscope slide to examine for eggs of the pinworm.

Anti-helminth treatment is a course of mebendazole which is effective against numerous human intestinal nematode infections and causes minimal side effects [1, 7]. There are other anti-helminth agents including levamisole and thiabendazole. Medical supervision should be obtained when treating mixed helminth infection involving *A. lumbricoides* as ineffective treatment can stimulate this roundworm to migrate to other locations and cause complications [8, 9]. Effective treatment for ascariasis is piperazine citrate as it causes paralysis of the worm. Treatment is recommended for all positive testing including asymptomatic carriage particularly in treating ascariasis as future migration of the worm to extra-intestinal locations can occur.

Intestinal obstructions secondary to worm bolus will often resolve with conservative management using medical therapy, i.e. 'starve the worm and hydrate the patient' with intravenous fluids, analgesia and nil by mouth [8]. Most of the morbidities and mortalities are accounted for within the paediatric population due to volvulus with gangrenous bowel and delayed presentation [10, 11]. Less common presentations are appendicitis, severe or chronic colitis, proctitis, rectal prolapse, volvulus and intussusception in children. Hepatobiliary presentations rarely include liver abscess, obstructive jaundice, acalculous cholecystitis, choledocholithiasis, cholangitis and pancreatitis secondary to *Ascaria* as the primary offender due to its migratory nature through the ampulla of Vater [8–17]. Perforation is most commonly found in the blind-ending structures including the appendix, Meckel's diverticulum or on occasion is found in the small intestine; however, there have been case reports of perforation in the large intestine [18].

Diagnosis of complications should be carried out with at least plain film radiography which can show radiolucent regions with cigar bundle appearance, whirlpool sign, pneumoperitoneum in case of perforation and multiple air-fluid levels [9]. It is also useful if volvulus is present showing coffee bean sign or Frimann-Dahl sign and absent rectal gas in sigmoid volvulus which can be treated in most cases with endoscopic decompression [9, 19]. Surgical management is recommended if there is a failure to decompress endoscopically or for recurrent volvulus. Likewise, caecal volvulus can be found on plain film with a kidney-shaped dilated caecum >9 cm usually positioned in the left upper quadrant or midline and will require surgical intervention. Ultrasound (US) when available has a 88% sensitivity for worm bolus. This is only true when US is viewed in real time, as the writhing movements of the worm can be appreciated, particularly with hepatobiliary imaging. US is also used for detection of intussusception where a target sign is serially found as gold standard in diagnosis [10, 19, 20]. Air enema is used for successful treatment of intussusception; however, failed management leads to surgery. Ultimately the best modality for complications of roundworm infestation is CT scan when available.

Surgery is rarely required for enteric nematode infection once diagnosis is confirmed and anti-helminth treatment is commenced [18, 21]. However close observation and early surgical intervention are warranted for patients with features of toxaemia and peritonitis as it may save bowel and reduce mortality. Intestinal perforation, or unresolved small bowel obstruction secondary to enteric nematode infection, is relatively rare. The type of surgery required is very dependent on the findings intraoperatively.

For a small perforation such as that found within the appendix or a Meckel's diverticulum, the standard surgery is to milk out the worm bolus and resect the appendix or Meckel's diverticulum [11, 18, 19]. For a sigmoid volvulus, a sigmoid colectomy with primary anastomosis or Hartmann's procedure is performed, while a caecal volvulus in a stable patient warrants a right hemicolectomy. In an unstable patient with caecal volvulus and bowel compromise, a right hemicolectomy with end ileostomy can be performed.

Midline laparotomy in the prepared patient is preferred to laparoscopic techniques due to possibility of contamination of the peritoneal cavity with nematodes [10, 18]. The affected area of bowel can be eviscerated out of the midline laparotomy wound for inspection of contents, protecting the surgical area with a sterile sponge or towel to avoid contamination of contents. Once the affected region of bowel is confirmed, atraumatic bowel clamps can be applied to the bowel to minimise movement of the worms and milk the worm bolus toward the caecum. If there is no perforation, a small longitudinal enterotomy can be performed over the bolus to gently milk the worms out of the intestine. Once bowel and worms are removed, the bowel can be closed in two layers transversely. In cases of compromised or gangrenous bowel, volvulus or intussusception or in cases of perforation, milk the contents towards the perforated area or towards the area of intestine to be resected, apply proximal and distal bowel clamps, and perform a limited resection of the bowel to preserve bowel length. Once bowel and worms are removed, an end-to-end handsewn or stapled anastomosis can be performed, or if small perforation, again close the perforation in two layers transversely without resection to preserve bowel length.

For hepatobiliary complications conservative management is the frontline treatment as the worm may migrate out of the biliary tract [13, 21]. Conservative management includes keeping the patient nil by mouth, intravenous fluids, analgesia, antispasmodics and empiric broad-spectrum antibiotics. Repeat ultrasound is recommended for re-evaluation after 3 days. Directed Ascaris therapy should be avoided until the worm has migrated out of the biliary tree. Endoscopic retrograde cholangiopancreatography (ERCP) can be used to grasp and extract the worms without sphincterotomy for failed conservative management. Sphincterotomy increases the risk of future migration of Ascaris into the biliary tree; however, balloon catheter can be considered. Where this fails, nasobiliary drainage can be used to decompress the biliary tree. Difficulty occurs when the worm is impacted/dead or calcified or once the worm enters the hepatic ducts or pancreatic duct. These patients carry a poor prognosis. A technique described as 'whirlpool jet technique' suggests injecting contrast material into the duct to flush it and then extracting by basket [22]. Given that invasive procedures lead to increased risk of reinfection of Ascaris into

the biliary tree, surgery has become rare, with less than 1% of cases being surgically managed.

If refractory biliary disease is present, choledotomy or choledochoduodenostomy and intraoperative ductal syringing can be performed to increase pressure in the ducts and facilitate washout of the worms [23]. If stricturing disease has occurred secondary to biliary ascariasis, a hepato-jejunostomy can be performed. If hepatic abscess occurs, a percutaneous drainage under ultrasound guidance can be performed. Alternatively, for a large hepatic abscess localised to one lobe, then a lobectomy can be performed if the patient has failed alternative management with persistent infection. Ascariasis of the gall bladder itself is very rare, but cholecystectomy is indicated in the event that this occurs [21].

Liver abscess formation can occur secondary to high worm load where the parenchyma of the liver is invaded followed by inflammation, necrosis and subsequent abscess formation [21, 24]. This complication again has been described in <1% of patients; however, ascariasis is a frequent cause of liver abscess in endemic regions. Early identification of ascariasis is important for liver abscess as it frequently requires surgical intervention and mortality rate is high.

Prevention

Prevention is by improved sanitation, hand hygiene, education, health promotion and treatment [1, 2, 4]. Control measures in low socio-economic areas where these infections are prevalent, has been focused on public health measures aimed at reducing infection rates by deworming all school children. A pilot trial performed in the Philippines aimed at eradication of soil helminths by periodic mass treatment [27]. Over a 3-year period, the prevalence of Ascaris dropped from 78% of the population to less than 1% of the population. Special attention also needs to be paid to families with diagnosed index cases for screening (as parasitic infections is often spread through households) and to high-risk environments including daycare centres, schools and other similar institutions [1, 4]. Schools, daycare centres and other institutions should be alerted to infection to relay treatment to other members of these centres and their families. Finally, there is no vaccine available for the soil helminth diseases in humans; however, research is continuing into vaccine production. The major dilemma for vaccine development has been the incomplete understanding of human immunity to parasitic nematodes; however, there has been progress with successful vaccination of livestock against a parasitic nematode infection using recombinant proteins.

References

1. Human info NGO. Essential Medicines and Health Products Information Portal A World Health Organization resource. WHO model prescribing information: drugs used in parasitic diseases. 2nd ed. Updated 2019. https://apps.who.int/medicinedocs/en/d/Jh2922e/3.2.html. Accessed 4 June 2019.

2. Ananthakrishnan S, Nalini P, Pani S. Intestinal geohelminthiasis in the developing world. Natl Med J India. 1997;10(2):67–71. http://archive.nmji.in/approval/archive/Volume-10/issue-2/review-article.pdf. Accessed 3 June 2019.
3. Cross J. Medical microbiology. 4th ed. Galveston: University of Texas Medical Branch at Galveston; 1996. https://www.ncbi.nlm.nih.gov/books/NBK8261/. Accessed 4 June 2019.
4. Stepek G, Buttle D, Duce I, Behnke J. Human gastrointestinal nematode infections: are new control methods required? Int J Exp Pathol. 2006;87(5):325–41. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2517378/. Accessed 6 June 2019.
5. Riddle D, Blumenthal T, Meyer B, Priess J. C. Elegans. 2nd ed. New York: Cold Spring Harbour Press; 1997.
6. Inglis W. Nematoda. Aust J Zool. 1983;31(2)243–55. http://www.publish.csiro.au/ZO/ZO9830243. Accessed 3 June 2019.
7. Centre for disease control. Parasites [Internet]. Atlanta; 2018. [cited 2019 June 6th]. Available from: https://www.cdc.gov/parasites/.
8. Sanai F, Al-Karawi M. Biliary ascariasis: report of a complicated case and literature review. Saudi J Gastroenterol. 2007;13(1):25–32. http://www.saudijgastro.com/article.asp?issn=1319-3767;year=2007;volume=13;issue=1;spage=25;epage=32;aulast=Sanai. Accessed 3 June 2019.
9. Poppy H, Lamberton P. Human ascariasis: diagnostics update. Curr Trop Med Rep. 2015;2(4):189–200. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630244/. Accessed 4 June 2019.
10. Ramareddy R, Alladi A, Siddapa O, Deepti V, Akthar T, Mamata B. Surgical complications of *Ascaris lumbricoides* in children. J Indian Assoc Pediatr Surg. 2012; 17(3):116–9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3409899/. Accessed 5 June 2019.
11. Mishra PK, Agrawal A, Joshi M, Sanghvi B, Shah H, Parelkar SV. Intestinal obstruction in children due to Ascariasis: a tertiary health centre experience. Afr J Paediatr Surg. 2008;5(2):65–70. https://www.ncbi.nlm.nih.gov/pubmed/19858669/. Accessed 5 June 2019.
12. Stephenson L, Latham M, Kinoti S, Kurz K, Brigham H. Improvements in physical fitness of Kenyan schoolboys infected with hookworm, Trichuris trichiura and Ascaris lumbricoides following a single dose of albendazole. Trans R Soc Trop Med Hyg. 1990;84(2): 277–82. https://www.ncbi.nlm.nih.gov/books/NBK19684/. Accessed 3 June 2019.
13. Khuroo M, Zargar S, Yattoo G, Koul B, Khan B, Dar M, et al. Ascaris-induced acute pancreatitis. Am J Surg. 1992;79:1335–8.
14. Justiniano M, Duran A, Uechi C. Biliopancreatic ascariasis: endoscopic approach. J Gastroenterol. 2002;37:97–9.
15. Khuroo M. Ascariasis. Gastroenterol Clin North Am. 1996;25:553–77.
16. Pawlowski Z. Ascariasis. Trop Geogr Med. 2nd ed. McGraw Hill; 1995. p. 369–78. Accessed 4 June 2019.
17. Katz D, Taylor D. Parasitic infections of the gastrointestinal tract. Gastroenterol Clin North Am. 2001;30(3):797–815. https://www.sciencedirect.com/science/article/pii/S0889855305702119?via%3Dihub. Accessed 4 June 2019.
18. Sanai F, Al-Karawi M. Biliary ascariasis: Report of a complicated case and literature review. Saudi J Gastroenterol. 2007;13(1)25–32. http://www.saudijgastro.com/article.asp?issn=1319-3767;year=2007;volume=13;issue=1;spage=25;epage=32;aulast=Sania#ref32. Accessed 5 June 2019.
19. Glick Y, Gaillard F. Radiopedia [Internet]. USA. Trend, 2018. [cited 2019, June 6th]. Available from: http://www.radiopedia.org.
20. Das A. Hepatic and biliary ascariasis. J Glob Infect Dis. 2014;6(2):65–72. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049042/. Accessed 3 June 2019.
21. Khuroo M, Zargar S. Biliary ascariasis: a common cause of biliary and pancreatic disease in an endemic area. Gastroenterol. 1985;88:418–23.
22. Mukhopadhyay M. Biliary ascariasis in the Indian subcontinent: a study of 42 cases. Saudi J Gastroenterol. 2009;15(2):121–4. https://www.ncbi.nlm.nih.gov/pubmed/19568577/. Accessed 5 June 2019.

23. Al-Karawi M, Sanai F, Yasawy M, Mohammed A. Biliary strictures and cholangitis secondary to ascariasis: endoscopic management. Gastrointest Endosc. 1999;50:695–7.
24. Ali M, Khan A. Sonography of hepatobiliary ascariasis. J Clin Ultrasound. 1996;24:235–41.
25. Chen Y, Den B, Huang B, Xu L. Endoscopic diagnosis and management of Ascaris-induced acute pancreatitis. Endoscopy. 1986;18(4):127–8.
26. Nisbet A, McNeilly T, Wildblood L, Morrison A, Bartley D, Bartley Y, et al. Successful immunization against a parasitic nematode by vaccination with recombinant proteins. Vaccine. 2013;31(37):4017–23. https://doi.org/10.1016/j.vaccine.2013.05.026.
27. Bundy D, Cooper E, Thompson D, Anderson R, Didier J. Age-related prevalence and intensity of Trichuris trichiura infection in a St. Lucian community. Trans R Soc Trop Med Hyg. 1987;81(1):85–94. https://www.ncbi.nlm.nih.gov/pubmed/3445330. Accessed 4 June 2019.

The Role of Surgery in Treating Parasitic Diseases of the Digestive System from Trematodes

6

Ashley Jenkin, Andrew Phillip Maurice, Amanda Hamilton, Robert Edward Norton, and Yik-Hong Ho

Introduction

Over 40 million people are infected with food-borne trematodes, and 750 million, more than 10% of the world's population, are at risk. It is an endemic condition without pathonogmonic features and, as such, has often been overlooked. Intestinal trematodiasis is considered a neglected tropical disease along with liver flukes and the like. Although only rarely associated with significant morbidity, surgical intervention can play a role in management in certain patients.

Taxonomy and Morphology

Trematodes are multicellular helminths with a complex life cycle and multiple virulence factors that promote its endemic nature. Each trematode species varies in morphology but tends to be symmetrical. Most have oral suckers, often positioned ventrally, that allow them to adhere to the wall of the host organism's intestine. Many species also have sensory papillae [1]. The body surface, or tegument, of these parasitic flatworms is covered by a syncytial epithelium. Trematodes' tegument has important roles in nutrient absorption, osmoregulation, sensory function, and secretion [1]. Trematodes lack respiratory and circulatory systems, and thus these functions are predominantly performed through the worm's epithelium [1]. The tegument also plays an important role in immune response protection, which acts to limit fulminant host immune reaction. The molecules and proteins that trematodes produce to modulate the immune system to produce a more tempered,

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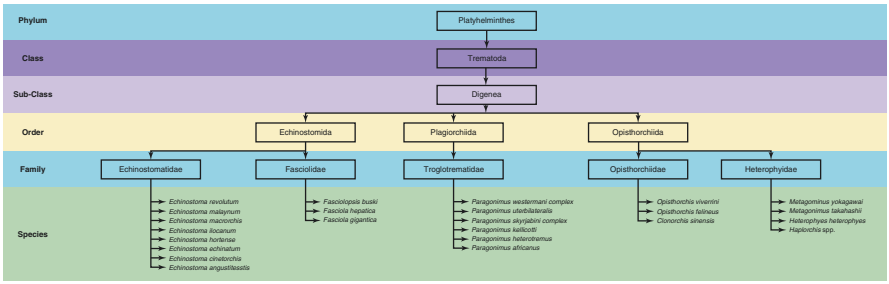

Fig. 6.1 Relevant taxonomy [1]

chronic approach are not clear [2]. It has however been demonstrated that most helminths stimulate T-helper and T-regulatory cell-mediated reactions and thus result in chronic granuloma formation and fibrosis [2].

The various intestinal trematode species vary in their length and general size. For example, *Echinostoma* species are usually 3–10 mm length in adulthood [3]. In contrast, *Heterophyes heterophyes* and *Metagonimus yokogawai* are considered minute flukes, averaging <0.5 mm length in adulthood. This is particularly different in comparison to the leaf-like liver flukes, which tend to grow much larger. *Opisthorchis viverrini* tend to be the smallest of the liver flukes ranging 5–10 mm long, in contrast to *Clonorchis sinensis* that average 10–25 mm [1, 4, 5]. The liver flukes' eggs however often have a similar appearance to the minute flukes, creating a diagnostic dilemma from faecal studies [6].

Trematodes are of subclass Digenea, derived from the phylum Platyhelminthes as seen in Fig. 6.1. Approximately 70 trematode species have been isolated from humans [1]. These organisms can be divided according to their final human habitat – liver, lung, blood, and intestinal. Liver flukes, for example, *Fasciola*, *Clonorchis*, and *Opisthorchis*, reside in bile ducts in their adult form. Although liver flukes are considered increasingly important in the literature in relation to their carcinogenic potential, the first reported large outbreak of acute *C. sinensis* was in Shanghai in the 1940s [4]. Of the known intestinal trematode species, there are four that are documented in the literature to have this most significant impact on human lives: *Fasciolopsis*, *Heterophyes*, *Metagonimus*, and *Echinostoma*. In the past, *Stellantchasmus falcatus*, *Haplorchis* spp., and *Procerovum spp*. have reportedly caused significant disease burden in humans [7].

Life Cycle

Trematodes are both hermaphroditic and digenic. This means they contain both male and female reproductive organs, and perform both self- and cross-fertilization in a definitive vertebrate host, but also reproduce asexually in a snail intermediate [8]. Although the life cycles differ in terms of the location the larvae can be found, the overall principle is similar between species as shown in Figs. 6.2 and 6.3.

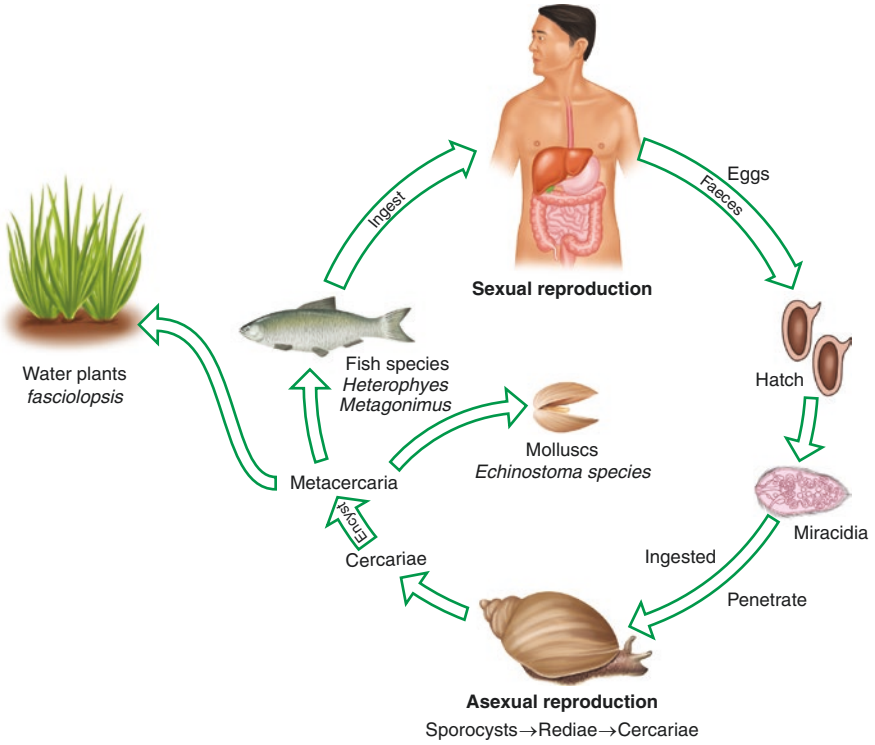

Fig. 6.2 Intestinal trematode life cycle

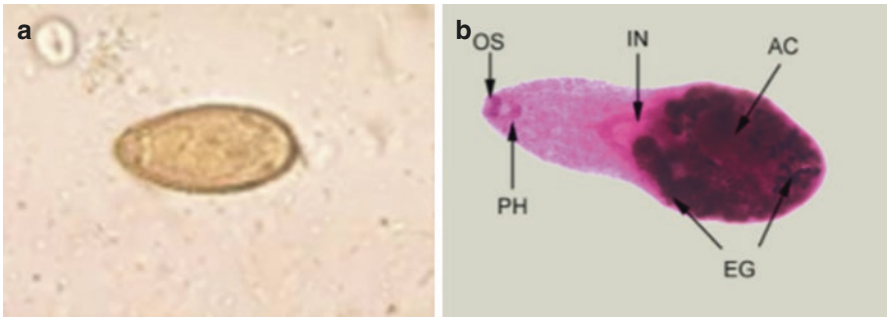

Fig. 6.3 Stages of trematode growth. (**a**) H. heterophyes egg. (**b**) H. heterophyes adult stained with carmine. The following structures are labelled: oral sucker (OS), pharynx (PH), intestine (IN), ventral sucker, or acetabulum (AC), and eggs within the uterus (UT) (cdc.gov/dpdx/heterophyasis/index)

Within a definitive vertebrate host, whether human, fowl, or beast, the adult trematode lays eggs that contaminate bodies of water via faeces. Ciliated miracidia hatch from the eggs to swim freely and penetrate or are eaten by snails that they then infect. Within the snail host, trematodes undergo several stages of asexual reproduction through sporocysts and then rediae. Once they develop into cercariae, they are released from the snail and encyst as metacercaria. It is at this stage that the life cycles somewhat diverge. For example, *Fasciola* sp. metacercariae encyst on certain water-based plants (water chestnuts, mint, parsley, watercress, etc.) where they are then consumed by humans, pigs, and so forth up to a year later. The metacariae excyst in the duodenum and attach to the intestinal wall where they can then mature into adult worms. The minute flukes however, *Heterophyes* and *Metagonimus,* encyst within the tissue of fish species that are then consumed. Interestingly, the *Opisthorchis* sp. are dependent upon water temperature and the species of fish they invade to determine the latency period between infecting the fish and being able to infect human/mammalian hosts [9]. *Echinostoma* species' metacariae tend to reinfect snails or clams and so forth and are transmitted to humans on ingestion of these molluscs raw [8].

The liver flukes differ in the life cycle once entering the duodenum of their definitive host as they reach their final tissue destination. *Fasciola* sp. penetrate the gut wall, migrating through the peritoneal cavity for up to 7 weeks to enter via the Glisson capsule to infect the hepatic tissue where they mature and begin to produce eggs [4, 8, 10]. *Opisthorchis* and *Clonorchis* sp. however access the liver via the ampulla of Vater in the second part of the duodenum [4, 8].

The adult worms need to fully mature prior to producing eggs, which is species specific. For example, *F. buski* develops over 3 months to produce approximately 25,000 eggs per day. Each adult intestinal trematode can live up to 1 year in its mammalian host. However, some liver flukes have been shown to survive for up to 30 years in a human host [4].

Intestinal Trematodes

Clinical Manifestation

Given its endemic nature, intestinal trematodiasis is an occult disease associated with limited clinical features. Morbidity and mortality have been associated, particularly with high worm burden in a smaller subset of the infected population (~5–10%). The prevalence and intensity of infection both tend to peak between ages 10 and 30 years [8]. Pathology may be caused by both the worms and their eggs, which cause inflammation, fibrosis, and granuloma formation by local damage and obstruction [8]. The mature embryo, or miracidium, tends to secrete antigenic molecules and enzymes that induce granuloma formation and antibody production [8]. Some of the immune response stimulated by these molecules is considered protective and actually mediates resistance to reinfection [8]. As aforementioned, the immune response generated by intestinal trematodes is T-helper cell-mediated and

does not produce a fulminant acute response from the host [2]. This moderated response results in the subclinical nature of most intestinal trematode infections.

The symptoms of intestinal fluke infection are only associated with severe disease but are similar across more common trematode species. Clinical manifestations of disease are more common in children and tend to develop between 9 and 60 days following exposure depending on the trematode species [3]. As many species tend to reside within the crypts of the small intestinal villi, symptomatic patients will report diarrhoea, generalized abdominal pain, anorexia, vomiting, and weight loss [6, 8]. Dyspepsia is a common symptom particularly with *Heterophyes* and *Metagonia* species [3]. Occasionally, these minute species are haematogenously spread to other sites, and patients can exhibit symptoms from granulomatous lesions in the liver, spleen, heart, lungs, or central nervous system [3]. Symptoms from *Echinostoma* species are more severe and associated with more significant mucosal damage [3].

Fasciolopsia species are considered more pathogenic than other species of trematodes, likely due to their larger size. The adult worms grow from 2 to 7.5 cm in length [3]. Although most infections are also associated with little or no symptoms, there are reported cases of severe disease. Attachment of *F. buski* to the duodenal or jejunal wall and its effect on the secretion of intestinal fluids and mucous can result in microabscesses, as well as ulceration and gastrointestinal bleeding [8]. This can result in clinically apparent anaemia. High worm burden (>500) with *Fasciolopsia* species has been associated with malabsorption, which can result in oedema, ascites, and vitamin B12 deficiency [3]. Large worm volumes rarely can be associated with obstruction and perforation [11]. Obstruction from trematodes can also occur secondary to successful treatment with large volumes of dead worms acting as a bolus [3].

Diagnosis

The mainstay of diagnosing infection with intestinal flukes is by visualization of eggs or adult worms in bodily fluids. Most commonly they are demonstrated in faeces but can also be found in bile, gastric washings, duodenal samples, or vomitus. The Kato-Katz thick smear method is a widely adopted diagnostic technique for detecting trematode infections as demonstrated in Fig. 6.4. It is used as a qualitative and semi-quantitative method that allows determination of worm concentration as well as species. This is important, as the likelihood of developing disease associated with intestinal trematodes is directly correlated to the intensity of infection or worm burden [8]. In this technique, faecal samples are run through a sieve to remove large particles. A portion of the sample is then placed within a template on a slide, which is then examined under the microscope for eggs. In this way, both the type of egg, as well as the volume of egg burden, can be assessed.

Formalin ether concentration or sedimentation technique (FECT) is another method of microscopic techniques for the diagnosis of intestinal worms (see Fig. 6.4). This method takes advantage of the higher specific gravity of trematode

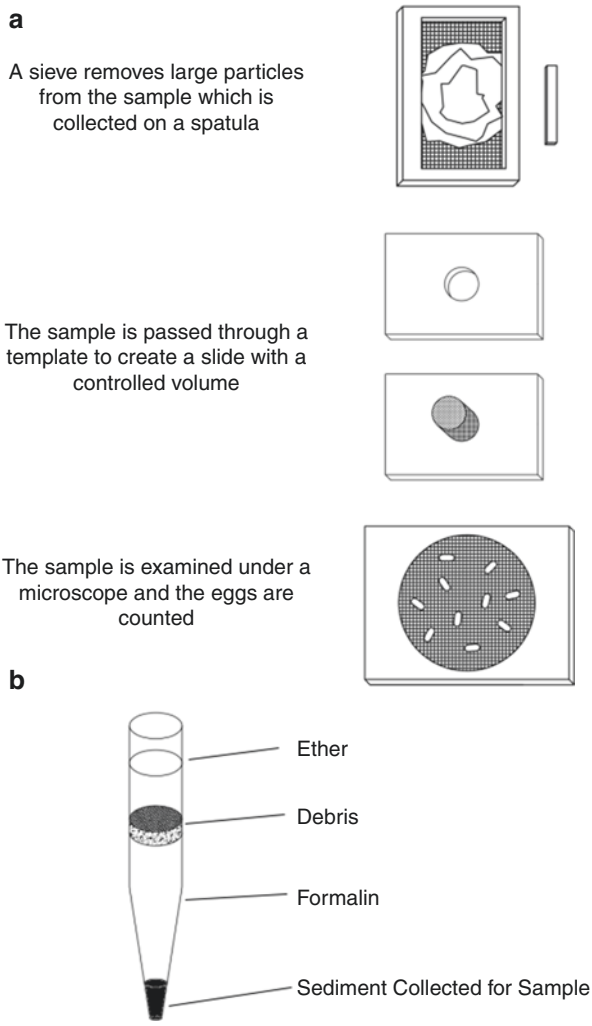

Fig. 6.4 (**a**) A demonstration of the Kato-Katz smear technique. (**b**) Formalin ether sedimentation technique

eggs as compared to water, allowing them to separate out of the specimen. It is particularly useful when the number of parasites is too low for direct smear and thus improves sensitivity. The formalin used fixes the morphology of the specimen to improve identification. The sample can then be directly visualized and counted.

Parasitological techniques relying solely on egg excretion have limitations. The presence of eggs in faecal material will not occur immediately following infection as the worms must mature to their adult form. Furthermore, different species of trematodes can have similar appearing eggs creating a diagnostic dilemma. *Heterophyidae* and *Clonorchis sinensis* (a liver fluke) both have rough, thick egg shells thus reducing the diagnostic specificity of the test [6]. Low worm burdens may also obscure results as these techniques rely on direct visualization.

The detection limit of FECT, for example, has been shown to be 20 worms or approximately 1000 eggs per gram (epg). This may result in underestimating the disease prevalence by up to 20% [12]. The ease of sample collection of the techniques means these non-invasive tests have remained the gold standard. Although antigen-, antibody-, and DNA-based techniques have been developed for liver and blood flukes [6], the same is not true for intestinal trematodes. No immunodiagnostic technique has been developed that is accurate enough to reliably diagnose them [13].

Treatment

The primary treatment of intestinal trematode infection is medical, though surgery has been reported as management of several infection complications. The mainstay of medical management is a 1-day course of oral praziquantel. The World Health Organization (WHO) recommends a dose of 25 mg/kg. Praziquantel effects cell membrane permeability and induces vacuolisation and disintegration of the fluke's integument [14]. This induces rapid contraction of the fluke and tends to affect adult worms more than immature worms. Praziquantel is rapidly absorbed orally but is subject to first pass metabolism that is thought to occur via the CYP450 enzyme system [14]. The drug and its metabolites are excreted by the kidney [14]. Praziquantel's effect is therefore influenced by renal failure and certain medications that compete for metabolism. Maximal serum concentration occurs within 3 hours of dosing. There have been no known studies testing the efficacy and safety of praziquantel in pregnancy, but it has been shown to be excreted in breast milk [14]. The side effect profile of this medication is rather benign, causing predominantly vague symptoms such as malaise, fatigue, and gastrointestinal upset. Few serious hypersensitivity reactions have been noted [14].

Surgical intervention is rarely required in intestinal trematode infection compared to the high number of infections these parasites cause. As a result, there are no published guidelines to direct the surgical management. There have however been reported cases of stricture and perforation in the setting of *F. buski*, though this is not the norm [11]. Small bowel resection may be indicated as sequelae of a high worm burden causing obstruction or ulceration with bleeding and/or necrosis [3]. Due to the granulomatous reactions induced by the fluke's enzymes, strictures can also occur in isolation. Depending on the location of the diseased segment of bowel, this may confound the diagnosis of other pathology such as inflammatory bowel disease.

The principles of surgical management have been described mostly in case series and case reports as opposed to rigorous trials. If surgery is required, preservation of bowel length is recommended. Open techniques are also preferred to laparoscopic in order to prevent contamination of the peritoneal cavity with either eggs or adult worms. In the instance of obstruction, in an appropriately prepared supine patient, the bowel can be accessed via a small midline laparotomy incision. The affected small bowel can be delivered outside of the wound for inspection, protecting the

wound edges with a sterile towel. When the affected segment is identified, it is sometimes possible to massage the bolus onward toward the caecum. This relies upon healthy small bowel and a more distally effected segment. In cases where this is not possible, or if the bowel appears friable and inflamed, non-crushing bowel clamps can be applied distally. Attempt to knead the bolus more proximally away from the diseased segment. A longitudinal enterotomy as in Fig. 6.5 can be made overlying the bolus to gently extract the content. Once the contaminants are removed, close the bowel in one or two layers transversely. If the bowel appears

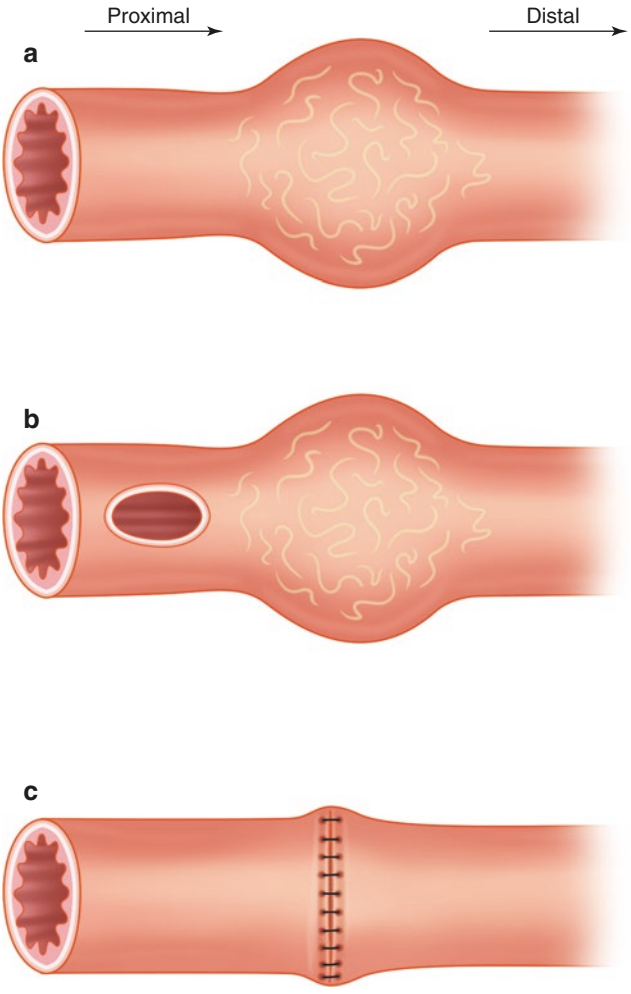

Fig. 6.5 Open surgical management of helminth-associated obstruction. (**a**) An obstructing bezoar of worms. (**b**) A longitudinal incision is made proximal to the obstruction. (**c**) The incision is closed transversely to help prevent stricture

compromised or its viability is threatened, a limited small bowel resection can be performed. An end-to-end hand-sewn anastomosis and stapled anastomosis are acceptable options.

When intestinal trematodiasis is associated with strictures secondary to microabscesses and fibrosis, treatment is similar to that seen in Crohn's disease. If the strictured segment appears grossly inflamed over a short area of involvement, primary resection is preferred. Otherwise, stricturoplasty may be appropriate. The tightness of the stricture can be evaluated via a small enterotomy as described above. Balloon catheter dilatation is appropriate in strictures with a diameter greater than 20 mm. Strictures tighter than this, less than 20 mm, require a longitudinal full-thickness incision to be carried over the entire effected segment. This incision should be continued for approximately 1 cm beyond into normal tissue. The bowel is then closed transversely in one or two layers. In longer strictured segments, primary resection and anastomosis are preferred.

Liver Trematodes

Liver flukes are endemic in many regions, particularly Southeast Asia. These flukes reside within the biliary system, sometimes for decades, and are well recognized for their propensity to cause chronic infection and cholangiocarcinoma. Infestations from intestinal flukes tend to cause similar clinical presentations regardless of the underlying organs; however the clinical manifestations and relevance of liver flukes differ between the few most important families. The particular symptoms, diagnostic features, and clinically relevant complications will be discussed separately.

Clinical Manifestations

Fasciolopsis

Infection with fascioliasis is often characterized by three distinct phases that correspond to different periods in the worm's life cycle. The invasive or acute phase occurs at approximately 6–12 weeks when the juvenile parasite penetrates and then migrates randomly through the liver parenchyma [4, 5, 8]. This results in acute inflammation from mechanical irritation and toxic secretions [8]. The outcome is hepatic cell loss, tissue necrosis, abscess formation, fibrosis, and haemorrhage [5]. This acute phase can last several months and results in clinically apparent disease. This is characterized by marked eosinophilia, right upper quadrant pain, intermittent fever, malaise, weight loss, urticaria, anaemia, and sometimes hepatomegaly [4, 5, 8]. Mild derangement of hepatic enzymes will only occasionally be seen [4]. Some patients will also develop secondary respiratory symptoms from the development of right-sided pleural effusions. When aspirated, these effusions tend to show increased eosinophils [15].

In the latent phase, the flukes have entered the larger bile ducts, they mature, and they begin to produce eggs. At this stage, symptoms tend to decline and often completely resolve [8]. An unknown proportion of patients progress to the chronic phase of infection. Patients with chronic fascioliasis are susceptible to biliary obstruction either through strictures and fibrosis or worm burden [4]. This can result in intermittent epigastric or right upper quadrant pain that mimics biliary colic or cholecystitis [4]. More rarely patients will present with ascending cholangitis with fevers, jaundice, and abdominal pain [4].

Clonorchis and Opisthorchis

Unlike fascioliasis, acute infection with *Clonorchis* or *Opisthorchis* sp. does not produce an initial syndrome. This is attributed to these trematodes atraumatically entering the biliary system through the ampulla [5, 8]. Patients do not tend to suffer significant signs or symptoms despite mild inflammation to the smaller bile ducts and portal connective tissue [16]. As the hepatic trematodiasis progresses, patients can develop diarrhoea, an irregular appetite, and oedema [5]. This corresponds to the necrosis of bile duct epithelial cells and hepatocytes and associated regeneration [16]. This results in hyperplasia of the bile ducts and adenoma formation [16]. The inflammation can occur with or without inducing granulomatous reactions leading to periductal and portal scarring with resolution [16]. Some patients will subsequently suffer severe chronic infection characterized by multilobular cirrhosis, portal hypertension, cholangitis, and potentially cholangiocarcinoma [4, 5, 8, 16, 17]. The likelihood of progressing to the symptoms and complications described is proportional to the burden of infestation.

Symptomatic patients manifesting chronic disease may report intermittent right upper quadrant pain, fatigue, dyspepsia, and occasionally hepatomegaly [4]. Biliary complications are not uncommon in liver fluke infestation. The helminth's presence within the bile duct results in proliferation of biliary epithelium as well as periportal fibrosis [16]. This can lead to biliary stasis and the production of soft, muddy, intrahepatic pigment stones as well as the associated symptoms of obstruction [5, 18]. The direct mechanical obstruction of bile ducts full of trematodes also contributes to this pathology, which involves the pancreas in 30% of cases [5, 16]. Secondary bacterial cholangitis and pyogenic liver cholangitis can develop also as opportunistic pathogens take advantage of the poor biliary drainage and tend to recur. These episodes are characterized by repeated phases of chills, fever, jaundice, right upper quadrant pain, Gram-negative sepsis, and leucocytosis [18].

Opisthorchis, *Clonorchis*, and Cholangiocarcinoma

Probably the most clinically significant outcome from hepatic trematodiasis is the development of cholangiocarcinoma. The WHO's International Agency for Research on Cancer (IARC) has listed *Opisthorchis viverrini* as a class 1 carcinogen since 1994, and *Clonorchis sinensis* is considered a probable carcinogen [17]. The evidence is inconclusive regarding the role *O. felineus* may play in the development of this cancer [4, 5, 16]. The first large case series reporting the link between *O. viverrini* and cholangiocarcinoma was from Bangkok in the 1960s [19]. Liver

examination of autopsy specimens identified a striking increase in cholangiocarcinoma incidence with the presence of the fluke [19]. In non-endemic regions, cholangiocarcinoma makes up approximately 15% of all hepatobiliary tumours [4, 9, 20]. However in endemic regions, the ratio of cholangiocarcinoma to hepatocellular tumours is 4:1, with an incidence 6–10 times higher than non-endemic regions [9]. The risk of cholangiocarcinoma is particularly increased in patients with high worm burdens [4].

The mechanism of carcinogenesis of liver flukes is a topic of great interest in current research as a potentially preventable risk factor in a malignancy known to have high mortality. Recurrent obstruction and inflammation with liver fluke infestation leads to several pathological changes within the liver and biliary system. These include biliary dilatation, desquamation of the bile duct epithelium, proliferative hyperplasia, fibrosis, and metaplasia [21–23]. These changes have been attributed to mechanical injury from the fluke's ventral suckers, as well as the metabolites they secrete to survive a hostile environment [4, 16, 22–24]. *O. viverrini* in particular has been shown to synthesize genotoxic agents that result in DNA damage that predisposes to development of malignancy over time [9]. Chronic inflammation is also associated with the generation of free radicals and nitrogen species that damage DNA, initiate mutations and genetic instabilities, and promote malignant transformation [16, 23, 25]. Interestingly, the mutations in RAS oncogenes frequently evident in intra-hepatic cholangiocarcinoma in non-endemic areas are less common in cases with liver flukes, suggesting an atypical pathway of genetic damage [26].

While liver flukes can be carcinogenic, they do not cause cholangiocarcinoma independently but rather act as a significant cofactor for the development of this malignancy. The incidence of cholangiocarcinoma is still low despite the high prevalence of this endemic disease [16]. Furthermore, there is no evidence to suggest that eradicating hepatic trematodiasis eliminates the malignancy risk of an individual patient, particularly if the flukes have already caused significant changes to the biliary system [27]. It will however significantly improve clinical symptoms as well as changes seen on imaging [28, 29].

The majority of fluke-induced cholangiocarcinomas are adenocarcinomas [16, 28]. *O. viverrini* can often be found within or adjacent to the tumour, surrounded by associated adenomatous proliferation of bile ductal epithelium [16]. The tumour location is predominantly central (60%) or peripheral (20%) type and found in the right lobe of the liver [16, 28]. Of the extrahepatic lesions, the majority affect the proximal ductal region [28].

Diagnosis

The mainstay for diagnosing liver fluke infection is still faecal microscopy given their simplicity, economics, and accessibility. However other methods are becoming more prevalent in the developed world to differentiate between the species and target therapy. While *Opisthorchis* and *Clonorchis* egg counts are relatively stable, *F. hepatica* eggs are not seen in the acute phase because the worms are still

immature [4]. Thus, for fascioliasis diagnosis must be based initially on the typical clinical syndrome or immunodiagnostic techniques [4]. Furthermore, low egg counts can also paradoxically be seen in very heavy infections with either families due to obstruction of the biliary tree or because ascending cholangitis has killed the adult worms [4].

Immunodiagnostic techniques have been variably successful and include immunofluorescence assays, enzyme-linked immunosorbent assay (ELISA), indirect haemagglutination, complement fixture, and countercurrent electrophoresis [4]. The advantage of these techniques is that they are applicable in any stage of disease and can even be used to monitor improvement post-treatment [4, 10]. However, the sensitivity of these techniques is dependent on the specificity of the worm extract used and is often unable to distinguish between active and past infection [4, 6].

Fasciola

The effect of *F. hepatica* on liver function tests (LFTs) varies throughout the course of infection [10]. During the acute phase, transaminases are often normal but tend to significantly increase 4 weeks post infection [10]. Later on, after 3 months, values tend to normalize before gamma-glutamyl transpeptidase (GGT) activity increases [10]. Thus, LFTs are not particularly reliable for diagnosis.

Since bloods tests are unreliable and faecal microscopy can be negative acutely, the initial syndrome is easily mistaken for more common pathology. Therefore, imaging has begun to play an increasing role in the diagnosis of fascioliasis, and features change based on the phase of disease. In the parenchymal phase when immature worms migrate through the liver, CT and MR are the most useful as seen in Fig. 6.6 [10]. Initially, ultrasound (US) findings are nonspecific and may demonstrate small volume ascites [15] or focal hypoechoic lesions with a surrounding halo [10]. In mild infections however, diffuse increase in echogeneity of the liver may be the only finding [10].

During the parenchymal (acute) phase, CT will demonstrate multiple small, hypodense lesions with peripheral enhancement measuring 2–10 mm [10, 30]. The position, attenuation, and shape of the hepatic lesions tend to change, starting with more peripheral lesions and progressing to tortuous clusters by 6 weeks [10, 31]. These lesions tend to be filled with necrotic material and occasionally will be surrounded by necrotic tracks and fibrosis [4]. These microabscesses can be confirmed on liver biopsy [4]. The liver capsule will also have notable focal thickening and enhancement initially where the trematodes have penetrated [10].

MR imaging in the parenchymal phase can often clearly demonstrate the characteristic evolution and life cycle of *F. hepatica*, without the use of contrast or radiation. It is also able to provide additional information about lesion complications such as haemorrhage and abscess formation [10]. Haemorrhage can be life-threateningly severe and when seen with eosinophilia, should raise the suspicion of hepatic trematodiasis [10]. On T2-weighted images, the aforementioned Glisson's thickening is seen as hyperintense areas, with clustered hyperintense parenchymal lesions that demonstrate peripheral enhancement with contrast [10]. Early

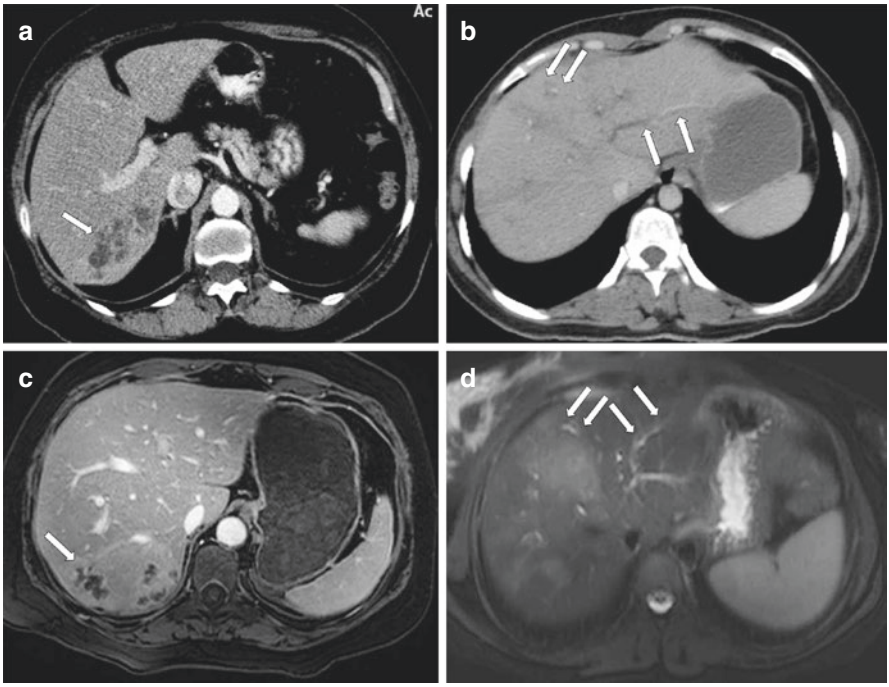

Fig. 6.6 Examples of key imaging findings in *F. hepatica* infection. (**a**). Contrast CT demonstrating clustered hypodense lesions with peripheral enhancement. (**b**) CT showing low attenuation tracks throughout the parenchyma representing trematode migration (**c**) T1-weighted MR of the same patient's (A) lesions (**d**) T2-weighted MR showing hyperintense tracks along portal veins [10]

migration routes can be demonstrated as hypointense on T1-weighted, or hyperintense on T2, subcapsular lines [10].

At the end of the parenchymal phase as the worms enter the ductal systems around week 8, the hepatic lesions tend to regress [10]. During the ductal phase, ductal ectasia can be seen. The biliary dilatation appears initially as thin, hypoechoic lines parallel to portal areas and progresses to tortuous distention toward week 12 [10]. This is poorly seen on MR initially; however capsular and subcapsular scarring and intermittent signal-filling defects representing worms can often be seen within the ducts [10]. US can also occasionally demonstrate intraluminal masses representing mobile flukes within the gallbladder or biliary tree [4, 10]. Eventually in chronic infestation areas of calcification can be identified, particularly on CT [10].

As discussed, the chronic stage of fascioliasis features recurrent episodes of biliary colic and cholecystitis. The biliary inflammation is seen as ductal dilatation with irregular areas of wall thickness [10]. Unlike pyogenic abscesses, the hepatic microabscesses demonstrated in fascioliasis do not tend to coalesce but similarly show a thick, minimally enhancing rim surrounded by oedema [10].

With cholangitis the lesions and biliary involvement tend to be distributed more centrally [10].

Missed or late diagnosis of *F. hepatica* frequently occurs, leading to unnecessary operations [10]. In this chronic phase, eggs can be found in the stool but can also be seen intraoperatively when eggs or adult worms are found to cause obstruction [4]. Endoscopic retrograde cholangiopancreatography (ERCP) can thus be useful for defining bile duct changes but also to directly visualize the trematodes including their location [5]. When laparoscopy is performed, raised grey-white or yellow nodules with short vermiform cords can often be seen on the liver surface [32, 33].

Opisthorchis and Clonorchis

Since egg counts are reasonably reliable for non-*Fasciola* liver fluke infestations, the imaging findings are less crucial to diagnosis. In opisthorchiasis, US shows clusters of dilatations of intrahepatic bile ducts that are pathognomonic [4]. There is also often gallbladder enlargement with sludge and stones, but clearly obstructing worms are less likely [4]. Numerous hypoechoic lesions with adjacent linear intraductal echoes may be seen [4]. ERCP in opisthorchiasis and clonorchiasis tend to show diffuse tapering and dilatation of intra- and extrahepatic ducts in combination, creating a mulberry-like appearance that is characteristic [34]. This may be associated with solitary cysts similar to a liver abscess cavity [34].

Treatment

Fasciola

Unlike other trematodes, *Fasciola* sp. is more often resistant to praziquantel [4]. Medical management of this hepatic fluke is predominantly with triclabendazole as a single 10 mg/kg dose or as two doses 12 hours apart [4]. Repeat treatment may be necessary to complete eradication, and increasing resistance to the drug has been noted [4]. In patients suffering a severe acute parenchymal stage, a short course of systemic steroids may be warranted [4].

The biliary epithelial hyperplasia that occurs in *F. hepatica* infection results in thickening and dilatation of the ducts as well as the gallbladder. In the context of cholecystitis, a laparoscopic cholecystectomy is recommended, preceded by antihelminthic medical therapy. Often treatment can reverse the trematode-associated gallbladder abnormalities, but in the context of significant wall thickening (>4 mm), surgery has been advocated [5]. Dilatation and chronic inflammation may increase the risk of bile leak from the cystic stump and preclude the use of 5 mm metal clips. As a result, the application of polydioxanone (PDS) endoloops is preferable over standard clip application. Other options for securing the cystic duct include a stapling device, suture ligation, or the use of locking clips. Effort should be made to avoid gallbladder perforation to avoid helminth spillage, and needle decompression is not recommended.

Since the adult worms have a proclivity toward central bile ducts, cholangiography is recommended in all cholecystectomies with associated *F. hepatica*

infestation. On occasion a linear opacity can be demonstrated that represents a dead adult worm. The parasite should be retrieved to prevent ongoing biliary obstruction and risk of cholangitis. This can be achieved via ERCP or common bile duct exploration. A non-dilated bile duct (<8–10 mm) is a relative contraindication to laparoscopic exploration due to the risk of stricture following healing of the choledochotomy, but is rarely encountered in this setting. Bile duct exploration should only be performed by experienced surgeons. The peritoneum overlying the supraduodenal bile duct should be divided to expose approximately 2 cm anteriorly. A longitudinal choledochotomy of 1 cm is made, and a 5 mm laparoscopic sucker is used to clear bile. A lithotripsy basket can be deployed distal to the obstructing trematode to clear the ducts with care made not to damage the posterior wall of the bile duct. A choledochoscope can be used to ensure duct clearance of the parasites. These techniques are similar to those used in standard gallstone disease.

Open surgical drainage of liver abscesses in the context of trematodiasis or otherwise is rarely indicated. Percutaneous drainage is the mainstay for large abscesses, but the majority will resolve following medical eradication. Abscess resolution can be monitored with regular US of the liver. If surgical management is indicated due to failed interventional management, the abscess cavity should be incised and the contents debrided. Adequate haemostasis can be achieved using diathermy coagulation, CUSA, or by applying two adjacent vertical mattress sutures and resecting the wedge of tissue between.

Opisthorchis and *Clonorchis*

Similar to the intestinal trematodes, oral praziquantel is the drug of choice for *Opisthorchis* and *Clonorchis* infection [13]. The recommended dose is 25 mg/kg three times daily for 2 days, but retreatment may be required in areas of high resistance such as Vietnam [4]. Medical cure in patients not developing cholangiocarcinoma has ranged from 73% to 100%, and infection intensity is greatly reduced in those patients not cured [5]. Antibiotics may also be required to treat associated sepsis or secondary bacterial infection with recurrent pyogenic cholangitis [4]. Surgical management of intrahepatic obstruction associated with secondary strictures, stones, and abscesses is often required [4]. Patients may also require biliary bypass or even transplant if the fibrosis doesn't resolve with medical eradication [16].

Cholangiocarcinoma is understandably the most significant complication arising from liver fluke infection requiring surgical management. Except in the presence of advanced disease or an unresectable tumour, resection should be performed [16]. This is true even as an effective palliative measure for obstructive jaundice [16]. There is however no indication for prophylactic resection in the presence of liver flukes to reduce the risk of cholangiocarcinoma [5]. The operative options do not differ from standard, non-trematodiasis-related cholangiocarcinoma and include a Longmire bypass (intrahepatic cholangiojejunostomy) and hemihepatectomy [5].

Similar to outcomes in cholangiocarcinoma without associated hepatic trematodiasis, non-jaundiced patients have better long-term outcomes, as do those with peripheral lesions [16]. Almost 75% of patients diagnosed with cholangiocarcinoma

will already have lymphatic or vascular invasion, or peritoneal seeding, and aggressive surgical treatment is often not beneficial [35]. Appropriate work-up and staging is imperative in surgical decision-making, and post-operative survival is similar for cholangiocarcinoma regardless of the cause [35]. Without an operation, 3-year survival is approximately 10% [5].

Prevention

Prevention in endemic areas is paramount to the long-term management of intestinal trematode infection. Given its wide distribution and the prevalence of international food imports and intercontinental immigration in the twenty-first century, population-based management is increasingly important. Sporadic cases of human infection have been in seen in most parts of the world [8].

Since trematodes mostly infect younger population groups, focus has been centred in endemic countries on mass drug administration (MDA) in schools. This has proven effective in reducing the incidence and prevalence of soil- and water-based helminth pathogens in Kenya [36] and Korea [37]. Not only do younger people tend to excrete more eggs than adults, but they also tend to develop recurrent infections following treatment with re-exposure [8]. Older individuals, when reinfected, tend to have lower worm burdens [8]. This may be associated with a stronger immune response associated with higher immunoglobulin levels from previous primary infection.

Understanding trematodes life cycle and transmission patterns is critical in disease prevention. In this regard, population health measures should focus on three main areas:

1. Preventing contaminated excrement from entering water systems
2. Education on food preparation
3. Reducing endemic populations disease burden

In order to limit egg-containing excrement from contaminating water sources, primary or secondary prevention strategies can be employed. Use of non-faecal fertilizers on crops can reduce transmission rates. This would limit the volume of eggs deposited into water systems, which interrupts the trematode life cycle. Alternatively, the control of snail populations with the use of molluscicides would also be effective. Without an intermediate host, trematode populations are likely to dwindle. Water sanitation methods can also assist with this method, but direct contact could still result in infection.

Infection with most intestinal flukes can also be limited by education on appropriate food preparation. Cultural practices of pickling fish and so forth encourage the transmission of *Heterophyes* and *Metagonia* species. Smoking and freezing meat similarly do not kill the metacariae. Awareness of which foods contain trematodes and on their recommended cooking of fresh water fish, crustaceans, and vegetables can limit occult disease transmission [38]. Furthermore, imported items of freshwater foods from endemic areas should be stringently monitored to prevent wider disease distribution throughout the world.

As aforementioned, initiatives targeting school children have been successful in the treatment and prevention of trematode-associated infection. MDA and other population-based measures can reduce the incidence and prevalence of trematode-related disease. Praziquantel as a single dose has been recommended by the WHO, and can be widely distributed to at-risk populations [13]. Large-scale treatment like this has been proven to reduce the rate of reinfection in endemic areas.

The mainstay of trematode treatment will be prevention, but unlike intestinal trematodes some early success has been seen in veterinary disease for vaccines against *Fasciola* [4]. However, no vaccines have been developed yet for human infection, likely due to the more complex T1 and T-helper interactions of the human immune system [4]. There have also been advances on developing antitumour compounds for cholangiocarcinoma, namely, triptolide [39]. With further development these therapies could contribute to possible eradication and complication prevention in hepatic trematodiasis in particular. In the future, these neglected tropical diseases may be eliminated.

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References

1. Keiser J, Utzinger J. Food-borne trematodiases. Clin Microbiol Rev. 2009;22(3):466–83.
2. Jackson JA, Friberg IM, Little S, Bradley JE. Review series on helminths, immune modulation and the hygiene hypothesis: immunity against helminths and immunological phenomena in modern human populations: coevolutionary legacies?. [published correction appears in Immunology. 2009 Mar;126(3):446]. Immunology. 2009;126(1):18–27.
3. Sripa B, Kaewkes S, Intapan PM, et al. Food-borne trematodiases in Southeast Asia epidemiology, pathology, clinical manifestation and control. Adv Parasitol. 2010;72:305.
4. Mahanty S, Maclean JD, Cross J. Liver, lung, and intestinal fluke infections. Trop Infect Dis. 2006:849–351.
5. Osman M, Lausten LB, El-Sefi T, Boghdadi I, Rashed MY, Jensen SL. Biliary parasites. Dig Surg. 1998;15:287–96.
6. Johansen MV, Lier T, Sithirhaworn P. Towards improved diagnosis of neglected zoonotic trematodes using a one health approach. Acta Trop. 2015;141:161–9.
7. WHO, 1995. Control of foodborne trematode infections. WHO Technical Report No. 849. pp. 1–157.
8. Doughty BL. Schistosomes and other trematodes. In: Baron S, editor. Medical microbiology. 4th ed. Galveston: University of Texas Medical Branch at Galveston; 1996. Chapter 88.
9. Pakharukova M, Mordvinov V. The liver fluke Opisthorchis felineus: biology, epidemiology and carcinogenic potential. Trans R Soc Trop Med Hyg. 2016;110:28–36.
10. Dusak A, Onur MR, Firat U, Ren T, Dogra VS. Radiological imaging features of Fasciola hepatica infection – a pictorial review. J Clin Imaging Sci. 2012;2:2.
11. Singh UC, Kumar A, Srivastava A, et al. Small bowel stricture and perforation: an unusual presentation of Fasciolopsis buski. Trop Gastroenterol. 2011;32:320.
12. Sithithaworn P, Tesana S, Pipitgool V, Kaewkes S, Pairojkul C, Sripa B, Paupairoj A, Thaiklar K. Relationship between faecal egg count and worm burden of Opisthorchis viverrini in human autopsy cases. Parasitology. 1991;102:277–81.

13. WHO. Position paper on food-borne trematode (FBT) infections. In: WHO expert meeting on food-borne trematode infections and taeniasis/cysticercosis in Vientiane, Lao People's Democratic Republic, 12–16 October, 2009. Geneva: World Health Organisation; 2009.
14. MIMS Online [Internet]. Crow's Nest (NSW): MIMS Australia Pty Ltd; 2018. Praziquantel.
15. Pulpeiro JR, Armesto V, Varela J, et al. Fascioliasis: findings in 15 patients. Br J Radiol. 1991;64:798.
16. Watanapa P, Watanapa WB. Liver fluke associated cholangiocarcinoma. Br J Surg. 2002;89:962–70.
17. International Agency for Research on Cancer. Infection with liver flukes (Opisthorchis viverrini, Opisthorchis felineus and Clonorchis sinensis). IARC Monogr Eval Carcinog Risks Hum. 1994;61:121–75.
18. Hou PC. The pathology of Clonorchis sinensis infestation of the liver. J Pathol Bacteriol. 1995;70:53.
19. Bhamarapravati N, Virranuvatti V. Liver diseases in Thailand. An analysis of liver biopsies. Am J Gastroenterol. 1966;45:267–75.
20. Vennervald BJ, Polman K. Helminths and malignancy. Parasite Immunol. 2009;31:686.
21. Rim HJ. Clonorchiasis in Korea. Kisaengchunghak Chapchi. 1990;28(suppl):63.
22. Upatham ES, Brokleman WY, Viyanant V, et al. Incidence of endemic Opisthorchis viverrini infection in a village in Northeast Thailand. Am J Trop Med Hyg. 1985;34:903–6.
23. Sripa B, Kaewkes S. Localisation of parasite antigens and inflammatory responses in experimental opisthorchiasis. Int J Parasitol. 2000;30:735–40.
24. Sripa B, Brindley PJ, Mulvenna J, Laha T, Smout MJ, Mairiang E, Bethony JM, Loukas A. The tumorigenic liver fluke *Opisthorchis viverrini* –multiple pathways to cancer. Trends Parasitol. 2012;28(10):395–407.
25. Mayer DA, Fried B. The role of helminth infections in carcinogenesis. Adv Parasitol. 2007;65:239.
26. Shirai T, Pairojkul C, Ogawa K, Naito H, Thamavit B, Bhundhisawat W, Ito N. Histopathological characteristics of cholangiocellular carcinoma in Northeast Thailand, where a region infection with the liver fluke, *Opisthorchis viverrini* is endemic. Acta Pathol Jpn. 1992;42:734–9.
27. Thamavit W, Moore MA, Sirisinha S, Shirai T, Ito N. Time- dependent modulation of liver lesion development in Opisthorchis-infected Syrian hamster by an antihelminthic drug, praziquantel. Jpn J Cancer Res. 1993;84:135–8.
28. Flavell DJ. Liver fluke infection as an aetiological factor in bile- duct carcinoma of man. Trans R Soc Trop Med Hyg. 1981;75:814–24.
29. Pungpak S, Viravan C, Radomyos B, Chalermrut K, Yemput C, Plooksawasdi W, et al. Opisthorchis viverrini infection in Thailand: studies on the morbidity of the infection and resolution following praziquantel treatment. Am J Trop Med Hyg. 1997;56:311–4.
30. Arjona R, Riancho JA, Aguado JM, et al. Fascioliasis in developed countries: a review of classic and aberrant forms of the disease. Medicine (Baltimore). 1995;74:13.
31. MacLean JD, Graeme-Cook FM. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case12-2002:a 50-year-old man with eosinophilia and fluctuating hepatic lesions. N Engl J Med. 2002;346:1232.
32. Cosme A, Alzate L, Orive V, Recasens M, Torrado J, Ruiz I, Arenas J. Laparoscopic findings in liver fascioliasis: study of 13 cases. Rev Esp Enferm Dig. 1990;78:359–62.
33. Uribarrena R, Borda F, Munoz M, et al. Laparoscopic findings in eight cases of liver fascioliasis. Endoscopy. 1985;17:137.
34. Leung J, Sung JY, Ling T, Chung S, Metreweli C. Filamentous filling defects on ERCP is pathognomonic of hepatic clonorchiasis (abstract). Gastrointest Endosc. 1988;34:189–90.
35. Uenishi T, Hirohashi K, Kubo S, Yamamoto T, Hamba H, Tanaka H, et al. Histologic factors affecting prognosis following hepatectomy for intrahepatic cholangiocarcinoma. World J Surg. 2001;25:865–9.
36. Mwandawiro C, Okoyo C, Kihara J, Simiyu E, Kepha S, Campbell SJ, Freeman MC, Brooker SJ, Njenga SM. Results of a national school-based deworming programme on soil-transmitted helminth infections and schistosomiasis in Kenya: 2012-2017. Parasit Vectors. 2019;12:76.

37. Bahk YY, Park YK, Na BK, Sohn WM, Chai JY, Kim TS. Survey on intestinal helminthic infection status of students in two counties, Hadong-gun and Goseong-gun, Korea. Korean J Parasitol. 2018;56(4):335–9.
38. Sithiathaworn P, Sripa B, Kaewkes S, Haswell-Elkins M. Food-borne trematodes. In: Cook GC, Zumla AI, editors. Manson's tropical diseases. 22nd ed. London: Saunders; 2009. p. 1461–76.
39. Tengchaisri T, Chawengkirttikul R, Rachaphaew N, Reutrakul V, Sangsuwan R, Sirisinha S. Antitumor activity of triptolide against cholangiocarcinoma growth in vitro and in hamsters. Cancer Lett. 1998;133:169–75.

Part III

Hydatid Disease

What a Surgeon Needs to Know About the Diagnosis and (Medical) Treatment of Hydatid Disease

7

Shauna H. Gunaratne and Rocio Hurtado

In Whom Should We Suspect Hydatid Disease? Epidemiology and Public Health Burden

Echinococcal disease is an important neglected disease that affects many people worldwide. It is one of the World Health Organization's (WHO) 17 neglected tropical diseases and is a priority neglected zoonotic disease [1]. Cystic echinococcosis affects approximately 1.2 million people around the world and is estimated to be responsible for 3.6 million disability-adjusted life years (DALYs) per year [2]. It is estimated to have a higher socioeconomic cost than Chagas disease or leprosy [3]. Highest concentrations of echinococcal disease are found in Eastern Europe, the Middle East, South America, and parts of China [4, 5] where rates can be as high as 50 per 100,000 person-years [4]. It has been estimated that the prevalence can be 2–6% within endemic populations. Risk factors for disease acquisition in these areas include close proximity of livestock slaughter to humans and dogs, such as on farms or at home, as well as sheep raising and large dog populations [6]. Within the continental United States, echinococcal disease exists mainly in the southwestern states. Risk factors include home slaughter of sheep and having pets, particularly canines, that are allowed to eat raw sheep organs and meat. Most cystic echinococcal cases in Alaska and Canada occur in native populations [7].

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Cystic echinococcal (CE) disease is caused by *E. granulosus*, of which strain G1 is most commonly responsible for infections in humans. *E. multilocularis* causes alveolar echinococcus (AE), which has distinct disease characteristics from the cystic form [4]. *E. multilocularis* is mostly transmitted by wild canines such as foxes, wolves, etc. and is found in Northern Asia, Europe, North America, and the Arctic [6]. Two other species, *E. vogeli* and *E. oligarthrus*, cause polycystic echinococcus, but these are much rarer [4]. *E. vogeli* is similar to alveolar echinococcal disease and found in Central and South America. *E. oligarthrus* is less aggressive and also found in Central and South America [6].

Alveolar echinococcus (AE) incidence has increased over the last few years, mostly in part due to increasing wild canine populations [6, 8]. In Switzerland, a highly endemic area for *E. multilocularis*, the incidence has increased to 0.26/100,000 between 2001 and 2005 due to increasing fox populations [8].

Clinical Manifestations

Canines (particularly dogs) are definitive hosts for echinococcus, and sheep and cattle are intermediate hosts [4, 6]. *Echinococcus granulosus* sensu stricto prefers sheep as its intermediate host [5]. The intermediate hosts (sheep, cattle, humans) ingest an egg from the environment which can remain infectious for weeks [6]. The definitive hosts, in this case dogs, release the egg into the environment through their feces. This egg hatches in the gastrointestinal tract of the intermediate host and releases an oncosphere, traverses the gut wall, and travels through the portal system, eventually to the liver or lungs where it becomes a cyst. When the dogs (definitive hosts) eat this cyst in the tissues of the intermediate hosts, the cyst then becomes a tapeworm in their gastrointestinal tract, completing the life cycle. The tapeworm does not exist in the intermediate host. Humans are accidental intermediate hosts as dogs do not consume the infected human tissue with cysts and do not continue the life cycle of the cestode [6].

In humans, the cyst is comprised of an endocyst, which is the germinal membrane, and a pericyst, which is a fibrous capsule and a result of the host response around the cyst [4]. The cyst is filled with fluid that often contains protoscolices, which can cause infection if they come in contact with other tissues. The cysts often grow very slowly at a rate of 1–10 millimeters per year [4, 5]. Since the parasite enters through the portal system, the liver is the most commonly affected area of cystic disease, in about 70% of cases [4]. The lungs are the second most commonly affected site, making up about 20% of cases. In 85–90% of CE cases, only one organ is affected, and greater than 70% of cases have only one cyst [4]. Less than 10% are found in other sites, including the bone [6]. The spine is the most commonly affected site of bony echinococcal disease [9].

Due to the very slow rate of growth, the cysts often remain clinically silent. They eventually manifest based on complications or mass effect from the enlarging cyst [5]. The parasite has also been able to adapt to minimize the host inflammatory

response [5]. The site of cyst formation dictates clinical manifestations. Liver cysts grow at a slower rate than lung cysts, which can therefore present earlier in life [10]. For example, liver cysts can cause nausea, vomiting, or abdominal pain or, if they exert compression on the biliary system, can cause jaundice and obstruction or fistulization. Lung cysts can cause cough, dyspnea, pleuritic chest pain, or even hemoptysis [4]. If lung cysts compress airways, they can cause post-obstructive pneumonia or atelectasis. Cystobronchial fistulae can cause patients to cough up contents of the cyst, which is characteristically described as "salty water and grape skin," and can even lead to aspiration. Cystobronchial and cystopleural fistulae can lead to pneumothoraces [9].

Under 10% of patients with echinococcal disease develop complications such as compression, rupture, or superinfection [6]. Rupturing of the cyst can cause significant challenges and often lead to clinical symptoms as the antigens are released and recognized by the immune system. In a contained rupture, the pericyst is still intact, but the endocyst is torn, and the cyst remains the same size on imaging. In a communicating rupture, the endocyst is torn, and the cyst contents may be released into fistulae within the pericyst. On imaging, a contained rupture appears smaller than previously imaged, with the addition of a now mobile membrane. A direct rupture is when both endocyst and pericyst are torn and there is direct communication of cyst contents with the outside space, and this often leads to disseminated echinococcal disease [4]. The protoscolices of active cysts can infect other organ systems to cause secondary or disseminated disease. Rupture into the biliary tract can cause cholangitis. Anaphylaxis can be seen when the cysts suddenly rupture, due to type 1 hypersensitivity reaction to the antigens [4, 9]. Rupture into the systemic circulation can cause embolic disease [9]. Bacterial superinfection is another not uncommon complication; it is estimated that 7.3% of all cysts become superinfected, which is a cause of significant morbidity in hydatid disease [4].

Alveolar echinococcal disease, caused by *E. multilocularis*, behaves differently than cystic echinococcus. It is more aggressive and has been described as behaving similarly to a malignancy. Its incidence is estimated at about 0.02 to 1.4/100,000 worldwide [6]. Its mortality rate is much higher than CE, estimated to be greater than 90% after 10–15 years if untreated, as compared to untreated CE, which is estimated to be 2–4% [10]. Torgerson et al. provide similar numbers of estimated 29% survival at 10 years and 0% survival at 15 years [8] though survival rates have improved over the years. The major predictor of survival in these studies was earlier diagnosis. For patients diagnosed in 2005, survival has now increased to about 90% for men and 94% for women [8]. Alveolar echinococcus (AE) almost always affects the liver and most commonly the right lobe [10]. It does not form cysts, and the larva directly invades surrounding tissue. It also remains clinically silent for many years. It is estimated to manifest with jaundice in 33% of cases and abdominal pain in another 33%, and the other 33% are found incidentally during other workup [10].

Diagnostic Considerations

Diagnosis of echinococcal disease can be challenging but relies on clinical and epidemiologic history and imaging, with serology as an adjunct. The differential diagnosis for echinococcus depends on the stage of cyst and appearance on imaging but can include simple cysts, cystadenomas, and metastases [9]. Brunetti et al. outline case definitions, with a possible case defined as clinical or epidemiologic history plus imaging findings or positive serology. A probable case has clinical history, epidemiologic risk factors, consistent imaging, and positive serology on two tests (usually a highly sensitive antibody then confirmed by a highly specific antibody). A confirmed case is a probable case with the following criteria: either protoscolices seen in cyst fluid or changes in ultrasound imaging spontaneously or after medication. Clinical criteria include a cyst seen on imaging, anaphylaxis from a ruptured cyst, or an incidentally found cyst [10].

Imaging

Ultrasound remains the cornerstone of diagnosis, staging, and follow-up for CE. Computed tomography (CT) is less useful than magnetic resonance imaging (MRI) as a secondary imaging modality [9]. Secondary imaging (MRI) is recommended if there is sub-diaphragmatic disease, disseminated disease, extra-abdominal disease, or complicated cysts with suspected abscess or fistulae [10]. For AE, ultrasound also is the imaging modality of choice, especially since the disease is primarily abdominal. However, as opposed to the staging approach described below for CE, AE is described similar to malignancy with a PMN staging system denoting involvement of other organs and metastases [10].

The WHO informal working group on echinococcus created a stage approach for CE based on ultrasound findings. They grouped the cysts into four different classes: active, transitional, inactive, and undefined [1]. The WHO classification is similar to prior classification systems such as Gharbi's, with some key differences: the order of CE2 and CE3a is reversed, a new CE3b grouping was created, and the cysts are grouped based on their activity. There is also the addition of the CL classification, which is undefined [11].

CE1 and CE2 cysts are classified as active [1]. CE1 cysts are anechoic and simple and have a double-line sign that is characteristic and seen more prominently on ultrasound, less so on MRI or CT [9]. CE1 cysts have pathognomonic signs on ultrasound which involve a "snowflake" sign and a cyst wall that is apparent [1]. CE2 cysts are multivesicular and often have multiple septae [9]. As a result, on ultrasound they can appear "wheel-like," "rosette-like," or "honeycomb-like" [1].

C3a and C3b are both transitional stages of cyst where the membranes are degenerating and set apart in that CE3a is liquid where CE3b is mucinous or solid [9]. CE3 has a pathognomonic "water-lily sign" seen on ultrasound which represents the endocyst that has become detached [1, 9]. C3b cysts often have daughter cysts but

have solid content as stated above, and these daughter cysts are often not visualized on CT and therefore can be misclassified [9].

CE4 can be described as "ball of wool" which is the appearance on ultrasound of the collapsing membranes [1]. They are solid and heterogeneous in appearance with the characteristic degenerating membranes, which can often be missed on CT. As a result, these cysts can be mistaken for active CE1 cysts [9]. CE5 is characterized by a thick, heavily calcified wall [1]. This is the only stage where the cyst characteristics are better seen on CT rather than ultrasound [9].

Stojkovic et al. conducted a retrospective analysis of patients with abdominal CE and studied 107 patients with 187 cysts. They compared the agreement coefficient for WHO staging between CT and MRI, and the agreement coefficient was lower for CT than for MRI for stages CE1 to CE4. However in stage CE5, CT was better than MRI [12] probably due to ability of seeing calcification better on CT than MRI.

This staging approach has implications for treatment as the imaging findings correlate with activity of the cyst. Hosch et al. conducted a metabolic viability assessment of cysts. The gold standard of determining viability is injection of cyst material or fluid into mice and resulting development of echinococcal disease. Alternative methods such as light microscopy have been used, and Hosch's group utilized the technique of proton magnetic resonance spectroscopy. They found that the WHO staging was mostly associated with viability of cysts. They found CE4 and CE5 cysts were usually nonviable, whereas many CE1 and CE2 cysts were viable. CE3a cysts tended to be viable and nonviable in equal proportion, whereas CE3b cysts tended toward being more viable. They also found that albendazole therapy interfered with cyst viability [13].

Solomon et al. also looked at reliability of the WHO classification and found high rates of intra-observer reliability and very high rates of inter-observer reliability for pathognomonic signs [14]. This staging approach is routinely used to guide management but has been slow to become adopted in certain regions of the world. Solomon et al. looked at the literature in the last 15 years and found that publications utilizing the WHO classification have increased over time, from <50% from 2004 to 2010 to as high as 96% in 2017. There is a significant amount of regional variation, where European, North American, and South American publications often use WHO classification, whereas the rates are much lower in publications from Africa. This does suggest that the WHO classification is becoming more utilized over time [14].

Ultrasound is also effective as a screening tool. Del Carpio et al. screened 1054 children in the Rio Negro area of Argentina, and sensitivity was 100%; specificity was 95.6% [15].

Serology and Laboratory Testing

Serology should be used as an adjunct to imaging in the diagnosis of echinococcal disease. Very early, active cysts can have negative serology since the endocyst is tightly sealed and prevents antigens from crossing and being recognized by the

immune system. Later stages of cyst with calcified walls can also be seronegative for the same reason: the calcified wall prevents antigens from being exposed to the immune system [9]. Cyst rupture can be the only time when the antigens are exposed to the host immune response [9]. Moreover, cysts in protected sites such as the brain or eye often have negative serology [2]. It is also thought that the laminated layer has complement avoidance mechanisms; pathology has often showed a non-inflamed layer of tissue adjacent to the hydatid cyst [5].

Significant gaps remain in testing, including lack of standardization in different methods of testing, for example, antigen preparation [2]. False positives can also occur with some methods if the serology cross-reacts with other cestodes or other antibodies. Antibody titers are not reliable in detecting recurrence as it can remain elevated even after cystectomy [2].

In the United States, a Western blot for antibodies is available through the Centers for Disease Control (CDC) [6]. Serology is thought to be 80–100% sensitive and 88–96% specific for liver cysts. Test characteristics drop off significantly for extrahepatic disease, with only about 50–56% sensitivity for lung cysts and 20–56% sensitivity for disease in other organs [6]. Sarkari et al. looked at the literature and found rates of negative serology from 15% to 37.5%. They remark upon one study of pulmonary disease, where unruptured cysts had 80% positive serology [2].

Hydatid cyst fluid, or HCF, is the most common source of antigens for serology testing. The fluid includes components both from the parasite and host proteins. Antigen 5 has been studied heavily, as it is one of the most immunogenic components. However, it unfortunately has high rates of cross-reactivity with normal blood and other helminths, including tapeworms, flukes, and roundworms. Sensitivity appears to be approximately 50%. Newer studies with purified antigen 5 may have better specificity. Antigen B is the main antigen of HCF and very specific and sensitive for CE. Immunoblot can be 100% sensitive and 80% specific and enzyme-linked immunosorbent assay (ELISA) 92.5% sensitive and 97% specific. Recombinant AgB testing performance appears similar to that of native AgB. They have also found that the test has improved characteristics when AgB is derived from sheep and humans, as opposed to other intermediate hosts. Combination of AgB and Ag5 testing was studied in one report with 96.8% sensitivity and 87.5% specificity but unfortunately cross-reacted with other cestodes and even normal blood. However, free antigen testing alone is less sensitive than antibody testing, in part because it may be trapped in the cyst and also because circulating free antigen may be bound in immune complexes and not detectable by assay [2].

Interestingly, different antigen immunoblots are correlated with disease activity and stage of cyst. Mariconti et al. looked at patients with hepatic cysts, healthy controls, and patients with other helminths. They found distinct patterns of bands for AgB and Ag5 that differentiated CE1, CE2, CE3a, C3b, and CE4/5 cysts [16].

Unfortunately, traditional antibody testing performs poorly. Different stages of immunoglobulin G (IgG) are associated with activity of the cyst. Immunoglobulin G (IgG) is associated with the growth and development of the cyst, where IgG1,

IgG2, and IgG3 are associated with the involutive phase. IgG4 may be more sensitive in relapse. Immunoglobulin G (IgG) subclasses have been shown to be more correlated with disease activity than IgG alone [2].

These poor test characteristics also make serology unhelpful for follow-up. As stated previously, antibodies may be positive for years. One study has reported that antibodies to AgB disappeared 3 months after therapy; hence additional studies will be needed to confirm whether this may be helpful in monitoring for response to therapy [2]. Stojkovic et al. looked at recombinant antigens EgP29 and 2B2t in follow-up of surgically treated patients. Unfortunately, the rates of positivity of these tests at the beginning of monitoring were only around 34–60%, and these tests did not turn positive in the setting of relapse, making them unreliable markers for follow-up [17].

Other laboratory abnormalities are also not reliable. Liver function tests (LFTs) have low sensitivity and are only elevated in 40% of patients. Of these, alkaline phosphatase elevation is seen most commonly. Eosinophilia is seen in only up to 40% of patients – again because the parasite is sealed in the endocyst leading to a minimal host response [4].

In AE, serology is more reliable, and serology using *E. multilocularis* antigens is estimated to have a sensitivity of 90–100% and specificity of 95–100%. Antibodies drop quickly after surgery and may be more useful for follow-up than in CE [10].

Therapeutic Considerations

There are four main approaches to treatment in CE: chemotherapy, surgery, percutaneous intervention, and the watch and wait approach. Choice of treatment is dictated by staging and cyst size, as outlined in the WHO model; see Fig. 7.1, Approach to treatment. For CE1 and CE3a cysts greater than 5 cm, puncture-aspiration-injection-reaspiration (PAIR) plus albendazole therapy is recommended, whereas for smaller CE1 and CE3a cysts less than 5 cm, albendazole alone is often sufficient. CE2 and CE3b cysts should be intervened upon with percutaneous therapy (catheterization, non-PAIR) with albendazole or surgery with albendazole therapy. Surgery is recommended for almost all large cysts greater than 10 cm in all active and transitional stages (CE1, CE2, CE3a, CE3b). CE4 and CE5 cysts should be observed with no intervention or medical therapy, regardless of size [1, 9–11].

Chemotherapy

Benzimidazoles first became available in the 1970s, starting with mebendazole (MBZ). When this was used, very high doses were needed due to poor absorption. Attention turned to albendazole (ABZ) with studies being conducted in the 1980s for treatment of echinococcal disease. Albendazole (ABZ) is also poorly absorbed, similar to MBZ, and requires food for improved bioavailability [18]. Absorption ranges from 5 to 20%, with the first-pass metabolism in the intestinal wall, and is mostly metabolized by the time it reaches the bloodstream [11]. However, one

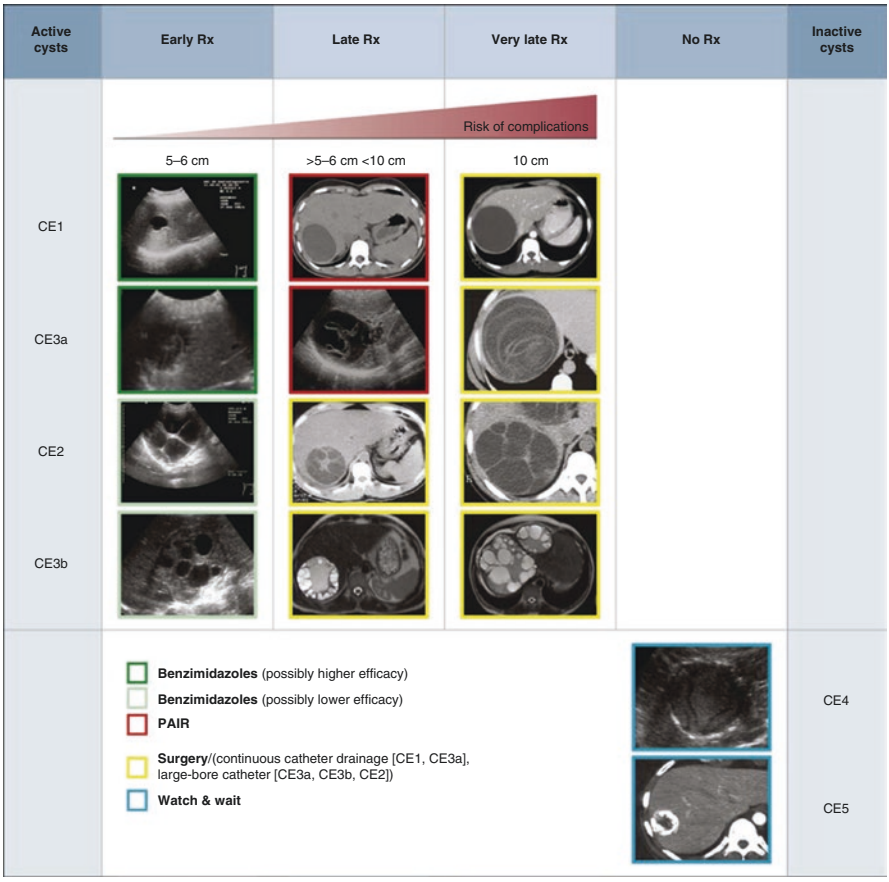

Fig. 7.1 Approach to treatment [50]. (Reprinted with permission)

advantage of ABZ over MBZ is that its metabolite, albendazole sulfoxide, is also antihelminthic. Intermittent dosing of ABZ was initially used given concern for adverse effects and that the drug may be mutagenic, and several older studies therefore used intermittent dosing strategies. However, one center in Italy has been using continuous dosing of ABZ with no increase in adverse effects seen, so intermittent dosing has fallen out of favor [18]. Standard dosing now is 400 mg twice daily [6]. Early data from the 1980s showed that there was a 39% successful response rate to ABZ. After review of the literature, Horton estimated ABZ had a 32.7% cure rate for liver cysts and 39.5% cure rate for lung cysts [18].

Stojkovic et al. conducted a systematic review where they analyzed 612 patients in the literature with 1159 liver and peritoneal cysts. Inactive cysts were defined as cysts in stage CE4 or CE5 or if cysts had resolved on imaging. In active CE1 cysts, 50–75% of those cysts resolved with ABZ therapy. Only 30–55% of CE2 and CE3 cysts resolved with therapy. A Cox proportional hazards model showed that CE1

responded better to medical therapy than CE3 after 1 year, $p = 0.04$. They also stratified by size and found that cysts smaller than 6 cm were more likely to respond to medical treatment ($p = 0.006$ in Cox proportional hazards model). However, 25% of treated cysts became active within about 18–24 months. It was estimated that after 2 years, about 40% of cysts had failed medical therapy and were likely still active or had relapsed [19]. This again supports the staging approach and choosing medical therapy for smaller, active cysts as recommended by WHO guidelines.

There have been very small, randomized controlled trials examining albendazole use versus placebo in CE [20, 21]. Gil-Grande et al. conducted a 3-arm trial with 18 patients as a control, 18 patients receiving 1 month of ABZ therapy, and 19 patients receiving 3 months of ABZ therapy. They did comparison ultrasounds before and after therapy, and all patients underwent surgery, with the cyst fluid being injected into mice to determine the viability of the protoscolices. The average cyst size or number of patients with greater than one cyst did not vary significantly among the three arms. Results showed that 50% of the control cysts were nonviable, compared to 72% of cysts treated with 1 month of ABZ and 94% of cysts treated with 3 months of ABZ. Both protoscolex and cyst viability were significantly reduced in treatment arms compared to the control arm ($p = 0.039$ and $p = 0.018$, respectively). 68% of cysts treated for 3 months showed changes on ultrasound [20]. Keshmiri et al. conducted a randomized controlled trial of 29 patients with 240 cysts that received ABZ (cyclical dosing) versus placebo and looked at radiographic evolution. 82% of cysts in the treatment arm had cure or improvement versus 1% of control cysts that had improvement; none of the control cysts had cure [21].

A longitudinal series by Nahmias looked at 68 patients with CE who were treated with ABZ on a cyclic schedule. 41% of liver patients were cured, 17% showed improvement (which was defined as a contraction of the cyst), and 15% had no change. 72% of lung cysts were cured, whereas 18% had no changes. They observed recurrence of cysts at a very low rate, in 0.03% of patients [22].

Liver function test (LFT) abnormalities are seen very commonly in treatment of CE with ABZ, reported up to 20% [18]. However, it has been observed that elevated LFTs were associated with treatment efficacy; moreover, LFTs would not necessarily continue to worsen on treatment. As such, it has been hypothesized that the LFTs are not true drug adverse effect, but instead inflammation and an immune response after albendazole destroys the cyst and antigens are being presented [18]. Albendazole (ABZ) also can suppress bone marrow and cause pancytopenias [18]. Albendazole is thought to be teratogenic, but these effects have not been seen in women thus far exposed in the first trimester [18, 23]. Bradley and Horton reviewed case series and other series conducted in West Africa and South Asia. At the time of their writing, ABZ had been available for 20 years, but there were no reports of birth defects or adverse maternal-fetal outcomes associated with ABZ. However, it is still recommended that its use be avoided during pregnancy [23]. Alopecia is also seen in 1–5% [11] as the hair is particularly sensitive to the anti-tubulin effects of albendazole. Given the above effects on laboratory testing, it is recommended to have complete blood cell count (CBC) and LFTs obtained at baseline, at days 5, 14, and 28 of therapy and then every other week through course of therapy [9].

In terms of metabolism of ABZ, its absorption is increased when taken with food, particularly a fatty meal. Taking ABZ with fatty food has been shown to increase drug levels by a factor of five [18]. It is thought to be metabolized by cytochrome P450 (CYP) enzymes. Nagy et al. looked at serum concentration of its metabolite, albendazole sulfoxide, when given with water, a fatty meal, grapefruit juice, and grapefruit juice with cimetidine (both CYP enzyme inhibitors). Serum concentrations were 6.5 times higher with a fatty meal when compared to taking it with water and 3.2 times higher with grapefruit juice, both statistically significant. The serum concentration was lower when taking ABZ with grapefruit juice and cimetidine than taking it with grapefruit juice, by 46%. The area under the curve was 9.4 times higher with a fatty meal and 3.1 times higher with grapefruit juice, both statistically significant. A similar reduction in AUC was seen when taking ABZ with juice plus cimetidine versus juice alone [24].

There may be a role for combination therapy with praziquantel (PZQ) to be given in addition to albendazole, but this has not been studied in randomized clinical trials [3], and there are currently no recommendations on duration or dosing. Praziquantel (PZQ) has greater than 80% bioavailability, which is improved when administered with food. It undergoes first-pass metabolism in the liver and is generally well tolerated with few adverse side effects [25], most commonly gastrointestinal symptoms and upset [3]. Homeida et al. looked at the pharmacokinetics when administering PZQ and ABZ concurrently; they found that the area under the curve of ABZ metabolite was 4.5 times higher when given with PZQ, 8 times higher when given with food, and 12 times higher when given with PZQ and food [26]. Of note, PZQ concentrations did not seem to be affected by ABZ [26]. Bygott and Chiodini reviewed the data on praziquantel thus far at time of publication (2009), and in vitro studies have shown that PZQ has protoscolicidal activity and is usually more effective in smaller cysts. In combination therapy with ABZ and PZQ, an increased rate of nonviable protoscolices has been reported than compared to treatment with ABZ alone. They found similar reports of the pharmacokinetics of combination therapy as Homeida et al., where levels of the active ABZ metabolite were higher in combination therapy than ABZ alone. However, they concluded there was not adequate data to fully support the use of PZQ and no data for frequency or duration of its use in echinococcal disease [25].

Alvela-Suárez et al. conducted a retrospective observational study of 57 patients on combination therapy with ABZ and PZQ in Spain. 81% of the patients they observed had complications of hydatid disease, such as compression, superinfection, or fistula formation. Patients were on standard dosing of ABZ 400 mg twice daily along with varying doses of PZQ from 20 to 75 milligrams per kilogram per day. Average length of treatment duration was 68 weeks, and 65% of patients received more than 1 year of combined therapy. Only 14% of patients had adverse effects, most commonly gastrointestinal side effects such as stomach upset, nausea, vomiting, and diarrhea. These were also reversible after discontinuation of combination therapy or after discontinuation of PZQ. The authors also mention possible combination therapy with nitazoxanide, another antihelminthic agent, but this needs to be studied further [3].

Besides the stage-specific approach mentioned above, indications for medical treatment include multiple cysts in the lung or liver, especially those that may be

inoperable [4, 5]. Other indications include multiple cysts in two or more organs and peritoneal cysts or disseminated disease [10]. Contraindications to medical treatment include large cysts that are at high risk of rupture, treatment in early pregnancy, treatment of inactive cysts, or pre-existing liver or bone marrow disease (which can be exacerbated by effects of albendazole) [4, 9]. Albendazole (ABZ) also has a role as adjunctive therapy for percutaneous treatment or surgery to reduce risk of disseminated disease during intervention and decreased viability of the cysts before intervention [4, 18]. Preoperative treatment for 1 to 3 months before intervention reduces number of cysts found intraoperatively [6]. Preoperatively, albendazole is recommended at a minimum 3 days before, for 4 to 8 weeks postoperatively for uncomplicated cysts, and up to 3 to 6 months postoperatively for complicated cysts [4].

Albendazole (ABZ) is recommended to be used for 1 month after PAIR to prevent secondary echinococcosis [18]. Smego et al. conducted a meta-analysis of PAIR with either albendazole or mebendazole given 1 week before and 4 weeks after drainage. They looked at 769 patients who underwent PAIR and either ABZ or MBZ therapy versus 952 matched controls who underwent surgery. There was a statistically significant higher rate of cure in the PAIR plus chemotherapy group ($p < 0.0001$), with 95.8% cure rates in the PAIR plus chemotherapy group versus 89.9% in the surgery group. The recurrence rate was also significantly lower in PAIR plus chemotherapy (1.6%) versus surgery (6.3%, $p < 0.0001$). They also noted an increased rate of major complications and longer hospital stays in the surgery group [27]. Arif et al. looked at ABZ as an adjuvant to standard surgical management from patients at one institute in India. The patients were sorted into four groups: those who underwent surgery alone, those who underwent 8 weeks of preoperative ABZ then surgery, those who underwent 8 weeks of preoperative and postoperative ABZ, and those who had surgery and then 8 weeks postoperative ABZ. At the time of surgery, 97% of medically untreated patients had cysts, compared to 9% of those receiving preoperative ABZ ($p < 0.01$). Recurrence was highest in the surgery alone group and lowest (0%) in the group that received pre- and postoperative ABZ [28].

Albendazole (ABZ) in AE is essential to therapy and is used in all stages of disease. Albendazole (ABZ) therapy is used as an adjunct after surgery for as long as 2 years, even in those patients undergoing transplant, due to the possibility of residual disease. In those patients that do not undergo surgery or other intervention, chemotherapy is lifelong. Preoperative ABZ is only recommended in advance of liver transplantation, but not for resection. Praziquantel (PZQ) is not used for AE [10].

PAIR and Percutaneous Methods

Percutaneous methods have been shown to be most effective for moderately sized CE1 and C3a cysts [1, 9–11]. Percutaneous methods vary between puncture-aspiration-injection-reaspiration (PAIR), standard catheterization, and modified catheterization technique. Indications for PAIR include patients that are

contraindicated for surgery or have relapsed after surgery. It is contraindicated in patients younger than 3 years old [29]. An important consideration before injecting protoscolidal agents is to ensure there are no cystobiliary or cystobronchial fistulae, as this will cause sclerosis and irreversibly damage human tissue. Of note, contrast or dye studies sometimes cannot reveal a fistula if the endocyst has not ruptured yet, as the fistulae are preformed in the pericyst and only become direct communications when the endocyst ruptures and the cyst material travels through the pericyst. The pericyst often contains biliary vessels or bronchi [9]. Puncture-aspiration-injection-reaspiration (PAIR) is contraindicated in cysts with fistulae [10] for this reason. Endoscopic techniques such as endoscopic retrograde cholangiopancreatography (ERCP) are often used preoperatively in surgical patients and/or in patients under consideration for PAIR to help determine if fistulization is present [30]. Additional contraindications to PAIR include cysts that have ruptured into the peritoneum or superficial cysts at risk of rupturing into the abdominal cavity [11]. Continuous catheter drainage is thought to be best for cysts larger than 10 centimeters [10] and other percutaneous methods for cysts that have relapsed after PAIR [11]. Puncture-aspiration-injection-reaspiration (PAIR) is also not helpful for spinal or paraspinal cysts [11]. Brunetti et al. looked at nearly 3000 patients who underwent percutaneous drainage and found complication rates as follows: anaphylaxis leading to death at 0.05%, major complications (such as death, secondary echinococcal disease from contamination, sclerosis) at 0.38%, and recurrence rates at 1.27% [11].

Khuroo et al. conducted two studies looking at percutaneous therapy versus medical therapy or surgery for hepatic cysts [31, 32]. In the randomized study with hepatic cysts receiving percutaneous drainage versus albendazole therapy, all cysts with percutaneous drainage had significant changes in size and in ultrasound characteristics compared to ABZ alone. The maximum reduction in size was seen in cysts that were percutaneously drained followed by ABZ treatment, $p < 0.05$ [31]. Their group also compared outcomes of percutaneous drainage to surgery in uncomplicated hepatic cysts. The final cyst diameter was not significantly different between both groups ($p = 0.2$), and cyst resolution was also similar in both groups ($p = 0.29$). However, there was a significant increase in complications in the surgical group ($p < 0.001$) [32]. These trials showed that percutaneous drainage in experienced hands could be more effective in some cysts than albendazole and as efficacious and safer than surgery in the studied populations.

Additional centers have published their experience with percutaneous treatment noting that this treatment modality is safe and effective. Yagci et al. looked at one center in Turkey of 355 patients with 510 liver cysts between 1992 and 2003 that either underwent open surgery, laparoscopic surgery, or percutaneous therapy. Recurrence rates were significantly higher for open surgery than laparoscopic or percutaneous methods [33]. Giorgio et al. published data after following patients for 11 years from 1988 to 1999 with median follow-up time of 48 months. These patients had double percutaneous treatment with alcohol, with no reaspiration. Inactive cysts were excluded from treatment. They observed 47% of treated cysts resolved and 45.8% of treated cysts then became solid (thought to be transitioning). The relapse rate was around 5%. Their overall morbidity rate was 9%, and mortality rate was 1.3% [34].

Two observational studies have shown that PAIR is not optimal treatment for CE2 and CE3b cysts and larger active cysts [35, 36]. Akhan et al. looked at 73 patients with CE2 and CE3b cysts that underwent percutaneous treatment from 1991 to 2008. Equal proportions were treated with PAIR, standard catheterization, and modified catheterization. Rates of recurrence were much higher in PAIR (47.8%) versus standard catheterization (3.8%) and modified catheterization (3.8%), and this difference was found to be statistically significant with a $p < 0.05$ [35]. Golemanov et al. looked at 230 patients with 348 cysts treated with PAIR that were followed for 12 months. 77.6% of cysts showed some obliteration. All CE1 and CE3a cysts showed some degree of obliteration, whereas the cysts that had no change in size/structure were all CE2 and CE3b. They also observed that 11.5% cysts needed repeat PAIR or aspiration, and these all ended up being CE1 cysts that were larger than 10 cm [36]. This supported the hypothesis that PAIR is inadequate for CE2 and CE3b cysts as well as large CE1 cysts, and other percutaneous methods should be pursued for treatment.

Men et al. looked at catheterization of 15 large abdominal cysts, which were classified as large if the estimated volume of a cyst was greater than 15 cm in diameter. They did not see recurrence in any cases with a mean follow-up time of 53 months [37].

Radiofrequency thermal ablation has been attempted as treatment, but unfortunately most cysts relapsed, so this is not recommended [11, 38].

Surgery

Surgical treatment of liver cysts has been quoted to have a morbidity rate of 32%, a mortality rate of 8%, and a relapse rate around 20%. Morbidity and mortality for surgical intervention of lung cysts are estimated around 0–13% and 0–5%, respectively. Surgery is the treatment of choice for large cysts, cysts in certain locations (such as bone or heart), and complicated cysts that can rupture, are superinfected, or have fistulization [10, 11].

Surgical approaches vary between conservative (partial cystectomy) and radical (total cystectomy, hepatectomy, or other tissue resection). Georgiou et al. observed 232 patients in Greece who underwent either total pericystectomy or hepatectomy or partial cystectomy and found no difference in mortality between groups undergoing total or partial cystectomies. Recurrence rate was slightly higher in the partial cystectomy group at 3 years [39]. Radical procedures generally have a higher risk intraoperatively but a lower rate of relapse, whereas conservative procedures are safer intraoperatively but have a higher rate of relapse [29].

To prevent secondary spread of echinococcus from accidental spillage, the surrounding tissues in the surgical field should be protected with towels soaked in protosolicidal agents (such as hypertonic saline) that will inactivate the cyst content [9, 10]. Adjuvant medications should also be administered as described above. The residual cavity, if left behind such as in partial pericystectomy, also poses a risk for infection or fistulization [11]. This cavity also needs to be treated; options in the liver include suctioning and filling it with omental tissue and in the lungs suturing or using capitonnage to close the cavity [11].

In AE, resection of all the infected tissue is treatment of choice and has been associated with increased survival [8, 10]. Torgerson et al. looked at survival curves in Switzerland and found that those who underwent radical resection had increased survival rates compared to those who did not [8].

Watch and Wait

Several cohort studies have shown that the watch and wait approach is safe for inactive cysts and that these cysts (CE4 and CE5) have very low rates of reactivation [40–43]. Piccoli et al. looked at a cohort of 38 patients with liver cysts from March 1994 to October 2013; these patients had inactive cysts and had not previously received any chemotherapy. They were followed for at least 24 months (though the median follow-up time was 52 months). Of these cysts, 97.4% remained inactive during follow-up. Serology was not found to be a reliable marker of inactivity of the cysts [40]. Stojkovic et al. hypothesized that medically induced inactive cysts behaved differently than naturally inactive cysts. They looked a prospective cohort of 223 patients and defined relapse as going from CE4 or CE5 back to an active stage. They had two groups – watch and wait, which contained 30 patients with 46 inactive cysts who had never previously received chemotherapy, and a medication group with 15 patients with 17 cysts. There were no relapses in the watch and wait group; however, half the cysts (8/17 or 47%) in the medication group relapsed. These cysts mostly moved to CE3b stage. Their interpretation from this cohort study was that cysts that become inactive with chemotherapy do behave differently than naturally progressed inactive cysts with higher rates of relapse. They suggested a time period of 5 years for follow-up for inactive cysts based on their experience [41].

Rinaldi et al. looked to see whether the watch and wait approach could be applied to C3b cysts, studying retrospective data of 60 patients with this cyst stage over 27 years. There was no association between the approach (watch and wait) and relapse with a $p = 0.09$, and no difference in the rate of complications. Their conclusion was that watch and wait may be an option if CE3b cysts are asymptomatic and not able to be surgically removed [42]. Lissandrin et al. recently released an update in 2018 to add to their prior report from 2014. They analyzed 53 patients from 1991 to October 2017 with CE4 or CE5 liver cysts who had never received treatment and had to be followed by ultrasound for at least 24 months. Of these patients, 98.5% remained inactive, and 1.9% (only one patient) had reactivation of one cyst [43].

Follow-Up

Follow-up varies depending on the intervention. Generally ultrasound is the method of choice and recommended every 6 months for the first 2 years and then annually if stable. Up to a 10-year period of follow-up is recommended given the possibility of relapse [4, 11]. As mentioned previously, serology is not helpful in this context [4]. Also of note, after intervention, ultrasound should be conducted to establish a baseline and discern postoperative changes from recurrence [9].

Management of Complicated Hydatid Disease

Complicated echinococcal disease often requires a different approach, with surgical intervention most commonly utilized as the preferred strategy. Symeonidis et al. conducted a retrospective study looking at 227 patients with 322 liver cysts between 1980 and 2010. Complicated cysts were classified as those that had intrabiliary rupture, intrabronchial rupture, intraoperative diagnoses of peritoneal perforation, or cyst fluid that was bile-stained (suggestive of biliary communication) or purulent (secondarily infected). The most common complications observed were intrabiliary rupture, followed by superinfection of cysts. They found a similar rate of medical complications between complicated and uncomplicated cysts, but there was a significantly higher rate of surgical complications in the complicated group ($p = 0.011$). However, the mortality rate was similar as well as length of hospitalization. They recommended indications for endoscopic retrograde cholangiopancreatography (ERCP) to include acute cholangitis and if hydatid material is found in the biliary system [44].

Endoscopic retrograde cholangiopancreatography (ERCP) plays an important role in the management of complicated hydatid cyst disease, particularly in the management of intrabiliary rupture. Dolay and Akbulut reviewed the role of preoperative and postoperative ERCP in these cases. Diagnostic preoperative ERCP is considered to examine possible communication between the cyst and biliary tree, classified as simple/minor if there is no obstruction and therefore asymptomatic, or major if there is obstruction. There are no recommendations for when this should be used, but some suggest using it when the rate of communication may be more probable, for example, in disease with large or multiple cysts. It should also be used when PAIR reveals presence of bile-stained cystic fluid. The authors do not recommend using preoperative diagnostic ERCP when the patient has no biliary symptoms and when there is no evidence of biliary obstruction or pathology on laboratory results or various imaging modalities. In rupture, the hydatid membranes are seen in the duodenum endoscopically, and on imaging, the membranes and cysts are seen as filling defects. Preoperative diagnostic ERCP is limited as it sometimes cannot detect minor communications and can miss rupture, obstruction, or cysts in the intrahepatic ducts [30].

Endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy are also helpful therapeutically in intrabiliary rupture [30]. Data is mixed on whether they decrease rates of fistulization. One advantage is treatment of obstruction, which allows for surgery for removal of the cyst to be elective instead of emergent. In some cases, they have seen cure rates of 25% in patients with rupture who no longer require surgery thereafter. Small case series have shown high rates of success with ERCP, and the authors of the study also have high cure rates with a modified procedure of drainage and ERCP. Endoscopic retrograde cholangiopancreatography (ERCP) also has a therapeutic role postoperatively to treat complications such as fistulae and strictures. Fistulae are the most common postoperative complication, with rates as high as 50–63%, and are defined as persisting 10 days postoperatively (before 10 days it is classified as postoperative drainage). Endoscopic retrograde cholangiopancreatography (ERCP) is recommended to treat fistulae and

particularly earlier in the course if there is a large amount of drainage or the drainage is persistent and not dropping off, suggesting that spontaneous resolution will be less likely [30].

Dziri et al. conducted a systematic review of complicated and disseminated cystic disease. In terms of liver cysts that have ruptured into the biliary tract, they were only able to examine retrospective data, which supported the use of ERCP or intraoperative cholangiography to remove cyst fluid and contents from the biliary tree [45]. This approach for ERCP is also recommended by Stojkovic [9]. Literature also supported 3 months of antihelminthic therapy post-procedurally. They found that ERCP and preoperative endoscopic sphincterotomy can decrease fistulization from 11.1% to 7.6%. Options for treatment of cystobiliary fistulae include suturing, creating a tract through the skin for drainage, or transfistulary drainage. For liver cysts in the thorax with bronchobiliary fistulae, surgical treatment is recommended. For cysts found in the spleen, lung, bone, and heart, surgical approaches are recommended but vary from cystopericystectomy for CE in the heart to splenectomy for multiple, large CE in the spleen [45].

Prousalidis et al. conducted a retrospective review of 44 years of experience with infected cysts in Greece. They identified 16.8% of CE cases had superinfected cysts. 90% of these patients had partial pericystectomy, whereas the other 10% had a cystopericystectomy. Microbiologic diagnosis was available in 61 out of 77 cases; most commonly isolated organisms were *Enterobacter* spp. in 23%, followed by *Pseudomonas*, *E. coli*, *Proteus*, and *Klebsiella*. Notably, in 34% of these, no organisms were isolated. Their postoperative complication rate was 19%, and their recurrence rate was 6.5%, but they did not find any correlation between recurrence and use of antihelminthic therapy, type of procedure, or number or size of cysts. Based on their review, they recommended open surgery for treatment of infected cysts to minimize the risk of spillage and contamination of infected material to other areas but preferred conservative approaches over radical ones [46].

Future Developments

Vaccines are in development for prevention of echinococcal disease in both definitive and intermediate hosts [4, 47–49]. A pilot field trial of the EG95 vaccine in sheep in Argentina found that after vaccination, the prevalence decreased from 56% to 21% over 6 years ($p = 0.03$). Moreover, there were fewer cysts per animal after vaccination as compared to controls [47]. Zhang et al. vaccinated dogs and found that these were 97–100% effective in preventing worm growth and egg production [48]. Heath et al. conducted studies of vaccines with recombinant EG95 in sheep and cattle in parts of China, Argentina, and New Zealand. They found greater than 85% immunity after two injections and greater than 95% after three injections [49]. Prior public health campaigns have been effective in eradicating echinococcal disease from Iceland, New Zealand, and Tasmania, mostly by preventing farm or at home slaughter of sheep [4]. These new developments may one day help to eradicate echinococcal disease.

References

1. Group WHOIW. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Trop. 2003;85(2):253–61.
2. Sarkari B, Rezaei Z. Immunodiagnosis of human hydatid disease: where do we stand? World J Methodol. 2015;5(4):185–95. https://doi.org/10.5662/wjm.v5.i4.185.
3. Alvela-Suarez L, Velasco-Tirado V, Belhassen-Garcia M, Novo-Veleiro I, Pardo-Lledias J, Romero-Alegria A, et al. Safety of the combined use of praziquantel and albendazole in the treatment of human hydatid disease. Am J Trop Med Hyg. 2014;90(5):819–22. https://doi.org/10.4269/ajtmh.13-0059.
4. Bhutani N, Kajal P. Hepatic echinococcosis: a review. Ann Med Surg (Lond). 2018;36:99–105. https://doi.org/10.1016/j.amsu.2018.10.032.
5. Diaz A. Immunology of cystic echinococcosis (hydatid disease). Br Med Bull. 2017;124(1):121–33. https://doi.org/10.1093/bmb/ldx033.
6. King CH, Fairley JK. 291 - tapeworms (Cestodes). 2015.
7. Cerda JR, Buttke DE, Ballweber LR. Echinococcus spp. tapeworms in North America. Emerg Infect Dis. 2018;24(2):230–5. https://doi.org/10.3201/eid2402.161126.
8. Torgerson PR, Schweiger A, Deplazes P, Pohar M, Reichen J, Ammann RW, et al. Alveolar echinococcosis: from a deadly disease to a well-controlled infection. Relative survival and economic analysis in Switzerland over the last 35 years. J Hepatol. 2008;49(1):72–7. https://doi.org/10.1016/j.jhep.2008.03.023.
9. Stojkovic M, Weber TF, Junghanss T. Clinical management of cystic echinococcosis: state of the art and perspectives. Curr Opin Infect Dis. 2018;31(5):383–92. https://doi.org/10.1097/QCO.0000000000000485.
10. Brunetti E, Kern P, Vuitton DA. Writing panel for the W-I. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114(1):1–16. https://doi.org/10.1016/j.actatropica.2009.11.001.
11. Junghanss T, da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. Am J Trop Med Hyg. 2008;79(3):301–11.
12. Stojkovic M, Rosenberger K, Kauczor HU, Junghanss T, Hosch W. Diagnosing and staging of cystic echinococcosis: how do CT and MRI perform in comparison to ultrasound? PLoS Negl Trop Dis. 2012;6(10):e1880. https://doi.org/10.1371/journal.pntd.0001880.
13. Hosch W, Junghanss T, Stojkovic M, Brunetti E, Heye T, Kauffmann GW, et al. Metabolic viability assessment of cystic echinococcosis using high-field 1H MRS of cyst contents. NMR Biomed. 2008;21(7):734–54. https://doi.org/10.1002/nbm.1252.
14. Solomon N, Fields PJ, Tamarozzi F, Brunetti E, Macpherson CNL. Expert reliability for the world health organization standardized ultrasound classification of cystic echinococcosis. Am J Trop Med Hyg. 2017;96(3):686–91. https://doi.org/10.4269/ajtmh.16-0659.
15. Del Carpio M, Moguilansky S, Costa M, Panomarenko H, Bianchi G, Bendersky S, et al. Diagnosis of human hydatidosis. Predictive value of a rural ultrasonographic survey in an apparently healthy population. Medicina (B Aires). 2000;60(4):466–8.
16. Mariconti M, Bazzocchi C, Tamarozzi F, Meroni V, Genco F, Maserati R, et al. Immunoblotting with human native antigen shows stage-related sensitivity in the serodiagnosis of hepatic cystic echinococcosis. Am J Trop Med Hyg. 2014;90(1):75–9. https://doi.org/10.4269/ajtmh.13-0341.
17. Stojkovic M, Adt HM, Rosenberger K, Boubaker G, Hernandez-Gonzalez A, Junghanss T, et al. Follow-up of surgically treated patients with cystic echinococcosis: can novel recombinant antigens compete with imaging? Analysis of a patient cohort. Tropical Med Int Health. 2017;22(5):614–21. https://doi.org/10.1111/tmi.12859.
18. Horton J. Albendazole for the treatment of echinococcosis. Fundam Clin Pharmacol. 2003;17(2):205–12.

19. Stojkovic M, Zwahlen M, Teggi A, Vutova K, Cretu CM, Virdone R, et al. Treatment response of cystic echinococcosis to benzimidazoles: a systematic review. PLoS Negl Trop Dis. 2009;3(9):e524. https://doi.org/10.1371/journal.pntd.0000524.
20. Gil-Grande LA, Rodriguez-Caabeiro F, Prieto JG, Sanchez-Ruano JJ, Brasa C, Aguilar L, et al. Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. Lancet. 1993;342(8882):1269–72. https://doi.org/10.1016/0140-6736(93)92361-v.
21. Keshmiri M, Baharvahdat H, Fattahi SH, Davachi B, Dabiri RH, Baradaran H, et al. Albendazole versus placebo in treatment of echinococcosis. Trans R Soc Trop Med Hyg. 2001;95(2):190–4. https://doi.org/10.1016/s0035-9203(01)90162-2.
22. Nahmias J, Goldsmith R, Soibelman M, el-On J. Three- to 7-year follow-up after albendazole treatment of 68 patients with cystic echinococcosis (hydatid disease). Ann Trop Med Parasitol. 1994;88(3):295–304. https://doi.org/10.1080/00034983.1994.11812870.
23. Bradley M, Horton J. Assessing the risk of benzimidazole therapy during pregnancy. Trans R Soc Trop Med Hyg. 2001;95(1):72–3. https://doi.org/10.1016/s0035-9203(01)90338-4.
24. Nagy J, Schipper HG, Koopmans RP, Butter JJ, Van Boxtel CJ, Kager PA. Effect of grapefruit juice or cimetidine coadministration on albendazole bioavailability. Am J Trop Med Hyg. 2002;66(3):260–3. https://doi.org/10.4269/ajtmh.2002.66.260.
25. Bygott JM, Chiodini PL. Praziquantel: neglected drug? Ineffective treatment? Or therapeutic choice in cystic hydatid disease? Acta Trop. 2009;111(2):95–101. https://doi.org/10.1016/j.actatropica.2009.04.006.
26. Homeida M, Leahy W, Copeland S, Ali MM, Harron DW. Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. Ann Trop Med Parasitol. 1994;88(5):551–9. https://doi.org/10.1080/00034983.1994.11812903.
27. Smego RA Jr, Bhatti S, Khaliq AA, Beg MA. Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. Clin Infect Dis. 2003;37(8):1073–83. https://doi.org/10.1086/378275.
28. Arif SH, Shams Ul B, Wani NA, Zargar SA, Wani MA, Tabassum R, et al. Albendazole as an adjuvant to the standard surgical management of hydatid cyst liver. Int J Surg. 2008;6(6):448–51. https://doi.org/10.1016/j.ijsu.2008.08.003.
29. Menezes da Silva A. Hydatid cyst of the liver-criteria for the selection of appropriate treatment. Acta Trop. 2003;85(2):237–42.
30. Dolay K, Akbulut S. Role of endoscopic retrograde cholangiopancreatography in the management of hepatic hydatid disease. World J Gastroenterol. 2014;20(41):15253–61. https://doi.org/10.3748/wjg.v20.i41.15253.
31. Khuroo MS, Dar MY, Yattoo GN, Zargar SA, Javaid G, Khan BA, et al. Percutaneous drainage versus albendazole therapy in hepatic hydatidosis: a prospective, randomized study. Gastroenterology. 1993;104(5):1452–9.
32. Khuroo MS, Wani NA, Javid G, Khan BA, Yattoo GN, Shah AH, et al. Percutaneous drainage compared with surgery for hepatic hydatid cysts. N Engl J Med. 1997;337(13):881–7. https://doi.org/10.1056/NEJM199709253371303.
33. Yagci G, Ustunsoz B, Kaymakcioglu N, Bozlar U, Gorgulu S, Simsek A, et al. Results of surgical, laparoscopic, and percutaneous treatment for hydatid disease of the liver: 10 years experience with 355 patients. World J Surg. 2005;29(12):1670–9. https://doi.org/10.1007/s00268-005-0058-1.
34. Giorgio A, Tarantino L, de Stefano G, Francica G, Mariniello N, Farella N, et al. Hydatid liver cyst: an 11-year experience of treatment with percutaneous aspiration and ethanol injection. J Ultrasound Med. 2001;20(7):729–38.
35. Akhan O, Salik AE, Ciftci T, Akinci D, Islim F, Akpinar B. Comparison of long-term results of percutaneous treatment techniques for hepatic cystic echinococcosis types 2 and 3b. AJR Am J Roentgenol. 2017;208(4):878–84. https://doi.org/10.2214/AJR.16.16131.
36. Golemanov B, Grigorov N, Mitova R, Genov J, Vuchev D, Tamarozzi F, et al. Efficacy and safety of PAIR for cystic echinococcosis: experience on a large series of patients from Bulgaria. Am J Trop Med Hyg. 2011;84(1):48–51. https://doi.org/10.4269/ajtmh.2011.10-0312.

37. Men S, Yucesoy C, Edguer TR, Hekimoglu B. Percutaneous treatment of giant abdominal hydatid cysts: long-term results. Surg Endosc. 2006;20(10):1600–6. https://doi.org/10.1007/s00464-005-0627-2.
38. Brunetti E, Filice C. Radiofrequency thermal ablation of echinococcal liver cysts. Lancet. 2001;358(9291):1464. https://doi.org/10.1016/S0140-6736(01)06518-7.
39. Georgiou GK, Lianos GD, Lazaros A, Harissis HV, Mangano A, Dionigi G, et al. Surgical management of hydatid liver disease. Int J Surg. 2015;20:118–22. https://doi.org/10.1016/j.ijsu.2015.06.058.
40. Piccoli L, Tamarozzi F, Cattaneo F, Mariconti M, Filice C, Bruno A, et al. Long-term sonographic and serological follow-up of inactive echinococcal cysts of the liver: hints for a "watch-and-wait" approach. PLoS Negl Trop Dis. 2014;8(8):e3057. https://doi.org/10.1371/journal.pntd.0003057.
41. Stojkovic M, Rosenberger KD, Steudle F, Junghanss T. Watch and wait management of inactive cystic echinococcosis - does the path to inactivity matter - analysis of a prospective patient cohort. PLoS Negl Trop Dis. 2016;10(12):e0005243. https://doi.org/10.1371/journal.pntd.0005243.
42. Rinaldi F, De Silvestri A, Tamarozzi F, Cattaneo F, Lissandrin R, Brunetti E. Medical treatment versus "Watch and Wait" in the clinical management of CE3b echinococcal cysts of the liver. BMC Infect Dis. 2014;14:492. https://doi.org/10.1186/1471-2334-14-492.
43. Lissandrin R, Tamarozzi F, Mariconti M, Manciulli T, Brunetti E, Vola A. Watch and wait approach for inactive echinococcal cyst of the liver: an update. Am J Trop Med Hyg. 2018;99(2):375–9. https://doi.org/10.4269/ajtmh.18-0164.
44. Symeonidis N, Pavlidis T, Baltatzis M, Ballas K, Psarras K, Marakis G, et al. Complicated liver echinococcosis: 30 years of experience from an endemic area. Scand J Surg. 2013;102(3):171–7. https://doi.org/10.1177/1457496913491877.
45. Dziri C, Haouet K, Fingerhut A, Zaouche A. Management of cystic echinococcosis complications and dissemination: where is the evidence? World J Surg. 2009;33(6):1266–73. https://doi.org/10.1007/s00268-009-9982-9.
46. Prousalidis J, Kosmidis C, Anthimidis G, Fachantidis E, Harlaftis N, Aletras H. Forty-four years' experience (1963-2006) in the management of primarily infected hydatid cyst of the liver. HPB (Oxford). 2008;10(1):18–24. https://doi.org/10.1080/13651820701854669.
47. Larrieu E, Mujica G, Gauci CG, Vizcaychipi K, Seleiman M, Herrero E, et al. Pilot field trial of the EG95 vaccine against ovine cystic echinococcosis in Rio Negro, Argentina: second study of impact. PLoS Negl Trop Dis. 2015;9(10):e0004134. https://doi.org/10.1371/journal.pntd.0004134.
48. Zhang W, Zhang Z, Shi B, Li J, You H, Tulson G, et al. Vaccination of dogs against Echinococcus granulosus, the cause of cystic hydatid disease in humans. J Infect Dis. 2006;194(7):966–74. https://doi.org/10.1086/506622.
49. Heath DD, Jensen O, Lightowlers MW. Progress in control of hydatidosis using vaccination--a review of formulation and delivery of the vaccine and recommendations for practical use in control programmes. Acta Trop. 2003;85(2):133–43.
50. Stojkovic M, Gottstein B, Junghanss T. 56 - Echinococcosis. 2014.

Management of Hepatic Echinococcal Disease and Its Complications

8

Ender Dulundu

Overview

Hydatid liver disease (HLD) is a zoonosis caused by echinococcus granulosus larvae [1]. Although it is highly prevalent in ovine breeding areas, it has become a global disease owing to population migration from endemic to nonendemic countries [2]. Dogs are definitive hosts for *E. granulosus*, with sheep being the major intermediate host (yaks, goats, and camels are other relevant intermediate hosts). Man is only incidentally infected when ingesting tapeworm eggs [6]. The eggs penetrate the intestinal wall, with the resulting larvae infiltrating the blood and lymphatic circulation system. Then, through the portal vein into the liver, lungs, and other tissues, the larvae develop into hydatid cyst [7, 8]. The liver is the most frequent site for the cystic lesions (52–77%) [6, 8, 9].

The disease course is typically slow growth rate (1–5 mm per year), and the patients tend to remain asymptomatic for many years [5, 10]. Often the diagnosis is incidental [11]. Some patients present with vogue abdominal pain. Others present with complications such as intraperitoneal leakage, anaphylaxis, cholangitis, and rupture to adjacent structures (i.e., biliary or bronchial tree) [8]. While most HLD patients have a single cyst, 20–40% tend to harbor multiple cysts [10].

Diagnosis

Many HLD cases are asymptomatic for years, and diagnosis is still challenging due to the absence of pathognomonic signs. For this reason, it is frequently underdiagnosed and detected only incidentally or when complications arise [11]. Diagnosis and

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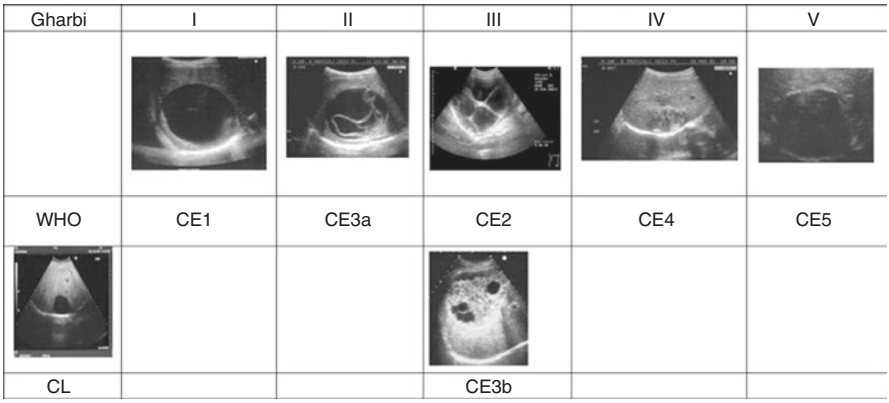

Fig. 8.1 Comparison of Gharbi's and WHO-IWGE ultrasound classification [4]

follow-up of HLD patients are mainly based on imaging techniques. Serological tools supporting imaging techniques would be desirable. However, the available tests are based on antibodies against crude antigens and thus marred by poor sensitivity and specificity, with low or no usefulness for the follow-up of patients during the treatment. Ultrasonography (US), a noninvasive, readily available, sensitive, and cost-effective imaging technique, should be diagnostic method of choice. Several classifications have been proposed for ultrasonic images: Gharbi and WHO-IWGE classifications are the most frequently used (Fig. 8.1) [4, 12, 13]. Computed tomography (CT) is a helpful tool for confirming the diagnosis and can reveal calcified cystic walls, daughter cysts, and exogenous cysts, as well as evaluate their volume and density. CT is essential for planning surgical treatment [8, 14, 15]. Magnetic resonance imaging (MRI) may show a characteristic intense rim, but it is expensive for routine use. Endoscopic retrograde cholangiopancreatography (ERCP) may be helpful during the diagnostic evaluation.

Treatment

There are four treatment options for HLD: surgery, chemotherapy, percutaneous drainage, and just observation. Surgery was first reported in 1820, use of benzimidazole was first reported in 1977, and successful percutaneous drainage was first reported in 1985 [16–18]. The 2010 World Health Organization (WHO) expert consensus has recently reported the indications for surgery, percutaneous treatment, anti-infective drugs, and watch and wait strategy, according to the type of cysts (based on the WHO International Radiological Classifications and the presence of cyst complications) [4, 13].

Surgical Treatment

While surgical treatment was once the most commonly used treatment modality, currently reserved for complicated cysts (such as cysts that develop biliary fistula or

perforated cysts), or is applied to the cysts that contain daughter cysts (CE2, CE3b), it is a suitable treatment option for superficial cysts that are at high risk of rupture and cysts exerting pressure on adjacent vital organs for cases not suitable for percutaneous treatment [4, 19–21].

Surgical procedures for HLD aim to remove the whole parasitic cyst content and to prevent local recurrence, regardless of the type of procedure performed [4, 21]. However, when surgery is advocated, there is a low level of evidence concerning the type of procedure that should be performed.

Indeed, surgical treatments of HLD can be summarized as a debate between two opposing approaches: (1) a conservative approach which is supported by general surgeons from endemic areas that emphasize the need for a safe and reliable first-line treatment and (2) a radical approach which is primarily supported by hepatobiliary surgeons that emphasized the importance of complete pericyst removal [22–25].

Due to the controversial results of former reported studies [7], the 2010 consensus states that "the more radical the intervention, the higher the operative risk, but the likelihood of fewer relapses, and vice versa" [4].

The conservative procedures are safer and easier to perform, and it includes removal of the cyst contents only, deroofing, and partial simple cystectomy (with or without omentoplasty, capitonnage, marsupialization, tube drainage, or other methods for management of residual cavity) [6, 7]. Among all conservative procedures, partial cystectomy is the best possible choice and is considered easy and safe [4, 26], but it leaves a residual cavity that theoretically exposes to specific complications [7, 25].

Surgical techniques for partial cystectomy: A J shape or a midline incision is made. After abdominal exploration, the liver is mobilized in order to explore the entire cystic cavity. Surgical gauzes soaked in 20% sodium chloride solution are placed around the cyst to protect the surrounding tissues from spread of parasites during cyst evacuation. Then, the cyst is punctured and/or incised at its most accessible part (Fig. 8.2). All contents are aspirated with a large bore catheter (Fig. 8.3). If deeply located and/or multiple cyst is existed, intraoperative ultrasonography can be used for not to miss and left behind any cystic region. The most commonly used protoscolicidal agent during surgery is 20% hypertonic saline. The hypertonic saline

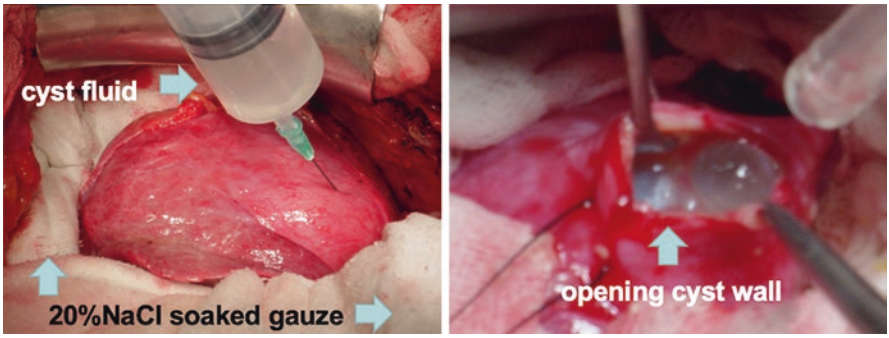

Fig. 8.2 The cyst is punctured and/or incised at its most accessible part

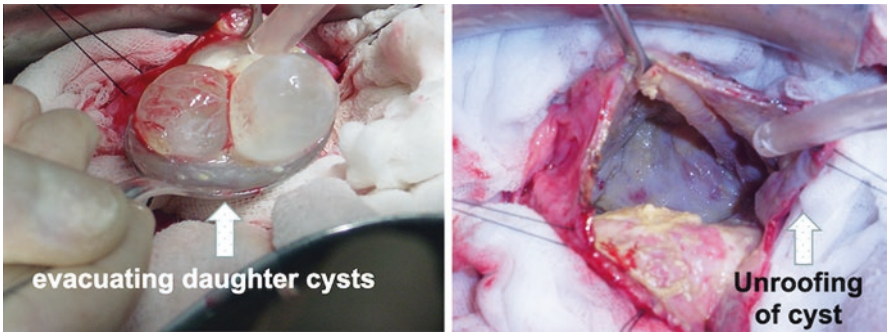

Fig. 8.3 After unroofing all contents are evacuated and aspirated with a large bore catheter

is injected to the cystic cavity and should be in contact with the germinal membrane for at least 10 min than the cystic cavity is aspirated again. Subsequently the cystic incision is enlarged, and cyst content is completely evacuated. The germinative membrane is removed with forceps. The extraparenchymal part of the cystic wall is excised with either a vessel-sealing energy device, harmonic scalpel, or an electrocautery. The inner surface of the cyst is brushed softly with saline-soaked gauzes. In case of intraoperative evidence of bilio-cystic communication, no scolicidal agent should be applied within the cyst in order to avoid sclerosis, cholangitis, and pancreatitis [4]. Meticulous search should be performed, and the orifice is closed using absorbable sutures. The cut edge of the cystic wall is also oversewn with absorbable sutures in a continuous, locked fashion to achieve hemostasis and the closure of any bile ducts opening in this area.

Management of cystic cavity: Obliteration of the remaining cavity can be done as the surgeon's discretion (omentoplasty, capitonnage, drainage). Accumulation of seroma, hematoma, or bile leakage within the residual cavity is a potential source of infection. The omentum is an excellent tissue for obliterating internal cavities and patching the gastrointestinal defects in cases where the formation of a closed dead space is a concern [27–29] (Figs. 8.4 and 8.5). However, the role of omentoplasty in the prevention of septic complications and bile leakage of the cystic cavity is controversial [30, 31]. Omentoplasty has a potential to interfere with the interpretation of follow-up imaging modalities, and it can be quite difficult for a radiologist to distinguish between omentoplasty site and recurrent HLD.

Radical surgery refers to the removal of the cyst along with the pericystic membrane (pericystectomy) and may also include liver resection if indicated figure [6]. Some surgeons suggest that, whenever possible, radical methods should be the mainstay of surgical treatment. They claim that the advantages of radical surgery are lower rates of early and late complications. Despite this trend, it can simply say that there is no clear evidence, yet that radical surgery has lower early or late complication rates. There is very limited randomized controlled trial that compares radical and conservative methods [25].

Resection of small pedunculated and peripherally placed cysts is simple and safe, but in the majority of cases, cystectomy involves a major liver resection with

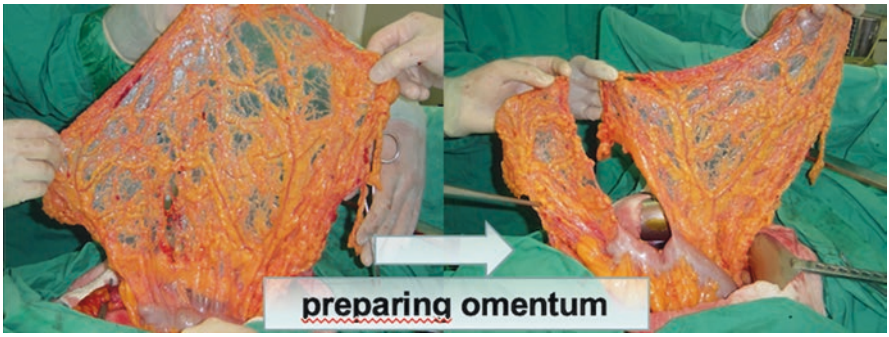

Fig. 8.4 Preparing omental flap for omentoplasty

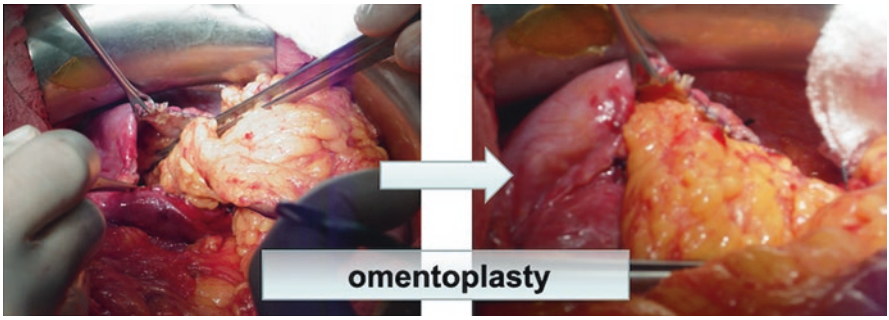

Fig. 8.5 Filling cyst cavity with omentum (omentoplasty)

attendant increase in operative risk. Liver surgery for HLD is predominantly performed by general surgeons. Surgeons who do not have extensive training and experience in liver resection should not be tempted to resect for HLD. Meticulous and careful conservative surgery for this benign disease gives good results, and unnecessary operative mortality will certainly outweigh the merit of totally removing the cyst [32].

A recent study reported a series of 103 patients with liver hydatidosis. A total of 32 patients (31%) had a liver cyst in contact with the inferior vena cava. Radical surgery was performed in 60% of patients. In radical surgery group morbidity rate was 35%, and mortality was 5% [33]. Liver hydatid cysts grow very slowly, and most of them are asymptomatic. When they are diagnosed, clinicians usually ruminate on the most catastrophic scenarios for this benign disease. Favoring preventive radical surgery for the potential reduction of hydatid cyst complications does not justify selecting over conservative methods. The incidence of the most feared complications (peritoneal perforation, jaundice, portal hypertension) is almost 10% when they occur. The mortality rate reported in the literature ranges from 0% to 6.6% [23–25, 34–37]. In the natural course of hydatid liver cyst, the mortality risk of an undiagnosed hydatid liver cyst due to complications is approximately 0.5%. In other words, all the treatment modalities on HLD should try to achieve an overall

mortality less than 0.5%. Performing a radical surgery for a benign disease with a high mortality with the aim of preventing potential complications is not acceptable [38]. The performance of radical procedures not only demands significant expertise in hepatobiliary surgery but also is not suitable for all HLD [39]. Propensity scoring is a statistical technique for dealing with selection bias in observational studies [40]. In a recent study, propensity score-matched analyses were used to compare conservative and surgical procedures in an experienced hepatobiliary surgical unit and to reduce the bias inherent to retrospective studies. Among 493 patients, radical treatment was performed in 86 patients (17.4%), and a conservative approach was used in 407 (82.6%). They found no statistically significant differences in postoperative mortality, morbidity, or recurrence rates after median follow-up of 8 years, between the two groups [34].

Putting a suture may not be safe to close biliary communication in the residual cavity especially if the thick and calcified pericyst is existed. In this instance, some authors favor pericystectomy to reduce the risk of postoperative biliary fistula and liver abscess and lessen the recurrence of the diseases [3, 41]. Subadventitial cystectomy consisted of an excision of the cyst using a cleavage plane located within the pericyst, which comprises two layers according to Peng's description [42]. In this technique, the inner layer or exocyst, which is related to the host granulomatous reaction, is resected. The outer layer or adventitia, which consists of a thin layer of fibrotic parenchyma resulting from liver compression, is left in place. Both approaches require a careful surgical technique especially cases where parts of the cysts are in close relation with great vessels and major biliary ducts.

Hepatic resection can be considered in following instances; when the major biliary structures are involved, if the liver parenchyma anatomically replaced by the cyst, small cyst located peripherally, or in pedunculated cyst. If the patient has a large cysts liver mobilization or blood vessel control is hazardous and there is also a risk of injury of nearby organs (colon, diaphragm, stomach, and duodenum). In such instances it is safer to adopt a conservative approach and perform conservative surgery. Hepatic resection: When the major biliary structures are involved, liver parenchyma anatomically replaced by the cyst, small cyst located peripherally, or in pedunculated cyst can be considered. In patients with large cysts, when liver mobilization or blood vessel control is hazardous or there is a risk of injury nearby organs (colon, diaphragm, stomach, and duodenum), it is safer to adopt a conservative approach and perform conservative surgery.

The first laparoscopic surgery for HLD was reported in 1993 [43]. Although the laparoscopic hydatid surgery offers some advantages in selected cases, this approach has not gained widespread acceptance because of the limited working space that increase the operative risk and potential spillage of cyst content [21, 44–46]. Especially deep-seated cysts in the hepatic parenchyma, posterior cysts close to the vena cava, multiple cysts (>3), and cysts with calcified walls are unsuitable for laparoscopic surgery [21, 47, 48].

There are limited studies to compare laparoscopy with open procedures. In a recent review including 914 patients in published 57 articles, the authors concluded that laparoscopic approach is safe and comparable to open surgery [49]. But this

study has several drawbacks that are open to discussion, because majority of patients are selected cases. And, there is a need a prospective comparative study.

Postoperative Period and Follow-Up

After the operation albendazole therapy is resumed when the patient starts oral feeding and is continued for 3 months. And, is extended to 6 months if gross contamination occurred during the operation. Postoperative recurrence of HLD is rare and can be difficult to distinguish from a new manifestation [50]. Recurrence may become symptomatic 3–4 years after surgery and range from 4% to 25% [3, 35, 36, 51–53]. Although Little et al. reported that recurrence is mostly seen during the first 3 years after surgery, published recurrence rate is higher with longer follow-up postoperatively [25].

After the operation albendazole therapy is resumed when the patient starts oral feeding and is continued for 3 months. And, is extended to 6 months if gross contamination occurred during the operation.

Patients can be followed up by abdominal ultrasonographic surveillance, every 6 months for 4 years and annually thereafter. In general, a period of 5 years without recurrence is considered sufficient [54]. Abdominal CT can be performed in patient with suspicion of liver hydatid cyst recurrence on ultrasound examination. If doubt persisted between recurrence and residual cavity after surgical treatment, despite CT or MRI, especially in the event of a negative immunological test, fine needle aspiration cytology (FNAC) can be carried out [55]. Immunological test is not used routinely for diagnosis because they are less sensitive and specific than radiological imaging [52].

In endemic areas those with less than optimal medical facilities, the radical approach can lead to high postoperative morbidity and mortality rates, and conservative approach represents a valid choice. On the other hand, recent technological developments and the availability of intraoperative ultrasonography, ultrasonic dissection, thermodiffusion, vessel sealers, metal bands, and radiofrequency may allow radical approaches if such equipment is available. This by itself becomes a big issue in developing countries, where the patient load is high and both resources and skilled liver surgeons are limited. Today, in Western European countries and the USA, patients with hydatid liver disease are referred, as a rule, to centers specializing in liver surgery. In this surgical environment, radical operations can be carried out with low operative morbidity, but this is not a case in most of the endemic areas [52].

Complications

Operative complications still occur frequently, accompanied by prolonged hospital stays and increased costs. The most common complication of HLD is the infection and the contact with the biliary tree. The improvement of these early postoperative outcomes has been challenging in the field of hepatobiliary surgery [27, 56].

The complication rates of the surgical treatment options vary between 3% and 25%, while the recurrence rates vary between 2% and 40% [26, 36, 57, 58]. The complication and recurrence rates tend to differ based on the location and size of the cyst, as well as the experience of the surgeon and the selected treatment method.

Hydatid cyst-specific surgical complications can be defined as deep abdominal complications, including deep bleeding or hematoma, deep infection (intrahepatic or subphrenic abscess or generalized peritonitis), and bile leakage [27, 56].

It is not clear which one of the given treatment options is the safest and most effective. However, recurrence and complication rates tend to be higher with conservative surgery as compared to those with radical surgery [25]. Many retrospective studies have revealed similar results [23, 58]. On the other hand, in a recent study, the overall postoperative complication rate was 15.7 percent (16 of 102 patients) [59]. The recurrences usually occur due to failure of complete removal of the endocysts and/or their dissemination during surgery. For this reason, special attention should be paid to prevent spread during the operation [60, 61].

Leakage of cyst contents into the blood circulations during surgery is a known triggering factor for anaphylaxis. Anaphylactic reactions may range from mild reactions to severe anaphylactic shock as a result of high antigenicity. Allergic reactions after liver hydatid cyst rupture have been reported to occur at a rate of 16.7–25%, while possibly fatal anaphylactic reactions at a rate of 1–12.5% [62].

The surgical management of ruptured liver hydatid cysts is more complex than an un-ruptured cyst. Scolices can spill into the abdomen, and surgeons address both disease in the liver and the removal of intra-abdominal protoscoleces. The main goals of surgery are to eliminate local disease, prevent complications, and minimize the morbidity, mortality, and recurrence risk. In a retrospective case series of 16 patients with intraperitoneal liver hydatid cyst rupture in 7 patients (44%), spontaneous rupture was observed, while 9 (56%) had a history of trauma [63].

Postoperative bile leak is the major source of morbidity and mortality. It is usually related to persistent biliary fistula linked to a thick, calcified, or infected remaining pericyst, suboptimal drainage of the residual cavity, or raw hepatic resection surface in radical or in conservative surgical patients [34].

Natural history of HLD, which consist of growth through the hepatic parenchyma followed by compression and/or trapping of adjacent intrahepatic vessels, can often lead to cystobiliary communications, and the contact of the cyst with the biliary tracts is encountered in 3–7% of all cases [64, 65]. Cystobiliary communication has multiple predisposing factors. The cyst diameter is an independent factor that is associated with a high risk of cystobiliary communication in clinically asymptomatic patients. In cases where the diameter of the cyst is >7.5 cm, the sensitivity of the contact of the cyst with the biliary tract is reported to be 73%, while its specificity is indicated to be 79% [66]. Multilocularity of cysts, the location of the cyst close to the liver hilum are other predisposing factor that should have to take into account [66].

Cystobiliary communications should be suspected preoperatively when the patient presented with jaundice or cholangitis in the history or when the preoperative imaging shows bile duct dilatation and/or intrabiliary material, and alkaline phosphatase, bilirubin, and gamma-glutamyl transferase levels may predict cystobiliary

communication preoperatively [64, 66–68]. Despite continuous improvements in hepatobiliary imaging, preoperative diagnosis of cystobiliary communication, particularly when cystobiliary communications are <5 mm, is difficult [69]. Magnetic resonance cholangiography seems to have a greatest efficacy (92% sensitivity and 83% specificity) for diagnosing [70]. In case of preoperative evidence of opening of the cyst into the biliary tract, clearing of the biliary tract and lowering of the common bile duct pressure can be achieved preoperatively through an endoscopic sphincterotomy, avoiding common bile exploration at operation, and decrease the risk of postoperative external fistula from 11.1% to 7.6% [59, 71].

Cystobiliary communication can be confirmed intraoperatively by visualizing opening bile duct orifice in the cystic cavity or by assessing the infected and/or bile-stained cyst content (Fig. 8.6). Some methods can be used to detect bile leakage

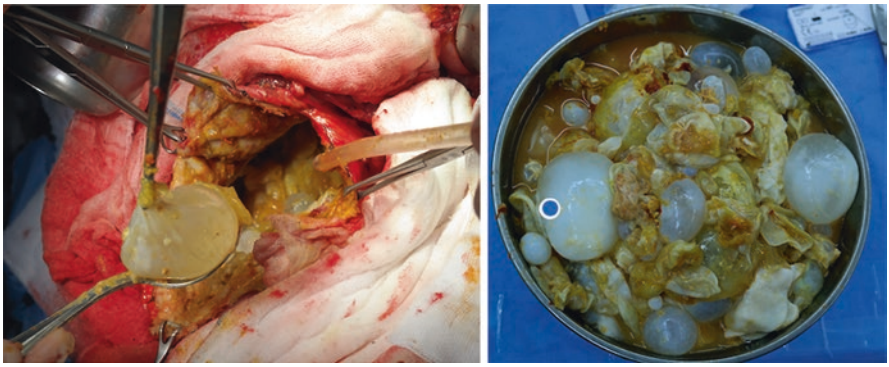

Fig. 8.6 Bile-stained cyst content

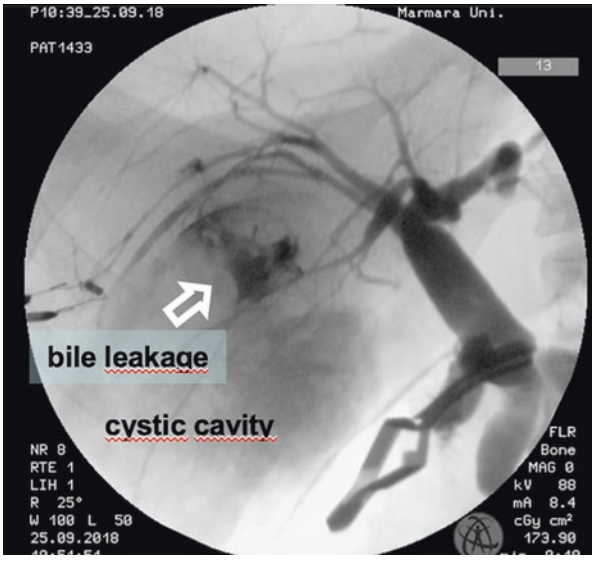

Fig. 8.7 Intraoperative cholangiography, bile leakage to cystic cavity

during the operation. After the cystic cavity had been fully evacuated and complete hemostasis had been achieved, saline-soaked gauzes were stained with bile. If the source of accumulated bile cannot be identified or the newly placed gauzes are again bile-stained, the next step is the bile leakage test in which the cystic duct stump is cannulated and normal saline or methylene blue is injected through the catheter while exposing the entire cystic cavity [30] (Video 1). Any site of leakage is oversewn. Finally, an intraoperative cholangiogram is evaluated for not only the detection of any contrast extravasation but also the definition of the anatomy of the biliary tree and confirmation of patency of the common bile duct [70] (Fig. 8.7). If any obstructing lesion such as HLD membranes within the common bile duct is detected, common bile duct exploration is considered [72, 73]. Performing curettage of the inner surface of the cystic cavity to debride the cuticula of the cyst and thereby visualize the hidden orifices of the cystobiliary communications beneath may result in bleeding that can make the exploration of the cystic cavity more difficult and should be done carefully if necessary [26, 45, 74].

Any openings of biliary communications with the cyst can be sutured individually with absorbable sutures. Intracystic closure of the communication associated with transduodenal sphincteroplasty to clear hydatid material in the common bile duct can be another option for preventing high pressure in the common bile duct in the postoperative period [59]. The involvement of the biliary confluence, the association with fibrotic and/or calcified pericysts, can make direct repair of cystobiliary communication difficult. In such instances, a conservative procedure (i.e., Roux-en-Y hepaticojejunostomy) can be done.

For a patient with the presence of large cystobiliary communications and/or with liver atrophy, a more radical approach can be chosen. The surgeon's experience is very important to choose decision.

Postoperative biloma or high flow biliary fistula requires ERCP and sphincterotomy along with nasobiliary drainage or biliary stenting [75, 76].

References

1. Li H, Song T, Shao Y, Aili T, Ahan A, Wen H. Comparative evaluation of liposomal albendazole and tablet-albendazole against hepatic cystic echinococcosis: a non-randomized clinical trial. Medicine (Baltimore). 2016;95:e2237.
2. Budke CM, Carabin H, Ndimubanzi PC, Nguyen H, Rainwater E, Dickey M, et al. A systemic review of the literature on cystic echinococcosis frequency worldwide and its associated clinical manifestations. Am J Trop Med Hyg. 2013;88:1011–27.
3. Safioleas MC, Misiakos EP, Kouvaraki M, Stamatakos MK, Manti CP, Felekouras ES. Hydatid disease of the liver: a continuing surgical problem. Arch Surg. 2006;141:1101–8.
4. Brunetti E, Kern P, Vuitton DA, Writing Panel for WHO IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114:1–16.
5. Rinaldi F, Brunetti E, Neumayr A, Maestri M, Goblirsch S, Tamarozzi F. Cystic echinococcosis of the liver: a primer for hepatologists.World. J Hepatol. 2014;6:293–305.
6. Smego RAJR, Sebanego P. treatment options for hepatic cystic echinococcosis. Int J Infect Dis. 2005;9:69–76.

7. Dziri C, Haouet K, Fingerhut A. Treatment of hydatid cyst of the liver: where is the evidence? World J Surg. 2004;28:731–6.
8. Sayek I, Tirnaksiz MB, Dogan R. Cystic hydatid disease: current trends in diagnosis and management. Surg Today. 2004;34:987–96.
9. McManus DP, Zhang W, Li J, et al. Echinococcosis. Lancet. 2003;362:1295–304.
10. Nunnari G, Pinzone MR, Gruttadauria S, Celesia BM, Madeddu G, Malaguarnera G, Pavone P, Cappellani A, Cacopardo B. Hepatic echinococcosis: clinical and therapeutic aspects. World J Gastroenterol. 2012;18:1448–58.
11. Manzano-Roman R, Sanchez-Ovejero C, Hernandez-Gonzales A, Casulli A, Siles-Lucas M. Serological diagnosis and follow- up of human cystic echinococcosis: a new hope for the future? Biomed Res Int. 2015;2015:428205.
12. Gharbi HA, Hassine W, Brauner M, Dupuch K. Ultrasound examination of the hydatid liver. Radiology. 1981;139:459–63.
13. WHO Informal Working Group. International classification of the ultrasound images in cystic echinococcosis for application in clinical field and epidemiological setting. Acta Trop. 2003;85:253–61.
14. Schipper HG, Kager PA. Diagnosis and treatment of hepatic echinococcosis, an overview. Scand J Gastroenterol Suppl. 2004;214:50–5.
15. Voros D, Katsarelias D, Polymenas G, et al. Treatment of hydatid liver disease. Surg Infect (Larchmt). 2007;8:621–7.
16. Bremser JG. Etwas u'ber echinococcus hominus. Rud Den Arch Physiol. 1820;6:292.
17. Bekhti A, Schaaps JP, Capron M, Dessaint JP, Santoro F, Capron A. Treatment of hepatic hydatid disease with mebendazole: preliminary results in four cases. Br Med J. 1977;2:1047–51.
18. Mueller PR, Dawson SL, Ferrucci JT Jr, Nardi GL. Hepatic echinococcal cyst: successful percutaneous drainage. Radiology. 1985;155:627–8.
19. Junghanss T, da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. Am J Trop Med Hyg. 2008;79:301–11.
20. WHO informal Working Group on Echinococcosis. Guidelines for treatment of cystic and alveolar echinococcosis in humans. Bull World Health Organ. 1996;74:231–42.
21. Dervenis C, Delis S, Avgerinos C, Maradiaga J, Milicevic M. Changing concepts in the management of liver hydatid disease. J Gastrointest Surg. 2005;9:869–77.
22. Birnbaum DJ, Hardwigsen J, Barbier L, Bouchiba N, Le Treut YP. Is hepatic resection the best treatment for hydatid cyst? J Gastroinst Surg. 2012;16:2086–93.
23. Tagliaccozzo S, Miccini M, Amore Bonapasta S, Gregori M, Tocchi A. Surgical treatment of hydatid disease of the liver: 25 years of experience. Am J Surg. 2011;201:797–804.
24. Motie MR, Ghaemi M, Aliakbarian M, Saremi E. Study of the radical vs. conservative surgical treatment of the hepatic hydatid cyst: a 10 year-experience. Indian J Surg. 2010;72:448–52.
25. Yuksel O, Akyurek N, Sahin T, Salman B, Azili C, Bostanci H. Efficacy of radical surgery in preventing early local recurrence and cavity-relate complications in hydatic liver disease. J Gastrointest Surg. 2008;12:483–9.
26. Buttenschoen K, Carli BD. Echinococcus granulosus infection: the challenge of surgical treatment. Arch Surg. 2003;388:218–30.
27. Dziri C, Paquet JC, Hay JM, Fingerhut A, Msika S, Zeitoun G, et al. Omentoplasty in the prevention of deep abdominal complication after surgery for hydatid disease of the liver: a multicenter, prospective, randomized trial. French Associations for Surgical Research. J Am Coll Surg. 1999;188:281–9.
28. Hofstetter C, Segovia E, Vara-Thorbeck R. Treatment of uncomplicated hydatid cyst of the liver by closed marsupialization and fibrin glue obliteration. World J Surg. 2004;28:173–8.
29. Rakas FS, el-Mufti M, Mehta PM, Abuthina H, Challeni CR. Omentoplasty or tube drainage for the management of the residual cavity following the removal of a hepatic hydatid cyst. Hepatogastroenterology. 1990;37:55–7.
30. Kayaalp C, Aydin C, Olmez A, Isik S, Yilmaz S. Leakage test reduce the frequency of biliary fistulas following hydatid liver cyst surgery. Clinics (Sao Paulo). 2011;66(3):421–4.

31. Silva MA, Mirza DF, Bramhal ISR, Mayer AD, McMaster P, Buckels JA. Treatment of hydatid disease of the liver. Evaluation of a UK experience. Dig Surg. 2004;21:227–33.
32. Pascal G, Azoulay D, Belghiti J, Laurent A. Hydatid disease of the liver. In: Jarnagin WR, editor. Blumgard's surgery of the liver biliary tract, and pancreas. 6th edn. Philadelphia: Elsevier; 2017. p. 1102–1121.
33. Ramia J, Serrablo A, De la Plaza R, Esarte J, Gijon L, Sarria L, Figueras J, Garcia-Parreno J. Is radical surgery feasible in liver hydatid cyst in contact with the inferior vena cava? World J Surg. 2014;38(11):2940–5.
34. El Malki HO, Souadka A, Benkabbou A, Mohsine R, Ifrine L, Abouqal R, et al. Radical versus conservative surgical treatment of liver hydatid cysts. Br J Surg. 2014;101:669–75.
35. Zaouche A, Haouet K, Jouini M, El Hachaichi A, Dziri C. Management of liver hydatid cyst with a large biliocystic fistula: multicenter retrospective study. Tunisian Surgical Association. World J Surg. 2001;25:28–39.
36. Gollackner B, Langle F, Auer H, Maier A, Mittlbock M, Agstner I, et al. Radical surgical therapy of abdominal cystic hydatid disease: factors of recurrence. World J Surg. 2000;24:717–21.
37. Akbulut S, Senol A, Sezgin A, Cakabay B, Dursun M, Satici O. Radical vs conservative surgery for hydatid liver cyst: experience from single center. World J Gastroenterol. 2010;16:953–9.
38. Kayaalp C. Is radical surgery for liver hydatid cyst the right way? Worl J Surg. 2016;40:486–7.
39. Zeybek N, Dede H, Balci D, Coskun AK, Ozerhan IH, Peker S, Peker Y. Biliary fistula after treatment for hydatid disease of the liver: when to intervene. World J Gastroenterol. 2013;19(3):355–61.
40. Hemmila MR, Birkmeyer NJ, Arbabi S, Osborne NH, Wahl WL, Dimick JB. Introduction to propensity scores: a case study on the comparative effectiveness of laparoscopic vs open appendectomy. Arch Surg. 2010;145:939–45.
41. Cirenei A, Bertoldi I. Evolution of surgery for liver hydatidosis from 1950 to today: analysis of a personal experience. World J Surg. 2001;25:87–92.
42. Peng X, Li J, Wu X, Zhang S, Niu J, Chen X, Yao J, Sun H. Detection of osteopontin in the pericyst of human hepatic echinococcus granulosus. Acta Trop. 2006;100:163–71.
43. Katkhouda N, Fabiani P, Benizri E, Mouiel J. Laser resection of a liverhydatid cyst under videolaparoscopy. Br J Surg. 1992;79:560–1.
44. Yaghan R, Heis H, Bani-Hani K, Matalka I, Shatanawi N, Gharaibeh K, Bani-Hani A. Is fear of anaphylactic shock discouraging surgeons from more widely adopting percutaneous and laparoscopic techniques in the treatment of liver hydatid cyst? Am J Surg. 2004;187:533–7.
45. Zaharie F, Bartos D, Mocan L, Zaharie R, Iancu C, Tomus C. Open or laparoscopic treatment for hydatid disease of the liver? A 10-year single-institution experience. Surg Endosc. 2013;27:2110–6.
46. Yagci G, Ustunsoz B, Kaymakcioglu N, Bozlar U, Gorgulu S, Simsek A, et al. Results of surgical, laparoscopic, and percutaneous treatment for hydatid disease of the liver. 10-year experience with 355 patients. World J Surg. 2005;29:1670–9.
47. Bickel A, Daud G, Urbach D, Lefler E, Barasch EF, Eitan A. Laparoscopic approach to hydatid liver cysts. Is it logical? Physical, experimental, and practical aspects. Surg Endosc. 1998;12:1073–7.
48. Baskaran V, Patnaik PK. Feasibility and safety of laparoscopic management of hydatid disease of the liver. JSLS. 2004;8:359–63.
49. Tuxun T, Zhang JH, Zhao JM, Tai QW, Abudurexti M, Ma HZ, Wen H. World review of laparoscopic treatment of liver cystic echinococcosis-914 patients. Int J Infect Dis. 2014;24:43–50.
50. El Malki HO, El Mejdoubi Y, Souadka A, Zakri B, Mohsine R, Ifrine L, Abouqal R, Belkouchi A. Does primary surgical management of liver hydatid cyst influence recurrence? J Gastrointest Surg. 2010;14:1121–7.
51. Little JM, Hollands MJ, Ekberg H. Recurrence of hydatid disease. World J Surg. 2001;25:28–39.
52. Yorganci K, Sayek I. Surgical treatment of hydatid cysts of the liver in the era of percutaneous treatment. Am J Surg. 2002;184:63–9.
53. Mottaghian H, Saidi F. Postoperative recurrence of hydatid disease. Br J Surg. 1978;65:237–42.
54. Brunetti E, White AC. Cestode infestations: hydatid disease and cysticercosis. Infect Dis Clin North Am. 2012;26:421–35.

55. Kim AR, Park SJ, Gu JM, Choi JH, Kim JH. Fine needle aspiration cytology of hepatic hydatid cyst: a case study. Korean J Pathol. 2013;47:395–8.
56. El Malki HO, El Mejdoubi Y, Souadka A, Mohsine R, Ifrine L, Abouqal R, et al. Predictive factors of deep abdominal complications after operation for hydatid cyst of the liver: 15 years of experience with 672 patients. J Am Coll Surg. 2008;206:629–37.
57. Daradkeh S, El-Muhtaseb H, Farah G, Sroujieh AS, Abu-Khalaf M. Predictors of morbidity and mortality in the surgical management of hydatid cyst of the liver. Langenbecks Arch Surg. 2007;392:35–9.
58. Aydin U, Yazici P, Onen Z, Ozsoy M, Zeytunlu M, Kilic M, Coker A. The optimal treatment of hydatid cyst of the liver: radical surgery with a significant reduced risk of recurrence. Turk J Gastroenterol. 2008;19:33–9.
59. Agaoglu N, Mustafae NA, Turkyilmaz S, Arslan MK. Surgical treatment of hydatid cyst of the liver. Br J Surg. 2003;90:1536–41.
60. Kapan M, Kapan S, Goksoy E, Perek S, Kol E. Postoperative recurrence in hepatic hydatid disease. J Gastrointest Surg. 2006;10:734–9.
61. Lissandrin R, Agliata S, Brunetti E. Secondary peritoneal echinococcosis causing massive bilateral hydronephrosis and renal failure. Int J Infect Dis. 2013;17:141–2.
62. Bozdag Z, Yilmaz EE, Gul M. A rare reason for acute abdomen: intraperitoneal liver hydatid cyst rupture. Dig Liver Dis. 2016;48:98–101.
63. Czermak BV, Akhan O, Hiemetzberger R, Zelger B, Vogel W, Jaschke W, et al. Echinococcosis of the liver. Abdom Imaging. 2008;33:133–43.
64. El Malki HO, El Mejdoubi Y, Souadka A, Mohsine R, Ifrine L, Abouqal R, et al. Predictive model of biliocystic communication in liver hydatid cysts using classification and regression tree analysis. BMC Surg. 2010;16:10–6.
65. Kumar R, Reddy SN, Thulkar S. Intrabiliary rupture of hydatid cyst: diagnosis with MRI and hepatobiliary isotope study. Br J Radiol. 2002;75:271–4.
66. Kilic M, Yoldas O, Koc M, Keskek M, Karakose N, Ertan T, Gocmen E, Tez M. Can biliary-cyst communication be predicted before surgery for hepatic hydatid disease: does size matter? Am J Surg. 2008;196:732–5.
67. Derbel F, Ben Mabrouk M, Ben Hadj Hamida M, Jaafar M, Youssef S, Ali BA. Hydatid cysts of the liver-diagnosis, complications and treatment. In: Derbel F, editor. Abdominal surgery. Croatia: INTECH Open Access Publisher; 2012. p. 105–37.
68. Pedrosa I, Saiz A, Arrazola J, Ferreiros J, Pedrosa CS. Hydatid disease: radiologic and pathologic features and complications. Radiographics. 2000;20:795–817.
69. Ramia JM, Figueras J, De la Plaza R, Garcia-Parreno J. Cystobiliary communication in liver hydatidosis. Langenbecks Arch Surg. 2012;397:881–7.
70. Peker KD, Gumusoglu AY, Seyit H, Kabuli HA, Salik AE, Gonenc M, Kapan S, Alis H. Prevention of postoperative bile leak in partial cystectomy for hydatid liver disease: trick of the trade. J Gastroentest Surg. 2015;19:228–34.
71. Galati G, Sterpetti AV, Caputo M, Adduchi M, Lucandri G, Brozzetti S, et al. Endoscopic retrograde cholangiography for intrabiliary rupture of hydatid cyst. Am J Surg. 2006;191:206–10.
72. Bedirli A, Sakrak O, Sozuer EM, Kerek M, Ince O. Surgical management of spontaneous intrabiliary rupture of hydatid liver cyst. Surg Today. 2002;32:594–7.
73. Erzurumlu K, Dervisoglu A, Polat C, Senyurek G. yetim I, Hokelek M. Intrabiliary rupture: an algorithm in the treatment of controversial complication of hepatic hydatidosis. Worl J Gastroenterl. 2005;11:2472–6.
74. Prousalidis J, Tzardinoglou E, Kosmidis C, Katsohis K, Aletras O. Surgical management of calcified hydatid cyst of the liver. HPB Surg. 1999;11(4):253–9.
75. Agarwal S, Sikora SS, Kumar A, Saxena R, Kapoor VK. Bile leaks following surgery for hepatic hydatid disease. Indian J Gastroenterol. 2005;24:55–8.
76. Chowbey PK, Shah S, Khullar R, Sharma A, Soni V, Baijal M, et al. Minimal access surgery for hydatid cyst disease: laparoscopic, thoracoscopic, and retroperitoneoscopic approach. J Laparoendosc Adv Surg Tech A. 2003;13:159–65.

9 Asymptomatic Liver Hydatid Cysts: Is There a Role for Nonoperative Management?

Tarek Nammour and Kassem Barada

Introduction

Echinococcosis, also known as hydatid disease, is a parasitic infection caused by tapeworms of the genus *Echinococcus*. It is considered by the World Health Organization (WHO) to be an important public health issue especially in endemic areas [1]. The life cycle includes a definitive host (mainly dogs) and an intermediate host (such as sheep or cattle). Humans are infected when they ingest the parasite eggs in contaminated food or water. They are considered as incidental hosts and do not play a role in the transmission of disease. Most cases occur where dogs and livestock are raised closely [2].

Human echinococcosis mainly affects the liver and lungs, although any organ can be involved. The two most common species affecting humans are *E. granulosus* and *E. multilocularis* causing cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively. CE has a global distribution including highly endemic areas such as the Middle East, North Africa, Eastern Europe, South America, China, and Central Asia. New endemic areas are being recognized as Echinococcosis is re-emerging as a health problem in certain countries [3]. The economic consequences have been estimated to reach a loss of at least one million disability-adjusted life years (DALYs) and three billion dollars in annual expenses, including treatment and loss of livestock [4]. The exact prevalence is difficult to determine with the absence of overall population surveys, especially in endemic areas. However, increased detection of new cases is currently observed with better diagnostic abilities and surveillance programs. Prevalence can reach 5–10% in endemic regions [5].

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Clinical Manifestations

CE has a long incubation period as most infected cases are usually asymptomatic in the initial phase and clinical manifestations can appear years later. The spectrum of clinical presentations can range from completely asymptomatic to severe and even fatal disease with a reported mortality of 2–4% [6]. Signs and symptoms depend on the size and location of the cysts. They can remain asymptomatic or can present with symptoms secondary to mass effect, obstruction of nearby vessels and structures, or from complications such as cyst rupture, infections, or anaphylactic reaction. The liver is the most frequently affected organ by hydatid cyst (70% of cases). The lungs are involved in 20% of cases, and less frequently other organs such as the kidneys, spleen, muscles, and bones [7]. *E. granulosus* tends to involve a single organ (up to 90% of cases) and usually presents as a solitary cyst (up to 70% of cases). The growth rate in the liver is variable with a reported 1–5 mm growth in diameter per year. The right lobe is more frequently involved due to the nature of portal blood flow [8].

The signs and symptoms of liver CE include hepatomegaly, abdominal distention, right upper quadrant/epigastric pain, nausea, vomiting, loss of appetite, and weight loss. Growing cysts can cause portal vein and bile duct obstruction. Cyst rupture in the peritoneal cavity can lead to secondary CE. Rupture in the biliary tree can lead to secondary cholangitis, biliary obstruction by daughter cysts, portal hypertension, ascites, and abscess formation. Cyst leakage or rupture can lead to a systemic immunological response and a life-threating anaphylactic reaction induced by sensitization from a previous leakage into the systemic circulation during the life of the cyst [7].

Diagnosis

The diagnosis of CE is based on history, clinical examination, imaging, and serologic testing. The vast majority of cases are usually found incidentally on imaging. In the case of symptomatic patients, a careful medical history should be obtained that focuses on contact with dogs or wild animals as well as living in endemic areas. Proper physical exam should be conducted, and liver imaging with or without serology testing is usually needed to confirm the diagnosis. In most cases, an ultrasound is sufficient to make the diagnosis. When in doubt, serological tests are available with variable sensitivity based on cyst location, size, and stage. Clinical laboratory tests are nonspecific in CE patients. Most will have normal serum liver enzymes tests and complete blood count tests will show eosinophilia in around 40% of patients [9]. In patients that require diagnostic aspiration, sampled fluid can be sent for microscopic examination, though this is rarely indicated. Observing protoscolices and/or free hooklets confirms the diagnosis [10].

Ultrasound has played a major historical role in the diagnosis of CE. The disease was previously only detected late as complications occur or incidentally on autopsies. It is now being detected in its earliest stages in asymptomatic affected

individuals. Ultrasound has allowed for population-based surveys of CE and has uncovered the true prevalence rates across the world. It has been the preferred imaging modality in CE due to its global availability, lack of radiation, and excellent ability to diagnose stage and follow up most abdominal cysts. In addition, field surveys are easily performed with portable ultrasound as a screening tool [11]. This led to the development of classification systems based on ultrasound findings. Gharbi et al. developed the first widely implemented CE ultrasound classification system in 1981 [12]. The WHO Informal Working Group on Echinococcosis (WHO-IWGE) improved the previous system and developed in 1995 a standardized classification that can be universally applied and replaced the plethora of previous classifications [13]. The WHO system divides the cysts into three categories: active, transitional, and inactive (Table 9.1). This classification has important implications in terms of prognosis and treatment decision-making [14]. CE1 and CE2 are active, usually fertile cysts with viable protoscoleces. CE3 is classified as transitional and is divided into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). Some studies based on magnetic resonance spectroscopy (MRS) have suggested that CE3b are usually viable and should be considered more active as compared to CE3a that tend to be more transitional and equally likely to be viable or nonviable [14]. CE4 and CE5 are considered inactive.

Cysts can also be assessed using other modalities including computed tomography (CT) and magnetic resonance imaging (MRI). MRI is superior to CT in detecting the structural components and stage-defining features of cysts that are usually seen on ultrasound. However, it has a limited role in detecting cyst wall calcification. MR cholangiopancreatography (MRCP) plays a role in the preoperative evaluation of cysto-biliary fistulas. It has been reported that it can be as sensitive as endoscopic retrograde cholangiopancreatography (ERCP) in detecting biliary obstruction as a noninvasive technique [10].

Table 9.1 World Health Organization Informal Working Group (WHO-IWG) ultrasound classification of cystic echinococcosis

Cyst	Status	Ultrasound features
CE1	Active	Unilocular simple cyst with uniform anechoic content
CE2	Active	Multivesicular multiseptated cysts Daughter cysts may partly or completely fill the mother cyst
CE3a	Transitional	Anechoic content with detached laminated membrane Floating membrane "water-lily" sign
CE3b	Transitional	Unilocular cyst with anechoic daughter cysts and echoic areas "Complex mass" appearance
CE4	Inactive	Heterogeneous hypoechoic cyst without daughter cysts "Ball of wool" indicating degenerative membrane
CE5	Inactive	Thick calcified wall with cone-shaped shadow

Adapted from 2003 World Health Organization Informal Working Group (WHO-IWG) International classification of ultrasound images in cystic echinococcosis [15]

Treatment

The available treatment options for CE include surgery, percutaneous drainage, chemotherapy, and the "watch and wait" approach. The decision to choose the best therapeutic approach should be based on the cyst stage, size and location, the available medical and surgical expertise, and adherence of patients to long-term monitoring. The WHO has issued recommendations on the best treatment approach based on the cyst stage (Table 9.2). However, despite the WHO attempts, a consensus is still lacking on a standardized disease management for CE. The best individual treatment option for patients is still controversial as the evidence supporting any of the four available modalities from solid clinical studies is limited. The reasons are mainly due to the chronicity of the disease requiring years of follow-up on the effectiveness of treatment, the relatively small number of patients presenting with homogenous conditions to allow adequate comparison, and finally the heterogeneity of studies in the literature that hinders appropriate comparison [16]. The current evidence is based on small randomized trials, cohort studies, and case series with few controlled studies to compare the four treatment options [17].

Historically, surgery has been considered the only definitive curative option for CE. However curative surgery is not always feasible and has considerable risks of morbidity and relapse. The overall recurrence rate is around 6%, and mortality can range between 0.5% and 4% depending on the type of surgery and the available surgical experience and medical facility [18]. In addition, surgery cannot be applied in cases where general contraindications for surgery apply such as pregnancy and very small or unreachable cysts. PAIR (puncture-aspiration-injection-reaspiration) procedure and laparoscopic surgical approach have been introduced as minimally invasive techniques, but morbidity, recurrence, and mortality rates, albeit low, should be considered. This has paved the way for implementing less invasive

Table 9.2 Treatment of uncomplicated CE stratified by cyst stage

Cyst	Surgery	Percutaneous	Medical therapy	Watch and wait	Expert consensus recommendation
CE1		✓	✓		< 5 cm ABZ > 5 cm PAIR + ABZ
CE2	✓	✓	✓		Other PT + ABZ Or surgery + ABZ
CE3a		✓	✓		< 5 cm ABZ > 5 cm PAIR + ABZ
CE3b	✓	✓	✓		Other PT + ABZ Or surgery + ABZ
CE4				✓	
CE5				✓	

Adapted and reprinted from 2010 WHO Informal Working Group on Echinococcosis (WHO-IWGE) stage-specific treatment approach [13] with permission from Elsevier
Abbreviations: *ABZ* albendazole, *PAIR* puncture, aspiration, injection, reaspiration, *Other PT* other percutaneous procedure

treatment strategies such as the "wait and observe" approach and the option of medical therapy.

Asymptomatic hydatid cyst can be defined as the incidental finding of a cyst in patients who do not have any symptoms or have symptoms not attributed to CE. The diagnosis can be made during ultrasound or other imaging techniques for other abdominal conditions or during mass surveys for CE in endemic areas [18]. Mass ultrasound surveys allowed a better understanding of the natural course of the disease and demonstrated that the vast majority of cases are asymptomatic at diagnosis. The current practice is that all asymptomatic hydatid cysts must be subjected to a type of treatment. The rationale behind such belief is the fear for any future complications that can happen if the cyst is left untreated. This practice, however, is not supported by strong evidence [19]. The major risk for any hepatic hydatid cyst is the possibility of rupture and leakage which can lead to serious complications such as anaphylactic shock and seeding to nearby structures. The host's defenses, however, are capable of containing the disease leading to cyst calcification which can remain dormant and inactive for years. The questions remain if asymptomatic hydatid cysts should be treated, what the best treatment approach would be, and if there is a role for nonoperative management.

The "Watch and Wait" Approach

The "watch and wait" approach corresponds to regular ultrasound follow-up on an asymptomatic uncomplicated hydatid cyst without any further interventions. According to the WHO-IWG guidelines, it is the current recommended approach for CE4 and CE5 inactive cysts. This recommendation was based on long-term follow-up of asymptomatic hydatid cysts, and it was shown that the majority of patients remain symptom-free for years with a low risk for complications. The widespread use of ultrasound and the incidental detection of asymptomatic hydatid cysts lead to a controversy on the best way to manage them. The current evidence to support a "watch and wait" approach is still based on a limited number of studies with a small number of patients [18]. In recent years, experience at some referral centers showed promising results to support a watchful approach to asymptomatic cysts. A study at a referral center in Italy using an ultrasound-based follow-up of at least 2 years on 53 patients with 66 inactive cysts (CE4 and CE5) showed that 52 (98.1%) patients remained stable with no complications and only one patient (1.9%) had a documented reactivation [20]. Such an approach would have promising socioeconomic implications in managing large numbers of asymptomatic carriers, especially in endemic areas. Adapting this strategy requires close follow-up with ultrasound monitoring to avoid unnecessary treatment and/or the risk of any therapeutic intervention. A prospective survey was carried in an endemic area on 127 patients with 137 liver cysts with a median follow-up of 6 years. It showed that while 81% of the cysts have favorable outcomes, 5.8% of the cysts developed complications, and the size increased in 13% [19]. This highlights the importance of close monitoring as experts recommend a minimum

follow-up of 5 years to confirm the stability of inactive cysts [21]. Another study on the "watch and wait" showed that this approach is also feasible on CE3b cysts [16]. To note, cysts that reached inactivity by means of medical treatment have a higher relapse rate (up to 50% within 2 years) as compared to naturally inactivated cysts and should be followed up more closely [21]. The exact biological mechanism to explain the process of inactivation or reactivation remains unknown. Clinical experiences in recent years have suggested that a conservative approach for selected asymptomatic hydatid cysts is reasonable. This was based on the observation that a good proportion of cysts becomes calcified and inactivated without treatment, and asymptomatic cysts that do not affect nearby structures seem to stabilize and remain quiescent. However, it is important to stress on the necessity of an adequate and regular follow-up using ultrasound in addition to a good doctor-patient relationship when the "watch and wait" approach is selected. Currently, this option should be offered to selected patients with CE4 and CE5 cysts. The evidence for this appealing approach is still far from ideal and deserves better evaluation to specify the indications and limitations.

Medical Therapy

The current available options for medical therapy are the benzimidazoles (albendazole and mebendazole) and praziquantel. The introduction of benzimidazole as a main treatment option has been a landmark in the management of CE. Heath et al. were the first to establish a larvicidal effect of mebendazole (MBZ) in animal models in 1975 [22]. After that, mebendazole was introduced in small clinical trials, and Bekhti et al. reported the first successful results of treating CE with MBZ in 1977 [23]. High doses were required to achieve a pharmacological effect. Albendazole (ABZ) was later introduced, and it was shown that its metabolite albendazole sulfoxide has its own active larvicidal effect enabling more practical dosing regimens [24]. They both inhibit microtubules formation, with impairment of glucose absorption through the wall of the germinative cell layer of the larva. This leads to glycogen depletion and degeneration of the endoplasmic reticulum and mitochondria of the germinal cells leading to an increase in lysosomes and eventually cellular death [24]. The WHO guidelines of 1996 have played a key role in promoting the role of benzimidazole as an important therapeutic option in the management of CE. This expanded the design and conduction of clinical trials to assess the activity of MBZ and ABZ against the parasitic disease.

Praziquantel (PZQ) is an isoquinoline discovered in the 1980s to have antiparasitic activity against CE. It was introduced as a more tolerated and less toxic therapeutic agent than the benzimidazoles. It increases the permeability of the parasite's cell membrane to calcium leading to strong contraction and paralysis of its musculature resulting in detachment from the host tissue [24]. PZQ was demonstrated to have an active scolicidal activity in vitro and in animal models. Few clinical studies, however, have analyzed its use in hydatid disease as a monotherapy or in combination with benzimidazoles.

The Role of Medical Therapy

Currently, the role of medical therapy in CE is highlighted in the WHO recommendations. The indications and the suggested medical therapy are summarized in Tables 9.3 and 9.4.

The value of medical agents in CE can be appreciated as a nonoperative, noninvasive treatment option. As previously discussed, complete curative surgery is not always feasible. There is a risk of relapse when choosing the options of surgery or PAIR, as well as a small but significant mortality risk. Antiparasitic drugs can be used on patients of any age and are not limited by the status of the patient as compared to surgery or PAIR. The role of medical treatment was mainly recommended for inoperable patients and patients with multiple organ involvement. Over the past decade, several studies have emphasized the role of chemotherapy as an alternative to operative management in uncomplicated cysts, increasing the use of medical drug therapy over the years. As with CE in general, the evidence to support chemotherapy is limited and based on a few randomized trials and case series with abundant heterogeneity among studies. Randomized studies have shown the superiority of albendazole when compared to mebendazole or placebo [25]. Although poorly absorbed from the gastrointestinal tract, ABZ reaches higher plasma concentration as compared to MBZ (15–49 times higher); thus lower daily doses are required. ABZ is metabolized in the liver, and the primary metabolite has also anthelminthic activity [26].

Benzimidazole use is expected to cure around 30% of patients. Another 30 to 50% will show signs of cyst degeneration and/or cyst reduction. However, 20 to 30% will show no changes with chemotherapy after 12 months of follow-up [18]. Franchi et al. [25] studied the effect of benzimidazoles on 929 hydatid cysts (from 448 patients) that were followed up for at least 1 year. They showed that 74% of the cysts treated with MBZ and ABZ had detectable degenerative changes, whereas 26% remained unchanged. Those changes were more frequent in the ABZ-treated than in MBZ-treated cysts (82.2% vs. 56.1%). Stojkovic et al. [27] reviewed data collected from 711 patients with 1308 cysts from 6 centers. They showed that after 1–2 years of benzimidazole therapy, 50–75% of active CE1 cysts can be classified as inactive or disappeared. CE2 and CE3 cysts were found to be less responsive (30% to 55%). They also observed multiple

Table 9.3 Indications for antiparasitic drug treatment in CE according to WHO-IWGE

Inoperable patients with liver CE
Patients with multiple cysts in two or more organs or peritoneal cysts
Small (<5 cm) CE1 and CE3a cysts
Prevention of recurrence following surgery or PAIR

Adapted from 2010 WHO Informal Working Group on Echinococcosis (WHO-IWGE) stage-specific treatment approach [13]
Abbreviations: *CE* cystic echinococcosis, *PAIR* puncture, aspiration, injection, reaspiration

Table 9.4 Suggested medical therapy protocol for cystic echinococcosis

Drug therapy	Drug	Dose	Duration
Definitive medical therapy	Albendazole	10 to 15 mg/kg/day (up to 400 mg twice daily)	Continuous for 3 to 6 months
	Mebendazole	40 to 50 mg/kg/day (three times daily)	Continuous for 3 to 6 months
	Praziquantel	40 mg/kg once weekly	In combination with albendazole for 3 to 6 months
Uncomplicated perioperative prophylaxis	Albendazole	10 to 15 mg/kg/day (up to 400 mg twice daily)	4 to 30 days preoperatively and for at least 1 month postoperatively
	Mebendazole	40 to 50 mg/kg/day (three times daily)	4 to 30 days preoperatively and for at least 3 months postoperatively
Complicated perioperative prophylaxis	Albendazole	10 to 15 mg/kg/day (up to 400 mg twice daily)	Recommend extending the postoperative course for 3 to 6 months
	Mebendazole	40 to 50 mg/kg/day (three times daily)	Recommend extending the postoperative course for 3 to 6 months

relapses with 25% of the cysts that initially responded reverting to active status within the first 2 years.

Some data showed that clinical and ultrasound improvement (> 25% reduction in cyst size, membrane separation, or cyst calcification) will increase with longer duration of therapy [7]. Previously, it was debatable whether cysts were inactivated by benzimidazoles or they spontaneously progressed to calcification, questioning the need for treatment. To study the effect of treatment, 80% of cysts in patients who were treated with albendazole in one study showed evidence of changes as compared to 13% of cysts in patients who received no treatment [28]. A surgical-based study demonstrated that pretreating with albendazole affects the cysts' viability and infectivity during surgical evaluation in mice models [29].

As suggested by the WHO recommendations, medical therapy is more effective for small CE1 and CE3a cysts. Benzimidazoles are less effective against CE2 and CE3b. Chemotherapy is also more effective among young patients. The outcome of treatment is also related to the size and age of the parasite. "Recent" small cysts with thin walls, as well as secondary cysts, are mostly susceptible to medical therapy as compared to "old" cysts with thick or calcified walls. Patients who experience relapse are sensitive to retreatment in the majority of cases [13].

Praziquantel is mentioned in a few studies in the literature to play a role for perioperative prophylaxis and in combination with albendazole for medical treatment.

It was introduced as a more tolerated, less toxic, and better-absorbed agent. A study suggested that a combination of PZQ plus ABZ for 1 month prior to surgery had a higher efficacy as compared to ABZ monotherapy [30]. While ABZ is potentially teratogenic, PZQ is safe in pregnancy. The currently available evidence is insufficient to guide the use of PZQ. Although it is ineffective as monotherapy, some evidence exists for a role of PZQ and ABZ combination [14].

Benzimidazoles have also an essential role to play when it comes to operative therapeutic options. Treatment outcomes were shown to be better when surgery or PAIR is combined with pre- and/or postprocedure benzimidazole therapy [17]. Blidik et al. [31], Gil-Grande et al. [29], Khuroo et al. [32], and Shams-UI-Bari et al. [33] studied this aspect of medical therapy and showed the significance of perioperative ABZ. They assessed the outcome of ABZ plus operative management as compared to operative management alone by analyzing the viability of scolex as an endpoint. The number of nonviable scolices was higher in the combination of ABZ and procedure as compared to operative procedure alone.

Risks and Contraindications

Benzimidazoles are contraindicated in early pregnancy and in cysts at risk of rupture (such as large or superficially located cysts). ABZ was found to be teratogenic in animal models. Although the risk of exposure in early human pregnancy is low and no abnormal birth outcomes have been recorded in humans following ABZ exposure, ABZ should be avoided in pregnancy unless the benefits significantly outweigh the potential risks [13]. Benzimidazoles should be used with caution in patients with chronic liver diseases and should be avoided in patients with bone marrow depression. Benzimidazoles monotherapy is ineffective in large cysts (>10 cm) as their effect is slow in large volumes of fluid. Calcified inactive cysts should not be treated unless they become complicated [13].

Dosage and Duration

Albendazole and mebendazole are water-soluble compounds and poorly absorbed in the gastrointestinal tract. Gastric pH and intraluminal degradation contribute to a further decrease in bioavailability. Administering PZQ with ABZ can result in a four to fivefold increase in the bioavailability of ABZ [34]. To improve absorption, benzimidazoles should be taken with fatty meals. This can lead to a four to eightfold improvement in the bioavailability of ABZ and MBZ.

Albendazole is given orally at a dose of 10 to 15 mg/kg/day in two divided doses with a fatty meal to a maximum of 400 mg twice daily. It should be administered continuously without the previously recommended cyclic treatment and weekly interruption. Long-term toxicity data was not available when ABZ was first introduced and cyclic treatment was recommended. The continuous

treatment approach was followed in several centers for years now, with no evidence of any increased adverse events [35]. In cases where ABZ is not tolerated or not available, mebendazole can be used as an alternative. It is given orally at a dose of 40 to 50 mg/kg/day in three divided doses with a fatty meal. Higher doses of MBZ are required to reach a similar drug concentration level as ABZ. Praziquantel is given in a dose of 40 mg/kg once weekly in combination with ABZ [13]. The optimal duration of medical therapy with benzimidazoles has not been formally assessed. Currently, it is recommended to give ABZ for at least 3–6 months when given as a primary treatment option. Studies on large number of patients suggested an increased evidence for clinical and/or radiological improvement when longer treatment duration is applied. However, the proportion of patients with cure, defined as calcified or disappeared cysts, did not change [36].

When ABZ is given as a perioperative prophylaxis, it is recommended to start it 1 month before surgery or percutaneous procedure and to be continued for up to 1–3 months. In case of complicated cases, some recommend continuing ABZ for 3–6 months postprocedure [37]. As discussed previously, ABZ treatment before surgery leads to a higher rate of nonviable cysts at the time of surgery. A randomized controlled trial showed that patients who received ABZ for 12 weeks prior and 12 weeks after surgery had no recurrences as compared to 17% recurrence in patients who received no medical therapy [33].

Adverse Events and Monitoring

The safety profile of benzimidazole is generally reassuring. Although the evidence is limited, adverse events are seen. Clinically, they can cause alopecia in 1–5% of cases. Gastrointestinal symptoms have been reported but are rarely severe to consider stopping treatment. Benzimidazoles have the potential to cause bone marrow suppression with reported cases of aplastic anemia and thrombocytopenia. Regular monitoring with complete blood count is required. As previously mentioned, treatment with benzimidazoles should be avoided during pregnancy as embryotoxicity and teratogenicity have been reported in animal models [38]. One of the best-known long-term effects of benzimidazoles is the rise in liver enzymes. It was reported in up to 20% of cases undergoing treatment [39]. The effect is usually limited, and liver enzymes normalize after treatment cessation. Although there is a possibility for drug-induced hepatocellular damage, it is believed that the rise in enzymes is due to the damage to the parasite and the local release of antigens by the antiparasitic drugs. Elevated liver transaminases are not seen, for example, when benzimidazoles are used to treat extra-hepatic echinococcal cysts or neurocysticercosis [39]. A retrospective study on the effect of benzimidazoles on liver function showed that the majority (85%) of elevated liver enzymes cases had liver cysts with associated structural changes [40]. Currently, it is recommended to monitor liver enzymes while on treatment, and unless changes are progressive, treatment can be continued. As previously discussed, monitoring

should be individualized as no clear evidence-based approach is currently available. It depends on the available resources and patient characteristics. Ultrasound follow-up (alternatively CT or MRI can also be used) at intervals of 3–6 months should be applied until stability is reached. After that, yearly ultrasound monitoring is advised to screen for recurrence. If stable, screening can be discontinued after 3–5 years.

Conclusion

In conclusion, the management of liver hydatid cysts remains controversial. The approach to treatment should follow the stage-specific WHO recommendations. It is not clear if asymptomatic uncomplicated cysts should be subjected to a specific treatment protocol. The majority of hydatid cysts have a favorable outcome and do not always require invasive surgical or percutaneous intervention. Considering the operative morbidity and mortality risk as well as the risk of relapse, two nonoperative strategies should be recognized. The "watch and wait" approach is a safe noninvasive option that should be considered in inactive uncomplicated cysts. The current evidence supports its use on WHO stages CE4 and CE5 cysts. This approach should be coupled with a good doctor-patient relationship and regular ultrasound monitoring. Antiparasitic drug therapy has emerged as another important noninvasive treatment option. Enough experience in treating centers has allowed the regular implementation of benzimidazole-based therapy into current practice. Small cysts less than 5 cm (WHO stages CE1 and CE3a) can be treated with albendazole only with an expected favorable outcome in the majority of cases. An important limitation of the current treatment recommendations should be mentioned. While it is safe to assume that the majority of affected individuals are usually asymptomatic, most of the studies on medical therapy do not specify whether the treated patients are asymptomatic or not. Patients should be informed about the different therapeutic options and the risks and benefits of each approach. Treatment of CE should be individualized by taking into account the patient characteristics as well as the available resources and expertise. Finally, randomized clinical studies are needed to compare the different treatment options to provide evidence-based guidance for treatment decision-making.

References

1. Echinococcosis [Internet]. World Health Organization. World Health Organization; 2018 [cited 2019Mar23]. Available from: https://www.who.int/echinococcosis/en/.
2. Chrieki M. Echinococcosis--an emerging parasite in the immigrant population. Am Fam Physician. 2002;66(5):817–20.
3. Jenkins DJ, Romig T, Thompson RC. Emergence/re-emergence of Echinococcus spp.–a global update. Int J Parasitol. 2005;35(11–12):1205–19.
4. Budke CM, Deplazes P, Torgerson PR. Global socioeconomic impact of cystic echinococcosis. Emerg Infect Dis. 2006;12(2):296–303.

5. Moro P, Schantz PM. Cystic echinococcosis in the Americas. Parasitol Int. 2006;55(Suppl):S181–6.
6. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. Bull World Health Organ. 1996;74(3):231–42.
7. Nunnari G, Pinzone MR, Gruttadauria S, Celesia BM, Madeddu G, Malaguarnera G, et al. Hepatic echinococcosis: clinical and therapeutic aspects. World J Gastroenterol. 2012;18(13):1448–58.
8. Pakala T, Molina M, Wu GY. Hepatic echinococcal cysts: a review. J Clin Transl Hepatol. 2016;4(1):39–46.
9. Symeonidis N, Pavlidis T, Baltatzis M, Ballas K, Psarras K, Marakis G, et al. Complicated liver echinococcosis: 30 years of experience from an endemic area. Scand J Surg. 2013;102(3):171–7.
10. Agudelo Higuita NI, Brunetti E, McCloskey C. Cystic Echinococcosis. J Clin Microbiol. 2016;54(3):518–23.
11. Brunetti E, Tamarozzi F, Macpherson C, Filice C, Piontek MS, Kabaalioglu A, et al. Ultrasound and cystic echinococcosis. Ultrasound international open. 2018;4(3):E70–e8.
12. Gharbi HA, Hassine W, Brauner MW, Dupuch K. Ultrasound examination of the hydatic liver. Radiology. 1981;139(2):459–63.
13. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114(1):1–16.
14. Brunetti E, Junghanss T. Update on cystic hydatid disease. Curr Opin Infect Dis. 2009;22(5):497–502.
15. WHO Informal Working Group. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Trop. 2003;85(2):253–61.
16. Rinaldi F, De Silvestri A, Tamarozzi F, Cattaneo F, Lissandrin R, Brunetti E. Medical treatment versus "Watch and Wait" in the clinical management of CE3b echinococcal cysts of the liver. BMC Infect Dis. 2014;14:492.
17. Velasco-Tirado V, Alonso-Sardon M, Lopez-Bernus A, Romero-Alegria A, Burguillo FJ, Muro A, et al. Medical treatment of cystic echinococcosis: systematic review and meta-analysis. BMC Infect Dis. 2018;18(1):306.
18. Frider B, Larrieu E. Treatment of liver hydatidosis: how to treat an asymptomatic carrier? World J Gastroenterol. 2010;16(33):4123–9.
19. Saidi F, Habibzadeh F. The non-operative management of asymptomatic liver hydatids: ending echinococcophobia. J Gastrointest Surg. 2018;22(3):486–95.
20. Lissandrin R, Tamarozzi F, Mariconti M, Manciulli T, Brunetti E, Vola A. Watch and wait approach for inactive echinococcal cyst of the liver: an update. Am J Trop Med Hyg. 2018;99(2):375–9.
21. Stojkovic M, Rosenberger KD, Steudle F, Junghanss T. Watch and wait management of inactive cystic echinococcosis - does the path to inactivity matter - analysis of a prospective patient cohort. PLoS Negl Trop Dis. 2016;10(12):e0005243.
22. Heath DD, Christie MJ, Chevis RA. The lethal effect of mebendazole on secondary Echinococcus granulosus, cysticerci of Taenia pisiformis and tetrathyridia of Mesocestoides corti. Parasitology. 1975;70(2):273–85.
23. Bekhti A, Schaaps JP, Capron M, Dessaint JP, Santoro F, Capron A. Treatment of hepatic hydatid disease with mebedazole: preliminary results in four cases. Br Med J. 1977;2(6094):1047–51.
24. Kern P. Medical treatment of echinococcosis under the guidance of Good Clinical Practice (GCP/ICH). Parasitol Int. 2006;55(Suppl):S273–82.
25. Franchi C, Di Vico B, Teggi A. Long-term evaluation of patients with hydatidosis treated with benzimidazole carbamates. Clin Infect Dis. 1999;29(2):304–9.
26. Smego RA Jr, Sebanego P. Treatment options for hepatic cystic echinococcosis. Int J Infect Dis. 2005;9(2):69–76.

27. Stojkovic M, Zwahlen M, Teggi A, Vutova K, Cretu CM, Virdone R, et al. Treatment response of cystic echinococcosis to benzimidazoles: a systematic review. PLoS Negl Trop Dis. 2009;3(9):e524.
28. Keshmiri M, Baharvahdat H, Fattahi SH, Davachi B, Dabiri RH, Baradaran H, et al. Albendazole versus placebo in treatment of echinococcosis. Trans R Soc Trop Med Hyg. 2001;95(2):190–4.
29. Gil-Grande LA, Rodriguez-Caabeiro F, Prieto JG, Sanchez-Ruano JJ, Brasa C, Aguilar L, et al. Randomised controlled trial of efficacy of albendazole in intra-abdominal hydatid disease. Lancet. 1993;342(8882):1269–72.
30. Cobo F, Yarnoz C, Sesma B, Fraile P, Aizcorbe M, Trujillo R, et al. Albendazole plus praziquantel versus albendazole alone as a pre-operative treatment in intra-abdominal hydatisosis caused by Echinococcus granulosus. Trop Med Int Health. 1998;3(6):462–6.
31. Bildik N, Cevik A, Altintas M, Ekinci H, Canberk M, Gulmen M. Efficacy of preoperative albendazole use according to months in hydatid cyst of the liver. J Clin Gastroenterol. 2007;41(3):312–6.
32. Khuroo MS, Dar MY, Yattoo GN, Zargar SA, Javaid G, Khan BA, et al. Percutaneous drainage versus albendazole therapy in hepatic hydatidosis: a prospective, randomized study. Gastroenterology. 1993;104(5):1452–9.
33. Arif SH, Malik AA, Khaja AR, Dass TA, Naikoo ZA. Role of albendazole in the management of hydatid cyst liver. Saudi J Gastroenterol. 2011;17(5):343–7.
34. Garcia HH, Lescano AG, Lanchote VL, Pretell EJ, Gonzales I, Bustos JA, et al. Pharmacokinetics of combined treatment with praziquantel and albendazole in neurocysticercosis. Br J Clin Pharmacol. 2011;72(1):77–84.
35. Horton J. Albendazole for the treatment of echinococcosis. Fundam Clin Pharmacol. 2003;17(2):205–12.
36. Stojkovic M, Weber TF, Junghanss T. Clinical management of cystic echinococcosis: state of the art and perspectives. Curr Opin Infect Dis. 2018;31(5):383–92.
37. Bhutani N, Kajal P. Hepatic echinococcosis: a review. Ann Med Surg. 2018;36:99–105.
38. Bradley M, Horton J. Assessing the risk of benzimidazole therapy during pregnancy. Trans R Soc Trop Med Hyg. 2001;95(1):72–3.
39. Junghanss T, da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. The American journal of tropical medicine and hygiene. 2008;79(3):301–11.
40. Teggi A, Giattino M, Franchi C, Lastilla M. A hypothesis on the significance of an increase in serum transaminases in patients with hydatidosis treated with benzimidazole carbamates. Recenti Prog Med. 1997;88(10):452–8.

Management of Thoracic Hydatid Disease and Its Complications

10

Alberto R. Ferreres

Introduction

Hydatid disease of the lung or lung echinococcosis is caused due to an infection with the cestode *Echinococcus granulosus* predominantly. The three types of echinococcosis are cystic echinococcosis caused by *E. granulosus*, alveolar echinococcosis caused by *E. multilocularis*, and polycystic echinococcosis caused by *E. vogeli* or *E. oligathrus*, being the first one the predominant, by far [1].

The term hydatid recognizes its first use from the French *hydate* around 1680, which comes from the Greek *hydatis/hydatos*, meaning vesicle with serous liquid, and this last, from *hydor/hydatos*, which means water or liquid.

This parasite has been known from the times of Hippocrates and Galen. Magnúson described the presence of the *E. granulosus* in German dogs circa 1200, but the first description belongs to the German anatomist Adam Christian Thebesius (1686–1732) in the seventeenth century. Zabert and Van Deinsen considered this disease to have originated in Iceland and introduced to Europe by the dogs of whale hunting ships [2]. In 1808 Karl Asmund Rudolphi (1771–1832), known as the "father of helminthology," was the first one to coin the term "hydatid cyst" to refer to the disease in humans [3].

In 1889, John Davies Thomas (1844–1893), an Australian surgeon based in Adelaide, was the first to propose the surgical treatment of pulmonary hydatidosis [4, 5]. Some years later, in 1899, Alejandro Posadas (1870–1902) performed in Buenos Aires, Argentina, a thoracic procedure for the treatment of hydatid disease in what is considered the first recorded surgical procedure in world surgery [6]. His technique included the performance of a thoracoplasty with the "harpooning" or "anchorage" of the lung to prevent its collapse and the aperture of the pericystic layer to remove the germinative layer and the cyst content [7].

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Parasite Biology and Cycle

The life cycle of *E. granulosus* requires two host types, an intermediate and a definitive one. The first are represented most commonly by sheep, however cattle such as horses, goats, pigs, and camels may be potential intermediate hosts. Humans are intermediate but accidental or aberrant intermediate hosts due to infestation or contact with diseased dogs, but do not play a role in the biological cycle.

The definitive hosts are dogs or other canines, such as foxes or wolves. The adult worm inhabits the small intestine of the definitive host; the size ranges from 2 to 7 mm long and gets attached to the intestinal mucosa by a double row of hooklets placed in its scolex and has at least three proglotides with several eggs. These eggs pass out in the stool and stick to the fur or fall to the grass. They can survive for at least 1 year in the outside world, time during which they are widely dispersed, even with the help of the wind. When intermediate or accidental hosts become infected, either by contact with infected dogs or by ingestion of eggs from contaminated food, water, or soil, the embryos are released after hatching in the intestinal mucosa and then enter the portal circulation making their first station the liver, or otherwise the lung [8]. The parasite then grows to form a cyst filled with fluid. Since two mammal species are required for completion of the life cycle of the parasite, direct transmission from human to human is not possible.

The fully developed cyst is organized in three layers, composed of both host and parasite tissue:

(a) The outer layer, or pericyst, is the adventitia and is formed by inflammatory fibrous tissue from the host as a reaction to a foreign body (parasite).
(b) The middle layer is known as the exocyst or laminated layer and is an acellular membrane composed by mucopolysaccharides.
(c) The inner layer is the endocyst, which is the germinal layer of the parasite and gives rise to larvae scolices which bud internally. The fluid contained inside is antigenic and contains hooklets and scolices and is known as "hydatid sand." There is an average 5 cc of this hydatid sand which contains half a million hooklets and scolices, which indicates its huge aggressiveness.

The cyst exists in different forms: intact or ruptured, single or multiple, unilateral or bilateral, exclusively located in the lung or in other locations (the liver, pleura, pericardium, rib cage, spine, etc.). The hydatid cysts are able to grow faster and larger in the lung due to the structure of these organs, which is easily collapsible, in comparison to the liver parenchyma.

The hydatid cyst can be classified according to its morphology:

- Type I: simple cyst
- Type II: cyst with daughter cysts and matrix
  - Daughter cysts at the periphery.
  - Larger daughter cysts which fill most of the mother cyst.
  - Cyst with calcifications and daughter cysts. Calcifications in the lung are partial and in spots, quite different from the calcification of liver cysts.
- Type III: calcified cyst, which means that the cyst is not viable, and cannot infect the host
- Type IV: complicated cyst, e.g., ruptured cyst

Epidemiology

Cystic echinococcosis can be seen worldwide, while endemic areas are represented by South and Central America, the Middle East, North and sub-Saharan Africa, Eurasia, Australia and New Zealand, China, and Russia [9].

A huge distinction needs to be made with alveolar echinococcosis caused by *E. multilocularis*, which is significantly less frequent than hydatid disease by *E. granulosus*. Definitive hosts include small rodents and the borders of endemic areas of alveolar echinococcosis never cease to expand [10].

Regarding the geographical distribution in Argentina, 30% of our territory carries risk of infection (1.271.912 km2) and 8% of our entire population (about 2.850.000 inhabitants) are at risk for acquiring the disease [11].

In children, the lung is the most common location for the cystic hydatid disease [12]; 20 to 40% of patients with thoracic involvement also present with liver cysts [13]. According to a multicenter Argentinian experience, 30% are multiple pulmonary cysts, 20% are bilateral, and 60% are located in lower lobes [14].

Clinical Presentation and Diagnosis

Pulmonary hydatidosis is the second most frequent location of cystic hydatid disease caused by *E. granulosus*. The lower lobes are more frequently affected than the upper ones, and one in five cases are bilateral. The size ranges from 1 to 20 cm and is the organ where hydatid cyst can become the largest due to the easy compressibility of lung tissue. Calcification of lung hydatid cysts is very rare, contrary to the liver ones.

Pulmonary hydatid cysts can present themselves in a variety of ways, making the diagnosis difficult and requiring high suspicion from the physician. The background of the patient in reference to the birthplace and residence in rural regions is very important and should be particularly targeted. Lung cysts may remain asymptomatic and thus silent for years, appearing when chest X-rays are requested for screening or due to other reasons. Initial symptoms include cough, discomfort, chest pain, fever, and hemoptysis. The development of an anaphylactic reaction and the appearance of vomiting are indicative of rupture of the cyst. In this latter case, the sputum direct study may reveal the presence of echinococcus granulosus' hooklets. When confronted with an initial thoracic hydatid cyst, it is mandatory to preclude the presence of a liver location [15].

A simple chest X-ray may provide the first suspicion and let the treating team know if this is a complicated or non-complicated cyst. Next diagnostic steps include serology together with imaging modalities, such as ultrasound and CT scans not only of the thorax but also of the abdominal and pelvic cavity.

Serological tests include the following modalities:

- Casoni intradermal reaction and complement fixation test have been abandoned in clinical practice.
- Indirect hemagglutination test: it is positive in just 50% of patients with pulmonary hydatidosis and in 90% of those with liver cysts. False-positive reactions with other helminthic diseases should be taken into account.

- Arc 5 test: this test measures antibodies against antigen 5, which is a major parasite antigen found in the inner aspect of the germinal layer, in daughter vesicles (brood capsule) and protoscolices. It achieves low sensibility but high specificity, and the subunit 8 kDa (located in the protoscolices) offers greater specificity [16]. Nonetheless the sensibility for lung hydatid cysts is in the range of 35%.
- ELISA (enzyme-linked immunosorbent assay): the immunoglobulin G enzyme-linked immunosorbent assay test represents the most sensitive technique. When this test shows a positive result, it should be confirmed by a western blot determination.

The diagnosis is usually performed by combining the clinical background, serology, and imaging modalities. It is important to highlight the role of screening X-ray examinations among the population in endemic places [17].

Differential diagnosis includes tuberculoma or tuberculous cavern, malignant tumor (primary or metastatic), lung abscess, bronchopulmonary infections, Wegener's granulomatosis, bronchiectasis, pneumothorax, and empyema, among others.

Puncture is not recommended due to the risks of cyst rupture, anaphylactic reaction, and risk of seeding the pleural cavity. Bronchoscopy is usually not necessary; besides the location of the cysts tends to be peripheral and not central.

Plain chest radiograph is helpful and may provide useful information regarding the status of a pulmonary hydatid cyst. When the cyst is intact, the typical image is that of a round or oval mass with clean borders surrounded by normal lung tissue (Figs. 10.1 and 10.2). The size may be variable and sometimes is not single. Sometimes the cyst shows an air-fluid level (Fig. 10.3). When the cyst is ruptured or infected, the typical image achieves the "water lily" or "hyacinth" sign. Due to the rupture or if bronchial erosion has occurred, an air fluid level can be found or the thin crescent or meniscus sign. From a clinical point of view, the patient will present with vomiting, with expulsion of cyst content (scolices and daughter vesicles).

Rupture or perforation of a pulmonary cyst represents its most frequent complication, with an incidence close to 50% of the cases. In 90% of the cases, the rupture is to the bronchial tree, and in the rest of the cases, the opening is toward the pleural cavity. The CT can provide further details as can be seen in Figs. 10.4 and 10.5 ("water lily sign" and presence of parasites). Two conditions should be considered regarding the hydatid cyst rupture: (a) the adventitial layer of lung cysts does not develop as well as in the liver and is more prone to rupture, and (b) the increase in the size of the cyst causes an increase in the intrathoracic pressure and can also favor the rupture. Rupture also conveys the risk of subsequent infection, with a similar course as that of a pulmonary abscess.

Simultaneous lung and liver locations for hydatid cysts are observed in less than 10% of the cases [18]; nonetheless when the patient initially presents with a thoracic location, liver involvement must be ruled out by ultrasound and CT scan.

Manterola introduced the concept of the thoracic involvement of hepatic echinococcosis, TIHE [19]. The hydatid cyst of the ruptured liver in the thoracic cavity is a rarely reported clinical entity whose frequency appears to be declining [20].

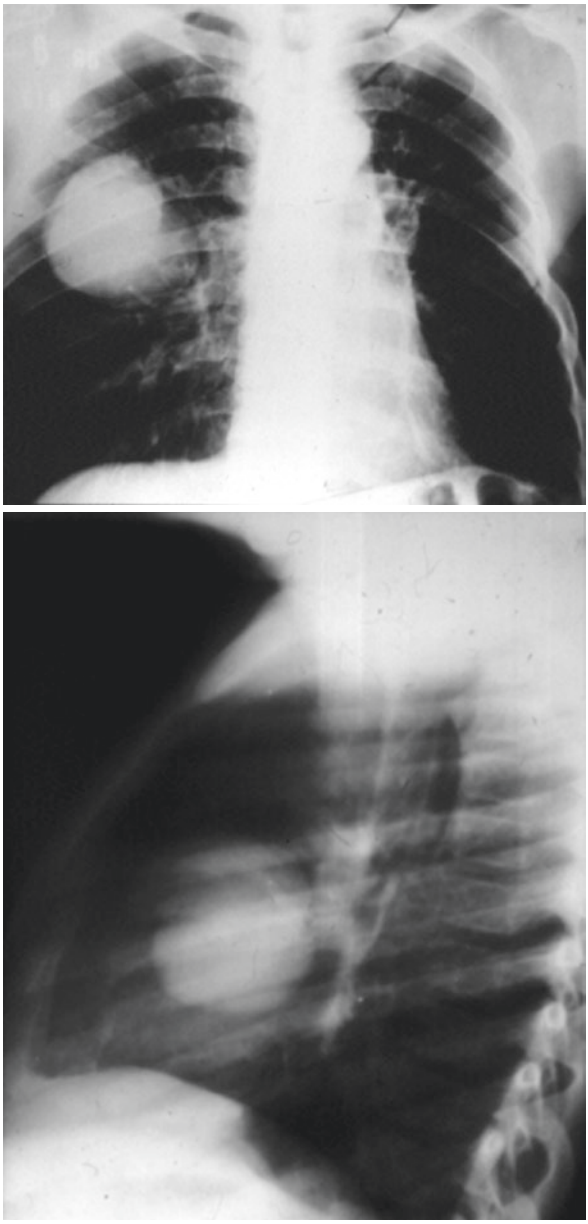


Fig. 10.1 Hydatid cyst, right lung (chest X-ray, front and profile position)

Compromise of both the liver and the thoracic cavity by hydatid cysts can be seen in Figs. 10.6, 10.7, 10.8, 10.9, and 10.10.

According to the degree of evolution of the diaphragmatic and/or thoracic involvement, the following five stages or grades have been described [13]:

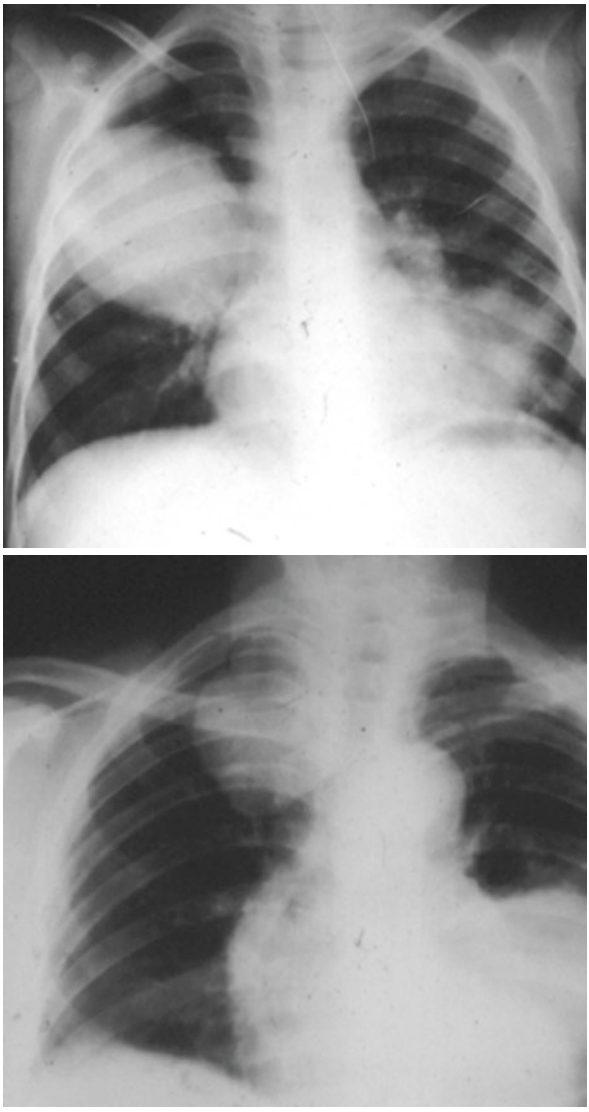


Fig. 10.2 Another case (chest X-ray, front position)

1. Adhered cyst, firm adherences between the cyst surface and the diaphragm but no perforation.
2. Hydatid transit, with perforation of the diaphragm, but little or no invasion of the thoracic cavity.
3. Pleurothoracic vesiculation, the cyst perforates the muscle and grows inside the thoracic cavity, and daughter vesicles are established in the pleura.

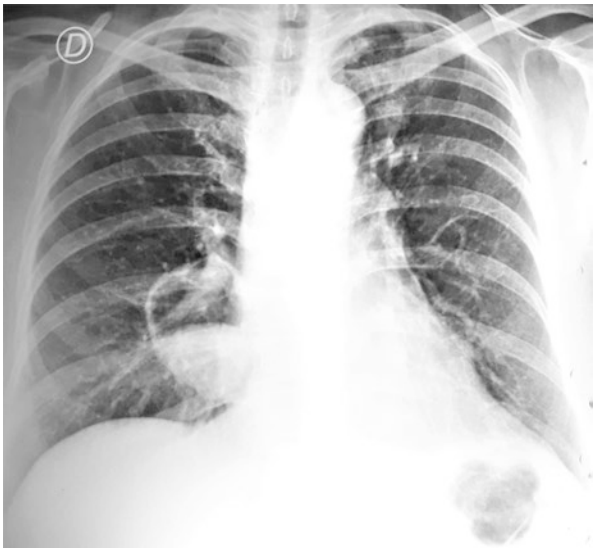


Fig. 10.3 Air/fluid level in a right lung hydatid cyst (chest X-ray front position)

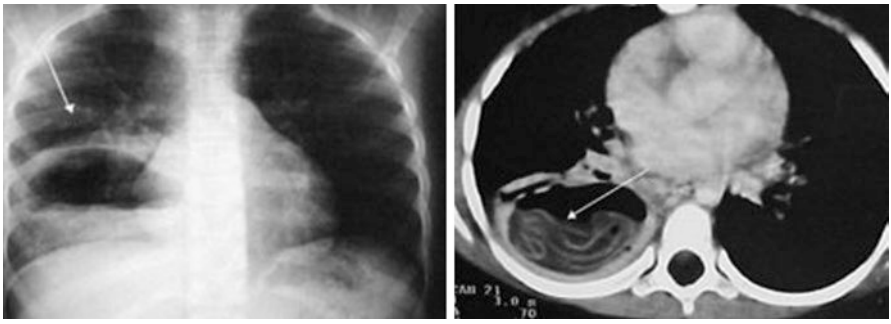


Fig. 10.4 Ruptured hydatid cyst, chest X radiograph, and CT scan (water lily sign). Parasites can be seen in the CT scan

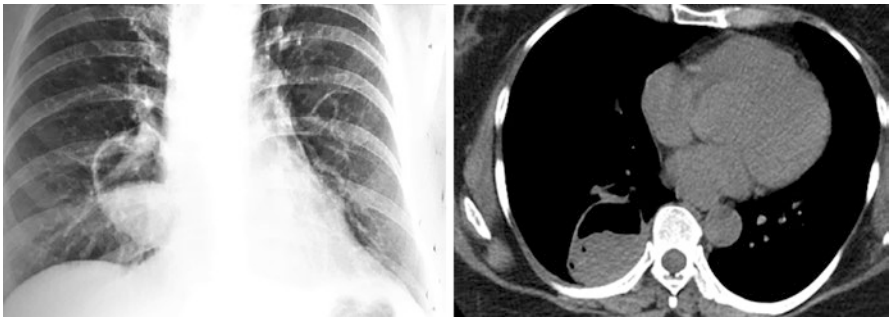


Fig. 10.5 Ruptured hydatid cyst, chest X radiograph, and CT scan (water lily sign)

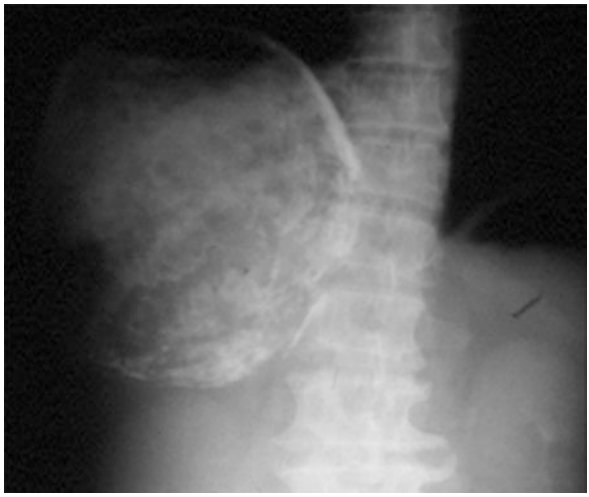


Fig. 10.6 Liver cyst with thoracic evolution (chest X-ray)

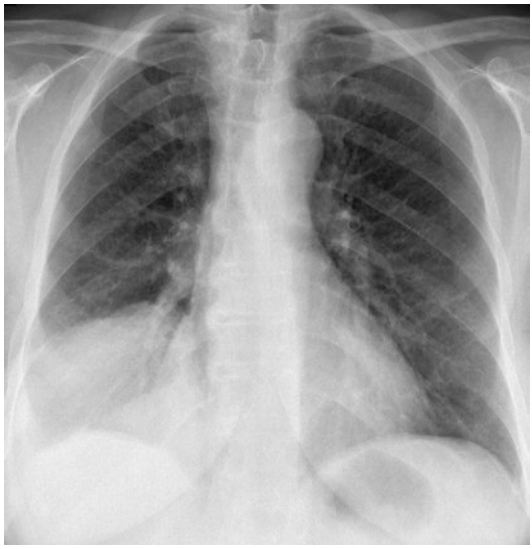


Fig. 10.7 Liver cyst with thoracic evolution (chest X-ray)

4. Disease of the pulmonary parenchyma, the cyst connects to the bronchi, or there may be compression and/or atelectasis of the pulmonary parenchyma.
5. Chronic bronchial fistula, either postoperative or usually as a result of the spontaneous evolution of the abdominal hydatid disease.

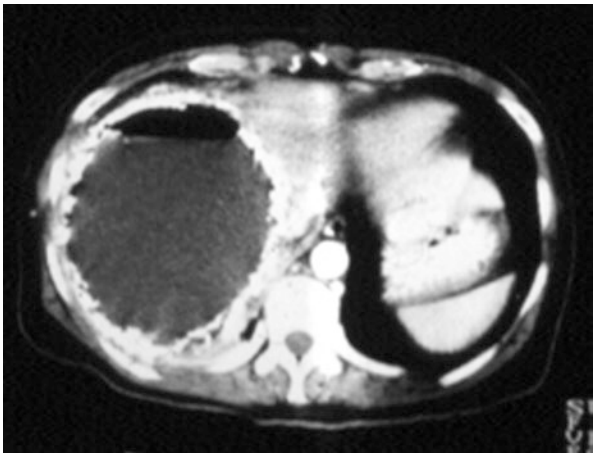


Fig. 10.8 Liver cyst with thoracic evolution (CT scan)

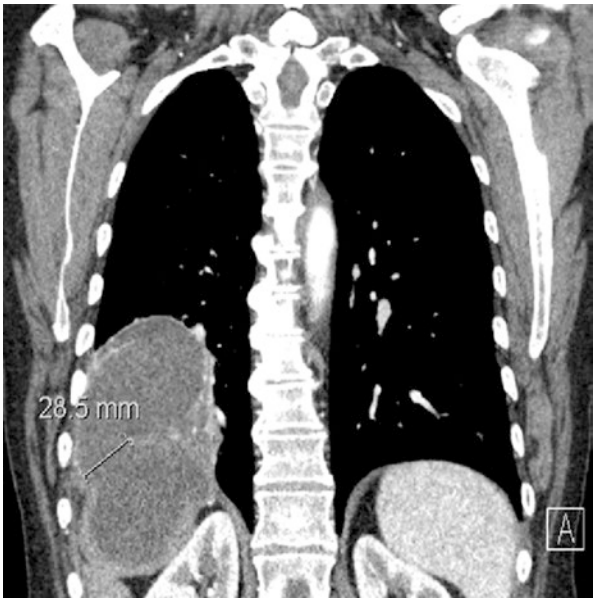


Fig. 10.9 Liver cyst with thoracic evolution (CT scan)

A condition that favors the upward migration is the negative pressure in the thoracic cavity and the obstruction of the bile duct system by parasites. Sometimes, the final evolution is the establishment of an abdominothoracic fistula, which is an uncommon but severe complication of hydatid disease. Biliptysis is pathognomonic of a biliary-bronchial fistula communication. The fistula usually is organized through trans-diaphragmatic penetration, which leads to a large cyst's rupture into the lung lower lobe. Though uncommon, the underlying cause is the perforation

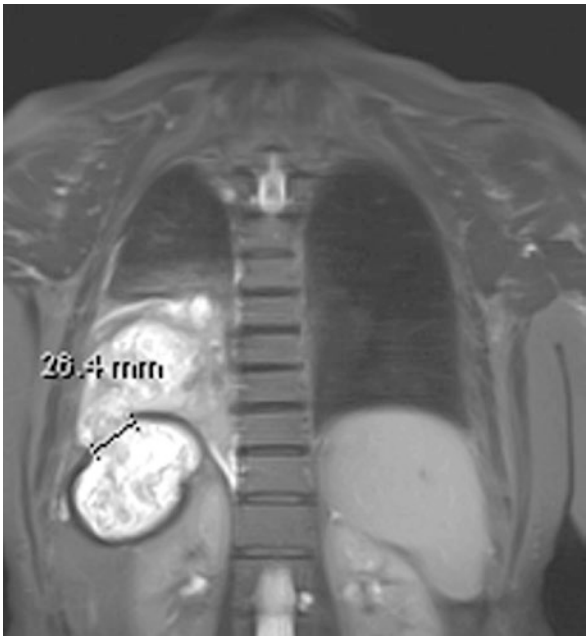


Fig. 10.10 Liver cyst with pleural and bronchial communication (CT scan)

Table 10.1 Classification of the hydatid liver cysts migrating to the lung (after Mestiri, 22)

Type I: direct fistulization of the cyst in the bronchi
IA: small-sized bronchial fistula
IB: large-caliber bronchial fistula
Type II: intrapulmonary cavern
IIA: without bronchial fistula or bronchiolar fistula
IIB: with large bronchial fistula
Type III: encysted intrapleural intermediate pocket
IIIA: without bronchial fistula
IIIB: with bronchial fistula
IIIC: with fistula on the wall
Type IV: rupture in the large pleural cavity
IVA: acute rupture: biliohydatic pleurisy
IVB: secondary pleural hydatidosis

from the right subphrenic space into the posterior basal segment of the right lower lobe [21]. Mestiri et al. proposed a classification for the migration of liver cysts to the lung emphasizing the importance of small bronchial fistulas over the biliary fistulas [22], as seen in Table 10.1.

Although calcification occurs frequently in liver cysts, it requires a lapse between 5 and 10 years at least, whereas it rarely happens in pulmonary cysts.

Other thoracic locations include the pleural cavity, the pericardium, the spine, and the rib cage. Pleural compromise can be achieved by different mechanisms: (a) spread of the cyst's (either hepatic or thoracic) content after its rupture which allows the nesting of daughter vesicles in the pleural space, (b) direct infestation with the

parasite, (c) hematogenous or lymphatic route, and (d) postoperative sequelae. Primary pleural hydatidosis is neglected by most authors [23]. The surgical treatment mandates thoracotomy and pleural decortication.

Location in the mediastinum is very rare but should be suspected in patients with a mediastinal mass coming from or living in an endemic area [24]. Surgery is mandatory due to the need to confirm the diagnosis and rule out malignancy if the images are not definitive and also due to the presence of vital structures. According to the location of the mediastinal hydatid cyst, the approach may be by right or left thoracotomy or thoracoscopy or even through a median sternotomy [25].

Pericardial hydatid involvement may be due to migration (secondary hydatidosis) or due to the rupture of a hydatid cyst located in the left heart (cardiac muscle). The role of magnetic nuclear resonance is very useful to show cardiac involvement (Fig. 10.11a, b). Pulmonary arteries are rare locations for hydatid cysts, with the most frequent cause arising from embolism originating in a primary cardiac location; another possibility is that the embryos of *Echinococcus granulosus* pass through the liver and then into the inferior vena cava and from there to the pulmonary arteries through the right cardiac chambers.

Hydatid compromise of the spine is very seldom seen [26]. CT and MRI usually show a lobulated lesion with some compromise of the epidural space of one or several thoracic vertebrae (Fig. 10.12a, b). The course is usually aggressive, with compromise of the spinal cord and thus neurological symptoms, recurrence is not infrequent, and surgery usually involves resection and vertebral instrumental stabilization [27, 28].

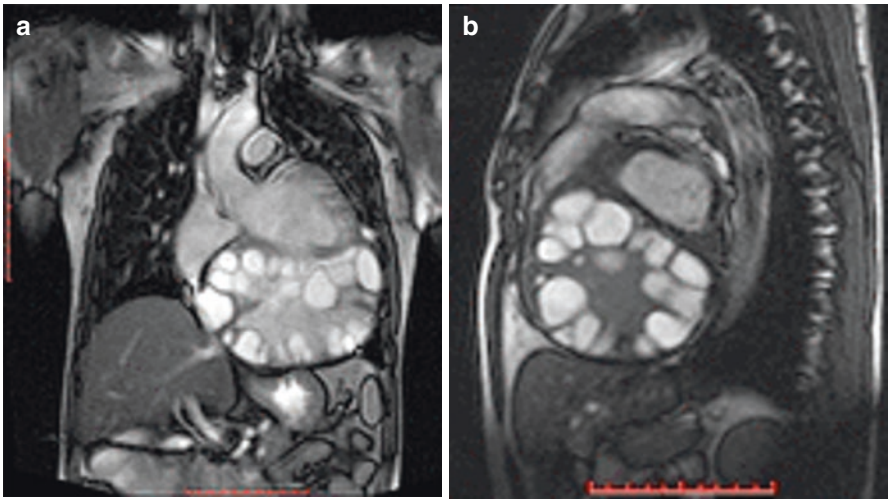


Fig. 10.11 (**a**) Pericardial hydatid disease (CT scan, sagital view). (**b**) Pericardial hydatid disease (CT scan, lateral view)

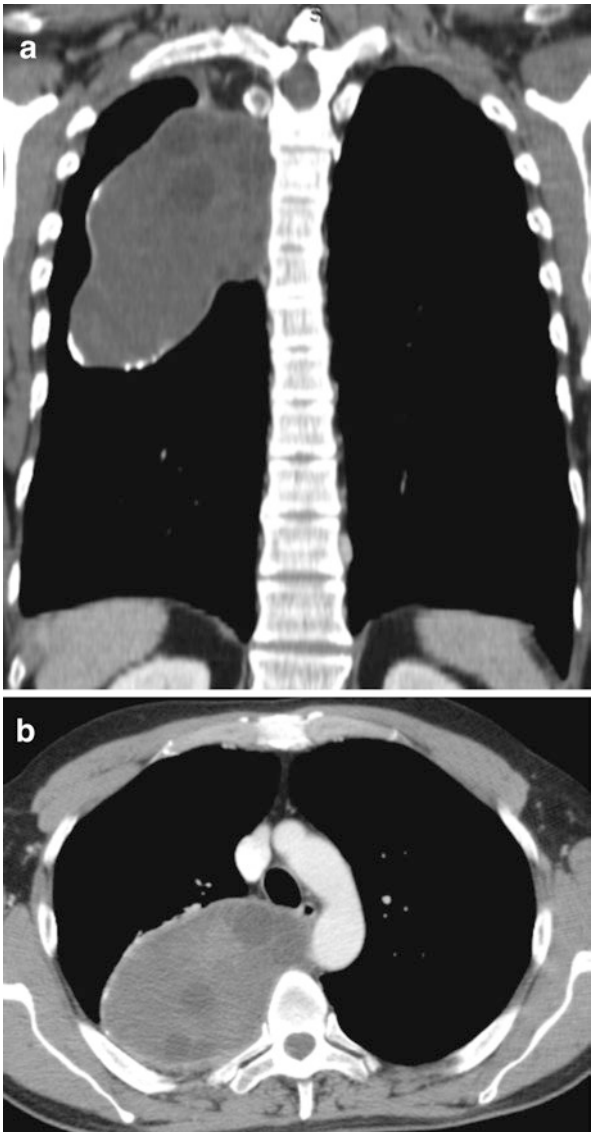


Fig.10.12 (**a**) Hydatid disease of the spine. (**b**) Hydatid disease of the spine

The chest wall is a rare location of secondary hydatidosis, but it may occur after the rupture of a lung cyst, from a liver cyst invading the diaphragm into the pleural cavity, following previous hydatid thoracic surgery, or by hematogenous spread of embryos with a diameter of less than 0.3 mm, which may escape from the liver or from the lung capillaries to involve any organ via the systemic circulation [29].

The rib location of hydatid cysts (Fig. 10.13) mandates differential diagnosis with the following entities, among others: fibrous dysplasia, tuberculosis, simple bone cysts, plasmacytoma, osteo- or chondrosarcoma, and other primary and metastatic bone tumors.

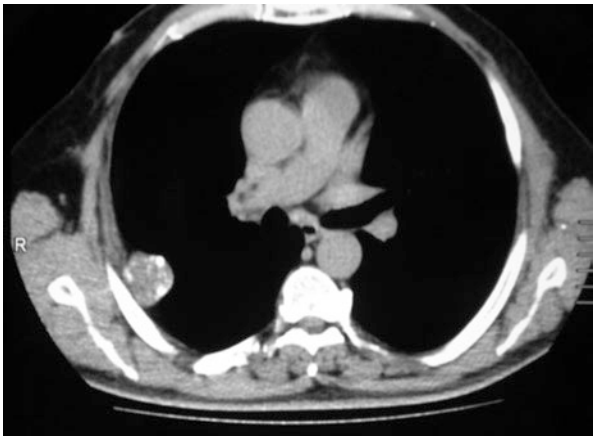


Fig. 10.13 Hydatid disease affecting the rib cage, posterior arch

Surgical Treatment

Initial treatment with albendazole before scheduled surgery is always recommended [30]. The dosage is 10 mg/kg/day twice a day, and the recommendation is after lunch and dinner rich in lipids, so as to improve absorption of the drug, with a maximum dosage of 800 mg/day [31]. If possible, preoperative prophylaxis is recommended for at least 15 days and for up to 3 months postoperatively [32].

Surgery should be considered for every thoracic hydatid cyst; initially, the surgical treatment consisted of simply performing the marsupialization of the cyst [33]. Currently, the goal of the surgical treatment for hydatid cysts of the lung is the complete excision of the disease process together with the maximum preservation of lung tissue, together with the elimination of the parasite and the prevention of recurrences and/or seedings [3]. The WHO guidelines mandate surgical intervention in the following cases: impending cyst rupture, compromise of vital organs due to mass effect, hemoptysis, secondarily infected cysts, infection due to obstruction, and unmanageable pain [34].

It is essential to prevent the contamination of the operative field due to rupture and/or spillage of the cyst's content, as its result may be the implant of scolices and the production of secondary cysts [35]. The approach maybe through a conventional or vertical thoracotomy, whereas a median sternotomy is reserved for those infrequent cases of bilateral cysts. The minimally invasive treatment of pulmonary hydatid disease was introduced by Becmeur et al. for the treatment of children [36], and though many surgeons do not feel comfortable with this access due to safety issues, the feasibility of this access has been proven by others [37, 38]. Alpay considers that video-assisted thoracic surgery treatment of pulmonary hydatid cysts is superior to conventional thoracotomy due to shorter operative time, lower chest drainage volume, shorter duration of tube placement, and less postoperative pain [39]. The minimally invasive or thoracoscopic approach is reserved for small and peripheral cysts, which after puncture and drainage are resected "en bloc" with the aid of mechanical sutures. Contraindications to this approach include larger pulmonary cysts (larger than 5/6 cm), multiple cysts and those with a hilar location.

It is important to bear in mind that the total enucleation of an unruptured pulmonary hydatid cyst, which can be safely performed in open surgery, cannot always be safely performed via a thoracoscopic approach since the small size of the incisions would prevent the safe removal of the cyst.

The conservative procedures include the following:

- Enucleation (intact endocystectomy): known as the "delivery" or the Armand Ugón technique [40], it may be used when the cyst is relatively small and not complicated, and the risk of rupture is low. The hydatid delivery requests the expertise and the attention of the whole team, including the anesthesiologist who must not ventilate the lung while the surgeon makes an opening in the adventitial layer, and introduces the finger to dissect the adherences between the cyst and the wall. After the parasite is fully freed from the surrounding tissues, the insufflation of the lungs will aid in the delivery, pushing the parasite through the air expelled through the bronchi (Fig. 10.14). Irrigation with saline solution during the whole procedure is recommended in order to prevent desiccation and a leak on the membrane [41].
- Removal after insertion of a trocar-suction device (R. Finochietto), for adequate parasite and cyst's content aspiration (Fig. 10.15). The puncture plus aspiration is a precision maneuver which necessitates avoidance of injury to the lung parenchyma, as well as spillage of the cyst's content. Care should be taken to prevent membranes falling into the pleural space.
- Cystotomy (marsupialization): is a conservative technique with usually very good results, frequently with an added capitonnage.
- Capitonnage: consists of the obliteration of the cavity with purse string sutures. There is no clear agreement regarding its use, and one of its main consequences is the distortion of the pulmonary parenchyma, especially when large cysts have been removed [42].

All the abovementioned techniques leave the adventitial layer is left in site.

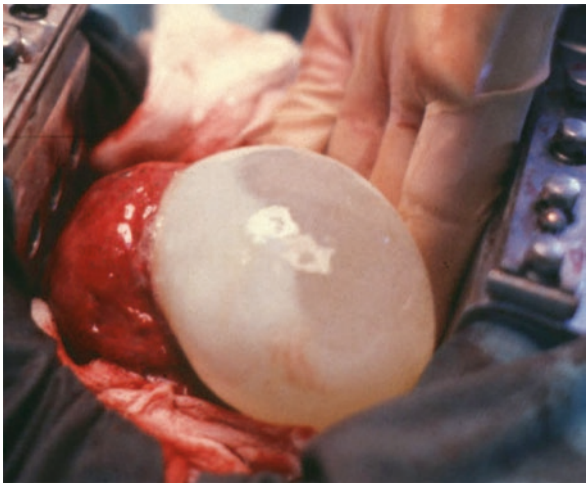


Fig. 10.14 Delivery of hydatid cyst

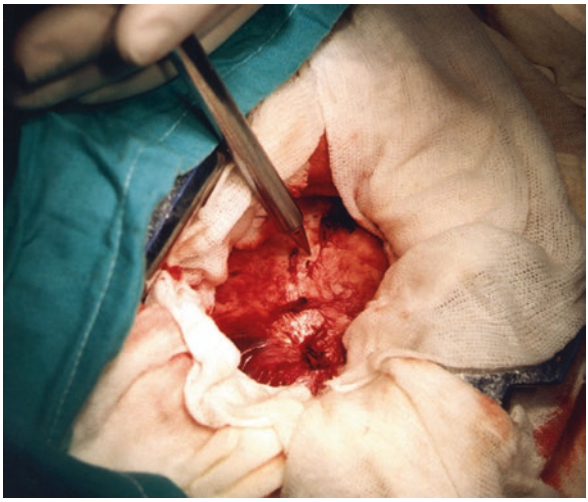


Fig. 10.15 Finochietto trocar-suction aspirator

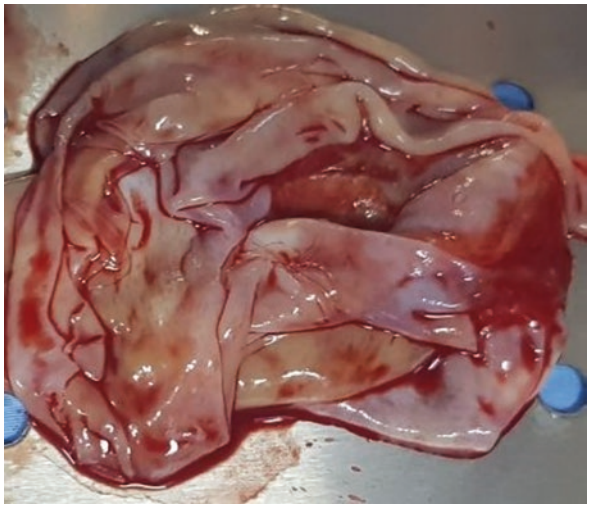


Fig. 10.16 Final result of a capsule resection (pericystectomy)

- Pericystectomy (capsule resection): known as the Pérez-Fontana method, consists in the removal of the cyst with the perycystic layer and the adventitia and the posterior obliteration of the residual cavity, Fig. 10.16 [43].

The use of the PAIR (puncture, aspiration, injection, and reaspiration) technique, originally described for the treatment of abdominal hydatid cysts, is not favored for thoracic locations since several contraindications have been reported [44].

The radical procedures, which include lung parenchymal resections, should be reserved for specific situations. They should be considered in the following cases:

- When the hydatid cysts have produced simultaneous and irreversible alterations in the surrounding lung parenchyma

- Multiple cysts in a lung segment or lobe
- When a large cyst replaces a small lobe (lingula or medium)

The options include the following:

- Pulmonary resection (e.g., "wedge"), when the size of the cyst is not large and there is no peripheral impact on the lung parenchyma.
- Segmentectomy, characterized by a high morbidity.
- Lobectomy: most of the times it is considered as the technique of choice. The surgical team should rely on this approach when confronted with large cysts involving more than 50% of the lobe, cases with severe pulmonary suppuration, multiple unilobar cysts and sequelae such as pulmonary fibrosis, bronchiectasis, and hemorrhage.
- Pneumonectomy: strictly only in cases of necessity.

Some general principles that should be taken into consideration are:

- Double lumen intubation is recommended to keep ipsilateral lung collapse during the procedure and in this way facilitate the surgical maneuvers.
- Protection of the pleura and the adjacent tissues may be achieved with towels soaked in 20% hypertonic saline solution.
- Avoidance of spillage of hydatid liquid to the bronchi.
- Injection of scolicide agents in the cyst: usually some fluid from the cyst is aspirated and replaced with hypertonic saline solution for about 15 minutes before the cyst's contents are evacuated with a powerful and wide aspirator.
- Treatment of the adventitial layer: according to the local conditions, the resection will include only the protruding or emergent part or its entirety. If the complete excision is prone to excessive risk, the remaining adventitial layer should be left on sit with a meticulous hemostasis of the borders.
- Closure of small bronchi: after the partial or full resection of the pericystic areas, and since the bronchi are opened to the cyst cavity in a tangential fashion, it is imperative to achieve a safe closure of the opening in a very thorough and detailed fashion with simultaneous irrigation and ventilation to observe bubbles from the opened bronchi. The folds of the remaining adventitial layer should be checked to prevent any bronchi from being closed. A hydrostatic test should be performed to check the closure.
- Management of the residual cavity: by means of a capitonnage or leaving it open so as to be resolved by the pulmonary expansion [45].

Intraoperative complications are represented mainly by the rupture of the hydatid cyst and bleeding. The first one is, by large, the most frequent and the cause of severe sequelae in the long-term follow-up (Fig. 10.17). All the protective measures should be taken to prevent the perforation and, if it happens, the spillage of its contents.

Postoperative complications may be *immediate* or *delayed*. Among the first ones, the bronchopleural fistula, hemopneumothorax, empyema, and atelectasis should be considered and will be briefly addressed.

- Bronchopleural fistula: usually due to an inadvertent bronchial opening that was not sutured during the operation. Usually, it tends to be self-limited and resolves

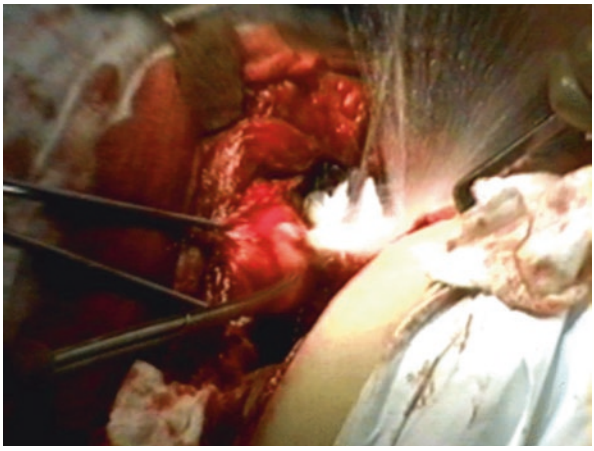


Fig. 10.17 Intraoperative spillage

with the pleural drainage favoring the parenchymal expansion of the lung, adhering itself to the parietal pleura.

- Hemo- and hemo-pneumo-thorax, their treatment does not differ from other situations.
- Empyema: usually develops in patients with long-standing and infected cysts, with compromise of the lung parenchyma.
- Atelectasis: is the most frequent postoperative complication. Usually due to secretions, the presence of hydatid membranes occluding the bronchial tree should be ruled out. Fiberoptic bronchoscopy is the treatment of choice and is both diagnostic and therapeutic.

Delayed postoperative complications are represented by:

- Residual cavity, usually treated as simple lung air cysts: no treatment is needed, but the risk is bacterial colonization and posterior pulmonary abscess (Fig. 10.18).
- Seeding: it is secondary to the intraoperative rupture of a hydatid cyst. The pleura are not a very fertile location for the nesting of the scolices, but when it is compromised, the prognosis is severe (Fig. 10.19). Bronchial seeding is by far a more serious complication and is the consequence of the filling of the bronchial tree with hydatid liquid and sand. The immediate consequence is the development of an anaphylactic shock, frequently during the operation and the patient under general anesthesia. It may be followed by the quick development, between 2 to 3 months, of multiple intrapulmonary cysts in the alveoli (Fig. 10.20).
- Local recurrence: due to the persistence of membrane remainders in the residual cavity and the consequence will be the development of a new hydatid cyst.

The management of biliary bronchial fistulas has not changed much with the advent of years. The premises of the surgical treatment include the drainage of the pleural space and the treatment of the pleural and lung lesions and the interruption

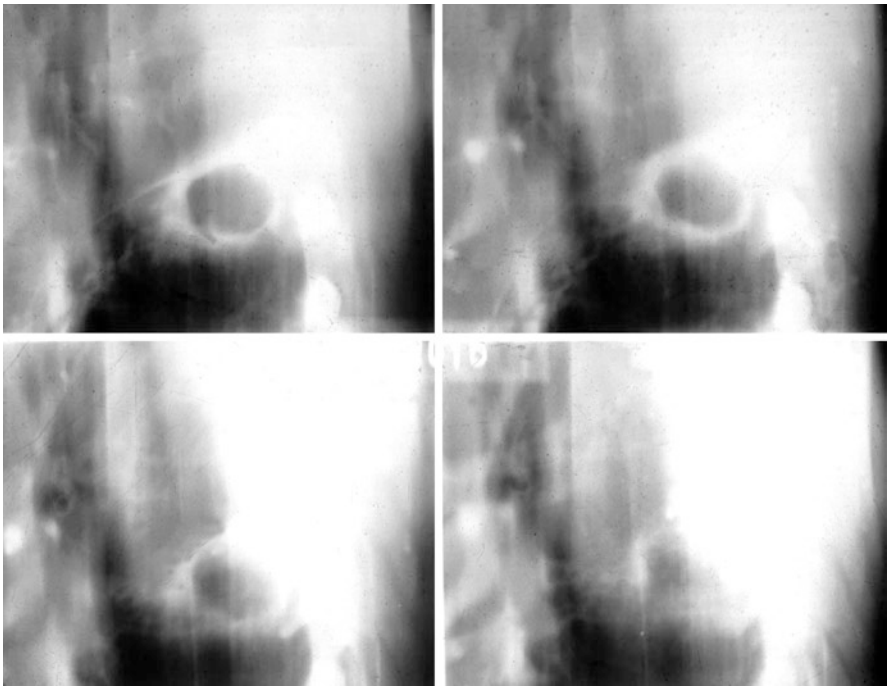
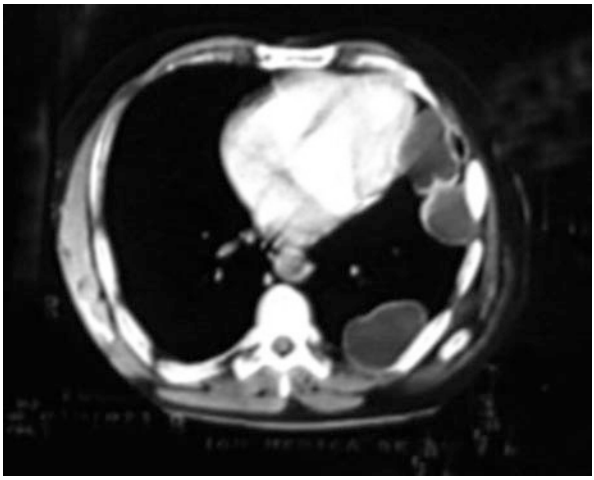


Fig. 10.18 Residual cavities

Fig. 10.19 Pleural seeding



of the communication between the liver, the diaphragm, the pleura, and the lung, the so-called pleura-peritoneal "divorce" or "splitting" [46, 47]. The approach tends to be simultaneous and the approach is through a thoraco-phreno-laparotomy with simultaneous treatment of the structures: the liver, diaphragm, pleura, and lungs.

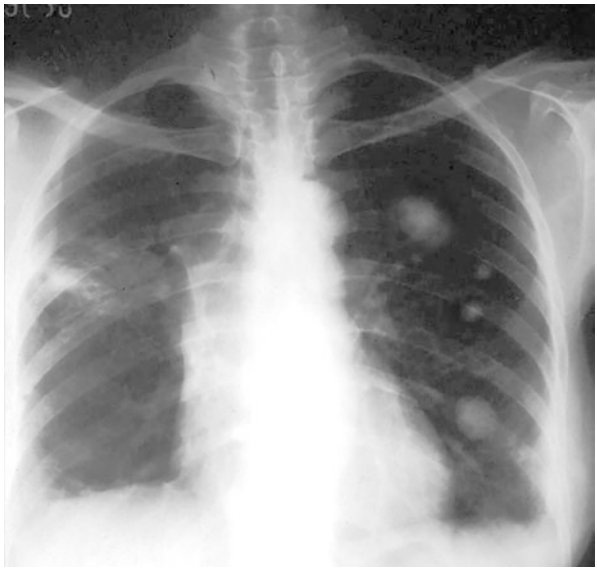


Fig. 10.20
Bronchogenic seeding

Key Points

- Diagnosis based on background, epidemiology, chest X-ray.
- Serology (arc 5 test, ELISA, and western blot).
- Surgery remains the primary choice of treatment in cystic pulmonary hydatid echinococcosis.
- Prevention should be the goal for the cestode infestation.
- A better understanding of hydatid immunoregulation may pave the way to rational immunotherapy and a future vaccine development.

References

1. Thompson RCA, McManus DP. Aetiology: parasites and life cycles. In: Eckert J, Gemmell MA, Meslin F-X, Pawlowski ZS, editors. WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern. Paris: Office Internationale des Epizooities; 2001. p. 1–19.
2. Magnúson G. Yfirlit yfir sogu sullaveikinnar a Islandi (review of the echinococcosis history in Iceland). Reykjavik: Prentsmidjan Gutenberg; 1913.
3. Aletras H, Symbas PN. Hydatid disease of the lung. In: Shields TW, LoCicero J, Ponn RB, editors. General thoracic surgery. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 1113–22.
4. Thomas JD. The treatment of pulmonary cysts by the establishment of large openings into the sac and subsequent free drainage. Br Med J. 1885;
5. Thomas JD. The operative treatment of hydatid cyst of the liver and lungs. Melbourne: Stillwell & Co; 1889. p. 80–2.
6. Venturini AH. La primera anestesia filmada en el mundo se hizo en Buenos Aires. Anestesia. 2011;69:56–60. Available at https://www.anestesia.org.ar/search/articulos_completos/1/1/1426/c.pdf. Accessed 19 Jan 2019.
7. Esteva H. Alejandro Posadas, Argentinian pioneer: thoracic surgery in the western world in his time. Ann Thorac Surg. 2004;78:741–5.

8. https://www.cdc.gov/parasites/echinococcosis/biology.html. Accessed 20 Feb 2019.
9. Gemmell MA, Lawson JR. Epidemiology and control of hydatid disease. In: RCA T, editor. *The Biology of* Echinococcus *and Hydatid Disease*. London: RCA Thompson Pub. George Allen and Unwin Ltd; 1986. p. 189–216.
10. Vuitton DA, Wang Q, Zhou HX, et al. A historical view of alveolar echinococcosis, 160 years after the discovery of the first case in humans: part 1. What have we learnt on the distribution of the disease and on its parasitic agent? Chin Med J. 2011;124:2943–53.
11. http://www.msal.gob.ar/images/stories/bes/graficos/0000000067cnt-01-guia-medica-hidatidosis.pdf. Accessed 19 Jan 2019.
12. Thumler J, Munoz A. Pulmonary and hepatic echinococcosis in children. Pediatr Radiol. 1978;7:164–71.
13. Gómez R, Moreno E, Loinaz C, et al. Diaphragmatic or transdiaphragmatic thoracic involvement in hepatic hydatid disease: surgical trends and classification. World J Surg. 1995;19:714–9.
14. Campana JM, Pochat CA. Hidatidosis toracica (Relato Oficial XLIV Congreso Argentino de Cirugia Toracica). Available at http://www.sact.org.ar/docs/hidatidosis_campana_pochat.pdf. Accessed 20 Jan 2019.
15. Morar R, Feldman C. Pulmonary echinococcosis. Eur Resp J. 2003;21:1069–77.
16. Zhang W, Li J, McManus DP. Concepts in immunology and diagnosis of hydatid disease. Clin Microbiol Rev. 2003;16:18–36.
17. Morar R, Feldman C. Pulmonary echinococcosis. Eur Resp J. 2003;21:1069–77.
18. Qian Z. Thoracic hydatid cysts. A report of 842 cases treated over a thirty year period. Ann Thorac Surg. 1988;46:342–6.
19. Manterola C, Otzen T. Hepatic echinococcosis with thoracic involvement. Clinical characteristics of a prospective series of cases. Ann Hepatol. 2017;16:599–606.
20. Kilani T, El Hammani S, Horchani H, et al. Hydatid disease of the liver with thoracic involvement. World J Surg. 2001;25:40–5.
21. Gulamhussein MA, Pararajasingham J, Adams B, et al. Hepatopulmonary fistula: a life threatening complication of hydatid disease. J Cardiothoracic Surg. 2015;10:103–7.
22. Mestiri S, Kilani T, Thameur H. Thoracic migrations of hydatid cysts of the liver: proposal for a classification. Lyon Chir. 1987;83:12–6.
23. Oguzkaya F, Akcali Y, Kahraman C, et al. Unusually located hydatid cysts: intrathoracic but extrapulmonary. Ann Thorac Surg. 1997;64:334–7.
24. Tulay CM. Primary mediastinal hydatid cysts. Ann Thorac Cardiovasc Surg. 2014;20:316–9.
25. Eroglu A, Kurkcuoglu C, Karaoglanoglu N, et al. Primary hydatid cysts of the mediastinum. Eur J Cardiothorac Surg. 2002;22:599–601.
26. Jacquier M, Piroth L. Vertebral hydatidosis. N Engl J Med. 2018;379:2.
27. Bhake A, Agrawal A. Hydatid disease of the spine. J Neurosci Rural Pract. 2010;1:61–2.
28. Prabhakar MM, Acharva AJ, Modi DR, et al. Spinal hydatid disease: a case series. J Spinal Cord Med. 2005;28:426–31.
29. Akbulut S. Parietal complication of the hydatid disease. Comprehensive literature review. Medicine. 2018;97:21–8.
30. Fattahi Masoom SH, Lari SM, Fattahi AS, et al. Albendazole therapy in human lung and liver hydatid cysts: a 13 year experience. Clin Resp J. 2018;12:1076–83.
31. Kurkcuoglu IC, Eroglu A, Karaoglanoglu N, et al. Complications of albendazole treatment in hydatid disease of the lung. Eur J Cardio Thorac Surg. 2002;22:649–50.
32. Ammann RW, Eckert J. Cestodes, Echinococcus. Gastroenterol Clin N Am. 1996;25:655–89.
33. Aarons BJ. Thoracic surgery for hydatid disease. World J Surg. 1999;23:1105–9.
34. Brunetti E, Kern P, Vuitton DA, et al. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114:1–16.
35. Ulku R, Onen A, Onat S. Surgical treatment of pulmonary hydatid cysts in children: report of 66 cases. Eur J Pediatr Surg. 2004;14:255–9.
36. Becmeur F, Chaouachi B, Dhaoui R, et al. Video-assisted thoracic surgery of hydatid cysts of the lung in children. J Chir (Paris). 1994;131:541–3.

37. Paterson HS, Blyth DF. Thorascopic evacuation of dead hydatid cysts. J Thorac Cardiovasc Surg. 1996;111:1280–1.
38. Eroglu A, Aydin Y, Altuntas B. Video-assisted thorascopic surgery is safe and effective in the treatment of pulmonary hydatid cyst. Ann Thorac Surg. 2016;101:829.
39. Alpay L, Lacin T, Ocakcioglu I, et al. Is video-assisted thoracoscopic surgery adequate in treatment of pulmonary hydatidosis? Ann Thorac Surg. 2015;100:258–62.
40. Ugon CV. Therapy of hydatid cysts of the lungs and their complications. J Int Chir. 1952;12:155–78.
41. Ugon AV. Técnica de la extirpación de los quistes hidatídicos de pulmón. Bol Soc Cir Uruguay. 1947;18:167–72.
42. Sokouti M, Golzari S, Aghdam BA. Surgery of uncomplicated pulmonary hydatid cysts: capitonnage or uncapitonnage? Int J Surg. 2011;9:221–4.
43. Pérez FV. Nuevo método de operar en el quiste hidatídico de pulmón. Arch Int Hidatid. 1947;7:267.
44. Lashkaman HP, Monhammed MA, Suraj KP. Pleuropulmonary hydatid disease treated with thorascopic instillation of hypertonic saline. Lung India. 2008;25:34–7.
45. Nabi MS, Waseem T, Tarif N, et al. Pulmonary hydatid disease: is capitonnage mandatory following cystostomy? Int J Surg. 2010;8:373–6.
46. Arce J. Fistula bronquio-bilio-cutanea, quiste hidatidico abierto a los bronquios. Bol y Trab Acad Arg Cirug. 1945;29:658.
47. Sahin E, Enon S, Kayi Cangir A, et al. Single- stage transthoracic approach for right lung and liver hydatid disease. J Thorac Cardiovasc Surg. 2003;126:769–73.

Management of Extrahepatic Abdominal Echinococcal Disease and Its Complications

11

Walid Faraj, Hussein Nassar, Ahmad Zaghal, and Mohamad Khalife

Introduction

Hydatid disease is a common disease in agricultural and animal raising societies and is endemic in the Middle East, Far East, Mediterranean, South America, Australia, and Turkey [1, 2]. It is one of the major zoonotic diseases carrying significant burden on public health and economy [3]. Hydatidosis is the most pathogenic zoonoses in humans in the northern hemisphere with an annual incidence of up to 1.2 per 100,000 [4]. It is caused by the infection with the tapeworm *Echinococcus* which belongs to the family Taeniidae. Four species of *Echinococcus* potentially infect humans, with *E. granulosus* and *E. multilocularis* being the most common. The two other species are *E. vogeli* and *E. oligarthrus*, and these have only rarely been associated with human infection [5]. The chief morphological difference between the species of *Echinococcus* is the length of the tapeworm, where *E. granulosus* can reach up to 7 mm in length. The type of disease that occurs in humans depends on the species of *Echinococcus* involved. Three forms of *Echinococcus* infection have been identified: cystic, alveolar, and polycystic. The most common form is cystic echinococcosis which is caused by *E. granulosus*. The other forms, alveolar and polycystic echinococcosis, are rarely encountered in humans and are not as widespread as cystic echinococcosis. Infection with *E. multilocularis* is rare; however, it is the most virulent species and can cause alveolar echinococcosis [3].

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The clinical course of echinococcal infection is highly variable and depends on the localization, extent, and proliferation of the larval tissue as well as on the host reaction. The clinical presentation of *Echinococcus* infection depends on the site of the cysts and their sizes. Small and/or calcified cysts may remain asymptomatic indefinitely. However, symptoms due to mass effect within organs, obstruction of blood or lymphatic flow, or complications such as rupture or secondary bacterial infections can occur [6]. Many infections are acquired in childhood but do not cause clinical manifestations until adulthood. Also, latent periods before symptoms arise have been reported. While approximately 50% of detected cases occur in asymptomatic patients, many more cases remain undiagnosed or are found incidentally at autopsy. Humans are considered the incidental intermediate host. Upon ingestion, the larval stage will emerge in the bowels, invade into the blood vessels, and migrate into almost every organ of the body [7] The liver is the most commonly affected organ with *Echinococcus* infection, followed by the lungs. However, any other human organ can potentially be involved. Primary extrahepatic hydatid disease has been reported in the abdominal cavity, retroperitoneum, spleen, kidneys, adrenals, and even myocardium [8, 9].

Normally parasites spread through portal circulation. Other courses of spread include lymphatic invasion by the parasite. The spread of hydatid disease in the abdomen can be along peritoneal fluid circulation or intra-abdominal recesses, which may explain intraperitoneal seeding. After infection with this disease, patients can remain asymptomatic for long time before presenting with symptoms. Most patients with abdominal extrahepatic hydatid disease present with abdominal discomfort, some may present with anaphylaxis or fever. However, a sudden abdominal pain in these patients may indicate intracystic bleed, rupture, or infection, with intracystic bleeding being the most dangerous complication [10]. Diagnostic challenges are imposed on clinicians due to the non-specific clinical presentation of this disease, especially in extra-abdominal hydatid disease. Ultrasound (US) and computed tomography (CT) scan usually confirm the diagnosis with a sensitivity of 93–98% and 97%, respectively. Most patients have a single organ involvement (most commonly the liver), and a single cyst is present in more than 70% of cases [11].

Treatment of small hydatid calcified cysts doesn't always require surgical treatment and can be managed conservatively. Treatment alternatives mainly involve anthelminthic therapy and interventional procedures including PAIR (puncture, aspiration, injection, respiration), PPDC (percutaneous puncture with drainage and curettage), conservative surgical approach (open cystectomy with or without omentoplasty), and radical surgical resection (absolute pericystectomy or hepatectomy). Palliative treatment comprises of drainage of infected cysts. Laparoscopic or open drainage procedures include aspiration, injection of scolicidal agent, deroofing, evacuation, and conversion of the cyst into a non-dependent cavity [12].

Life Cycle

The life cycle of *Echinococcus* infection was first described by Haubner [12]. The disease is transmitted when food/water containing parasitic eggs is eaten, or through a close contact with an infected animal. The eggs are released in the stool of

carnivores that are infected by the parasite. Commonly infected animals include dogs, foxes, and wolves. An adult worm resides in the small intestine of a definitive host. The eggs get released from gravid proglottids that are passed in the feces that get ingested by an intermediate host. The eggs hatch in the intestines of the intermediate host and release oncospheres that penetrate through the intestinal wall and target organs such as the liver and lungs developing into a cyst(s). The membranes and capsule provides the parasite with immunity against destruction. The cyst gets enlarged, creating protoscolices with daughter cyst. These cysts may contain thousands of protoscolices, and this fast reproductive potential poses a problem in the intermediate host. The definitive host then becomes infected after ingesting the infected intermediate host. After ingestion, the protoscolices attach and then develop into adult worms, and the cycle starts all over again. Humans get infected when they get in contact with infected animal hosts [13].

Extrahepatic Anatomical Locations of Disease

Splenic Hydatidosis

The first case report of splenic hydatid disease discovered on autopsy was published by Berthelot in 1790 [14]. Splenic hydatidosis accounts for around 0.5% of all patients with echinococcosis and up to 4% of the abdominal hydatid disease [9]. Patients are classified as either primary or secondary (more common) with other organs involved. The rare isolated contamination of the spleen by echinococcus is related to the anatomy of the portal vein system and the flow of the embryos of the tapeworms via blood. Sometimes, the eggs may penetrate the circulation without forming cysts in the liver, thus allowing them to settle in other organs via the blood stream. However, it is also possible that when a human host has a fissured cyst, scolices or daughter hydatid cysts can migrate through the wall of the cyst. They can be released to the body and may form new cysts in nearby or distant organs, such as the spleen, and this is known as secondary echinococcosis [7, 11]. Other hypotheses also attempted to explain the spread of this disease directly to the spleen, including a portal vein retrograde extension from the liver to the spleen or via systemic dissemination. The long-term outcome is variable and many patients remain asymptomatic. The splenic hydatid cyst exhibits a variety of clinical features, requiring a high index of suspicion for diagnosis [13]. The rarity of splenic hydatid disease imposes a diagnostic challenge for clinicians, especially in non-endemic areas. Splenic hydatid disease is quite a slowly progressing disease rendering patients completely asymptomatic for years [15]. Accordingly, diagnosis is made either as an incidental finding or as part of workup for non-specific abdominal complaints. Today, the diagnosis of splenic hydatid disease is greatly aided by ultrasonography (US) and computed tomography (CT) [15, 16]. Differential diagnosis of splenic cysts includes cystic neoplasms, abscesses, and benign cysts, which are categorized into true cysts and pseudocysts. True cysts include parasitic (hydatid) and non-parasitic cysts (epidermoid, dermoid, hemangiomas, and lymphangiomas). Pseudocysts are mainly traumatic (hematoma). Several therapeutic options are

present. However, the most effective methods comprise excision of the infected tissues, either surgically or the through less invasive procedures such as puncture-aspiration-injection-reaspiration (PAIR) approach. Treatment options are usually individualized based on presentation and medical status of patients. Nevertheless, it is still controversial if performing total splenectomy is more beneficial than performing spleen sparing surgical approaches [14]. Literature that focuses on splenic hydatid disease is still based on individual cases with weak evidence to support splenectomy, spleen-preserving surgery, or interventional treatment options. It has been described that large or multiple splenic cysts are best managed surgically eliminating the higher risk of rupture and its complications including anaphylaxis, septic shock, and bleeding. A spleen sparing approach is advisable when the cysts are peripheral at the surface of the spleen [17]. However this approach potentially carries a higher risk of blood loss compared to unroofing and evacuation of hydatid cysts. Meimarakis et al. have advocated, based on their case series of ten patients, for total splenectomy as the best treatment option for complete removal of infected tissues and avoiding potentially infected remnant cavity, bearing in mind post-splenectomy complications [17]. Prophylactic antiparasitic therapy may reduce recurrence rates. In addition, preoperative or early postoperative vaccination is important for surgical patients in order to decrease the risk of post-splenectomy sepsis which can be life-threatening [17].

Pulmonary Hydatidosis

Hydatid disease of the lung can be primary or secondary. Initially, patients are asymptomatic. Of patients with pulmonary hydatid disease, around 20–40% also have liver involvement. Pulmonary involvement appears to be more common in pediatric population [18]. Usually, the evolution of a hydatid cyst in any sold organ is affected by several factors including the texture of the organ itself, and the elasticity of surrounding tissues and organs. The rate of growth of hydatid disease in the lungs is faster than that of the liver since lungs are softer in consistency compared to the liver. Accordingly, the growth rate of pulmonary hydatidosis is faster in children compared to adults, since children have more elastic tissues. In addition, the location of the lungs in the thorax puts it under negative pressure which may also accelerate the growth rate of hydatid cysts [18]. Imaging is the principal investigational modality for pulmonary hydatid cyst including chest X-ray, CT, or magnetic resonance imaging (MRI) of the lungs. Radiological presentation of hydatid disease varies based on the presence or absence of complications [18]. What is special about pulmonary hydatid disease is that it does not lead to calcification of cyst wall and rarely causes formation of daughter cysts, thus making the radiological diagnosis more challenging. The role of ultrasound is limited due to the ribcage, except when lesions are peripheral. Complications of pulmonary hydatidosis include rupture, secondary bacterial infection, pneumothorax, and bronchial fistulization, all of which are serious complications [18]. Rupture of cyst is the most frequent complication occurring in almost half of

patients. It can occur intrabronchially or into the pleural cavity. Intrabronchial rupture can cause hypersensitivity reactions and hydatoptysis which is the expectoration of cyst membranes and even parasites. Hydatid cysts can even erode into major vessels such as the aorta [19]. Echinococcosis can involve the pleural cavity, mediastinum, or chest wall. Secondary involvement of the diaphragm and thoracic cavity with hydatid disease occurs in 1–16% of cases of hepatic hydatid disease [20]. Surgical intervention in the treatment of pulmonary hydatid disease is the treatment of choice; however pharmacotherapy is helpful as an adjunct therapy. Surgery is indicated in most cases as operative mortality is low (1–2%), morbidity rates are acceptable, and the recurrence rate is also low (1–3%) [21]. Indications for surgical intervention include large cysts that are peripheral with risk of rupture, infection, anatomical location, and presence of substantial mass effect. The most important technical point is to remove the entire cyst and preserve as much lung parenchyma as possible. Surgical techniques include enucleation, pericystectomy, cystostomy, open aspiration, and lung resection [19]. Enucleation is suitable only for small cysts less than 5 cm in diameter. Surgical intervention for pulmonary hydatid disease is a safe intervention with good outcomes, very low morbidity, and mortality. A meta-analysis by Athanassiadi et al. of 4255 patients with pulmonary hydatid disease showed that surgical intervention had only a mortality rate of 1.45% and a morbidity rate up to 17% with excellent cure rate [22]. Video-assisted thoracoscopic surgery (VATS) is becoming a very useful technique in the field of thoracic surgery. It has been employed for the removal of peripheral and small cysts with lower morbidity compared to conventional surgery [19].

Renal Hydatidosis

Renal hydatid cyst is one of the rare presentations of hydatid disease and constitutes up to 3% of all cases. Patients may not report any symptoms for years [23]. Disease involving the kidney may progress slowly with vague complaints, leading to progressive damage of the kidney putting it at risk of loss of function. Early diagnosis is mandatory using a combination of modalities including proper clinical history, imaging, and laboratory testing. Cyst rupture into the urinary collecting system leading to hydatiduria is one of the complications although it is seen in only 10–20% of cases and is usually microscopic rupture only. Gross rupture and passage of cyst contents is uncommon, but if it is present, it makes the diagnosis much easier. Renal ultrasound helps in the diagnosis when daughter cysts and floating membranes are visualized; however the accuracy of ultrasound remains operator dependent. A CT scan remains the gold standard for proper diagnosis with an accuracy of 98% and extremely high sensitivity to visualize daughter cysts [24] PAIR is usually successful for renal hydatid cysts. However, surgery remains the best modality of treatment and disease control via renal sparing cystectomy avoiding renal parenchymal destruction [23, 24]. Nephrectomy must be reserved for extreme cases of destroyed kidneys only.

Rare Locations

Rare locations for hydatid disease have been reported and include the myocardium, brain, spine, adrenal gland, pancreas, gallbladder, ovaries, and bones.

Brain involvement with hydatid disease is rare and has been reported in up to 2% of all cases [25]. Patent ductus arteriosus and patent foramen ovale are recognized risk factors. Primary hydatid disease of the brain can present clinically as intracranial space occupying lesion with clinical manifestations based on the location of the cyst. This is more common in children. Surgery remains the best therapeutic option with acceptable rates of morbidity and low mortality [26].

Primary adrenal hydatid disease accounts for only 0.5% of all reported cases [27]. One of the reported cases included a case of adrenal hydatidosis complicated by fistulization to small bowels that was managed through laparotomy and en bloc resection of the mass.

The incidence of cardiac echinococcosis is about 0.03–1.1% of all cases of Echinococcosis. Surgery is mandatory in most cases due to the risk of rupture and anaphylactic shock. However, early detection of cardiac echinococcosis is challenging, since symptoms manifest only when the cyst is large enough to compress adjacent structures or to rupture. Cardiac hydatid cysts are characterized by multiple thin walls with a high tendency to invade the myocardium [28]. Cardiac magnetic resonance (CMR) imaging is a useful tool for the diagnosis and presurgical planning .

Hydatid disease can manifest initially in the pancreas in a small proportion of patients. The head of the pancreas is more commonly involved. It can be misdiagnosed as a pancreatic pseudocyst or cystic neoplasms of the pancreas. Thus, it should be thought of as part of the differential diagnosis in patients with cystic lesions of the pancreas in endemic regions [29]. Surgery remains the best definitive diagnostic and therapeutic tool available. Management options include laparoscopic cyst excision, percutaneous drainage, or cystectomy with deroofing and drainage [29].

The gallbladder is one of the least common anatomical locations for primary hydatid disease. So far, only five cases have been reported in the medical literature [30]. One of the hypotheses to explain the pathogenesis of gallbladder hydatid disease is the contamination of gallbladder via biliary route. Proper diagnosis can be difficult in terms of localization of primary gallbladder hydatid cysts, which is not always easy due the anatomical proximity of the gallbladder to the liver. Total pericystectomy with cholecystectomy is the classical surgical approach, with careful dissection at the pericystic wall to avoid any biliary injuries or radical liver resection [30, 31].

Hydatid disease can affect the spine in 0.2–1% of reported cases. Unless there is a clinical suspicion of hydatid disease of the spine to consider performing neuroimaging, this curable disease will be missed by most clinicians. It may manifest through compression symptoms, most commonly presenting with radiculopathy [32]. Magnetic resonance imaging (MRI) is the preferred imaging modality in the

diagnosis of spinal hydatid disease. The initial treatment option is surgical excision for neural decompression. The type of surgical intervention, extent of resection, and the need for spinal stabilization depend on the location and extent of destruction leading to spinal instability [33].

Role of Serological Testing

Laboratory tests for *Echinococcus* infection include Casoni intradermal skin test, Weinberg complement fixation (CF) test, hemagglutination inhibition (HAI), enzyme-linked immunosorbent assay (ELISA), and IgE testing. These tests help in establishing the diagnosis; however false-negative rates are concerning especially in cases of intact hydatid cysts whereby the antigens are sequestered [27, 34]. In addition, it has been shown that the rates of seropositivity are generally higher in liver hydatid disease compared to other organ involvement. Hepatic hydatid disease has been confirmed in 80–94% of the patients via immunologic tests, but extrahepatic hydatidosis was only confirmed in 65% of cases, even if multiple tests were applied.

Role of Anthelminthic Therapy

In most cases, pre- and postoperative courses of albendazole ought to be considered to sterilize the cyst, to diminish the opportunity of anaphylaxis, to diminish the pressure in the cyst wall, and to decrease the recurrence rate. Albendazole inhibits tubulin, causing blockage of glucose absorption, leading to glycogen consumption and degenerative alterations in the endoplasmic reticulum and mitochondria of the germinal layer, in this way enhancing lysosomal activity inducing cell autolysis [35]. A study demonstrated that surgery combined with antiscolicidal agents such as albendazole showed better results in terms of treatment and recurrence rates compared to surgery alone [36]. Albendazole therapy requires a minimum period of 11 days to have an incremental response, with a recommended dosage of 10–15 mg/kg/day, twice daily. However, there are several contraindications for anthelminthic therapy, including risk of rupture especially for large cysts, bone marrow suppression, and pregnancy especially in the first trimester [37].

Conclusion: Hydatid disease is a common disease in agricultural and animal raising societies and is considered endemic in the Middle East. It carries significant burden on public health and economy. Extrahepatic hydatid disease has been reported in several anatomical locations including the abdominal cavity, retroperitoneum, spleen, kidneys, adrenals, and even myocardium. Clinicians shall keep a low threshold for proper diagnosis of hydatid disease and consider the best curative approach whether surgical or conservative based on the clinical presentation, location, and extent of hydatid disease.

References

1. Rasheed K, Zargar SA, Telwani AA. Hydatid cyst of spleen: a diagnostic challenge. N Am J Med Sci. 2013;5(1):10–20.
2. Ramia-Angel JM, Gasz A, de la Plaza-Llamas R, Quinones-Sampedro J, Sancho E, Garcia PJ. Hidatidosis of the spleen. Pol Przegl Chir. 2011;83(5):271–5.
3. Sarkar M, Pathania R, Jhobta A, Thakur BR, Chopra R. Cystic pulmonary hydatidosis. Lung India. 2016;33(2):179–91.
4. Neil M, Burgkart RH, Guntmar G, Von Eisenhart-Rothe R. Primary extrahepatic alveolar echinococcosis of the lumbar spine and the psoas muscle. Ann Clin Microbiol Antimicrob. 2011;10:13.
5. Ameur HB, Affes N, Abdelhedi C, Kchaou A, Boujelbene S, Beyrouti MI. Hydatid cyst of the spleen: Tunisian series of 21 cases. Indian J Surg. 2015;77(Suppl 2):515–9.
6. Bourée P. Hydatidosis: dynamics of transmission. World J Surg. 2001;25:4–993.
7. Manouras AJ, Nikolaou CC, Katergiannakis VA, et al. Spleen-sparing surgical treatment for echinococcosis of the spleen. Br J Surg. 1997;84:1162.
8. Romig T. Epidemiology of echinococcosis. Langenbeck's Arch Surg. 2003;388:209–17.
9. Magistrelli P, Masetti R, Coppola R, Messia A, Nuzzo G, Picciochi A. Surgical treatment of hydatid disease of the liver. World J Surg. 1991;126:518–23.
10. Prousalidid J, Tzardinoglou K, Sgouradis L, Katsohis C, Aletras H. Uncommon sites of hydatid disease. World J Surg. 1998;22:17–22.
11. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev. 2004;17:107–35.
12. Brunt LM, Langer JC, Quasebarth MA, et al. Comparative analysis of laparoscopic versus open splenectomy. Am J Surg. 1996;172:596–601.
13. Mokhtari MAM, Spoutin A. Splenic hydatid cyst and relevation with anaphylaxis. Res J Med Sci. 2008;2:248–50.
14. Eris C, Akbulut S, Yildiz MK, et al. Surgical approach to splenic hydatid cyst: single center experience. Int Surg. 2013;98(4):346–53.
15. Caremani M, Benci A, Maestrini R, Accorsi A, Caremani D, Lapini L. Ultrasound imaging in cystic echinococcosis. Proposal of a new sonographic classification. Acta Trop. 1997;67:91–105.
16. Gossios KJ, Kontoyiannis DS, Dascalogiannaki M, Gourtsoyiannis NC. Uncommon locations of hydatid disease: CT appearances. Eur Radiol. 1997;7:1303–8.
17. Meimarakis G, Grigolia G, Loehe F, Jauch KW, Schauer RJ. Surgical management of splenic echinococcal disease. Eur J Med Res. 2009;14(4):165–70.
18. Sarkar M, Pathania R, Jhobta A, Thakur BR, Chopra R. Cystic pulmonary hydatidosis. Lung India. 2016;33(2):179–91.
19. Harris DG, Van Vuuren WM, Augustyn J, Rossouw GJ. Hydatid cyst fistula into the aorta presenting with massive hemoptysis. Case report and literature review. J Cardiovasc Surg. 2001;42:565–7.
20. Gomez R, Moreno E, Loinaz C, et al. Diaphragmatic or transdiaphragmatic thoracic involvement in hepatic hydatid disease: surgical trends and classification. World J Surg. 1995;19:714–9.
21. Dogan R, Yuksel M, Cetin G, et al. Surgical treatment of hydatid cysts of the lung: report on 1055 patients. Thorax. 1989;4(4):192–1999.
22. Athanassiadi K, Kalavrouziotis G, Loutsidis A, Bellenis I, Exarchos N. Surgical treatment of echinococcosis by a transthoracic approach: a review of 85 cases. Eur J Cardiothorac Surg. 1998;14:134–40.
23. Zmerli S, Ayed M, Horchani A, Chami I. El ouakdi M, Ben slama MR. Hydatid cyst of the kidney: diagnosis and treatment. World J Surg. 2001;25(1):68–74.
24. Reza HAM, Rreza G, Nastaran B, Mousa M. Renal hydatid cyst; a rare infectious disease. Oxf Med Case Reports. 2019;2019(3):omz011.

25. Senapati SB, Parida DK, Pattajoshi AS, Gouda AK, Patnaik A. Primary hydatid cyst of brain: two cases report. Asian J Neurosurg. 2015;10(2):175–6.
26. Ali M, Mahmood K, Khan P. Hydatid cysts of the brain. J Ayub Med Coll Abbottabad. 2009;21(3):152–4.
27. Ruiz-rabelo JF, Gomez-alvarez M, Sanchez-rodriguez J. Rufian peña S. complications of extrahepatic echinococcosis: fistulization of an adrenal hydatid cyst into the intestine. World J Gastroenterol. 2008;14(9):1467–9.
28. Su L, Yu J, Dai C, Liu Y, Peng L. Echinococcosis in left ventricle: a case report. Medicine (Baltimore). 2019;98(16):e15267.
29. Ahmed Z, Chhabra S, Massey A, et al. Primary hydatid cyst of pancreas: case report and review of literature. Int J Surg Case Rep. 2016;27:74–7.
30. Krasniqi A, Limani D, Gashi-luci L, Spahija G, Dreshaj IA. Primary hydatid cyst of the gall-bladder: a case report. J Med Case Rep. 2010;4:29.
31. Noomene R, Ben Maamer A, Bouhafa A, Haoues N, Oueslati A, Cherif A. Primary hydatid cyst of the gallbladder: an unusual localization diagnosed by magnetic resonance imaging (MRI). Pan Afr Med J. 2013;14:15.
32. Bhake A, Agrawal A. Hydatid disease of the spine. J Neurosci Rural Pract. 2010;1(2):61–2.
33. Khazim RM. Spinal hydatid disease. South Med J. 2006;99:114.
34. Illuri HR, et al. Hydatid disease: a 2 years retrospective study in a tertiary care center in South India. Inte Surg J. 2018;5(2):602–7.
35. Teggi A, Lastilla MG, De Rosa F. Therapy of human hydatid disease with mebendazole and albendazole. Antimicrob Agents Chemother. 1993;37:1679–84.
36. Karavias DD, Vagianos CE, Bouboulis N, et al. Improved techniques in the surgical treatment of hepatic hydatidosis. Surg Gynecol Obstet. 1992;174:176–80.
37. Stamatakis J. Hepatic hydatid disease. In: Johnson CD, Taylor I, editors. Recent advances in surgery (17). London: Churchill Livingstone; 1994. p. 35–48.

The Role of Surgery in the Management of *Echinococcus multilocularis*

12

Daniel Paramythiotis and Vasileios N. Papadopoulos

Introduction

Echinococcosis is a zoonosis caused by infestation with any of 4 (of the 16) members of the *Echinococcus* genus, namely, *Echinococcus granulosus*, *Echinococcus multilocularis*, *Echinococcus oligarthus*, and *Echinococcus vogeli*. Furthermore, human alveolar echinococcosis (AE) is a rare parasitic disease caused by the pseudo-cancerous hepatic development of the larval form (metacestode) of the cestode *Echinococcus multilocularis*. The developing cysts may become very dangerous because of their unlimited budding outwards and their ability to infiltrate nearby organs as well as metastasize to the brain, lungs, mediastinum, and other tissues [1, 2].

The endemic areas of the disease are located in the Central and Eastern Europe, Russia, Central Asia, China, northern Japan, Alaska, as well as in Canada and in the central-northern USA, where *E. multilocularis* infection is emerging. In Europe and in highly endemic areas, the annual incidence of AE is 2/100,000 of population; there has been an increase in the incidence in areas previously identified as endemic, and moreover, AE is now present in countries previously considered free from the disease, such as the Eastern-Central and Baltic States [2].

Definitive hosts for AE are mainly red foxes; however other carnivores may also contribute to the disease cycle. The intermediate hosts are typically small rodents and rarely humans. Growing fox populations in Europe, especially in urban areas, may indicate a potentially increased infection risk for humans with a lag phase of one to two decades. In addition to this, since AE is often not considered in the differential diagnosis, the disease remains under diagnosed in Europe [3].

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AE is characterized by an initial asymptomatic incubation period of 5–15 years and a subsequent chronic course with clinical symptoms that may include epigastric pain, fever, jaundice, and hepatomegaly. Diagnosis depends on imaging examinations, serologic tests, and pathologic findings, because the clinical presentation is usually nonspecific. Ultrasonography (US), computed tomography (CT) scan, and magnetic resonance (MR) imaging are the most useful methods of diagnostic imaging. Without timely diagnosis and therapy, the prognosis is grim, as in the era prior to antihelminthic treatment, the cumulative lethality for AE was about 90% 10 years after the diagnosis [3]. Surgery remains the cornerstone of treatment, combined with parasite-static chemotherapy.

Radical Resection

The World Health Organization-Informal Working Group on Echinococcosis (WHO-IWGE) PNM classification system (Table 12.1), based on imaging findings, has been established as a standardized method for reporting the extent of the disease, while it may also guide therapeutic decisions (Table 12.2) and help estimate the resectability of the lesion, or else the likelihood of achieving radical resection [4]. Analogous to the TNM classification for malignant tumors, it reports the extension of the parasitic mass in the liver (P), the involvement of neighboring organs (N), and the presence or absence of metastases (M).

Based on the PNM classification, alveolar echinococcosis is further described as follows:

- Stage I: P1 N0 M0.
- Stage II P2 N0 M0.
- Stage IIIA: P3 N0 M0.
  IIIB: P1–3 N1 M0 or P4 N0 M0
- Stage IV: P4 N1 M0 or Any P Any N and/or M1.

Table 12.1 The PNM classification for alveolar echinococcosis

P	*Hepatic localization of the parasite*
Px	Primary tumor cannot be assessed
P0	No detectable tumor
P1	Peripheral lesions without proximal vascular and/or biliary involvement
P2	Central lesions with proximal vascular and/or biliary involvement of one lobe
P3	Central lesions with hilar vascular or biliary involvement of both lobes and/or with involvement of two hepatic veins
P4	Any liver lesion with extension along the vessels (inferior vena cava, portal vein and arteries) and the biliary tree
N	*Extra-hepatic involvement of neighboring organs*
Nx	Not evaluable
N0	No regional involvement
N1	Regional involvement of contiguous organs or tissues
M	*The presence of distant metastasis*
Mx	Not completely evaluated
M0	No metastasis (chest x-ray and brain computed tomography negative)
M1	Metastasis

Table 12.2 Consensus view on stage-specific approach to alveolar echinococcosis

WHO-IWGE classification	Surgery	Interventional treatment	Drug therapy	Suggested approach	Resources setting
P1N0M0				Radical resection (R0)	Optimal
			√	Antiparasitic drugs for 2 years	
	√			PET/CT controls	
				Radical resection (R0)	Minimal
				Antiparasitic drugs for 3 months	
P2N0M0				Radical resection (R0)	Optimal
			√	Antiparasitic drugs for 2 years	
	√			Radical resection (R0)	Minimal
				Antiparasitic drugs for 3 months	
P3N0M0				Antiparasitic drugs continuously	Optimal
			√	PET/CT/MRI scan initially and in intervals of 2 years	
				Antiparasitic drugs continuously	Minimal
P3N1M0				Antiparasitic drugs continuously + PET/CT/MRI scan initially and in intervals of 2 years	Optimal
		√	√	Surgery, if indicated	Minimal
P4N0M0				Antiparasitic drugs continuously + PET/CT/MRI scan initially and in intervals of 2 years	Optimal
		√	√	Surgery, if indicated	Minimal
P4N1M1				Antiparasitic drugs continuously + PET/CT/MRI scan initially and in intervals of 2 years	Optimal
		√	√	Surgery, if indicated	Minimal

WHO-IWGE has further suggested therapeutic approaches, according to the stage of the disease and the resources available to each facility.

Hepatectomy, as a means of radical resection of the lesion, remains the gold standard therapy for AE, when such a resection is feasible, even though this is often difficult to achieve because of echinococcal dissemination into host tissues. Additionally, the surgical therapy for hepatic AE should follow the operative principles guiding excision of malignant liver tumors and, more specifically, in toto removal of the tumor with an additional safety distance of 2 cm in order to achieve tumor free resection margins [3]. As mentioned above however, since in the majority of patients the disease has already advanced when the diagnosis is established, curative resection rates have been reported to be as low as 20%, with an estimated average of 35% [5].

When hepatectomy is performed, it ought to be classified according to the quality of resection: R0, no residual disease; R1, microscopic residual disease; and R2, macroscopic residual disease. Recently, studies have suggested that R1 resection, i.e., with a safety margin <1 cm and/or microscopic remnants, may lead to almost equal overall survival rates as R0 resection and almost 100% disease progression-free rate, when continuous antiparasitic treatment is employed. Such results should, however, be confirmed by prospective studies [6].

While it is true that the complete disappearance of the parasitic lesion until the last cell is the therapeutic goal in AE [6], the extent of hepatic resection must be adapted to the location and volume of the pseudo-tumorous mass, due to the risk of postoperative liver failure. If the lesion is solitary and peripheral, or limited to the left lobe, resection is simple; if there are multiple parasitic pseudo-tumors, the magnitude of surgery will depend on the possibility to safely resect all lesions. In most of the cases, this entails a right hepatectomy, often extended to segment IV or to segment I. In addition to this, since the intrahepatic common bile duct is frequently involved, it is often necessary to excise the bile duct bifurcation and reconstruct the biliary tract with similar techniques as those employed in the treatment of hilar cholangiocarcinoma [6].

Notwithstanding the fact that radical resection remains the primary goal, non-radical liver resections, which were regarded in the past as beneficial for reducing the burden of disease, are not currently considered as being superior to conservative treatment [6, 7]. Therefore, palliative surgery should be avoided whenever possible. However, the diversity of AE manifestations sometimes results in a case-by-case management, such as R1 or even R2 resections, which may be necessary to effectively deal with a septic focus, provided that R0 resection is impossible and/or if percutaneous or endoscopic drainage, which should be attempted first, is not effective [4].

Lesions not confined to the liver do not represent a contraindication to surgery per se; however curative procedures ought to meet the R0 resections criteria as well. Lesions in other organs (e.g., the brain) may be managed either by surgery or by conservative means [4]. AE patients with any kind of immunosuppression (cancer, hematological malignant disorder, chronic inflammatory disease) are still candidates for radical resection, provided that the associated condition allows for hepatic surgery [6].

Spread of AE to regional lymph nodes in man has not been encountered in the past, and thus, systematic lymph node dissection is not recommended as a standard procedure. However, in a fairly recent report, an excised regional hepatic lymph node was infested with the parasite, leading the authors to state that omitting the prophylactic regional lymph node resection would have allowed for remaining parasitic tissue, rendering the surgical procedure non-radical. The authors conclude that resection should be extended to the removal of regional lymph nodes as a routine, as a means of reducing the risk of persistent infection. Perhaps, a prospective study should look into the spread of AE to regional lymph nodes and the possibility of recurrence, in order to clarify this issue [8].

Finally, it has to be mentioned that nowadays, more than half of the patients are diagnosed incidentally after imaging procedures performed for unrelated conditions and that a marked trend toward a reduction in the percentage of surgical operations

is observed (albeit accompanied by an enormous increase in the percentage of radical operations/total number of operation). Furthermore, it is obvious that hepatic surgery for AE demands a highly specialized surgical team, as well as the appropriate resources for major hepatic surgery, since only in specialized centers may the intraoperative and immediate postoperative mortality of the procedure range as low as 0–2% [6]. It has been also reported that the most relevant factors for postoperative mortality are the presence of Budd-Chiari syndrome and hypoalbuminemia [5].

Postoperative antiparasitic drug treatment and long-term follow-up are mandatory in all cases after radical resection of the lesion, for a span of at least 2–10 years [4, 7].

Liver Transplantation

Based on the European Liver Transplant Registry data for the time period of 1968–2010, AE of the liver was treated with transplantation in 77 (0.09%) of 90,257 patients with a 69% 5-year survival rate in 63 of these patients [2]. Liver transplantation (LT) should be reserved for patients with severe liver failure or recurrent life-threatening cholangitis and the inability to perform a radical liver resection for AE (PNM stage IIIA, IIIB, and IV). On the other hand, long-term administration of immunosuppressive therapy may increase the risk of disease recurrence and the formation or growth of metastases. In addition to this, LT is contraindicated in the presence of extrahepatic locations of the disease and if immunosuppressive drugs and/or antiparasitic drugs cannot be administered [4, 7, 9].

Since the advent of the twenty-first century, LT for echinococcosis has decreased significantly in the Central Europe (especially in France), possibly as a result of better imaging techniques, as well as the development of highly sensitive diagnostic tests, leading to earlier diagnosis of the disease and therefore earlier treatment [6, 9]. Furthermore, in addition to the recommendations of Brunetti et al. [4], the shortage of donors, as well as the trend to promote antiparasitic drug treatment combined with nonsurgical interventional procedures in cases with advanced AE, have also contributed to the decrease of the number of liver transplantations (LT) [6]. Sporadic reports of LT for echinococcosis are still being published from different countries around the world, including Poland, China, Germany, Spain, Switzerland, Belgium, Kyrgyzstan, and the USA, and mostly from Turkey as an endemic country in the Middle East [9].

Due to the late diagnosis and previous surgical interventions, the echinococcosis-related LT procedure is often even more technically challenging. In addition to this, direct involvement of the adjacent organs may require extensive resection during the LT [2].

Pre-transplant administration of antiparasitic drug therapy is recommended by WHO-IWGE, preferably for at least 6 weeks, and recommencing it as soon as possible postoperatively, preferably during the first 2 weeks after transplantation, since recurrence of AE is the main risk of the late deaths after LT [2, 4, 10]. The duration of post-transplant antiparasitic therapy is largely unknown yet, unfortunately. A combination of assessing the dynamics of specific serological tests results, as well

as results from [18F]-2-fluoro-2-deoxyglucose positron emission tomography/CT (FDG PET/CT) in long-term follow-up, may be useful, although the point of time when negative findings should relatively safely allow for discontinuation of such therapy has yet to be established [2, 11]. Nevertheless, continuous administration of antiparasitic drug treatment for at least 2 years after LT is necessary [10].

The most significant problem after LT is recurrence of AE, mainly seen in the graft, lungs, diaphragm, spleen, brain, but also in mediastinum. The WHO-IWGE does not recommend transplantation in patients with metastases; therefore, thorough pre-transplantation evaluation for extrahepatic manifestation of the disease is of utmost importance. Metastases are observed in 20% of the cases, and PET scan may be helpful in the diagnosis of residual or recurrent lesions [4, 10, 11].

Presence of an extrahepatic lesion before LT and prolonged immunosuppression are two main risk factors for recurrence of AE. Immunosuppressive treatment after LT may promote a rapid growth of AE metastases by suppression of cellular immunity that is crucial for control of the parasite's growth [10, 11]. Even more, in addition to immunosuppression, a delayed reintroduction of antiparasitic drug treatment after LT is also an unfavorable factor for recurrence.

LT is associated with very good long-term outcomes, characterized by a 5-year survival rate of 85% [2].

Ex Vivo Liver Resection and Autotransplantation

Liver transplantation, albeit employed in the past in cases where radical resection of the AE lesions was not feasible, has several potential complications that have led to LT being even less and less utilized. Such short- and long-term post-transplant complications include possible disease recurrence associated with the administration of immunosuppressive agents, while the lack of donors and the high financial cost have also limited the current use of liver transplantation in the treatment of final stage AE [12].

To extend the limits of complete resection of the AE lesions, a team in China reported the use of ex vivo resection, followed by autotransplantation of the AE-free liver segments. This technique, which was developed and utilized by Rudolf Pichlmayr and his team in Germany for the treatment of "unresectable" hepatic tumors in the 1990s, could potentially represent an alternative to liver allotransplantation in AE. What makes this technique especially interesting is the fact that AE represents a chronic tumorlike infectious disease exquisitely sensitive to immunosuppressive therapy; therefore autotransplantation and the subsequent avoidance of such therapy may lead to fewer complications and less recurrence of the disease [6]. Conventional hepatic surgery was not considered adequate when the lesion invaded the hepatocaval region with the three hepatic veins and the retrohepatic vena cava, and the lesion invaded the tertiary portal and arterial supply, requiring a complex reconstruction beyond the time that the liver can tolerate [12].

The pioneer surgeons insisted on a very thorough preoperative evaluation and strict patient selection, as the procedure itself is very demanding for both the surgeon as a technique and for the patient's physiology. Computed tomography and magnetic resonance imaging were routinely used for the assessment of the pseudo-tumor's location, its extension, hepatocaval and portal hilum involvement, and the presence or absence of extrahepatic metastasis. Autograft volumes were calculated by using three-dimensional (3D) imaging and furthermore weighed during the operation. Preoperative positron emission tomography scanning was routine for monitoring the disease activity, any remote metastasis or recurrence, and postoperatively, in order to monitor the subsequent liver regeneration. Phlebography was also carried out so as to identify the collateral circulation caused by the chronic obliteration of the retrohepatic vena cava. Additionally, preoperative percutaneous transhepatic biliary drainage (PTBD) was routinely performed in patients with obstructive jaundice, in order to relieve the biliary obstruction, aiming at a total bilirubin level less than twice the upper limit of the normal value [12].

The median autograft volume was 788cm^3 (range 370–1180 cm^3), while the median intraoperative weight of autograft was 706 g (380–1000 g), and the median operative time was 15.5 h (range 11.5–20.5 h). There was no intraoperative mortality; however a patient died from hepatic failure 12 days after surgery, despite a satisfactory remnant liver volume/function as evaluated before surgery: three patients, including the one mentioned before, experienced postoperative complications Clavien-Dindo grade IIIa or higher. During the anhepatic phase, both temporary interpositioned inferior vena cava and portosystemic shunts were necessary to maintain hemodynamic stability and to prevent intestinal congestion in 7 out of 15 patients. Thirteen patients were followed for a median of 21.6 months with no AE relapse; it should be noted that during surgery, the safe resection margin was guaranteed through repeated frozen sections and pathological examination in all cases [6, 12].

At this point, it is important to note that since the parasite grows toward the portal trunk, once the main portal branch becomes obstructed, decreased portal blood flow may lead to atrophy of the affected lobes, especially of the right lobe, and hypertrophy of disease-free lobes. As in most end-stage AE liver lesions, the right portal vein is completely obliterated, and the left lobe becomes hypertrophied due to increased portal blood flow, resulting as a matter of fact in a natural PV embolization [12].

The authors of the study conclude that patients with end-stage hepatic AE may be suitable for ex vivo liver resection and autotransplantation due to the parasite's specific growth patterns and sufficient resulting autograft volumes (left lateral lobe). Since this technique requires no organ donor and no postoperative immunosuppressive therapy, there are relatively lower costs compared to orthotopic liver transplantation. The early postoperative mortality was low with acceptable morbidity; however thorough preoperative assessment is necessary, and strict patient selection is of the utmost importance [12].

Conclusion

In the past 30 years, a major improvement of the prognosis of AE patients worldwide has been shown, due to the use of antiparasitic drug therapy, the improvement of existing surgical techniques, and the development of new surgical and nonsurgical interventional procedures. In the absence of any controlled study, management recommendations are currently based only on the published experience of referral centers or the expert opinion of international collaborations, a fact that should and could change if appropriate funding to support prospective, multicenter studies became available.

Whatever the therapeutic plan for a given patient, the treating strategy should be discussed within a multidisciplinary team, while antiparasitic treatment should be administered in all situations (regardless of the operative treatment). Finally, long-term follow-up of the patient is essential in order to timely diagnose a lesion's progression or recurrence.

References

1. Ambregna S, Koch S, Sulz MC, Grüner B, Öztürk S, Chevaux JB, Sulima M, de Gottardi A, Napoléon B, Abergel A, Bichard P, Boytchev I, Deprez P, Dumortier J, Frossard JL, Kull E, Meny B, Moradpour D, Prat F, Vanbiervliet G, Thevenot T, Vuitton DA, Bresson-Hadni S, Vuitton L. A European survey of perendoscopic treatment of biliary complications in patients with alveolar echinococcosis. Expert Rev Anti-Infect Ther. 2017;15:79–88.
2. Patkowski W, Kotulski M, Remiszewski P, Grąt M, Zieniewicz K, Kobryń K, Najnigier B, Ziarkiewicz-Wróblewska B, Krawczyk M. Alveococcosis of the liver - strategy of surgical treatment with special focus on liver transplantation. Transpl Infect Dis. 2016;18:661–6.
3. Atanasov G, Benckert C, Thelen A, Tappe D, Frosch M, Teichmann D, Barth TFE, Wittekind C, Schubert S, Jonas S. Alveolar echinococcosis-spreading disease challenging clinicians: a case report and literature review. World J Gastroenterol. 2013;19:4257–61.
4. Brunetti E, Kern P, Vuitton DA, Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114:1–16.
5. Dulger AC, Esen R, Begenik H, Aytemiz E, Demirtas L, Aslan M. Alveolar echinococcosis of the liver: a single center experience. Pol Arch Med Wewn. 2012;122:133–8.
6. Vuitton DA, Azizi A, Richou C, Vuitton L, Blagosklonov O, Delabrousse E, Mantion GA, Bresson-Hadni S. Current interventional strategy for the treatment of hepatic alveolar echinococcosis. Expert Rev Anti-Infect Ther. 2016;14:1179–94.
7. Nunnari G, Pinzone MR, Gruttadauria S, Celesia BM, MadedduG MG, Pavone P, Cappellani A, Cacopardo B. Hepatic echinococcosis: clinical and therapeutic aspects. World J Gastroenterol. 2012;18:1448–58.
8. Buttenschoen K, Kern P, Reuter S, Barth TF. Hepatic infestation of Echinococcus multilocularis with extension to regional lymph nodes. Langenbeck's Arch Surg. 2009;394:699–704.
9. Aliakbarian M, Tohidinezhad F, Eslami S, Akhavan-Rezayat K. Liver transplantation for hepatic alveolar echinococcosis: literature review and three new cases. Infect Dis (Lond). 2018;50:452–9.
10. Sulima M, Wołyniec W, Oładakowska-Jedynak U, Patkowski W, Wasielak N, Witczak-Malinowska K, Borys S, Nahorski W, Wroczyńska A, Szostakowska B, Lass A, Krawczyk M. Liver transplantation for incurable alveolar echinococcosis: an analysis of patients hospitalized in department of tropical and parasitic diseases in Gdynia. Transplant Proc. 2016;48:1708–12.

11. Bresson-Hadni S, Blagosklonov O, Knapp J, Grenouillet F, Sako Y, Delabrousse E, Brientini MP, Richou C, Minello A, Antonino AT, Gillet M, Ito A, Mantion GA, Vuitton DA. Should possible recurrence of disease contraindicate liver transplantation in patients with end-stage alveolar echinococcosis? A 20-year follow-up study. Liver Transpl. 2011;17:855–65.
12. Wen H, Dong JH, Zhang JH, Duan WD, Zhao JM, Liang YR, Shao YM, Ji XW, Tai QW, Li T, Gu H, Tuxun T, He YB, Huang JF. Ex Vivo liver resection and autotransplantation for end-stage alveolar echinococcosis: a case series. Am J Transplant. 2016;16:615–24.

The Role of Emergency Surgery in Hydatid Liver Disease

13

Alberto Porcu, Alessandro Fancellu, Giuseppe Cherchi, and Giuseppe Nigri

The liver is the most frequently involved organ by hydatid cysts (70% to 85% of cases) [1, 2] The majority of patients with hydatid cysts of the liver are asymptomatic or mildly symptomatic. In general, some form of treatment is required including medical, percutaneous, or surgical treatment, with the exception of small, calcified, and inactive cysts. Appropriate treatment can usually been planned depending on the biological activity of the parasite, the size and number of the cysts, and their location in the liver. In about 30% of cases, patients with liver hydatidosis present with complications, such as anaphylaxis, cyst suppuration, adjacent organ compression, and rupture [3–6]. In a few circumstances, complications of hydatid cysts may be life-threatening and necessitate surgical intervention in urgency or emergency situations. Complications can occur for either infection of the cyst fluid or rupture of the cyst. The aim of this chapter is to describe those challenging clinical situations, analyzing the diagnostic features and the aspects of surgical treatment. The following scenarios will be addressed:

1. Abscess formation of the cyst
2. Rupture of the cysts in the biliary tree
3. Rupture of the cyst in the peritoneal cavity
4. Liver cysts with thoracic involvement

Sporadic reports exist in the literature regarding extremely rare complications, such as hydatid cyst rupture into hollow viscera such as the gallbladder, stomach, duodenum, and in pericardium and vessels such as the aorta and inferior cava vein [7, 8].

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The objectives of emergency treatment of complicated hydatid cysts should include the control of the infectious process, as well as the evacuation of the content of the cyst and the prevention of cyst recurrence.

Abscess Formation of the Cyst

Infection or abscess formation of the cyst represents the most common complication along with intrabiliary rupture [2, 6]. Superinfection and suppuration of the cyst can be due to the invasion of bacteria from small cysto-biliary communications through the pericystium or, more rarely, through the hematogenous route. Secondary infections after non-radical cyst removal or incomplete PAIR procedures can also occur. Abscess formation in the liver is a severe condition which can clinically manifest with either mild signs of infection or even with septic shock [1–3]. Fever with chills and right upper quadrant pain are the most common presenting symptoms. Jaundice can be another clinical sign when the suppurated cyst fistulizes into the biliary tract. A broad spectrum of nonspecific symptoms, including malaise, nausea, and vomiting, can be present. The optimal treatment of liver hydatid abscess is still a matter of debate, although open surgical approach remains the warranted management along with wide-spectrum antibiotic therapy [9]. Traditionally, surgical approach consisting in simple drainage, or surgical drainage associated with total pericystectomy or various form of unroofing with debridement of the residual cavity, has been considered the treatment of choice in suppurated liver hydatid cysts. Although theoretically suppuration of the cyst may result in parasite death, patients treated with simple surgical drainage usually need delayed surgery for the treatment of the cyst; indeed new episodes of infection and chronic complications may occur. When emergency surgery is warranted, radical treatment including total pericystectomy, eradication of the parasites, and closing of the cysto-biliary fistulas can be difficult to achieve. Percutaneous drainage has been considered a contraindication for years due to the risk of anaphylactic reaction and possible parasitic dissemination. Recently, however, percutaneous CT-guided drainage has been used as a first therapeutic step prior to surgery in few selected cases [9]. The purulent material obtained is sent for culture, in order to give antibiotic therapy adapted to the antibiotic sensitivity testing along with anti-parasitic therapy. *Escherichia coli* is the most frequently isolated bacterium. According to some authors, percutaneous drainage can be useful as a therapeutic bridge to more radical and safer surgery.

Rupture of the Cyst in the Biliary Tree

Biliary rupture is considered the most common complication, accounting for 60% of total complications, and occurs in 10–25% of patients affected by liver hydatid cysts [10, 11]. This complication occurs more often in the biliary ducts of the right lobe (55–60%), less commonly in those of left lobe (30–35%), and rarely in the common bile duct [12]. Cysto-biliary communication can arise from compression

of cyst on the bile ducts or from the trapping of small biliary radicals in the pericystic wall. The cysts sited in the central segments and those with diameter over 10 cm are more likely to form communications with the biliary system, as well as multivescicular cysts [13, 14]. Depending on the size and location of cysts, rupture and fistulization can occur in small-caliber ducts or major biliary ducts, leading to different clinical situations, which can range from asymptomatic to jaundice, cholangitis, liver abscess, and septicemia [12]. Related cholangitis should be suspected in a patient, coming from an endemic area, presenting with sudden onset of jaundice, fever, and abdominal pain. Rarer clinical complications, such as acute cholecystitis and acute pancreatitis caused by hydatid remnants within the bile ducts, have been described [10, 12]. Minimal leakages between the laminated membrane of the cyst and the surrounding pericystium may cause scarce adsorption from small biliary ducts and result in an asymptomatic picture, although some forms of sensitivity to the hydatid antigen can occur. Large unilocular cysts can compress the surrounding parenchyma and the bile ducts, causing erosion of their wall and subsequent spillage of the hydatid fluid through the interrupted laminated membrane and the pericystium. This fact allows the passage of the cyst contents into the duct once the frank intrabiliary rupture takes place [15]. Multilocular cysts contain a variable number of vital daughter cysts floating in a turbid semi-liquid material, which can pass into the biliary system in case of rupture. Cysto-biliary communications greater than 5 mm allow the contents of the cyst to drain into the bile duct, while in smaller communications cystic material barely drains into the ductules [10]. The possibility of complete evacuation of unilocular cyst fluid through a large-boring biliary fistula has been described, with consequent spontaneous clinical resolution. However, cysts ruptured in the biliary system usually cause symptoms related to biliary infection. Common symptoms are jaundice, abdominal pain, fever, nausea, vomiting, and urticaria. A mass in the right upper quadrant may be palpable. Positive hydatid serology has been reported in 75–86% of patients with intrabiliary rupture [10]. Laboratory exams show leukocytosis with eosinophilia, direct hyperbilirubinemia, and abnormal liver tests. When dealing with a jaundiced patient having hydatid cyst of the liver, intrabiliary rupture should be suspected, although the presence of jaundice in those patients can be also related to other causes, such as compression of the main biliary ducts by one or more large intact cysts. Cysto-biliary fistulization can be visualized preoperatively with CT scan and/or magnetic resonance cholangiography, which have sensitivity of 75% and 92% for the diagnosis of frank intrabiliary rupture, respectively [10]. When a cysto-biliary communication is diagnosed through CT scan or MRI, and hydatid elements are clearly seen in the bile ducts, endoscopic retrograde cholangiopancreatography (ERCP) with or without plastic biliary stent placement may represent the first treatment step, which can lead to resolution of the jaundice and the signs of infection (Fig. 13.1). According to some studies, such an approach can be useful to overcome acute cholangitis and biliary obstruction prior to elective surgery for cyst treatment. Furthermore, ERCP may reduce the risk of postoperative persistent biliary leakage [10, 12]. In the absence of preoperative drainage and decompression of the biliary tree by means of ERCP, patients with cysts ruptured into the biliary system should have urgent surgery, due

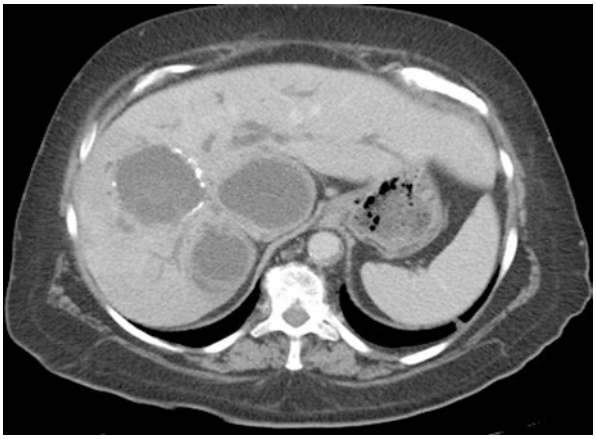

Fig. 13.1 Contrast-enhanced CT scan of the abdomen in a 76-year-old woman presenting with jaundice, fever, and abdominal pain. The image shows three large hydatid cysts of the liver, one of which presents partially calcified wall. Preoperative ERCP, with endoscopic sphincterotomy and a biliary occlusion balloon, permitted empying of the biliary tree from hydatid membranes and relief of symptoms of cholangitis

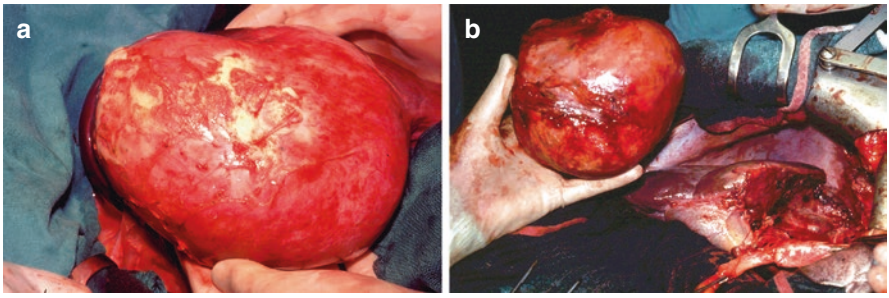

Fig. 13.2 (**a**, **b**) Radical pericystectomy in patients with large hydatid cysts of the liver ruptured in the biliary tree

to the high risk of severe cholangitis, abscess formation, and sepsis. The objectives of surgery are the treatment of the cyst, the repair of the cysto-biliary fistula, and the cleaning of the biliary ducts. Radical pericystectomy is ideally the best form of treatment for those patients and can be performed by surgeon expert in the treatment of liver hydatidosis (Fig. 13.2). However, in the majority of cases, surgical operations mostly consist of various forms of conservative techniques, such as combination of deroofing, partial cystectomy, cleaning and drainage of the cyst cavity, and omentoplasty. Communicating ducts of limited size are sutured on healthy liver parenchyma after removal of the cyst wall. In patients with large frank intrabiliary fistulae and in whom opening of the common bile duct is needed, the placement of a T tube is warranted after proper treatment of the cyst, closure of the fistula, and extensive intrabiliary washing. It can be used for intraoperative and postoperative cholangiography, and it can allow for removal of residual cyst material. Undiagnosed

communications between the cyst and the biliary ducts sometimes are seen intraoperatively and are commonly suspected when bile is present in the cyst content. In uncertain cases, intraoperative cholangiography, use of methylene blue injection from the cystic duct through a catheter can be used for visualizing the cysto-biliary communications. Surgical treatment of cysto-biliary communications in patients having hydatid liver cysts is linked to significant mortality and morbidity. Ramia et al. reported postoperative mortality in frank intrabiliary rupture ranging from 1.25% to 7% and postoperative morbidity between 16.7% and 55% [10]. Postoperative formation of biliary fistulae is the most common complication, with a reported incidence higher than 50% of cases [12, 16]. Low output fistulas (less than 200 mL/day) usually close spontaneously, while high-volume persistent fistulas require prompt treatment by means of ERCP. Redo surgery with jejuno-biliary anastomosis is seldom necessary in refractory cases.

Rupture of the Cysts in the Peritoneal Cavity

Intraperitoneal rupture of hydatid cysts is a complication seen in 1–16% of cases and may result from trauma or from spontaneously increasing of intracystic pressure [1, 3, 16–18]. While the exact mechanism leading to spontaneous rupture is not clearly defined, it is mostly seen in patients with large (≥10 cm) subcapsular cysts. In such situations, in fact, there is no hepatic parenchyma surrounding the cyst and the cyst content spills into the peritoneum with hydatid fluid and daughter cysts. Contamination of the peritoneal cavity by cyst content bears the immediate risk of anaphylactic reaction, which can also be fatal [6, 8]. The contact of the hydatid fluid and protoscoleces in the peritoneal surfaces, indeed, can cause various grades of allergy-related reactions, which were reported to be present in about 25% of cases during intraperitoneal rupture of hydatid cysts. While the small wall leakages are the more common form of ruptured cysts in the peritoneal cavity, massive ruptures may also occur. Free ruptures of liver hydatid cysts of the liver, when systemic anaphylactic reaction does not occur, can result in disseminated abdominal hydatidosis. When minimal fissures present in the cyst surface, diffuse implantation of scolices in the peritoneum and surface of abdominal organs may lead to so-called forms of "metastatic hydatidosis." In those cases, slow-arising ascites and abdominal distension can occur [18]. In cases of peritoneal effusion of uncertain diagnosis, a battery of serologic tests is available to evaluate antibody response against *Echinococcus granulosus*, but all are limited by low sensitivity and specificity. In the absence of allergic reactions, the symptoms are related to the type of rupture and the rapidity to peritoneal cavity invasion. Large and sudden leakages may result in acute peritonitis and hemodynamic instability. The typical symptoms of frank hydatid cyst rupture are epigastric pain and vomiting, along with clinical signs of shock and peritoneal irritation. The possibility of a ruptured hydatid cyst should be taken into account in the differential diagnosis of the acute abdomen in patients residing in an endemic area.

Ultrasound is nowadays the first image approach in patients with acute abdomen and can be helpful in correctly visualizing the hepatic cyst and the peritoneal fluid collection; however, contrast-enhanced CT scan of the abdomen and pelvis remains

the gold standard to confirm the diagnosis and to identify co-existing complications. CT scan findings are free intra-abdominal fluid along with a liver cyst with a detached membrane and signs of rupture, while rarely the scanner allows direct visualization of the solution in continuity with the cyst wall. Ruptured hydatid cysts should be promptly diagnosed, as they require emergency intervention. A rapid diagnosis and emergency surgery play a pivotal role in decreasing patient deaths and postoperative complications related to this rare clinical entity. In patients presenting with hemodynamic shock, resuscitation with intravenous fluids and hydrocortisone is usually required immediately before emergency laparotomy. Aims of surgical management are the treatment of peritonitis and broken hydatid cyst. Abundant peritoneal washing with isotonic solution and drainage along with sampling of peritoneal effusion for bacteriology are mandatory, even in cases of clear peritoneal effusion. Use of hypertonic saline, which does have a scolicidal activity, is usually reserved for washing of the residual cavity of the cyst, because its use may be associated with hypernatremia. As for treatment of the ruptured hydatid cyst, conservative methods such as either partial pericystectomy or unroofing and drainage of the remnant cavity are the preferred techniques in the emergency setting. Attention should be given to removing all of the cyst contents, including hydatid sand. Radical surgery, such as pericystectomy, in the case of rupture may be difficult to perform and may be considered in very select cases. After surgical operation, albendazole therapy is generally started to prevent recurrences.

Peritoneal cavity needs to be washed with isotonic saline and drained.

Liver Cysts with Thoracic Involvement

Intra-thoracic rupture of cysts occurs in 1% of patients with liver hydatidosis and represents a serious complication with high rates of mortality and morbidity, in spite of advances in surgical techniques and critical care. Liver cysts can rupture in the thoracic cavity spontaneously or following a trauma [19–21]. That complication occurs more frequently in patients with large hydatid cysts of the liver abutting the diaphragm, located in the superoposterior segments, especially if the content and the wall of the cystic lesion are infected. Gradual growing and increasing of intracystic compression cause adhesion and erosion of the muscle fibers of the diaphragm. During the initial phases, persistent inflammation results in adhesion and formation of sterile pleural effusion, with silent or asymptomatic clinical pictures. As the inflammation progresses, the wall of the cyst erodes into the pleural cavity through the diaphragm, with possible formation of pleural empyema or hydropneumothorax causing fever, thoracic pain, cough, and dyspnea. Purulent leakage of the cystic content in the pleural cavity may result in intra-thoracic dissemination of daughter cysts (pleural hydatidosis). Extension of the infectious process to the inferior lobe of the lungs may cause pneumonia, pulmonary abscess, and/or cysto-bronchial communications [21, 22]. In such situations the clinical manifestations are various, ranging from mild forms presenting with fever and dry cough to severe pictures with worsening dyspnea, acute respiratory failure, and anaphylactic shock. Frank rupture of the cyst into the bronchial tree represents a

very serious event associated with dismal prognosis and usually manifests with severe dyspnea and emission of hydatid membrane and daughter cysts with cough and expectoration. Early diagnosis of liver cyst communications with the pleural cavity or the pulmonary parenchyma is of paramount importance in order to plan appropriate treatment. Emission of bile with expectoration can be present and is a clear sign of bronchobiliary fistula. Chest x-ray usually shows subdiaphragmatic calcifications and pleural effusion. CT scan of the thorax and abdomen is the mainstay for demonstrating pulmonary involvement, and it is essential for surgical planning [21]. Surgical approach changes depending on site and size of the cyst, extension of diaphragm erosion, and size of the fistula. The surgical management of patients with thoracic complications of liver hydatidosis is a complex one due to fact of contemporaneous involvement of the liver, diaphragm, and lung [21]. Some authors suggest only treating the hydatid liver cyst and repairing the diaphragm, as the pulmonary infection may resolve after the abolition of the cysto-thoracic communication; however, a simultaneous treatment of liver cyst along with its thoracic complication is warranted [22]. While sometimes thoracotomy access allows pleural washing and debridement, along with repair of the diaphragm defect and partial resection of the liver cyst, thoraco-abdominal access is warranted in cysts ruptured in the thoracic cavity [21, 23]. Radical pericystectomy remains the treatment of choice; however conservative treatments could be considered safer in cases in which the inflammation process is particularly severe or the cysts are large and in close proximity to hepatic veins. The diaphragm should be closed in layers. In general, use of meshes for diaphragmatic repair should be avoided because of the infection; however when primary repair is not possible, a biological mesh should be considered. In some cases, in which pulmonary necrosis or large pulmonary involvement is present, atypical pulmonary resections are needed (Fig. 13.3). Attention should be paid to meticulous repair of possible bronchial fistulas. When bronchobiliary fistula is present or suspected, postoperative ERCP is suggested

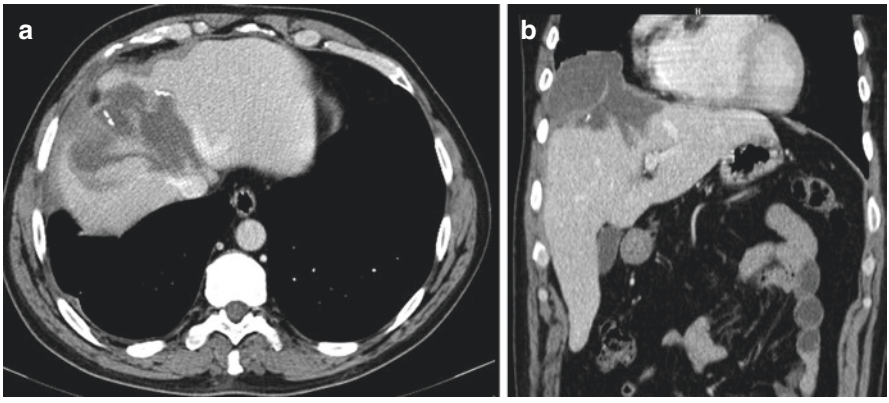

Fig. 13.3 (**a**, **b**) Axial and coronal contrast-enhanced CT scan in a 44-year-old man. The images show a large hepatic hydatid cyst eroding the diaphragm and involving the inferior lobe of the right lung, with broncho-biliary communication. Through a thoraco-abdominal incision, radical pericystectomy, direct diaphragmatic repair, and atypical pulmonary resection was performed

[21, 24]. Pleural decortication may help lung expansion. A water seal drainage tube is placed before closing the thoracotomy.

References

1. Alghofaily KA, Saeedan MB, Aljohani IM, et al. Hepatic hydatid disease complications: review of imaging findings and clinical implications. Abdom Radiol (NY). 2017;42:199–210.
2. Aghajanzadeh M, Hassanzadeh R, Rimaz S, et al. Managements and outcome of complicated liver hydatid cysts. Clin Surg. 2017;2:1820.
3. Bhutani N, Kajal P. Hepatic echinococcosis: a review. Ann Med Surg (Lond). 2018;36:99–105.
4. Yahya AI, Shwereif HE, Ekheil MA, et al. The role of emergency surgery in hydatid liver disease. World J Emerg Surg. 2014;9:12.
5. Keong B, Wilkie B, Sutherland T, Fox A. Hepatic cystic echinococcosis in Australia: an update on diagnosis and management. ANZ J Surg. 2018;88:26–31.
6. Dinc T, Kayilioglu SI, Akturk OM, Coskun F. Surgical management of liver hydatid cyst related non-traumatic emergencies: single center experience. Iran J Parasitol. 2016;11:574–9.
7. Niolu P, Marogna P, Dessanti A, et al. Rare localizations of hydatidosis. Ann Ital Chir. 1994;65:655–7.
8. Akbulut S. Parietal complication of the hydatid disease: comprehensive literature review. Medicine (Baltimore). 2018;97:e10671.
9. Lopez-Marcano AJ, Ramia JM, Arteaga V, et al. Percutaneous drainage as a first therapeutic step prior to surgery in liver hydatid cyst abscess: is it worth it? World J Hepatol. 2017;9:114–8.
10. Ramia JM, Figueras J, De la Plaza R, García-Parreño J. Cysto-biliary communication in liver hydatidosis. Langenbeck's Arch Surg. 2012 Aug;397(6):881–7. https://doi.org/10.1007/s00423-012-0926-8.
11. Toumi O, Ammar H, Gupta R, et al. Management of liver hydatid cyst with cystobiliary communication and acute cholangitis: a 27-year experience. Eur J Trauma Emerg Surg. 2018; https://doi.org/10.1007/s00068-018-0995-7.
12. Dolay K, Akbulut S. Role of endoscopic retrograde cholangiopancreatography in the management of hepatic hydatid disease. World J Gastroenterol. 2014;20:15253–61.
13. Atli M, Kama NA, Yuksek YN, et al. Intrabiliary rupture of a hepatic hydatid cyst: associated clinical factors and proper management. Arch Surg. 2001;136:1249–55.
14. Bedirli A, Sakrak O, Sozuer EM, et al. Surgical management of spontaneous intrabiliary rupture of hydatid liver cysts. Surg Today. 2002;32:594–7.
15. Elbir O, Gundogdu H, Caglikulekci M, et al. Surgical treatment of intrabiliary rupture of hydatid cysts of liver: comparison of choledocoduodenostomy with T-tube drainage. Dig Surg. 2001;18:289–93.
16. Somani SK, Srivastava AP. Resolution of hepatic hydatid cyst with biliary communication with ERCP. J Gastroint Dig Syst. 2012;2:114.
17. Toumi O, Noomen F, Salem R, et al. Intraperitoneal rupture of hydatid cysts. Eur J Trauma Emerg Surg. 2017;43:387–91.
18. Limeme M, Yahyaoui S, Zaghouani H, et al. Spontaneous intraperitoneal rupture of hepatic hydatid cyst: a rare cause of ascites. BMC Surg. 2014; https://doi.org/10.1186/1471-2482-14-99.
19. Amin MU, Tahir A, Akhtar MS, et al. Transdiaphragmatic rupture of huge hepatic hydatid cyst with formation of bronchopleural fistula. J Coll Physicians Surg Pak. 2007;17:431–2.
20. Gomez R, Moreno E, Loinaz C, et al. Diaphragmatic or transdiaphragmatic thoracic involvement in hepatic hydatid disease: surgical trends and classification. World J Surg. 1995;19:714–9. discussion 719
21. Gulamhussein MA, Patrini D, Pararajasingham J, et al. Hepatopulmonary fistula: a life threatening complication of hydatid disease. J Cardiothorac Surg. 2015;10:103.

22. Dziri C, Haouet K, Fingerhut A, Zaouche A. Management of cystic echinococcosis complications and dissemination: where is the evidence? World J Surg. 2009;33:1266–73.
23. Rabiou S, Lakranbi M, Ouadnouni Y, et al. Surgical management of hydatid Bilio-bronchial fistula by exclusive thoracotomy. Int J Surg. 2017;41:112–8.
24. Hady HR, Baniukiewicz A, Luba M, et al. Bronchobiliary fistula as a complication after long-term stenting of hepatic ducts, applied by ERCP after hepatobiliary surgery due to hydatid cyst. Endoscopy. 2011;43(Suppl 2):E178–9.

Management of Cystic Echinococcosis Complications and Dissemination

14

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Echinococcosis in humans results from infection by the larval stages of Taenia echinococcus. So far, six different species have been recognized, but four are of particular public concern [1]. Despite our increased medical knowledge and better control of echinococcal disease, it still remains a major public concern in several countries. The highest incidence of echinococcosis is noted in southern South America, Mediterranean countries, the Middle East, southern and central parts of the former Soviet Union, Central Asia, Australia, China, and parts of Africa. Echinococcosis is not a common disease in the USA, but increased rates have been noted in Alaska, California, Utah, Arizona, and New Mexico [1–3]. The most common sites for hydatid disease in humans include the liver and the lungs [4]. Due to the slow growth of the cysts, patients with echinococcosis can sometimes be diagnosed by the development of complications, some of which may be life-threatening. Due to the great number of organs that may be affected (liver, lungs, spleen, CNS, kidneys, etc.), there are various complications described in the literature, mainly in the form of case-reports (cancer, portal hypertension, Budd-Chiari syndrome, esophageal and gastric variceal bleeding, cerebral vessel aneurysms, hemorrhagic strokes, etc.) [5–10]. The aim of this chapter is to describe the predominant complications associated with echinococcosis, as well as the management of disseminated disease.

Genesis of Complications

The complications seen in patients with hydatid cyst can be divided into two categories, based on the growth phase of the cyst. In the first phase of growth, the cyst is filled with liquid. If the pressure of the liquid exceeds the resistance of the pericysts,

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there is increased risk of rupture. During this stage of development, rupture of the cyst wall can lead to acute anaphylactic reactions, secondary infections, and compression with "mass effect" of adjacent structures. The second phase of growth is characterized by the replacement of the fluid by scolices and membranes, together with the formation of daughter cysts. The host is mounting an inflammatory reaction that leads to the classic cystic wall calcifications. During this stage of growth, the most common complication includes biliary rupture, either through a fissure or due to fistula formation [11].

Liver Hydatid Cyst Rupture in the Biliary Tract

Rupture of a liver hydatid cyst in the biliary system is probably the most common complications with an incidence documented to be between 5% and 25% [12–14]. Cyst-biliary tree communications occur more often in patients with hydatid cysts located centrally in the liver, with cysts close to the liver hilum and in more advanced stage and/or multivesicular cysts [15]. It is a serious complication that makes management and surgical approach technically difficult. It has been shown that the intracystic pressure rises as the diameter of the cyst increases, and this causes the spontaneous rupture in adjacent bile ducts [16]. Another hypothesis postulates that the first step is compression of the wall of the bile duct with subsequent ischemic necrosis and erosion into the bile duct [15]. Patients with rupture in the biliary tract can be classified in two subcategories: those with occult rupture (reported to be up to 90% of cases) that leads to suppuration only and those with significant rupture and cyst – bile duct communication – that leads to passage of cystic material in the bile (Fig. 14.1) [13, 15, 16]. Presence of cystic material in the bile duct has also been associated with the diameter of the fistula. If the communication is <5 mm, the chance of having passage of debris and membranes in the bile duct is slim [15]. Independent predictors for the presence of occult leakage include history of nausea and vomiting, ALP >144 U/L, total bilirubin >0.8 mg/dL, and cystic diameter >14.5 cm. Presence of nausea and vomiting is thought to be due to the toxic effects of hydatid material. Similarly, independent predictors for the presence of frank rupture include history of jaundice or jaundice present currently on physical examination, cyst diameter >10.5 cm, presence of suggestive ultrasonographic findings, and a type IV cyst on ultrasound [16]. Type IV cysts include any complicated cyst, i.e., internal or external rupture, expansion to adjacent structures, and secondary infection (Table 14.1) [17]. The cut-off for diameter in frank rupture is lower, probably because frank rupture causes better cyst evacuation. In a different study, presence of a fibrotic and/or calcified cyst was identified in univariate analysis as a sign that increased the risk of a fistula being present [18]. Based on the above, a surgeon should always suspect the presence of an intrabiliary rupture in patients with larger cysts that present with or without symptoms and have laboratory documentation of cholestasis, even if ALP and bilirubin are slightly increased. Bile duct dilation does not always signify the presence of a communication, since large-sized cysts can cause external

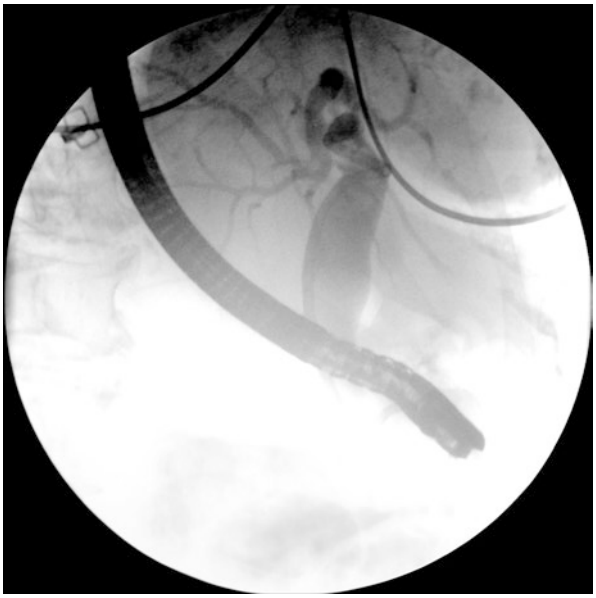

Fig. 14.1 Endoscopic retrograde cholangiopancreatography on a patient with spontaneous rupture of an echinococcal cyst into the common bile duct. There is distention of the common bile duct diameter, and the cyst material is seen as filling defect within the bile duct. Presence of membranes and debris in the common bile duct can also lead to obstruction of the cystic or pancreatic duct leading to cholecystitis or pancreatitis. In the appropriate candidate, ERCP can be both diagnostic and therapeutic, with a sphincterotomy and potential stent placement which will empty the cyst material in the duodenum. (Archives of our department)

Table 14.1 Types of hydatid disease and radiographic description of the findings [17]

Types of hydatid disease	Description
Type I	Initial-active phase. Three layers of the cystic wall are intact. Ultrasound shows anechoic, well-defined cystic lesions with small echogenic foci (hydatid sand). CT scan may reveal contrast enhancement from host tissue compression
Type II	Active-dissemination phase. Outpouching of new cysts from main cavity (hourglass appearance). CT density of mother cyst is higher than the daughter ones. Scattered calcifications may be seen
Type III	Inactive phase. Disease cannot spread. Thick continuous (rim-like) wall calcifications are seen, with possible decrease in cyst size
Type IV	Complicated cyst (e.g., rupture of cyst, superinfection, mass effect)

compression of the duct or can be associated with choledocholithiasis [19]. Increased clinical suspicion leads to proper preoperative work-up that can decrease the rates of redundant intraoperative bile duct explorations.

Patients with intrabiliary rupture of a liver hydatid cyst are usually asymptomatic [20]. If they develop symptoms, this commonly include right upper quadrant pain, jaundice, fever, and chills. In symptomatic patients, the most common finding is

tender hepatomegaly. Patient presentation is very similar to that of biliary obstruction and cholangitis. Laboratory and serologic exams are not specific and usually not helpful in diagnosing intrabiliary rupture [21]. The work-up should always include liver imaging. The two most common diagnostic modalities used are abdominal ultrasound and computed tomography (CT) scans that show the space-occupying lesion in the liver. Presence of a cystic liver lesion with dilated common bile duct and/or jaundice should always include hydatid cyst with potential intrabiliary rupture, especially in patients with history of travel or residence in endemic regions. CT scans can sometimes show the wall defect on the cystic wall and can detect cystic material as low-attenuating substance in the bile duct [15]. Importantly, imaging techniques lose their sensitivity in patients with occult intrabiliary rupture. The clinical suspicion of intrabiliary rupture should preferably be assessed with a magnetic resonance cholangiopancreatography (MRCP) which can show the communication of the bile ducts and the hydatid cyst [22]. Endoscopic retrograde cholangiopancreatography (ERCP) can also visualize the biliary system and potential fistula, and in addition it offers the potential for bile duct manipulation. ERCP has been recommended as standard of care in patients presenting with a stage IV cyst and have a diameter that is greater than 10.5 cm [16]. However, ERCP has also been associated with potential complications and should be used cautiously in patients with vesicles, debris, and hydatid remnants in the biliary duct or in patients with post-inflammatory changes that lead to bile stasis. Communication of the cyst with the bile ducts can also be documented with a percutaneous transhepatic cholangiography (PTC); however, this technique carries an increased risk for anaphylactic reactions, due to the potential spillage of antigenic material within the abdominal cavity, and should be reserved for patients who due to preexisting anatomy their duodenum and ampulla are not readily available with upper endoscopy [16].

The cornerstone of management of patients with intrabiliary rupture includes surgical cystectomy/cystotomy with removal of all daughter cysts, membranes, and debris followed by surgical exploration of the common bile duct. The rates of radical surgical procedures used in patients with frank rupture are reportedly low in the literature, especially due to the high complexity of the surgical procedure and the need for an experienced hepatobiliary surgeon. A radical procedure is recommended in patients with peripheral cysts, since only radical procedures can treat both the communication and the cyst and have been shown to have lower postoperative complications (decreased bile leakage, bilomas, and bile peritonitis rates) [20, 23, 24]. When non-radical techniques are used, the surgeon should decrease the size of the cyst as much as possible, address the cyst-biliary communication, and leave a drain in place [15]. Obtaining an intraoperative cholangiogram, recommended in all patients, can protect patients from unnecessary bile duct explorations [16]. A very useful intraoperative technique for the identification of a communication path between the cyst and the bile ducts include placing a gauze in the cyst after evacuation, filling the cyst with serum, and inserting air in the cystic duct through a catheter, or using dyes, such as methylene blue [25, 26]. Intraoperative identification of bile in the cystic cavity is not a criterion for frank rupture. Nevertheless, whenever possible, the site of bile leakage has to be identified and sutured. Care has to be

given during suturing, to avoid the development of an iatrogenic biliary tree obstruction [16]. All patients should receive broad-spectrum antibiotics, since higher rates of infectious complications are expected due to the bile communications [16]. Potential delay in the surgical management of these patients can lead to suppurative infection of the bile ducts, septicemia, and liver abscesses. Bile duct obstruction caused by missed diagnosis or delayed treatment has been associated with a 50% mortality rate [27]. Presence of membranes and debris in the common bile duct can also lead to obstruction of the cystic or pancreatic duct leading to cholecystitis or pancreatitis [28, 29]. Biliary cirrhosis has also been suggested to be a late sequela of intrabiliary hydatid cyst rupture [30]. Therefore, it is imperative to ensure unobstructed passage of bile to the duodenum. It is important to assess the sphincter of Oddi for presence of sclerotic inflammatory changes. In the case of obstruction, sphincterotomy or sphincteroplasty must be done. If sphincterotomy fails and patient has biliary tree obstruction and incomplete clearing of cystic material, a choledochoduodenostomy or choledochojejunostomy has to be performed [31]. Use of a T-tube can be an alternative to choledochoduodenostomy. It is faster, it carries lower morbidity rates, and it allows for postoperative bile duct monitoring with acceptable results, although there is a small risk of spillage of cyst contents in the peritoneal cavity [15]. In small case series in the literature, some authors also suggest a cholecystectomy, in cases of cholelithiasis or cholecystitis [16]. Either cystectomy/cystotomy or common bile duct exploration alone is not sufficient to address the issue and reduce recurrences. There are different techniques that can be used in the treatment of the residual cystic cavity. Decision depends on the location and size of the cyst, cyst's proximity to the hilum and vascular structures, and surgeon's preference [21]. Right or left lobectomy can be used in patients with large cysts that occupy the entire liver lobe, only if the remnant liver volume is sufficient [32]. Omentoplasty should be avoided in patients with suppurated cysts or patients that have cyst-biliary tree communication. There is some controversy in the literature regarding the utilization of hypertonic solution in these patients, mainly because of concerns for acute hypernatremia and delayed adverse effects (e.g., sclerosing cholangitis) [33, 34]. Also, evidence in the literature recommends against the utilization of anti-helminthic agents in patients with suspected intrabiliary rupture due the increased risk of reactive sclerosing cholangitis [15]. Potential postoperative complications include the formation of an external bile fistula (rates of 5–27%), surgical site infections, bile collections, bleeding, and abscess formation [15, 16]. Laparoscopic approach in patients with liver hydatid cyst and rupture in the biliary tree is proven to provide acceptable results in terms of disease source control, without increased postoperative morbidity [35].

Intraperitoneal Rupture of Hydatid Cyst

Spontaneous intraperitoneal rupture of a hydatid cyst is a rare complication that is associated overall with significant morbidity and mortality. The incidence of intraperitoneal rupture is reported to range from 1% to 16% [36–38]. It is most

commonly the result of liver cysts, but there have been reports of intraperitoneal ruptures in patients with splenic hydatid cysts too. Rupture of the cyst usually follows an increase in the intracystic pressure. This may be the result of abdominal trauma or after significant cyst enlargement [39]. Cysts closer to the liver surface, with larger size, and viable cysts with higher pressures are more likely to rupture [40]. The most important predisposing factors for rupture are young age and more superficial location [41]. Younger age may be due to increased risk for blunt abdominal trauma and also because elderly patients tend to go to the hospital for associated comorbidities more often than young patients. This can lead to earlier diagnosis and management of hydatid cysts. Rupture of the endocyst with an intact pericyst does not result in antigenic dissemination, and anaphylactic reactions are rare. This type of rupture can be diagnosed using imaging procedures that will show indulation of the cystic wall without changes in the cavity size. Complete rupture of the pericyst wall too leads to spillage of the cystic content in the abdomen, and it can be fatal. The most common cause of death in these patients is anaphylactic shock. However, there have been some cases in the literature with death secondary to the development of late peritonitis [42]. Compared to elective cases, emergent surgical management for patients with complicated, ruptured hydatid cyst has higher mortality rates [36].

Contact of the highly antigenic content of the cyst with the peritoneal surface is usually followed by abdominal pain and activates an alternative complement pathway that can lead to allergic and anaphylactic reactions [36, 43]. Minor allergic reactions after hydatid cyst rupture occur in 17–25% of the patients. More severe anaphylactic reactions occur in 1–12% of patients. Incidence of severe anaphylactic shock is reported to be 1.4% [44]. The initial presentation is usually severe and alerting with peritoneal signs (rebound tenderness and guarding) [40]. The first signs of anaphylaxis develop within minutes after the rupture. Patients develop high fever, pruritus, urticaria, angioedema of the face, dyspnea, shortness of breath, and stridor, followed by cardiovascular collapse [45, 46]. In some patients, initial rupture is associated with a decrease in abdominal pain, due to the rapid shrinkage of the hydatid cyst's size. This can delay surgical treatment in patients not developing an immediate allergic reaction and may gravely affect patient's prognosis. Treating physicians should always bear in mind this initial brief pain relief and monitor patients closely [42, 47].

Usually the first imaging test is an abdominal US. On US the most common findings include regression of the size of the liver cyst (in case there has been previous imaging and measurement). In CT scans, the diagnosis of rupture can be easier. The wall enhances after contrast administration. Detection of wall irregularity usually represents the probable rupture site [42]. Furthermore, intraperitoneal free fluid can be identified [45]. In equivocal cases, MRI of the abdomen can help differentiate the cystic lesion in the liver and diagnose the rupture. Some patients with equivocal imaging findings may benefit from a diagnostic laparoscopy.

Immediate surgical procedure is necessary after the rupture is diagnosed. If definitive treatment is delayed, peritonitis, allergic reaction, and anaphylaxis may develop. Prior to going to the operating room, appropriate medical management for

the allergic reaction is necessary. Intraoperatively the objective is to decrease complication rates and eliminate primary disease. Radical procedures may be more difficult to perform in an emergency setting. Conservative approaches with unroofing, cavity filling, and external drainage are easier, faster, and safer [45]. Conservative approaches are usually complicated by recurrences and cavity-related morbidity [41]. Radical procedures may also be hard to perform in patients with rupture following abdominal trauma, due to the concurrent organ injuries. In these patients conservative surgical management combines ease and fast source control [47]. Efforts should be made to carefully remove all protoscoleces from the peritoneum, and the surgeon should irrigate the abdomen with scolicidal agents (hypertonic normal saline, formalin, silver nitrate, povidone-iodine, chlorhexidine) and then with normal saline, to reduce recurrence rates [40]. Intra-abdominal dissemination with development of secondary foci and peritoneal hydatidosis is a major concern in these patients [39]. Another complication that can appear after liver hydatid cyst surgery is bile leakage. To avoid this complication, the surgeon has to carefully examine the cyst and identify and suture any possible connections with the biliary tree. Diagnosis of postoperative bile leakage may require ERCP and biliary stenting [44]. Postoperative follow-up of the patients with imaging of the abdomen, US or preferentially CT scans, and serology is indicated, in view of the increased risk for secondary hydatidosis [45, 48]. Albendazole treatment has been shown to be effective in reducing recurrence and peritoneal hydatidosis and should be administered for prolonged periods postoperatively (3–6 months) [36]. Recurrence rates vary widely in the literature [47, 49].

Intrathoracic Rupture

Liver hydatid cysts (especially in the liver dome) can also rupture into the thorax (Fig. 14.2a–c) [50]. Intrathoracic rupture is a rare complication, with an incidence ranging from 0.6% to 16% that is associated with increased morbidity and mortality (9–43%) [51–53]. Rupture can occur to the mediastinum, lung, pleural cavity, or pericardium [53]. It has been hypothesized that intrathoracic rupture can be promoted by the pressure gradient that exists between the abdominal and thoracic cavities, that aids in thoracic expansion, or due to the hepatomegaly from the hydatid cyst and the surrounding inflammation that obliterates the hepatodiaphragmatic space, compresses the diaphragm, and causes ischemia. In addition to that, it has been postulated that in patients with cystic-biliary communications bile can cause chemical injury to the diaphragm and subsequently to the lungs and pleura [54].

The clinical signs and symptoms of patients are predominantly from the respiratory system. The most common symptom is irritating cough. Acute rupture in the pleural cavity usually leads to sudden pain, and it has also been associated with anaphylactic reactions with high mortality. Other symptoms include expectoration, purulent sputum, chest pain, shortness of breath, and dyspnea. Some patients may also present with fever, due to the infected daughter cysts present in the pleural

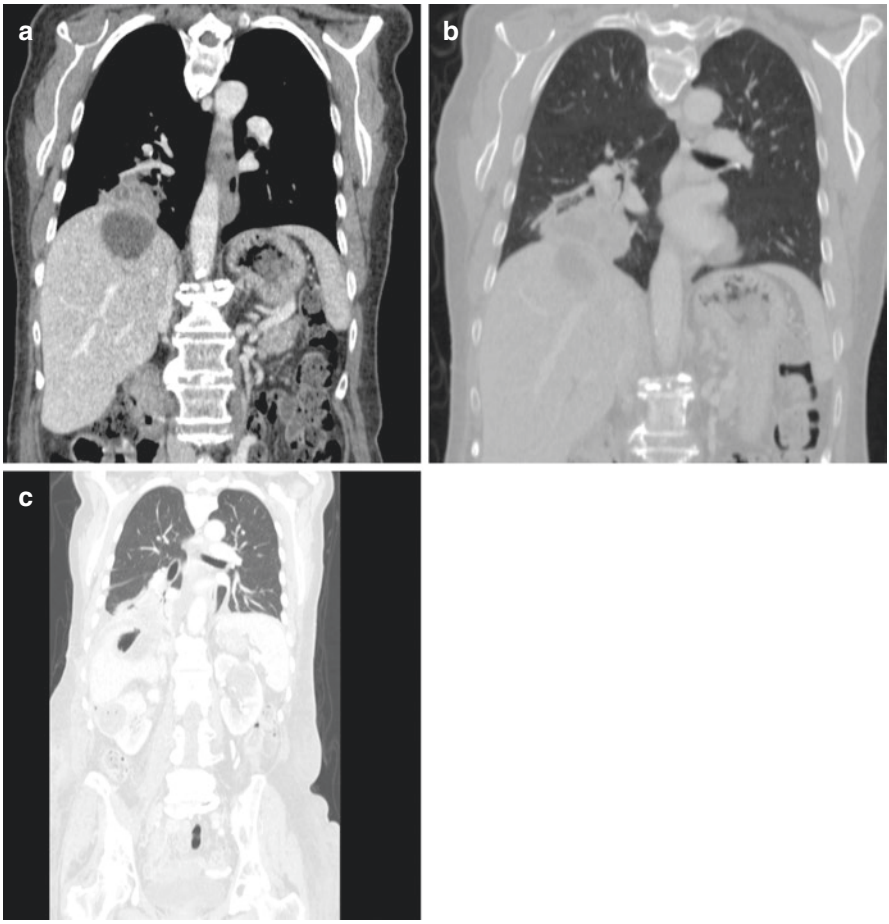

Fig. 14.2 Coronal CT imaging of a patient with hepatic dome cyst rupture. The cyst has ruptured through the diaphragm, with erosion of pulmonary parenchyma and bronchi, with bronchobiliary fistula and hemoptysis. (Archives of our department.) (**a**) Abdominal window. (**b**) Lung window. (**c**) After surgical exploration and cyst removal

cavity or the lung parenchyma. Abdominal symptoms do not predominate and, if present, are commonly subtle. Presence of jaundice or elevation of cholestatic enzymes in laboratory work-up should always raise concern for a concurrent presence of an intrabiliary rupture [54]. A serious complication that may result from rupture of a hydatid cyst in the thorax is the development of a bronchobiliary fistula. A bronchobiliary fistula should be suspected in patients with history of hydatid cyst or patients coming from endemic countries, which present with cystic fluid expectoration and/or hemoptysis. Other potential complications include pneumonitis and lung abscesses. A reactive pneumonitis can also happen when the cyst ruptures into a bronchus and there is cystobiliary communication, with free bile passage into the bronchi and lung parenchyma [53].

Diagnostic work-up usually starts with chest imaging, most commonly a chest x-ray. Findings typically include the presence of right lower lobe opacities and/or pleural effusions. Abdominal imaging is indispensable for the diagnosis. An abdominal ultrasound followed by a CT scan of the abdomen is usually performed and helps in visualization of the hydatid cyst in the liver and potential communication with the thorax, and they also allow for assessment of the size, location, and association of the cyst with other hepatic structures. These findings can help determine the extent of the disease, identify the thoracic communication site, and determine the best surgical approach for the patient [51, 54, 55]. Due to the predominance of respiratory symptoms, some patients undergo bronchoscopy first. Expected findings include the presence of fluid mixed with daughter vesicles and fragments of the cystic membrane. In cases with a co-existing cyst-biliary fistula, bile may also be seen in lung lobes. Bronchoscopy also offers a better assessment of the extent of the inflammatory process in the lungs [54].

The treatment of choice for intrathoracic rupture of hydatid cyst is surgical management. Access to the thoracic cavity is usually done with a posterolateral thoracotomy. First step is the evacuation of the pleural cavity, followed by pulmonary decortication. After identification of the diaphragmatic rupture site, if access to the liver is not sufficient, the surgeon can elect to further dissect the diaphragm or reposition the patient and perform a laparotomy. After addressing the hepatic hydatid cyst, drains should be left in place, and the diaphragm should be closed in layers. The next step includes treatment of lung pathology, as well as drainage of the chest [54]. In case there is a separate lung hydatid cyst identified intraoperatively, it should be resected en bloc. The surgeon should look for presence of fistulas that should be taken down, with suturing of the pulmonary cavity. Lung resections should not be the standard of care. Pneumonectomies need to be performed selectively, usually in patients with severely damaged lung parenchyma. The goal is to remove the infected material, leave a drain, and re-expand the lung as soon as possible [53]. Reported surgical complications include hemorrhage, biliary leaks, iatrogenic injuries to the inferior vena cava, and respiratory complications from the thoracotomy that may lead to acute respiratory failure with cardiac arrest [54]. Hydatid cyst rupture in the pleural cavity is associated with higher recurrence rates, compared to rupture in the bronchi, but this should never encourage the surgeon to perform a pleuropneumonectomy. In the majority of cases, more limited procedures will clear the cysts and fistulae [53].

Intrapleural Rupture of Pulmonary Hydatid Cyst

Pulmonary hydatidosis can lead to expansion of the cyst with rupture in the pleural cavity. Rupture is more frequently the result of more superficially located and larger lung or liver lesions but can also be secondary to chest trauma or iatrogenic (needle aspiration/biopsy). This is a rare event that leads to fluid and scolices deposited in the pleural cavity [56]. Rupture can be a potentially lethal complication, as it can lead to anaphylactic shock or secondary acute respiratory failure [57]. Intrapleural

rupture may also lead to asthmatic attacks and give rise to secondary foci that can decrease the feasibility of a complete resection and increase the chance of recurrence. Delayed diagnosis (usually 10–15 days after the rupture) may lead to secondary bacterial infections, empyema, and lung abscesses [56]. Two separate patterns of rupture have been identified. First, when there are no adhesions in the pleural cavity, rupture can lead to pneumothorax or hydropneumothorax. Usually there is a small bronchial tree fistula that is not large enough to spontaneously drain cyst contents. Second, if there are adhesions in the pleural cavity, rupture is not as common, because of the protective pleural effect. However, it may still occur and lead to pleural antigen seeding [58].

In the literature, the incidence of intrapleural rupture of pulmonary hydatid cysts ranges from 1.5% to 6% [59]. The most common clinical symptoms include chest pain, dyspnea, and cough. Other symptoms may include expectoration or fever. Hemoptysis and vomiting can be seen in patients with concomitant bronchial rupture [59]. A small percentage of patients may be asymptomatic and diagnosed incidentally during physical examination or chest imaging for other reasons. Intrapleural rupture may be clinically challenging to diagnose, mainly because of the broad spectrum of differential diagnosis including mainly cancer, tuberculosis, and infections. In addition, the lack of clinical symptoms or pathognomonic signs of echinococcosis can be confusing. Chest x-ray in these patients shows the presence of pleural fluid with or without pneumothorax [60]. Laboratory testing in the acute setting may show signs of infection with increased white blood cell counts. Specific serologic testing for echinococcosis can be positive in 60% of the cases [59]. Uncomplicated, intact cysts trigger a minimal antibody response and have increased rates of false-negative serologic testing. On the other hand, ruptured or leaking cysts trigger a stronger immune reaction and are more likely to have positive antibody testing [1].

Surgery is the mainstay of treatment for patients with lung echinococcosis and intrapleural rupture [59, 61]. Considering the risk of respiratory failure and secondary infections, surgery has to be performed as soon as possible after the diagnosis, preferably in the first 5 days. Surgery includes evacuation of the pleural cavity and pleural decortication [62]. This way, full lung expansion is promoted, and the risk of recurrence is reduced. When pleural effusion is significant or there is a severe pleural empyema, management can include the placement of a chest tube for a few days, as a temporary control measure, followed as soon as possible by surgery [59]. Thoracoscopy may be used, before surgery, as a means to fully assess the pleural cavity and perform adhesiolysis [63]. After addressing the rupture and dissemination in the pleural cavity, the pulmonary hydatid cyst can be resected in the standard fashion [64, 65]. The most common and immediate postoperative complications include the development of hemothorax, pneumothorax, or pyothorax. The longer the time to definitive treatment (especially if more than 10 days into the disease), the higher the rates of bronchopleural fistula and empyemas [59]. While not indicated in all cases, patients with advanced and/or disseminated disease may benefit from additional medical treatment. Long-term follow-up is needed for early detection of recurrences [58].

Other Complications

Secondary infection of a hydatid cyst is a common complication [66]. In many cases, due to the asymptomatic nature and slow development of the primary cyst, a bacterial infection can be the first symptom of the disease. Bacterial contamination of the hydatid cyst usually occurs from bacteria present in nearby structures (e.g., biliary tree, bronchi) or from bacteremia that allows seeding of the cyst from microorganisms present in the blood [43]. However, infections usually occur in patients with no history of biliary disease. Therefore, it has been assumed that the hydatid cyst in the liver causes local mass effects that alters the anatomy of the biliary tree and helps bacterial proliferation locally that secondarily invade the cyst. Suppuration usually presents with fever, hepatomegaly, and abdominal tenderness in the right upper quadrant. There are cases in the literature of patients with superinfections that presented with allergic reactions and angioedema [43]. Laboratory findings are not trustworthy for the diagnosis of a hydatid cyst superinfection. Leukocytosis and increased eosinophils are present in 30–40% of patients [43]. Drainage of the cyst in patients with suspected secondary infections can be diagnostic and therapeutic. Drainage can be performed either surgically (marsupialization) or percutaneously and patients should also receive antibiotic treatment after the procedure. Fluid retrieved must be cultured, even though microbiologic diagnosis may not be achieved in all patients. In some cases, polymicrobial infections occur [14].

Cystic hemorrhage is a rare complication. Usually, bleeding complications are the result of iatrogenic interventions (percutaneous or surgical) or result from abdominal trauma [67]. However, there are a few cases in the literature with nontraumatic bleeding in the setting of echinococcosis. This can be the result of cyst erosion into a vessel (e.g., hepatic vein) [68]. This usually leads to severe bleeding with hypotension and shock and is usually associated with a grave prognosis or can lead to severe intraoperative bleeding after surgical manipulations and cystic exploration. In the hemodynamically stable patient, angiography and embolization may be an option; however, surgical exploration is often the only definitive treatment and should not be delayed especially in the presence of hemodynamic instability [69].

Occasionally a liver hydatid cyst may lead to the formation of pseudoaneurysms in the hepatic vessels with bleeding in the cyst or to the formation of subcapsular hematomas [67]. Pseudoaneurysms are hypothesized to be the result of local inflammation that can affect vessel wall integrity or may be the result of cystic calcifications that mechanically damage the vessel's anatomy [70]. If there is a concomitant cyst-biliary connection, bleeding in the cyst may present with hemobilia and anemia. These cases are best managed with angiography and coil embolization [67]. If the patient presents with hemodynamic instability, emergent surgical exploration is mandated [67].

Another rare complication is recurrent upper GI bleeding after the formation of a gastric fistula. In both published cases, patients were treated surgically with infection source control and fistula take down [71].

Management of Disseminated Disease

As mentioned above, the most common locations for cystic lesions is the liver (60%), followed by the lungs (20%). However, all tissues in the human body can be infected [72]. Other sites infected in <10% of patients include the spleen, kidneys, orbits, heart, central nervous system, and the bones [73]. There is controversy over which is the best surgical approach in patients with echinococcal disease and whether radical or conservative surgical approach should be implemented. In radical procedures, the cyst is completely removed [74]. Surgery still remains the standard of care for echinococcosis; however Simon et al. showed that there may be place for attempted medical management alone in patients that are poor surgical candidates [75]. Apart from the risk of disseminated disease at presentation, it is important that the surgeon always keeps in mind that hydatid cysts may recur, not only in the initial organ but also in remote areas of the body [73].

Splenic cystic echinococcosis Hydatid cysts of the spleen can be asymptomatic for an extended period of time. If symptoms are present, these usually include pain in the left upper quadrant with concomitant splenomegaly (palpable mass). Diagnosis is established with imaging, mainly CT scans and abdominal US. They can reveal the characteristic morphology of echinococcal cysts with peripheral calcification and at the same time can help identify the borders, relations with adjacent structures and potential complications. Serologic tests can be used to increase the specificity of the diagnosis. Existing serologic tests for the diagnosis of echinococcosis include the indirect hemagglutination test, the ELISA test (positive in 90% of infected patients), the complement fixation test, the radioallergosorbent test, and the counterimmunoelectrophoresis test [76]. The mainstay of treatment is surgical excision, in combination with medical treatment. Antiheminthic treatment usually starts 2–3 weeks before elective hydatid cyst surgery and is continued postoperatively for 6–8 weeks [44]. The treatment of choice is splenectomy, but conservative procedures with cyst enucleation, unroofing with omentoplasty, or partial splenectomies have been described. More conservative approaches are used in patients with an uncomplicated solitary cyst located in the periphery of the splenic parenchyma that can be surgically removed, or in children, where preservation of splenic function is important for immune system regulation [77].

Osseous cystic echinococcosis Bones rarely get infected with echinococcus, except perhaps in the immunocompromised host (0.5–2.5%). Typically, it is one of the hardest forms of the disease to treat, because at the time of diagnosis, lesions are diffuse. The disease is usually asymptomatic, while the infection spreads in the bone, and symptoms predominantly of pain appear in advanced stages. When long bones are affected some patients may present with pathologic fractures, while if the vertebra are involved, neurologic deficits and chronic pain commonly arise from compression of the spinal canal and nerves. Local disease is different in bones, as the rigid tissue prevents the formation of a capsule and infection spreads through

mechanical expansion, compression atrophy of surrounding bone, and activation of osteoclasts [78]. The resistant nature of bony tissue slows the rate of expansion [79]. Bone disruption can lead to extraosseous invasion of soft tissues with the formation of a hydatid abscess [78].

Cystic structures are not common in bone hydatidosis. Macroscopically, small vesicles can be identified, without a clear margin between healthy and diseased bone. Furthermore, the microscopic invasion is more extensive and guides recurrences, even after seemingly wide resections. A conventional x-ray at the bone sites where symptoms predominate can help identify the disease. However, radiographic findings usually lag behind bone invasion. Typical findings include not clearly demarcated lacunar lesions without a periosteal reaction or clear transition points from diseased to normal bone and without any morphological bone changes. In patients with suspected hydatid disease of the bones, MRI is the preferred imaging test. Percutaneous aspiration of the cyst should not be used. It can increase the risk of dissemination and can also lead to anaphylactic reactions [79]. Radiographic findings can raise concern for bone hydatidosis in a patient with the suitable clinical background. Final diagnosis can be confirmed with positive serological testing. Major differential diagnoses that have to be ruled out are tuberculosis of the bones, osteomyelitis, and benign and malignant tumors [78].

Locations that can be involved include the spinal and pelvic skeleton. Vertebral involvement, usually cervical and lumbar, is the most common form of osseous hydatidosis. Vertebral involvement has a high risk of being associated with neurologic deficits and surgical approach is challenging. At the advanced stages of disease, when clinical symptoms are usually apparent, multiple vertebral levels are commonly infected. Patients with pelvic echinococcosis also present at advanced disease stages. The clinical latency leads to invasion of the sacroiliac and pelvic-femoral joints completely altering disease prognosis and management options [78].

The mainstay of treatment is surgical. In vertebral body involvement the surgical approach has to be two-staged, because of the involvement of both the anterior and posterior arches. The first step includes the removal of the posterior arch with spinal cord decompression and osteosynthesis, while the second step includes resection of the anterior arch. In pelvic disease, total removal of disease burden is associated with many technical difficulties. Prosthetic materials are not indicated because of the potential risk for infection. As a result, trochanteroiliac coaptation or femoral head and neck resections are performed, with the aim to achieve a long-term disease-free interval. When long bones are involved, if disease is isolated to the bone, complete en bloc resection of the long bone can be sufficient to control the disease. However, if disease has already spread amputation of the limb is the only solution that offers long-term remission. The combination of surgical management with medical treatment remains debated in patients with osseous hydatidosis [78]. If medical treatment is used, it has been suggested that long postoperative duration is needed. Follow-up imaging has to be performed, to assess for recurrence after surgical management or for cystic size reduction in patients treated medically [79]. Correlation studies between the location of the disease and the recurrence rates have

shown that osseous hydatid cysts that involve the epidural space have small vesicles that rupture and increase recurrence rates. To decrease the risk of recurrence the use of hypertonic saline as a scolicidal has been proposed [79].

Cystic echinococcosis of the heart and pericardium Heart involvement is rare. Larvae reach the myocardium through the coronary circulation. Patients with heart echinococcosis have high mortality rates [80]. The most common location of a hydatid cyst in the heart is the left ventricle, probably due to the dominance of the left coronary artery or the higher mass of the left ventricle [81]. Sudden death can follow acute intracavitary rupture. Large cystic fragments and membranes can obstruct ventricular outflow tract, cause massive pulmonary embolism with acute right heart failure, or cause bilateral emboli to the CNS. Shower emboli throughout the human body may also happen after rupture in the left cardiac cavities. Intrapericardial rupture may lead to acute death due to tamponade [81]. If the patient survives, the acute rupture can lead to secondary dissemination of disease with metastatic foci. Heart echinococcosis may be asymptomatic, or patients may complain about chest pain, dyspnea, and palpitations. Heart involvement can also simulate valvular disease, coronary artery disease, acute myocardial infarction, and heart failure. In cases when the interventricular septum is involved, hydatid cysts in the heart may affect the conduction pathway and cause arrhythmias or recurrent syncopal episodes [81]. However, because the initial symptoms are subtle and generally well tolerated by the patients, diagnosis can be further delayed. Pericardial cysts usually result from rupture of a primary hydatid cyst site, most commonly the heart. Intrapericardial rupture may also lead to pericarditis from the exudative allergic reaction, transient chest pain, and fever [81]. Furthermore, pericardial hydatid cysts may also lead to external compression of the cardiac cavities or can lead to constrictive pericarditis. Diagnosis is made with ultrasound and serological tests. US findings suggesting the diagnosis can include a fluid-filled cyst, in a favorable clinical context. A detached membrane is the only diagnostic sign. US findings are not easy to interpret and differentiate from heart tumors or mural thrombi in patients with complicated or ancient hydatid cysts in the degeneration phase. In these patients, an echogenic mass is visualized on US. Surgical planning can be safely based on the results of the US; however, unless it is an emergent case, additional imaging with CT or MRI should be sought [81]. Chest x-ray commonly shows abnormalities in the cardiac silhouette, and in some cases, it may show cystic wall calcifications.

The cornerstone of treatment is surgical excision of the cyst. Surgery can be avoided only in patients that have small, calcified cysts without any symptoms that compromise hemodynamic stability or blood supply through the coronary arteries [81]. In difficult cases that involve heart chambers, standard cardiopulmonary bypass can be used with arrest of heart function. In patients with right-sided cysts, it is important to add a filter to the bypass machine, in order to avoid passage of cystic membranes and debris. The pericardial cavity has to be carefully examined in all operative patients. The cyst should be injected with scolicidal agents and then

incised. Cystic bed and pericardial tissues should be washed with hypertonic saline. Formalin should not be used due to its toxic action on the myocardium [81]. If the cystic wall is thin and the location is away from all important vascular structures, a cystectomy may be performed. The cystic bed and the residual cavity need additional management. They constitute an area of myocardial fragility that may postoperatively lead to myocardial wall aneurysms or rupture. The cavity should be closed with superficial sutures. Capitonage should not be used, to avoid the risk of blockage. Perioperative mortality ranges from 5% to 10% in the literature [82, 83]. Bleeding seems to be a complication with high risk of occurrence after open heart procedures for hydatid cysts. Medical treatment (e.g., albendazole) can be used in the postoperative period, to decrease recurrence rates [80, 81]. Pericardial recurrences are more common than myocardial. These may be the result of intraoperative dissemination or missed small cysts if the pericardium was incompletely examined [80, 81].

Cystic echinococcosis of the kidney Kidneys can be involved in up to 4% of patients. As in all other regions of the body, the cysts enlarge slowly. They are initially a single vesicle, but as they enlarge, they become multivesicular. In the majority of the cases, renal hydatid cysts are solitary. When symptomatic, patients usually present with flank pain and a palpable mass that is tense and mobile. Abdominal pain with distention, bloating, and vomiting can also be noted. As the cyst is increasing in size, it expands toward the surface of the kidney and looks like an external structure, even though it is always below the renal capsule. Increased compression to the kidney leads to elongation and atrophy of the calyces. Some patients may also have hematuria. Rupture into the urinary system leads to hydatiduria (22%) that can be easily recognized from the passage of daughter cysts in the urine. Abdominal x-ray scans may show calcifications (35%). IVP can be used to show the anatomy of the urinary system and external compression or obstruction by the cyst. Ultrasound can provide more information and can diagnose the presence of a renal hydatid cyst. In equivocal cases, CT scan can follow that can show the classic pattern of cystic wall calcifications. Diagnosis can be supported by the positive serological tests. Treatment is surgical and includes cystectomy, performed using a lumbar approach, which provides sufficient exposure irrespectively of the size of the cyst. In patients with damaged kidneys from old, infected or ruptured cysts a total nephrectomy has to be performed. Initial cyst excision can help visualize and assess the viability of the renal parenchyma before the nephrectomy. Medical treatment should be given postoperatively with close follow-up for recurrences [84].

Cystic echinococcosis of the central nervous system Central nervous system infection by Echinococcus occurs in 1–2% of patients. Increased rates have been recorded in the pediatric population. The cysts are usually intraparenchymal and solitary. Cysts can initially be asymptomatic, but as they increase in size symptoms occur [85]. Apart from the size, number, and location of cysts, development of symptoms also depends on the host's immune reaction. Symptoms of increased intracranial pressure predominate and include headache, nausea, vomiting,

papilledema, and focal neurologic symptoms. Diagnosis requires head imaging, with CT or MRI. The cysts appear as a well-defined lesion without surrounding edema and usually without calcifications [85, 86]. Presence of calcifications usually signifies death of Echinococcus, while any disruption in the wall of the cyst may signify a previous rupture. The fluid included in the cyst has the same density with cerebrospinal fluid. Serological tests have low sensitivity for diagnosis of intracranial infections. Diagnosis of echinococcal infection of the central nervous system can be supported by positive serological titers. Treatment is surgical and includes a large craniotomy, with careful cyst removal. Dowling's technique remains the most commonly used technique that utilizes hydrostatic dissection to separate the cyst from the surrounding healthy brain parenchyma. Intraoperative ultrasound can be helpful in determining cyst's outline. Hypertonic saline swabs can be helpful if cyst rupture occurs (care should be taken to limit systemic absorption). Intraoperative cyst rupture necessitates postoperative medical treatment with antihelminthic drugs (e.g., albendazole) [85].

If a patient presents with more than one organ affected, the surgical strategy should focus on minimizing the risk of postoperative morbidity and mortality for the patient. If there is no risk for the patient's life, all organs can be addressed during one elective operation. In patients that are poor surgical candidates and cannot undergo such an extensive procedure, therapeutic management should begin with the complicated hydatid cysts and address all of the infected organs in a step-wise surgical approach [87].

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References

1. Moro P, Schantz PM. Echinococcosis: a review. Int J Infect Dis. 2009;13(2):125–33.
2. Burgos R, Varela A, Castedo E, Roda J, Montero CG, Serrano S, et al. Pulmonary hydatidosis: surgical treatment and follow-up of 240 cases. Eur J Cardiothorac Surg. 1999;16(6):628–34; discussion 34–5.
3. Thapa B, Sapkota R, Kim M, Barnett SA, Sayami P. Surgery for parasitic lung infestations: roles in diagnosis and treatment. J Thorac Dis. 2018;10(Suppl 28):S3446–S57.
4. Safioleas M, Misiakos EP, Dosios T, Manti C, Lambrou P, Skalkeas G. Surgical treatment for lung hydatid disease. World J Surg. 1999;23(11):1181–5.
5. Dulger AC, Kucukoglu ME, Akdeniz H, Avcu S, Kemik O. [Case report: Budd-Chiari syndrome and esophageal variceal bleeding due to alveolar echinococcosis]. Turkiye Parazitol Derg. 2010;34(3):187–90.
6. Kantarceken B, Cetinkaya A, Bulbuloglu E, Demirpolat G. Splenic hydatic cyst as a cause of sinistral portal hypertension and isolated gastric variceal bleeding. Turk J Gastroenterol. 2010;21(3):317–20.
7. Poyrazoglu OK, Ataseven H, Bektas S, Aydin A, Yalniz M, Celebi S, et al. Portal hypertension due to Echinococcus alveolaris: a case report. Acta Med (Hradec Kralove). 2007;50(1):57–9.

8. Assad F, Lins E. [Mycotic aneurysm of the middle cerebral artery in echinococcal infestation]. Neurochirurgia (Stuttg). 1984;27(3):89–92.
9. Turhan N, Esendagli G, Ozkayar O, Tunali G, Sokmensuer C, Abbasoglu O. Co-existence of Echinococcus granulosus infection and cancer metastasis in the liver correlates with reduced Th1 immune responses. Parasite Immunol. 2015;37(1):16–22.
10. Kanj AH, Fares YH, Yehya RR, Hamzeh FF. Unusual appearance of a cerebral hydatid cyst as a hemorrhagic infarct. Neurosciences (Riyadh). 2010;15(4):275–6.
11. Derbel F, Mabrouk MB, Hamida MBH, Mazhoud J, Youssef S, Ali AB, et al. Hydatid cysts of the liver-diagnosis, complications and treatment. Abdominal Surgery. 2012;5:105–38.
12. Vignote ML, Mino G, de la Mata M, de Dios JF, Gomez F. Endoscopic sphincterotomy in hepatic hydatid disease open to the biliary tree. Br J Surg. 1990;77(1):30–1.
13. Dadoukis J, Gamvros O, Aletras H. Intrabiliary rupture of the hydatid cyst of the liver. World J Surg. 1984;8(5):786–90.
14. Erguney S, Tortum O, Taspinar AH, Ertem M, Gazioglu E. [Complicated hydatid cysts of the liver]. Ann Chir. 1991;45(7):584–9.
15. Ramia JM, Figueras J, De la Plaza R, Garcia-Parreno J. Cysto-biliary communication in liver hydatidosis. Langenbeck's Arch Surg. 2012;397(6):881–7.
16. Atli M, Kama NA, Yuksek YN, Doganay M, Gozalan U, Kologlu M, et al. Intrabiliary rupture of a hepatic hydatid cyst: associated clinical factors and proper management. Arch Surg. 2001;136(11):1249–55.
17. Polat P, Atamanalp SS. Hepatic hydatid disease: radiographics findings. Eurasian J Med. 2009;41(1):49–55.
18. El Malki HO, El Mejdoubi Y, Souadka A, Mohsine R, Ifrine L, Abouqal R, et al. Predictive model of biliocystic communication in liver hydatid cysts using classification and regression tree analysis. BMC Surg. 2010;10:16.
19. Prousalidis J, Kosmidis C, Anthimidis G, Fachantidis E, Harlaftis N, Aletras H. Forty-four years' experience (1963-2006) in the management of primarily infected hydatid cyst of the liver. HPB (Oxford). 2008;10(1):18–24.
20. Avcu S, Unal O, Arslan H. Intrabiliary rupture of liver hydatid cyst: a case report and review of the literature. Cases J. 2009;2:6455.
21. Paksoy M, Karahasanoglu T, Carkman S, Giray S, Senturk H, Ozcelik F, et al. Rupture of the hydatid disease of the liver into the biliary tracts. Dig Surg. 1998;15(1):25–9.
22. Borahma M, Afifi R, Benelbarhdadi I, Ajana FZ, Essamri W, Essaid A. Endoscopic retrograde cholangiopancreatography in ruptured liver hydatid cyst. Indian J Gastroenterol. 2015;34(4):330–4.
23. Safioleas MC, Misiakos EP, Kouvaraki M, Stamatakos MK, Manti CP, Felekouras ES. Hydatid disease of the liver: a continuing surgical problem. Arch Surg. 2006;141(11):1101–8.
24. Zaouche A, Haouet K, Jouini M, El Hachaichi A, Dziri C. Management of liver hydatid cysts with a large biliocystic fistula: multicenter retrospective study. Tunisian Surgical Association. World J Surg. 2001;25(1):28–39.
25. Kilic M, Yoldas O, Koc M, Keskek M, Karakose N, Ertan T, et al. Can biliary-cyst communication be predicted before surgery for hepatic hydatid disease: does size matter? Am J Surg. 2008;196(5):732–5.
26. Pedrosa I, Saiz A, Arrazola J, Ferreiros J, Pedrosa CS. Hydatid disease: radiologic and pathologic features and complications. Radiographics. 2000;20(3):795–817.
27. Lewall DB, McCorkell SJ. Rupture of echinococcal cysts: diagnosis, classification, and clinical implications. AJR Am J Roentgenol. 1986;146(2):391–4.
28. Saez-Royuela F, Yuguero L, Lopez-Morante A, Perez-Alvarez JC, Martin-Lorente JL, Ojeda C. Acute pancreatitis caused by hydatid membranes in the biliary tract: treatment with endoscopic sphincterotomy. Gastrointest Endosc. 1999;49(6):793–6.
29. Abou-Khalil S, Smith BM, MacLean JD, Poenaru D, Fried GM, Bret P, et al. Acute cholecystitis and cholangitis caused by Echinococcus granulosus. Am J Gastroenterol. 1996;91(4):805–7.
30. Kattan YB. Intrabiliary rupture of hydatid cyst of the liver. Ann R Coll Surg Engl. 1977;59(2):108–14.

31. Yang H, Tang J, Peng X, Zhang S, Sun H, Lv H, et al. Treatment of complicated hepatic cystic hydatidosis with intrabiliary rupture by pericystectomy in combination with Roux-en-Y hepaticojejunostomy. J Huazhong Univ Sci Technolog Med Sci. 2012;32(2):205–9.
32. Belli L, del Favero E, Marni A, Romani F. Resection versus pericystectomy in the treatment of hydatidosis of the liver. Am J Surg. 1983;145(2):239–42.
33. Wanninayake HM, Brough W, Bullock N, Calne RY, Farman JV. Hypernatraemia after treatment of hydatid. Br Med J (Clin Res Ed). 1982;284(6325):1302–3.
34. Belghiti J, Benhamou JP, Houry S, Grenier P, Huguier M, Fekete F. Caustic sclerosing cholangitis. A complication of the surgical treatment of hydatid disease of the liver. Arch Surg. 1986;121(10):1162–5.
35. Chopra N, Gupta V, Rahul, Kumar S, Joshi P, Gupta V, et al. Liver hydatid cyst with cystobiliary communication: laparoscopic surgery remains an effective option. J Minim Access Surg. 2018;14(3):230–5.
36. Derici H, Tansug T, Reyhan E, Bozdag AD, Nazli O. Acute intraperitoneal rupture of hydatid cysts. World J Surg. 2006;30(10):1879–83. discussion 84-5
37. Unalp HR, Yilmaz Y, Durak E, Kamer E, Tarcan E. Rupture of liver hydatid cysts into the peritoneal cavity. A challenge in endemic regions. Saudi Med J. 2010;31(1):37–42.
38. Kurt N, Oncel M, Gulmez S, Ozkan Z, Uzun H. Spontaneous and traumatic intra-peritoneal perforations of hepatic hydatid cysts: a case series. J Gastrointest Surg. 2003;7(5):635–41.
39. Karakaya K. Spontaneous rupture of a hepatic hydatid cyst into the peritoneum causing only mild abdominal pain: a case report. World J Gastroenterol. 2007;13(5):806–8.
40. Mouaqit O, Hibatallah A, Oussaden A, Maazaz K, Taleb KA. Acute intraperitoneal rupture of hydatid cysts: a surgical experience with 14 cases. World J Emerg Surg. 2013;8:28.
41. Dirican A, Yilmaz M, Unal B, Tatli F, Piskin T, Kayaalp C. Ruptured hydatid cysts into the peritoneum: a case series. Eur J Trauma Emerg Surg. 2010;36(4):375–9.
42. Erdogmus B, Yazici B, Akcan Y, Ozdere BA, Korkmaz U, Alcelik A. Latent fatality due to hydatid cyst rupture after a severe cough episode. Tohoku J Exp Med. 2005;205(3):293–6.
43. Garcia MB, Lledias JP, Perez IG, Tirado VV, Pardo LF, Bellvis LM, et al. Primary superinfection of hydatid cyst--clinical setting and microbiology in 37 cases. Am J Trop Med Hyg. 2010;82(3):376–8.
44. Yilmaz M, Akbulut S, Kahraman A, Yilmaz S. Liver hydatid cyst rupture into the peritoneal cavity after abdominal trauma: case report and literature review. Int Surg. 2012;97(3):239–44.
45. Toumi O, Noomen F, Salem R, Rabeh H, Jabra SB, Korbi I, et al. Intraperitoneal rupture of hydatid cysts. Eur J Trauma Emerg Surg. 2017;43(3):387–91.
46. Bitton M, Kleiner-Baumgarten A, Peiser J, Barki Y, Sukenik S. [Anaphylactic shock after traumatic rupture of a splenic echinococcal cyst]. Harefuah. 1992;122(4):226–8.
47. Akcan A, Akyildiz H, Artis T, Ozturk A, Deneme MA, Ok E, et al. Peritoneal perforation of liver hydatid cysts: clinical presentation, predisposing factors, and surgical outcome. World J Surg. 2007;31(6):1284–91.
48. Kalantari N, Bayani M, Abbas-Zadeh M. Rupture of hydatid liver cyst into peritoneal cavity following blunt abdominal trauma; a case report. Emerg (Tehran). 2015;3(1):45–7.
49. Acharya AN, Gupta S. Peritoneal hydatidosis: a review of seven cases. Trop Gastroenterol. 2009;30(1):32–4.
50. Sakhri J, Ben Ali A, Letaief R, Derbel F, Dahmen Y, Ben Hadj Hmida R. [Hydatic cysts of the liver ruptured into the thorax. Diagnostic and therapeutic aspects]. J Chir (Paris) 1996;133(9–10):437–41.
51. Gomez R, Moreno E, Loinaz C, De la Calle A, Castellon C, Manzanera M, et al. Diaphragmatic or transdiaphragmatic thoracic involvement in hepatic hydatid disease: surgical trends and classification. World J Surg. 1995;19(5):714–9; discussion 9.
52. Karydakis P, Pierrakakis S, Economou N, Ninos A, Raitsiou B, Bobotis E, et al. [Surgical treatment of ruptures of hydatid cysts of the liver]. J Chir (Paris). 1994;131(8–9):363–70.
53. Xanthakis DS, Katsaras E, Efthimiadis M, Papadakis G, Varouchakis G, Aligizakis C. Hydatid cyst of the liver with intrathoracic rupture. Thorax. 1981;36(7):497–501.

54. Kabiri EH, El Maslout A, Benosman A. Thoracic rupture of hepatic hydatidosis (123 cases). Ann Thorac Surg. 2001;72(6):1883–6.
55. Low VH. Transdiaphragmatic rupture of calcified hepatic hydatid cyst. Australas Radiol. 1991;35(2):199–202.
56. Hankins J, Dutz W, Kohout E. Surgical treatment of ruptured and unruptured hydatic cysts of the lung. Ann Surg. 1968;167(3):336–41.
57. Ozer Z, Cetin M, Kahraman C. Pleural involvement by hydatid cysts of the lung. Thorac Cardiovasc Surg. 1985;33(2):103–5.
58. Issoufou I, Harmouch H, Belliraj L, Ammor F, Rabiou S, Younssa H, et al. Management for hydatid cysts of the lung ruptured in the pleural cavity. Med Sante Trop. 2018;28(3):292–6.
59. el Kabiri H, Caidi M, al Aziz S, el Maslout A, Benosman A. Surgical treatment of hydatidothorax. Series of 79 cases. Acta Chir Belg. 2003;103(4):401–4.
60. Turgut AT, Altinok T, Topcu S, Kosar U. Local complications of hydatid disease involving thoracic cavity: imaging findings. Eur J Radiol. 2009;70(1):49–56.
61. Daghfous H, Zendah I, Kahloul O, Tritar-Cherif F. [Pleural complications of pulmonary hydatid disease]. Tunis Med. 2014;92(1):6–11.
62. Solak H, Ceran S, Ozpinar C, Yeniterzi M, Yuksek T, Sunam GS, et al. Lung hydatid cyst rupture and its surgery. Indian J Med Sci. 1994;48(7):155–7.
63. Oto O, Silistreli E, Erturk M, Maltepe F. Thoracoscopic guided minimally invasive surgery for giant hydatic cyst. Eur J Cardiothorac Surg. 1999;16(4):494–5.
64. Yaldiz S, Gursoy S, Ucvet A, Yaldiz D, Kaya S. Capitonnage results in low postoperative morbidity in the surgical treatment of pulmonary echinococcosis. Ann Thorac Surg. 2012;93(3):962–6.
65. Vasquez JC, Montesinos E, Peralta J, Rojas L, DeLaRosa J, Leon JJ. Need for lung resection in patients with intact or ruptured hydatid cysts. Thorac Cardiovasc Surg. 2009;57(5):295–302.
66. Chen YC, Yeh TS, Tseng JH, Huang SF, Lin DY. Hepatic hydatid cysts with superinfection in a non-endemic area in Taiwan. Am J Trop Med Hyg. 2002;67(5):524–7.
67. Bracha M, Khoury T, Marom G, Gazla SA, Adeleh M, Bloom AI, et al. Successful embolization of hemorrhagic hepatic hydatid cyst followed by surgical resection: report of two cases and review of the literature. Ann Vasc Surg. 2019;60:474.e1.
68. Colovic R, Perisic-Savic M, Bilanovic A. [Injury of the left hepatic vein by a large hepatic echinococcal cyst]. Acta Chir Iugosl. 1991;38(1):121–31.
69. Coskun I, Esenturk M, Yoruk Y. The rupture of hepatic hydatid disease into the right hepatic vein and bile ducts: a case report. Hepato-Gastroenterology. 1996;43(10):1006–8.
70. Lakshminarayan R, Anuradha C. Haemobilia--a rare presentation of intrabiliary hydatid disease. J Med Imaging Radiat Oncol. 2012;56(6):650–3.
71. Yildiz SY, Berkem H, Hengirmen S. A rare complication of intraabdominal hydatid disease: gastric fistula and recurrent gastric bleeding. Am J Surg. 2010;200(5):e59–60.
72. Stoot JH, Jongsma CK, Limantoro I, Terpstra OT, Breslau PJ. More than 25 years of surgical treatment of hydatid cysts in a nonendemic area using the "frozen seal" method. World J Surg. 2010;34(1):106–13.
73. Arinc S, Alpay L, Okur E, Koksal C, Sogukpinar O, Kosif A, et al. Recurrent pulmonary hydatid disease: analysis of ten cases. Surg Today. 2008;38(11):983–6.
74. Franciosi CM, Romano F, Porta G, Caprotti R, De Fina S, Colombo G, et al. Surgical treatment of hydatid disease of the liver. An experience from outside the endemic area. Chir Ital. 2002;54(5):667–72.
75. Simon D, Koegelenberg CF, Sinha Roy S, Allwood BW, Irusen EM. Can large hydatid cysts resolve with medical treatment alone? Respiration. 2016;92(6):428–31.
76. Kouskos E, Chatziantoniou J, Chrissafis I, Anitsakis C, Zamtrakis S. Uncommon locations of hydatid cysts. Singap Med J. 2007;48(4):e119–21.
77. Narasimharao KL, Venkateswarlu K, Mitra SK, Mehta S. Hydatid disease of spleen treated by cyst enucleation and splenic salvage. J Pediatr Surg. 1987;22(2):138–9.
78. Zlitni M, Ezzaouia K, Lebib H, Karray M, Kooli M, Mestiri M. Hydatid cyst of bone: diagnosis and treatment. World J Surg. 2001;25(1):75–82.

79. Awasthy N, Chand K. Primary hydatid disease of the spine: an unusual case. Br J Neurosurg. 2005;19(5):425–7.
80. Gurbuz A, Tetik O, Yilik L, Emrecan B, Ozsoyler I, Ozbek C. Cardiac involvement of hydatid disease. Jpn J Thorac Cardiovasc Surg. 2003;51(11):594–8.
81. Thameur H, Abdelmoula S, Chenik S, Bey M, Ziadi M, Mestiri T, et al. Cardiopericardial hydatid cysts. World J Surg. 2001;25(1):58–67.
82. Dibello R, Abo JC, Cortes R, Zubiaurre L, Folle LE, Urioste HA, et al. Hydatid cyst of the left ventricle of the heart: mitral insufficiency after surgical treatment. J Thorac Cardiovasc Surg. 1965;49:854–9.
83. Tellez G, Nojek C, Juffe A, Rufilanchas J, O'Connor F, Figuera D. Cardiac echinococcosis: report of 3 cases and review of the literature. Ann Thorac Surg. 1976;21(5):425–30.
84. Zmerli S, Ayed M, Horchani A, Chami I, El Ouakdi M, Ben Slama MR. Hydatid cyst of the kidney: diagnosis and treatment. World J Surg. 2001;25(1):68–74.
85. Padayachy LC, Dattatraya M. Hydatid disease (Echinococcus) of the central nervous system. Childs Nerv Syst. 2018;34(10):1967–71.
86. Turkoglu OF, Solaroglu I, Tun K, Beskonakli E, Taskin Y. Secondary infection of intracranial hydatid cyst with Clostridium ramosum. Childs Nerv Syst. 2005;21(11):1004–7.
87. Feki W, Ghozzi S, Khiari R, Ghorbel J, Elarbi H, Khouni H, et al. Multiple unusual locations of hydatid cysts including bladder, psoas muscle and liver. Parasitol Int. 2008;57(1):83–6.

Is There a Role for Minimally Invasive Surgery in the Management of Hydatid Liver Disease?

15

Constantine P. Spanos

Introduction

Over the past 30 years, minimally invasive techniques in surgery have revolutionized surgical practice. In abdominal surgery, laparoscopy has established itself as the standard of care in the most common surgical disorders, namely, cholecystopathy, appendicitis, and hernia surgery. The adoption of minimally invasive approaches for surgical diseases extended to endocrine surgery, foregut surgery, colorectal surgery, and bariatric surgery. In most of these fields, the learning curve is steeper, and more cases are required to master the techniques.

The increased use of laparoscopy and minimally invasive techniques has been driven by several factors [1]:

- Smaller incisions, with the benefit of cosmesis and reduced incidence and severity of hernia
- Less superficial surgical trauma with a decrease in surgical site infections
- Reduced postoperative pain
- Enhanced recovery

Minimally invasive surgery introduced new surgical skills. Complex precise dissection is now performed under magnification; attention is given to anatomical structures not previously taken into account in open surgery. Novel instrumentation, such as high-resolution optics, energy devices, and surgical techniques, such as suturing, has led to the adoption of minimally invasive techniques to most of the spectrum of intra-abdominal and gastroenterological surgery.

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Laparoscopic Hepatectomy

Laparoscopic hepatic procedures have been added to the armamentarium of liver surgery. However, it has not enjoyed the same adoption rate as other surgical techniques. There are several reasons for this:

- The anatomical complexity of the liver
- The proximity of major vascular structures
- Difficulties in hepatic mobilization, lack of working space
- The possibility of insufficient oncologic resection
- Parenchymal transection exposes a risk of hemorrhage and CO2 gas embolization
- Difficult laparoscopic control of vessels
- Lack of training among hepatobiliary experts in advanced laparoscopic techniques [1, 2]

It is highly desirable to combine the qualifications of an expert hepatobiliary surgeon and an advanced laparoscopic surgeon to perform minimally invasive hepatic procedures [3].

Additionally, liver procedures comprise a large variety and standardization of the procedure is more difficult, thus prolonging the learning curve [1–4].

An important point is that a minimally invasive hepatic procedure should achieve the same surgical "quality" as an open procedure with regard to technical aspects and oncological outcomes [2].

Hydatid Cyst

Echinococcus granulosus is a small tapeworm that typically infects carnivores such as dogs and foxes, after consumption of infected intermediate host viscera (sheep and pigs). The parasite enters the small intestine and remains firmly attached to the mucosa. Later, it sheds proglottids which are excreted in the infected animal's feces. Proglottids (or eggs) are ingested by *intermediate hosts* (sheep, humans), where they mature into cysts and daughter cysts.

A hydatid cyst usually develops in the liver parenchyma of an intermediate host. Humans are accidental intermediate hosts [5].

Hydatid cysts contain a clear, colorless, odorless hydatid fluid with a large amount of protoscolices (400,000/mm^3). This fluid is highly irritating to tissues. The mature cyst consists of three layers:

- The *germinal layer*: this is the inner layer, and it surrounds the fluid-filled central hydatid cavity. It is the living component of the parasite. It produces protoscolices, which are released directly into the cyst fluid or an endogenous daughter cyst. Protoscolices are the future taenia heads. The germinal membrane is the source of both the cyst fluid and daughter cysts. Multivesicular hydatid cysts are the result of multiple daughter cysts.
- The *laminated layer*: this supports the germinal layer externally. It is acellular, always separable from the pericyst, with a thickness of 1–2 mm. The layer is permeable to water, K+, Cl-, Ca++, and urea. It protects the cysts from bacteria, enzymes, and bile.

- The *adventitial layer*: this has an abundant blood supply and does not have a clear cleavage plane between itself and the surrounding normal host tissue. A fibrous capsule that develops from the host tissue as an inflammatory reaction is the ectocyst or pericyst. With time the adventitial tissue may partially or totally calcify [5, 7].

If rupture of the cyst occurs, secondary hydatidosis results from implantation of protoscolices and daughter cysts on the surrounding viscera [5, 7, 8].

Cyst morphology and cyst integrity are instrumental to the surgical approach of hydatid disease. All aspects of surgical technique are based on knowledge of these specific anatomical details.

Cyst Complications

- Compression. Hydatid cysts may cause compression toward Glisson's capsule, compression of the bile ducts with obstructive jaundice, and compression of the hepatic veins resulting in Budd-Chiari syndrome. Presinusoidal portal hypertension can occur; sinistral portal hypertension is a result of splenic vein compression.
- Cyst infection. Hydatid cysts can become infected as a result of a bacteremic episode or communication with bile ducts. Clinical presentation is similar to that of a pyogenic liver abscess.
- Rupture into the biliary tract. This is the most common complication of hepatic hydatid cysts and leads to cystobiliary communication. Such communications can be major or minor. Major cystobiliary communication can lead to obstructive jaundice, cholangitis, or both.
- Rupture into the bronchial tree. This may occur with hepatic hydatid cysts located in segments IVa, VII, and VIII of the liver. Bronchio-biliary fistula is the main clinical presentation.
- Rupture into the peritoneum. This may occur as a result of trauma or spontaneously. Multiple cysts usually develop. Patients with intraperitoneal rupture may be asymptomatic or have acute abdominal pain, nausea and vomiting, and, rarely, anaphylactic reactions.
- Rupture into organs or cavities [8].

The WHO Ultrasound (US) Classification System

Ultrasound is the first-line imaging technique for hepatic hydatid disease. The WHO classification system [6] classifies hydatid cysts into six types:

1. CL (cystic lesion) type: This is a well-circumscribed liquid image with a clearly defined wall that may be difficult to differentiate from a simple biliary cyst. These cysts are active.
2. CE1: A concentric, hyperechoic halo is present around the cyst, which may contain free-floating hyperechoic foci called hydatid sand. These cysts are active.

3. CE2: Multivesicular daughter cysts present. A honeycomb or rosette image is characteristic. These cysts are active.
4. CE3: There is partial or total detachment of the laminated layer with floating and undulating hyperechoic membranes showing the dual wall. Water-lily sign. These cysts are transitional.
5. CE4: Cystic and solid components are present. Daughter cysts are absent. The cysts are inactive.
6. CE5: Cysts with matrix or amorphous mass, solid or semisolid appearance, calcification in wall, complete or incomplete. The cysts are inactive.

Indications for Surgery

- Large CE2–CE3 cysts with multiple daughter cysts.
- Single liver cysts located superficially, as these may rupture spontaneously.
- Infected cysts.
- Cystobiliary communication.
- Cysts exerting pressure on adjacent organs.
- Surgery is contraindicated in patients with inactive asymptomatic cysts, cysts which are difficult to access surgically, and very small cysts [8].

Surgical Objectives

The principal objectives of surgery are removal of the entire parasite, removal of the residual cavity, and identification and treatment of biliary leak. The main operative procedures offered are conservative surgery and radical surgery. Conservative surgery includes cystectomy or cyst unroofing, whereas radical surgery includes total pericystectomy, total cystectomy, and hepatectomy. The major pitfalls of hepatic hydatid surgery are uncontrolled spillage of active cystic contents, insufficient extirpation of cystic contents and components, bile leakage, and poor access secondary to location [8, 9].

Preoperative Evaluation

Preoperative evaluation for hydatic disease includes standard tests such as an electrocardiogram, complete blood count and electrolyte panel, and renal function tests. Of great importance is recent high-quality cross-sectional imaging. This is done to exclude hidden or occult pelvic, retroperitoneal, and chest hydatid cysts. A hepatic triphasic CT is performed to evaluate major vascular structures. Finally, MR cholangiography should be performed for central cysts located close to the hilum, to evaluate for possible biliary fistula [8, 9].

Perioperative Benzimidazoles

Perioperative adjunctive drug therapy with benzimidazoles (albendazole, mebendazole) is administered to prevent secondary seeding of the peritoneal cavity in case of intraoperative cyst rupture. Usually, either albendazole or mebendazole is given 4 days prior to surgery. Mebendazole is continued for 3 months postoperatively, whereas albendazole is continued for 1 month postoperatively [5, 7–9, 15].

Operative Strategy During Cystectomy or Cyst Unroofing for Hydatid Disease

Cystectomy is the most commonly performed surgical procedure for hepatic hydatidosis. It consists of puncture and cyst aspiration, injection of a scolicidal agent, hydatidectomy (removal of hydatid sand, daughter cysts, laminated and germinal layers), and unroofing. The main risk during hydatid surgery is twofold: intraoperative spillage and missing a biliary leak [8, 15, 20].

One of the important adjunctive intraoperative measures taken in hydatic surgery is the placement of scolicidal-soaked gauzes around the hepatic surface at the cyst location. The most common scolicidal agent used is 20% hypertonic saline and povidone-iodine [8, 9, 15].

Below is a step-by-step brief outline of cystectomy for hepatic hydatid disease [8, 9, 15, 17].

1. Cyst puncture. This is performed using a large-gauge needle. A three-way stopcock is used ideally. Aspiration is performed as much as possible. The color of the aspiration fluid is carefully noted for pus or bile.
2. Scolicidal solution Injection. If the fluid is clear, 20% hypertonic saline is injected into the cyst. The ideal contact time is 6 minutes [21]. The goal of this step is to sterilize the cyst contents thus preventing recurrence.
3. Cyst aspiration. Usually the laminated membrane will collapse into the cystic cavity at this stage.
4. Cyst incision. This is done in order to inspect cyst contents initially and to remove them subsequently. The typical contents are clear fluid, hydatid sand, and daughter cysts. After drainage of the fluid, the laminated membrane collapses into the cavity and the cyst contents including daughter cysts can be evacuated. The laminated membrane is removed by forceps. It is important to inspect the cavity for bile staining. Scolicidal injection should never be done in this case, as this poses a risk for sclerosing cholangitis [22].
5. Removal of cyst roof.
6. Management of residual cavity.

As mentioned above, careful inspection of the cyst contents is performed for detection of biliary leakage. This can be done with direct inspection of the cyst cavity, placement of a dry gauze in the cavity with inspection upon removal, methylene

blue testing, and intraoperative cholangiography. Obvious small biliary leaks can be sutured, whereas large ones may necessitate endoscopic drainage (ERCP), T-tube drainage, or Roux-en-Y hepaticojejunostomy [8, 9, 15, 17].

The residual cavity is packed with omentum adequately mobilized from the transverse colon. With large cavities, a drain is placed along with the omentoplasty [8, 9, 15, 17].

Radical Operations

Pericystectomy

This technique involves creating a surgical plane outside the pericyst layer. This will prevent inadvertent opening of the cyst during surgery, and an en bloc resection of the lesion is thus achieved. Of note, a clear anatomic plane does not exist; adjunctive tools such as the ultrasonic aspirator or other energy devices may be used to facilitate parenchymal transection as in hepatic resection. If the hydatid cyst is in proximity of major hepatic veins, the venal cava, or the liver hilum, pericystectomy should be avoided [8, 20].

Liver Resection

Liver resection is indicated for infection with *E. multilocularis* [20]. In cases of *E. granulosus*, resection is considered in cases of peripherally sited cysts such as the left lateral segment, in cases of pedunculated cysts, as well as in cases of hepatic atrophy secondary to biliary obstruction. When a major bile leak occurs during hepatic hydatid surgery, liver resection may be performed if endoscopic or surgical biliary drainage or diversion is not deemed effective [20].

The Laparoscopic Approach

The adoption of minimally invasive techniques in hepatic surgery is unquestionable. Surgery for hepatic hydatidosis has been no exception to this trend. However, widespread adoption of minimally invasive techniques for this specific indication has not been widespread. It has not replaced standard time-tested open approaches even with conservative surgical options such as cystectomy. Strict selection criteria based on location and size of the lesion, experience in minimally invasive surgery, and available instrumentation are extremely important for consideration of a laparoscopic approach to hydatidosis. Overall, minimally invasive approaches are reserved for uncomplicated cysts in the anterior liver segments [1, 8].

Significant pitfalls for laparoscopy are as follows:

- Limited space for instrumentation.
- Complexity in controlling spillage after cyst puncture.

- Difficulty in aspirating degenerated thick cystic contents.
- Pneumoperitoneum can increase risk of hydatid fluid contamination and has been reported as a risk factor for spillage and recurrence [16].
- Difficulty in controlling hemorrhage.
- Steep learning curve [8, 15].

In centers with extensive experience in treating hepatic hydatidosis, exclusion criteria for minimally invasive surgery are intraparenchymal cyst location, the presence of more than 3 cysts, and a thick, calcified cyst wall. Hydatid cysts in proximity to major vessels and relapsed cysts are also contraindications to the minimally invasive approach.

Both conservative and radical procedures have been utilized in minimally invasive hepatic hydatid surgery [8, 15, 20].

Positioning and Access

The "French" position, supine with legs spread apart, surgeon between the legs and assistants on either side, is frequently employed. Trocar sites vary according to location and size of cyst. Usually a supraumbilical port is placed for the optics; a 30-degree laparoscope is frequently used. On average, four trocars are placed in total. A pneumoperitoneum at 12 mm pressure is established. With laparoscopic cystectomy, the same principals are followed as with open surgery. Gauzes soaked with scolicidal fluid (20% hypertonic saline or povidone-iodine) are carefully placed around the hydatid cyst. The cyst is punctured, aspirated, and filled with the scolicidal fluid, and re-aspirated after 10 min. A cystotomy is performed with electrocautery. The laparoscope can be introduced in to the cyst cavity and enhanced magnification and high optic resolution can be useful to explore for remnant daughter cysts, laminated membranes, and bile leakage. Laparoscopic sutures or clips are used to ligate biliary-cyst communications. Omentoplasty is employed for the residual cavity and drains can be placed [8, 9].

Special laparoscopic techniques and instruments have been used in minimally invasive hydatid surgery. Most of these are a result of surgical enterprise, using relatively cheap components to achieve a cost-effective solution to a problem endemic in specific geographical areas. A perforator-grinder-aspirator has been used to access and evacuate hydatid cysts [13, 14]. A specialized trocar (umbrella-shaped) enables suspension of the cyst wall against the abdominal wall for facilitated evacuation of cyst contents [19]. Bickel and Eitan described the use of a transparent large cannula with a beveled tip for safe aspiration of hydatid cyst contents [12]. Hemmati described a laparoscopic system for access and evacuation of hydatid cysts using a Maryland laparoscopic grasper/dissector, standard laparoscopic trocar, and a modified endotracheal tube [17]. All these techniques are designed to achieve access and evacuation of hydatid cysts with minimal spillage and risk of contamination and recurrence. Perihepatic irrigation creating a pool of scolicidal solution has been recommended by some experts [15, 18].

Berberoglu et al. [15] described laparoscopic cystectomy with gasless laparoscopy. Theoretical advantages of this approach are the amelioration of dissemination/contamination as a result of positive pressure exerted by the CO_2 gas; the use of high-volume suction and irrigation systems without loss of pneumoperitoneum; as well as avoidance of hemodynamic and metabolic changes attributable to pneumoperitoneum. In addition, CO_2 embolization can be avoided.

Review of Literature

Minimally invasive technique for treatment of hydatic hepatic cystic disease was first described by Katkhouda et al. [10]. In the ensuing decades, a significant body of literature has accumulated regarding minimally invasive techniques for hepatic hydatid disease. Tuxun et al. [11] reviewed the world literature on laparoscopic treatment of hepatic cystic hydatid disease. The study included 914 patients. The patient age range was 3–70 years; the cyst diameter range was 3–18 cm. The majority (84%) were 5–10 cm in diameter. There were 466 males and 368 female patients. The location of the hepatic cysts were as follows: in 643 patients, right lobe; 295 patients, left lobe and 32 patients, both lobes. The procedures performed were:

- Cystectomy: 75.16%
- Partial pericystectomy: 14.77%
- Pericystectomy: 5.84%
- Left lobectomy: 1.09%
- Left lateral segmentectomy: 0.98%

Pneumoperitoneum was used in 89.17% of cases and gasless laparoscopy in 5.58%.

The conversion rate to an open procedure observed in this review was 4.92% overall. Reasons for conversion included adhesions, bleeding, poor exposure, inappropriate staging, inability to identify cyst laparoscopically, imminent risk of rupture and uncontrolled spillage, and inadequate evacuation. The operative time ranged from 50 to 144 min. This decreased as experience accumulated. The average length of hospital stay was 1–8 days. Overall mortality was 0.22%. The range of morbidity in the report included within this review ranged from 0% to 53%. Overall morbidity was 15%. The incidence of bile leak was 6.24%. Treatment for bile leak included endo-biliary stenting and sphincterotomy. Abscess was formed in 2.2% of patients. Anaphylactic shock occurred in three patients in this review. Complications reported in the review included port-site infection, incisional hernia, subphrenic abscess, small bowel perforation, fever of unknown origin, subcutaneous hematoma, pleural effusion, empyema, pneumonia, and drug-induced fever. Recurrence of hydatid disease was 1.09% overall. The authors concluded that minimally invasive approaches are safe in selected patients, comparable to open surgery with acceptable morbidity and mortality. Conservative and radical surgery is feasible laparoscopically [11]. Finally, few cases of robotic-assisted surgery have been reported. Goja et al. [20] described robotic-assisted cysto-pericystectomy. Reported

advantages of this approach include three-dimensional visualization, tremor reduction, motion scaling, and additional degrees of freedom allowing for improved dissection, parenchymal transection, intracorporeal suturing, and hemostatic control [20].

Conclusion

Minimally invasive techniques have been added to the armamentarium of surgeons treating patients with hepatic hydatid cystic disease. These should be employed in carefully selected patients. High-quality cross-sectional imaging is important for patient selection. In general, minimally invasive approaches are reserved for uncomplicated cysts in the anterior liver segments. Special instrumentation for access and cyst aspiration may be necessary. All the important steps taken in open surgery should be reproduced in laparoscopic hepatic hydatic cases. This includes field protection of cyst area with scolicidal-soaked gauze, meticulous care to prevent spillage during puncture and aspiration, careful inspection of the cyst cavity for remnant daughter cysts and bile leakage, and making an effort to perform omentoplasty in the remaining cavity. Careful use and selection of scolicidal solutions may prevent complications such as sclerosing cholangitis and chemical peritonitis. Laproscopic hydatid surgery requires expertise in both the treatment of hydatid disease and advanced laparoscopic techniques. Conversion to open surgery should not be considered a failure. There should be a low threshold for conversion when exposure is inadequate or deemed unsafe, access to the cyst itself is unsatisfactory, cyst rupture and uncontrolled spillage are imminent or apparent, or daughter cysts cannot be removed. Inability to control a bile leak is an indication for conversion. Of note, no randomized controlled trials have been performed to compare the various therapeutic options for hepatic cystic hydatidosis.

References

1. Liu R. Laparoscopic anatomical hepatectomy. In: Liu R, editor. Laparoscopic liver resection. Theory and techniques. Gordecht: Springer; 2017.
2. Cherqui D, Lin CW, Kluger M. Minimally invasive techniques in hepatic resection. In: Jarnagin W, editor. Blumgart's surgery of the liver, biliary tract and pancreas. Philadelphia: Elsevier; 2017. p. 1597–612.
3. Martin RCG, Scoggins CR, McMasters KM. Laparoscopic hepatic lobectomy: advantages of a minimally invasive approach. J Am Coll Surg. 2010;210:627–36.
4. Komatsu SO, Goumard C, et al. Development process and technical aspects of laparoscopic hepatectomy: learning curve based on 15 years of experience. J Am Coll Surg. 2017;224:841–50.
5. Pakala T, Molina M, Wu GY. Hepatic echinococcal cysts: a review. J Clin Transl Hepatol. 2016;4:39–46.
6. WHO Informal Working Group. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. 2003;85:253–61.
7. Bhutani N, Kajal P. Hepatic echinococcosis: a review. Ann Med Surg (Lond). 2018;36:99–105.

8. Pascal G, Azoulay D, Belghiti J, Laurent A. Hydatid disease of the liver. In: Jarnagin W, editor. Blumgart's surgery of the liver, biliary tract and pancreas. Philadelphia: Elsevier; 2017. p. 1597–612.
9. Ertem M, Karahasanoglu T, Yavuz N, et al. Laparoscopically treated liver hydatid cysts. Arch Surg. 2002;137:1170–3.
10. Katkhouda N, Fabiani P, Benizri E, et al. Laser resection of a liver hydatid cyst under videolaparoscopy. Br J Surg. 1992;79:560–1.
11. Tuxun T, Zhang J, Zhao J, et al. World review of laparoscopic treatment of liver cystic echinococcosis-914 patients. Int J Infect Dis. 2014;24:43–50.
12. Bickel A, Eitan A. The use of a large, transparent cannula, with a beveled tip, for safe laparoscopic management of hydatid cysts of the liver. Surg Endosc. 1995;9:1304–5.
13. Saglam A. Laparoscopic treatment of liver hydatid cysts. Surg Laparosc Endosc. 1996;6:16–21.
14. Avtan LA. A new 'perforator-grinder-aspirator apparatus (PGAA)' for the minimal access surgery of cystic hydatidosis. Hepato-Gastroenterology. 2005;52:339–42.
15. Berberoglu M, Taner S, Dilek ON, et al. Gasless vs gaseous laparoscopy in the treatment of hepatic hydatid disease. Surg Endosc. 1999;13:1195–8.
16. Jerraya H, Khalfallah M, Osman SB, et al. Predictive factors of recurrence after surgical treatment for liver hydatid cyst. Surg Endosc. 2015;29:86–93.
17. Hemmati SH. How to build a simple and safe hydatid evacuation system. JSLS. 2014;18:e2014.00314.
18. Palacios-Ruiz JA, et al. Hypertonic saline in hydatid disease. World J Surg. 2002;1398.
19. Seven R, Berber E, Mercan S, et al. Laparoscopic treatment of hepatic hydatid cysts. Surgery. 2000;128:36–40.
20. Goya S, Saha SK, Yadav SK, et al. Surgical approaches to hepatic hydatidosis ranging from partial cystectomy to liver transplantation. Ann Hepatobiliary Pancreat Surg. 2018;22:208–15.
21. Besim H, et al. Scolicidal agents in hydatid cyst surgery. HBP Surg. 1998;10:347–51.
22. Belghiti J, et al. Caustic sclerosing cholangitis. A complication of the surgical treatment of hydatid disease of the liver. Arch Surg. 1986;121:1162–5.

The Role of the WHO in the Global Management of Hydatid Disease. Lessons Learned in the Field

16

Enrico Brunetti and Calum N. L. Macpherson

Background

Hydatid disease or cystic echinococcosis (CE) is a complex, chronic disease with a cosmopolitan distribution. Caused by the larval stage (metacestode) of *Echinococcus granulosus*, it is endemic in sheep raising areas and is one of the most neglected diseases.

Despite a global burden calculated at 1,009,662 DALYs, CE remains excluded from funding for conditions related to low socioeconomic status. A landmark paper published in 2006 showed that if funding for CE was placed on the same scale as TDR-supported diseases, based on estimated DALYs lost, CE should have received approximately US$1,200,000 annually [1].

Due to its many clinical variables, such as number, anatomical location, dimension of the cysts, and presence or absence of complications, its clinical spectrum in humans ranges from asymptomatic infection to severe and, on occasion, can be fatal.

This complexity is compounded by the existence of four clinical management options: surgery, percutaneous techniques, drug treatment for active cysts, and the so-called "watch and wait" approach for asymptomatic inactive cysts. Allocation of patients to these treatments should be based on cyst stage, size and location, available clinical expertise, and comorbidities. However, clinical decision algorithms, efficacy, relapse rates, and costs have never been properly evaluated.

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Comparative clinical trials of the four treatment options are not available to resolve important questions such as stage-specific allocation of treatments, adverse events, and long-term relapse rates.

Data is mostly derived from case series and small clinical trials, and treatment guidelines remain at the level of expert opinion [2].

As randomized clinical trials are expensive and CE is neglected, funding is hard to come by.

The WHO Informal Working Group on Echinococcosis

To address the neglect for this zoonosis and given its wide geographical distribution, in 1985 the WHO set up the Informal Working Groups on Echinococcosis to promote international cooperation, scientific standards, and methodology.

For 10 years, under the leadership of Prof. Jonas Eckert, a parasitologist based in Zurich, Switzerland, these working groups contributed to exchanges between interested scientists in their respective areas. In 1995, the Veterinary Public Health Unit, at WHO, merged the Groups into a single one. The Working Group brought together clinicians and scientists involved in research on Echinococcosis irrespective of their specialty, field of interest, or species of Echinococcus studied.

Neither WHO nor the Informal Working Group provided financial support, but they served to provide information on funding sources and organized meetings for specialists to discuss and develop guidelines on different aspects of CE.

The History of Clinical Management of CE

A rational choice for the clinical management of CE was not possible before the development and implementation of imaging techniques that could clearly visualize the organs in the abdomen, which are the most common locations of echinococcal cysts. Prior to this, surgeons performed laparotomies on the suspicion of discovering cysts of unknown size, number, condition, or location.

The introduction of ultrasound (US) in the late 1970s and, later, computed tomography (CT) and magnetic resonance imaging (MRI), revolutionized the clinical management of CE which hugely benefited the patients and clinicians alike. The images provided, for the first time, the ability to preoperatively evaluate the best interventional method. It is difficult to explain just how difficult it was to care for patients with CE prior to the introduction of imaging techniques.

US, which is harmless with no ionizing radiation, providing instant recordable results, allowed physicians to not only see cysts, their location, number, size, and their internal composition but also permitted longitudinal monitoring of changes in the internal composition of cyst over time. Portable US scanners, which have been available since the early 1980s, enabled large community based surveys which, for the first time, through the detection of asymptomatic cyst together with longitudinal studies monitoring cyst changes, enabled a better understanding of

the natural history of CE. Cysts may evolve from one stage to another, either with a reduction in fluid content and size that begins with the detachment, collapse, and folding of the endocyst until the cyst become "solid" or with the growth of daughter vesicles either within an inactive cyst or within an active cyst that was previously unilocular.

CE3a cysts can reactivate and the cavity is progressively filled with daughter vesicles. When CE4 cysts reactivate, daughter vesicles are seen in the context of solid matrix (CE3b).

US was used in many endemic regions of the world and:

- Facilitated screening of remote, rural populations where the prevalence of the disease had been previously unknown [3–7] and consequently revealed the extent of the disease in at risk communities
- Enabled a definitive diagnosis of CE for those CE cases with pathognomonic signs in US accessible locations
- Enabled the collection of data on the natural history of untreated CE (Fig. 16.1)
- Permitted a more rational selection of the best form of treatment
- Allowed the in vivo monitoring of cyst changes over time with the introduction of chemotherapeutic candidates and new treatment options (Fig. 16.1)

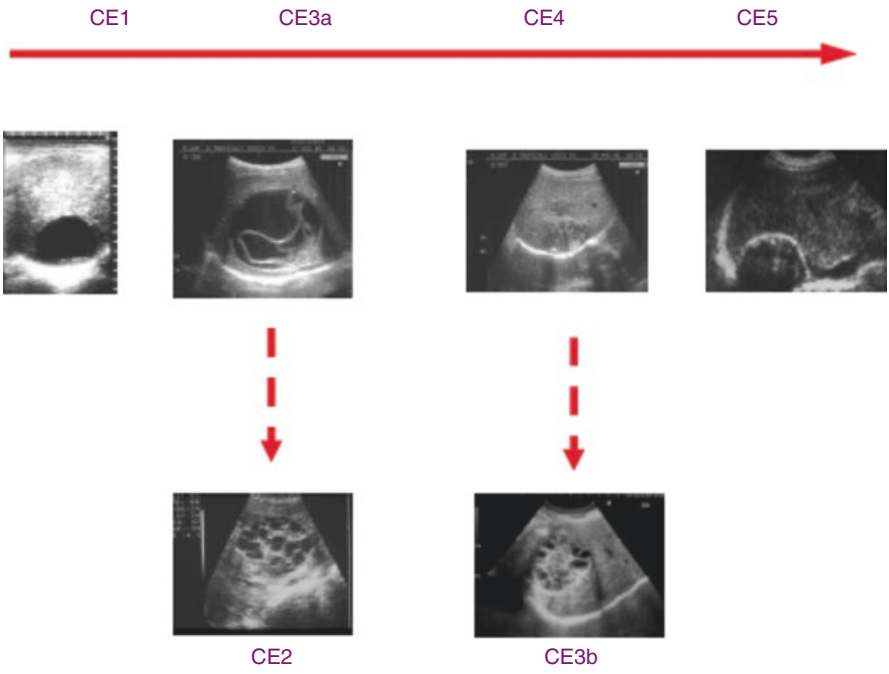

Fig. 16.1 The natural history of echinococcal cyst as observed on ultrasound. Early cyst (CE1) changes into CE3a after detachment of the endocyst (CE3a), and its cavity is filled with pseudocaseous inflammatory material that confers a "solid" appearance (CE4) with a thin, calcified rim (CE5). This involution is seen in the top row

- Enabled multiple and frequent observations facilitating close follow-up following treatment thanks to the painless and harmless properties
- Enabled longitudinal evaluation of control programs [8, 9] with repeated cross-sectional US prevalence
- Provided a milestone in clinical medicine that cannot be overstated and produced a dramatic change to our understanding of the natural history, epidemiology, and response to treatment for not only CE but also for many other parasitic diseases [10] (Macpherson 1992)

The increasing use of US in all CE endemic areas saw the development of a number of US-based cyst classifications, the most widely adopted of which was that published by Gharbi and colleagues [11] (1981). Many other US cyst classifications quickly followed over the next decades leading to difficulty in comparing the results obtained from any one particular study. In 1994, the IWGE proposed that WHO should take the lead in developing a non-eponymous classification that would utilize all the information that was being increasingly generated from cross-sectional field epidemiological studies, as well as from clinical interventions. After an initial review of the plethora of published classifications, the IWGE group decided to use the original Gharbi classification for the basis for the WHO classification. The WHO standardized US classification for CE was eventually agreed upon and published in 2001 in the WHO/OIE Manual on Echinococcosis in Humans and Animals and as a formal WHO classification in 2003 [12]. This standardized classification differed from the original Gharbi classification through the addition of a cystic lesion (CL) potentially early undifferentiated cystic stage and the swapping of the Gharbi type 2 with the CE 3 stage and adding two subgroups. These modifications were thought to more accurately represent the variety of appearances (e.g., in the Gharbi classification there was no distinction between CE2 and CE3b) (Fig. 16.2) and, therefore, be of greater clinical value for clinicians treating patients with CE. The WHO standardized US classification for CE has been adopted by some but far from uniformly [13] although this might change in the future and appears to be function of the geographic area where the authors are working [14].

The WHO IWGE classification of active, inactive, and transitional stages is perfectly in line with the metabolic activity profiles of the cysts, with the exception of CE3b, which appears vigorously active in 1H MRS, a finding that corresponds well with clinical experience. This was shown by an assessment of

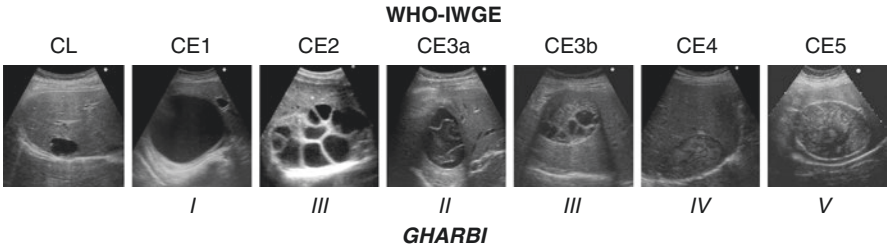

Fig. 16.2 Figure comparing the WHO and the Gharbi classifications. In the latter, no distinction was made between CE2 and CE3b cysts

metabolic profiles of cyst stages with high-field proton magnetic resonance spectroscopy (1H MRS) [15].

Field-Based Studies

With the availability of portable US equipment, powered either by solar panels and batteries or with the use of a portable generator, remote community-based US screening programs for CE became possible for the first time in the early 1980s. These community-based US surveys have to-date been conducted in most of the known endemic foci within a large number of CE endemic countries throughout the world [6, 7]. The cross-sectional nature of these surveys facilitates the collection of images of all cyst space-occupying structures from the earliest possible lesions (CE1) to those which are asymptomatic, inactive, and the last stages of their existence (CE4 and CE5) (Fig. 16.3). Such data can be categorized into the various WHO treatment modalities which include medicinal, interventional, surgical, or a watch and wait strategy [16]. Those space occupying legions without pathognomonic signs, such as CL and some CE types 4 and 5, present different diagnostic and clinical challenges. CL cases may represent the earliest, undifferentiated stage of CE, are invariably asymptomatic, and represent a clear opportunity if they can be differentially diagnosed from other simple cyst or space-occupying legions by fine-needle aspiration biopsy (FNAB) to detect *E. granulousus* antigens or protoscolices and if shown to be parasitic should be treated appropriately. The finding of CE1 and CE3a stages represents recent *E. granulosus* transmission and provides the earliest possible treatment opportunity, thus preventing the insidious progression of the disease and, in many cases, less successful subsequent treatment outcomes [17]. In CE4 and CE5 cases, provided that they are asymptomatic and not complicated, these stages present an opportunity to conduct a longitudinal "wait and watch" option [18, 19].The withholding of treatment for these stages may be justified by their asymptomatic nature and the expectation that they will usually not result in clinical disease and may resolve spontaneously without any treatment intervention. Questions remain regarding the frequency of assessment and the availability and adequacy of follow-up, as increased diligence is required in this group of patients.

Classification

The WHO standardized US classification for CE (Fig. 16.4) has five distinct stages with two substages. In general, the presence of fluid indicates presence of protoscolices with the exception of CE3a, in which viable protoscolices are found in approximately 50% of cases [15] .

The most frequent location of CE cysts is the liver. Prior to US, all space-occupying lesions in the liver were operated surgically. The introduction of US permitted, for the first time, the ability for the clinician to choose a management option based on the revelation by US of the CE stage, dimension, number, and location in the liver (Fig. 16.5). US also permitted the examination of the impact of any

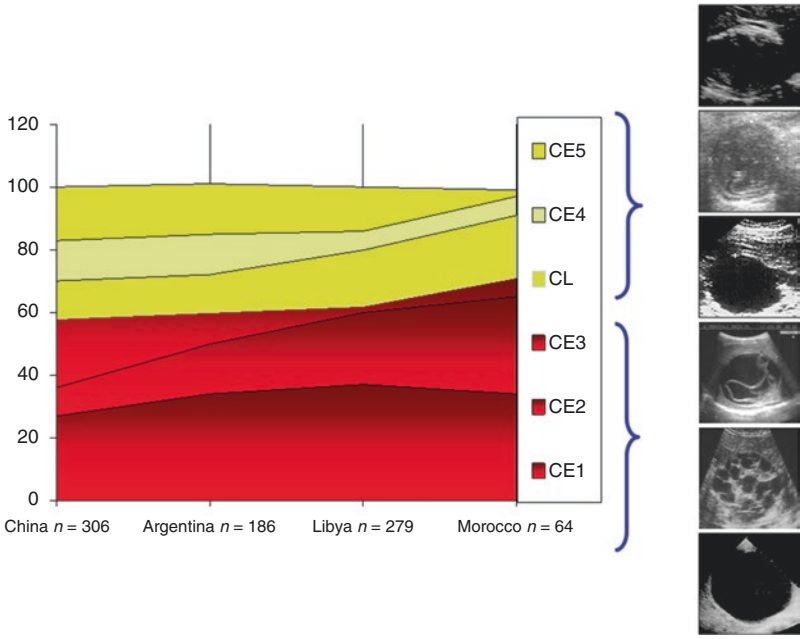

Fig. 16.3 The case mix proportions found during a US rural community-based study in China [20], Libya [5], Argentina (Palaez et al. unpublished), and Morocco [21]. If the cost of the different treatment modalities is known, then the economic cost of treating all the patients found during such surveys can be calculated. Cross-sectional prevalence US surveys, if accompanied by relevant questionnaires, may also reveal the retrospective clinical interventions for CE in the community studied [21] . This provides a much clearer picture of the importance of human CE in that community. The involvement of local physicians in such surveys helps with patient follow-up and subsequent treatment. It provides an important opportunity for the education of local physicians on the WHO IWGE treatment guidelines recommended for each cystic type discovered during the surveys

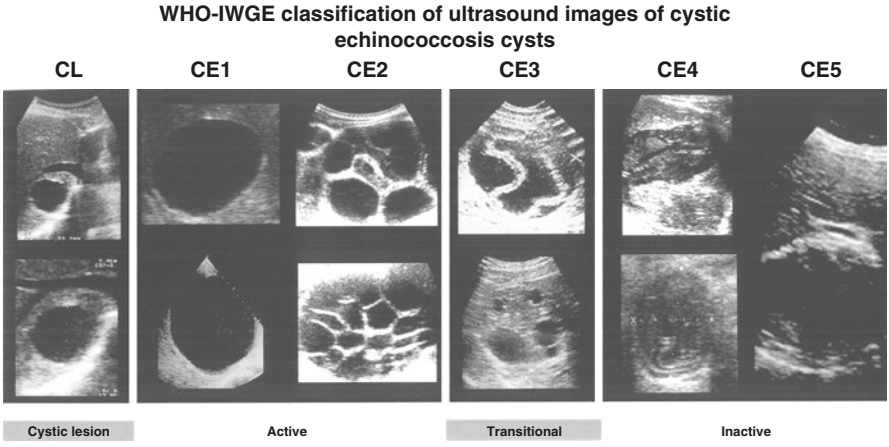

Fig. 16.4 The original WHO IWGE standardized classification. A further distinction between CE3a (transitional column, top) and CE3b (bottom) was introduced at a later stage due to their different response to non-surgical treatments

	Surgery	PAIR	Percutaneous Treatments other than PAIR *	Drug Therapy	Watch and Wait §
CE1		O		X	
CE2	X		O		
CE3a		O		X	
CE3b	X		O		
CE4					X
CE5					X

* Require interventional radiology expertise
§ For uncomplicated CE4 and CE5 only

Fig. 16.5 A stage-specific approach to treatment for hepatic CE. From: Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans [2]

space-occupying lesions on the liver's function. There had been numerous advances in US, which will undoubtedly continue to be made, as our understanding of the properties of ultrasound and the ability of computers to use these properties to evaluate structures in an ever sophisticated manner are developed. These developments will potentially shed new light into our understanding of the different stages of CE and our ability to assess their viability and natural history.

The treatment choices are based on data obtained through following up a large number of patients over many years. Patients with cysts CE1 and CE3a tend to respond well both to medical and percutaneous treatments. Patients with cyst CE2 or CE3b respond to medical and percutaneous treatment becoming solidified, but this response is only temporary. The biological explanation for this temporary response is still unclear. Inactive (CE4 and CE5) cysts that are not complicated can be managed through a "watch and wait" approach with the important proviso that cysts that have become spontaneously inactive tend to remain inactive much more often than those that have reached these stages as a result of treatment [18, 19, 22].

Treatment

Surgery

Surgery can be performed as an open procedure, with radical or conservative techniques, or through a laparoscopic approach. Today, there remains controversies about the criteria to be used to allocate patients to the various options. Additionally,

differences in technical resources need to be considered across the wide range of clinical settings where patients are in need of treatment.

Radical surgery aims to remove the entire cyst, including the pericyst, with or without hepatic resection. In conservative surgical procedures, only the parasitic material is removed, while part of the pericyst may be left in situ. The residual cavity is usually managed with omentoplasty [23].

Radical procedures are generally found to bear greater intraoperative risks and less postoperative complications (biliary fistula, superinfection) and relapses compared to conservative surgical procedures. These retrospective studies should be interpreted with caution, as they may be biased by the selection of candidate patients, surgical team experience, historical period considered, and, with regard to relapse rates, differences in the length of follow-up.

Medical Treatment

To this day, the only compounds that have been registered for treatment of CE in humans are mebendazole (MBZ) and albendazole (ABZ), which were introduced in 1976 and in 1982, respectively. ABZ gradually replaced MBZ as the treatment of choice, due largely to its better intestinal absorption and lower daily doses. Surprisingly, at the time of this writing, we have no definitive answers to questions such as what are the stage-specific efficacy and relapse rates, therapeutic intracystic concentrations of the drugs and of active metabolites, optimal dosing regimens, duration of treatment, and rate of adverse events. Over the years the indications for treating patients with benzimidazoles have changed. Based on a series of studies, mostly case series, it has been suggested that medical treatment could be an alternative to surgery in patients with uncomplicated (CE1, CE2, CE3a) cysts [24].

A systematic review on the efficacy of benzimidazoles conducted by Stojkovic et al. [25] provided evidence that, 1–2 years after initiation of benzimidazole derivatives treatment, 50–75% of active CE1 cysts were subsequently classified as inactive/disappeared compared to 30–55% of CE2 and CE3 cysts. A more detailed examination of the available evidence revealed that 50–60% of cysts <6 cm either became inactive or disappeared compared to only 25–50% of cysts >6 cm after 1–2 years of treatment. Unfortunately many relapses occurred and up to 25% of cysts reverted to active status within 1.5–2 years. Relapses were recorded in 60% of patients 2 years after receiving 2–3 treatments with MBZ. Two years after treatment initiation, 40% of cysts were still active or had become reactivated. The review concluded that the overall efficacy of benzimidazoles had been overstated in the past and that there was a need for a pragmatic randomized controlled trial to compare standardized benzimidazole therapy on responsive cyst stages with outcomes obtained using other treatment modalities.

Praziquantel (PZQ) is often mentioned in the literature as a compound that can be used peri-operatively as a prophylactic agent or in combination with ABZ for medical treatment. A recent thorough review indicates that “at present, there is insufficient published evidence to support a clear recommendation for the use of PZQ in prolonged chemotherapy” and “there is some evidence to support a role for the use of PZQ in combination with ABZ in pre- and post-intervention therapy” [26].

Percutaneous Treatments

Percutaneous treatments (PTs) for abdominal CE were introduced in the mid-1980s following the introduction of US. This option has subsequently become a viable alternative to surgery and benzimidazole derivatives for certain cyst stages.

PTs implemented with US guidance aim to either destroy the germinal layer with scolecidal agents or to evacuate the entire endocyst.

The most popular method in the first group is puncture, aspiration, injection of a scolecidal agent, and re-aspiration (PAIR), while several modified catheterization techniques belong to the second group and are generally reserved for cysts which are difficult to drain or tend to relapse after PAIR (multivesiculated cysts or cysts with predominantly solid content and daughter cysts) [27].

Catheterization techniques are based on the aspiration of the "solid" content of the cyst, the germinal and the laminated layer, through a large-bore catheter or device. Several variants of these techniques are in use, in particular Percutaneous EVACuation (PEVAC), the Modified Catheterization Technique (MoCaT), and Dilatable Multi-Function Trocar (DMFT) [27] .

The puncture of echinococcal cysts was strongly discouraged because of the risk of anaphylactic shock due to spillage of the fluid and potential seeding of the abdominal cavity with protoscolices. However, a growing number of articles have reported its safety in treating abdominal, especially liver, CE cysts. A total of 4209 cysts have been punctured, either for diagnostic or therapeutic purposes, and 16 cases of anaphylactic shock, 2 of them fatal (0.05%), have been reported [28]. Peritoneal seeding using the PT technique has never been reported, but it is difficult to assess the accuracy of this statement due to the short follow-up time periods. Prophylactic administration of ABZ for at least 30 days after puncture is a cautionary measure that should always accompany PAIR [2].

PAIR is performed with several variants of the standard protocol and is generally successful as judged by the change in cyst becoming inactive with a solidified appearance in CE1 and CE3a cysts. A few studies with long-term follow-up indicate that multivesiculated cysts (CE2,CE3b) tend to relapse repeatedly after PAIR [29].

The experience with catheterization techniques in CE2 and CE3b cysts is more recent and somewhat smaller than that with PAIR, so the results from series with long-term follow-up are needed before concluding on their long-term efficacy.

A meta-analysis concluded that PAIR compares favorably with surgery in terms of efficacy and length of hospital stay [30], and, given the wide range of technical variants and short follow-up of many reports, a systematic evaluation of this technique is overdue.

Percutaneous treatments is one of the areas where the WHO IWGE was instrumental in promoting something that for a long time was seen as dangerous (Fig. 16.6). The authors are old enough to recall conversations with members of the IWGE admitting to not believing in the safety of PT, and many conversations with surgeons not exactly happy to accept a nonsurgical intervention in their prior exclusive domain. At the time, medical treatment as an alternative was not considered.

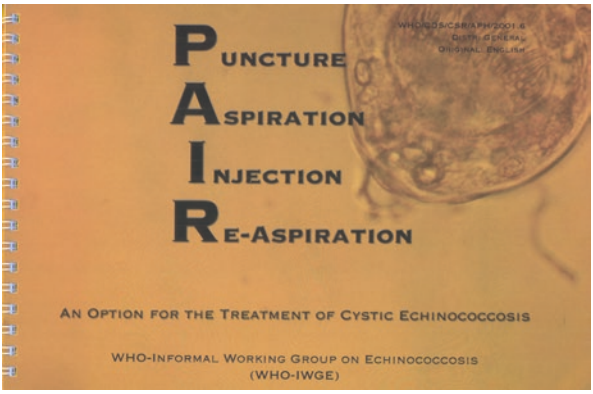

Fig. 16.6 Cover of the PAIR Booklet issued by the WHO-IWGE in 2001 https://www.who.int/echinococcosis/resources/who_cds_csr_aph_2001.6/en/

The category of watch and wait (uncomplicated CE4, CE5) entered the field at a later stage and only, after a few centers were able to report on the safety of this approach, which requires sustained long-term follow-up.

It took years to have enough patients treated, with a sufficiently long follow-up and the publication of these results to convince many of those involved in the field that PT provided a viable option for patients with specific CE cyst types. Some of the taboos (anaphylactic shock, dissemination) had been addressed in the initial efforts of the pioneers, but again it took decades of published experience and someone willing to sift through hundreds of descriptive studies of small cohorts to show that the risk of death due to anaphylactic shock following a puncture of an CE cysts was actually smaller than that of anaphylactic shock following an injection of penicillin [28].

Besides being based on low-grade evidence, treatment of CE patients is carried out in very different settings depending on experience, numbers of patients, and the available resources. Until data from appropriate comparative clinical trials are available to design algorithms which can be confidently followed by non-experts, patients should be managed in centers where appropriate expertise is available.

The current stage-specific treatment approach evolved with different centers conducting interventions under the WHO umbrella.

Almost 10 years after the publication of the Expert Consensus, the WHO IWGE is now at the final stage of the production of a WHO Technical Manual which provides an overview of the best practices gained from evidence obtained during this time.

References

1. Budke CM, Deplazes P, Torgerson PR. Global socioeconomic impact of cystic echinococcosis. Emerg Infect Dis. 2006;12(2):296–303.
2. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Trop. 2010;114(1):1–16.

3. MacPherson CN, Romig T, Zeyhle E, Rees PH, Were JB. Portable ultrasound scanner versus serology in screening for hydatid cysts in a nomadic population. Lancet. 1987;2(8553):259–61.
4. Perdomo R, Alvarez C, Geninazzi H, Ferreira C, Monti J, Parada R Jr, et al. Early diagnosis of hydatidosis by ultrasonography. Lancet. 1988;1(8579):244.
5. Shambesh MK, Macpherson CN, Beesley WN, Gusbi A, Elsonosi T. Prevalence of human hydatid disease in northwestern Libya: a cross-sectional ultrasound study. Ann Trop Med Parasitol. 1992;86(4):381–6.
6. Chebli H, Laamrani El Idrissi A, Benazzouz M, Lmimouni BE, Nhammi H, Elabandouni M, et al. Human cystic echinococcosis in Morocco: Ultrasound screening in the Mid Atlas through an Italian-Moroccan partnership. PLoS Negl Trop Dis. 2017;11(3):e0005384.
7. Tamarozzi F, Akhan O, Cretu CM, Vutova K, Akinci D, Chipeva R, et al. Prevalence of abdominal cystic echinococcosis in rural Bulgaria, Romania, and Turkey: a cross-sectional, ultrasound-based, population study from the HERACLES project. Lancet Infect Dis. 2018;18(7):769–78.
8. Salviti JC, Sobrino M, Del Carpio M, Mercapide C, Uchiumi L, Moguilensky J, et al. [Hydatidosis: Ultrasonographyc screening in the Rio Negro Province 25 years after the first screening]. Acta Gastroenterol Latinoam. 2014;44(4):311–5.
9. Solomon N, Zeyhle E, Subramanian K, Fields PJ, Romig T, Kern P, et al. Cystic echinococcosis in Turkana, Kenya: 30 years of imaging in an endemic region. Acta Trop. 2018;178:182–9.
10. Macpherson CN. Ultrasound in the diagnosis of parasitic disease. Trop Dr. 1992;22(1):14–20.
11. Gharbi HA, Hassine W, Brauner MW, Dupuch K. Ultrasound examination of the hydatic liver. Radiology. 1981;139(2):459–63.
12. Pawlowski Z, Eckert J, Vuitton D, Ammann R, Kern P, Craig P, et al. Echinococcosis in humans: clinical aspects, diagnosis and treatment. In: Eckert J, Gemmell MA, Pawlowski K, aM F-X, editors. WHO/OIE manual on echinococcosis in humans and animals. Paris; 2001. p. 20–71.
13. Tamarozzi F, Nicoletti GJ, Neumayr A, Brunetti E. Acceptance of standardized ultrasound classification, use of albendazole, and long-term follow-up in clinical management of cystic echinococcosis: a systematic review. Curr Opin Infect Dis. 2014;27(5):425–31.
14. Mirabile E, Solomon N, Fields PJ, Macpherson CNL. Progress towards international adoption of the World Health Organization ultrasound classification of cystic echinococcosis. Acta Trop. 2019;189:6–9.
15. Hosch W, Junghanss T, Stojkovic M, Brunetti E, Heye T, Kauffmann GW, et al. Metabolic viability assessment of cystic echinococcosis using high-field 1H MRS of cyst contents. NMR Biomed. 2008;21(7):734–54.
16. Strohaker J, Nadalin S. [Diagnostics and management of intra-abdominal Echinococcus manifestation]. Chirurg. 2019;90(10):823–32.
17. Del Carpio M, Mercapide CH, Salvitti JC, Uchiumi L, Sustercic J, Panomarenko H, et al. Early diagnosis, treatment and follow-up of cystic echinococcosis in remote rural areas in Patagonia: impact of ultrasound training of non-specialists. PLoS Negl Trop Dis. 2012;6(1):e1444.
18. Lissandrin R, Tamarozzi F, Mariconti M, Manciulli T, Brunetti E, Vola A. Watch and wait approach for inactive echinococcal cyst of the liver: an update. Am J Trop Med Hyg. 2018;99(2):375–9.
19. Stojkovic M, Rosenberger KD, Steudle F, Junghanss T. Watch and wait management of inactive cystic echinococcosis - does the path to inactivity matter - analysis of a prospective patient cohort. PLoS Negl Trop Dis. 2016;10(12):e0005243.
20. Schantz PM. The burden of echinococcosis. Am J Trop Med Hyg. 2005;73(1):1.
21. Macpherson CN, Kachani M, Lyagoubi M, Berrada M, Shepherd M, Fields PF, et al. Cystic echinococcosis in the Berber of the Mid Atlas mountains, Morocco: new insights into the natural history of the disease in humans. Ann Trop Med Parasitol. 2004;98(5):481–90.
22. Stojkovic M, Weber TF, Junghanss T. Clinical management of cystic echinococcosis: state of the art and perspectives. Curr Opin Infect Dis. 2018;31(5):383–92.
23. Al-Saeedi M, Khajeh E, Hoffmann K, Ghamarnejad O, Stojkovic M, Weber TF, et al. Standardized endocystectomy technique for surgical treatment of uncomplicated hepatic cystic echinococcosis. PLoS Negl Trop Dis. 2019;13(6):e0007516.

24. Horton J. Albendazole for the treatment of echinococcosis. Fundam Clin Pharmacol. 2003;17(2):205–12.
25. Stojkovic M, Zwahlen M, Teggi A, Vutova K, Cretu CM, Virdone R, et al. Treatment response of cystic echinococcosis to benzimidazoles: a systematic review. PLoS Negl Trop Dis. 2009;3(9):e524.
26. Bygott JM, Chiodini PL. Praziquantel: neglected drug? Ineffective treatment? Or therapeutic choice in cystic hydatid disease? Acta Trop. 2009;111(2):95–101.
27. Tamarozzi F, Vuitton L, Brunetti E, Vuitton DA, Koch S. Non-surgical and non-chemical attempts to treat echinococcosis: do they work? Parasite. 2014;21:75.
28. Neumayr A, Troia G, de Bernardis C, Tamarozzi F, Goblirsch S, Piccoli L, et al. Justified concern or exaggerated fear: the risk of anaphylaxis in percutaneous treatment of cystic echinococcosis-a systematic literature review. PLoS Negl Trop Dis. 2011;5(6):e1154.
29. Golemanov B, Grigorov N, Mitova R, Genov J, Vuchev D, Tamarozzi F, et al. Efficacy and safety of PAIR for cystic echinococcosis: experience on a large series of patients from Bulgaria. Am J Trop Med Hyg. 2011;84(1):48–51.
30. Smego RA Jr, Bhatti S, Khaliq AA, Beg MA. Percutaneous aspiration-injection-reaspiration drainage plus albendazole or mebendazole for hepatic cystic echinococcosis: a meta-analysis. Clin Infect Dis. 2003;37(8):1073–83.

Part IV

Surgical Management of Non-gastrointestinal Parasitic Diseases

Surgical Management of Parasitic Diseases Involving the Heart

17

Georgios T. Karapanagiotidis and Kyriakos Anastasiadis

Introduction

A parasite is an organism that lives in another organism, called the host, and often harms it; it depends on its host for survival. Thus, without a host, a parasite cannot live, grow and multiply. Therefore, it rarely kills the host; however, it can spread diseases, and some of these can be fatal. Parasites, unlike predators, are usually much smaller than their host, and they reproduce at a faster rate.

There are three main types of parasites. Protozoa are a single-celled organism known as *Plasmodium* (which can only multiply, or divide, within the host); helminths are worm parasites and ectoparasites that live on rather than in their hosts. In general, the heart involvement by parasites should be considered in the differential diagnosis especially of myocardial and/or pericardial diseases of unknown aetiology in both immunocompetent and immunocompromised individuals.

The heart and pericardium may be affected directly or indirectly by a variety of parasites (Table 17.1). The involvement of the heart may be part of a more generalized illness. This involvement may manifest in different ways, but the syndromes resulting from impairment of the myocardium and pericardium are the most frequent. The myocardium may be invaded by parasites that trigger local inflammatory response with subsequent myocarditis or cardiomyopathy. The pericardium is the structure of the heart most frequently involved with consequent pericardial effusion, acute pericarditis, cardiac tamponade or constrictive pericarditis. Intracardiac rupture of a parasitic cyst can cause membrane or secondary cysts embolization to either the lungs or to other organs supplied by the systemic circulation. Chronic parasitic infections, especially filarial, have been associated with the development of tropical endomyocardial fibrosis, a severe form of

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Table 17.1 Types of parasites in human parasitic diseases

Parasites that preferentially involve the myocardium or cause pancarditis	Parasites that occasionally involve the pericardium	Miscellaneous syndromes
Trypanosomes	*Echinococcus*	*Schistosoma*
Toxoplasma	*Entamoeba histolytica*	*Dirofilaria immitis*
Trichinella	*Taenia solium*	*Wuchereria bancrofti*
		Brugia malayi
		Helminth
		Toxocara canis
		Toxocara cati
		Baylisascaris procyonis
		Sarcocystis

restrictive cardiomyopathy. Lung vasculature involvement may cause pulmonary hypertension and cor pulmonale [1, 2]. Due to growing migration, population displacement and travel, clinicians anywhere around the globe must be aware of the potential cardiac manifestations of parasitic diseases.

Types of Parasites in Human Parasitic Diseases: Parasites That Preferentially Involve the Myocardium or Cause Pancarditis

Trypanosomes

There are several types of trypanosomes, but the most common is *Trypanosoma cruzi* (*T. cruzi*) that causes Chagas disease also known as American trypanosomiasis. This comprises a zoonotic tropical disease caused by this flagellate protozoan parasite. Most infections occur through vector-borne transmission by triatomine insects in areas of endemicity, but they can also occur through blood transfusion or organ transplantation (vertically from mother to infant) and, more rarely, by ingestion of food or liquid contaminated with *T. cruzi* (i.e. due to accidents among laboratory personnel who work with live parasites) [3]. A minority of patients will develop an acute syndrome of 4–8 weeks duration, which invariably involves prolonged fever in addition to a variable constellation of symptoms, which include inflammation at the portal of entry, subcutaneous oedema (localized or generalized), lymphadenopathy, hepatosplenomegaly, myocarditis and, more rarely, meningoencephalitis. The manifestations of the acute phase resolve spontaneously for the vast majority of individuals even if the infection is not treated with an antiparasitic drug. About 60% to 70% of these patients will never develop clinically apparent diseases. They remain asymptomatic and infected life long, being recognized only if serological tests are performed (the so-called indeterminate form of chronic Chagas disease). Roughly 30–40% of infected patients will subsequently develop the cardiac and/or digestive (megaesophagus and megacolon) form of chronic Chagas disease, usually 10–30 years after the initial infection [4].

Historically, the disease disproportionately affected the poor because the transmission of *T. cruzi* infection occurred mainly in rural areas where humans live in poor-quality houses and in close contact with potential vectors [5]. As a result of these dynamic changes in the population and the coordinated efforts of countries where disease is endemic to interrupt vectorial and transfusional transmission, the prevalence and incidence of the disease are constantly changing. In the 1980s the overall prevalence of *T. cruzi* infection was estimated to reach 17 million cases in 18 countries where disease is endemic, with 100 million people at risk. According to the most recent estimates, there are currently 7.6 million people infected with *T. cruzi* in Latin America. Although precise figures documenting the total burden of cardiac involvement with *T. cruzi* are not available, it can be assumed that 20–30% of the 7.6 million infected individuals are or will potentially be developing chronic cardiac lesions. Chagas cardiomyopathy, in turn, is thought to represent the principal cause of cardiac morbidity and mortality among young adults in countries where T. cruzi is endemic and has been estimated to result in at least 21,000 deaths annually [6].

The pathogenesis of myocarditis and subsequent myocardial dysfunction during *T. cruzi* infection is still a matter of strong debate. It has been postulated that a repetitive inflammatory response resulting in progressive neuronal damage, microcirculatory alterations and heart matrix deformation are the main pathogenic features in Chagas cardiomyopathy [7].

However, recent evidence has suggested that the chronic chagasic cardiomyopathy appears to be a continuous process associated with the persistence of the parasites in the myocardium [8]. In addition, there are findings that supported by the frequent reactivation of Chagas disease among HIV-infected individuals. Therefore, there is a growing consensus that elimination of *T. cruzi* in myocardial tissue is a prerequisite to halt the progression of the disease [9]. Acute myocarditis as evidenced by autopsy studies probably happens in close to 100% of patients with acute Chagas disease. However, acute chagasic myocarditis is diagnosed for only 1–40% of them [10].

The initial descriptions of the cardiac involvement in Chagas disease were completed by Carlos Chagas in the early twentieth century. In his early descriptions, he eloquently described the occurrence of significant cardiac conduction abnormalities, arrhythmias and sudden cardiac death in his patients [11]. Currently, we recognize that Chagas disease has three different clinical phases. The acute phase follows the entry and invasion of the bloodstream by the protozoan parasite. After the acute phase, the infected individual enters the chronic phase, which has a variable duration usually more than 10 or 20 years. At its end, the disease may follow three different paths: (i) develop of megasyndromes, (ii) end up to myocarditis with associated fibrosis which is considered the terminal form (with highest mortality) (iii) or remain asymptomatic for the rest of live [12]. The cardiomyopathy associated with Chagas disease manifests as a biventricular failure with both systolic and diastolic dysfunction and associated cardiac arrhythmias or sudden cardiac death. Sudden cardiac death accounts for 55–65% of deaths in Chagas disease [13]. Pulmonary or systemic embolism arising from mural thrombi in dilated cardiac

chambers may be identified at autopsies of patients who died of Chagas disease. Chagas disease has become an important opportunistic infection among patients with human immunodeficiency virus (HIV) – infection or other types of immune-suppression such as organ transplantation causing reactivation of chronic latent *T. cruzi* infection and manifested as myocarditis or meningoencephalitis [14].

The diagnosis of *T. cruzi* infection is made by epidemiological, clinical and serological criteria [14]. ECG findings are numerous but consist mainly of bundle branch blocks and various degrees of atrioventricular blocks (Fig. 17.1). The principal electrocardiographic (ECG) alterations are first-degree atrioventricular (AV) block, low QRS voltage and primary T-wave changes [14]. A chest radiograph frequently shows variable degrees of cardiomegaly, and pericardial effusion is the most frequently reported echocardiographic abnormality [15]. Echocardiograms may reveal apical aneurysms, segmental wall motion abnormalities or diffuse hypokinesis [16]. Brain natriuretic peptide (pro-BNP) measurements could be a useful method to screen patients with Chagas disease [16]. Death in the acute phase occurs occasionally (for 5–10% of symptomatic patients) as a result of congestive heart failure (due to severe myocarditis) and/or meningoencephalitis [14].

The treatment of Chagas heart disease is a combination at eradicating the parasite and targeting the cardiac manifestations [17, 18]. Benznidazole and nifurtimox are used in the acute phase and in reactivation under immunosuppressive conditions. Chemotherapy can shorten the acute phase and achieve a parasitological cure in 50% of the cases but causes significant toxicity. However, there is no evidence that drug treatment of persons in the chronic phase can alter the natural history of the disorder [19]. On the other hand, heart failure and arrhythmias in Chagas disease are treated similar to other aetiologies of heart failure. Surgical management of the disease includes, in several times, cardiac transplantation. The procedure, despite the lack of donors and the high surgical risk, has been successfully performed in selected patients, and survival was better compared to patients transplanted for other types of cardiac disease. Moreover, there is still the option of heart transplantation

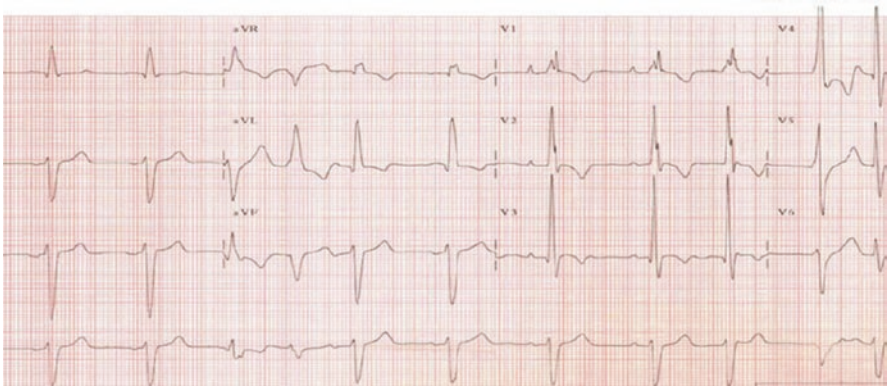

Fig. 17.1 Electrocardiogram from a patient with dilated cardiomyopathy due to Chagas Disease showing a complicated right bundle branch block and premature ventricular complexes

in very advanced stages of chagasic cardiomyopathy [20]. Cardiomyoplasty and partial ventriculectomy are considered in few patients. The former utilizes stimulated skeletal muscle grafts mainly form latissimus dorsi muscle to reinforce ventricular wall [21]. The later seeks to restore left ventricular function by reducing cardiac volume (and left ventricular wall tension) through the resection of the posterolateral wall of the left ventricle [22] and was described by the Brazilian cardiac surgeon Randas Batista, known afterwards as the Batista procedure [23]. However, the results from these heart operations are controversial [24]. Also, patients at high risk of sudden death can benefit from implantable defibrillator for cardioversion therapy [25].

Regarding other trypanosomes, *Trypanosoma brucei* (*T. brucei*) *rhodesiense* (in east and southern Africa) and *Trypanosoma brucei Gambiense* (in west and central Africa) are the two flagellate parasites responsible for human African trypanosomiasis (HAT). The disease is caused by the bite of the tsetse fly (*Glossina*). Cardiac manifestations are not a prominent feature of *T. brucei*, but they have been described for HAT. Studies looking at clinical aspects of HAT have focused mainly on central nervous system signs and symptomatology [26]. Dyspnoea upon exertion, cough, palpitations, abnormal cardiac rhythms, heart murmurs, hepatojugular reflux, hepatomegaly and peripheral oedema were all more commonly seen in patients with *T. brucei Gambiense* HAT. Moreover, all of these symptoms resolved with the treatment of HAT and without specific treatment for heart failure [27]. It is still unclear whether cardiac involvement is present during early stages or whether the changes observed during late-stage HAT can evolve years later to an established cardiomyopathy. Usually, there is no need for specific surgical management. Signs and symptoms of heart failure in patients with HAT are relatively mild and do not correlate with ECG abnormalities or with laboratory markers of LV dysfunction, such as pro-BNP. Summing up, these nonspecific signs and symptoms usually resolve with the etiological treatment of HAT [27]. However, when myocarditis occurs, occasional pancarditis may occasionally develop during the hemolymphatic stage, leading to arrhythmias and heart failure with *T. brucei rhodesiense* infection. The pathophysiology of cardiac involvement in African trypanosomiasis is secondary to endarteritis and fibrosis caused by perivascular infiltration by trypanosomes and lymphocytes [28]. ECG abnormalities are present in half the cases sometimes manifested as cardiac conduction delays. A chest radiograph may show cardiomegaly, and echography can identify ventricular dilatation and/or pericardial thickening. Surgical treatment is usually not necessary due to most frequently signs and symptoms are resolved with the etiological treatment.

Toxoplasma

Toxoplasma gondii (*T. gondii*) causes toxoplasmosis which is a worldwide zoonosis capable of causing several distinct clinical syndromes in immune-competent and immune-compromised individuals. *T. gondii* is a parasite of members of the cat family, with humans and other warm-blooded animals serving as intermediate hosts

[29]. Humans become infected by eating of undercooked meat, ingestion of contaminated water and faecal-oral transmission from feline faeces, congenitally through transplacental transmission, blood transfusion or transplantation [30]. Indeed, toxoplasmosis is the most commonly reported parasitic disease occurring after heart transplantation and may simulate organ rejection. Disseminated toxoplasmosis with associated myocarditis can lead to a fatal outcome if no prior prophylaxis is given to transplant patients [31]. The diagnosis of toxoplasmosis is based on serology or the identification of tachyzoites in myocardial tissue [31]. IgG antibodies appear early, peak within 6 months of infection and remain detectable for life; IgM antibodies may persist for years after infection and should not be used as the sole diagnostic criteria for recent infection [32]. Patients may have slight lymphocytosis, and hepatic transaminase levels may be slightly elevated. Kean and Grocott first described 'toxoplasmosis-like cysts' in the myocardium in 1945, while Adams subsequently described fluctuating ST changes in glandular-type toxoplasmosis [33, 34]. It has to be noted that endomyocardial biopsy has identified the organism even in heart transplant patients [31]. In general, local necrosis with oedema and an inflammatory infiltrate upon biopsy are typical. Myocardial abscesses have also been reported; however, abscesses are not common pathological features of toxoplasmosis [35]. Polymerase chain reaction (PCR) has been reported to diagnose toxoplasma more frequently than histology of cardiac biopsy specimen samples in the transplant setting [36].

Myocarditis, pericardial effusion, constrictive pericarditis, arrhythmias and congestive heart failure have been described in patients infected with *T. gondii* [14]. In patients with the HIV infection, the heart is the second most commonly affected organ after the brain [37]. Prevalence varies according to various studies, and diagnosis is usually made post-mortem since cardiac involvement is usually clinically silent. Approximately 12–22% of HIV-positive patients had evidence of endomyocardial involvement by *T. gondii* at autopsy. Prevalence of cardiac toxoplasmosis confirmed at autopsy in the highly active antiretroviral era has been reported to be less than 10% [38]. *Toxoplasma gondii*-associated myocarditis can also occur in transplant patients either due to a reactivation or to de novo infection from a seropositive donor to a seronegative recipient [39]. In fact, toxoplasmosis is the most commonly reported parasitic disease occurring after heart transplantation. Disseminated toxoplasmosis with associated myocarditis can lead to a fatal outcome if no prior prophylaxis is given in transplant patients. The diagnosis of toxoplasmosis relies on serology or identification of the bradyzoites in myocardial tissue [31, 40].

The treatment of choice is based on a combination of pyrimethamine and sulfadiazine or pyrimethamine and clindamycin [41, 42]. Prevention is important for seronegative pregnant women and immune-deficient patients. Prevention is accomplished through physician-patient education and prophylaxis prescription, where appropriate. Teaching/education should focus on the avoidance of contact with materials potentially contaminated with cat faeces, washing of hands after contact with raw meat, 'well done' cooking of meat, washing of fruits and vegetables before

consumption and using of single used gloves when handling cat litter or gardening. Surgical management of the disease is personalized from patient to patient regarding the signs and symptoms that affecting the heart but usually in the majority of cases is decided to follow conservative medical treatment.

Trichinella

Trichinella spiralis (*T. spiralis*) and other *Trichinella* species are common worldwide and causing trichinellosis. Humans become infected when eating undercooked contaminated meat [43]. The clinical picture of trichinellosis is manifesting with two clinical stages: the intestinal stage and the muscular stage [43]. Larval migration into the muscles can cause periorbital and facial oedema, subungual, conjunctival and retinal haemorrhages, myalgias, weakness and fever [43]. The tropism of *T. spiralis* for striated muscle may lead to involving the myocardium in 21–75% of infected patients [44, 45]. *Trichinella spiralis* is associated myocarditis, which is not caused by the direct larval invasion of the myocardium with encystations; it is more likely induced by an eosinophilic-enriched inflammatory response resulting in eosinophilic myocarditis similar to the pathogenic process associated with tropical endomyocardial fibrosis. Trichinellosis myocarditis may initially manifest with chest pain and mimic an acute myocardial infarction. Reports suggest that ECG evidence of myocardial involvement was found for up to 75% of patients. Complications such cardiac arrhythmias are considered the most common cause of death associated with trichinellosis. In addition, pericardial effusions have also been reported during *T. spiralis* infection [46, 47].

As far as the diagnosis of the disease is concerned, there is no direct relationship between the severity of eosinophilia and clinical course [48]. Confirmation is based on serology and muscle biopsy specimens [45]. Serology is generally reliable and first becomes positive about 3 weeks after infection [49]. Antibody levels may remain positive for longer than a year after clinical resolution. The finding of larvae in a muscle biopsy specimen provides a definitive diagnosis; however, biopsy is rarely necessary. The ECG findings are considered nonspecific without an association with poor prognosis [50]. Rarely, the presence of pericardial effusion is the most common cardiac manifestation of trichinellosis, affecting up to 10% of patients [45]. In addition, cardiac magnetic resonance imaging (MRI) may provide supportive evidence of myocardial involvement, although the MRI findings are not specific to trichinellosis [51].

Treatment of T. spiralis infection consists of the administration of albendazole or mebendazole in conjunction with steroids for severe cases [48, 49]. Although albendazole and mebendazole are relatively contraindicated in pregnancy, both have been used in patients without adverse foetal effects [52]. Adjunctive steroids are commonly utilized for 10–15 days. Surgical management of trichinellosis consists mainly of pericardial effusion drainage whenever this exists.

Types of Parasites in Human Parasitic Diseases: Parasites That Occasionally Involve the Pericardium

Echinococcus

Echinococcosis in humans is mainly due to the parasite *Echinococcus granulosus* or *Taenia echinococcus*. There are other rare forms like *Echinococcus multilocularis* or *Echinococcus sibericensis* and *Echinococcus oligarthous* and *Echinococcus vogeli*. The parasite can cause disease to the human, but the true prevalence is unknown [53]. It is known that humans are infected with swallowing contaminated ova with the parasite of grass, water and vegetables. It is noted that the ova are extremely resistant to fossil and chemical agents [54]. Following the ingestion of the eggs by an intermediate host, the eggs hatch and release oncospheres, which cross the small intestine and spread to encyst in various visceral organs. Hydatid cysts develop over months to years. Most of them will remain asymptomatic, but some of them become large enough to cause symptoms [55].

Cardiac hydatid disease was first reported by Williams in 1836. Cardiac hydatid cysts are rare and have been described for 0.5–3% of echinococcosis cases [54, 56–58]. The heart is haematogenically inflamed through the coronary circulation and rarely through the thoracic duct (lymphangitic spread), which is ultimately drained into the subclavian vein [59]. Hydatid cysts of myocardium are primary cysts that are mainly located in the left ventricular myocardium due to its richer blood flow. In contrast, hydatid cysts of pericardium are secondary cysts due to their wall rupture [54, 56]. Hydatid cysts are located in the left ventricular myocardium (43–77%), in the right ventricular myocardium (15–20%), in the left atrium myocardium (1.6–8%), in the intraventricular septum (5–19%), in pulmonary artery (7–8%), in the right atrium myocardium (3–11.2%) and in the pericardium (5%) [60, 61]. Isolated cardiac hydatid cysts without liver involvement are uncommon [56].

Echinococcal disease is often diagnosed as an incidental finding during imaging for other reasons. Clinical presentations of cardiac echinococcosis include arrhythmias, myocardial infarction, cardiac tamponade, pulmonary hypertension, syncope, purulent pericarditis and sudden cardiac death [56, 57]. Hydatid cysts can even mimic ST segment elevation myocardial infarction upon electrocardiography [62]. Rarely, an atrial or ventricular thrombus may mimic a hydatid cyst [63, 64]. Diagnosis relies on positive serological testing and radiographic findings [2, 65]. Echocardiography (Fig. 17.2) is the most appropriate imaging test to evaluate potential myocardial or pericardial hydatid cysts [66]. Chest computed tomography (CT) imaging and MRI (Fig. 17.3) may also demonstrate specific signs, including the calcification of the cysts walls, the presence of daughter cysts, and membrane detachment [67, 68].

Unruptured hydatid cysts are asymptomatic in 40% of cases [54]. Unruptured cysts are presenting with symptoms in the rest 60% of cases, either because of enlargement of them or because of the anatomical area that located and create pressure to adjacent structures. The main symptoms in these circumstances are thoracic

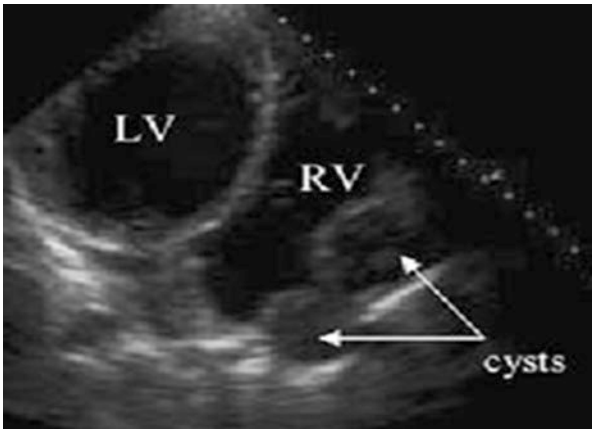

Fig. 17.2 Pericardial hydatid cysts occupy space and cause pressure in the right ventricle

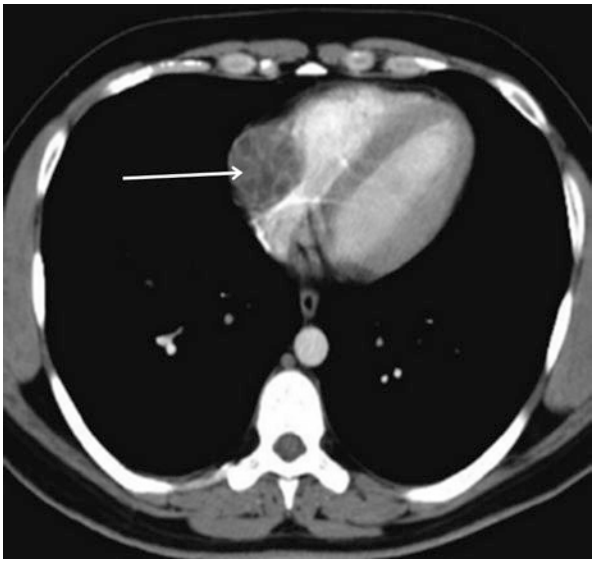

Fig. 17.3 Computed tomography (CT) image of a hydatid cyst into the right ventricle

pain, shortness of breath, angina and palpitations [53, 54]. Rupture of hydatid cysts of myocardium or pericardium is an emergency situation that can even cause sudden death [69]. Four phases after the rupture of a cardiac hydatid cyst are described: (i) symptoms of anaphylactic reaction or shock and sudden death may occur because of allergic shock, ventricular or valve obstruction, massive pulmonary embolism and carotid occlusion; (ii) spreading of parasites through systemic or pulmonary circulation; (iii) appearance of symptoms due to secondary location; and (iv) appearance of complications due to secondary location [54]. It is worth mentioning that in 25% cases, a 'silent uncomplicated' rupture of the cyst from myocardium to pericardium has been reported [56].

The drug of choice for the treatment of echinococcosis is albendazole or mebendazole. Antiparasitic therapy should be started at least 4 days before surgery and be continued for at least 1 month (albendazole) or 3 months (mebendazole) after surgery. Patients should be on antiparasitic therapy prior to surgery to reduce the risk of cyst dissemination [70, 71]. Surgery, when feasible, is the most common form of treatment of echinococcosis [70]. Management of hydatid disease carries a substantial risk of complications and recurrence. The ultimate goal of surgery is to kill the parasites, evacuate the cyst, remove the germinal layer and obliterate the residual cavity all while preserving the healthy cardiac tissue. The first successful surgical intervention in heart was performed by Long in 1932. By 1964, only 42 successfully treated cases had been reported in the literature. In 1962, Arturico and colleagues reported the first successful operation for cardiac echinococcosis with the use of extracorporeal circulation [72].

According to the World Health Organization (WHO), surgery is not recommended for pregnant women, those with multiple or difficult-to-access cysts or patients with dead or totally calcified cysts. Asymptomatic cysts, if heavily calcified and presumed nonviable, may be monitored without specific therapy [70]. Although it is generally published in the literature that whenever echinococcosis is diagnosed, the treatment of choice for even asymptomatic cases is surgery, due to the risk of cystic rupture [59, 73]. The puncture, aspiration, injection and respiration (PAIR) technique is an option for inoperable cysts [70]. The operation is performed through a median sternotomy in most of the times; operations through left or right thoracotomy may perform only in pericardium hydatid cysts. As far as the procedure is concerned, patients may be operated with or without the use of cardiopulmonary bypass (Fig. 17.4), while the latter is the treatment of choice in the majority of cases. As a rule, the heart should not be manipulated before the application of the cross-clamp to stop and isolate the heart from the systemic circulation. In operations for cysts located in the right side of the heart, the pulmonary artery can be clamped to avoid pulmonary embolism. Usually, the operative field was wrapped with towels moistened with 1% povidone-iodine solution, which was also instilled into the

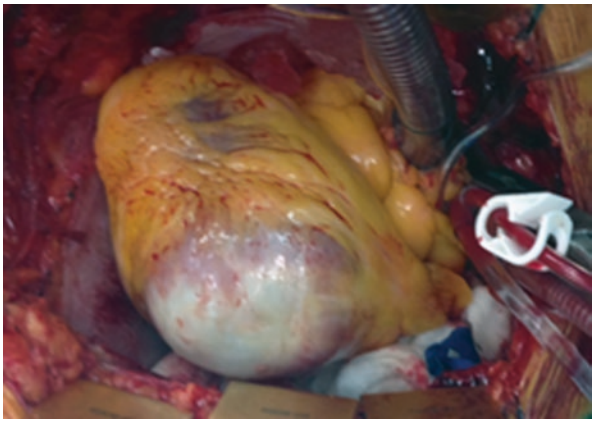

Fig. 17.4 Hydatid cyst located in posterolateral wall of the left ventricle. The patient is connected to the extracorporeal circulation for subsequent excision of the cyst

cysts. In superficially located cysts, the cavity could left open at the end of cystectomy. Technique of capitonnage was performed in several cases to obliterate the cystic cavity [60, 72–74]. Operative mortality varies from 4.8% to 10% [56, 69].

Entamoeba histolytica

Amoebiasis is caused by a protozoan *Entamoeba histolytica* transmitted by the faecal-oral route. It is the third most common cause of parasitic death [75]. Particular high-risk groups include children, pregnant women and malnourished individuals [76]. Invasive amoebiasis may be more common among HIV patients, prompting some to call for routine HIV testing of those diagnosed with the disease [77]. Involvement of the pericardium is very rare but is considered a serious complication of amoebiasis. The suppurative feature of amoebic pericarditis may cause it to be confused with tuberculous pericarditis [78, 79]. Amoebic pericarditis may present as either a pericardial rub with electrocardiographic changes associated with an abscess of the left lobe or purulent pericarditis from the perforation of the abscess into the pericardium [80]. Amoebic abscesses in the right lobe of the liver have also been reported to communicate with the pericardium [81]. The presenting clinical syndrome is usually either sudden onset as cardiac tamponade with chest pain, shortness of breath and shock or progressive effusion with a slower course to develop fever, dyspnoea and pain [82]. Amoebic pericarditis has been more frequently described for paediatric populations in which the association of concomitant intestinal amoebiasis may be as high as 20% [83].

Diagnosis is usually established by serology with a very high sensitivity of about 90% [84]. However, a distinguishing factor between tuberculous and amoebic pericarditis is that there is a predominance of neutrophils in patients with amoebiasis [78]. Positive serology does not distinguish between acute and past infections. Aspirated pus is usually sterile, and diagnosis should not be excluded based on its gross characteristics [85]. Imaging with CT scan and echocardiography can be useful given the potential to demonstrate a liver abscess in continuity with the pericardium and fluid within the pericardial sac, with or without the fistulous tract [79].

Treatment of pericardial amoebiasis requires usually a combination of surgical drainage and metronidazole [79]. Metronidazole should be given three times daily for 7–10 days. Clinical improvement is expected within 48 h to 72 h. If clinical improvement does not occur, bacterial superinfection should be considered and treated if found, and metronidazole therapy may be prolonged [86].

Taenia solium

Ingestion of the eggs of *Taenia solium* may produce cerebral cysticercosis as the most serious complication. The condition can also present as ocular, spinal, cutaneous, muscular or cardiac lesions [87, 88]. Cardiac involvement in cysticercosis is extremely rare, but autopsy studies have shown prevalence of 20–25% in patients

with concomitant documented neurocysticercosis [89]. Cardiac cysticercosis is often asymptomatic and discovered during cardiac surgery or at autopsy. Cysticerci are usually multiple and randomly distributed in cardiac tissues including the subpericardium, subendocardium and myocardium [88, 89]. The inflammatory response can be variable; granuloma formation can be present as well as fibrosis, leading to arrhythmias and conduction abnormalities [58, 89]. The role of albendazole and praziquantel or surgery in cardiac cysticercosis is still unclear [58, 88, 89].

Types of Parasites in Human Parasitic Diseases: Miscellaneous Syndromes

Schistosoma

Schistosomiasis is caused by parasite schistosoma due to the accumulation of *Schistosoma* eggs, which induce a local granulomatous response [90]. Involvement of the myocardium or pericardium is rare, while the induced granulomatous response may lead to myocarditis or pericarditis [91]. Chronic schistosomiasis could end up to severe liver fibrosis secondary to hepatosplenic schistosomiasis. This process involving portal hypertension may be associated with a hepatopulmonary syndrome manifested as dyspnoea on exertion, right ventricular hypertrophy and ultimately cor pulmonale [92, 93]. Endothelial damage to the pulmonary circulation results from the shunting of *Schistosoma* eggs through portosystemic shunts. In addition, thrombosis in situ, particularly, of the right pulmonary artery may occur, as well as cardiac arrhythmias and sudden cardiac death syndromes [92, 93]. The treatment of schistosomiasis (all species) is pharmaceutical and comprises praziquantel or, alternatively, oxamniquine for *Schistosoma mansoni* [91].

Dirofilaria immitis

It is a common parasite of dogs, and other canids prevalent in many areas of the world can occasionally affect humans, and it causes zoonotic filariasis. Once injected by a mosquito vector, the adult worms live in the right chambers of heart where they can induce myocarditis [94]. Although adult *Dirofilaria immitis* worms have been found on several occasions in the heart and major vessels of humans at necropsy, the usual finding is for immature worms to be located in partially or completely occluded by small pulmonary arteries, where the obstruction has produced a pulmonary infarct and eventually a well-circumscribed coin lesion containing the parasite [94]. These lesions are usually identified in asymptomatic individuals undergoing routine chest radiographs. Other filarial species, such as lymphatic-dwelling human filariae (*Wuchereria* spp. and *Brugia* spp.), may also be identified as pulmonary nodules [95, 96]. The occurrence of severe and occasionally lethal, myocardial involvement that often occurs in dogs and other canids has not been described for humans [95].

Wuchereria bancrofti and *Brugia malayi*

Wuchereria bancrofti and *Brugia malayi* are parasites that can cause tropical pulmonary eosinophilia. This syndrome manifested as chronic pulmonary infiltrates with eosinophilia and may result in permanent deficits in pulmonary function [97]. Clinical symptoms usually include cough, dyspnoea and nocturnal wheezing [98]. Eosinophils located in the lung, as a response to the presence of filariae in the pulmonary circulation, degranulates and leads to the production of toxic oxygen radicals that contribute to a chronic pulmonary inflammatory process [97, 99]. These restrictive pulmonary function deficits may result in pulmonary hypertension that subsequently contributes to cor pulmonale [98, 99]. The treatment of choice recommended by WHO is conservative with the oral antifilarial drug diethylcarbamazine (DEC) for 3 weeks [98].

Helminth (Macroparasite Worms)

Helminth-induced hypereosinophilia has been associated with tropical endomyocardial fibrosis. The exact aetiology of this entity remains unknown. Filariae and schistosomiasis are the nematodes most frequently found to induce chronic eosinophilia with consequent endomyocardial fibrosis [100, 101]. The proposed immune pathogenesis suggests that when eosinophilia is persistent, blood eosinophils may undergo characteristic changes that have been associated with cellular activation and eosinophil-induced tissue damage [101, 102]. This results in endomyocardial fibrosis, which is manifested clinically as restrictive cardiomyopathy [101]. The clinical presentations of tropical endomyocardial fibrosis are similar to those of the idiopathic hypereosinophilic syndrome involving the heart [100, 102]. This process leads to endomyocardial fibrosis, mural thrombus formation, arrhythmias and pericarditis with effusion in some cases. Echocardiographic criteria such as endomyocardial plaques, thrombi or spontaneous contrast without severe ventricular dysfunction, retraction of the right ventricular apex and atrioventricular valve dysfunction caused by adhesion of the valvular apparatus are utilized to diagnose endomyocardial fibrosis (Fig. 17.5a) [103]. MRI scan has been reported to have a supportive emerging role [104]. A tailored, individualized approach of combined surgical and medical therapy is the optimal plan of care [105]. Open heart surgery increases survival compared with medical treatment [106]. Endomyocardial fibrosis may be successfully treated with surgical endocardectomy and valve repair or replacement (Fig. 17.5b). The use of cavopulmonary connections may be helpful in pure right-sided endomyocardial fibrosis with a small right ventricular cavity. Although the early postoperative mortality is high and may be up to 20%, variable rates of recurrence after surgery have been reported. Timely surgical treatment still appears to be the only option to substantially improve outcomes at present [107]. It is of noted that patients with end-stage endomyocardial fibrosis and clinical signs of advanced disease (gross and long-standing ascites, chronic pulmonary thromboembolism, extensive endocardial fibrosis, right ventricular hypoplasia or extreme

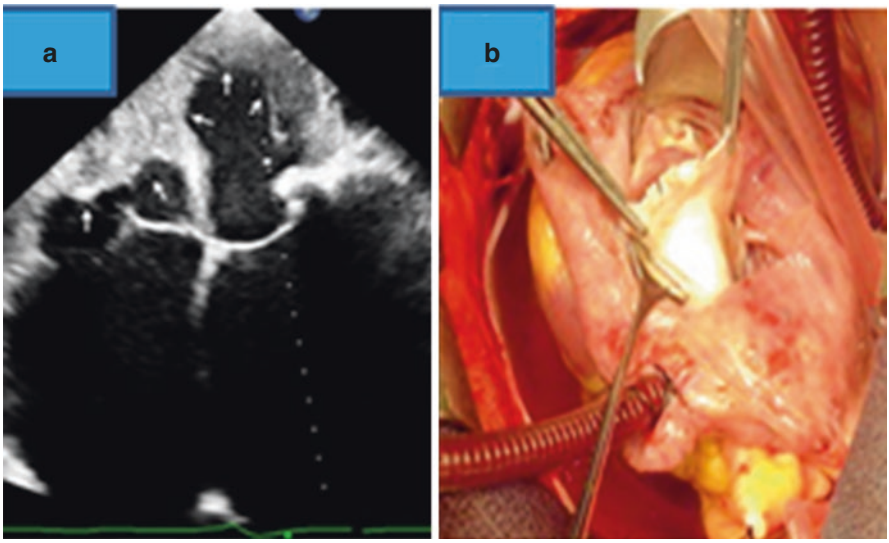

Fig. 17.5 (**a**) Echocardiographic image of severe biventricular endomyocardial fibrosis causing clinically restrictive clinical syndrome as well as severely dilated atria; (**b**) intraoperative image of endocardial resection from the ventricular cavity of tropical endomyocardial fibrosis. (Adapted from Mocumbi et al. [105])

cachexia) are not suitable for surgery [107, 108]. In general, prognosis is poor, while death often results from complications of the chronic heart failure and its associated morbidities.

Toxocara canis, *Toxocara cati* and *Baylisascaris procyonis*

Visceral larva migrans is caused primarily by infection with *Toxocara canis* and less frequently by *Toxocara cati* or *Baylisascaris procyonis.* The syndrome is characterized by eosinophilia, fever and hepatomegaly and has presented predominantly in children [109, 110]. Although almost any human organ can be affected, the liver is most frequently involved, while eosinophilia is a hallmark of the disease. Cardiac manifestations have included endomyocarditis, cardiac pseudotumor and cardiac tamponade [111, 112]. The diagnosis can be definitively confirmed by finding larvae in the affected tissue by histological examination. Toxocara antibody titers may not be useful in definitively establishing the diagnosis. Many patients recover without therapy, while no single agent has been proven to be particularly effective. However, in the setting of severe cardiac disease, treatment with albendazole, mebendazole or thiabendazole is recommended to be applied. In general, clinical vigilance must remain high for the possibility of a treatment-provoked inflammatory response that may respond to corticosteroids. Pericardial drainage must be performed in case of acute life-threatening cardiac tamponade [113].

Sarcocystis

Sarcocystis is a zoonotic coccidian protozoal parasite, and more than 120 different species have been reported and cause sarcocystosis. Humans may serve as definitive hosts for pork and cattle sarcocystis when ingested with poorly cooked or raw meat. Southeast Asia is the source of most human case reports [114, 115]. In ethnic groups that routinely consume undercooked pork or beef, the prevalence has been reported to be up to 22%. Most individuals are asymptomatic. However, clinical manifestations usually comprise myalgia, fever, transient pruritic rashes, lymphadenopathy and subcutaneous nodules associated with eosinophilia and elevated creatinine kinase levels [116]. Serology is highly specific, and muscle biopsy may be useful for individuals with symptoms [117]. *Sarcocystis* can be found in the muscles of the limbs, tongue, oesophagus and diaphragm but also in neural tissue in the brain and in the spinal cord [118]. It is worth mentioning that several cases of sarcocystosis have been detected in patients with various types of cancer [119]. Cardiac conduction abnormalities are due to myocardial involvement [118]; it is interesting that *Sarcocystis* was found in Purkinje fibres [120]. Treatment strategies may be adapted from experimental animal studies and from therapeutic procedures of related protists in humans; they can provide guidance for treatment of muscular sarcocystosis when diagnosis is made early in infection, before sarcocystis formation begins [120]. In general, there is no specific treatment for sarcocystis, although albendazole was reported to suppress human symptoms [118].

Summary

The heart can be affected, though rarely, directly or indirectly by a variety of parasites. This involvement may manifest in different ways. The clinical syndromes resulting of impaired myocardial function and pericardial involvement are the most frequent. Both the myocardium and the pericardium while invaded by parasites trigger local inflammatory response with subsequent myocarditis or cardiomyopathy, either pericarditis or pulmonary hypertension. Chronic persistence of some parasites in the heart leads to an immune-pathogenic mechanism of cardiac injury. Therefore, parasitic infections should be included in the differential diagnosis of myocardial and pericardial diseases in any place worldwide. As far as the therapeutic protocols are concerned, limited number of drugs is effective for most of the human parasitic diseases. The lack of effective vaccines, efficient chemoprophylaxis or successful pharmacologic therapies to control the majority of the parasitic diseases of the heart, renders such disease as one of the current key public health challenges. Regarding the surgical management of cardiac parasitic diseases, this comprises mainly the control of complications rather than a radical treatment. Only in few parasitic diseases, surgical procedures such as pericardial drainage, parasitic cyst excision, endocardectomy with or without concomitant heart valve repair or replacement and ultimately heart transplantation may be of clinical value.

References

1. Nunes MC, Guimaraes Junior MH, Diamantino AC, Gelape CL, Ferrari TC. Cardiac manifestations of parasitic diseases. Heart. 2017;103:651–8.
2. Hidron A, Vogenthaler N, Santos-Preciado JI, et al. Cardiac involvement with parasitic infections. Clin Microbiol Rev. 2010;23(2):324–49.
3. Strickland GT. American trypanosomiasis. In: Hunter's tropical medicine and emerging diseases. 8th ed. Philadelphia: WB Saunders; 2000. p. 653–64.
4. Laranja FS, Dias E, Nobrega G, Miranda A. Chagas' disease; a clinical, epidemiologic, and pathologic study. Circulation. 1956;14:1035–60.
5. Moncayo A. Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. Mem Inst Oswaldo Cruz. 2003;98:577–91.
6. Rassi A, Rassi A Jr, Little WC. Chagas' heart disease. Clin Cardiol. 2000;23:883–9.
7. Machado FS, Koyama NS, Carregano V, et al. CCR5 plays a critical role in the development of myocarditis and host protection in mice infected with Trypanosoma cruzi. J Infect Dis. 2005;191:627–36.
8. Urbina JA, Docampo R. Specific chemotherapy of Chagas disease: controversies and advances. Trends Parasitol. 2003;19:495–501.
9. Anez N, Carrasco H, Parada H, et al. Myocardial parasite persistence in chronic chagasic patients. Am J Trop Med Hyg. 1999;60:726–32.
10. Parada H, Carrasco HA, Anez N, Fuenmayor C, Inglessis I. Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study. Int J Cardiol. 1997;60:49–54.
11. Punukollu G, Gowda RM, Khan IA. Early twentieth century descriptions of the Chagas heart disease. Int J Cardiol. 2004;95:347–9.
12. De Faria JB, Alves G. Transmission of Chagas' disease through cadaveric renal transplantation. Transplantation. 1993;56:1583–4.
13. Samuel J, Oliveira M, Correa De Araujo RR, Navarro MA, Muccillo G. Cardiac thrombosis and thromboembolism in chronic Chagas' heart disease. Am J Cardiol. 1983;52:147–51.
14. Paredes CF, Rouphael N, Mendez J, et al. Cardiac manifestations of parasitic infections part 2: parasitic myocardial disease. Clin Cardiol. 2007;30:218–22.
15. Groom ZC, Protopapas AD, Zochios V. Tropical diseases of the myocardium: a review. Int J Gen Med. 2017;10:101–11.
16. Scanavacca M, Sosa E. Electrophysiologic study in chronic Chagas heart disease. Sao Paulo Med J. 1995;113:841–50.
17. Ribeiro AL, dos Reis AM, Barros MV, et al. Brain natriuretic peptide and left ventricular dysfunction in Chagas disease. Lancet. 2002;360:461–2.
18. Pinto Dias JC. The treatment of Chagas disease (South American trypanosomiasis). Ann Intern Med. 2006;144:772–4.
19. Villar JC, Marin-Neto JA, Ebrahim S, Yusuf S. Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection. Cochrane Database Syst Rev. 2002;1:CD003463.
20. Bocchi EA, Fiorelli A. The paradox of survival results after heart transplantation for cardiomyopathy caused by Trypanosoma cruzi. First Guidelines Group for Heart Transplantation of the Brazilian Society of Cardiology. Ann Thorac Surg. 2001;71:1833.
21. Moreira LF, Stolf NA, Bocchi EA, et al. Latissimus dorsi cardiomyoplasty in the treatment of patients with dilated cardiomyopathy. Circulation. 1990;82(Suppl):IV257–63.
22. National Institute for Health and Clinical Excellence - NICE. Partial left ventriculectomy (the Batista procedure). Interventional procedures guidance 2004; nice.org.uk/guidance/ipg41.
23. Batista RJ, Santos JL, Takeshita N, Bocchino L, Lima PN, Cunha MA. Partial left ventriculectomy to improve left ventricular function in end-stage heart disease. J Card Surg. 1996;11:96–7.

24. Moreira LF, Seferian P, Bocchi EA, et al. Survival improvement with dynamic cardiomyoplasty in patients with dilated cardiomyopathy. Circulation. 1991;84(Suppl):III296–302.
25. Rodriguez H, Munoz M, Llamas G, et al. Automatic, implantable cardioverter-defibrillator in a patient with chronic Chagas cardiopathy and sustained ventricular tachycardia. Arch Inst Cardiol Mex. 1998;68:391–9.
26. Blum J, Schmid C, Burri C. Clinical aspects of 2541 patients with second stage human African trypanosomiasis. Acta Trop. 2006;97:55–64.
27. Blum JA, Burri C, Hatz C, Kazumba L, Mangoni P, Zellweger MJ. Sleeping hearts: the role of the heart in sleeping sickness (human African trypanosomiasis). Tropical Med Int Health. 2007;12:1422–32.
28. Bertrand E. Cardiac involvement in human African trypanosomiasis. Med Trop (Mars). 1987;47:91–3.
29. Dubey JP, Lindsay DS, Speer CA. Structures of Toxoplasma gondii tachyzoites, bradyzoites, and sporozoites and biology and development of tissue cysts. Clin Microbiol Rev. 1998;11:267–99.
30. Matturri L, Quattrone P, Varesi C, Rossi L. Cardiac toxoplasmosis in pathology of acquired immunodeficiency syndrome. Panminerva Med. 1990;32:194–6.
31. Wagner FM, Reichenspurner H, Uberfuhr P, Weiss M, Fingerle V, Reichart B. Toxoplasmosis after heart transplantation: diagnosis by endomyocardial biopsy. J Heart Lung Transplant. 1994;13:916–8.
32. Liesenfeld O, Press C, Montoya JG, et al. False-positive results in immunoglobulin M (IgM) toxoplasma antibody tests and importance of confirmatory testing: the Platelia Toxo IgM test. J Clin Microbiol. 1997;35:174–8.
33. Kean BH, Grocott RG. Sarcosporidosis or toxoplasmosis in man and guinea-pig. Am J Pathol. 1945;21:467–83.
34. Adams JL. Acute toxoplasmosis with involvement of the heart. N Z Med J. 1962;61:20.
35. Roldan EO, Moskowitz L, Hensley GT. Pathology of the heart in acquired immunodeficiency syndrome. Arch Pathol Lab Med. 1987;111:943–6.
36. Holliman R, Johnson J, Savva D, Cary N, Wreghitt T. Diagnosis of toxoplasma infection in cardiac transplant recipients using the polymerase chain reaction. J Clin Pathol. 1992;45:931–2.
37. Politi Okoshi M, Rubens MM. Pathology of the heart in AIDS. Study of 73 consecutive necropsies. Arq Bras Cardiol. 1996;66:129–33.
38. Hoffman P, Bernard E, Michiels JF, Thyss A, Le Fichoux Y, Loubiere R. Extracerebral toxoplasmosis in the acquired immunodeficiency syndrome (AIDS). Pathol Res Pract. 1993;189:894–901.
39. Gallino A, Maggiorini M, Kiowski W, et al. Toxoplasmosis in heart transplant recipients. Eur J Clin Microbiol Infect Dis. 1996;15:389–93.
40. Sahasrabudhe NS, Jadhav MV, Deshmukh SD, Holla VV. Pathology of Toxoplasma myocarditis in acquired immunodeficiency syndrome. Indian J Pathol Microbiol. 2003;46:649–51.
41. Wreghitt TG, Gray JJ, Pavel P, et al. Efficacy of pyrimethamine for the prevention of donor-acquired Toxoplasma gondii infection in heart and heart-lung transplant patients. Transpl Int. 1992;5:197–200.
42. Centers for Disease Control and Prevention. Treating opportunistic infections among HIV-1 adults and adolescents. MMWR. 2004;53:1–112.
43. Moorhead A, Grunenwald PE, Dietz VJ, Schantz PM. Trichinellosis in the United States, 1991–1996: declining but not gone. Am J Trop Med Hyg. 1999;60:66–9.
44. Compton SJ, Celum CL, Lee C, et al. Trichinosis with ventilatory failure and persistent myocarditis. Clin Infect Dis. 1993;16:500–4.
45. Lazarevic AM, Neskovic AN, Goronja M, et al. Low incidence of cardiac abnormalities in treated trichinosis: a prospective study of 62 patients from a single-source outbreak. Am J Med. 1999;107:18–23.
46. Siwak E, Dron D, Pancewicz S, et al. Changes in ECG examination of patients with trichinosis. Wiad Lek. 1994;47:499–502.

47. Kirschberg GJ. Trichinosis presenting as acute myocardial infarction. Can Med Assoc J. 1972;106:898–9.
48. Kociecka W. Trichinellosis: human disease, diagnosis and treatment. Vet Parasitol. 2000;93:365–83.
49. Murrell KD, Bruschi F. Clinical trichinellosis. Prog Clin Parasitol. 1994;4:117–50.
50. Puljiz I, Beus A, Kuzman I, Seiwerth S. Electrocardiographic changes and myocarditis in trichinellosis: a retrospective study of 154 patients. Ann Trop Med Parasitol. 2005;99: 403–11.
51. Kerebel S, Paule P, Jego C, et al. Myocarditis caused by Trichinella spiralis: a case report. Ann Cardiol Angeiol (Paris). 2008;57:127–30.
52. Gyorkos TW, Larocque R, Casapia M, Gotuzzo E. Lack of risk of adverse birth outcomes after deworming in pregnant women. Pediatr Infect Dis J. 2006;25:791–4.
53. McManus DP, Zhang W, Bartley PB. Echinococcosis. Lancet. 2003;362:1295–304.
54. Patta BN. Parasitic diseases of the heart. In: Silver MD, editor. Cardiovascular pathology. 2nd ed. New York: Churchill Livingstone; 1991. p. 1288–90.
55. Khuroo MS. Hydatid disease: current status and recent advances. Ann Saudi Med. 2002;22:56–64.
56. Thameur H, Abdelmoula S, Chenic S, et al. Cardiopericardial hydatid cysts. World J Surg. 2001;25:58–67.
57. Uysalel A, Yazicioglu L, Aral A, Akalin H. A multivesicular cardiac hydatid cyst with hepatic involvement. Eur J Cardiothorac Surg. 1998;14:335–7.
58. Paredes CF, Rouphael N, Mendez J, et al. Cardiac manifestations of parasitic infections part 3: pericardial and miscellaneous cardiopulmonary manifestations. Clin Cardiol. 2007;30:277–80.
59. Miralles A, Bracamonte L, Pavie A, et al. Cardiac echinococcosis. Surgical treatment and results. J Thorac Cardiovasc Surg. 1994;107:184–90.
60. Birincioglou LC, Bardakci H, Kucuker SA, et al. A clinical dilemma: cardiac and pericardial echinococcosis. Ann Thorac Surg. 1999;68:1290–4.
61. Kaplan M, Demitras M, Cimen S, Ozler A. Cardiac hydatid cysts with intracavitary expansion. Ann Thorac Surg. 2001;71:1587–90.
62. Eroglu E, Gemici G, Ergenoglu M, Yildiz C, Kucukaksu S, Degertekin M. Giant hydatid cyst of the interventricular septum mimicking acute myocardial infarction on ECG: an unusual cause of ST segment elevation. J Cardiovasc Med (Hagerstown). 2009;10:425–7.
63. Ozlu MF, Ozcan F, Tufekcioglu O. Left ventricular apical cystic thrombus mimicking a hydatid cyst. Can J Cardiol. 2009;25:e266.
64. Singh AV, Walsh JT, Birdi IS. Right atrial thrombus masquerading as intracardiac cyst: a case report. Asian Cardiovasc Thorac Ann. 2008;16:e35–6.
65. Eckert J, Deplazes P. Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Clin Microbiol Rev. 2004;17:107–35.
66. Lioulias AG, Kokotsakis JN, Foroulis CN, Skouteli ET. Images in cardiovascular medicine. Multiple cardiac hydatid cysts: consistency of echocardiographic and surgical findings. Tex Heart Inst J. 2002;29:226–7.
67. Dursun M, Terzibasioglu E, Yilmaz R, et al. Cardiac hydatid disease: CT and MRI findings. Am J Roentgenol. 2008;190:226–32.
68. Garot J, Unterseeh T, Morice MC. Comprehensive cardiovascular magnetic resonance for diagnosis of cardiac hydatid cyst. Eur Heart J. 2008;29:2069.
69. Di Bello R, Mendez H. Intracardiac rupture of hydatid cyst of the heart: a study based on three personal observations and 101 cases in the world literature. Circulation. 1963;27:366–74.
70. Erentug V, Bozbuga N, Kirali K, et al. Cardiac hydatid cysts: surgical treatment and results. J Card Surg. 2004;19:358–60.
71. Teggi A, Lastilla MG, De Rosa F. Therapy of human hydatid disease with mebendazole and albendazole. Antimicrob Agents Chemother. 1993;37:1679–84.
72. Yaliniz H, Tokcan A, Salih OK, Ulus T. Surgical treatment of cardiac hydatid disease: a report of 7 cases. Tex Heart Inst J. 2006;33:333–9.

73. Abid A, Ben Omrane S, Kaouel K, et al. Intracavitary cardiac hydatid cyst. Cardiovasc Surg. 2003;11:521–5.
74. Rossouw GJ, Knott-Craig CJ, Erasmus PE. Cardiac echinococcosis: cyst removal in a beating heart. Ann Thorac Surg. 1992;53:328–9.
75. Walsh JA. Problems in recognition and diagnosis of amebiasis: estimation of the global magnitude of morbidity and mortality. Rev Infect Dis. 1986;8:228–38.
76. Wanke C, Butler T, Islam M. Epidemiologic and clinical features of invasive amebiasis in Bangladesh: a case-control comparison with other diarrheal diseases and postmortem findings. Am J Trop Med Hyg. 1988;38:335–41.
77. Hung CC, Ji DD, Sun HY, et al. Increased risk for Entamoeba histolytica infection and invasive amebiasis in HIV seropositive men who have sex with men in Taiwan. PLoS Negl Trop Dis. 2008;2:e175.
78. Ibarra-Perez C. Thoracic complications of amebic abscess of the liver: report of 501 cases. Chest. 1981;79:672–7.
79. Samsuzzaman SM, Hashiguchi Y. Thoracic amebiasis. Clin Chest Med. 2002;23:479–92.
80. MacLeod IN, Wilmot AJ, Powell SJ. Amoebic pericarditis. Q J Med. 1966;35:293–311.
81. Supe AN, Sathe SS, Redkar RG, Dalvi AN, Kulkarni BA, Shah PP. Amebic pericarditis following ruptured right liver lobe abscess. Indian J Gastroenterol. 1991;10:111.
82. Heller RF, Gorbach SL, Tatooles CJ, Loeb HS, Rahimtoda SH. Amebic pericarditis. JAMA. 1972;220:988–90.
83. Li E, Stanley SL Jr. Protozoa. Amebiasis. Gastroenterol Clin North Am. 1996;25:471–92.
84. Rosenblatt JE, Sloan LM, Bestrom JE. Evaluation of an enzyme-linked immunoassay for the detection in serum of antibodies to Entamoeba histolytica. Diagn Microbiol Infect Dis. 1995;22:275–8.
85. Sharma MP, Rai RR, Acharya SK, Ray JC, Tandon BN. Needle aspiration of amoebic liver abscess. BMJ. 1989;299:1308–9.
86. Cameron EW. The treatment of pleuropulmonary amebiasis with metronidazole. Chest. 1978;73:647–50.
87. Schantz PM, Cruz M, Sarti E, Pawlowski Z. Potential eradicability of taeniasis and cysticercosis. Bull Pan Am Health Organ. 1993;27:397.
88. Lio Junior Rde S, Ribeiro PM, Antonelli EJ, et al. Developmental characteristics of Cysticercus cellulosae in the human brain and heart. Rev Soc Bras Med Trop. 2002;35:617–22.
89. Lino RS Jr, Reis MA, Teixeira VP. Occurrence of encephalic and cardiac cysticercosis (Cysticercus cellulosae) in necropsy. Rev Saude Publica. 1999;33:495–8.
90. Mangoud AM, Morsy TA, Ramadan ME, Makled KM, Mostafa SM. The pathology of the heart and lung in Syrian golden hamsters experimentally infected with Leishmania d. infantum on top of pre-existing Schistosoma mansoni infection. J Egypt Soc Parasitol. 1998;28:395–402.
91. De Cleva R, Herman P, Pugliese V, et al. Prevalence of pulmonary hypertension in patients with hepatosplenic Mansonic schistosomiasis–prospective study. Hepato-Gastroenterology. 2003;50:2028–30.
92. Cheever AW, Kamel IA, Elwi AM, Mosimann JE, Danner R, Sippel JE. Schistosoma mansoni and S. haematobium infections in Egypt. III. Extrahepatic pathology. Am J Trop Med Hyg. 1978;27:55.
93. Denie C, Vachiery F, Elman A, et al. Systemic and splanchnic hemodynamic changes in patients with hepatic schistosomiasis. Liver. 1996;16:309–12.
94. Orihel TC, Eberhard M. Zoonotic filariasis. Clin Microbiol Rev. 1998;11:366–81.
95. Goldstein JD, Smith D. Dirofilaria immitis in a portal shunt. Hum Pathol. 1985;16:1172–3.
96. Ciferi K. Human pulmonary dirofilariasis in the United States: a critical review. Am J Trop Med Hyg. 1982;31:302–8.
97. Boggild AK, Keystone JS, Kain KC. Tropical pulmonary eosinophilia: a case series in a setting of nonendemicity. Clin Infect Dis. 2004;39:1123–8.
98. Vijayan VK. Tropical pulmonary eosinophilia: pathogenesis, diagnosis and management. Curr Opin Pulm Med. 2007;13:428–33.

99. Rom WN, Vijayan VK, Cornelius MJ, et al. Persistent lower respiratory tract inflammation associated with interstitial lung disease in patients with tropical pulmonary eosinophilia following conventional treatment with diethylcarbamazine. Am Rev Respir Dis. 1990;142:1088–92.
100. Berger PB, Duffy J, Reeder GS, Karon BL, Edwards WD. Restrictive cardiomyopathy associated with the eosinophilia-myalgia syndrome. Mayo Clin Proc. 1994;69:162–5.
101. Rashwan M, Ayman AM, Ashour S, Hassanin MM, Zeina AA. Endomyocardial fibrosis in Egypt: an illustrated review. Br Heart J. 1995;73:284–9.
102. Olsen EG, Spry CJ. Relation between eosinophilia and endomyocardial disease. Prog Cardiovasc Dis. 1985;27:241–54.
103. Berensztein CS, Pineiro D, Marcotegui M, Brunoldi R, Blanco MV, Lerman J. Usefulness of echocardiography and Doppler echocardiography in endomyocardial fibrosis. J Am Soc Echocardiogr. 2000;13:385–92.
104. Qureshi N, Amin F, Chatterjee D, Prasad S, Al-Obaidi M, Missouris C. MR imaging of endomyocardial fibrosis (EMF). Int J Cardiol. 2011;149:e36–7.
105. Mocumbi AO, Sidi D, Vouhe P, Yacoub M. An innovative technique for the relief of right ventricular trabecular cavity obliteration in endomyocardial fibrosis. J Thorac Cardiovasc Surg. 2007;134:1070–2.
106. Grimaldi A, Mocumbi AO, Freers J, et al. Tropical endomyocardial fibrosis: natural history, challenges, and perspectives. Circulation. 2016;133:2503–15.
107. Russo PA, Wright JE, Ho SY, Maneksa JR, Clitsakis D. Endocardectomy for the surgical treatment of endocardial fibrosis of the left ventricle. Thorax. 1985;40:621–5.
108. Tang A, Karski J, Butany J, David T. Severe mitral regurgitation in acute eosinophilic endomyocarditis: repair or replacement? Interact Cardiovasc Thorac Surg. 2004;3:406–8.
109. Glickman L, Schantz P. Epidemiology and pathogenesis of zoonotic toxocariasis. Epidemiol Rev. 1981;3:230.
110. Jones W, Schantz P, Foreman K, et al. Human toxocariasis in a rural community. Am J Dis Child. 1980;134:967.
111. Boschetti A, Kasznica J. Visceral larva migrans induced eosinophilic cardiac pseudotumor: a cause of sudden death in a child. J Forensic Sci. 1995;40:1097–9.
112. Vargo TA, Singer DB, Gillatte PC, Fernbach DJ. Myocarditis due to visceral larva migrans. J Pediatr. 1977;90:322–3.
113. Herry I, Philippe B, Hennequin C, Danel C, Lejeunne C, Meyer G. Acute life-threatening toxocaral tamponade. Chest. 1997;112:1692–3.
114. Wong K, Pathmananthan R. Review of human skeletal muscle sarcosystis in Southeast Asia. Trans R Soc Trop Med Hyg. 1992;86:631–2.
115. Kan S, Pathmananthan R. Review of sarcocystis in Malaysia. Southeast Asian J Trop Med Public Health. 1991;22(Suppl):129–34.
116. Pamphlett R, O'Donoghue P. Sarcocystis infection of human muscle. Aust NZ J Med. 1990;20:705–7.
117. Jeffrey HC. Sarcosporidiosis in man. Trans R Soc Trop Med Hyg. 1974;68:17–29.
118. Arness MK, Brown JD, Dubey JP, Neafie RC, Granstrom DE. An outbreak of acute eosinophilic myositis attributed to human Sarcocystis parasitism. Am J Trop Med Hyg. 1999;61:548–53.
119. Amarasinghe HK, Usgodaarachchi US, Johnson NW, Lalloo R, Warnakulasuriya S. Betel-quid chewing with or without tobacco is a major risk factor for oral potentially malignant disorders in Sri-Lanka: a case-control study. Oral Oncol. 2010;46:297–301.
120. Fayer R, Esposito D, Dubey JP. Human infections with Sarcocystis species. Clin Microbiol Rev. 2015;28:295–311.

18 Surgical Management of Parasitic Diseases Involving the Brain and Peripheral Nervous System

Houssein A. Darwish

Introduction

Central nervous system parasitic infections are highly morbid infections that could affect immune-competent and immune-compromised patients. It has been associated with multiple neurological presentations ranging from meningitis, encephalitis, increased intracranial pressure, seizures, and or neurological deficits. These manifestations affect millions of adults and children in endemic areas of third world countries [1]. There are different types of parasites that affect the central nervous system. Parasites include the cestodes, trematodes, and protozoans. The most common is cysticercosis; less frequent infections are toxoplasmosis, echinococcosis, and schistosomiasis. And the most rare parasitic diseases are toxocariasis, malaria, onchocerciasis, Chagas disease (CD), and human African trypanosomiasis. Cestodes and trematodes are platyhelminthes, which are characterized by total dependence on the host for its existence and thus cannot live outside a host. Cestodes are usually referred to as tapeworms, whereas trematodes are referred to as flukes. The cestode *Taenia solium* causes neurocysticercosis which is considered the most common parasitic infection of the central nervous cyst. Another common cestode is *Echinococcus* (hydatid disease) that leads to the development of hydatid cysts in the brain. These are associated with morbidity since the most common treatment would be surgical with special precaution of not rupturing the thin layered cyst wall and causing intraoperative spillage which is highly mortal and morbid [2]. Several other central nervous system parasitic infections are treated differently; this depends on the type of the organism and the presentation. Medical and surgical managements are both implicated and sometimes even complement each other. We will focus in this chapter on the surgical

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management of the parasitic central nervous system infections. We will focus on *Echinococcus* hydatid cyst formation since it is the parasitic infection that is mostly treated with surgery. This includes extensive description of the presentation of the disease, radiological presentation, and the surgical management. In addition we will discuss other common parasitic infections and its modality surgical treatment like sparganosis caused by the larval form of tapeworms from the genus *Spirometra* or *Diphyllobothrium*. And finally schistosomiasis (bilharzia) that when it presents with large granuloma should be resected surgically. Other types of parasitic infections are treated with antiparasitic medications and steroids and thus won't be discussed in the chapter.

Echinococcus (Hydatid Disease)

Hydatid disease is a worldwide most commonly seen in the Middle East, Mediterranean countries, South America, Africa, New Zealand, and Australia [3]. It is developed from the larval stage of the *Echinococcus* tapeworm, with the most frequently encountered type in humans being *E. granulosus* and to a lesser extent *E. multilocularis* [3]. The latter is half the size of *E. granulosus*, causing alveolar hydatid disease mostly seen in Alaska, Central Europe, Turkey, and China [4]. Involvement of the central nervous system is around 1% of all cases [3]. Overall, intracranial hydatid disease is a rare cause of intracranial space occupying lesions representing only 1–2% [5].

The parasite is transferred to human adults by ingestion of food containing eggs or scolex. In pediatrics the transfer of the parasite is rather through direct contact with the feces of dogs. The disease reaches the brain by passing through the liver first then the lungs [6]. Mostly it affects pediatrics age group in around 73% of cases in one report from turkey where the average age group was around 7 years [6]. So it is usually diagnosed during childhood and is often solitary [7]. However multiple intracranial hydatid cysts are very rare, and they are usually the result of cyst rupture whether spontaneous or induced by trauma or surgery [8].

Hydatid cyst can be located anywhere in the brain, but it is mostly present in the supratentorial area and more specifically in the parietal region and rarely in the posterior fossa or intraventricular [9].

Hydatid cysts are composed of three layers:

1. The pericyst which is the outermost layer representing the reaction of the host to the parasite
2. Then the acellular membrane comprising the middle layer. This is the layer responsible for nutrients passage to the parasite.
3. The inner thin and translucent germinal layer from where the scolices are formed [10].

Intracranial hydatid cyst will start causing symptoms when it reaches a large size, thus start causing mass effect on the surrounding brain tissue and thus causing seizures, weakness, headaches, and sometimes hydrocephalus if it causes CSF flow

obstruction. Headache and vomiting are the most common presentations followed by motor weakness and seizures [11].

Differential Diagnosis

The differential diagnosis of intracranial cyst is wide and ranges from abscesses to necrotic malignancies or any other benign such as low-grade gliomas or arachnoid cysts. The hydatid cyst has no rim enhancement nor any surrounding edema; this can help differentiate it from brain abscess and cystic tumor in the addition to the presence of the mural nodule seen in hydatid cyst. In addition arachnoid cysts and porencephalic cysts are rarely spherical and usually extra-axial surrounded by brain tissue as in hydatid cysts. But despite all this differentiation, it is very crucial for the proper management and in order to decide whether medical or surgical and even if surgery to be done, we should have some sort of certainty about the lesion, since surgical technique is different among the different types of lesions. Since we are not allowed to rupture of the hydatid cyst in the brain while other lesions can be fenestrated. Based on this we have different diagnostic tools that are used each with variable specificity and sensitivity.

Diagnosis

It is very difficult to establish an exact diagnosis before surgery for such lesions. Indirect hemagglutination test, indirect fluorescence antibody test, and enzyme-linked immunosorbent assay (ELISA) are serological tests used for preoperative diagnosis, and these are carried out directly after suspecting an intracranial hydatid cyst on brain imaging [12]. However the sensitivity is around 20% for ELISA which is very low [6]. Lumbar puncture and CSF studies may show cyst wall membranes or scolices, but most of the times, we won't be able to do it due to mass effect of the lesion and fear of brain downward herniation [13]. All patients should undergo chest and abdominal imaging searching of other lesions that might give a hint about the diagnosis. This is to be done despite the fact that only 20% of cases with intracranial hydatid cysts have other organ involvement [13].

In addition to the above, brain imaging plays some role. Regular CT brain and MRI show a well-defined spherical/oval homogeneously looking cystic lesion with a thin wall smooth surroundings with fluid characteristics of CSF. On unenhanced CT, the cyst wall will be isodense or hyperdense on an unenhanced CT [14]. However on MRI the cyst wall is rather low signal on T1- and T2- weighted images. Wall calcifications occur in only <1% of all cases [15]. Despite the mass effect, surrounding edema and wall enhancement are absent. New MR modalities like diffusion-weighted images and spectroscopy have been recently used to further help in the differential diagnosis. In vivo MR spectroscopy analysis in a patient of

intracranial hydatid cyst found a large resonance for pyruvate [16]. This same result was found by Chand et al. where the hydatid cyst demonstrated a large peak of lactate, pyruvate, and acetate [17]. The same was demonstrated by Taslakian and Darwish [10]. Thus pyruvate might be considered as a specific in vivo marker for cestodal, in particular hydatid cysts.

But despite all diagnostic measures and modalities, it may be impossible at times to arrive at a definite preoperative diagnosis. And care must be taken when performing surgical management that will be described next.

Surgical Management

Surgery is the gold standard of treatment for intracranial hydatid cyst. The resection should be radical and extracystic without any spillage of the cyst material to the surrounding brain tissue and or ventricles. There has been different techniques for resection of hydatid cyst, all of which emphasize avoidance of cyst wall breach. The most famous technique is the Dowling [18]. This technique was later improved by Arana-Iniguez and San Julian [19]. And now it is the most widely used technique for resection of hydatid cysts. Basically, the technique is about doing wide cranial exposure with the position of the head in way that the cyst be pushed by gravity. Then in an atraumatic fashion the dura is opened wider than the cyst's largest diameter. Then depending on where the cyst wall is brain parenchyma and cortex overlying the cyst over an area with a diameter no less than three quarters of the diameter of the cyst, we proceed with normal saline irrigation between the cyst wall and the surrounding brain parenchyma with the help of the gravity and brain pulsation, and the cyst wall is dissected from the brain parenchyma and is delivered unruptured. But this would be the perfect scenario; however, cysts are not always easy to dissect. So the cyst wall might be stuck to the brain parenchyma, and thus a cotton is used on the cyst wall to find the plane in an atraumatic fashion which is not easy knowing the fragility of the cyst wall. Another obstacle would be deep-seated cysts that are abutting the wall of the ventricles. Sometimes the wall is very stuck to the ventricle wall and the irrigation technique won't work and thus extremely careful microsurgical dissection is warranted to prevent a disastrous spillage in the ventricles [20]. If this happens, irrigation with saline is not recommended since this will disseminate the scolices more and cause anaphylactic reaction, chemical meningitis, subsequent death, or serious neurological deficits [21]. Other times the hydatid cyst touching the dura might be large enough; in this situation care must be taken not to breach the dura above the cyst when doing the craniotomy and or opening the dura. In some cases there may be multiple hydatid cysts, then removal of the largest first with the Dowling technique, followed by the smaller ones with the same technique during the same setting if feasible [20]. All surgeries should be performed with the help of surgical microscope and neuro-navigation. In case of spillage to the surrounding brain parenchyma, the surgical site should be repeatedly irrigated with a solution of 3% NaCl or 10% formaldehyde [22]. Despite the fact that surgery is the main stay of treatment, different authors suggest using preoperative albendazole to sterilize the cyst and thus decrease the chance of anaphylaxis if spillage happens as well as decrease the risk of recurrence [23–25].

Sparganosis

Central nervous system proliferative disease is caused by the larval form of tapeworms from the genus *Spirometra* or *Diphyllobothrium*. Two species are the most common, *Spirometra mansoni* and *Spirometra mansonoides*, with the first one being more common in Asia and the second one in the Gulf States of North America. It causes infection by eating undercooked fish [26, 27]. Definitive hosts are cats, dogs, and other wild carnivores. Human beings are incidental hosts that are usually infected by ingesting fish. The larva of the adult worm lives in the intestine where it completes the life cycle and then spreads to the body tissues and muscles. The adult worm may live in the host for more than 20 years [28, 29].

Infection can happen in immune-competent and immune-compromised patients. It is mainly a proliferative disease that presents differently depending on the location of the infection in the brain. The main presenting symptom is seizures in addition to other symptoms like progressive weakness, headaches, and vomiting [30].

Diagnosis

Antisparganum ELISA is very sensitive and specific for the diagnosis [31].

Blood eosinophilia is usually associated with central nervous system infection [32]. Definitive diagnosis is however determined by the direct biopsy from the brain tissue that if sometimes not possible, then ELISA will be the net best option [33].

Brain imaging with CT and MRI has typical appearance for sparagnosis. Calcospherules, which are calcifications inside the parasite, are pathognomonic of the disease and are better seen by CT scans that are more sensitive then MRI [34].

Follow-up images with enhanced CT are highly recommended to check for an increasing in size lesions and or enhancing ones since both should be surgically removed [30].

MRI shows lesions that are located in the white matter hypodense and with heterogeneous enhancement; also it might represent space occupying lesion with vasculopathy [35].

Surgery

Praziquantel is the treatment of choice for peripheral infection. However since praziquantel is useless against the parasite in the central nervous system, then surgery is the best modality for treatment. Surgery comprises surgical excision of the parasite or any enhancing nodule whether or not causing mass effect [36].

This surgical resection may not be feasible in all cases especially when it is very proliferative and disseminated. In this situation treatment is very limited, and prognosis is very decimal [37].

Schistosomiasis (Bilharzia)

Schistosomiasis is caused by five different species of blood trematodes: *Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. intercalculatum*, and *S. mekongi*. The central nervous system involvement is most commonly due to infection with *S. mansoni*, *S. haematobium*, and *S. japonicum* [38]. Transmission of the disease is through water that is infected with schistosomiasis especially in countries with poor sanitary facilities. Humans are considered definitive hosts.

Initially the main vector of infection is the forked tail of the larvae that penetrates human skin. Later the larva sheds off the tail and migrates into the venous system. Each species has a predilection for invading the venous system: *S. haematobium* the peri-bladder veins, *S. japonicum* the superior mesenteric veins, and *S. mansoni* the inferior mesenteric veins [39].

Depending on the size of the eggs, different species infect different areas of the central nervous system. The smaller eggs of *S. japonicum* have tendency to migrate to the brain than other species, and actually they comprise 60% of all schistosomal brain infections. On the other hand, *S. mansoni* with the larger egg size migrates to the spinal cord [40].

S. haematobium may migrate either to the brain or spinal cord. The access to the central nervous system whether to the brain or spinal cord is through the Batson's venous plexus. After migration to the central nervous system, the eggs never develop into worms nor adult worms are able to enter the central nervous system. Thus at any time, no adult worms are found in the central nervous system. The eggs after entry rather induce a granulomatous response as the brain attempts to surround the hostile organism. This creates granulomas that might become necrotic in chronic conditions. These granulomas may cause mass effect and increase intracranial pressure. Sometimes the granulomas might invade vascular structures and thus present with intracranial hemorrhage [38]. Cauda equina syndrome or necrotic myelitis can occur when spinal cord is involved [41].

Diagnosis

Biopsy with identification of the eggs from the affected tissue is the definitive diagnosis. But if this is not feasible, then antibody detection against the eggs can used for diagnosis not a marker for the response of treatment since this remains positive after eradication of the parasite. In addition stool and urine detection of eggs is highly sensitive for the disease [42]. For patients with spinal cord infection, CSF ELISA IgG is highly sensitive and specific [43].

Brain imaging shows granulomatous formation with surrounding edema that could be mistaken for any form of neoplasm. On CT and MRI, there could single or multiple granulomas that hyperdense and with heterogeneous enhancement. MRI might show the typical arborized appearance with multiple enhancing satellite nodules [44, 45].

Surgery

In 60–90% of patients, praziquantel is the curative treatment of choice for all *Schistosoma* spp. [46]. In cases where there is severe edema around the granulomas, steroids are added and are very beneficial to decrease the intracranial pressure, thus ameliorating the symptoms. Medical treatment is considered as long as the patient clinically is able to tolerate the high intracranial pressure. However in situations where the lesion is big and the patient is deteriorating clinically, then surgery is advised for resection of the granuloma and relieving of the high pressure.

References

1. Walker M, Kublin JG, Zunt JR. Parasitic central nervous system infections in immunocompromised hosts: malaria, microsporidiosis, leishmaniasis, and African trypanosomiasis. Clin Infect Dis. 2006;42:115–25.
2. Walker M, Zunt J. Semin Neurol. 2005;25(3):262–77.
3. Pedrosa I, Saíz A, Arrazola J. Hydatid disease: radiologic and pathologic features and complications. Radiographics. 2000;20:795–817.
4. Algros MP, Majo F, Bresson-Hadni S. Intracerebral alveolar echinococcosis. Infection. 2003;31:63–5.
5. Kern P, Bardonnet K, Renner E. European echinococcosis registry: human alveolar echinococcosis, Europe, 1982–2000. Emerg Infect Dis. 2003;9:343–9.
6. Khaldi M, Mohamed S, Kallel J, Khouja N. Brain hydatidosis: report on 117 cases. Childs Nerv Syst. 2000;16:765–9.
7. Gupta S, Desai K, Goel A. Intracranial hydatid cyst: a report of five cases and review of literature. Neurol India. 1999;47:214–7.
8. Vaquero J, Jiménez C, Martínez R. Growth of hydatid cysts evaluated by CT scanning after presumed cerebral hydatid embolism. Case report. J Neurosurg. 1982;57:837–8.
9. Nazaroğlu H, Ozateş M, Bilici A. Multilocular cerebral hydatid disease with extracalvarial extension. AJR Am J Roentgenol. 1999;172:1455–6.
10. Taslakian B, Darwish H. Intracranial hydatid cyst: imaging findings of a rare disease. Case reports. BMJ. 2016;2016:bcr2016216570.
11. Eşgin M, Aktaş M, Coşkun S. The investigation of antibody presence in the sera of patients with a suspicion of cystic echinococcosis by using indirect hemaglutination test (IHA). Turkiye Parazitol Derg. 2007;31:283–7.
12. Turgut M. Intracranial hydatidosis in Turkey: its clinical presentation, diagnostic studies, surgical management, and outcome. A review of 276 cases. Neurosurg Rev. 2001;24:200–8.
13. Sherwani RK, Abrari A, Jayrajpuri ZS, Srivastava VK. Intracranial hydatidosis. Report of a case diagnosed on cerebrospinal fluid cytology. Acta Cytol. 2003;47:506–8.
14. Bükte Y, Kemaloglu S, Nazaroglu H. Cerebral hydatid disease: CT and MR imaging findings. Swiss Med Wkly. 2004;134:459–67.
15. Nurchi G, Floris F, Montaldo C. Multiple cerebral hydatid disease: case report with magnetic resonance imaging study. Neurosurgery. 1992;30:436–8.
16. Kohli A, Gupta RK, Poptani H. In vivo proton magnetic resonance spectroscopy in a case of intracranial hydatid cyst. Neurology. 1995;45(Pt 1):562–4.
17. Chand K, Kanodia AK, Manpreet G. In vivo proton magnetic resonance spectroscopy in a known case of intracranial hydatid cyst. Neurol India. 2005;53:337–8.
18. Carrea R, Dowling E Jr, Guevera A. Surgical treatment of hydatid cysts of the central nervous system in the pediatric age (Dowling's technique). Childs Brain. 1975;1:4–21.
19. Arana-Iniguez R, San Julian J. Hydatid cyst of the brain. J Neurosurg. 1955;12:323–35.

20. Izci Y, Tuzun Y, Secer HI, Gonul E. Neurosurg Focus. 2008;24(6):E15.
21. Ozek M. Complications of central nervous system hydatid disease. Pediatr Neurosurg. 1994;20:84–91.
22. Najjar MW, Rajab Y, El-Beheiri Y. Intracranial hydatid cyst. Dilemma in diagnosis and management. Neurosciences (Riyadh). 2007;12:249–52.
23. Tuzun Y, Kadioglu HH, Izci Y, Suma S, Keles M, Aydin IH. The clinical, radiological and surgical aspects of cerebral hydatid cysts in children. Pediatr Neurosurg. 2004;40:155–60.
24. Singounas EG, Leventis AS, Sakas DE, Hadley DM, Lampadorios DA, Karvounis PC. Successful treatment of intracerebral hydatid cysts with albendazole: case report and review of the literature. Neurosurgery. 1992;31:571–4.
25. Horton RJ. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. Acta Trop. 1997;64:79–93.
26. Lee KJ, Bae YT, Kim DH. A seroepidemiologic survey for human sparganosis in Gangweondo. Korean J Parasitol. 2002;40:177–80.
27. Landero A, Hernandez F, Abasolo MA. Cerebral sparganosis caused by Spirometra mansonoides. Case report. J Neurosurg. 1991;75:472–4.
28. Norman SH, Kreutner A Jr. Sparganosis. Clinical and pathologic observations in ten cases. South Med J. 1980;73:297–300.
29. Mueller JF. Potential longevity of life history stages of Spirometra spp. J Parasitol. 1974;60:376–7.
30. Chang KH, Chi JG, Cho SY. Cerebral sparganosis: analysis of 34 cases with emphasis on CT features. Neuroradiology. 1992;34:1–8.
31. Nishiyama T, Ide T, Himes SR Jr. Immunodiagnosis of human sparganosis mansoni by microchemiluminescence enzyme-linked immunosorbent assay. Trans R Soc Trop Med Hyg. 1994;88:663–5.
32. Fan KJ, Pezeshkpour GH. Cerebral sparganosis. Neurology. 1986;36:1249–51.
33. Sarma DP, Weilbaecher TG. Human sparganosis. J Am Acad Dermatol. 1986;15:1145–8.
34. Moon WK, Chang KH, Cho SY. Cerebral sparganosis: MR imaging versus CT features. Radiology. 1993;188:751–7.
35. Jeong SC, Bae JC, Hwang SH. Cerebral sparganosis with intracerebral hemorrhage: a case report. Neurology. 1998;50:503–6.
36. Kim DG, Paek SH, Chang KH. Cerebral sparganosis: clinical manifestations, treatment, and outcome. J Neurosurg. 1996;85:1066–71.
37. Torres JR, Noya OO, Noya BA. Treatment of proliferative sparganosis with mebendazole and praziquantel. Trans R Soc Trop Med Hyg. 1981;75:846–7.
38. Pittella JE. Neuroschistosomiasis. Brain Pathol. 1997;7:649–62.
39. Haedicke TA. Cerebral schistosomiasis. A report of 10 cases caused by Schistosomiasis japonica. Minn Med. 1972;55:1105–14.
40. Pittella JE. The relation between involvement of the central nervous system in schistosomiasis mansoni and the clinical forms of the parasitosis. A review. J Trop Med Hyg. 1991;94:15–21.
41. Liu LX. Spinal and cerebral schistosomiasis. Semin Neurol. 1993;13:189–200.
42. Brinkmann UK, Powollik W, Werler C, Traore M. An evaluation of sampling methods within communities and the validity of parasitological examination techniques in the field. Trop Med Parasitol. 1988;39:162–6.
43. Ferrari TC, Moreira PR, Oliveira RC. The value of an enzyme-linked immunosorbent assay for the diagnosis of schistosomiasis mansoni myeloradiculopathy. Trans R Soc Trop Med Hyg. 1995;89:496–500.
44. Ching HT, Clark AE, Hendrix VJ. MR imaging appearance of intracerebral schistosomiasis. AJR Am J Roentgenol. 1994;162:693–4.
45. Preidler KW, Riepl T, Szolar D, Ranner G. Cerebral schistosomiasis: MR and CT appearance. AJNR Am J Neuroradiol. 1996;17:1598–600.
46. Kardaman MW, Amin MA, Fenwick A, et al. A field trial using praziquantel (BiltricideR) to treat Schistosoma mansoni and Schistosoma haematobium infection in Gezira, Sudan. Ann Trop Med Parasitol. 1983;77:297–304.

Parasitic Infections of the Vascular System

19

Tamam Tulimat and Jamal J. Hoballah

Introduction

Parasitic infections of the vascular system are very rare in the Western world and are typically encountered in travelers or immigrants from endemic areas. However, in tropical or endemic regions, parasitic vascular infections are common and represent a major health hazard recognized by the World Health Organization (WHO) [1, 2]. Parasitic infections can affect the lymphatic and arterial systems. Filariasis is the most common and affects the lymphatic system. Hydatid disease can very rarely affect the arterial system. They both represent the focus of this chapter.

Lymphatic Filariasis

Filarial parasites can infect and damage the lymphatic system causing abnormal limb enlargement of various parts of the body. The damaged lymphatics can result in lymphedema with disfiguring limb swelling, elephantiasis, and scrotal edema leading to severe disability, social embarrassment, and suffering. The scope of this disease is enormous, and as such it is a global health problem. According to WHO, in 2018, 893 million people living in 49 countries were at risk of becoming infected with filariasis. Estimates from 2000 showed that approximately 120 million people were infected with filarial parasites. Of these, it was estimated that approximately 40 million were disfigured by this disease and suffered major disability. Twenty-five million were due to scrotal edema, and 15 million were due to limb lymphedema [1, 2].

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Pathophysiology

Lymphatic filariasis is attributed to infection by three related nematode worms: *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. *Wuchereria bancrofti* is responsible for 90% of the disease and is typically found in tropical and subtropical areas. *Brugia* worms are responsible for the remaining 10% and are in a more restricted geographical distribution [3].

All three share a similar life cycle. Mosquitoes carrying infectious stage larvae L3 transmit this disease through their bites into the human skin. The larvae will then creep into the skin and find their way into the lymphatics and then lymph nodes where they further develop into L4 larvae and adult worms. Mating of these adult worms will release microfilariae (mf) which ultimately get into the blood circulation. Mosquitoes biting and sucking blood from such patients will also ingest these microfilariae which will further develop inside the mosquito into L2 and L3 Larvae completing the life cycle.

Different types of mosquitoes can transmit the disease. These include the *Culex* mosquito that is prevalent across urban and semi-urban areas, the *Anopheles*, usually in rural areas, and the *Aedes* typically in endemic islands in the Pacific [3].

The filarial infection induces a complex immunological response which determines the clinical manifestations. This immunologic response is not fully understood; however it is believed to be primarily an antigen-specific T-helper 2 response along with an increase in the CD4+T cells and a decreased T-helper 1 response which explains the chronic infection despite a heavy parasite load [4].

Clinical Manifestations

Although filarial infection is not a fatal disease, it can cause significant pain, deformity, and disability. The disease can be asymptomatic or may present itself with acute or chronic manifestations. In addition there is a large group of individuals who are exposed but not yet infected. The exposed but uninfected group, also referred to as endemic normal, represents 0–90% of the population in endemic areas [5].

As such patients may be classified into five categories [3]. These are exposed but uninfected, infected but asymptomatic, acutely symptomatic with or without microfilaremia, chronically infected with pathological conditions, and with tropical pulmonary eosinophilia (TPE).

The asymptomatic group includes acutely infected patients with or without microfilaremia who do not have clinical symptoms; however their blood tests will show evidence of microfilariae in the blood or circulating parasite antigen which is an indicator for the presence of live worms in the patients' body. These patients will become carriers of the disease, and those with positive microfilaremia will serve as the reservoir for the infection and can carry a very large load of infective microfilariae. Although clinically asymptomatic, thorough evaluation will reveal evidence of

subclinical pathology in the lymphatic channels. These include dilated and tortuous lymphatic vessels, increased and abnormal lymphatic flow, collateral lymphatic channels, scrotal lymphangiectasia, and microscopic hematuria or proteinuria.

Symptomatic patients with acute manifestations present with recurrent attacks of fever and inflamed lymphatic channels and lymph nodes typically inguinal, axillary, or epitrochlear. Patients infected with the *Brugia* parasite tends to have more frequent recurrent attacks of fever, lymphangitis, or lymphadenitis. Those infected with the Bancroft parasite tend to express more insidious type of symptoms and may also affect the male genital lymphatics presenting with epididymitis and/or orchitis. Usually fever may not be present, but pain is a key element. The acute lymphadenitis is believed to be a manifestation of the immunologic response to the dead or dying adult worm. Another acute manifestation termed acute dermatolymphangitis is considered to be due to a recurrent bacterial infection of the lymphatic system and tend to ascending in nature and associated with significant fever and chills related to the superimposed bacterial infection.

Patients with chronic infection develop chronic manifestations related to the immune response the presence of the worm within the afferent lymphatics. The initial immune interaction leads to a coexistence with limited reaction and lymphangiectasia and progressive dysfunction of the lymphatics and lymphatic flow. Dead and dying worms result in significant inflammatory changes with granuloma formation which then results in further lymphatic destruction. As a result, lymphedema starts developing in the extremity and starts as pitting and later progresses into amore chronic firm with skin thickening and later hyperpigmentations and hyperkeratosis. Skin folding and crevices develop and become a supportive milieu for bacteria and fungi. Skin excoriations and cracks later develop and become an ideal nidus and source of entry for bacterial and fungal infection which later causes further inflammation and lymphatic destruction. Bancroft worms also have an affinity for the scrotal lymphatics which also leads to massive scrotal swelling and edema. It may also progress and result rarely in milky urine or chyluria. Bungro infections are specially known to cause significant tissue destruction and deformity below the knee causing elephantiasis (Figs. 19.1 and 19.2).

Management

The management is focused on controlling the transmission of the disease in the hope of eradicating it and treating its disabling complications. The World Health Assembly realized years ago that this debilitating disease can be eradicated if proper measures are taken. As such, the Global Programme to Eliminate Lymphatics Filariasis (GPELF) was established in 2000 by WHO with a goal of having the disease eliminated as a public health problem by 2020. A mass drug administration strategy (MDA) was established with the objective of eradication of the transmission by the administration of antifilarial drugs to the entire population at risk annually. The rational for this preventive chemotherapy was to halt the spread of infection.

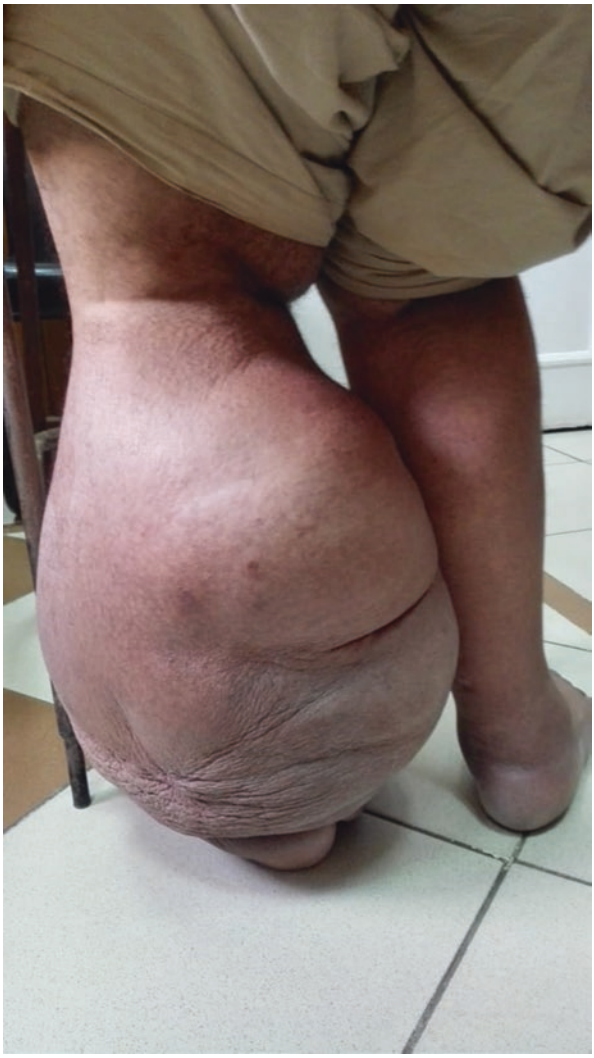

Fig. 19.1 Filarial infection causing lower extremity lymphedema and elephantiasis. (Courtesy of Dr Emad Hussein. Ein Shams University, Cairo, Egypt)

Although such medications had a very limited effect on the adult worms, these drug therapies significantly lower the density of the microfilariae in the blood stream in infected patients, thus breaking the life cycle of the disease by preventing the spread of the larvae to the mosquitoes. The drug therapy utilized varies depending on the presence of other filarial disease that may be endemic in the region and includes albendazole, ivermectin, and diethylcarbamazine. Originally a two-drug regimen was proposed, but a three-drug regimen was found to be even more effective at clearing the bloodstream from the microlarvae within few weeks rather than years. As such, the current recommendation by WHO for MDA regimen in countries without onchocerciasis (river blindness) is ivermectin (200 mcg/kg) together with

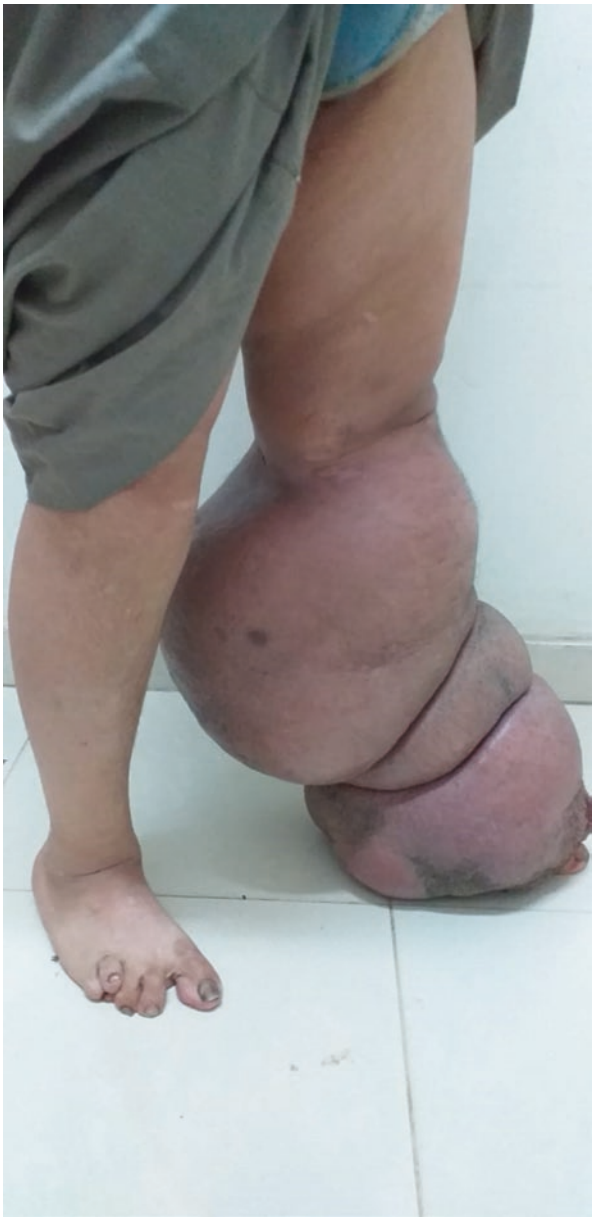

Fig. 19.2 Filarial infection causing lower extremity lymphedema, elephantiasis, and disfiguring changes. (Courtesy of Dr Emad Hussein. Ein Shams University, Cairo, Egypt)

diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in certain settings. The success of this program depends on abiding by the regimen, its duration, and the proportion of the population at risk ingesting the drugs. Since the inception of the GPELF, 10 of the 81 countries that were considered endemic no longer need preventive chemotherapy. Over an 18-year span, 2000–2018, 7.7 billion

treatments to more than 910 million people have been given in 68 countries. As such the population requiring MDA declined by 42%, down to 597 million with a saving of an estimated US$100 billion in economic loss from the debilitating disease. As of 2018, preventive chemotherapy is still required in 49 countries. In the following countries and territories (Cambodia, the Cook Islands, Egypt, Kiribati, Maldives, Marshall Islands, Niue, Palau, Sri Lanka, Thailand, Togo, Tonga, Vanuatu, Viet Nam, Wallis and Futuna, and Yemen), lymphatic filariasis is no longer considered as a public health problem. Seven additional countries have successfully implemented recommended strategies, stopped large-scale treatment, and are under surveillance to demonstrate that elimination has been achieved.

In addition to the mass drug administration, vector control is a very valuable supplemental strategy that can be utilized to decrease transmission of mosquito-borne infections. These measures, supported by WHO, include insecticide-treated nets, indoor residential spraying, and personal protection and can contribute to the elimination of this disease.

The second element of care focuses on the management of the morbidities, mainly the lymphedema and the hydrocele.

Lymphedema and Elephantiasis

The lymphedema tends to affect most commonly the lower extremities but can also affect the upper extremities, the breast and the genitalia. It may be unilateral or bilateral and tends to be asymmetric. The lymphedemal has several stages. In the early stages, it tends to be pitting and reversible with leg elevation. As it progresses to stage, it becomes non-pitting and does not reverse with elevation. Progression to stage 3 is marked by skin changes and thickening, which becomes large folds, warty-like skin changes, and very disfiguring swelling in stage 4.

In all stages, a key part of the management includes simple measures of proper hygiene and extremity washing with soap and water. This is essential because it decreases the chances of superimposed bacterial and fungal infections which may exacerbate the situation further and causes severe attacks of acute lymphadenitis which can also cause further damage to the already damaged lymphatic system. In the early stages, leg elevation and the use of compression devices can be very valuable. The later stages are more challenging to manage. Several surgical procedures have been tried with limited success. Excisional procedures of excessive skin and soft tissues with skin grafts of the excised areas have been tried with variable results. Although these debulking procedures can be performed safely, their long-term outcomes are marked by excoriations and drainage and nonhealing wounds. Lymphatic reconstruction and pedicle transfers, including omentum transfer, have been attempted. More recently,excision along with nodal and lymphatic pedicle microvascular transfer have been reported to offer promising results yet to be reproduced and attempted at larger scale [6].

Hydrocele Management

The management of hydrocele has been more effective than that of lymphedema as it may lend itself to curative surgical therapy. Several stages of hydrocele exist. For the early stages, hydrocelectomy with excision of the tunica vaginalis and

simple closure of the scrotum are typically offered. For the later advanced stages and disfiguring hydroceles, referrals to high-level care centers for hydrocelectomy with excision of the tunica vaginalis and scrotal reduction are recommended [7].

Major strides have been achieved by WHO with specific guidelines for the management of patients with filariasis. Through WHO and its GPELF program the aim is to provide a minimum package of care to patients with chronic manifestations of filariasis to alleviate suffering and improve quality of life. This package includes treatment of the episodes of acute adenolymphangitis, guidance in lymphedema management, surgical management of hydroceles, and treatment of infected people with antifilarial drugs. The implementation of WHO programs provides the real hope for eliminating this debilitating disease.

Echinococcosis

Echinococcosis is a zoonotic infection caused by cestodes of the genus *Echinococcus* of the family Taeniidae. There are two main diseases related to *Echinococcus* infection, cystic echinococcosis (CE) mostly caused by *Echinococcus granulosus* and alveolar echinococcosis (AE) caused by *Echinococcus multilocularis* [8, 9]. CE is more common with annual incidence ranging from <1 to 200 per 100,000, while that of AE ranging from 0.03 to 1.2 per 100,000 [9]. AE has a mortality rate of more than 90% if left untreated within 10–15 years of diagnosis. The CE has a much lower mortality rate of 2–4%. To our knowledge, there's no vascular complications related to AE apart from local hepatic vascular complications. Cystic echinococcosis, however, is reported to cause arterial occlusion [10], aortic aneurysmal dilatation [11], and cardiac involvement with subsequent embolization to the pulmonary or systemic circulation [12]. CE is listed by the World Health Organization (WHO) as one of the target diseases for control or elimination by 2050. According to their report, 200,000 new cases are diagnosed annually with an annual cost of treatment and losses to the livestock industry of US$2 billion (http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD _2012.1_eng.pdf).

Biology Life Cycle

Echinococcus spp. is maintained in carnivores as definitive hosts (canids and felids) and by intermediate hosts which are usually herbivorous (sheep, goats, cattle, camels, cervids). Hundreds to thousands of *Echinococcus* spp. adult worms develop in the intestine of their definitive hosts producing eggs that are released into the host's feces to the external environment [9]. Eggs ingested by humans or intermediate hosts hatch in the intestine releasing oncospheres that pass through the portal and lymphatic vessels to reach the liver. Oncospheres may also settle in the lungs, brain, bones, heart, or peripheral vessels. Oncospheres develop into larvae (metacestodes or hydatid cysts) [9]. The definitive host gets infected by ingesting the protoscoleces which are the fertile forms produced by the hydatid cyst. When ingested, the

protoscoleces envaginate their scoleces which attach to the intestinal wall and develop into an egg-producing adult worm [9].

Epidemiology and Transmission

Cystic echinococcosis has a cosmopolitan distribution and is considered endemic in Peru, Chile, Argentina, Uruguay, Southern Brazil, Central Asia, Western China, the Mediterranean region, and East Africa [13]. CE has been eliminated in Iceland, New Zealand, Tasmania, Falkland Islands, and Cyprus [14].

Humans at risks are those living in pastoral regions in which sheep or other livestock are raised and in which dogs are kept for guarding or herding. The incidence increases with age, and women are more likely to be infected [13, 15]

Clinical Features

CE cysts are slow-growing lesions, usually, depending on the location of the lesion, taking many years to develop symptoms [16]. The onset of symptoms is related to the infected organ, the size and location of the cyst, and complications related to the rupture of the cyst or secondary infection. Most of the lesions occur in the liver (70%) and the lungs (20%), with the remainder occurring in the brain, spleen, bone, heart, muscles, and arteries [9]. Most patients have a single organ disease (80%), while the other 20% have multiple organs involved [17]. Hepatic cysts develop symptoms when the cyst reaches more than 10 cm diameter or cause mechanical compression on the bile ducts, hepatic artery, vein, or portal vein [9]. Rupture of cyst into the biliary system causes cysto-biliary fistula [16]. Patients with cysts in the liver may present with vague abdominal pain or discomfort, poor appetite, abdominal distension, or jaundice [9]. Compression or damage to the bronchia in the lung can cause symptoms of cough, chest pain, and hemoptysis [16]. Rupture of the cyst into the bronchi may cause coughing hydatid material and cystic membranes [16]. Rupture of hydatid cyst at any location may induce fever, urticaria, eosinophilia, and anaphylactic shock [16]. Symptoms in other organs are related to mechanical compression to vital structures, occlusion of lumens, and rupture of the cyst or the organ. Also, secondary bacterial infection of the cyst or the cavity created by the cyst can lead to symptoms [16, 17]. It's not unusual for the disease to be discovered incidentally on imaging studies done for other purposes [16].

Hydatid Vascular Manifestations

Hydatid vascular manifestations are numerous though rare. Cardiac hydatid disease is well-described in the literature [18] with incidence of 0.5–2% of hydatid manifestations [19] and can manifest by distal embolization to the pulmonary [20] and

systemic circulation [21] or by rupture of the cyst to the pericardium [18]. Vascular hydatid disease can also present primarily in an artery or in an adjacent structure compressing or involving the vessel [22]. Major vessels can be involved such as the descending thoracic aorta or abdominal aorta [23–25]. As such, patients may present with symptoms such as pulmonary embolism, pericardial effusion, or tamponade manifested by chest pain, angina, syncope, or sudden death [18]. Patients may also present with symptoms related to systemic vascular occlusion, acute or chronic, with acute limb ischemia, claudication, or stroke.

Acute Limb Ischemia

CE can present with symptom of acute limb ischemia with hydatid membranes extracted during embolectomy of the occluded vessels. The primary source of emboli is mostly a membrane rupture in left ventricle of the heart but can also be from ruptured hydatid cyst in the descending thoracic or abdominal aorta [25]. Treatment is often successful with embolectomy of the hydatid membrane and simultaneous or staged excision of the primary hydatid disease through a sternotomy (Figs. 19.3, 19.4, and 19.5). Medical treatment with mebendazole is described from anywhere between a month to a year postoperatively with no described recurrences.

Chronic Limb Ischemia

Symptoms of claudication and impotence are described for hydatid disease primarily involving the vessel and aorta [26] or invading the vessel from adjacent structures [22], also in one case of recurrence 5 years following excision of hydatid disease from the femoral arteries area [27]. Treatment is with excision of the disease along with the involved vessels and re-establishing the anatomy with a graft [10, 22]. Incomplete excision of the disease might lead to local and distal

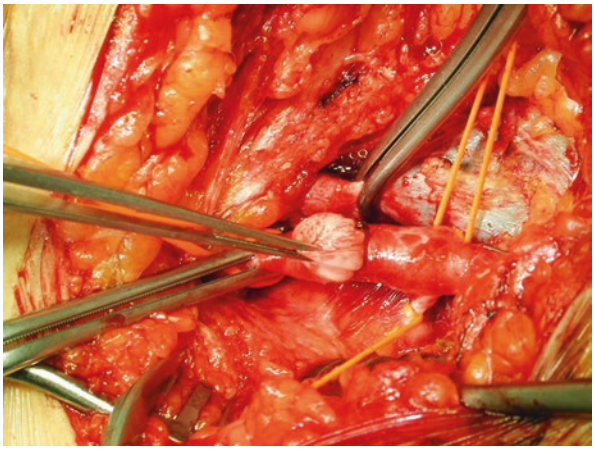

Fig. 19.3 The beginning of the extraction of the daughter cyst from the right common femoral artery. (Courtesy of Dr Bassem Chaab)

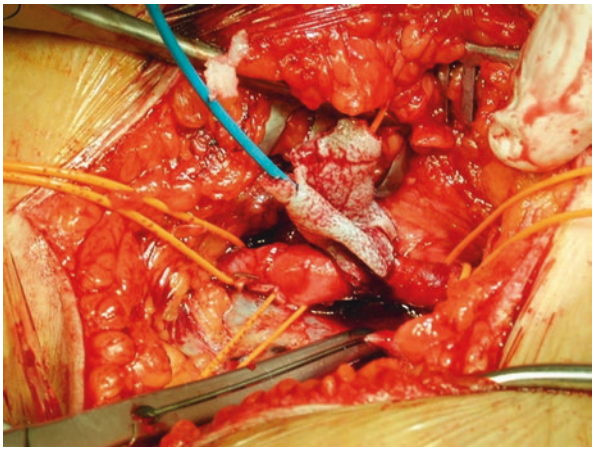

Fig. 19.4 The final stage of the extraction of the daughter cyst. (Courtesy of Dr Bassem Chaab)

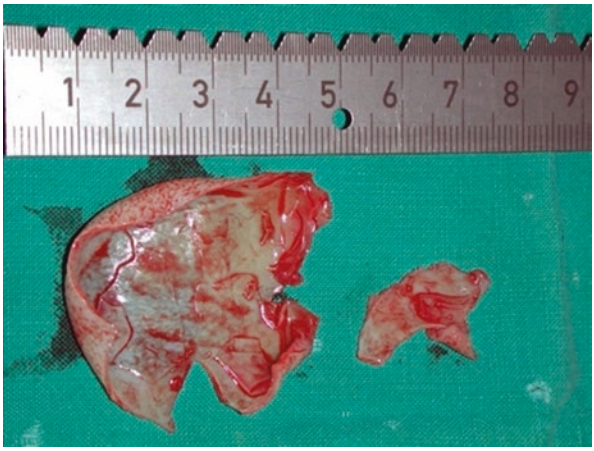

Fig. 19.5 The hydatid cyst. (Courtesy of Dr Bassem Chaab)

recurrence [28, 29]. Endovascular treatment was described by Volpe et al. [29] for descending thoracic aorta pseudoaneurysm due to hydatid disease. The aortic pseudoaneurysm was successfully excluded by an endovascularly inserted stent. The disease, however, continued to progress invading adjacent structures and displacing the stent 5 years later [29].

References

1. World Health Organisation. World Health Organization Global Programme Global Programme To Eliminate Lymphatic Filariasis. 2010:1–93.
2. World Health Organization (WHO). Lymphatic filariasis. https://www.who.int/lymphatic_filariasis/en/. Accessed 25 Jan 2020.
3. Shenoy RK. Clinical and pathological aspects of filarial lymphedema and its management. Korean J Parasitol. 2008;46(3):119–25. https://doi.org/10.3347/kjp.2008.46.3.119.

4. Babu S, Nutman TB. Immunology of lymphatic filariasis. Parasite Immunol. 2014;36(8):338–46. https://doi.org/10.1111/pim.12081.
5. Babu S, Nutman TB. Immunopathogenesis of lymphatic filarial disease. Semin Immunopathol. 2012;34(6):847–61. https://doi.org/10.1007/s00281-012-0346-4.
6. Chilgar RM, Khade S, Chen H-C, et al. Surgical treatment of advanced lymphatic filariasis of lower extremity combining vascularized lymph node transfer and excisional procedures. Lymphat Res Biol. 2019;17(6):637–46. https://doi.org/10.1089/lrb.2018.0058.
7. Lim KHA, Speare R, Thomas G, Graves P. Surgical treatment of genital manifestations of lymphatic filariasis: a systematic review. World J Surg. 2015;39(12):2885–99. https://doi.org/10.1007/s00268-015-3220-4.
8. Buris L, Takacs P, Varga M. Sudden death caused by hydatid embolism. Z Rechtsmed. 1987;98(2):125–8. https://doi.org/10.1007/BF00200469.
9. Wen H, Vuitton L, Tuxun T, et al. Echinococcosis: advances in the 21st century. Clin Microbiol Rev. 2019;32(2):1–39. https://doi.org/10.1128/CMR.00075-18.
10. Öz N, Türkay C, Gölbaşi I, et al. Primary vascular echinococcosis: an uncommon cause of chronic iliofemoral arterial occlusion. Tex Heart Inst J. 2000;27(2):209–11.
11. Dar AM, Kawoosa NU, Ahangar AG, et al. Hydatid embolism from a thoracic aortic pseudoaneurysm presenting as gangrenous toes. Gen Thorac Cardiovasc Surg. 2010;58(7):344–7. https://doi.org/10.1007/s11748-009-0543-9.
12. Díaz-Menéndez M, Pérez-Molina JA, Norman FF, et al. Management and outcome of cardiac and endovascular cystic echinococcosis. PLoS Negl Trop Dis. 2012;6(1). https://doi.org/10.1371/journal.pntd.0001437.
13. Pham H, Kupshik D, King C, Romano P. Cystic echinococcosis. Appl Radiol. 2019;48(5):42–3. https://doi.org/10.1128/JCM.02420-15.Editor.
14. Craig PS, McManus DP, Lightowlers MW, et al. Prevention and control of cystic echinococcosis. Lancet Infect Dis. 2007;7(6):385–94. https://doi.org/10.1016/S1473-3099(07)70134-2.
15. Deplazes P, Rinaldi L, Alvarez Rojas CA, et al. Global distribution of alveolar and cystic echinococcosis. Vol 95. Elsevier Ltd; 2017. https://doi.org/10.1016/bs.apar.2016.11.001.
16. Mcmanus DP, Zhang W, Li J, Bartley PB. Echinococcosis. 2003;362:1295–304.
17. Kern P, Menezes da Silva A, Akhan O, et al. The echinococcoses: diagnosis, clinical management and burden of disease. Adv Parasitol. 2017;96:259–369. https://doi.org/10.1016/bs.apar.2016.09.006.
18. Abhishek V, Avinash V. Cardiac hydatid disease: literature review. Asian Cardiovasc Thorac Ann. 2012;20(6):747–50. https://doi.org/10.1177/0218492312460774.
19. Hèla BJ, Abir B, Majdi G, et al. Interventricular septum hydatid cyst presenting with acute lower limb ischemia: a case report. Libyan J Med. 2015;10:4–6. https://doi.org/10.3402/ljm.v10.28634.
20. Bayraktaroglu S, Ceylan N, Savaş R, Nalbantgil S, Alper H. Hydatid disease of right ventricle and pulmonary arteries: a rare cause of pulmonary embolism - Computed tomography and magnetic resonance imaging findings (2009: 5b). Eur Radiol. 2009;19(8):2083–6. https://doi.org/10.1007/s00330-008-1165-9.
21. Ceyran H, Tasdemir K, Tezcaner T, et al. A rare cause of peripheral arterial embolism: ruptured cardiac hydatid cyst. Vasa - J Vasc Dis. 2002;31(2):129–31. https://doi.org/10.1024/0301-1526.31.2.129.
22. Yörökoğlu Y, Zengin M, Dolgun A, et al. Primary muscular hydatid cyst causing arterial insufficiency: case report and literature review. Angiology. 1993;44(5):399–401. https://doi.org/10.1177/000331979304400509.
23. Zakhariev T, Startkev M, Baev B, Iliev R, Tschirkov A. A rare case of hydatid cyst perceived as false aneurysm of thoracic aorta. J Thorac Cardiovasc Surg. 1997;113(4):792–3. https://doi.org/10.1016/S0022-5223(97)70239-3.
24. Posacioglu H, Bakalim T, Cikirikcioglu M, Yuce G, Telli A. Intramural hydatid cyst of descending aorta complicated by false aneurysm. Scand Cardiovasc J. 1999;33(4):242–4. https://doi.org/10.1080/14017439950141687.

25. Rosenberg T, Panayiotopoulos YP, Bastounis E, Papalambros E, Balas P. Acute abdominal aorta embolism caused by primary cardiac echinococcus cyst. Eur J Vasc Surg. 1993;7(5):581–5. https://doi.org/10.1016/S0950-821X(05)80375-5.
26. Cockcroft DW, Faaaai F, Nair P, Frcpc F, Nair P, Frcpc F. Reproduced with permission of the copyright owner. Further reproduction prohibited without. J Allergy Clin Immunol. 2012;130(2):556. https://doi.org/10.1016/j.jaci.2012.05.050.
27. Erdogan A. Recurrent primary vascular echinococcosis. Tex Hear Inst J. 2005;32(1):113. http://www.ncbi.nlm.nih.gov/pubmed/15902840.
28. Hadjiat N, Graba A, Mansouri H. Rupture of retroperitoneal hydatid cyst into the abdominal aorta. Ann Vasc Surg. 1987;1(4):483–5.
29. Volpe P, Dalainas I, Ruggieri M, Nano G, Paroni G. Endovascular treatment of the descending thoracic aorta in a patient with a hydatid pseudoaneurysm. J Vasc Surg. 2006;44(5):1097–100. https://doi.org/10.1016/j.jvs.2006.07.026.

Surgical Management of Parasitic Diseases of the Genitourinary Tract

20

Nassib Abou Heidar, Aline Yaacoubian, and Yaser El-Hout

Introduction

Many parasites affect or infect the urogenital tract. Even though physicians rarely encounter these entities, it is of utmost importance for the physician to have a complete understanding of the organism, its mode of infection, when to suspect and how to diagnose it, as well as its best modes of treatment. Parasitic pathogens of the urogenital tract include schistosomiasis, enterococcus, amebiasis, enterobiasis, filariasis, hirudiniasis, and *Paragonimus*.

Schistosoma

Life Cycle and Clinical Manifestations

Schistosomes are white 1 cm flukes or trematodes that can infect and live in the bloodstream of human host while evading the host immunity and can live up to 30 years in the host. There are three species that are known to infect humans: *Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*. The first two species mainly infect the liver and gastrointestinal tract, whereas the latter affects the genitourinary tract, which will be our emphasis [1]. The life cycle of these flukes is complex, and mode of transmission to the human host is from secondary larvae (cercariae) from fresh water that penetrate the dermis. They migrate as schistosomulae in the bloodstream and mature in the portal system and liver. The final destination of *S. haematobium* is the lower ureter and bladder through the venous anastomotic channels between the inferior mesenteric, periureteric, and

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perivesical veins [1, 2]. Around 200 million people are infected worldwide by schistosomiasis according to the World Health Organization (WHO) [3]. About 112 million people are infected with *S. haematobium*, and attributable mortality reaches nearly 150,000 annually [4]. Transmission increases near dams with less running water and in communities with poor sanitation [5]. For unclear reasons, children 5–15 years of age are more affected, partly due to more contact with water but probably also have an inherent susceptibility [6]. Proteases secreted by the cercarea aid in skin penetration initiating immunologic responses [7]; however, these responses are localized to the skin only due to the parasitic immunological alteration [8]. The acute phase of the infection is characterized by a local urticarial that can last from a few hours to days. Later on, Katayama fever can ensue, which is characterized by a protracted flu-like constellation of symptoms that can last up to 2–3 weeks [1]. Adult *Schistosoma* are able to evade immunologic response by their double lipid bilayer and its antigenic mimicry and immunomodulation [9]. The main pathologic responses of the body are at the level of the urinary system. This is triggered by the ova that are deposited in the urothelial walls that lead to granuloma formation [10]. These ova have two eventual destinations: expulsion or persistence. Eggs that are expelled develop in aquatic snails into cercarea and can reinfect human hosts. On the other hand, persistent ova calcify and decrease the compliance of the urinary tract [11], mainly the distal portion of the ureter, and can lead to azotemia. Chronic urinary schistosomiasis can lead to increased risk of bacterial infections and urolithiasis [1]. More importantly, schistosomiasis is linked to squamous cell carcinoma of the bladder; this link is supported by both epidemiologic and experimental studies [12]. *Schistosoma haematobium* is classified as a class I carcinogenic agent by the International Agency for Research on Cancer within the World Health Organization [13].The herald signs of chronic schistosomal infection are painless hematuria or irritative lower urinary tract symptoms [14]. An often overlooked entity is female genital schistosomiasis; this occurs when the eggs are deposited in the female genital tract and can cause abnormal uterine bleeding as well as dyspareunia [15].

Diagnosis and Medical Management

Currently, the gold standard for diagnosis of a schistosomal infection is microscopic finding of ova in the urine after proper centrifugation and filtration. It is preferable for the collection to occur around noon due to the circadian rhythm of egg shedding [16]. Serological tests are available and are very sensitive and specific by enzyme-linked immunosorbent assay. PCR is the most sensitive tool for diagnosis of *Schistosoma* from urine samples; however, PCR is more costly and needs trained technicians [17].

Whenever the diagnosis of schistosomal infection is confirmed, a proper imaging of the genitourinary system must be done. The best first imaging of choice is ultrasonography since it can properly visualize bladder or ureteral mural thickening,

hydroureteronephrosis, polyps, or calcifications [18]. Computed tomography can better anatomically visualize lesions especially if done with intravenous contrast and delayed phase; moreover, it gives the physician an idea of the genital tract be it in females or males.

The only recommended drug by the WHO is praziquantel; two 20 mg/kg oral doses are given 6–8 hours apart [5]. Efficacy of praziquantel approaches 90% [19], and efficacy can be increased in highly endemic areas by adding artemisinin.

Surgical Management

Due to the high efficacy of praziquantel, most patients would deserve a trial of medical therapy before elective procedures are undertaken [20]. However, there are certain instances whereby procedures need to be expedited. For instance, gross hematuria with clot urinary retention and/or severe hemorrhage requiring blood transfusions is an example whereby genitourinary surgeons must be called to manage the hemorrhage whether by cystourethroscopy or traditional transvesical approach. The authors suggest that cystourethroscopy takes precedence due to it being less invasive and significant amount of energy for stopping the hemorrhage can easily be used, be it with monopolar or bipolar electrocautery or even laser.

Genital Tract

Scrotal induration, scrotal pain, and epididymal enlargement and testicular enlargement due to ova deposition have been reported [21]. These cases have been operated on for the risk of testicular tumors due to sonographic evidence of calcifications. As for the prostate, its enlargement is uncommon in schistosomiasis, and very scarce literature has been reported on bladder outlet obstruction from the prostate due to *Schistosoma*. However, there are few reports on association with *Schistosoma* and prostate cancer but nothing of high evidence [22]. In addition, it is well established that bilharzia negatively impacts male infertility by pretesticular, testicular, and post-testicular mechanisms. In case of infertility, oligospermia management would be similar to non-helminthic causes, if obstructive a surgical repair might be of slight benefit; if pretesticular or testicular, a microdissection for sperm extraction might be needed for assisted reproduction.

Bladder

Vesical schistosomiasis prompts the specialized urologist to perform a diagnostic cystoscopy (Fig. 20.1) to better visualize the pathology of the inflammation that has ensued polyps, ulcers, erythematous changes, lesions suspicious for malignancy, fibrosis of the bladder neck or at the ureteral orifice, and contracted bladder. Depending on the clinical context and the imaging available, the surgeon must decide if his cystourethroscopy should be done under general/spinal anesthesia or under local anesthesia. Histopathological findings are pathognomonic and are shown in Figs. 20.2 and 20.3.

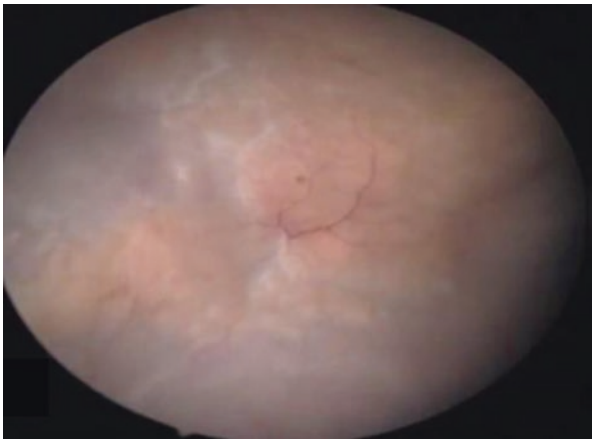

Fig. 20.1 Cystoscopic view of the bladder revealing a yellowish and calcified sessile-like lesion

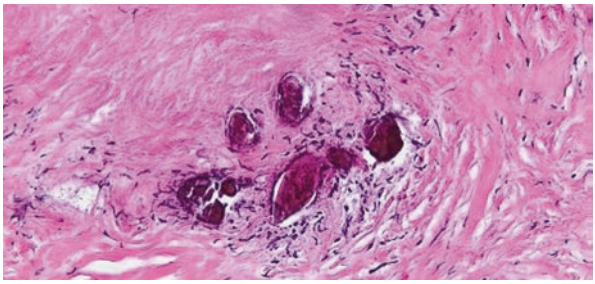

Fig. 20.2 Histopathology of bladder lesion: Hematoxylin and Eosin (H&E) staining of the bladder wall biopsies at higher magnification (×200) showing numerous calcified helminth eggs, with wide base and rounded tip, with the presence of a terminal spine. Each egg measured approximately 120–180 μ

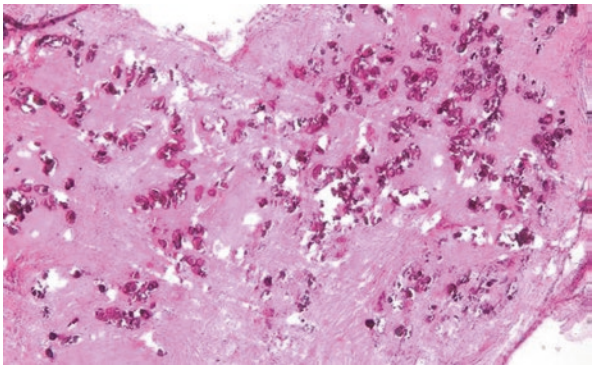

Fig. 20.3 Hematoxylin and Eosin (H&E) staining of the bladder wall biopsies (×40) showing the presence of scattered helminth eggs of Schistosoma within a milieu of smooth muscle cells of the bladder and reactive urothelium

For hyperplastic polypoid lesions, a proper resection/biopsy must be done similar to all other lesions with adequate sampling of detrusor muscle due to the risk of transitional cell carcinoma as well. The mode of resection is based on the surgeon's preference and expertise.

If ulcers are encountered during cystoscopy, a proper biopsy/resection must be done of the ulcer with its base due to risk of malignancy, as above. However, if the ulcer is deep, it is left to the judgment of the surgeon to proceed as stated or to convert to a partial cystectomy because fulguration might not be enough for adequate symptomatic relief or for risk of perforation. For irreversibly fibrosed and contracted bladders with very low capacity, surgical options are hydrodistention, enterocystoplasty, and urinary diversion (from least to most invasive). Hydrodistention is extrapolated from cases of interstitial cystitis best detailed by Nordling et al., whereby a rigid cystoscope is used with glycine irrigant at a height of 80 cm above the pelvis, the infusion fills the bladder till the irrigant stops, and then distention is kept for 3 minutes after which the bladder is emptied [23]. Enterocystoplasty/bladder augmentation was first described in 1899 by both Rutkowski and Mikulicz. Enterocystoplasty is a procedure that can be done with conventional surgery or a minimally invasive laparoscopic or robotic assistance. It entails incising the bladder and augmenting it with a segment of bowel, more commonly terminal ileum or a colonic segment. Other options for bladder augmentation are gastrocystoplasty, autoaugmentation by creating a diverticulum, and ureterocystoplasty (enterocystoplasty). Urinary diversion can be done with ureterosigmoidostomy, ileal conduit, or bilateral percutaneous nephrostomies.

Ureter

The most frequent and the most dreaded sequelae of schistosomiasis is the involvement of the ureter, which can lead to nephropathy [24]. Due to the fact that, early in the inflammatory phase, intra- and extramural polypoid lesions cause obstructive uropathy, medical management most of the times is enough for complete resolution of renal function. The surgeon's role in this entity is when a patient has a chronic urinary schistosomiasis or associated urolithiasis, whereby the anatomic obstruction is less amenable to medical management. The most common observed pathology is ureteral stenosis in up to 80% of patients with ureteral involvement [25]. The surgical approach to each patient depends on the clinical context and the location and extent of the stenosis.

Small distal strictures of the ureter not involving the intramural portion can be managed by balloon dilation [26]; however, mechanical dilation has a significant risk of recurrence. For strictures involving the intramural portion of the ureter, reimplantation of the ureter can be performed with an anti-refluxing reconstruction, be it a Politano-Leadbetter modification, a Lich-Gregoir, or nipple ureteroneocystostomy. Nowadays, with the advances in endourology, even intramural strictures can be attempted to be done endoscopically, whether retrograde or antegrade; endourologic procedures are effective for short segment strictures that are not completely obstructing or not recurrent; otherwise an open surgical approach would be preferable [27].

Long or multifocal strictures might necessitate excision and depending on ureteral length intraoperatively, a ureteroureterostomy, boari flap, psoas hitch, ileal conduit, and replacement of the ureter with an ileal segment. If all else fails, percutaneous nephrostomy can be placed to protect the renal function and bypass the diseased ureter.

Echinococcus

Clinical Overview

Echinococcus granulosus is a tapeworm that causes cystic echinococcus/hydatid cyst [28]. Urologic hydatid cysts are rare and comprise of 2–4% of all *Echinococcus granulosus* infections in the body (>90% are in the liver and lung) [29]. Endemic areas are pastoral communities mainly Mediterranean, Eastern Europe, and the Middle East, among others. *Echinococcus granulosus* are small worms measuring 0.5 cm; its eggs are excreted by canine feces and when ingested can infect humans by growing into cysts. Younger cysts are unilocular and have two layers, an external laminated layer and an inner germinal layer, from which daughter cysts develop (Fig. 20.4). Usually, hydatid cysts of the kidney are asymptomatic but can present due to symptoms of compression with flank pain or a palpable mass (Figs. 20.5 and 20.6) [30]. The pathognomonic sign, even though rare, is hydatiduria which is the passing of gelatinous material in the urine due to rupture of cyst in the renal collecting system [31].

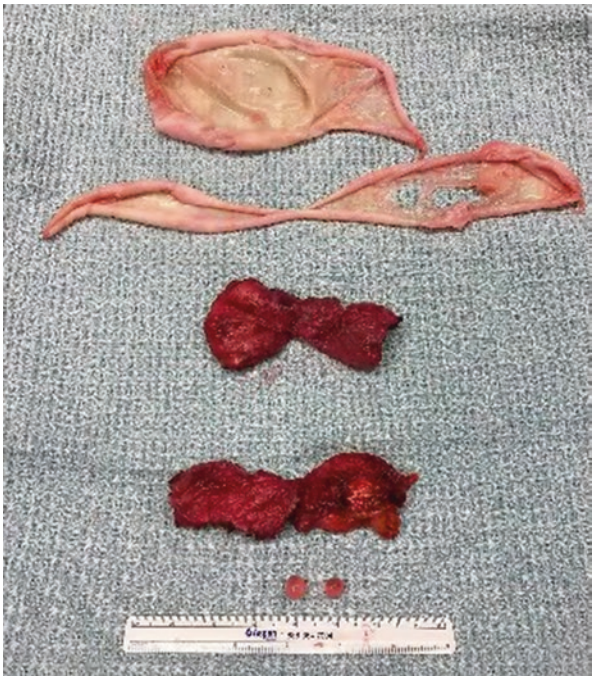

Fig. 20.4 Gross image after laparoscopic unroofing of hydatid cyst showing endocyst (upper 2) and exocyst (mid 2) with small daughter cysts

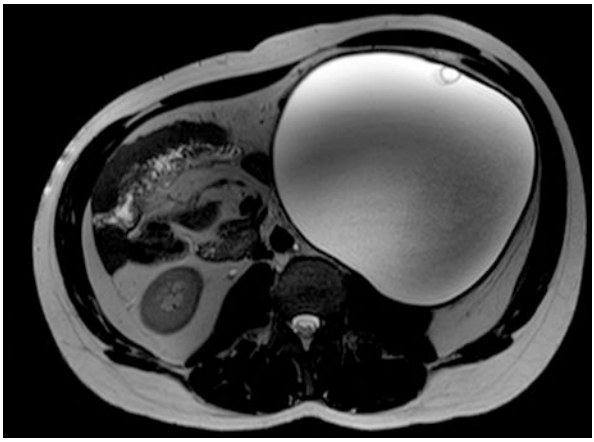

Fig. 20.5 Large left renal hydatid cyst evident on MR T2-weighted image showing small daughter cyst

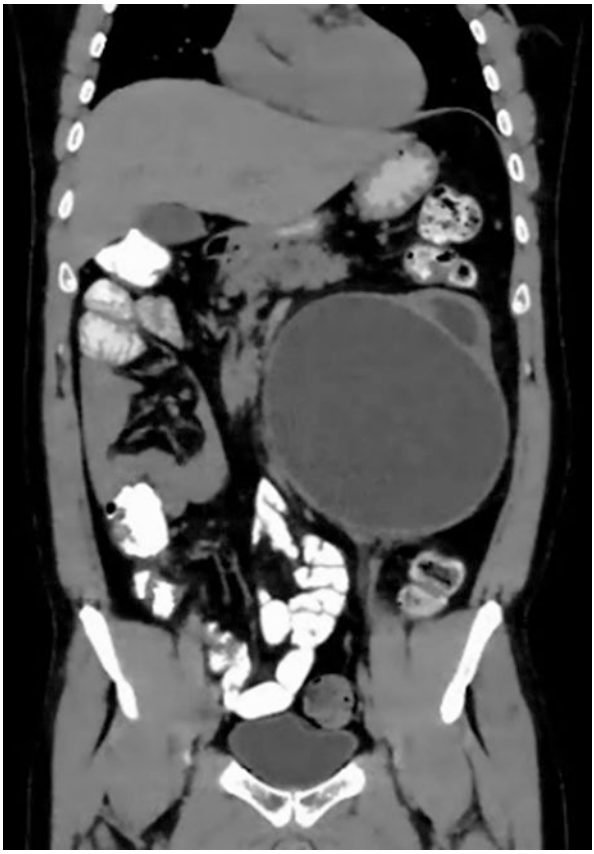

Fig. 20.6 CT scan showing large left renal hydatid cyst with obstruction of the upper pole of the kidney

Table 20.1 Echinococcus radiologic classification [34]

CL (cystic lesion)	Undifferentiated simple cyst
CE1	Unilocular fertile cysts with viable daughter cysts
CE2	Multilocular fertile cysts with viable daughter cysts
CE3	Transitional cysts before degeneration
CE4 and CE5	Heavily calcified inactive infertile cyst

The first step in diagnosis is the suspicion of the physician/radiologist of a hydatid, which should be present on the differential diagnosis of renal cysts, especially in endemic areas. Serology is useful for the diagnosis; however, renal echinococcus tend to have a lower rate of antibody response, and thus serology has a lower sensitivity (about 60%) [32]. Even if serology is positive, it is not definite; the false positives occur due to cross-reaction with other parasites such as *Schistosoma* [33]. Therefore, complementary imaging is necessary to serological testing at instances where serologies are negative.

On ultrasonography, the cyst is readily visualized along with its contents. The authors suggest extrapolating from liver hydatid and adopt the ultrasonographic characterization by the WHO that has been universally agreed on (Table 20.1).

The importance of this characterization in liver hydatid disease is its dictation of management strategies, whether surgery, PAIR (puncture, aspiration, injection, and reaspiration), or watchful waiting. Generally, active cysts CE 1, 2, and 3 require intervention because they indicate that the infection is in the active state. This has not been established in renal hydatid whereby most publications discuss surgery to hydatid cysts of the kidneys and there is not enough experience to be comfortable with expectant management. A more superior imaging modality is CT due to the better characterization of gas, calcifications, as well as better anatomical assessment for possible future intervention [35]. Anatomic cross-sectional imaging can be done to rule out malignant kidney lesions in cases of CE 4 and 5 [30].

Management

Due to the lack of a systemic scolicidal agent that can reach the cyst and kill the daughter cysts, surgical management remains the mainstay of treatment for echinococcus cysts. The surgical management should be dictated by the cyst size, location, relationship with adjacent tissue, and renal cortex preserved. Surgical options include a nephrectomy, partial nephrectomy, and endocystectomy plus closure, simple unroofing of the cyst with evacuation, with preference to nephron sparing surgery if possible [35]. Perioperative albendazole should be administered, especially after opening the cyst for drainage intraoperatively. Albendazole is a scolicidal agent that is given systemically and mainly decreases risk of anaphylaxis intraoperatively and decreases risk of recurrence and disseminated infection in the abdomen. Albendazole is started up to 1–2 weeks preoperatively and is given for up to 3 months postoperatively [36, 37]. Extrapolating from liver hydatid disease, inoperable cases are treated by PAIR; PAIR has not been tried for renal hydatid and has been treated mostly by surgery and/or medical therapy.

Filariasis

Filariasis refers to nematodes that infect the lymphatic tissue and cause lymphatic filariasis, such as *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. These organisms infect the human host when in the larval stage and inoculated by mosquito bites. These worms live in the afferent lymphatics in the inguinal, iliac, and para-aortic chains, as well as the male genital tract for *Wuchereria bancrofti* (testicle, epididymis, spermatic cord). Most of these cases occur in sub-Saharan Africa or in the tropical regions of South America [38].

Lymphatic filariasis causes hydroceles and genital edema and can lead to a debilitating elephantiasis. Hydrocele is the collection of fluid inside the tunica vaginalis that surrounds the testicle in each hemi-scrotum [39]; in the case of filariasis, hydroceles occur due to the fibrosis of the lymphatic tract that drain the tunical lymphatic fluid. Genital edema is the edema in the skin and subcutaneous tissue including the dartos fascia due to blocked lymphatic drainage. Another dreaded consequence of filariasis is chyluria. Chyluria or chyle in urine occurs due to the rupture of the lymphatic channels into the urinary collecting system. This happens after the recurrent lymphatic infection that renders the lymphatics incompetent after destruction of the lymphatic valves [40]. Another manifestation worth mentioning is epididymitis that has been mistaken for a tumor in many reports [41]. As other parasitic diseases, diagnosis is made by ELISA or more recently immunochromatographic card test [42].

Medical Management

Medical treatment is recommended for both symptomatic and asymptomatic patients with microfilaremia, especially those living in an endemic area. The first line of therapy is diethylcarbamazine 2 mg/kg orally three times daily for 1 day. Alternatively, albendazole 400 mg orally twice daily for 3 weeks can be given [43].

Surgical Management

Hydrocelectomy

A simple hydrocelectomy, without any scrotal excision or reconstruction, can be done and has been reported if the disease is confined to the tunica vaginalis. In the literature, tunical eversion [44], excision [45], or Lord's technique [46] has been tried with varying success; however, no comparison has been made between these techniques in terms of recurrence and hematoma formation in filariasis. It is the belief of the authors that if the lymphatic drainage is obstructed, then proper excision of the tunica involved should be done to prevent recurrence.

Scrotal Resection/Reconstruction

Many have published about scrotal excision with reconstruction in addition to hydrocelectomy. Most series perform reconstruction from adjacent healthy skin, with creating subcutaneous pockets for the testes or coverage with local flaps [47].

Another strategy is the coverage of the testes with a split thickness skin graft [48]. However, the authors acknowledge that long-term subfertility is a risk due to the higher temperature in the flaps. Moreover, the authors suggest the use of omentum as a free flap for coverage due to its success in volume reduction due to lymphedema after axillary dissection [49].

Chyluria

In milder cases of chyluria, medical treatment with albendazole can be tried. In more severe cases of chyluria, medical management fails as a stand-alone therapy, and a procedure must be done. Endoscopic injection of a sclerosing agent (betadine or silver nitrate) retrogradely into the ureter and pelvi-calyceal system over multiple times has been tried with moderate success in the past [50]. The most effective method for treatment of chyluria, which is typically reserved for severe cases, is the disconnection of the renal pedicle by either open or laparoscopic approach that mechanically disconnects the fistulous tracts between the lymphatic and urinary system [51].

Type of organism	Clinical manifestation	Medical treatment (first line)	Surgical treatment
Cestode (*Echinococcus granulosus*)	Hydatid cysts	Albendazole	Excision, unroofing
Trematodes (*Schistosoma haematobium*)	Schistosomiasis	Praziquantel	Resection, excision of diseased part
Nematodes (*W. bancrofti*)	Elephantiasis	Diethylcarbamazine	Excision for elephantiasis
	Chyluria		Renal pedicle disconnection
Onchocerca volvulus	Onchocerciasis	Ivermectin	

Onchocerciasis

Onchocerciasis is also known as river blindness in endemic areas. It is caused by *Onchocerca volvulus*, transmitted by *Simulium* black flies. It is found mainly in Africa and Latin America. Classical infection causes dermatitis, keratitis, and chorioretinitis (which may lead to blindness). Diagnosis is made by microscopy because blood testing is less developed for this organism. Urologically, onchocerciasis may cause the "hanging groin" due to recurrent lymphadenitis and loss of skin turgor and elasticity, which is usually manifested as genital swelling that is usually less severe as that of filariasis and inguinal adenopathy. The disease is also characterized by patchy depigmented skin areas, which may involve the genitalia, as well.

Medical Management

The first line of therapy is ivermectin 150 micrograms/kg orally once repeated every 6–12 months until the patient is asymptomatic. An alternative regimen proposed is doxycycline daily for 6 weeks [52].

Surgical Management

Surgical management is identical to that of filariasis, since similar clinical manifestations result; however, these manifestations are much less severe and rarely require surgical management. Surgery for individuals affected with this entity would be mostly cosmetic with excision and reconstruction.

Enterobiasis

Introduction

Enterobius vermicularis or the pinworm is the most common helminthic infection in the developed countries. It commonly infests the gastrointestinal tract and is transmitted by the fecal-oral route. The females migrate to the anus to lay their eggs, and from there, it has been proposed that pinworms can infest and infect the genitourinary tract. There has been evidence of abnormal uterine bleeding as well as vulvovaginitis in women with pinworms. Moreover, a published case report shows that *Enterobius* eggs were found in a surgical specimen of a removed kidney for another reason [53]. Epididymal involvement and infestation of inguinal hernias have been reported in the literature [41].

Management

There has been no report of a serious pinworm infestation of the genitourinary tract in humans that have necessitated a surgical procedure. Medically, mebendazole is not absorbed outside of the gastrointestinal tract and thus would be ineffective of treating extraintestinal enterobiasis. On the other hand, ivermectin is the drug of choice for treating extraintestinal pinworms.

Amebiasis

Amebiasis is the infection of the human with the parasite *Entamoeba histolytica*. Classically infection with this parasite causes colitis, dysentery, and liver abscesses after entering the portal venous system. Urologically, this organism can cause genital ulcers or genital amebiasis mostly in females, characterized by a foul bloody vaginal discharge [54]. Infection of the uterus and fallopian tubes has also been reported [55, 56]. On the other hand, in men it presents as painful genital ulcers. In both genders, diagnosis is based on microscopy of smears, and treatment is mainly medical with metronidazole [57].

There have been cases of amebic abscesses in the kidneys; the authors recollect two such cases. One patient had concomitant renal and hepatic abscesses. The kidney abscess was due to an evident fistula seen on imaging between the colon and right kidney, which explains the abscess formation. The patient had to undergo

surgery for excision of part of the colon, right kidney, and liver abscess drainage [58]. Another case of renal amebic abscess formation was reported in a diabetic patient with emphysematous pyelonephritis that had to undergo an open nephrectomy for infectious control [59].

Trichomoniasis

Trichomoniasis is caused by the parasitic flagellate *Trichomonas vaginalis* which is a very common sexually transmitted infection [60]. The WHO ranked trichomonas as higher than other sexually transmitted infectious agents such as chlamydia or gonorrhea [61]. It infects the male urethra and prostate as well as the female genital tract, which can be asymptomatic in up to 80% of affected men and 50% of women [62]. In women, manifestations range from cervicitis with the pathognomonic "strawberry cervix" due to petechial hemorrhages to pelvic inflammatory disease and preterm delivery and low birth weight [63]. Males, however, tend to show symptoms of cystoprostatitis and epididymo-orchitis [62]. Diagnosis is made by microscopy or real-time PCR [60]. Since it is transmitted sexually, treatment must be initiated to the patient and to the partner, using oral metronidazole. Surgical management of this infection is not necessary since the flagellate is highly treatable with systemic treatment. Other methods for prevention include barrier contraception [64] and male circumcision [65].

Hirudiniasis

Hirudiniasis is caused by leeches that infest the human by entering the body orifices, if the leech gains access to the urethra it can infest the bladder. The leech has a soft elongated segmented body with suckers at both ends. There are a few reports in the literature regarding leeches entering the bladder and causing hematuria or blood per urethra [66]. The bite of the leech causes continuous bleeding since it secretes an anticoagulant (hirudin) [67]. There are few reports of patients living in the tropics presenting with mainly hematuria that turned out to have hirudinasis or leech infestation. Some infestations were severe enough to cause bladder clot urinary retention requiring cystoscopic treatment of bleeding site [68]. Other infestations were treated by surgical removal by an open suprapubic cystotomy and manual removal [69].

Diagnosis is made mainly by ultrasonographic finding of the isoechoic elongated structure that can be motile [67]. The largest series of treatment was reported in the Journal of Pediatric Urology in 2007 that demonstrated successful expulsion of the leeches in 43 boys by inserting a Foley catheter and instilling 50 mL of normal saline and clamping the catheter for 3 hours before removing the catheter. All boys successfully urinated the leech within 24 hours without sequelae [66].

Paragonimus

Paragonimiasis is a disease cause by a trematode common in the Far East; the most common is *Paragonimus westermani*. It infests the human host after ingestion of raw seafood, after which the metacercial stage of the fluke infects the human host as cysts in the intestines and can penetrate intestinal walls and enter the abdominal cavity and manifest mainly due to the inflammation and fibrosis ensued by the fluke cysts [70]. This fluke has been rarely reported to affect the genitourinary tract including the bladder [70] and the kidney [71]. It is purely a disease of endemic regions, and treatment is usually medical with praziquantel and rarely requires surgery.

References

1. Gryseels B. Schistosomiasis. Infect Dis Clin N Am. 2012;26(2):383–97.
2. Barsoum RS. Urinary schistosomiasis: review. J Adv Res. 2013;4(5):453–9.
3. WHO (World Health Organization). The global burden of disease: update 2004. 2008. p. 1–160. URL: https://www.who.int/healthinfo/global_burden_disease/2004_report_update/en.
4. van der Werf MJ, de Vlas SJ, Brooker S, Looman CW, Nagelkerke NJ, Habbema JD, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. Acta Trop. 2003;86(2–3):125–39.
5. WHO (World Health Organization). Schistosomiasis. Strategy: control and preventive chemotherapy. 2014.
6. Anderson RM, Anderson B May RM. Infectious diseases of humans: Dynamics and control. Oxford University Press; 1992. p. 1–766.
7. Curwen RS, Ashton PD, Sundaralingam S, Wilson RA. Identification of novel proteases and immunomodulators in the secretions of schistosome cercariae that facilitate host entry. Mol Cell Proteomics MCP. 2006;5(5):835–44.
8. Jenkins SJ, Hewitson JP, Jenkins GR, Mountford AP. Modulation of the host's immune response by schistosome larvae. Parasite Immunol. 2005;27(10–11):385–93.
9. Abath FG, Werkhauser RC. The tegument of Schistosoma mansoni: functional and immunological features. Parasite Immunol. 1996;18(1):15–20.
10. Eriksson J, Reimert CM, Kabatereine NB, Kazibwe F, Ireri E, Kadzo H, et al. The 434(G>C) polymorphism within the coding sequence of Eosinophil Cationic Protein (ECP) correlates with the natural course of Schistosoma mansoni infection. Int J Parasitol. 2007;37(12):1359–66.
11. Cheever AW, Young SW, Shehata A. Calcification of Schistosoma haematobium eggs: relation of radiologically demonstrable calcification to eggs in tissues and passage of eggs in urine. Trans R Soc Trop Med Hyg. 1975;69(4):410–4.
12. Mostafa MH, Sheweita SA, O'Connor PJ. Relationship between schistosomiasis and bladder cancer. Clin Microbiol Rev. 1999;12(1):97–111.
13. WHO (World Health Organization). International agency for research on cancer. 2011. p. 102. URL: https://www.who.int/schistosomiasis/en/.
14. Wilson RA. Schistosomiasis. Trop Med Sci Pract. 2001;3.
15. Kjetland EF, Hove RJ, Gomo E, Midzi N, Gwanzura L, Mason P, et al. Schistosomiasis PCR in vaginal lavage as an indicator of genital Schistosoma haematobium infection in rural Zimbabwean women. Am J Trop Med Hyg. 2009;81(6):1050–5.
16. Gomes LI, Enk MJ, Rabello A. Diagnosing schistosomiasis: where are we? Rev Soc Bras Med Trop. 2014;47(1):3–11.
17. ten Hove RJ, Verweij JJ, Vereecken K, Polman K, Dieye L, van Lieshout L. Multiplex real-time PCR for the detection and quantification of Schistosoma mansoni and S. haematobium

infection in stool samples collected in northern Senegal. Trans R Soc Trop Med Hyg. 2008;102(2):179–85.
18. Kardorff R, Dohring E. Ultrasound diagnosis of bilharziasis. Ultraschall Med (Stuttgart, Germany: 1980). 2001;22(3):107–15.
19. Doenhoff MJ, Cioli D, Utzinger J. Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. Curr Opin Infect Dis. 2008;21(6):659–67.
20. Richter J. Evolution of schistosomiasis-induced pathology after therapy and interruption of exposure to schistosomes: a review of ultrasonographic studies. Acta Trop. 2000;77(1):111–31.
21. Rambau PF, Chandika A, Chalya PL, Jackson K. Scrotal swelling and testicular atrophy due to Schistosomiasis in a 9-year-old boy: a case report. Case Rep Infect Dis. 2011;2011:787961.
22. Figueiredo JC, Richter J, Borja N, Balaca A, Costa S, Belo S, et al. Prostate adenocarcinoma associated with prostatic infection due to Schistosoma haematobium. Case report and systematic review. Parasitol Res. 2015;114(2):351–8.
23. Nordling J, Anjum FH, Bade JJ, Bouchelouche K, Bouchelouche P, Cervigni M, et al. Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol. 2004;45(5):662–9.
24. Smith JH, Christie JD. The pathobiology of Schistosoma haematobium infection in humans. Hum Pathol. 1986;17(4):333–45.
25. El-Nahas AR, Shoma AM, El-Baz M. Bilharzial pyelitis: a rare cause of secondary ureteropelvic junction obstruction. J Urol. 2003;170:1946–7.
26. Jacobsson B, Lindstedt E, Narasimham DL, Sundin T, Vijayan P. Balloon dilatation of bilharzial ureteric strictures. Br J Urol. 1987;60(1):28–32.
27. Fasihuddin Q, Abel F, Hasan AT, Shimali M. Effectiveness of endoscopic and open surgical management in benign ureteral strictures. JPMA J Pak Med Assoc. 2001;51(10):351–3.
28. Schantz PM, Kern P, Brunetti E. Echinococcosis. In: Tropical Infectious Diseases: Principles, Pathogens and Practice, 3rd ed, Guerrant R, Walker DH, Weller PF (Eds), Saunders Elsevier, Philadelphia 2011. p.824.
29. Gogus C, Safak M, Baltaci S, Turkolmez K. Isolated renal hydatidosis: experience with 20 cases. J Urol. 2003;169(1):186–9.
30. Horchani A, Nouira Y, Kbaier I, Attyaoui F, Zribi AS. Hydatid cyst of the kidney. A report of 147 controlled cases. Eur Urol. 2000;38(4):461–7.
31. Gogus O, Beduk Y, Topukcu Z. Renal hydatid disease. Br J Urol. 1991;68(5):466–9.
32. Craig PS. Immunodiagnosis of echinococcosis granulosus and comparison of techniques for diagnosis of canine echinococcosis. In: Compendium on cystic echinococcosis in Africa and Middle Eastern Countries with special reference to Morocco. Provo: Brigham Young University; 1997. p. 85–118.
33. Botros BA, Moch RW, Barsoum IS. Echinococcosis in Egypt: evaluation of the indirect haemagglutination and latex-agglutination tests for echinococcal serologic surveys. J Trop Med Hyg. 1973;76(9):243–7.
34. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. Acta Trop. 2003;85(2):253–61.
35. Rexiati M, Mutalifu A, Azhati B, Wang W, Yang H, Sheyhedin I, et al. Diagnosis and surgical treatment of renal hydatid disease: a retrospective analysis of 30 cases. PLoS One. 2014;9(5):e96602.
36. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. Bull World Health Organ. 1996;74(3):231–42.
37. Arif SH, Shams Ul B, Wani NA, Zargar SA, Wani MA, Tabassum R, et al. Albendazole as an adjuvant to the standard surgical management of hydatid cyst liver. Int J Surg (London, England). 2008;6(6):448–51.
38. Taylor MJ, Hoerauf A, Bockarie M. Lymphatic filariasis and onchocerciasis. Lancet (London, England). 2010;376(9747):1175–85.
39. Cimador M, Castagnetti M, De Grazia E. Management of hydrocele in adolescent patients. Nat Rev Urol. 2010;7(7):379–85.

40. Zhang X, Zhu QG, Ma X, Zheng T, Li HZ, Zhang J, et al. Renal pedicle lymphatic disconnection for chyluria via retroperitoneoscopy and open surgery: report of 53 cases with followup. J Urol. 2005;174(5):1828–31.
41. Nutman TB, Kazura J. Lymphatic Filariasis. In: Tropical Infectious Diseases: Principles, Pathogens and Practice, 3rd ed, Guerrant R, Walker DH, Weller PF (Eds), Saunders Elsevier, Philadelphia 2011. p.729.
42. Weil GJ, Curtis KC, Fakoli L, Fischer K, Gankpala L, Lammie PJ, et al. Laboratory and field evaluation of a new rapid test for detecting Wuchereria bancrofti antigen in human blood. Am J Trop Med Hyg. 2013;89(1):11–5.
43. CDC (Centers for Disease Control and Prevention). Parasites – lymphatic filariasis: guidance for evaluation and treatment. 2013.
44. Thomas G, Richards FO Jr, Eigege A, Dakum NK, Azzuwut MP, Sarki J, et al. A pilot program of mass surgery weeks for treatment of hydrocele due to lymphatic filariasis in Central Nigeria. Am J Trop Med Hyg. 2009;80(3):447–51.
45. Noroes J, Dreyer G. A mechanism for chronic filarial hydrocele with implications for its surgical repair. PLoS Negl Trop Dis. 2010;4(6):e695.
46. Fasana F. Treatment of tropical hydrocele: a study of 273 cases. Medicom. 1982;4:73–5.
47. Lucas JW, Lester KM, Chen A, Simhan J. Scrotal reconstruction and testicular prosthetics. Translational Androl Urol. 2017;6(4):710–21.
48. Ollapallil JJ, Watters DA. Surgical management of elephantiasis of male genitalia. Br J Urol. 1995;76(2):213–5.
49. Chu YY, Allen RJ Jr, Wu TJ, Cheng MH. Greater Omental lymph node flap for upper limb lymphedema with lymph nodes-depleted patient. Plast Reconstr Surg Glob Open. 2017;5(4):e1288.
50. Tan LB, Chiang CP, Huang CH, Chou YH, Wang CJ. Experiences in the treatment of chyluria in Taiwan. J Urol. 1990;144(3):710–3.
51. Wang L, Ou Z, Chen H, Cao Z, Tang Z, Chen X, et al. Learning curve for retroperitoneoscopic renal pedicle lymphatic disconnection for intractable chyluria: a single surgeon's experience. Urol J. 2012;9(3):562–7.
52. Hoerauf A, Mand S, Adjei O, Fleischer B, Buttner DW. Depletion of wolbachia endobacteria in Onchocerca volvulus by doxycycline and microfilaridermia after ivermectin treatment. Lancet (London, England). 2001;357(9266):1415–6.
53. Cateau E, Yacoub M, Tavilien C, Becq-Giraudon B, Rodier MH. Enterobius vermicularis in the kidney: an unusual location. J Med Microbiol. 2010;59(Pt 7):860–1.
54. Antony SJ, Lopez-Po P. Genital amebiasis: historical perspective of an unusual disease presentation. Urology. 1999;54(6):952–5.
55. Othman NH, Ismail AN. Endometrial amoebiasis. Eur J Obstet Gynecol Reprod Biol. 1993;52(2):135–7.
56. Calore EE, Calore NM, Cavaliere MJ. Salpingitis due to Entamoeba histolytica. Braz J Infect Dis. 2002;6(2):97–9.
57. Richens J. Genital manifestations of tropical diseases. Sex Transm Infect. 2004;80(1):12–7.
58. Mourra N, Colignon N, Broudin C, Arrive L. Amoebic hepatic and renal abscesses complicating amoebic colitis. Clin Res Hepatol Gastroenterol. 2014;38(5):541–2.
59. Guvel S, Kilinc F, Kayaselcuk F, Tuncer I, Ozkardes H. Emphysematous pyelonephritis and renal amoebiasis in a patient with diabetes mellitus. Int J Urol. 2003;10(7):404–6.
60. Soba B, Skvarc M, Maticic M. Trichomoniasis: a brief review of diagnostic methods and our experience with real-time PCR for detecting infection. Acta dermatovenerologica Alpina, Pannonica, et Adriatica. 2015;24(1):7–10.
61. WHO (World Health Organization). Global incidence and prevalence of selected curable sexually transmitted infections – 2008. 2012. p. 20. URL: https://www.who.int/reproductivehealth/publications/rtis/stisestimates/en/.
62. Muzny CA, Schwebke JR. The clinical spectrum of Trichomonas vaginalis infection and challenges to management. Sex Transm Infect. 2013;89(6):423–5.

63. Sena AC, Bachmann LH, Hobbs MM. Persistent and recurrent Trichomonas vaginalis infections: epidemiology, treatment and management considerations. Expert Rev Anti-Infect Ther. 2014;12(6):673–85.
64. Bouchemal K, Bories C, Loiseau PM. Strategies for prevention and treatment of Trichomonas vaginalis infections. Clin Microbiol Rev. 2017;30(3):811–25.
65. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet (London, England). 2007;369(9562):643–56.
66. Alam S, Das Choudhary MK, Islam K. Leech in urinary bladder causing hematuria. J Pediatr Urol. 2008;4(1):70–3.
67. Deka PM, Rajeev TP. Unusual cause of Hematuria. Urol Int. 2001;66:41–2.
68. Hamid MS, Mohd Nor GR. Severe urological complication of leech bite in the tropics. Br J Urol. 1996;77(1):164–5.
69. Datta B, Sarkar AN, Ghosh MK. Vesical hirudiniasis: a rare case report. Urol J. 2011;8(3):242–3.
70. Yue X, Wei X, Zhu Y, Han P, Li X, Wei Q, et al. Vesical paragonimiasis diagnosed by histopathology: a case report. Urol Int. 2014;93(3):361–3.
71. Lin CM, Chen SK. Paragonimus calcified ova mimicking left renal staghorn stone. J Urol. 1993;149(4):819–20.

Part V

Special Situations

Parasitic Infestations Requiring Surgical Treatment in the Pediatric Population

21

Arwa El-Rifai, Samir Akel, and Ahmad Zaghal

Protozoa

Entamoeba histolytica

Entamoeba histolytica is a nonflagellated protozoan that causes the disease amebiasis, it occurs worldwide [2] and is transmitted via the fecal-oral route by ingestion of the infective cystic form which is usually found in fecally contaminated water, soil, or hand [3].

The estimated prevalence is around 50 million cases per year worldwide with up to 100,000 deaths as a result of the invasive sequelae [3].

Humans are the sole reservoir for this parasite, yet infected patients can remain asymptomatic in many cases, but they can also develop intestinal manifestations including but not limited to colitis, fulminant colitis, or even perforation. Moreover, they can develop extraintestinal manifestations via the invasive form of trophozoites and can present most commonly with a liver abscess but can also present with brain abscess, pleural disease, or even pericarditis [3].

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Diagnosis is established using stool microscopy, serology, and molecular testing using the polymerase chain reaction (PCR) [3]. Pharmacologic therapy is used in symptomatic patients as well as asymptomatic patients in nonendemic regions [4]. It includes metronidazole or tinidazole as well as a luminal agent such as paromomycin [4].

Some patients may present with a surgical abdomen and hence require surgical intervention. There aren't many reported cases in the literature; however the presentation in children doesn't differ much from that of adults. The underlying pathologies include perforated amebic colitis, massive gastrointestinal (GI) bleeding, toxic megacolon, and abscesses that failed medical therapy and percutaneous drainage [4, 5]. The colitis can be mild or severe with sloughing of the mucosa and blood per rectum [2] and can progress to the development of toxic megacolon requiring urgent colectomy [4].

Leishmania infantum/L. tropica/L. donovani

Leishmania infantum is a vector-borne parasite that is responsible for the disease leishmaniasis which is transmitted to humans by the bite of sandflies. Estimated incidence is 1.5 million cases of cutaneous leishmaniasis (Fig. 21.1) and 500,000 of

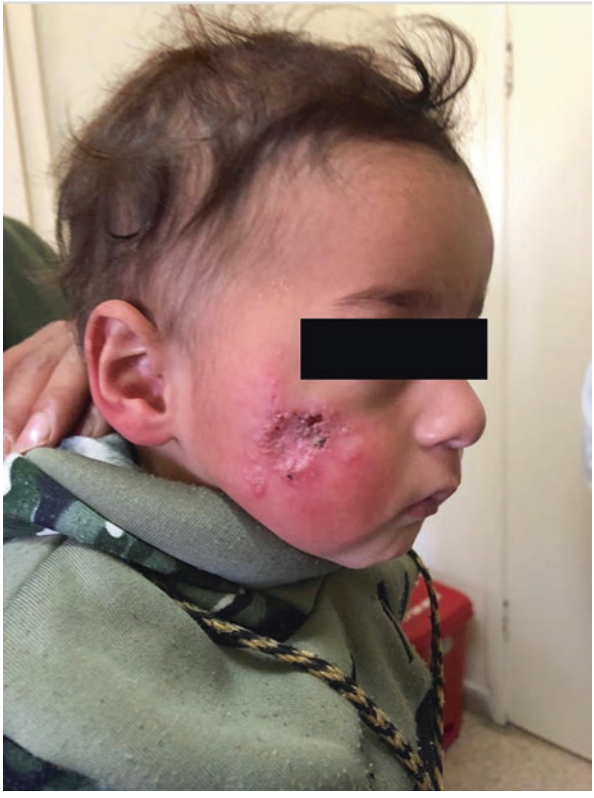

Fig. 21.1 Cutaneous leishmaniasis

visceral leishmaniasis worldwide [6]. The diagnosis depends on clinical evaluation and confirmed by PCR. Patients with cutaneous leishmaniasis present with a local ulceration at the site of the bite. For localized lesions, treatment may involve cryotherapy, thermotherapy, and even surgical excision followed by a course of amphotericin B or other drugs [7]. On the other hand, a more severe form of infection can occur which is visceral leishmaniasis. Patients can present with high-grade fever, anorexia, vomiting and diarrhea, as well as associated hepatosplenomegaly and will require pharmacotherapy [8].

Giardia duodenalis or *G. lamblia*

Giardia duodenalis or *G. lamblia* is a multi-flagellated parasite responsible for the disease giardiasis with a prevalence of up to 24% in endemic regions [9]. It is transmitted via ingestion of contaminated water or food or via fecal-oral route. More than half of the infected patients are asymptomatic; however, if symptoms ensue in the acute phase, they include diarrhea, most commonly, malaise, steatorrhea, as well as nausea, vomiting, and weight loss [10]. Symptoms of chronic infection can also occur including malabsorption and profound weight loss. On rare occasions, the parasite can spread into the biliary tree leading to cholangitis, cholecystitis, and hepatitis some of which may require a surgical intervention [10].

Helminthes

Ascaris lumbricoides

Ascaris lumbricoides is a large intestinal parasite also known as the roundworm, the transmission occurs through intake of fecal contaminated water or food containing the *Ascaris* eggs [11]. Globally, around 890 million people are infected [12] with around 20,000 deaths per year in endemic regions [13]; it is most common among children. The ingested eggs develop into larvae that can migrate through the intestinal mucosa and disseminate into the liver, heart, and lung [11]. Most patients are asymptomatic yet they warrant treatment. Pharmacologic therapy includes administration of anthelmintics such as albendazole or mebendazole.

The intestinal infection can be diagnosed via peripheral eosinophilia, stool microscopy, or visualization of the adult worms macroscopically. Furthermore, radiologic studies can be utilized including X-ray, barium swallows, and computed tomography (CT) scans.

When intestinal symptoms occur, they are often attributed to a high load of adult worms; another possibility is pulmonary manifestations from the larvae [11]. Bowel obstruction comprises up to 87% of *Ascaris*-related complications [14] and more commonly so in children between the ages of 1 and 5 years [15]. Most common presenting symptom is abdominal pain in up to 95% of cases followed by vomiting in 79% of cases [16]. It can present with intussusception, volvulus perforation, and

obstruction of the appendix presenting as appendicitis and bowel ischemia [13]. Moreover, they can migrate into the biliary tree accounting for around 10% of admissions [17] and can present as cholangitis, cholecystitis, and liver abscesses as well as perforation [18].

In cases of bowel obstruction, a trial of conservative management with decompression and adequate hydration is attempted and is successful in up to 83% of cases [16]; however if no adequate response is attained or if patient had worsening radiologic evidence or signs of peritonitis, then surgical exploration is warranted. Surgical options depend on the spectrum of presentation and may include [19] (1) appendectomy; (2) resection of ileum with primary anastomosis; and (3) peritoneal toileting and closure of perforation.

In cases of biliary-pancreatic involvement, it is noted on diagnostic ultrasound that in 80% of cases, the worms are in the CBD and in the gallbladder in 16% [17]. Endoscopic removal of the obstructing worms should be attempted and is often successful [17]; surgical intervention is required for persistent biliary obstruction that is documented on follow-up ultrasonography [17, 20]. Surgical options include open [21] and laparoscopic approaches [22]: (1) common bile duct (CBD) exploration; (2) cholecystectomy with CBD exploration; (3) drainage of liver abscess; (4) choledochodudenostomy; and (5) peritoneal lavage.

Schistosoma haematobium/S. mansoni/S. japonicum

Schistosoma haematobium and other species also known as bilharzia are responsible for the disease schistosomiasis or bilharziasis. They are parasitic flatworms that are transmitted when water is contaminated with the eggs which affect the intermediate snail host which then transmits them to humans [23]. In the human host, the larvae develop into the adult form and can release ova into the blood or into body tissues causing immune reaction and chronic changes including splenomegaly and development of esophageal varices [23].

The diagnosis is made after detecting the eggs in stool or urine samples in individuals with suspected infection, and the treatment is praziquantel [23]. Children can develop a rash at the site of penetration of the parasite, or they can develop acute schistosomiasis as a result of deposition of the eggs in the tissues [23]. This acute infection is seen in patients who are infected for the first time, and they present with fever, malaise, hematuria, and diarrhea [23]. The main surgical concern, however, is the development of obstructive uropathy, liver fibrosis, and its sequel of esophageal varices and GI bleeding as well as pulmonary hypertension, all due to chronic infection [23].

The onset of obstructive uropathy is due to the granulomatous reaction caused by *S. haematobium* that occurs in the distal ureters ultimately leading to fibrosis. In order to relieve the obstruction, nephrostomy or surgical reimplantation of the ureters may be needed [24]. The liver disease and its manifestations are due to *S. mansoni* and *S. japonicum* mainly causing the granulomatous response leading to hepatic fibrosis, portal hypertension, varices, and splenomegaly with hypersplenism

[23]. Surgical options include splenectomy with reimplantation into the omentum to decrease the risk of overwhelming post-splenectomy infection (OPSI) [25], sclerotherapy for the esophageal varices, and possibly shunting procedures.

Echinococcus granulosus

Echinococcus granulosus is a parasite that is responsible for the disease hydatidosis. It is transmitted via ingestion of the ova that can travel from the intestine to the liver and some even can pass into the lungs [26]. The parasite equally affects the liver and the lung in children with incidence of synchronous lesions in up to 16% of cases. Moreover, it can affect other organs such as the brain, spleen, and heart [26]. When suspected, the diagnosis of hydatidosis is supplemented by confirmatory imaging modalities such as ultrasound or computer tomography (CT) scan. On ultrasound, the cyst can appear as an anechoic cyst with appearance of "sand," or it can have a more complex appearance with internal septations, daughter cysts, and floating debris. Ultrasound can show the characteristic "water lily" sign of the cyst wall. On CT scan, calcifications, daughter cysts, and membranes can also be visualized [27]. Serologic testing is available but is considered to have low sensitivity [28].

Treatment is combined approach with pharmacotherapy and surgery. Without treatment, the risk of rupture increases as the size of the cyst increases, and this could lead to an anaphylactic reaction and death.

When the liver is involved, some children can remain asymptomatic and be incidentally discovered when investigated for other problems. When symptoms ensue, they often include abdominal pain in the majority of patients, and children can develop symptoms even when cysts are less than 5 cm. Some patients will have atypical symptoms such as jaundice and hepatomegaly [26]. The cysts can vary in size from less than 5 cm in most cases and can reach up to 20 cm which are commonly referred to as "giant" hydatid cysts [28].

As for open technique, the classic incisions are either a midline laparotomy or a subcostal incision; the cyst is identified and carefully punctured and aspirated then injected with hypertonic solution or other scolicidal agent. Then the cyst is aspirated and unroofed and daughter cysts evacuated with care to avoid spillage and special attention to inspect for any biliary fistulae [30].

Several scolicidal agents have been utilized intra-operatively, these vary in terms of their safety profile and potential complications. Formalin was historically used, however, it has been largely abandoned due to the risk of leakage into the peritoneal cavity resulting in chemical peritonitis as well as the risk of cardiac arrest in case of systemic leakage. Moreover, ethyl alcohol has been utilized as a scolicidal agent, yet the risk of sclerosing cholangitis is present. Cetrimide can be also used; however, there is associated risk of developing methemoglobinemia. Others have used hypertonic saline, hydrogen peroxide, and silver nitrate [29].

As for the laparoscopic approach, a three-hole approach is used with an umbilical trocar for the camera and two working trocars in each of the upper quadrants. Using ultrasound guidance, the cysts can be identified and carefully punctured,

aspirated, and then injected with hypertonic saline or glycerol solution for 10 minutes and then re-aspirated. After which the cyst is unroofed using an electrosurgical device and the germinative layer evacuated as well as the daughter cysts each in a protective bag to avoid contamination [30].

Surgical excision of the cyst with or without omentopexy with or without capitonnage is the mainstay therapy with an emerging role for laparoscopic approach [30]. All patients should be maintained on albendazole preoperatively, and the course should be completed for at least 4 weeks postoperatively and up to 3 months [28].

When the lung is involved (Fig. 21.2a–c), patients present with chest pain, fever, and cough; the condition, however, may be asymptomatic. The cyst size can vary and can reach a giant size of more than 10 cm which are more common in children than in adults [31]. Cysts can be unilateral, and in some cases it can be bilateral. Treatment is usually surgical with the aim to completely remove the parasite and prevent spillage. Timely surgical intervention is key as the risk of rupture increases with the size of the cyst, and there is a higher risk for perforation in cysts located in the right middle lobe and the lingual reaching up to 70% and 66.7%, respectively [32].

In cases of unilateral involvement, a thoracotomy on the affected side is performed with cyst excision and removal of the germinative layer and obliteration of the cavity by capitonnage [26]. Classically, another technique of cyst delivery has been described which is intact endocystectomy, also known as "Barrett's technique."

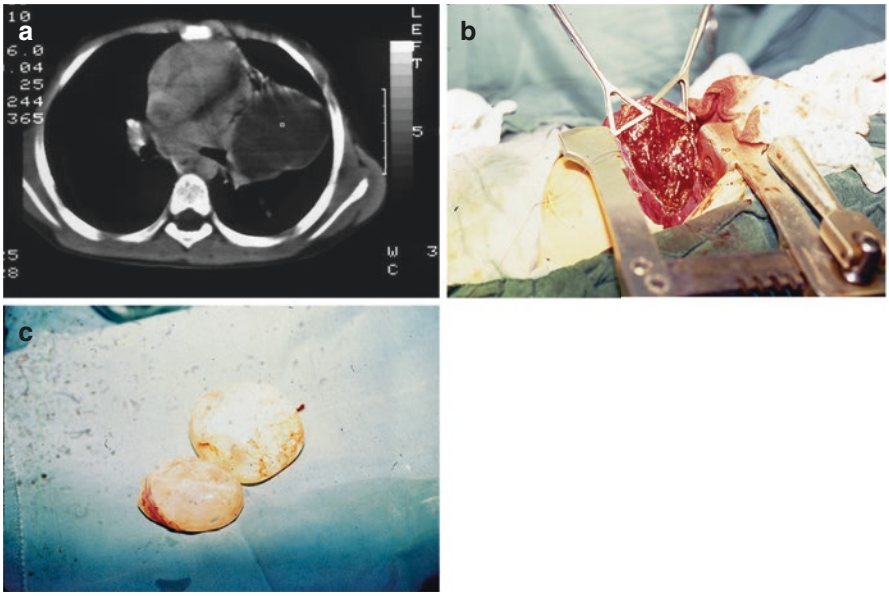

Fig. 21.2 (**a**) Axial CT scan showing cystic lesion in the lung of a 9-year-old boy. (**b**) Thoracotomy for excision of lung hydatid cysts in a 9-year-old boy. (**c**) Intact cysts after delivery from the lung parenchyma

It involves incision of the fibrous ectocyst until the whitish endocyst protrudes, and then with help of the anesthesiologist, the intrapulmonary pressure is increased and the cyst is delivered intact [33]. For giant cysts, lobectomy can be done if the cysts are large and involve more than 50% of the lobe; however, there is an emerging role for parenchymal saving surgery, namely, cyst drainage and capitonnage; this is to avoid the risk of excessive lung resection should the patients become reinfected especially in endemic regions [31]. Moreover, the role of thoracoscopic surgery for lung hydatid disease in children is emerging since technology and expertise in minimally invasive surgery are on the rise [34]. In cases of bilateral lung involvement, staged cysts-excision with three months' interval between the operations is a popular approach. If both the lungs and liver are affected, then surgery for the lung should be attempted first in view of the risks of anesthesia [26].

Spleen involvement occurs in about 1.9% of cases and presents with pain or discomfort of the left upper quadrant. Treatment involves partial pericystectomy, partial splenectomy with omentoplasty [35], and total splenectomy. However, the risk of OPSI with total splenectomy should be kept in mind, and attempts at spleen preserving approaches should be considered first.

Renal involvement occurs in about 1.9% of cases and can present with flank pain and can mimic renal colic; it can be associated with fever, hematuria, and dysuria [28]. Treatment involves partial pericystectomy or partial nephrectomy with omentoplasty depending on the extent of involvement [35].

Brain involvement is a rare occurrence and often in the form of single cysts. Children are more likely to have CNS involvement than adults with a ratio of 7:1 [36]. This presents with signs and symptoms of increased intracranial pressure such as headache and vomiting; treatment involves cyst excision [28].

Cardiac involvement usually has nonspecific presentation including chest pain, dyspnea, and palpitations but can also cause more serious complications such as arrhythmias, pulmonary emboli, and myocardial infarction. In the majority of the cases, it involves the left ventricle [28].

Hydatidosis can involve the soft tissues such as the abdominal wall or thigh muscles; it can also involve the retroperitoneum. Involvement of the omentum indicates spillage from a previous intervention for hydatid [35].

Enterobius vermicularis

The parasite *Enterobius vermicularis* is also known as pinworm, and humans are recognized to be its only host. It is considered to be the most common parasitic infestation in humans across all ages. The prevalence can be 50%, majority of which are below 18 years of age. Infection is through contact with contaminated hands or ingestion of contaminated food or water; the classic presentation is anal pruritus due to the irritation from the worms or the eggs [37]. The treatment is with mebendazole; however, reinfection can occur.

E. vermicularis, commonly considered to be harmless and easily treated, can be associated with ileocolitis, abscesses, and appendicitis [38]. The estimated

prevalence of pinworms in appendiceal specimens removed surgically for presumed appendicitis was around 1.4% in one study [38] but can be as high as 10% in some regions such as Turkey [39].

Dracunculus medinensis

Dracunculus medinensis, also known as the guinea worm, is responsible for the disease dracontiasis. It is transmitted via intake of contaminated water containing the water fleas that are infected by the parasite. It is estimated to affect around 3.5 million people and up to 21% of school children [40] in endemic regions, but the prevalence is decreasing due to global efforts. Infected individuals start to develop symptoms a year after acquiring the infection. They present as an erythematous and painful lower extremity ulcer associated with systemic symptoms [41]. The blister grows and eventually ruptures exposing the worm. There is no available pharmacological treatment; this is usually managed via gradual removal of the worm from its emerging point in the ulcer over several weeks, which is a painful procedure. The surgical concern arises with secondary infection as a result of the lack of access to healthcare; this allows for the development of cellulitis and abscesses including septic arthritis which requires surgical care [41].

Angiostrongylus costaricensis

Angiostrongylus costaricensis is the parasite that is responsible for the human abdominal angiostrongyliasis (HAA). Humans are accidental hosts of this parasite, and they acquire the infection after the ingestion of mollusks or contaminated vegetables. Afterward, the parasites mature and release their eggs in the mesenteric arteries often of the ileocecal region. It is thought to be more prevalent in boys less than 12 years of age [44]. Around 500 new cases are reported in endemic regions of South America [42]. Patients are often asymptomatic however can present with abdominal pain that can be localized to the right lower quadrant or even an acute abdomen that can be associated with fever, nausea, and vomiting.

Diagnosis can be done using serologic analysis; treatment with anthelmintics is controversial. Nonetheless when the disease progresses, the presentation can mimic appendicitis and can also present as bowel stenosis, necrosis, and perforation due to the severe inflammatory and granulomatous reaction in the intestinal wall and associated vasculitis [43, 44].

Dioctophyma renale

Dioctophyma renale is also known as the “giant kidney worm” which causes the disease dioctophymiasis. The parasite is found in flesh-eating mammals and is acquired via ingestion of raw fish or frogs. Few cases of human infection have been reported, some of which were in the pediatric age group. They can present with a

myriad of clinical symptoms such as abdominal pain, fever, hematuria, urgency, and anemia. The treatment is surgical removal of the worms as well as excision of the damaged portion of the kidney [45].

Fasciola hepatica/F. gigantica

Fasciola is a food- and water-borne parasite responsible for the disease fascioliasis or liver fluke disease. Cattle are the definite host for the parasite, and humans are incidental hosts; transmission of infection occurs via intake of contaminated water or ingestion of contaminated plants [46]. The parasite penetrates the duodenum and migrates into the liver capsule. In the acute liver phase, patient presents most commonly with abdominal pain, fever, anorexia, nausea, and vomiting associated with peripheral eosinophilia. They can present with hemobilia, and depending on severity of infection, parenchymal necrosis can occur and thus mimic a liver abscess [46]. The chronic biliary phase, beginning after 6 months of infection, can be asymptomatic. However, nonspecific symptoms such as abdominal pain, nausea, vomiting, and occasionally hepatomegaly can develop [46]. They can also present with cholangitis, cholelithiasis, cholecystitis, and cirrhosis as a sequel of chronic infection. Diagnosis is done via identification of the eggs in stool, duodenal fluid, or bile, and imaging can also be helpful in diagnosis [46]. Medical treatment with triclabendazole is available; however, endoscopic removal of the fluke or even surgery may be warranted [47].

Dirofilaria immitis/D. repens

Dirofilaria immitis is responsible for pulmonary dirofilariasis and *D. repens* for ocular or subcutaneous dirofilariasis. Several cases have been reported in literature including an infection of the scrotum in a pediatric patient [48]. No medical treatment is available, and the mainstay approach is extraction or surgical excision [49] .

Ectoparasites

Dermatobia hominis

Dermatobia hominis is a parasite that is also known as botfly that causes the disease myiasis. It is often found in Central and South America. The transmission occurs when the botfly transmits the eggs to other flies and ticks, and then the eggs hatch and larvae are transmitted to humans upon contact. They form a hole in the skin from which they feed and grow up to 3 cm; they also secrete their waste products. Infections involving the eyes, ears, nasopharynx, and urogenital as well as intestines can occur [50]. Treatment includes removal using suction, occlusion/suffocation using paraffin over the opening, or surgical excision and wound closure [50].

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References

1. Centers for Disease Control and Prevention (CDC), Global Health, Division of Parasitic Diseases. 2016. https://www.cdc.gov/parasites/about.html Accessed 05 May 2019.
2. Dhawan VK, et al. Pediatric Amebiasis. Available at: http://emedicine.medscape.com/article/996092-overview. Accessed 05 May 2019.
3. Leder, et al. Intestinal Entamoebahistolytica Amebiasis. https://www.uptodate.com/contents/intestinal-entamoeba-histolytica-amebiasis#H10. Accessed 05 May 2019.
4. Gonzales ML, Dans LF, Martinez EG. Antiamoebic drugs for treating amoebic colitis. Cochrane Database Syst Rev. 2009;15(2):CD006085.
5. Athié-Gutiérrez C, Rodea-Rosas H, Guízar-Bermúdez C, Alcántara A, Montalvo-Javé EE. Evolution of surgical treatment of amebiasis-associated colon perforation. J Gastrointest Surg. 2010;14(1):82–7.
6. Desjeux P. Leishmaniasis. Public health aspects and control. Clin Dermatol. 1996;14(5):417–23.
7. Koliou MG, Antoniou Y, Antoniou M, Christodoulou V, Mazeris A, Soteriades ES. A cluster of four cases of cutaneous leishmaniasis by Leishmania donovani in Cyprus: a case series. J Med Case Rep. 2014;8:354.
8. Pace D, Williams TN, Grochowska A, Betts A, Attard-Montalto S, Boffa MJ, et al. Manifestations of paediatric Leishmania infantum infections in Malta. Travel Med Infect Dis. 2011;9(1–4):37–46.
9. El Fatni C, Olmo F, El Fatni H, Romero D, Rosales MJ. First genotyping of Giardia duodenalis and prevalence of enteroparasites in children from Tetouan (Morocco). Parasite. 2014;21:48.
10. Leder, et al. Giardiasis: epidemiology, clinical manifestations, and diagnosis. https://www.uptodate.com/contents/giardiasis-epidemiology-clinical-manifestations-and-diagnosis. Accessed 20 Apr 2019.
11. Leder, et al. Ascariasis https://www.uptodate.com/contents/ascariasis Accessed 12 Apr2019.
12. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors. 2014;7:37.
13. Khuroo MS. Ascariasis. Gastroenterol Clin N Am. 1996;25(3):553–77.
14. de Silva NR, Guyatt HL, Bundy DA. Morbidity and mortality due to Ascaris-induced intestinal obstruction. Trans R Soc Trop Med Hyg. 1997;91(1):31–6.
15. Blumenthal DS, Schultz MG. Incidence of intestinal obstruction in children infected with Ascaris lumbricoides. Am J Trop Med Hyg. 1975;24(5):801–5.
16. Mir I, Wani N, Ahangar A, Shah O, Saleem K, Patnail R. Surgical ascariasis in children. JK-Practitioner. 2003;10(1):17–21.
17. Malik AH, Saima BD, Wani MY. Management of hepatobiliary and pancreatic ascariasis in children of an endemic area. Pediatr Surg Int. 2006;22(2):164–8.
18. Javid G, Wani NA, Gulzar GM, Khan BA, Shah AH, Shah OJ, et al. Ascaris-induced liver abscess. World J Surg. 1999;23(11):1191–4.
19. Pandit SK, Zarger HU. Surgical ascariasis in children in Kashmir. Trop Dr. 1997;27(1):13–4.
20. Rode H, Cullis S, Millar A, et al. Abdominal complications of Ascaris lumbricoides in children. Pediatr Surg Int. 1990;5:397–401.
21. Wani MY, Chechak B, Reshi F, Pandita S, Rather M, Sheikhet T. al. Our experience of biliary ascariasis in children. J Indian Assoc Pediatr Surg. 2006;11(3):129–32.
22. Cai M, Cheng J, Li W, Shuai X, Gao J, Cai K, et al. Combination of laparoscope and choledochoscope to treat biliary ascariasis: a CARE-compliant case report. Medicine (Baltimore). 2017;96(13):e6291.

23. Gray DJ, Ross AG, Li YS, McManus DP. Diagnosis and management of schistosomiasis. BMJ. 2011;342:d2651.
24. Antwi S, Aboah KE, Sarpong CK. The unacknowledged impact of urinary schistosomiasis in children: 5 cases from Kumasi, Ghana. Ghana Med J. 2014;48(4):228–33.
25. Brandt CT, da Mota Braga MV, Melo KL, Pinho Sá H, Carvalheira R. Surgical Hepatosplenic Mansonic schistosomiasis in adolescents: repercussions of the post-treatment Schistosomotic burden on the hepatic functional reserve. Mem Inst Oswaldo Cruz. 2001;96:113–5.
26. Talaiezadeh A, Maraghi S. Hydatid disease in children: a different pattern than adults. Pak J Med Sci. 2006;22(3):329–32.
27. Marrone G. Crino' F, Caruso S, Mamone G, Carollo V, Milazzo M, et al. multidisciplinary imaging of liver hydatidosis. World J Gastroenterol. 2012;18(13):1438–47.
28. Gupta R, Sharma S, Prabhakar G, Mathur P. Hydatid disease in children: our experience. Formosan J Surg. 2014;47(6):211–20.
29. Ekci B. Scolicidal agent use in hydatid cysts and complications. Yeditepe Med J. 2011;5(17):379–84.
30. Minaev SV, Gerasimenko IN, Kirgizov IV, Shamsiev AM, Bykov NI, Shamsiev JA, et al. Laparoscopic treatment in children with hydatid cyst of the liver. World J Surg. 2017;41(12):3218–23.
31. Onal O, Demir OF. Is anatomic lung resection necessary in surgical treatment of Giant lung hydatid cysts in childhood? Ann Thorac Cardiovasc Surg. 2017;23(6):286–90.
32. Onal O, Demir OF. The relation between the location and the perforation rate of lung hydatid cysts in children. Asian J Surg. 2018;41(5):422–6.
33. Qian ZX. Thoracic hydatid cysts: a report of 842 cases treated over a thirty-year period. Ann Thorac Surg. 1988;46(3):342–6.
34. Parelkar SV, Gupta RK, Shah H, Sanghvi B, Gupta A, Jadhav V, et al. Experience with video-assisted thoracoscopic removal of pulmonary hydatid cysts in children. J Pediatr Surg. 2009;44(4):836–41.
35. Durakbasa CU, Tireli GA, Sehiralti V, Sander S, Tosyali AN, Mutus M. An audit on pediatric hydatid disease of uncommon localization: incidence, diagnosis, surgical approach, and outcome. J Pediatr Surg. 2006;41(8):1457–63.
36. Carrea R, Dowling E Jr, Guevara JA. Surgical treatment of hydatid cysts of the central nervous system in the pediatric age (Dowling's technique). Childs Brain. 1975;1(1):4–21.
37. Cook GC. Enterobius vermicularis infection. Gut. 1994;35(9):1159–62.
38. Arca MJ, Gates RL, Groner JI, Hammond S, Caniano DA. Clinical manifestations of appendiceal pinworms in children: an institutional experience and a review of the literature. Pediatr Surg Int. 2004;20(5):372–5.
39. Helmy AH, AbouShousha T, Magdi M, Sabri T. Appendicitis; appendectomy and the value of endemic parasitic infestation. Egypt J Surg. 2000;19:87–91.
40. Ilegbodu VA, Kale OO, Wise RA, Christensen BL, Steele JH, Chambers LA. Impact of Guinea worm disease on children in Nigeria. Am J Trop Med Hyg. 1986;35(5):962–4.
41. Greenaway C. Dracunculiasis (Guinea worm disease). CMAJ. 2004;170(4):495–500.
42. Morera P. Abdominal angiostrongyliasis: a problem of public health. Parasitol Today. 1985;1(6):173–5.
43. Dard C, Nguyen D, Miossec C, de Meuron K, Harrois D, Epelboin L, et al. Angiostrongylus costaricensis infection in Martinique, Lesser Antilles, from 2000 to 2017. Parasite. 2018; 25:22.
44. Duarte Z, Morera P. Abdominal angiostrongyliasis in Nicaragua: a clinicopathological study on a series of 12 cases reports. Ann Parasitol Hum Comp. 1991;66(6):259–62.
45. Yang F, Zhang W, Gong B, Yao L, Liu A, Ling H. A human case of Dioctophyma renale (giant kidney worm) accompanied by renal cancer and a retrospective study of dioctophymiasis. Parasite. 2019;26:22.
46. Leder, et al. Liver flukes: Fascioliasis https://www.uptodate.com/contents/liver-flukes-fascioliasis. Accessed 20 Apr 2019.

47. Menon P, Sinha AK, Rao KL, Khurana S, Lal S, Thapa BR. Biliary Fasciola gigantica infestation in a nonendemic area — An intraoperative surprise. J Pediatr Surg. 2015;50(11):1983–6.
48. Tumolskaya NI, Pozio E, Rakova VM, Supriaga VG, Sergiev VP, Morozov EN, et al. Dirofilaria immitis in a child from the Russian Federation. Parasite. 2016;23:37.
49. Leder, et al. Miscellaneous nematodes https://www.uptodate.com/contents/miscellaneous-nematodes. Accessed 20 Apr 2019.
50. Whitcomb V, Hartwig E. An unexpected guest: a case of cutaneous Furuncular Myiasis. Pediatr Emerg Care. 2016;32(3):183–4.

Parasitic Infections in the Immunocompromised Host: Prevention, Diagnosis, and Management

22

Vijay G. Menon and Nahel Elias

Introduction

The National Institutes of Health defines an immunocompromised host as being unable to produce an adequate immune response [1]. An immunocompromised state can occur as a result of disease processes but also as a consequence of the treatment of disease or deliberately induced immunosuppression. In this chapter, we will primarily be discussing the latter scenario with regards to parasitic infestations as it relates to solid organ transplant though this can be applied to all immunocompromised states.

Multiple immunodeficient states can lead to disease, including humoral or B cell deficiencies resulting in from multiple myeloma, chronic lymphoid leukemia, and AIDS/HIV [2]. Complement deficiencies and asplenia, secondary to splenectomy or sickle cell disease [3], can also result in immunodeficiency as can states leading to T cell deficiency and neutropenia, including treatment modalities of chemotherapy and glucocorticoid therapy [4].

Organ transplantation has become a mainstay treatment for end-stage organ failure. As technical knowledge improved, maintaining the transplanted grafts became a challenge as early usage of radiation and steroids led to severely immunocompromised states or organ rejection [5]. The advent of cyclosporine was a turning point and currently there are multiple agents used individually or in combination to prevent rejection, preferably without over-immunosuppression resulting in infection or malignancy [6]. Another deliberately immunosuppressed state is in the treatment of autoimmune diseases such as Crohn's disease or rheumatoid arthritis, which require medications to counter a hyperactive component of the immune system.

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Table 22.1 Common parasites that cause infection in humans

Protozoa	Helminths	Ectoparasites
***Plasmodium*spp.**	*Ascaris lumbricoides*	Head louse
Entamoeba	Pinworm	Body louse
Giardia	*Strongyloides stercoralis*	Crab louse
***Trypanosoma*spp.**	*Toxocara*	Tick (Ixodoidea)
Toxoplasma gondii	Hookworm	Flea (Siphonaptera)
Acanthamoeba	Tapeworm	Mosquito (Culicidae)
Leishmania	Whipworm	Bed bug (*Cimex*)
Babesia	***Schistosoma***	Chiggers (Trombiculidae)
Balamuthia mandrillaris	*Gnathostoma*	Scabies mite
Cryptosporidium	*Paragonimus*	Red mite
Cyclospora	*Fasciola hepatica*	Tropical fowl mite
Naegleria fowleri	*Trichobilharzia regenti*	Northern fowl mite
		Tropical rat mite
		Spiny rat mite
		House mouse mite
		Demodex mite

Diseases in **bold** are discussed in detail in this chapter

In the United States, bacteria and viruses are the most commonly encountered infections in organ transplant recipients, and this is unsurprising given these organisms' prevalence in hospitals and the community [7]. Bacterial and viral pathogens are tested in the donor and recipient preoperatively and in the symptomatic individual. Recipients are routinely on a short course of prophylactic antibiotics and antivirals during the period where immunosuppression is greatest immediately after transplant or after treatment of rejection, in an effort to minimize transplant-related infections. Parasitic infections are less commonly seen in transplant recipients, but this depends on prevalence of infections in a given geographical location. Parasites that are pathogenic have been mentioned in other chapters but are briefly summarized in Table 22.1 [8].

In this chapter we will specifically address prevention of opportunistic parasitic infections as it relates to the screening of donors and recipients; diagnosing by epidemiology, symptoms and signs, imaging, and laboratory testing; as well as overall medical and surgical management.

Epidemiology and Prevention

Organ Procurement and Transplantation Network (OPTN) and Centers for Medicare and Medicaid Services policies require donor testing at the bare minimum to include hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), syphilis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and, as of 2017, toxoplasmosis [9]. Blood and urine cultures must also be obtained, and typically sputum and wound culture (if applicable) are also obtained. Unless there is a strong clinical suspicion, parasitic testing is not performed, except in the case of toxoplasmosis IgG.

Critical to screening is a thorough history to include past medical history, history of high-risk behavior, and travel history. In the United States, deceased donor transplantation is overall far more common than living donor, and as a result the screening history may be difficult to fully ascertain. After the procurement and transplant, the Organ Procurement Organization (OPO) continues to receive information about the donor and reports any positive infectious results to the receiving transplant center. Transmission of disease through transplantation is reported to the Disease Transmission Advisory Committee, which is a part of the OPTN, and they implement policies to reduce donor transmission.

The recipient themselves are usually able to provide a full history, but depending on their clinical state, the history may come from family members or hospital charts. Prior to transplantation, laboratory testing is routine as an active or latent infection can cause disastrous complications post-operatively if untreated.

Ultimately preventing a parasitic infection in an organ transplant recipient who is an immunocompromised host requires a comprehensive history from both the donor and recipient, as well as knowledge of epidemiology of parasitic infections in the region.

Within the United States as well as worldwide, there is tremendous variability in prevalence of communicable diseases. There are essentially three components to consider. Firstly, in a region without endemic disease, one needs to assess the donor's travel history in order to discern the likelihood of carrying a parasitic infection. Similarly, the recipient's travel history should also be investigated to ensure they do not have a parasitic infection leading into transplantation, with the subsequent immunosuppression causing clinical compromise. Secondly there are areas in the United States where parasitic infections are more common, and even within the donor and/or recipient hospitals, there may be greater prevalence than nationally. With this information, testing for parasitic infections may be prudent. Finally, worldwide there are known endemic areas for certain parasites and certainly both the donor and recipient should be more thoroughly tested for disease prior to the recipient becoming immunosuppressed after transplantation.

In the United States, there is variability of reporting of parasitic diseases to the Centers for Disease Control and Prevention, so often there are gaps in knowledge as to the true prevalence of disease [10]. Overall, World Health Organization data suggests that the majority of parasitic infections occur in South America, Africa, and Asia with relative sparing of the Northern Hemisphere and Australia [11]. Both organ transplantation in these regions and previous donor travel to high prevalence countries should alert physicians to the increased risk of transmission. For the most part, judgment as to risk of exposure and transmission is made on a case-by-case basis, and often the donor is not screened; instead the recipient is tested if clinical signs warrant suspicion.

Prevention or prophylactic regimens will be discussed in detail as it pertains to specific diseases in the following paragraphs. A generalized premise is that less intensive immunosuppression regimens, balancing rejection vs infection, lead to lower likelihood of infection, and in the event of infection, immunosuppression should be reduced as the disease is treated.

Table 22.2 Reported cases of opportunistic parasitic infections in solid organ transplant recipients

	Total cases	Kidney	Liver	Heart	Lung	Pancreas	Bowel	Multi-organ	Not specified
Toxoplasma gondii	162	**75**	19	55	1	1	1	6	4
Leishmania	151	**127**	13	8	3				
Trypanosoma cruzi	88	20	11	**53**	2			2	
Strongyloides	72	**38**	6	5	2	1	2	5	13
Babesia	5	**4**		1					
Plasmodium	27	**16**	5	2					4
Cryptosporidium	210	**177**	11	1	1		7		13
Microsporidia	77	**50**	10	1	1			3	12

Adapted from Fabiani et al. [12]
Most disease prevalent transplanted organ in **bold**

Other than travel to an endemic area, solid organ transplant recipients may acquire significant parasitic disease via four routes: donor-derived transmission with the graft, transmission through blood products, de novo infection, or reactivation of dormant infection due to immunosuppression. The latter three routes of transmission are applicable to all immunocompromised patients. Table 22.2 shows the current status of parasitic diseases in solid organ recipients that have been reported in the literature [12].

Toxoplasmosis

As discussed above, toxoplasmosis is routinely tested in donors, which is prudent given that over 60 million persons in the United States are chronically infected by *Toxoplasma gondii*, with 1.1 million new infections annually [8]. Worldwide the prevalence of seropositive persons is greater than 50%. Primary or de novo infection is through consumption of raw meat, contact with cat feces, and transplacental transmission.

Donor-derived transmission has been more of a concern in cardiac transplantion due to persistence of encysted toxoplasma in the myocardium that can proliferate and cause necrotizing inflammation in the immunosuppressed recipient and can become disseminated in seronegative recipients as they do not have toxoplasmosis-specific immunity [13]. Blood transfusion and reactivation of latent infection are rare.

There is a wide range of symptoms and outcomes for toxoplasmosis. The disease can manifest with nonspecific symptoms of fever and general malaise or with severe manifestations including retinochoroiditis (Fig. 22.1) [8], myocarditis, encephalitis, pneumonitis, and multiorgan failure [13–18]. The symptoms and signs correspond to the organ affected, and often the suspicion for toxoplasmosis is made as a diagnosis of exclusion in non-endemic areas or if the donor was known to be seronegative. The majority of donor-derived disease occurs within the first 3 months post-transplant where immunosuppression is at its highest [19], whereas

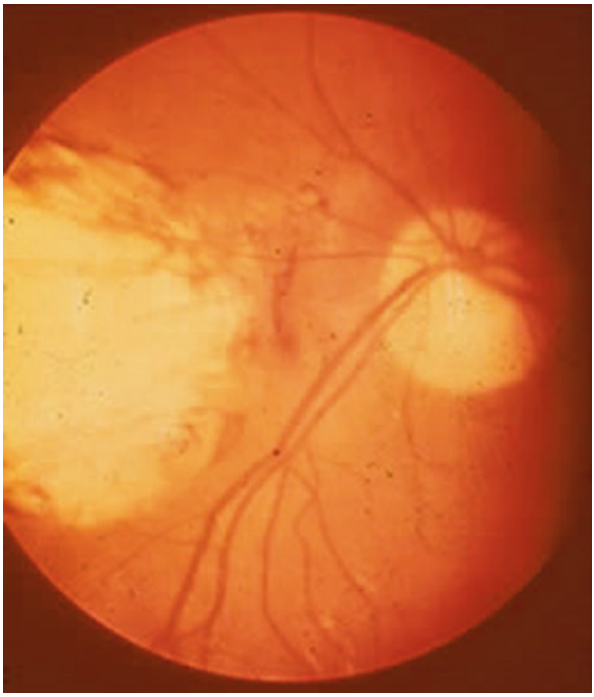

Fig. 22.1 Ocular toxoplasmosis (CDC)

reactivation or de novo infection occurs later after transplant, usually after Bactrim (TMP-SMX), commonly used for prophylaxis against pneumocystis pneumonia, is discontinued or the recipient has had rejection and required more intensive immunosuppressive therapy [20].

Diagnosis of infection is commonly made by toxoplasma PCR testing [21]. PCR of cerebrospinal fluid and bronchial lavage fluid can establish disease. In the case of organ failure, positive PCR of blood is suspicious for disseminated disease. ELISA testing of serum anti-*T. gondii* IgG/IgM can show seroconversion, indicating infection or reactivation. However, seroconversion that occurs in seronegative recipients doesn't necessarily indicate active disease, and conversely early infection in severely immunosuppressed patients may not result in seroconversion [22]. Identification of parasites in a biopsy sample is the definitive method of diagnosis, and this can be obtained from tissue such as the myocardium or from fluid, blood, or bone marrow [13].

Multiple regimens are available for treatment of toxoplasmosis with an oral regimen of pyrimethamine and sulfadiazine being first line [23]. Depending on absorption profiles, intravenous clindamycin and intravenous TMP-SMX is also an option.

Avoiding new infection after transplant can be as simple as avoiding cat litter and eating undercooked meat. However, the mainstay has been prophylactic treatment with TMP-SMX. In general, the main indication for TMP-SMX post-transplant is prevention of *Pneumocystis jirovecii* and at the very least is for 3 months. There are recommendations for longer duration in centers with higher incidence of

pneumocystis pneumonia, in endemic areas of toxoplasmosis, and in recipients who underwent treatment for acute rejection, as the higher doses of immunosuppression increase risk of opportunistic infections [24].

Leishmaniasis

Leishmania parasites are spread by sandflies and affect individuals in almost 100 countries. Worldwide the prevalence of leishmaniasis is around 12 million with approximately 2 million new infections annually (Fig. 22.2) [11]. Most cases in the United States reflect travel and immigration patterns.

There are three major clinical manifestations of disease [25]. Cutaneous disease is the most common form and usually occurs as a painless skin sore within a few weeks of the sandfly bite. Mucocutaneous disease occurs when there is spread from the skin into mucosal surfaces. The most severe form is visceral disease that affects the liver and spleen primarily and develops within months. Other manifestations of visceral disease include pancytopenia.

Cutaneous disease in transplant patients is rare, though reactivation can occur in T-cell-depleted patients as well as primary infection in endemic regions [26]. Most cases reported in the literature are that of visceral disease though this is also uncommon [27]. Most patients are renal transplant recipients, and the highest prevalence is seen in Italian transplant recipients [28, 29]. There is sparse literature describing donor-derived disease. Generally, reactivation occurs within 18 months, especially within the first 3 months when immunosuppression is most intense [29]. Infection after 18 months is usually de novo infection [30].

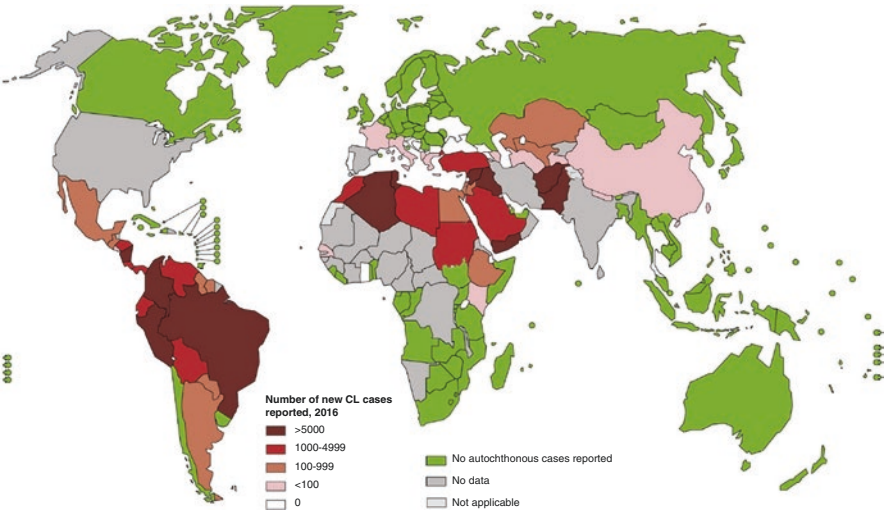

Fig. 22.2 Status of endemicity of leishmaniasis worldwide, 2016. (Adapted from WHO data)

Diagnosis of visceral disease is made by direct examination of the amastigotes parasite in bone marrow and spleen aspirates [29]. PCR and immunoassay can be used to identify disease of early onset [31].

Visceral disease is fatal if not treated expeditiously. Liposomal amphotericin B is the recommended treatment with a 95% cure rate in the immunocompetent patient and 84% cure rate in transplant recipients [32]. Miltefosine is an oral agent with excellent cure rates that can also be used [33]. Though there is no recommended primary prophylaxis, secondary prophylaxis is considered in relapses secondary to high-intensity immunosuppressive regimens.

There is no recommended donor screening, and recipient screening is not routine but should be considered in recipients who have traveled to endemic areas. Prevention of primary disease or de novo disease in endemic areas can be aided by use of insecticide netting and treating dogs, which are a large reservoir for disease.

Chagas Disease

At least 300,000 persons are infected with *Trypanosoma cruzi* (*T. cruzi*) in the United States, and more than 300 infected babies are born yearly [8]. *T. cruzi* leads to Chagas disease. Given this is a disease commonly seen in Latin America, estimates are based on migration patterns with the majority of cases seen in areas with a high Latin population. Infection is generally spread from a triatomine bite, though transfusion-related infection is increasingly more common.

In the United States, donor-derived infection has been observed in the rare instance where *T. cruzi* seropositive donor organs have been transplanted [34–38]. Infection is less common in liver and kidney recipients, compared to cardiac recipients. In Latin America, seropositive donors are routinely used for noncardiac transplants with acceptable outcomes [35].

Acute infection is generally self-limited, and patients are asymptomatic. Clinical manifestations can range from chagoma, fever, hepatosplenomegaly, lymphadenitis, to life-threatening encephalitis and myocarditis [39]. After an initial phase, 8–12 weeks later, individuals enter a chronic phase with approximately 60–70% remaining asymptomatic with 30–40% developing cardiomyopathy, megaesophagus (Fig. 22.3) [8], or megacolon over the course of 10–30 years due to repeated episodes of inflammation and fibrosis.

End-stage cardiomyopathy from Chagas disease is an indication for cardiac transplantation, and outcomes are excellent in these patients [40]. Though the risk of reactivation has been as high as 43%, advances in immunosuppression have improved these rates [41]. Currently cyclosporine and mycophenolate mofetil (MMF) have been reported to increase rate of reactivation [42, 43]. The rate of reactivation in liver and kidney transplant patients is approximately 20%, and again MMF has been shown to be a risk factor, as well as patients who receive intense immunosuppression, often following treatment of rejection episodes [44, 45].

Microscopic examination of anticoagulated blood, CSF or tissue biopsy, or blood smears stained with Giemsa can identify the *T. cruzi* parasite. Further breakdown of species and acute disease can be identified by PCR or immunoassay assessment [46].

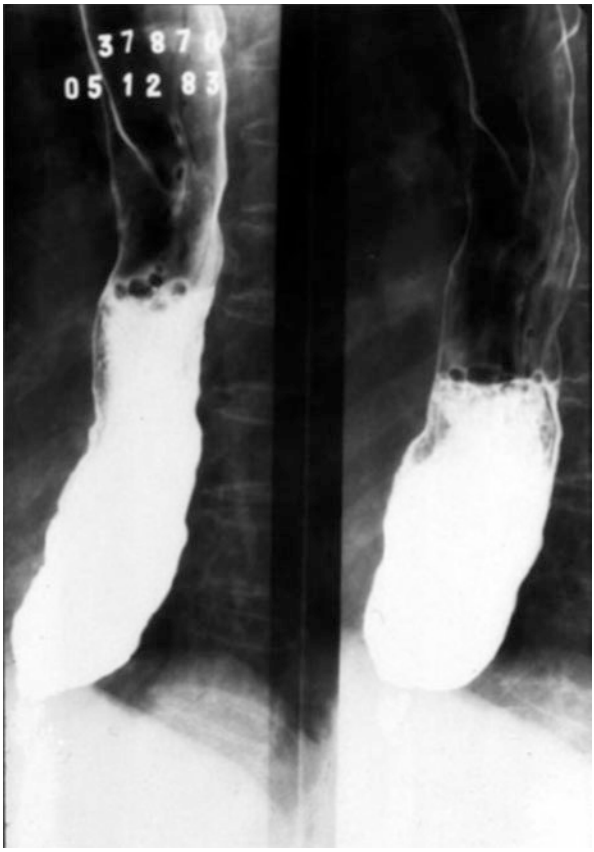

Fig. 22.3 Chagas megaesophagus (CDC)

Benznidazole and nifurtimox are the first- and second-line therapies, respectively, for acute disease with a 70% cure rate [47]. Given the toxicity associated with treatment, prophylaxis is not recommended for seropositive recipients pretransplant nor for recipients who received organs from a seropositive donor [48].

There is no routine screening of donors or recipients for *T. cruzi* in the United States, but those with a history of travel or receiving a blood transfusion in an endemic region should be tested. In Latin America, donor and recipient testing is routine. The use of insecticides and screening donated blood for disease can reduce incidence of de novo disease.

Strongyloidiasis

The global prevalence of strongyloidiasis is unknown but is estimated to be as high as 100 million persons [8]. Infection is most commonly encountered in the tropical climates and is associated with low socioeconomic status, institutionalization, rural areas, and agricultural activities. Infection occurs by contact with contaminated soil.

In immunocompromised patients, hyperinfection can exist due to persistent autoinoculation of *Strongyloides* and subsequent reactivation [49, 50]. Donor-derived transmission is rare but has been reported [51].

Strongyloidiasis can present with vague gastrointestinal symptoms, but accelerated autoinfection can result in 50% mortality with symptoms and signs of bloody diarrhea, ileus, and pneumatosis. Seeding from the GI tract or lungs can result in high fatality disseminated disease leading to sepsis or meningitis [52, 53]. Recipients are at highest risk of infections within the first 3 months of transplant, secondary to intense therapy post-transplant or due to treatment of rejection.

Stool, sputum, urine, and duodenal aspirates can be tested for the larvae, and often multiple samples are needed for diagnosis. Skin biopsies can be obtained if there are petechia and purpura. Serological testing for *Strongyloides* is sensitive but not specific due to cross-reactivity with other parasites [54, 55].

Treatment of disease is dependent on severity. A single oral dose of ivermectin or seven days of oral albendazole is usually sufficient, with repeat stool or sputum testing in 2 weeks to ensure clearance [56]. Treatment of hyperinfection and disseminated disease requires daily ivermectin until stool or sputum are tested negative for 2 weeks [57]. It is especially important to taper steroids rapidly and reduce immunosuppression during anti-*Strongyloides* therapy. Studies have shown that cyclosporin has a parasiticidal affect and may be considered in place of tacrolimus [58].

Recipient and donor screening should be considered in endemic areas and associated travel. Patients with known history of human T lymphocytic virus should also be screened given the strong association and the devastating consequences of hyperinfection [59]. Avoidance of travel post-transplant to endemic areas, proper hygiene, and avoidance of walking barefoot on soil can reduce de novo infection.

Babesiosis

Babesia is the rare opportunistic parasite more common in the United States and Europe than in the developing world [8]. Babesia is not routinely reported in the United States, in fact only 31 states reported cases in 2014, and these were most commonly in the Northeastern United States (Fig. 22.4) [8]. Babesia is generally spread by ticks but in transplant patients has been more frequently reported transmitted by transfusion [60].

Patients with babesiosis are often asymptomatic or have vague flu-like symptoms [61]. However, transplant patients and especially those who are asplenic can have potentially devastating disease, with manifestations including hemolytic anemia, impaired graft function, hemophagocytic syndrome, disseminated intravascular coagulation, and congestive heart failure [62].

Diagnosis of babesiosis is made by peripheral blood smear testing, which identifies babesia parasites in red blood cells, though PCR is increasingly being used [63].

Treatment consists of dual therapy. In mild to moderate cases, oral atovaquone and azithromycin can be used for a 7-day course. In severe disease clindamycin and quinine are first-line therapy [64]. Exchange transfusion can also be utilized to remove infected blood.

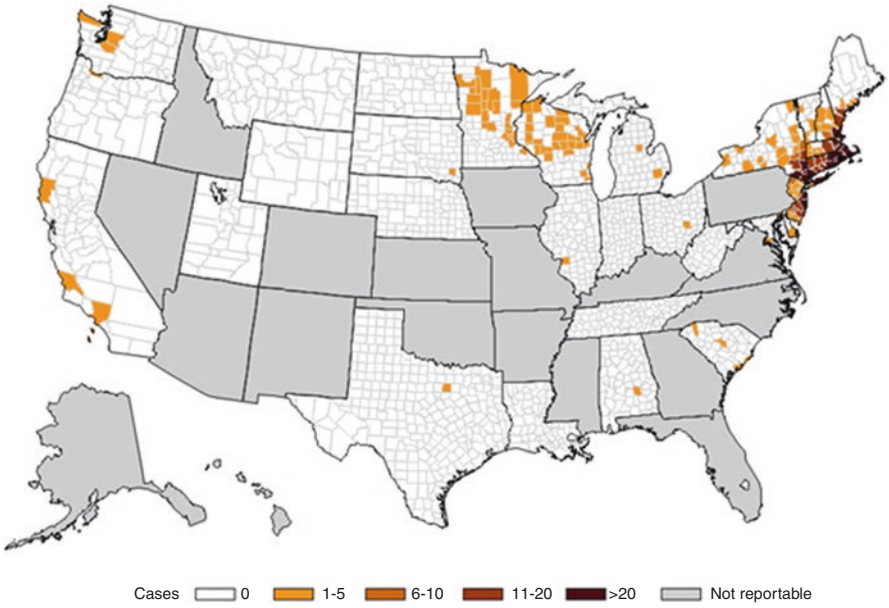

Fig. 22.4 Number of reported cases of babesiosis, by county of residence, 2014 (CDC)

There is no routine screening of donors or recipients as fewer than five cases of graft- or transfusion-related infection have been reported. Avoidance of areas endemic to ticks post-transplant is recommended as well as general caution to avoid tick bites.

Malaria

Though a major cause of morbidity and mortality worldwide, there have been rare instances of malaria in transplant recipients [65]. Primary infection is predominantly through the graft or transfusion, but de novo infection has been reported [66]. Reactivation of malaria is exceedingly rare. *Plasmodium vivax* usually is more benign with late onset compared to *Plasmodium falciparum*.

The disease course can be severe in transplant recipients, with symptoms including pyrexia, hemolytic anemia, and thrombocytopenia [67–70]. The disease can be fatal in liver transplant recipients, unsurprising as the allograft is a reservoir for parasitized hepatocytes which leads to early-onset disease with high-level parasitemia.

The gold standard for diagnosis is assessment of blood smears for the parasite. Antigen testing and PCR can also be used for low parasitemia [71]. Serology can be used for assessing past exposure.

Treatment of malaria in recipients can be difficult due to hepatoxicity associated with amodiaquine and sulfadoxine-pyrimethamine, as well as interactions with quinine and calcineurin inhibitors [72]. Uncomplicated *P. falciparum* can be treated

with artemisinin combinations or atovaquone-proguanil [8, 11, 72]. Severe *P. falciparum* requires intravenous artesunate or quinidine. Other strains of plasmodium can be treated with chloroquine.

There is no routine screening of donors or recipients, but there should be increased suspicion in patients from endemic areas. Routine malaria prophylaxis is not advocated, and usual avoidance of endemic areas and general care including insecticides and mosquito nets are recommended.

Alimentary Protozoa

Intestinal parasites are common in the general public and in transplant recipients. Cryptosporia and microsporidia are opportunistic in immunosuppressed patients.

Cryptosporidium is transmitted through contaminated water. The ensuing diarrhea and malabsorption can be lethal in immunocompromised patients. Diarrhea is commonly seen in transplant recipients secondary to antibiotics use and clostridium difficile or immunosuppressant side effects, but *Cryptosporidium* should be part of the differential diagnosis in the appropriate setting. Sclerosing cholangitis is another devastating manifestation that occurs in renal and liver transplant recipients and often requires surgical intervention [73, 74]. Diagnosis is made by acid fast staining of stool cysts and ELISA assessment of antigens [75, 76]. There is no optimal therapy, though nitazoxanide has been approved [77, 78]. Also, of note, tacrolimus levels have to be carefully monitored secondary to impaired intestinal absorption [79]. Cryptosporidium is not passed through blood, and as such most cases of infection are de novo infection from recipients drinking contaminated water or in contact with animal feces.

Microsporidiosis has been encountered in all solid organ transplants but has been most frequently described following renal transplant [80–85]. Disseminated disease is fatal in up to one third of patients, with CNS manifestations, cholangitis, and abdominal pain. Diagnosis is made by trichrome staining of stool or urine for spores [86, 87]. Immunofluorescence can be used for identifying species as the most common species *Enterocytozoon bieneusi* is mostly resistant to treatment [88, 89]. A combination of albendazole, metronidazole, and immunosuppression reduction has been used to treat all forms of infection [90].

Case Study

Schistosomiasis is not an opportunistic infection, and the trematodes that cause disease are not found in the United States. However, continuing the discussion of donor testing, we present an interesting case of intestinal schistosomiasis found during organ procurement [91]. The donor was a 25-year-old man, born in South America, who had been in a good state of health without any significant past medical history, who suffered a ventricular fibrillation arrest. Full work-up including blood testing with positive antibodies to CMV and EBV and negative for syphilis, HIV types 1 and 2, human T-lymphotropic virus (HTLV) types I and II, HCV, and HBV. Cardiac

catheterization, abdominal imaging, and end-organ perfusion and functional parameters were satisfactory to pursue recovery of the heart, lungs, liver, kidneys, and pancreas for organ transplantation.

After meeting criteria for brain death testing on hospital day 9, the patient was taken to the operating room on hospital day 11. During the recovery it was noted that there was abnormal thickening of the cecum and ascending colon. Correlation to imaging obtained preoperatively had suggested some thickened haustral folds, consistent with colitis. Though this was noted in the early mobilization, the decision was made to continue with the organ recovery before reevaluating the colon at the end of the case, so as to reduce risk of intestinal contamination. After all the organs to be transplanted had been recovered, the procuring surgeon obtained a full-thickness biopsy of the cecum with the concern for possible cancer or infection. The biopsy (Fig. 22.5) showed ova with lateral and terminal spines consistent with mixed species infection of schistosomes.

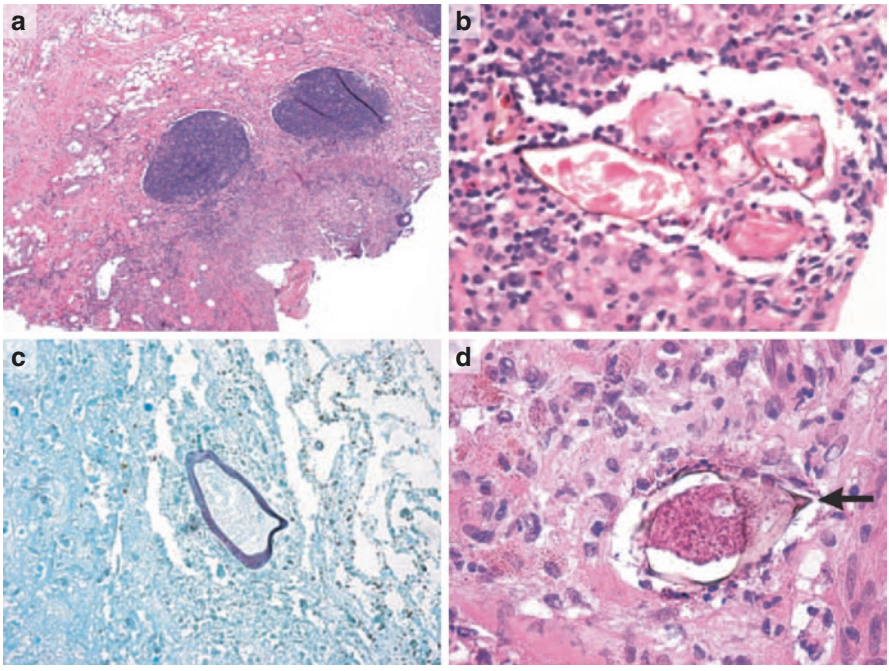

Fig. 22.5 Colon biopsy specimen (NEJM). An excisional biopsy of the cecum shows ischemic ulceration of the bowel wall (Panel **a**, hematoxylin and eosin). The cecal mucosa shows numerous circumoval granulomas with refractile ova (approximately 150 μm in length) surrounded by epithelioid histiocytes, plasma cells, and eosinophils (Panel **b**, hematoxylin and eosin). One ovum has lateral spines, which is morphologically consistent with the egg of *Schistosoma mansoni* (Panel **c**, Fite method). An ovum with a well-developed terminal spine (Panel **d**, arrow, hematoxylin and eosin) is consistent with the egg of *S. haematobium* or *S. intercalatum*

Urgent consultation was held with the infectious disease team and the OPO by the surgical teams. Of concern were the findings of active colitis presumed secondary to schistosomiasis. Adult schistosomes do not replicate within the human host, because they need snails to serve as the intermediate host. There was a concern about the transmission of nonreplicating adult worms, because they sometimes crawl into surgical sites and disrupt critical anastomoses. However, it was reassuring that a liver biopsy during the recovery showed no evidence of hepatic schistosomes.

We were not privy to the decision-making thoughts of the other teams, but our intended recipient was a patient with liver and kidney failure, with a model for end liver disease score of 30, requiring both a liver and a kidney transplant. We made the decision that the likelihood of death from liver disease was greater than the risk of infection and sequela of infection. In fact, all surgeons involved accepted all the organs despite the findings of intestinal schistosomiasis. Our recipient did well and was treated with praziquantel 20 mg/kg BID on post-operative days 1, 2, 3, 18, and 42.

Testings for *T. cruzi* and *Strongyloides* were subsequently done in the donor and were negative. However this case illustrates the lower threshold to test for parasites in patients with a history of foreign travel or birth in areas endemic of disease as well as the fastidious nature of the procuring surgeon in a time-consuming and time-sensitive operation involving multiple teams.

Conclusion

There are several opportunistic infections that can occur and cause severe morbidity and mortality in the immunocompromised host. Testing for and prophylaxis against disease is similar in various immunocompromised conditions. However, for transplantation surgery, there should also be stringent donor and recipient testing when a history is suspicious for possible transmission or de novo infection. The OPO, infectious disease teams, and donor hospital policies often dictate what tests are obtained, but this is evolving and ultimately should be tailored to the donor as necessary with the transplant team also tailoring testing of the recipient as appropriate to decrease and prevent parasitic infections in the immunocompromised host.

References

1. National Institute of Health. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunocompromised.
2. Buckley RH. Humoral immunodeficiency. Clin Immunol Immunopathol. 1986;40(1):13–24.
3. Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev. 2010;23(4):740–80.
4. Edgar JD. T cell immunodeficiency. J Clin Pathol. 2008;61(9):988–93.
5. Simmons RL, Balfour HH, Lopez C, Mauer SM, Kjellstrand CM, Buselmeier TJ, et al. Infection in immunosuppressed transplant recipients. Surg Clin North Am. 1975;55(6):1419–30.

6. van Sandwijk MS, Bemelman FJ, Ten Berge IJ. Immunosuppressive drugs after solid organ transplantation. Neth J Med. 2013;71(6):281–9.
7. Fishman JA. Infection in organ transplantation. Am J Transplant. 2017;17(4):856–79.
8. CDC. Available from: https://www.cdc.gov/parasites/az/index.html.
9. OPTN. Available from: https://optn.transplant.hrsa.gov › media › optn_policies.
10. Parise ME, Hotez PJ, Slutsker L. Neglected parasitic infections in the United States: needs and opportunities. Am J Trop Med Hyg. 2014;90(5):783–5.
11. WHO. Available from: https://www.who.int/neglected_diseases/en/.
12. Fabiani S, Fortunato S, Bruschi F. Solid organ transplant and parasitic diseases: a review of the clinical cases in the last two decades. Pathogens. 2018;7(3):65.
13. Petty LA, Qamar S, Ananthanarayanan V, Husain AN, Murks C, Potter L, et al. Cardiac toxoplasmosis after heart transplantation diagnosed by endomyocardial biopsy. Transpl Infect Dis. 2015;17(5):719–22.
14. Eza DE, Lucas SB. Fulminant toxoplasmosis causing fatal pneumonitis and myocarditis. HIV Med. 2006;7(6):415–20.
15. Petersen E, Kijlstra A, Stanford M. Epidemiology of ocular toxoplasmosis. Ocul Immunol Inflamm. 2012;20(2):68–75.
16. Mastrobuoni S, Dell'aquila AM, Herreros J. Fatal toxoplasma gondii dissemination in a heart transplant recipient: description of a case. Case Rep Transplant. 2012;2012:524279.
17. Aksoy A, Tanir G, Ozkan M, Oguz M, Yildiz YT. Acute disseminated encephalomyelitis associated with acute toxoplasma gondii infection. Pediatr Neurol. 2013;48(3):236–9.
18. Suvisaari J, Torniainen-Holm M, Lindgren M, Harkanen T, Yolken RH. Toxoplasma gondii infection and common mental disorders in the Finnish general population. J Affect Disord. 2017;223:20–5.
19. Campbell AL, Goldberg CL, Magid MS, Gondolesi G, Rumbo C, Herold BC. First case of toxoplasmosis following small bowel transplantation and systematic review of tissue-invasive toxoplasmosis following noncardiac solid organ transplantation. Transplantation. 2006;81(3):408–17.
20. Baden LR, Katz JT, Franck L, Tsang S, Hall M, Rubin RH, et al. Successful toxoplasmosis prophylaxis after orthotopic cardiac transplantation with trimethoprim-sulfamethoxazole. Transplantation. 2003;75(3):339–43.
21. Patrat-Delon S, Gangneux JP, Lavoue S, Lelong B, Guiguen C, le Tulzo Y, et al. Correlation of parasite load determined by quantitative PCR to clinical outcome in a heart transplant patient with disseminated toxoplasmosis. J Clin Microbiol. 2010;48(7):2541–5.
22. Botterel F, Ichai P, Feray C, Bouree P, Saliba F, Tur Raspa R, et al. Disseminated toxoplasmosis, resulting from infection of allograft, after orthotopic liver transplantation: usefulness of quantitative PCR. J Clin Microbiol. 2002;40(5):1648–50.
23. Fernandez-Sabe N, Cervera C, Farinas MC, Bodro M, Munoz P, Gurgui M, et al. Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. Clin Infect Dis. 2012;54(3):355–61.
24. Martin SI, Fishman JA, AST Infectious Diseases Community of Practice. Pneumocystis pneumonia in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):272–9.
25. Vieira-Goncalves R, Pirmez C, Jorge ME, Souza WJ, Oliveira MP, Rutowitsch MS, et al. Clinical features of cutaneous and disseminated cutaneous leishmaniasis caused by Leishmania (Viannia) braziliensis in Paraty, Rio de Janeiro. Int J Dermatol. 2008;47(9):926–32.
26. Roustan G, Jimenez JA, Gutierrez-Solar B, Gallego JL, Alvar J, Patron M. Post-kala-azar dermal leishmaniasis with mucosal involvement in a kidney transplant recipient: treatment with liposomal amphotericin B. Br J Dermatol. 1998;138(3):526–8.
27. Moroni G, Bossi L. Don't forget visceral leishmaniasis in transplant patients. Nephrol Dial Transplant. 1995;10(4):563–4.
28. Basset D, Faraut F, Marty P, Dereure J, Rosenthal E, Mary C, et al. Visceral leishmaniasis in organ transplant recipients: 11 new cases and a review of the literature. Microbes Infect. 2005;7(13):1370–5.

29. Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. Lancet Infect Dis. 2008;8(3):191–9.
30. Veroux M, Corona D, Giuffrida G, Cacopardo B, Sinagra N, Tallarita T, et al. Visceral leishmaniasis in the early post-transplant period after kidney transplantation: clinical features and therapeutic management. Transpl Infect Dis. 2010;12(5):387–91.
31. Gatti S, Gramegna M, Klersy C, Madama S, Bruno A, Maserati R, et al. Diagnosis of visceral leishmaniasis: the sensitivities and specificities of traditional methods and a nested PCR assay. Ann Trop Med Parasitol. 2004;98(7):667–76.
32. Martin-Davila P, Fortun J, Lopez-Velez R, Norman F. Montes de Oca M, Zamarron P, et al. transmission of tropical and geographically restricted infections during solid-organ transplantation. Clin Microbiol Rev. 2008;21(1):60–96.
33. Sunyoto T, Potet J, Boelaert M. Why miltefosine-a life-saving drug for leishmaniasis-is unavailable to people who need it the most. BMJ Glob Health. 2018;3(3):e000709.
34. Salvador F, Sanchez-Montalva A, Sulleiro E, Berastegui C, Jauregui A, Pont T, et al. Case report: successful lung transplantation from a donor seropositive for Trypanosoma cruzi infection (Chagas disease) to a seronegative recipient. Am J Trop Med Hyg. 2017;97(4):1147–50.
35. Goldaracena N, Wolf MM, Quinonez E, Anders M, Mastai R, McCormack L. Is it safe to use a liver graft from a Chagas disease-seropositive donor in a human immunodeficiency virus-positive recipient? A case report addressing a novel challenge in liver transplantation. Liver Transpl. 2012;18(8):979–83.
36. Corey AB, Sonetti D, Maloney JD, Montgomery SP, Rademacher BL, Taylor LJ, et al. Transmission of donor-derived Trypanosoma cruzi and subsequent development of Chagas disease in a lung transplant recipient. Case Rep Infect Dis. 2017;2017:5381072.
37. Bryan CF, Tegtmeier GE, Rafik N, Markham LE, Murillo D, Nelson PW, et al. The risk for Chagas' disease in the Midwestern United States organ donor population is low. Clin Transpl. 2004;18(Suppl 12):12–5.
38. Amato Neto V, Matsubara L, Uip DE, Strabelli TM, Bocchi EA, Stolf NA, et al. Heart transplantation: donor with Chagas' disease and clinical course of the receptor. Rev Hosp Clin Fac Med Sao Paulo. 1992;47(2):92–4.
39. Teixeira AR, Nitz N, Guimaro MC, Gomes C, Santos-Buch CA. Chagas disease. Postgrad Med J. 2006;82(974):788–98.
40. Bestetti RB, Theodoropoulos TA. A systematic review of studies on heart transplantation for patients with end-stage Chagas' heart disease. J Card Fail. 2009;15(3):249–55.
41. Campos SV, Strabelli TM, Amato Neto V, Silva CP, Bacal F, Bocchi EA, et al. Risk factors for Chagas' disease reactivation after heart transplantation. J Heart Lung Transplant. 2008;27(6):597–602.
42. Salvador F, Sanchez-Montalva A, Valerio L, Serre N, Roure S, Trevino B, et al. Immunosuppression and Chagas disease; experience from a non-endemic country. Clin Microbiol Infect. 2015;21(9):854–60.
43. Inga LAC, Olivera MJ. Reactivation of Chagas disease in a heart transplant patient infected by sylvatic Trypanosoma cruzi discrete typing unit I. Rev Soc Bras Med Trop. 2019;52:e20180512.
44. Riarte A, Luna C, Sabatiello R, Sinagra A, Schiavelli R, De Rissio A, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. Clin Infect Dis. 1999;29(3):561–7.
45. Chagas' Disease Argentine Collaborative Transplant Consortium, Casadei D. Chagas' disease and solid organ transplantation. Transplant Proc. 2010;42(9):3354–9.
46. Bern C. Chagas disease in the immunosuppressed host. Curr Opin Infect Dis. 2012;25(4):450–7.
47. Bern C. Antitrypanosomal therapy for chronic Chagas' disease. N Engl J Med. 2011;364(26):2527–34.
48. Aldasoro E, Posada E, Requena-Mendez A, Calvo-Cano A, Serret N, Casellas A, et al. What to expect and when: benznidazole toxicity in chronic Chagas' disease treatment. J Antimicrob Chemother. 2018;73(4):1060–7.

49. Dada-Adegbola HO, Oluwatoba OA, Bakare RA. Strongyloidiasis: prevalence, risk factors, clinical and laboratory features among diarrhea patients in Ibadan Nigeria. Afr J Med Med Sci. 2010;39(4):285–92.
50. Hira PR, Al-Ali F, Shweiki HM, Abdella NA, Johny M, Francis I, et al. Strongyloidiasis: challenges in diagnosis and management in non-endemic Kuwait. Ann Trop Med Parasitol. 2004;98(3):261–70.
51. Nordheim E, Olafsson Storro M, Natvik AK, Birkeland Kro G, Midtvedt K, Varberg Reisaeter A, et al. Donor-derived strongyloidiasis after organ transplantation in Norway. Transpl Infect Dis. 2019;21(1):e13008.
52. Khuroo MS. Hyperinfection strongyloidiasis in renal transplant recipients. BMJ Case Rep. 2014;2014.
53. Roxby AC, Gottlieb GS, Limaye AP. Strongyloidiasis in transplant patients. Clin Infect Dis. 2009;49(9):1411–23.
54. Dacal E, Saugar JM, Soler T, Azcarate JM, Jimenez MS, Merino FJ, et al. Parasitological versus molecular diagnosis of strongyloidiasis in serial stool samples: how many? J Helminthol. 2018;92(1):12–6.
55. Gottardi M, Paula FM, Corral MA, Meisel DM, Costa SF, Abdala E, et al. Immunofluorescence assay for diagnosis of strongyloidiasis in immunocompromised patients. Infect Dis (Lond). 2015;47(8):550–4.
56. Repetto SA, Ruybal P, Batalla E, Lopez C, Fridman V, Sierra M, et al. Strongyloidiasis outside endemic areas: long-term parasitological and clinical follow-up after Ivermectin treatment. Clin Infect Dis. 2018;66(10):1558–65.
57. Moura EB, Maia Mde O, Ghazi M, Amorim FF, Pinhati HM. Salvage treatment of disseminated strongyloidiasis in an immunocompromised patient: therapy success with subcutaneous ivermectin. Braz J Infect Dis. 2012;16(5):479–81.
58. Palau LA, Pankey GA. Strongyloides hyperinfection in a renal transplant recipient receiving cyclosporine: possible strongyloides stercoralis transmission by kidney transplant. Am J Trop Med Hyg. 1997;57(4):413–5.
59. Salvador F, Sulleiro E, Piron M, Sanchez-Montalva A, Sauleda S, Molina I. Seroprevalence of Strongyloides stercoralis infection among HTLV-I infected blood donors in Barcelona, Spain: a cross-sectional study. Acta Trop. 2017;176:412–4.
60. Munoz P, Valerio M, Eworo A, Bouza E. Parasitic infections in solid-organ transplant recipients. Curr Opin Organ Transplant. 2011;16(6):565–75.
61. Moniuszko-Malinowska A, Swiecicka I, Dunaj J, Zajkowska J, Czupryna P, Zambrowski G, et al. Infection with Babesia microti in humans with non-specific symptoms in north East Poland. Infect Dis (Lond). 2016;48(7):537–43.
62. Gubernot DM, Lucey CT, Lee KC, Conley GB, Holness LG, Wise RP. Babesia infection through blood transfusions: reports received by the US Food and Drug Administration, 1997-2007. Clin Infect Dis. 2009;48(1):25–30.
63. Souza SS, Bishop HS, Sprinkle P, Qvarnstrom Y. Comparison of Babesia microti real-time polymerase chain reaction assays for confirmatory diagnosis of Babesiosis. Am J Trop Med Hyg. 2016;95(6):1413–6.
64. Krause PJ. Human babesiosis. Int J Parasitol. 2019;49(2):165–74.
65. Fischer L, Sterneck M, Claus M, Costard-Jackle A, Fleischer B, Herbst H, et al. Transmission of malaria tertiana by multi-organ donation. Clin Transpl. 1999;13(6):491–5.
66. Pierrotti LC, Levi ME, Di Santi SM, Segurado AC, Petersen E. Malaria disease recommendations for solid organ transplant recipients and donors. Transplantation. 2018;102(2S Suppl 2):S16–26.
67. Rodriguez M, Tome S, Vizcaino L, Fernandez-Castroagudin J, Otero-Anton E, Molina E, et al. Malaria infection through multiorgan donation: an update from Spain. Liver Transpl. 2007;13(9):1302–4.
68. Alkhunaizi AM, Al-Tawfiq JA, Al-Shawaf MH. Transfusion-transmitted malaria in a kidney transplant recipient. How safe is our blood transfusion? Saudi Med J. 2008;29(2):293–5.
69. Lee PC, Lee PY, Lei HY, Chen FF, Tseng JY, Ching YT. Malaria infection in kidney transplant recipients. Transplant Proc. 1994;26(4):2099–100.

70. Mejia GA, Alvarez CA, Pulido HH, Ramirez B, Cardozo C, Suarez Y, et al. Malaria in a liver transplant recipient: a case report. Transplant Proc. 2006;38(9):3132–4.
71. Tangpukdee N, Duangdee C, Wilairatana P, Krudsood S. Malaria diagnosis: a brief review. Korean J Parasitol. 2009;47(2):93–102.
72. Cheaveau J, Marasinghe D, Akakpo S, Deardon R, Naugler C, Chin A, et al. The impact of malaria on liver enzymes: a retrospective cohort study (2010–2017). Open Forum Infect Dis. 2019;6(6):ofz234.
73. Denkinger CM, Harigopal P, Ruiz P, Dowdy LM. Cryptosporidium parvum-associated sclerosing cholangitis in a liver transplant patient. Transpl Infect Dis. 2008;10(2):133–6.
74. Abdo A, Klassen J, Urbanski S, Raber E, Swain MG. Reversible sclerosing cholangitis secondary to cryptosporidiosis in a renal transplant patient. J Hepatol. 2003;38(5):688–91.
75. Abdel Gawad SS, Ismail MAM, Imam NFA, Eassa AHA, Abu-Sarea EY. Detection of Cryptosporidium spp. in diarrheic immunocompetent patients in Beni-Suef, Egypt: insight into epidemiology and diagnosis. Korean J Parasitol. 2018;56(2):113–9.
76. Santana BN, Kurahara B, Nakamura AA, da Silva CV, Ferrari ED, da Silva GS, et al. Detection and characterization of Cryptosporidium species and genotypes in three chicken production systems in Brazil using different molecular diagnosis protocols. Prev Vet Med. 2018;151:73–8.
77. Rossignol JF, Kabil SM. el-Gohary Y, Younis AM. Effect of nitazoxanide in diarrhea and enteritis caused by Cryptosporidium species. Clin Gastroenterol Hepatol. 2006;4(3):320–4.
78. Sparks H, Nair G, Castellanos-Gonzalez A, White AC Jr. Treatment of Cryptosporidium: what we know, gaps, and the way forward. Curr Trop Med Rep. 2015;2(3):181–7.
79. Bonatti H, Barroso LF 2nd, Sawyer RG, Kotton CN, Sifri CD. Cryptosporidium enteritis in solid organ transplant recipients: multicenter retrospective evaluation of 10 cases reveals an association with elevated tacrolimus concentrations. Transpl Infect Dis. 2012;14(6):635–48.
80. Deltombe C, Lefebvre M, Morio F, et al. Cryptosporidiosis and microsporidiosis as causes of diarrhea in kidney and/or pancreas transplant recipients [published online ahead of print, 2019 Aug 28]. Med Mal Infect. 2019;S0399-077X(18)30713–3. https://doi.org/10.1016/j.medmal.2019.07.010.
81. Nagpal A, Pritt BS, Lorenz EC, Amer H, Nasr SH, Cornell LD, et al. Disseminated microsporidiosis in a renal transplant recipient: case report and review of the literature. Transpl Infect Dis. 2013;15(5):526–32.
82. Galvan AL, Sanchez AM, Valentin MA, Henriques-Gil N, Izquierdo F, Fenoy S, et al. First cases of microsporidiosis in transplant recipients in Spain and review of the literature. J Clin Microbiol. 2011;49(4):1301–6.
83. Mohindra AR, Lee MW, Visvesvara G, Moura H, Parasuraman R, Leitch GJ, et al. Disseminated microsporidiosis in a renal transplant recipient. Transpl Infect Dis. 2002;4(2):102–7.
84. Guerard A, Rabodonirina M, Cotte L, Liguory O, Piens MA, Daoud S, et al. Intestinal microsporidiosis occurring in two renal transplant recipients treated with mycophenolate mofetil. Transplantation. 1999;68(5):699–707.
85. Sax PE, Rich JD, Pieciak WS, Trnka YM. Intestinal microsporidiosis occurring in a liver transplant recipient. Transplantation. 1995;60(6):617–8.
86. Matos O, Lobo ML, Antunes F. Methodology of the diagnosis of microsporidiosis in urine and pulmonary specimens from AIDS patients. J Eukaryot Microbiol. 2001;Suppl:69S–70S.
87. Sianongo S, McDonald V, Kelly P. A method for diagnosis of microsporidiosis adapted for use in developing countries. Trans R Soc Trop Med Hyg. 2001;95(6):605–7.
88. Saffo Z, Mirza N. Successful treatment of Enterocytozoon bieneusi gastrointestinal infection with nitazoxanide in a immunocompetent patient. IDCases. 2019;18:e00586.
89. Alfa Cisse O, Ouattara A, Thellier M, Accoceberry I, Biligui S, Minta D, et al. Evaluation of an immunofluorescent-antibody test using monoclonal antibodies directed against Enterocytozoon bieneusi and Encephalitozoon intestinalis for diagnosis of intestinal microsporidiosis in Bamako (Mali). J Clin Microbiol. 2002;40(5):1715–8.
90. Aneke CI, Otranto D, Cafarchia C. Therapy and antifungal susceptibility profile of microsporum canis. J Fungi (Basel). 2018;4(3).
91. Kotton CN, Elias N, Delmonico FL, Kradin RL. Case records of the Massachusetts General Hospital. Case 15-2009. A 25-year-old man with coma after cardiac arrest. N Engl J Med. 2009;360(20):2118–25.

Parasitic Infestations in Pregnancy: Surgical Challenges and Dilemmas

23

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Introduction

Parasitic infections are a major global health concern. Not only they affect millions worldwide but also the manifestations of the diseases they cause have a wide spectrum, ranging from mild anemia to severe disease and even death. Until now, the majority of parasitic infestations are encountered in the tropics Southeast Asia, the Caribbean, and the Central and South America. With the rise of both immigration and international tourism, there has been noted a remarkable increase of incidence of parasitic infections in areas where they were not seen as often if not at all [1–3].

As a result, physicians are coming across these cases more and more. Keeping in mind that these diseases have atypical symptomatology, a detailed medical history with emphasis on the social history of the patient is on the utmost importance [1–3].

If an infection occurs during pregnancy that entail the infection of the maternal-fetal unit. The severity of the disease is linked to the parasitic species, the parasitic load, and the underlying maternal health state. Any infection can disrupt the pregnancy at three different levels: maternal, fetal, and placental, all of which are linked to each other. Thus, obstetricians and other obstetric care providers should understand and keep in mind the general pathophysiology of the parasitic diseases [2].

As in all cases, healthcare workers need to provide the best plan of action for both mother and fetus in order to minimize further complications in both and have a good perinatal outcome. Unfortunately, there are insufficient data concerning the

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safety of the antiparasitic medications during pregnancy, as well as about the effectiveness of a surgical management. All of the above make the decision of action even harder.

General Issues

On one hand we have a large number of people being infected by parasites every year and in some cases there might be concomitant parasitic infections, polyparasitism. And on the other hand, we come across the limited research and development and thus production of antiparasitic drugs. Even more, literature does not give much information about the safety of use during pregnancy, more precisely about dosage and embryotoxic/fetotoxic effects [4, 5]. Ethical implications should be taken into account as further investigations and large-scale trials by the pharmaceutical companies entail the "experimentation" on pregnant women and unborn infants [6, 7].

Before diving in the conservative and operative management of parasitic infections, it would be prudent to mention some general issues concerning infection during pregnancy.

Malaria

Malaria is on one of the most prevalent and serious parasitic diseases throughout the tropical and subtropical areas of the world [3].

Malaria is endemic in areas of the world where the anopheles mosquito species exist and the infected human population remains above critical density, which is required for sustained transmission [8].

Malaria is caused by the obligate intracellular protozoa of the genus *Plasmodium*. The four species known to infect human are *P. vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*. The disease is transmitted by the bite of an infected anopheline mosquito, blood contaminations through transfusion or contaminated needles, and congenitally. Pregnant women are more vulnerable to malaria with various unfavorable outcomes. A wide range of symptomatology is seen in both mother and fetus. The mother may experience anemia, and in such cases the disease may lead to death. The effects on the fetus may vary, from miscarriage, intrauterine growth restriction, stillbirth, or preterm birth. And as for the newborn which might be small for the gestational age, there is an increased possibility of perinatal death [8, 9].

Toxoplasmosis

It is estimated that 1/3 of the world's population is infected with *Toxoplasma gondii* [10]. Infection during the immunosuppressive state of pregnancy is quite dangerous possibly leading to congenital toxoplasmosis. During this severe situation,

maternal-fetal unit is threatened with possible spontaneous abortion, in utero fetal death, or other malformations (hydrocephalus, intracranial calcification, retinochoroiditis, organogenesis disorders) being the end result [7].

Leishmaniasis

Leishmaniasis is a chronic inflammatory disease of the skin, mucous membranes, or viscera caused by obligate intracellular protozoan parasites transmitted through the bite of infected female sandflies. There are about 20 different *Leishmania* species that can cause a disease [11]. There are three main forms of the disease: cutaneous, visceral (also known as Kala-Azar disease), and mucocutaneous [12].

The cutaneous form can be either anthroponotic or zoonotic. There has been reported a transplacental transmission in animals [12]. Cutaneous leishmaniasis has different clinical representation during pregnancy (usually larger and more prominent lesions), and it might be linked with increased adverse pregnancy outcomes in humans [13].

The visceral form has been linked with increased morbidity and mortality. There have been cases of congenital transmission of visceral-associated leishmaniasis which can potentially lead to fetal death [12, 14, 15].

Trypanosomiasis

Human African trypanosomiasis (HAT), also known as sleeping sickness, is caused by the protozoan parasites *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, which cause the West and East forms of the disease respectively [16]. The parasites are carried by the infected tsetse flies in endemic regions (eastern Africa, Botswana). The bite of the tsetse fly is painful, and medical attention must be sought promptly [7]. The East form is less common, and the West form accounts for the 10% of the global incidence [17].

American trypanosomiasis, also known as Chagas disease, is caused by the protozoan parasite *Trypanosoma cruzi* and is cared by the blood-sucking triatomine bugs ("kissing bugs" or "bug-nosed") [16]. But congenital transmission is the main and most persistent form of parasitosis in human population. Incidence rates of congenital Chagas disease reach approximately 14,000 per year in Latin America, 66–630 per year in United States, and about 20–180 per year in Europe [18, 19], although its effects in human fertility and risk of abortion or prematurity is inconclusive [20–23] .

All trypanosomes have the potential for transplacental transmission with resulting intrauterine infection of the fetus during maternal parasitemia [22]. There are studies that showed that the intrauterine infection may lead to premature delivery, low birth weight, premature rupture of membranes, polyhydramnios, and possible placental infection [24–28].

Helminthiasis

Helminthiasis is considered a tropical disease where there is a parasitic infection caused by various types of helminths – worms (roundworms, hookworms, and *Ascaris*) [29]. Soil-transmitted helminthiasis and schistosomiasis are the most important helminthiases.

The effects of these infections on pregnancy are indirect as the prolonged and untreated conditions cause anemia, malnutrition, and immunological symptoms and potentially lead to an increased risk of premature birth or low birth weight infants [30, 31].

Intestinal nematodes are often thought to be unimportant causes of infection in humans. Yet in many low-income and rural communities in the southeast United States, half of the population may suffer from infection with *Ascaris lumbricoides*, *Trichuris trichiura*, or both [3].

Maternal infection with these intestinal roundworms usually is benign with exception cases where there is a heavy worm load. Diagnosis is essential, especially in cases where there is symptomatology from the gastrointestinal track, but treatment can be delayed until the end of pregnancy. This is due to the known fact that a parasitic infection with nematodes is not associated either with severe complications of pregnancy or with any adverse fetal outcomes [3, 32].

Schistosoma

Even though untreated schistosomiasis is a life-threatening infection in the general population, the effects of the disease on pregnant women seem to be greater, as the infection will jeopardize the well-being of both the mother and the fetus [33–35].

The health status of the woman prior to pregnancy is a crucial factor in gestational morbidity and to the pregnancy outcome [36–39]. Poor nutritional state, unsanitary living conditions, and other infectious diseases also contribute to maternal and infant mortality and low birth weight (LWB) in least-developed countries (LDCs); understandably, women suffering from undernutrition, small stature, and anemic state and with coexisting infections are at increased risk of delivering low birth infants [40].

Ascaris lumbricoides

Ascariasis is the most widespread helminthiasis in the world [41].

Chu et al. [42] reported a single case of congenital ascariasis. They proposed various mechanisms to explain the case, with the only plausible one being the transplacental transmission of larvae via migration from the mothers' intestine to the maternal lymphatics and bloodstream and then into the fetal circulation and fetal small intestine where they developed into adult worms.

Ascariasis is associated with a high mortality rate (21%). This necessitates the application of a prompt and optimal method of treatment in order to reduce the complication rate. In endemic areas, routine anthelmintic treatment in women of childbearing age is applied to reduce the worm load and thus prevent biliary

ascariasis. Even with this mode of action, reinfection may be unavoidable. Possibly the only way to prevent transmission of ascariasis in humans is the improvement of sanitation especially in human excreta disposal in endemic areas mainly [43].

Enterobius vermicularis

Enterobius vermicularis, also known as pinworm, threadworm, or *Oxyuris*, is an intestinal nematode that may inhabit the human terminal ileum, colon, and appendix. Transmission occurs through direct anus-to-mouth spread from contact within infected person or through airborne eggs that have been dislodged from contaminated clothing of bed linens.

Extraintestinal enterobiasis is a rare and unusual entity that mostly involves the female genital and reproductive tract: the vagina, uterus, ovaries, fallopian tubes, pelvic peritoneum, and even the embryo [44–54]. The first case of vaginal enterobiasis was reported in 1950 [55].

Another rare localization of the worm is the embryo, and several cases have reported so [46, 48].

The recommended treatment for enterobiasis is oral pyrantel pamoate, according to the Center for Disease Control and Prevention (CDC) guidelines. Alternatively, a single dose of mebendazole can be given, even though most require two. Mebendazole is a category C drug; thus, potential benefit of treatment should exceed the possible risks. A study conducted to examine the pregnancy outcome after gestational exposure to mebendazole reported no significant increase in fetal malformation compared with control group results [56]. Conclusively, mebendazole use during pregnancy requires caution and should be given to the family member within the same household as well to minimize reinfection.

Echinococcus

Echinococcus granulosus is a parasite transmitted from canines to humans through fecal-oral route [57].

Echinococcus granulosus causes the hydatid disease. It is a rare zoonosis and manifests as multicystic fluid-filled spaces anywhere in the body.

During pregnancy, the disease is rare with a reported incidence of 1 in 20,000 to 1 in 30,000 [57–59]. The immunosuppresion seen in pregnancy may predispose pregnant women to the disease. Liver (50–70%) and lung involvement are the most reported sites of cyst formation during pregnancy, but other sites include the brain, bones, and abdominal cavity. Cardiac involvement is even rarer especially during pregnancy (0.5–2%) and is usually accompanied by other organ involvement.

Cystic echinococcosis can grow slowly or show rapid progression. The presentation may vary from asymptomatic to one with acute complicated from cyst rupture, anaphylaxis, and obstruction of labor. Cardiac hydatid cysts are usually asymptomatic but progression of the disease can lead to a life-threatening condition such as sudden death, anaphylactic shock, peripheral/pulmonary/cerebral emboli acute coronary syndrome, heart failure, and arrhythmias.

The disease can be managed either with medications or surgery. The drugs classically used against *E. granulosus* are the benzimidazoles. Their mechanism of action is based on inhibition of glucose uptake by the parasite which in turn generated metabolic and structural alterations in the parasite leading to its death. Albendazole has been used for this purpose since 1980 [60], but the Food and Drug Administration (FDA) of the United States has classified it as a category C drug. It has been shown to have teratogenic and embryogenic effects in rats and rabbits and thus is not recommended for use in the first trimester [61].

Surgical treatment in pregnancy has to be individualized. The obstetrician has to take into account not only the clinical condition of the pregnant woman and the size of the cyst but also his/her expertise. The suggested options seem to be the percutaneous drainage under ultrasonographic guidance or the surgical removal. Nowadays, surgery is the treatment of choice, performed conventionally or laparoscopically.

Pharmacological Treatment

Most drugs used until recently in the treatment of parasitic diseases are fetotoxic and with other major adverse reactions.

Nowadays there are new generation drugs to treat parasitic infections that generally are better tolerated and with wider spectrum of activity and less adverse effects.

This chapter focuses on the updated information about the antiparasitic drugs and their use during pregnancy.

Malaria is a serious parasitic infection that during pregnancy requires prompt treatment to minimize complications to both mother and fetus [62, 63]. Unfortunately, data concerning their safety, efficacy, and use during pregnancy, especially during the first trimester, are scarce at best since, for ethical reasons, there cannot be clinical trials [64–67].

Pregnant women are at increased risk of complications after malaria infection [8]. Even more susceptible are nonimmune women, particularly travelers, who are advised to avoid, if possible, visiting endemic regions during pregnancy [68]. But if the travel is unavoidable, these women are put on an effective chemoprophylaxis regiment [69]. The main chemoprophylactic antimalarial medications currently recommended include doxycycline and primaquine but are contraindicated in pregnancy [70, 71]. The two chemoprophylactic options currently available for pregnant women are chloroquine and mefloquine [72]. But due to widespread resistance of *Plasmodium falciparum* parasites to chloroquine, which limits its use to specific regions, the only option left for pregnant women is mefloquine. In some areas of Southeast Asia, there is resistance to mefloquine too, thus leaving no available option in that part of the world [69]. Lastly, atovaquone-proguanil is a combination drug that is recommended for effective malaria prophylaxis and treatment in nonpregnant travelers in regions with resistance to other antimalarial medications [73].

Aminoquinolines

4-Aminoquinolines

This category includes chloroquine. It has been used for many years with satisfactory gastrointestinal absorption. Overexposure to chloroquine has been linked with harmful effects in animal species. In human beings, chloroquine is not associated with abortions, fetal malformations, or intrauterine fetal deaths [74].

Chloroquine may be prescribed at any trimester of pregnancy. As a curative treatment, it can be administered without any restriction at a dose of 10 mg/kg on the first day, 10 mg/kg on the second day, and 5 mg/kg on the third day to treat uncomplicated malaria episodes caused by non-*Plasmodium falciparum* species [75].

8-Aminoquinolines

This category includes primaquine which is prescribed for the prevention of *P. vivax* and *P. ovale* malaria relapses. It is contraindicated in pregnant women as it is responsible for severe hemolytic anemia [75].

Alkanolamines

Natural Alkanolamines

This category includes quinine. There are reported ocular and hearing impairments in children whose mothers received high doses of quinine during pregnancy. Quinine remains the first-line treatment of uncomplicated *P. falciparum* episodes during the first trimester of pregnancy [63]. Its daily dosage is 25 mg/kg divided into three intakes, for 7 days.

Synthetic Alkanolamines

Experimental studies revealed that usage of mefloquine during pregnancy is associated with an increased risk of spontaneous abortions and in utero fetal death, even at low doses [76].

Although, mefloquine can be administered at any trimester. The recommended dose for prophylactic treatment is 250 mg every week and for curative treatment is 25 mg/kg over 1 day only, divided into two intakes of 15 mg/kg followed by 10/mg/kg 12 hours later or into three intakes of 8 mg/kg every 6–8 hours.

The curative treatment with mefloquine is prescribed to patients presenting with uncomplicated *Plasmodium falciparum* malaria only when Quinine is contraindicated [63].

Inhibitors of Folic Acid Synthesis

This category includes antifolic drugs of the sulfonamide class (sulfadoxine) and antifolates (proguanil, pyrimethamine).

Sulfonamides have good transplacental passage. In humans, when prescribed during the third trimester, they are associated with fetal jaundice and neonatal hemolysis if the child has glucose-6-phosphate dehydrogenase deficiency [7].

Pyrimethamine crosses the placental barrier and reaches high concentrations in the blood. Its administration during the first trimester has harmful effects in animal species [77].

Sulfadoxine-pyrimethamine combination is not prescribed in the first trimester, since the pharmacokinetic data existing from animal studies have linked its use with teratogenic effects [78]. Even so this combination is recommended as intermittent prevention of congenital malaria in endemic areas after the 16th week of gestation (three doses one month apart) [79].

Lastly, folic acid 0.4 mg per day or folinic acid 3–5 mg three times per week remains beneficial to prevent congenital disorders as well as cytopenia in mothers [80, 81].

Cyclins

Doxycycline is contraindicated in pregnancy since it has teratogenic effects on the fetus, especially during the second trimester [78]. It is associated with higher rates of neural tube defects, cleft palate, and other major congenital abnormalities (MCAs) [82].

Although, based on available data, accidental exposure of pregnant women to doxycycline is unlike to cause harm [83].

Artemisinin Derivatives

This class of medications is associated with teratogenic affects especially in animals (cardiac and long bone malformations). The major pathogenetic mechanism is the damage on embryonic erythroblasts unsettling in this way the angiogenesis possibly leading to intrauterine fetal death or spontaneous abortions [84].

Other Antimalarial Drugs

Atovaquone is an inhibitor of the pyrimidine biosynthesis, and it is used as part of a two-drug combination with an antifolate: proguanil.

Atovaquone-proguanil can be administrated for preventive treatment in pregnant women traveling in endemic areas where there is chloroquine/mefloquine resistance [78]. Suggested doses: 250 mg atovaquone, 100 mg proguanil, daily. Treatment must be continued daily for a week following the return home. Atovaquone has been associated, sometimes, with teratogenic effects in animal species [85–88].

Anti-toxoplasma Drugs

For curative treatment of congenital toxoplasmosis, the most widely used drug remains the combination of pyrimethamine-sulfadiazine [89]. Dosage: 1 mg/kg pyrimethamine until delivery and 100–150 mg/kg sulfadiazine [90]. For patients with hypersensitivity to sulfonamides, pyrimethamine alone in high doses or in combination with clindamycin/clarithromycin/azithromycin or atovaquone can alternatively be used [91, 92].

Other commonly used medications include spiramycin, azithromycin, and trimethoprim in combination with sulfamethoxazole [10]. All of them do not cross the feto-placental barrier and are prescribed during pregnancy to prevent congenital toxoplasmosis. Dosage: 3 million units 3 times per day until delivery or until congenital infection is confirmed [75].

Anti-leishmanial Drugs

Sodium Stibogluconate (SSB) and Meglumine Antimoniate (MA)

This category of drugs cross the placenta barrier and are embryotoxic [75].

Pentamidine

It has been replaced by amphotericin B, as pentamidine has been associated with first-trimester miscarriages and other teratogenic effects on fetus and thus is not recommended in pregnancy [75].

Amphotericin B

It also crosses the placental barrier, but its use has not been associated with embryotoxicity [15]. But it has been linked, in some cases, with renal failure leading to a decreased amount of amniotic fluid, but only at the end of the gestation. The liquid form of the drug has less harmful effects and is not related with abortions or malformations [93].

Antihuman African Trypanosomiasis (HAT) Drugs

Suramin

It is contraindicated in pregnancy, and it can only be given when pregnant women are at great risk at the neurological phase of trypanosomiasis. Recommended dose in these cases is 20 mg/kr via slow intravenous injections every 5–7 days [75].

Pentamidine

Pentamidine isethionate may be used to treat the mother and to reduce the vertical transmission risk during *Trypanosoma brucei gambiense* infection at the hemolytic phase [75]. Generally it is not recommended, but it can be used in cases where the benefits outweigh the risks (maternal neurological symptomatology). Recommended dose: 7–10 intramuscular injections of 4 mg/kg daily [94].

Eflornithine

It is embryotoxic based on finding from studies on animal species. It is associated with intrauterine growth restriction and central nervous system impairment in fetuses. Its topical use in pregnant women presenting with facial hirsutism was associated with spontaneous abortions, but the study lacked power to conclude on a real effect [95, 96].

Recommended dose: 100 mg/kg i.m. every 6 hours for 14 days. At the end of the treatment cycle, the cure rate reached 97% [97].

Melarsoprol

It is contraindicated in pregnancy. Obstetricians and other healthcare providers must either delay treatment until delivery or chose an alternative HAT drug [75].

Other American Trypanosomiasis Drugs

Drugs that can be used against Chagas disease include Benznidazole (a nitroimidazole derivative) and nifurtimox (a nitrofuran derivative). They are associated with medullary and neurological toxicity. After the first trimester, they can be used only in cases where the benefits outweigh the risks [75].

Anthelmintics

Management poses challenges to the attending physicians but can either be conservative or surgical. Conservative management include administration of antispasmodics and antibiotics. Mebendazole and albendazole are contraindicated due to their fetotoxic effects, but pyrantel, pamoate, and piperazine citrate are safe in late pregnancy [43]. The indications for pharmaceutical approach where given by Lee [43] and include gastrointestinal problems that persist and interfere with maternal health and parasite-related extraintestinal abnormalities. Resolution of symptoms will occur in most cases (68–80%) [98, 99], which comes from the return of the parasites to the small intestine. Failure of resolution seems to be the obstruction of parasite exit either due to stones, strictures, or mass of dead worms.

Benzimidazole Derivatives

Observational studies have not reported a significant excess of congenital anomalies following their use in human pregnancies.

This category includes albendazole, mebendazole, and its fluorinated derivative (flubendazole).

Benzimidazoles are mainly nematicidal – especially against hookworms, roundworms and *Oxyuris* – and to a lesser extent trematocidal and cestocidal.

When administered at the pre-implantation phase, albendazole was associated with a decreased bovine embryonic cell division capacity [100]. At the organogenesis phase, its prolonged use in pregnant rats was associated with skeleton impairment at concentrations close to those used in humans.

Mebendazole and flubendazole have teratogenic effects and at high doses are associated with embryonic lethality [56, 101].

Albendazole and mebendazole may be prescribed during the second and third trimester but only as second-line options during the first trimester [75].

Avermectins

Avermectin derivatives are used mainly against nematodes. Overexposure is associated with embryotoxicity, central nervous system defects, and cleft palate.

Ivermectin is the most frequently used drug from this category. It can be used as a curative treatment of nematosis, but there are controversial finding from studies concerning its safety of use during pregnancy [102].

Praziquantel

Neither animal studies nor a randomized double-blind clinical trial of pregnant women between 12th and 16th week linked its use with embryotoxicity, in utero deaths, spontaneous abortions, congenital malformations, or low birth weight [103].

Surgical Dilemmas

In some cases a surgical approach is required in the treatment of a parasitic infection. In the case of pregnancy, the obstetrician must balance his choice of surgical management between risks and benefits and calculate all the special circumstances dealt with a pregnant patient. The risks are different during pregnancy and out of it. The underlying cause, infection, in some cases, e.g., appendicitis, makes surgery the only path to take.

After the 13th week of gestation, all major organ systems of the fetus have been developed; thus, the risk of congenital malformations is minimal. After the 16th week, the uterus has been enlarged to a degree that is now an extra pelvic organ. This means that in a supine position, it can apply pressure to the inferior vena cava leading to decreased venous return and to supine hypotension. But, between 13th and 23rd week of gestation, the uterus is less sensitive to the stimuli caused by a surgery, and the risks of preterm labor are minimal. This is the optimal period to perform an unavoidable procedure with minimal risk but the patient must be placed in a left lateral tilt position to reduce venous and arterial compression.

After the 24th week, the surgical approach has three main possible complications: fetal hypoxia, infection, and preterm labor. Fetal hypoxia is a result of supine hypotension which may be exacerbated by an already compromised maternal health state.

Fetal brain injury and death can occur at any stage of pregnancy. The main cause is fetal hypoxia. Prolonged and severe supine hypotension is not the only etiology. A fall in the maternal hematocrit of more than 50%, a decrease in maternal blood pressure of 20%, or a maternal PaO_2 below 60 mmHg with O_2 saturation less than 90% will result in fetal hypoxia, acidosis, and thus fetal compromise. This hypoxic fetal stress might lead to fetal brain injury or stimulate hormonal triggers and lead to preterm labor. It must be remembered that a significant proportion of fetal

neurodevelopment occurs in the third trimester. Any infection or surgical complications, the anesthetic agents being used during surgery, all can potentially affect neonatal and child neurodevelopment.

Fetal infection may be the result of the primary disease affecting the mother or as a complication from surgery, hematogenous inoculation leading to chorioamnionitis, or indirectly as a result of preterm birth. The pathophysiological mechanism of preterm labor in these cases includes the circulating endotoxins and cytokines from distal infections that stimulated the decidual macrophages which in turn increase the prostaglandin production and thus initiating preterm labor. Also, endotoxins and cytokines that cross the placenta may have a direct adverse effect on the fetus.

Preterm labor and delivery is the most important risk when performing surgery in a pregnant patient. Hypoxia, infection, and genital tract manipulation may stimulate preterm labor. Before the 23rd week, preterm delivery results in neonatal death, and even after then, preterm labor in hospitals without neonatal unit and specialized and experienced neonatologists there is a significant risk of both perinatal death and long-term handicaps.

The prevalence of non-gynecologic causes or trauma that can lead to surgery during pregnancy is 1–10 per 1000 pregnancies.

Hydatid Disease

There are only case reports published about parasitic infections that require surgical management during pregnancy and from review of those, the most common infection was the hydatid disease caused by *Echinococcus granulosus* [104]. In all pregnant patients with a hydatid cyst, the physician can choose between surgical approach or percutaneous drainage based on the type, location, and condition of the cyst and taking into account the underlying condition of the patient. Generally management of pregnant women with hydatid disease is complicated due to the fact that data concerning their management are scarce and there is no internationally accepted course of action [105]. In the first study based on a literature review, Rodrigues et al. made several recommendations for managing the challenges presented in treating pregnant patients with hydatid disease, but many cases resulted in negative outcomes, mainly death of the fetus and/or mother [61]. Anaphylaxis following cyst rupture, during labor or surgical clearance, might endanger maternal life. The administration of antihistamines and steroids before the active stage of labor or preoperatively can reduce this possibility [106].

Most reported sites of cyst formation is the lung and liver. These cysts and cysts in the kidney or spleen may not affect the progression of pregnancy nor of the labor. But if the cyst is located in the pelvis, a rare event, these are likely to cause problems during labor. In case of vaginal delivery, dystocia must be anticipated. Delivery by ceasarean section is often suggested in these cases [106].

Management of hydatid disease during pregnancy must be individualized. If possible, surgical intervention should be postponed for the antenatal period, even though there is a controversy of whether to operate and excise the cyst or convert to

a pharmacological approach. Surgery during pregnancy is associated with increased intraoperative morbidity due to less space for maneuvers, increased risk of cyst rupture, uterine manipulation and preterm birth. On the other hand, if left in situ, the cyst may increase in size and pose problems during labor [104].

There is a dilemma of action in pregnant women with an asymptomatic hydatid disease. Pharmaceutical management with albendazole, after the first trimester, with close monitoring for adverse reactions can be considered in patients not willing to undergo surgery which should be postponed for after delivery or during if caesarean delivery is recommended [61].

Isolated Rupture of Interatrial Septal Cystic Echinococcosis During Pregnancy

Cardiac involvement of echinococcosis during pregnancy is quite rare. There are only few published case reports about the condition [107, 108].

There is a high risk of rupture, septic embolization, and other potentially life-threatening complications. Thus cardiac cystic echinococcosis should be treated surgically without delay even if the patient is asymptomatic in order to prevent later complications to both mother and fetus [109].

Management of Biliary Ascariasis in Pregnancy

Biliary ascariasis is one of the most common and well-described entities caused by the nematode *Ascaris lumbricoides*. In endemic areas pregnant women are prone to develop biliary ascariasis. Its management poses a great challenge to both the surgeon and the endoscopist [43].

Failure of the conservative treatment with antispasmodics and antibiotics necessitates a more invasive approach. One choice is the ERCP. Extra care and protection from ionizing radiation must be applied during the ERCP. The use of a lead apron to cover the abdomen, minimizing the fluoroscopic time, documentation of fetal exposure with dosimetry badges, and avoidance of spot radiographs are some of the techniques used nowadays to shield and protect the fetus. There are limited published data about the efficacy and safety of ERCP in the management of symptomatic choledocholithiasis during pregnancy [110, 111]. Complete extraction of the worms is not always possible especially in cases of friability of the living worms, fragmentation of the dead, high location of the worms within the intrahepatic ductal system, or spasm of the sphincter of Oddi [112].

Another choice of surgical approach is sphincterotomy. Sphincterotomy should be avoided as it appears to influence the recurrence of infestation by allowing easier access through the ampulla of Vater [113]. Although it may be necessary if there are stones obstructing passage of the endoscope. This surgical intervention, like any other surgery during pregnancy, cares the risk of premature labor. During the first trimester, it is believed that any type of surgery is highly associated with fetal loss and the rate with cholecystectomy reaches 5%. But the same operation performed

during the second trimester or later is safe and is not associated with fetal mortality [114], although there is an increased risk of premature labor ranging between 15 and 20% [115].

Bibliography

1. Sinniah B, Leopairut J, Neafie RC, Connor DH, Voge M. Enterobiasis: a histopathological study of 259 patients. Ann Trop Med Parasitol. 1991;85:625.
2. Dotters-Katz S, Kuller J, Heine RP. Parasitic infections in pregnancy. Obstet Gynecol Surv. 2011;66(8):515–25.
3. Reynolds SJ, Bollinger RC, Quinn TC. Parasitic diseases during pregnancy. Glob Libr Women's Med. 2009.
4. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Heal. 2014;2:e323.
5. Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: A systematic analysis by the un maternal mortality estimation inter-agency group. Lancet 2016.
6. Liu LX, Weller PF, Drugs A. Review article new eng. N Engl J Med. 1996;334:1178–84.
7. Boitel E, Desoubeaux G. Antiparasitic treatments in pregnant women: Update and recommendations. Med Mal Infect [Internet]. 2018; Available from: https://doi.org/10.1016/j.medmal.2018.09.008.
8. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis. 2007;7(2):93–104.
9. Saito M, Gilder ME, McGready R, Nosten F. Antimalarial drugs for treating and preventing malaria in pregnant and lactating women. Expert Opin Drug Saf [Internet]. 2018;17(11):1129–44. Available from: https://doi.org/10.1080/14740338.2018.1535593.
10. Wei HX, Wei SS, Lindsay DS, Peng HJ. A systematic review and meta-analysis of the efficacy of anti-toxoplasma gondii medicines in humans. PLoS One. 2015;10(9):1–12.
11. Assimina Z, Charilaos K, Fotoula B. Leishmaniasis: an overlooked public health concern. Heal Sci J. 2008.
12. G D. A review on biology, epidemiology and public health significance of leishmaniasis. J Bacteriol Parasitol. 2013.
13. Morgan DJ, Guimaraes LH, Machado PRL, D'Oliveira A, Almeida RP, Lago EL, et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. Clin Infect Dis. 2007;45:478–82.
14. Panagopoulos P, Mitsopoulos V, Papadopoulos A, Theodorou S, Christodoulaki C, Aloupogiannis K, et al. Visceral leishmaniasis during pregnancy: a rare case report from Greece. PLoS Negl Trop Dis. 2017;11:e0005134.
15. Figueiró-Filho EA, Duarte G, El-Beitune P, Quintana SM, Maia TL. Visceral leishmaniasis (kala-azar) and pregnancy. Infect Dis Obstetr Gynecol. 2004;12:31.
16. Cevallos AM, Hernández R. Chagas' disease: pregnancy and congenital transmission. Biomed Res Int. 2014;2014:1.
17. Nadjm B, Van Tulleken C, Macdonald D, Chiodini PL. East African trypanosomiasis in a pregnant traveler. Emerg Infect Dis. 2009;15(11):1866–7.
18. Basile L, Jansà JM, Carlier Y, Salamanca DD, Angheben A, Bartoloni A, et al. Chagas disease in european countries: the challenge of a surveillance system. Eur Secur. 2011.
19. Yadon ZE, Schmunis GA. Congenital chagas disease: estimating the potential risk in the United States. Am J Trop Med Hyg. 2009;81:927.
20. Gonzalez Cappa SM, Mirkin GA, Solana ME, Tekiel VS. Trypanosoma cruzi pathology. Strain dependent? Medicina (B Aires). 1999;59 Suppl 2:69–74.

21. Solana ME, Celentano AM, Tekiel V, Jones M, Cappa SMG. Trypanosoma cruzi: effect of parasite subpopulation on murine pregnancy outcome. J Parasitol. 2006.
22. Montes-Rincón LM, Galaviz-Silva L, González-Bravo FE, Molina-Garza ZJ. Trypanosoma cruzi seroprevalence in pregnant women and screening by PCR and microhaematocrit in newborns from Guanajuato. Mexico Acta Trop [Internet] 2016;164:100–6. Available from: https://doi.org/10.1016/j.actatropica.2016.08.029.
23. Cencig S, Coltel N, Truyens C, Carlier Y. Fertility, gestation outcome and parasite congenital transmissibility in mice infected with TcI, TcII and TcVI genotypes of trypanosoma cruzi. PLoS Negl Trop Dis. 2013;7(6):e2271.
24. Brabin L. The epidemiological significance of Chagas' disease in women. Mem Inst Oswaldo Cruz. 1992;87:73–9.
25. Duaso J, Rojo G, Cabrera G, Galanti N, Bosco C, Maya JD, et al. Trypanosoma cruzi induces tissue disorganization and destruction of chorionic villi in an ex vivo infection model of human placenta. Placenta. 2010;31(8):705–11.
26. Duaso J, Yanez E, Castillo C, Galanti N, Cabrera G, Corral G, et al. Reorganization of extracellular matrix in placentas from women with asymptomatic chagas disease: mechanism of parasite invasion or local placental defense? J Trop Med. 2012;2012:758357.
27. Apt W, Zulantay I, Arnello M, Oddó D, González S, Rodríguez J, et al. Congenital infection by Trypanosoma cruzi in an endemic area of Chile: a multidisciplinary study. Trans R Soc Trop Med Hyg. 2013;107:98–104.
28. Hernandez-Matheson IM, Frankowski RF, Held B. Foeto-maternal morbidity in the presence of antibodies to Trypanosoma cruzi. Trans R Soc Trop Med Hyg. 1983;77:405–11.
29. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical diseases. J Clin Investig. 2008;118:1311–21.
30. Mpairwe H, Tweyongyere R, Elliott A. Pregnancy and helminth infections. Parasite Immunol. 2014;36(8):328–37.
31. Shrinivas K, Radhika, Sreelatha R, Kavitha K. Study of helminthiasis in pregnancy and its correlation with haemoglobin level. J Clin Diagnostic Res. 2014;8(10):OC07–9.
32. Wekesa AW, Mulambalah CS, Muleke CI, Odhiambo R. Intestinal Helminth infections in pregnant women attending antenatal clinic at Kitale District Hospital, Kenya. J Parasitol Res. 2014;2014:823923
33. Engels D, Chitsulo L, Montresor A, Savioli L. The global epidemiological situation of schistosomiasis and new approaches to control and research. Acta Tropica. 2002;82:139–46.
34. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect Dis. 2006;6:411.
35. Chitsulo L, Loverde P, Engels D. Focus: schistosomiasis. Nat Rev Microbiol. 2004.
36. Steketee RW. Pregnancy, nutrition and parasitic diseases. J Nutr. 2018.
37. McGarvey ST, Aligui G, Graham KK, Peters P, Richard Olds G, Olveda R. Schistosomiasis japonica and childhood nutritional status in northeastern Leyte, the Philippines: a randomized trial of praziquantel versus placebo. Am J Trop Med Hyg. 1996;54:498–502.
38. Friedman JF, Kanzaria HK, Acosta LP, Langdon GC, Manalo DL, Wu H, et al. Relationship between Schistosoma Japonicum and nutritional status among children and young adults in Leyte, the Philippines. Am J Trop Med Hyg. 2005;72(5):527–33.
39. Coutinho HM, McGarvey ST, Acosta LP, Manalo DL, Langdon GC, Leenstra T, et al. Nutritional status and serum cytokine profiles in children, adolescents, and young adults with schistosoma japonicum –associated hepatic fibrosis, in Leyte, Philippines. J Infect Dis. 2005;92(3):528–36.
40. Kramer MS. The epidemiology of adverse pregnancy outcomes: an overview. J Nutr. 2018.
41. Hoi MT, Desjeux A, Bach TT, Barthet M, Grimaud J-C. Endoscopic management of biliary and pancreatic ascariasis in Viet-Nam. Report of a series of 91 cases. Gastroentérologie Clin Biol. 2002;26(11):968–72.
42. Chu WG, Chen PM, Huang CC, Hsu CT. Neonatal ascariasis. J Pediatr. 1972.

43. Shah OJ, Robanni I, Khan F, Zargar SA, Javid G. Management of biliary ascariasis in pregnancy. World J Surg. 2005;29(10):1294–8.
44. JN MM, Connolly CE, Long SV, Meehan FP, et al. Br Int J Obstet Gynaecol. 1984;91(3): 289–90.
45. Neri A, Tadir Y, Grausbard G, Pardo J, Ovadia J, Braslavsky D. Enterobius (Oxyuris) vermicularis of the pelvic peritoneum - a cause of infertility. Eur J Obstet Gynecol Reprod Biol. 1986;23:239–41.
46. Tandan T, Pollard AJ, Money DM, Scheifele DW. Pelvic inflammatory disease associated with Enterobius vermicularis. Arch Dis Child. 2002;86(6):439–40.
47. Khan JS, Steele RJC, Stewart D. Enterobius vermicularis infestation of the female genital tract causing generalised peritonitis case report. Br Int J Obstet Gynaecol. 1981;88:681–3.
48. Knuth KR, Fraiz J, Fisch JA, Draper TW. Pinworm infestation of the genital tract. Am Fam Physician. 1988;38(5):127–30.
49. Dundas KC, Calder AA, Alyusuf R. Enterobius vermicularis threadworm infestation of paraovarian tissue in a woman who has had a hysterectomy. Br Int J Obstet Gynaecol. 1999;106:605–7.
50. Smolyakov R, Talalay B, Yanai-Inbar I, Pak I, Alkan M. Enterobius vermicularis infection of female genital tract: a report of three cases and review of literature. Eur J Obstet Gynecol Reprod Biol. 2003;107:220–2.
51. Craggs B, De Waele E, De Vogelaere K, Wybo I, Laubach M, Hoorens A, et al. Enterobius vermicularis infection with tuboovarian abscess and peritonitis occurring during pregnancy. Surg Infect (Larchmt). 2009;10(6):545–7.
52. Shetty J, Prabhu V, Kulkarni D. Eggs containing larvae of Enterobius vermicularis in vaginal smear. J Cytol. 2012;29:94–6.
53. Powell G, Sarmah P, Sethi B, Ganesan R. Enterobius vermicularis infection of the ovary. BMJ Case Reports. 2013;2013.
54. Mendoza E, Jorda M, Rafel E, Simón A, Andrada E. Invasion of human embryo by Enterobius vermicularis. Arch Pathol Lab Med. 1987;111(8):761–2.
55. Ngui R, Ravindran S, Ong DBL, Chow TK, Low KP, Nureena ZS, et al. Enterobius vermicularis salpingitis seen in the setting of ectopic pregnancy in a Malaysian patient. J Clin Microbiol. 2014;52(9):3468–70.
56. Diav-Citrin O, Shechtman S, Arnon J, Lubart I, Ornoy A. Pregnancy outcome after gestational exposure to mebendazole: a prospective controlled cohort study. Am J Obstet Gynecol. 2003;188:282–5.
57. Lewis JW, Koss N, Kerstein MD. A review of echinococcal disease. Ann Surg. 1975;181(4):390–6.
58. Tunger O. Epidemiology of cystic Echinococcosis in the world. Turkish J Parasitol. 2013;37:47.
59. Kain KC, Keystone JS. Recurrent hydatid disease during pregnancy. Am J Obstet Gynecol. 1988;159:1216–7.
60. Vuitton DA. Benzimidazoles for the treatment of cystic and alveolar echinococcosis: what is the consensus? Expert Rev Anti Infect Ther. 2009;7(2):145–9.
61. Celik S, Okyay O, Karaman E, Sert ÖZ, Cim N, Okyay TY. Analysis of factors affecting outcomes of pregnancy complicated by Echinococcus: an algorithm for approach and management. Arch Gynecol Obstet [Internet]. 2018;298(1):103–10. Available from: https://doi.org/10.1007/s00404-018-4792-7.
62. Nosten F, et al. Case management of malaria in pregnancy. Lancet Infect Dis. 2007;7: 118–25.
63. Reyburn H. New WHO guidelines for the treatment of malaria. BMJ (Online). 2010.
64. D'Alessandro U. Existing antimalarial agents and malaria-treatment strategies. Expert Opin Pharmacother. 2009;10(8):1291–306.
65. Lutje V, Gerritsen A, Siegfried N. Randomized controlled trials of malaria intervention trials in Africa, 1948 to 2007: a descriptive analysis. Malar J. 2011;10:61.
66. Orton LC, Omari AAA. Drugs for treating uncomplicated malaria in pregnant women. Cochrane Database of Syst Rev. 2008;4:CD004912.

67. Gil VS, Ferreira MCR, d'Alva FSM, d'Abreu JA, Will IM, Gomes ML, et al. Efficacy of artesunate plus chloroquine for uncomplicated malaria in children in Sao Tome and Principe: a double-blind, randomized, controlled trial. Trans R Soc Trop Med Hyg. 2003;97:703–6.
68. Pasternak B, Hviid A. Atovaquone-proguanil use in early pregnancy and the risk of birth defects. Arch Intern Med. 2011;171(3):259–60.
69. Brunette GW, Kozarsky PE, Magill AJ, Shlim DR. CDC health information for international travel 2010. CDC Health Informat Brunetteion for International Travel 2010; 2009.
70. Tan KR, Magill AJ, Parise ME, Arguin PM. Doxycycline for malaria chemoprophylaxis and treatment: report from the CDC expert meeting on malaria chemoprophylaxis. Am J Trop Med Hyg. 2011;84(4):517–31.
71. Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: Report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg. 2006;75(3):402–15.
72. Global Health – Division of Parasitic Diseases and Malaria. CDC – malaria – travelers – choosing a drug to prevent malaria. CDC; 2012.
73. Looareesuwan S, Viravan C, Webster HK, Kyle DE, Hutchinson DB, Canfield CJ. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. Am J Trop Med Hyg. 1996;54(1):62–6.
74. Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Saf. 1996;14(3):131–45.
75. Boitel E, Desoubeaux G. Antiparasitic treatments in pregnant women: update and recommendations. Med Mal Infect. 2018;50(1):3–15.
76. Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, de Vries A, et al. The effects of mefloquine treatment in pregnancy. Clin Infect Dis. 2007.
77. McLeod R, Mack D, Foss R, Boyer K, Withers S, Levin S, et al. Levels of pyrimethamine in sera and cerebrospinal and ventricular fluids from infants treated for congenital toxoplasmosis. Antimicrob Agents Chemother. 1992;36(5):1040–8.
78. Saito M, Gilder ME, McGready R, Nosten F. Antimalarial drugs for treating and preventing malaria in pregnant and lactating women. Expert Opin Drug Saf. 2018;17(11):1129–44.
79. Kayentao K, Garner P, Van Eijk AM, Naidoo I, Roper C, Mulokozi A, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. JAMA - Journal of the American Medical Association. 2013;309:594–604.
80. Hernández-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. Obstet Gynecol Surv. 2003.
81. Van Der Ven AJAM, Schoondermark-van De Ven EME, Camps W, Melchers WJG, Koopmans PP, Van Der Meer JWM, et al. Anti-toxoplasma effect of pyrimethamine, trimethoprim and sulphonamides alone and in combination: Implications for therapy. J Antimicrob Chemother. 1996;38(1):75–80.
82. Bessières MH, Berrebi A, Cassaing S, Fillaux J, Cambus JP, Berry A, et al. Diagnosis of congenital toxoplasmosis: prenatal and neonatal evaluation of methods used in Toulouse University Hospital and incidence of congenital toxoplasmosis. Mem Inst Oswaldo Cruz. 2009;104:389.
83. Hellgren U, Rombo L. Alternatives for malaria prophylaxis during the first trimester of pregnancy: our personal view. J Travel Med. 2010;17:130–2.
84. Clark RL, TEK W, Clode SA, Gaunt I, Winstanley P, Ward SA. Developmental toxicity of artesunate and an artesunate combination in the rat and rabbit. Birth Defects Res Part B Dev Reprod Toxicol. 2004;71(6):380–94.
85. McGready R, Stepniewska K, Edstein MD, Cho T, Gilveray G, Looareesuwan S, et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol. 2003;59(7):545–52.
86. Na-Bangchang K, Manyando C, Ruengweerayut R, Kioy D, Mulenga M, Miller GB, et al. The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. Eur J Clin Pharmacol. 2005;61:573–82.

87. Wangboonskul J, White NJ, Nosten F, ter Kuile F, Moody RR, Taylor RB. Single dose pharmacokinetics of proguanil and its metabolites in pregnancy. Eur J Clin Pharmacol. 1993;44(3):247–51.
88. McGready R, Stepniewska K, Seaton E, Cho T, Cho D, Ginsberg A, et al. Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. Eur J Clin Pharmacol. 2003;59:553–7.
89. Guerina NG, Hsu H-W, Meissner HC, Maguire JH, Lynfield R, Stechenberg B, et al. Neonatal serologic screening and early treatment for congenital toxoplasma gondii infection. N Engl J Med. 2002.
90. Ambroise-Thomas P, Schweitzer M, Pinon JM, Thiebaugeorges O. Prevention of congenital toxoplasmosis in France. Risk assessment. Results and perspectives of prenatal screening and newborn follow up. Bull Acad Natl Med. 2001;185(4):665–83.
91. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic Encephalitis in Patients With Acquired Immune Deficiency Syndrome. JAMA J Am Med Assoc. 1984;252(7):913–7.
92. McLeod R, Kieffer F, Sautter M, Hosten T, Pelloux H. Why prevent, diagnose and treat congenital toxoplasmosis? Mem Inst Oswaldo Cruz. 2009;104(2):320–44.
93. Pilmis B, Jullien V, Sobel J, Lecuit M, Lortholary O, Charlier C. Antifungal drugs during pregnancy: an updated review. J Antimicrob Chemother. 2015;70(1):14–22.
94. Bronner U, Gustafsson L, Doua F, Ericsson O, Miezan T, Rais M, et al. Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with Trypanosoma gambiense sleeping sickness. Br J Clin Pharmacol. 1995;39:289–95.
95. Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, Mutombo W, et al. In-hospital safety in field conditions of Nifurtimox Eflornithine Combination Therapy (NECT) for T. b. gambiense sleeping sickness. PLoS Negl Trop Dis. 2012;6(11):e1920.
96. World Health Organization (WHO). Trypanosomiasis, human African (sleeping sickness). WHO fact sheets. 2018.
97. Haider BA, Humayun Q, Bhutta ZA. Effect of administration of antihelminthics for soil transmitted helminths during pregnancy. Cochrane Database Syst Rev. 2009;2:CD00554.
98. Rode H, Cullis S, Millar A, Cremin B, Cywes S. Abdominal complications of Ascaris lumbricoides in children. Pediatr Surg Int. 1990;5:397–401.
99. Sultan Khuroo M, Ali Zargar S, Nabi Yattoo G, Javid G, Yousuf Dar M, Iqbal Boda M, et al. Worm extraction and biliary drainage in hepatobiliary and pancreatic ascariasis. Gastrointest Endosc. 1993;39(5):680–5.
100. Elliott AM, Ndibazza J, Mpairwe H, Muhangi L, Webb EL, Kizito D, et al. Treatment with anthelminthics during pregnancy: what gains and what risks for the mother and child? Parasitology. 2011;138(12):1499–507.
101. Longo M, Zanoncelli S, Colombo PA, Harhay MO, Scandale I, Mackenzie C, et al. Effects of the benzimidazole anthelmintic drug flubendazole on rat embryos in vitro. Reprod Toxicol. 2013;36:78–87.
102. Nour NM. Schistosomiasis: health effects on women. Rev Obstet Gynecol. 2010;3(1):28–32.
103. Ndibazza J, Muhangi L, Akishule D, Kiggundu M, Ameke C, Oweka J, et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda: A Randomized Controlled Trial. Clin Infect Dis. 2010;50(4):531–40.
104. Tyagi S, Singh C, Tripathi R, Mala Y. Pregnancy complicated by abdominopelvic hydatid disease. BMJ Case Rep. 2012;2012:bcr2012007880.
105. Rodrigues G, Seetharam P. Management of hydatid disease (echinococcosis) in pregnancy. Obstet Gynecol Surv [Internet]. 2008;63(2):116–23. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2008046254.
106. Bhattacharyya SK, Bhattacharya S, Alam H, Patua B, Chattopadhyay P. Dilemmas encountered while dealing a pregnancy complicated by pelvic Hydatid disease. Arch Gynecol Obstet. 2013;288(5):965–6.
107. Soleimani A, Sahebjam M, Marzban M, Shirani S, Abbasi A. Hydatid cyst of the right ventricle in early pregnancy. Echocardiography. 2008;25(7):778–80.

108. Tetik O, Yilik L, Emrecan B, Ozbek C, Gurbuz A. Giant hydatid cyst in the interventricular septum of a pregnant woman. Tex Heart Inst J. 2002;29(4):333–5.
109. Ercan S, Gokaslan G, Davutoglu V, Inanc IH, Bosnak V, Deniz H. Isolated ruptured interatrial septal cystic echinococcosis during pregnancy. Echocardiography. 2013;30(8):E236–8.
110. Jamidar PA, Beck GJ, Hoffman BJ, Lehman GA, Hawes RH, Agrawal RM, et al. Endoscopic retrograde cholangiopancreatography in pregnancy. Am J Gastroenterol. 1995;90(8):1263–7.
111. Axelrad AM, Fleischer DE, Strack LL, Benjamin SB, Al-Kawas FH. Performance of ERCP for symptomatic choledocholithiasis during pregnancy: techniques to increase safety and improve patient management. Am J Gastroenterol. 1994;89(1):109–12.
112. Wani NA, Chrungoo RK. Biliary ascariasis: surgical aspects. World J Surg. 1992;16:976–9.
113. Saul C, Pias VM, Jannke HA, Braga NHM. Endoscopic Removal of Ascaris lumbricoides from the Common Bile Duct. Am J Gastroenterol. 1984;79(9):725–7.
114. Dixon NP, Faddis DM, Silberman H. Aggressive management of cholecystitis during pregnancy. Am J Surg. 1987;154:292–4.
115. Hamlin E, Bartlett MK, Smith JA. Acute surgical emergencies of the abdomen in pregnancy. Obstet Gynecol Surv. 2006.

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