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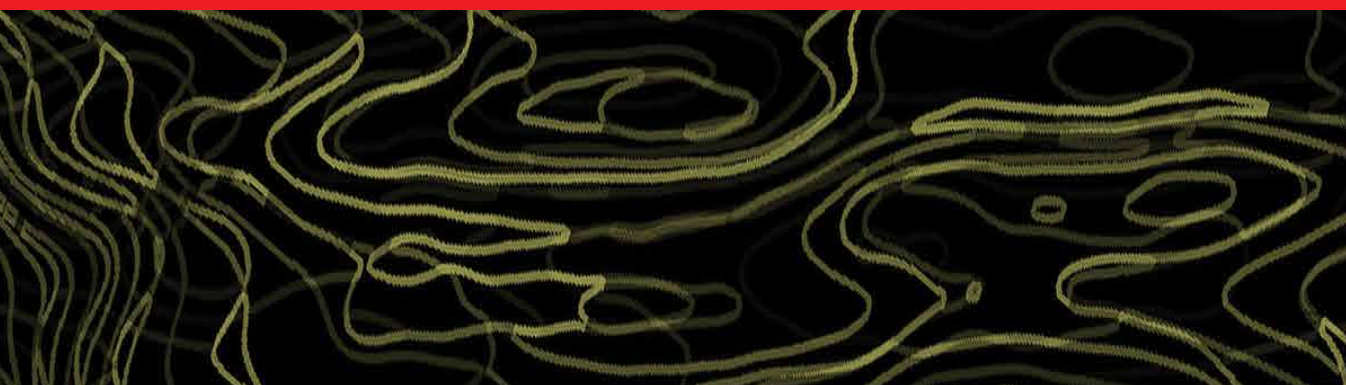
Echinococcosis

New Perspectives

Edited by Tonay Inceboz



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Infectious Diseases

Volume 19

Aims and Scope of the Series

This series will provide a comprehensive overview of recent research trends in various Infectious Diseases (as per the most recent Baltimore classification). Topics will include general overviews of infections, immunopathology, diagnosis, treatment, epidemiology, etiology, and current clinical recommendations for managing infectious diseases. Ongoing issues, recent advances, and future diagnostic approaches and therapeutic strategies will also be discussed. This book series will focus on various aspects and properties of infectious diseases whose deep understanding is essential for safeguarding the human race from losing resources and economies due to pathogens.

Meet the Series Editor

Dr. Rodriguez-Morales is an expert in tropical and emerging diseases, particularly zoonotic and vector-borne diseases (notably arboviral diseases), and more recently COVID-19 and Monkeypox. He is the president of the Publications and Research Committee of the Pan-American Infectious Diseases Association (API), as well as the president of the Colombian Association of Infectious Diseases (ACIN). He is a member of the Committee on Tropical Medicine, Zoonoses, and Travel Medicine of ACIN. Dr. Rodriguez-Morales is a vice-president of the Latin American Society for Travel Medicine (SLAMVI) and a member of the Council of the International Society for Infectious Diseases (ISID). Since 2014, he has been recognized as a senior researcher at the Ministry of Science of Colombia. He is a professor at the Faculty of Medicine of the Fundacion Universitaria Autonoma de las Americas, in Pereira, Risaralda, Colombia, and a professor, Master in Clinical Epidemiology and Biostatistics, at Universidad Científica del Sur, Lima, Peru. He is also a non-resident adjunct faculty member at the Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut, Lebanon, and an external professor, Master in Research on Tropical Medicine and International Health, at Universitat de Barcelona, Spain. Additionally, an invited professor, Master in Biomedicine, at Universidad Internacional SEK, Quito, Ecuador, and a visiting professor, Master Program of Epidemiology, at Diponegoro University, Indonesia. In 2021 he was awarded the "Raul Isturiz Award" Medal of the API and, the same year, the "Jose Felix Patiño" Asclepius Staff Medal of the Colombian Medical College due to his scientific contributions to the topic of COVID-19 during the pandemic. He is currently the Editor in Chief of the journal Travel Medicine and Infectious Diseases. His Scopus H index is 55 (Google Scholar H index 77) with a total of 725 publications indexed in Scopus.

Meet the Volume Editor

Tonay Inceboz is a senior lecturer of medical parasitology. He graduated from the Medical Faculty, Ege University, Turkey, in 1988 and obtained his MD and Ph.D. in Medical Parasitology at the same university in 1998. He became an associate professor in 2008 and a full professor in 2014. He is currently a professor in the Department of Medical Parasitology at Dokuz Eylul University in Turkey. He also works for the audit committee of quality and accreditation at hospitals and universities in Turkey. His main research interests are *Entamoeba histolytica, Blastocystis hominis, Echinococcus granulosus, Echinococcus multilocularis, Trichomonas vaginalis,* and ticks. He has given many lectures and presentations at different academic meetings. He has published more than sixty-seven articles, twenty-one book chapters, and books.

Contents

Preface

Echinococcosis is a disease caused by *Echinococcus* spp. cestode parasites. There are more than 20 species of this parasite. Four important species are *E. granulosus* (Batsch, 1786), which causes cystic echinococcosis (CE); *E. multilocularis* (Leuckart, 1863), which causes alveolar echinococcosis (AE); and *E. oligarthrus* (Diesing, 1863) and *E. vogeli*, both of which cause neotropical echinococcosis in polycystic and unicystic forms, respectively (Rausch and Bernstein, 1972). Definitive hosts of the parasite are widespread throughout the world, for example, foxes, cats, wolves, raccoon dogs, cervids, pigs, lions, jackals, wild canids/hunting dogs, and hyenas. *Echinococcus* spp. live in the intestines of these hosts and are transmitted to intermediate hosts by eggs that are spread around by the feces of the host. Intermediate hosts are also widespread and include humans, sheep, buffalo, horses, cattle, camels, and pigs. Although affected organs in intermediate hosts vary according to species, the liver, lungs, brain, and kidney are commonly involved.

Echinococcosis can last for 20–30 years and is more common in the northern hemisphere. It is especially common in Asia and Europe. Echinococcosis has a global distribution with an estimated 2–3 million people affected, and 200,000 new cases diagnosed annually. The World Health Organization (WHO) designated echinococcosis as one of the seventeen neglected diseases for 2050 and included this parasitic disease in its elimination program. The WHO and the Food and Agriculture Organization (FAO) of the United Nations list *Taenia solium, E. granulosus*, and *E. multilocularis* as foodborne parasitic diseases.

There are two main issues in echinococcosis that inspired us to write this book. First, it is a "neglected disease." Second, pollution of our world's waters and global warming due to industrialization are increasing the spread of the disease.

This book presents epidemiological information about *Echinococcus* species; classic, molecular, and serological diagnosis methods; medical and surgical treatment methods; control mechanisms; vaccine studies; and information and suggestions about what needs to be done in the future.

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Chapter 1

Introductory Chapter: Changes in Eco-System Change Echinococci - "One Health Concept" against Echinococci

Tonay Inceboz

1. Introduction

1.1 Historical perspective of echinococcosis

Echinococcosis or Hydatid disease has been "described" thousands of years ago [1]. The first implication of Echinococcosis dated back to Hippocrates (460–377 BC). He mentioned hydatids (clear fluid full of metacestods of *Echinococcus granulosus*) as "In those whose water stuffed liver opens into omentum, the belly is filled with water, and they die" [2]. Hydatid disease has been also mentioned by Galen (129–200 BC). Interestingly, Aretaeus (80–138 AD), ancient physician from Cappadocia, has stated his observation as "many small fluid-filled blisters may be present in some patients with ascites" (Neisser A. DieEchinococcen-Krankenheit. Verlag August Hirschwald Berlin 1877.) Thereafter, many observations have been reported, however, the animal nature of metacestodes and their parasitic character was first reported by Francesco Redi (1626–1697). Since then, there have been many observations and investigations that lead to our wide knowledge in 21st century [3].

1.2 *Echinococcus spp* and causative agent of echinococcosis

Echinococcus belongs to family of Taeniidea in the subclass of Cyclophillidea and the class of Cestoda in the phylum of Platyhelminthes. Although there have been more than 20 different species defined in *Echinococcus* (*E.*) spp., there are four species that are of health concern in humans; *E. granulosus* (Batsch, 1786), *E. multilocularis* (Leuckart, 1863), *E. oligarthrus* (Diesing, 1863) and *E. vogeli* (Rausch and Bernstein, 1972). The diseases in the human according to the types of Echinococci are "Cystic echinococcosis" by *E. granulosus*, "Alveolar echinococcosis" by *E. multilocularis*, "Polycystic echinococcosis" by *E. oligarthrus* and *E. vogeli*. There are two new species, namely *E. shiquicus* in small mammals from the Tibetan plateau and *E. felidis* in African lions, however the importance of these and the transmission from animals to humans are not known yet [4].

Adult forms of *Echinococcus spp.* are 1.2–6 mm in length and consist of a head (scolex), a neck (proliferation zone), and body (strobilia). The scolex contains four suckers and a rostellum with 25–50 hooks. The proglottids are formed from the

Proliferation zone (the neck). There are 2–6 chains called proglottids in strobilia; the first is immature, the second is mature and the others are gravid proglottids. Mature proglottid has both male and female reproductive organs (hermaphrodite). Gravid proglottids have many eggs [5–7].

In humans, two forms of Echinococci are utmost important clinically; *E. granulosus* (causative agent of "Cystic echinococcosis", CE) and *E. multilocularis*, (causative agent of "Alveolar echinococcosis", AE). For *E. granulosus*, dogs and other members of "familie canidea" (carnivores) are definitive hosts and hold the adult forms, whereas "the familie ungunatae" (such as sheep, goats, pigs, horses etc.) (herbivores) are the intermediate hosts where the larval stage of Echinococci exist. There are other intermediate hosts such as hares, marsupials, rabbits, rodents. Humans do not play a role in transmission (dead-end), they called as "aberrant intermediate hosts" [8]. For *E. multilocularis*, definitive hosts are mainly foxes (especially red foxes), domestic dogs, wolves, and intermediate hosts are their preys mainly rodents.

The life cycle of Echinococci is similar in different forms. The adult forms of the parasite reside in the mucosal layer of the definitive hosts' small intestines and release the eggs thru feces. The eggs are highly resistant to difficult environmental conditions. One example is that the eggs can survive 225 days at 6°C in water or wet sand [9]. When the embryonated eggs are ingested by the intermediate hosts, the egg shell is broken and the embryo (oncosphere) is released in the stomach. In the small intestines the oncospheres first attach to the mucosa and then penetrate it. Thereafter the oncospheres travel to various organs via blood steam and develop cysts. In the cysts, by enlarging, protoscolices and daughter cysts are being formed and fill the cysts. The life cycle is completed by ingestion of the cysts (via organs) by definitive hosts. Apart from consuming contaminated water of food, humans especially children may also take the eggs directly from the hair of infected dogs.

Although the life cycle of Echinococci is simple, the transmission pathways are complex due to involvement of different wild and domestic mammalian animals [10]. Due the changing climate and -in general- environment, both genotypic and phenotypic changes of the strains draw the curtain over the systems of transmission. Detailed data concerning the transmission according to geographic distribution would really be appreciable to provide a control in all over the world.

Until recently, the scientists tried to differentiate the types and subtypes. However, in recent years, holistic approach gained value as "*One Health Concept*". This is more realistic to eradicate the disease and agents in all over the world because, whether for all hosts and intermediate hosts, either domestic or wild, all types and subtypes are in the same eco-system. "*Cleverly*", the parasite can modify itself according to changing eco-system, thus escapes from the controls [11].

2. Control of echinococcosis

2.1 International organizations

Echinococcus spp. are important health causative agents in the World. The spread of the disease also causes economic losses. Infection with echinococci of the farm animals such as sheep and cattle leads to not only direct economic losses but also workload, treatment costs, risk of disease epidemics among organisms including humans. World Health Organization (WHO) accepted "echinococcosis" as one of the

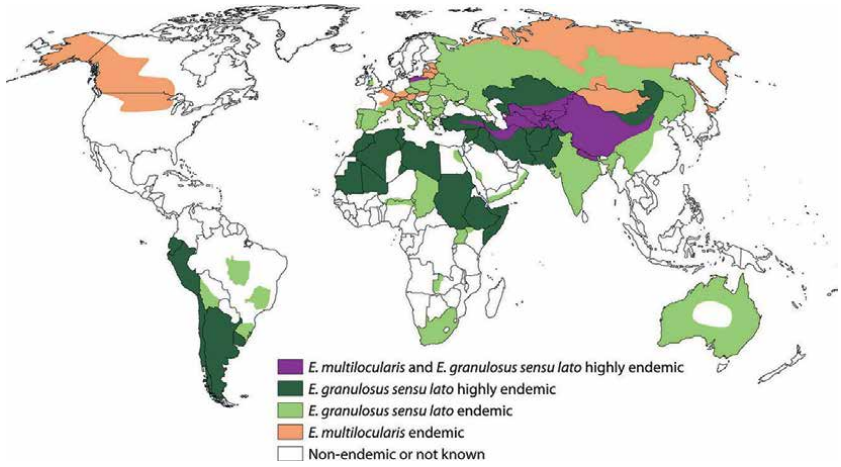

Figure 1.
The distribution of echinococcosis in the world [14].

17 neglected diseases for year 2050 and included this parasitic disease in "elimination program" [12]. Along with this program, the World Health Organization/Food and Agriculture Organization included *Taenia solium*, *E. granulosus*, and *E. multilocularis* in the food borne parasitic diseases [13]. Echinococcosis has a global distribution with an estimated 2–3 million people affected and 200,000 new cases diagnosed annually. Cystic echinococcosis can be seen with prevalence levels of up to 5–10% in Argentina, Peru, East Africa, Central Asia and parts of China (**Figure 1**) [15–17].

This map shows the worldwide distribution of *Echinococcus* spp. It is defined in different colors, taking into account the rate of infection of definitive and intermediate hosts.

2.2 Local organizations

There are many researches and preventive investigations on echinococcosis especially in Europe and Asia. Changes in eco-system have important effects on *Echinococcus* spp., leading to biologic diversities [18, 19]. These changes may cause health problems in animals and humans [20].

According to WHO report on 2021, cystic echinococcosis has a worldwide distribution except Antarctica, whereas alveolar echinococcosis is confined to northern hemisphere especially north central region [21]. However, precise mapping is still difficult to achieve in whole geographic areas.

3. The field of research and development

3.1 *Echinococcus* species

Up until now, people have been rude to the nature for their own interests. We used all-natural resources for ourselves only. To produce more food source, livestock-feed was increased. To achieve this, genetic alterations were used. Meantime, pollution of soil and water by industrial products risked the right to live of all living things. In the end, global warming destroyed the eco-system in the World.

3.2 Animals

3.2.1 Domestic animals

Echinococcus spp. may reside in many farm animals in close similarity to humans. These intermediate hosts are sheep, buffalo, horse, cattle, camel, pig. The definitive hosts are dogs and other members of canidea [10, 14].

3.2.2 Wild animals

It is difficult to combat against echinococcosis in wild-nature. The definitive hosts and intermediate hosts especially for *Echinococcus spp.* are in the wild-nature. The definitive hosts are wild animals such as fox, cat, wolf, raccoon–dog (*Nyctereutes procyonoides albus*), American cervid strain (European or Fennoscandian cervid strain), pigs, lions (*Panthera leo*), jackals (*Canis mesomelas* and *C. aureus*) wild canids (eg. hunting dogs (*Lycaon pictus*), hyaenas (*Crocuta crocuta*).

The intermediate hosts in the wild are plains zebras (*Equus quagga*), giraffe (*Giraffa camelopardalis*), moose (Alces alces), Wapiti (or elk) (*Cervus canadensis*) Muskox (*Ovibos moschatus*), as small mammals; rodents, *Soricidae*, *Talpidae*, *Sciuridae*, *Cricetidae* and *Dipodidae*, and pikas (*Ochotonidae*) (*meriones ungualitis, rattus norvegicus*) [10, 14, 22–25].

3.3 Humans

Humans are aberrant intermediate hosts (dead-ends). *E. granulosus* and then *E. multilocularis* are the top two most common in human echinococcosis.

3.4 Water

Echinococcus spp. eggs are highly resistant to tough conditions. Survival of the eggs mainly depends on humidity and temperature [26]. According to data, eggs protect their viability for 3 weeks at 30°C, 225 days at 6°C and even 32 days at 10-21°C in water and moist soil [27]. In waters from heavy rain and melting glaciers, *Echinococcus spp* eggs may stay long enough time until it is drunken by hosts [28]. Rain may also lead to increased vegetation and may also increase intermediate host [29].

4. Clinical characteristics

Echinococcosis may stay silent in human for many years. The liver is the most commonly involved organ in human. It may show itself by non-specific complaints such as loss of appetite, weight loss, hepatic enlargement (hepatomegaly), uneven and firm liver on palpation, sometimes ascites. The second most common involved organ is the lungs. There may be cough, chest and back pain, high fever, sputum, hemoptysis, dyspnea, allergic signs. Other exceptional signs may be due to cyst compression to the surrounding organs.

In laboratory analyses, hyperbilirubinemia, anemia, eosinophilia (>5%), lymphopenia, low prothrombin time may be present. In addition, high liver function tests (Gamma-glutamyl transferase (GGT), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT)) may be high [14].

4.1 Diagnosis

4.1.1 Radiological diagnosis

According to clinical findings, ultrasound (US) [22]. and/or direct radiograms [30, 31] can be used. Additionally, radiological examinations via computed tomography (CT) scans [32], Magnetic Resonance Imaging (MRI) [33], Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) [34],^{67}Ga Scintigraphy [35] can aid to diagnose "echinococcosis". In recent years, radiological methods do not only aid in diagnosis but also give a chance to treatment. Puncture, aspiration, injection, re-aspiration (PAIR) technique are widely being used in type I and Type IICE in non-complicated locations [36, 37].

4.1.2 Serological and molecular diagnosis

Indirect fluorescent antibody (IFA), indirect hemagglutination (IHA), Enzyme-linked immunosorbent assay (ELISA), Western blotting (EmWB) (LD BIO Diagnostics, Lyon, France) [38], 70–90 Em WB [39] are the serological methods for the diagnose. Molecular methods in the diagnoses of echinococcosis are DNA detection, real time PCR [40, 41], quantitative and/or nested PCR assays nested PCR [42], LAMP-based assays [43, 44], cell-free DNA (cfDNA) [45].

4.2 Treatment

Treatment of echinococcosis is mainly surgical. As anti-infective medical treatment, Benzimidazole carbamates, Albendazole (ABZ) (10–15 mg/kg/day, continuously), or Mebendazole (4.5 g/day) are in use. However, ABZ and Mebendazole act as parasitostatic, thus they just stop the growth of larvae [46].

4.3 Prevention

The World Health Organization (WHO) has listed echinococcosis as one of the 17 neglected diseases targeted for control or elimination by 2050 [12].

One arm of prevention would be the prevention of dissemination of the disease from the hosts. This may be achieved first the diagnose by using stool antigen tests in dogs. The second arm would be "vaccination". Although there is no vaccination against Echinococci for dogs, vaccination of sheep would be helpful. EG95 vaccine is a vaccine for *E. granulosus* and can be given as two doses monthly injection, thereafter as yearly booster [14, 47]. It is more difficult to find a way to control *E. multilocularis*, since the life cycle is tricky to break due to hosts in wild life, thus there is no vaccination [48]. The treatment of red foxes has been shown effective but sustainability of such method of prevention is difficult due to high cost [49].

4.4 Education

4.4.1 Training of educators

Multidisciplinary international meetings should be held to define strategies for action plans against echinococcosis.

Species	New classification	Natural definitive host species (excluding humans)	Human public health importance	intermediate host	Geographic Distribution	References
1.*E. granulosus*						
1.1.(G1) (sheep strain)	*E. granulosus sensu stricto*	carnivors (dogs, foxes, dingo, jackal, hyena)	High	Domestic (sheep, cattle, pigs, camels, and goats)	Australian mainland, Europe, USA, New Zealand, Africa, China, Middle East,South America and Russian Federation	[50–54]
1.2.E. granulosus (G2) (Tasmanian sheep strain)	Genotype G2 is no longer considered a valid genotype, but it is recognized as a microvariant of G3	carnivors (dogs, foxes)	High	Domestic (sheep, cattle)	Tasmania, Argentina	[10, 55]
1.3.E. granulosussensustricto (G3) (buffalo strain)	Manda	carnivors (dogs, foxes)	?		Asia	[5, 10]
1.4.E. granulosus (G4) (horse strain)	*E. equinus*	carnivors (dogs) lions (Panthera leo), black-backed jackals (Canis mesomelas)	No	Perissodactylids (horses) Donkeys, plains zebras (Equus quagga), red ruffed lemur (Varecia rubra)	Europe, Middle East, South Africa, (New Zealand? USA?)	[23, 56]
1.5.E. granulosus (G5) (cattle strain)	*E. ortleppi*	Domestic Dogs	Yes (rarely)	Cattle, Goats, pigs, zebra, oryx antelopes (Oryx gazella), giraffe (Giraffa camelop ardalis)	Europe, South Africa, India, Sri Lanka, Russian Federation, South America?	[57, 58]
1.6.E. granulosus (G6) (camel strain)		Dogs	Yes	Camels,sheep,	Middle East, Africa, China, Argentina	[59]

Species	New classification	Natural definitive host species (excluding humans)	Human public health importance	intermediate host	Geographic Distribution	References
1.7.E. granulosus (G7) (pig strain)	*E. canadensis (G6/G7)*	Pig-raising Domestic:Dogs Wild: wolf Camel-raising: domestic dogs and	Yes(moderate)	Pig-raising: Pigs other livestock (e.g., goats), Wild: wild boar Camel-raising: Camel, dromedaries house mouse (M. musculus)	Pig-raising regions of western Eurasia and South/Central America Camel-raising regions (from eastern and northern Africa through the Middle East to central Asia)	[10]
1.8.E. granulosus (G8) (American cervid strain)	*Echinococcus ortleppi*	Wolf, Dogs,	Yes	moose (Alces alces), Wapiti or elk (Cervus canadensis) Muskox (Ovibos moschatus) Cervids	North America, Canada, northeastern United States, Eurasia	[10]
1.9.E. granulosus (G9)	Dog		pig strain; cervid	Humans	Polonya	[14]
1.10. E. granulosus (G10)	*E. canadensis* (European or Fennoscandian cervid strain)	Domestic dog, wolf		Wild: moose, wapiti, caribou, moose Domesticated reindeer and moose Pig, camel, cervids	Canada Unitad States Mongolia Eurasia,	[10]
Lion strain	*E. felidis*	Lions (P. leo), potted hyenas (Crocuta crocuta),		Zebra, wildebeest, warthog, bushpig, buffalo, various Antelope, giraffe? hippopotamus? red river hogs (Potamochoerus porcus)	Africa	[10, 60]
Lagomorf (?)						
2.*E. multilocularis*						

Species	New classification	Natural definitive host species (excluding humans)	Human public health importance	intermediate host	Geographic Distribution	References
2.1. European isolate		Fox, dog, cat, wolf, raccoon–dog	Yes	Rodents (Microtus. levis), domestic and wild pig, dog, monkey	Europe, China?	[10, 17]
2.2. Alaskan isolate		Wolves (C. lupus), dog, cat	Yes	Rodents Tundra voles (Microtus oeconomus) singing vole (Microtus miurus)	Alaska	[10, 17]
North American isolate		Arctic foxes (Vulpes lagopus), dog, cat, coyote	Yes	Rodents	North America	[10, 17]
2.3. Hokkaido isolate		Fox, dog, cat, raccoon –dog	Yes	Rodents, pig, monkey, horse		[10, 17]
3. *E. vogeli*		Bush dog	Yes	Rodents (Paca)	Central and South America	[10, 17]
4.*E. oligarthra*		Wild felids	Yes	Rodents (Agouti)	Central and South America	[10, 17]
E. shiquicus		Tibetan fox		Pika	Tibetan plateau	[61]

Table 1.
Schematic phylogeny of interrelationships between members of the Echinococcus species, strains, isolates, genotypes, definitive host and intermediate host vertebrates.

4.4.2 Public education

Professions, those related to animals and animal products, especially farmers, shepherds, hunters, tanners, veterinarians and people in the endemic areas such as soldiers, climbers, athletes, scouts, hikers should be informed and educated periodically (**Table 1**) [62].

5. Conclusion

- Echinococcosis is *STILL* an important "neglected disease", and food borne parasitic diseases.
- Adaptive changes of *Echinococcus spp.* stemmed mainly from humans wrong attitude towards eco-system. To prevent this;
  - Global warming should be taken into consideration since endemic areas for Echinococci are also increased.
  - Dissemination of infected tissues to the environment and contamination should be prevented.
  - The spread of the disease causes economic losses.
- In this 21st century, new molecular-based and radiological methods should be investigated and developed.
- To increase the awareness of echinococcosis, national and international communication should be provided.
- To combat against the disease, cooperation among healthcare professionals, veterinarians, municipalities should be coordinated both in national and international levels. That is to say "One health concept" is important.

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Chapter 2

Perspective Chapter: Echinococcosis – An Updated Review

Narendra Nath Mukhopadhyay

Abstract

Common Name: Dog Tapeworm. *Echinococcus granulosus* is most prevalent and causes cystic hydatid disease. *Echinococcus multilocularis* is uncommon and responsible for alveolar hydatid disease. Hydatid disease is a significant health problem worldwide. It is a zoonosis. Adult worm lives in the small intestine of dog and rarely wolf and fox. Dog is the optimal definitive host. The larval stage (hydatid cyst) is found in herbivorous animal like sheep, goat, cattle. Man is the accidental intermediate host. Echinococcal infection occurs through ingestion of eggs that are passed through the feces of definitive host. After ingestion of eggs, the egg liberates embryo which passes through the intestinal mucosa in the portal circulation. Right lobe of the liver is the commonest site for liver hydatid cyst. The cyst wall consists of pericyst, ectocyst and endocyst. Endocyst or the germinal layer is the site of asexual reproduction giving rise to brood capsule and scolices. Symptoms mainly due to pressure effect. Rarely fatal anaphylaxis may occur due to spontaneous rupture or during surgery. USG and CT is the most valuable imaging technique. Serology is an adjunct to diagnosis. Classification of hydatid cyst by Gharvi et al. into five types based on sonographic analysis. Treatment modalities include chemotherapy, percutaneous treatment and surgery.

Keywords: echinococcosis, hydatid cyst, pair, pericystectomy

1. Introduction

Echinococcosis or hydatid disease caused by canine tapeworm *Echinococcus granulosus* and rarely by *Echinococcus multilocularis*. It is a significant health and socioeconomic problem globally and more than 1 million people are affected at any one time. Although hydatid cyst is a benign disease but treatment is difficult, recurrence rate is high and may cause life threatening complication. This chapter reflects updated review of evaluation, diagnosis and treatment of Echinococcosis.

Human Echinococcosis (Echinococcal cyst, Hydatidosis, Hydatid disease) is a parasitic disease caused by the tapeworm of the genus Echinococcus and the family Taeniidae. Hydatid disease has been described by Hippocrates who speaks of "Liver full of water." The word echinococcus is Greek origin means "hedgehog berry." Hydatid is also of Greek origin meaning a "water vesicle." In Latin hydatid means a "drop of water."

The genus Echinococcus contains four species:

1. *Echinococcus granulosus*.

2. *Echinococcus multilocularis*.

3. *Echinococcus vogeli*.

4. *Echinococcus oligarthus*.

E. granulosus is most common and causes cystic hydatid disease [1]. *E. multilocularis* is uncommon and causes alveolar hydatid disease. *Echinococcus vogeli* and *oligarthus* are rare entity and causes polycystic hydatid disease. Adult *E. granulosus* was described by Hartmann in the small intestine of dog in 1695 and the larval form (hydatid cyst) was recognized by Goeze in 1782.

Human Cystic Echinococcosis (CE) is a zoonosis and is prevalent in most parts of the world except Antarctica. It is most common in sheep and cattle raising areas of Australia, Africa, South America. It is also prevalent in Europe, China and Middle East. In endemic areas it is significant health and socio-economic problem. More than 1 million people are affected with Echinococcosis at any one time.

2. Habitat

Adult worm lives in the small intestine of dog and other canine carnivora like wolf and fox. The larval stage is found in sheep and other herbivorous animal like goat, cattle and horse. Human being is an accidental intermediate host.

3. Parasitology

Adult worm is a small tapeworm 3–6 mm in length and consists of scolex, a short neck and a strobila. The scolex is pyriform with four suckers and a prominent rostellum. Neck is short. The strobila is composed of three proglottides: (a) anterior immature, (b) middle mature (c) posterior gravid segment. The gravid proglottid contains about 200 and 800 ova. Adult worm survives 6–30 months.

4. Eggs

Ovoid in shape and brown in color. It contains an embryo which is called an oncosphere or hexacanth because it has six hooklets.

5. Larval form

Larval form develops into hydatid cyst in the various organs of intermediate host. It represents the structure of scolex of adult worm and remain invaginated within a vesicular body. After entering the definitive host the scolex with suckers and rostellar hooklets becomes exvaginated and mature into adult worm.

6. Lifecycle

Lifecycle is completed in two hosts.

6.1 Definitive host

Dog (The optimal host), wolf, jackal, fox.

6.2 Intermediate host

Sheep and cattle. Sheep is the ideal intermediate host. Man is the accidental intermediate host (dead end) and become infected when they accidentally ingest the eggs of the tapeworm during intimate handling of infected dogs or by consumption of vegetables, food and water contaminated with eggs.

Several distinct genotypes of *E. granulosus* are recognized but not all genotype causes human infection. The genotype causing CE in human is principally maintained in dog-sheep-dog cycle.

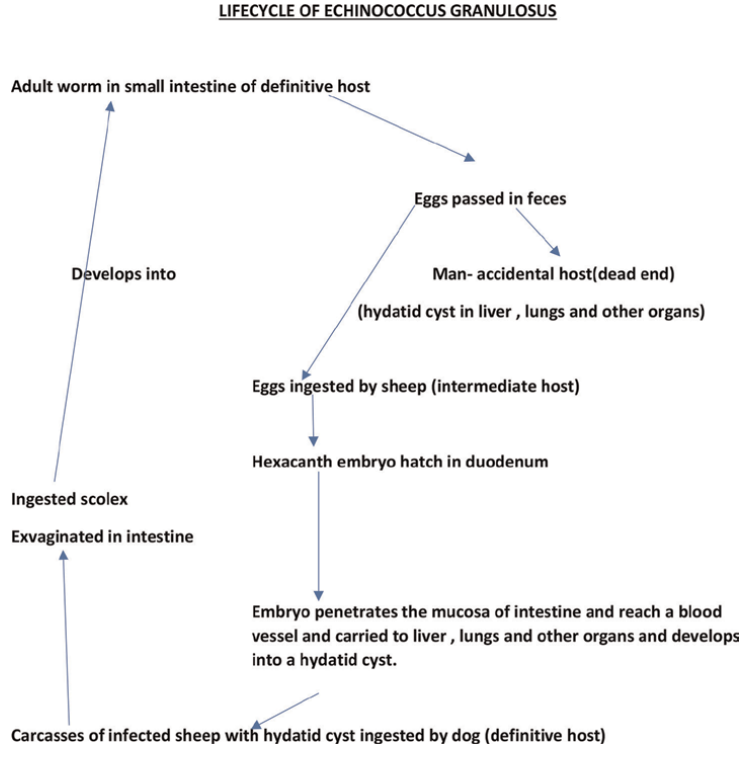
Alveolar echinococcosis (AE) usually occurs in wildlife cycle between foxes and other carnivores with small mammals (mostly rodent) acting as intermediate host. Domesticated dogs and cats can also act as a definitive host.

After ingestion of eggs hexacanth embryo hatch in the duodenum and penetrate the mucosa reaching into portal circulation and gets trapped in hepatic sinusoids and eventually develops into liver hydatid cyst (75%) which acts as a first filter.

Some embryo may pass through the liver and enters the right side of the heart and are caught in pulmonary circulation which acts as a second filter forming lung hydatid cyst (20%).

Few enters the systemic circulation and give rise to hydatid cyst of various other organ like spleen, kidney, eye, brain, bones [2].

Infection with echinococcal organism is the most common cause of liver cyst in the world [3].



7. Formation of hydatid cyst

Once the embryo is deposited in an organ it develops into a cyst filled with fluid. It enlarges slowly and reach a diameter of 0.5–1 cm in about 6 months. Mature cyst is able to survive within organs for years. The growing cyst evokes host tissue response with formation of fibrous capsule around it. Mature cyst has two layers:

1. Outer layer (Pericyst): It is a dense fibrous tissue layer and usually due to host response to the parasite. It is not present in pulmonary and brain hydatid cyst. Pericyst consists of two different layers. The inner layer of pericyst or exocyst is the result of an inflammatory and granulomatous reaction. It frequently contains osteopontin which regulates macrophage accumulation and calcium deposition. The outer layer is the adventitia and composed of biliovascular elements and tributaries of hepatic veins. Separating the exocyst from the adventitial layer is the basis of sub adventitial cystectomy.

2. Inner layer: It is further divided into two layers:

    a. Ectocyst: It is composed of acellular, chitinous, laminated hyaline material. It is efficient barrier for bacteria and an ultra-filter for protein.

    b. Endocyst: It is the inner germinal layer which is cellular and consists of number of nuclei within a protoplasmic mass and is very thin (22–25 μm). It is the vital layer of the cyst and responsible for production of hydatid fluid, ectocyst, brood capsule, scolices, and daughter cyst. From the inner wall of brood capsule protoscolices (new larva) develops which represents the head of the potential worm with invaginated scolex. Development of brood capsule from germinal layer indicates complete biologic development of cyst which occurs after 6 months of growth.

    Several thousands of protoscolices develop into mature hydatid cyst and thus it reflects a process of asexual reproduction.

    Daughter cyst formation is a defense mechanism. Any injury to hydatid cyst may cause daughter cyst formation. Daughter cysts are replica of mother cyst but without a pericyst. Even grand daughter cyst may develop. In uncomplicated cases the cyst cavity is filled with a sterile colorless antigenic fluid containing salt, enzymes, proteins and toxic sustances [4]. The formation of daughter cyst is called endogenic vesiculation. Exogenic vesiculation occurs when a small rupture or defect in the laminated membrane occurs and the germinal layer passes through it and creates a satellite hydatid cyst. This process is uncommon in *E. granulosus* but characteristic of larval stages of *E. multilocularis*. *In E. multilocularis* process of exogenic vesiculation is fulminant. Multiple vesicles are formed in all directions. The infected parenchyma has a multilocular appearance and centre becomes necrotic and spongy and filled with gelatinous fluid similar to that of mucoid liver carcinoma. Hepatic insufficiency is common and disease is often lethal [4].

8. Acephalocysts

Some cysts are sterile and may never produce brood capsule and some brood capsule may not produce scolices. These are called acephalocysts.

9. Clinical features

The clinical features of hydatidosis depend on the site, size, number, viability and stage of development of cyst [4]. Most of the time it is asymptomatic and incidentally discovered. Lung cyst gives rise to symptoms even if small. Liver cyst usually becomes symptomatic when it is more than 5 cm.

9.1 Clinical features of liver hydatid cyst

The symptoms can be non-specific or due to mass effect or cyst complications.

Symptoms	Signs
Right upper quadrant pain (74%)	Palpable mass in right upper quadrant (55%)
Vomiting	Fever
Dyspepsia	Jaundice
Non-specific fatigue	Malnutrition
Weight loss	Cholangitis
Fever	Pleural effusion
History of jaundice	Splenomegaly
Allergy	Ascites
Hydatid emesis	Skin rash
Hydatid enterica	Pancreatitis
	Hydatid cachexia (children in endemic areas)
	Hydatid thrill (if the cyst is present near lower margin of liver)

10. Clinical features of lung hydatid cyst

Cough, hemoptysis, chest pain, pneumothorax, dyspnoea.

11. Clinical features of H.C in other sites

Cerebral hydatid cyst may present with focal epilepsy.

Bone- Laminated layer is not well developed. The parasite migrate along the bony canal and erode the bone tissue. Erosion of bone may lead to pathological fracture.

12. Course of the disease

The hydatid cyst enlarges slowly and the growth rate depends on the immunological relationship between the parasite and the human and the resistance offered by

surrounding tissues. Rate of growth is usually 1 mm in diameter per month. Sometimes the hydatid cyst dies, the germinal layer disintegrated and the hydatid fluid is absorbed. Over time the pericyst calcifies [5]. However, not every calcified cyst is dead.

13. Complications related to hydatid cyst

1. Infection and suppuration: Most frequent cause of infection is cysto biliary communication (CBC). The clinical presentation is similar to a pyogenic liver abscess.

2. Mass- effect: In CNS and lung small cyst causes serious symptoms. In liver large cyst may give rise to pressure atrophy of surrounding hepatocytes and compensatory hypertrophy of remaining liver tissue. Large cyst can replace entire liver lobe. Portal hypertension and Budd-Chiari like syndrome have been described.

3. Rupture:

    a. Internal: Injury or bile leak can damage the laminated membrane and liberated protoscolices occupy the space within the pericyst cavity. A univesicular cyst converted into multivesicular cyst.

    b. Free rupture:

    - Intraperitoneal: The hydatid cyst is a high-pressure cyst (30–70 cm of water). Because of high intracystic pressure, both univesicular and multivesicular cyst can rupture. Sudden rupture may give rise to acute abdomen with severe anaphylactic reaction and circulatory collapse. Cyst rupture also leads to release of thousands of protoscolices leading to disseminated abdominal hydatidosis.

    - Intrathoracic: can give rise to pleural effusion, empyema, pneumonitis, lung abscess. Rupture into a bronchiole may give rise to appearance of cyst in sputum. Rarely there is formation of broncho biliary fistula.

    - Intra biliary: Rupture into the biliary tree can lead to obstruction by the daughter cyst producing cholangitis, obstructive jaundice and sometime pancreatitis. Leak into the biliary tree can lead to classical triad of biliary colic, jaundice and urticaria. Hydatid emesis and hydatid enterica may occur rarely.

      CBC can be of minor communication and major communication. Major communication has a fistula diameter of more than 5 mm.

      Reported incidence of rupture of hydatid cyst into bile duct ranges from 2.6 to 30%. If the cyst content is bile stained a meticulous search for CBC is necessary.

- Rupture into adjacent viscera: Rupture into digestive tract giving rise to hydatid emesis and in urinary tract hydatiduria.

  Rupture of hydatid cyst into Aorta, IVC and Heart with embolism have been reported.

14. Diagnosis

14.1 Imaging

a. Plain X-Ray: It is of limited value. Plain x-ray of the abdomen and chest may reveal elevation of right hemi diaphragm or a thin rim of calcification.

b. Ultrasound: It is the most common investigation used for the diagnosis of hydatid cyst and reported sensitivity of USG is 100% [6]. A cyst containing daughter cyst and hydatid sand are highly suggestive (**Figure 1**). A solitary anechoic liver cyst should be considered hydatid until proved otherwise.

US diagnostic features of hydatid cyst are:

a. multivesicular cyst has been termed as "cart wheel sign."

b. Daughter cyst gives rise to "rosette appearance."

c. separation of laminated membrane produces a split wall appearance and complete collapse resulting in "water lily sign."

d. calcification of cyst wall.

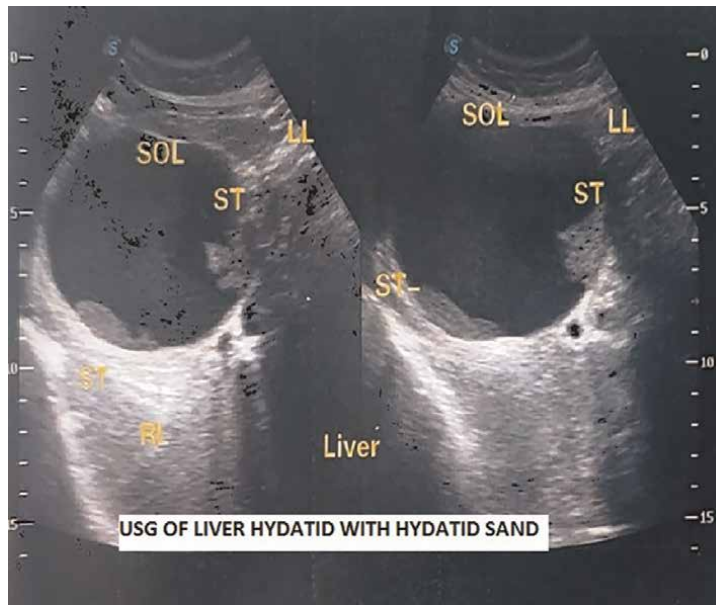


Figure 1.
USG of liver hydatid cyst.

Ultrasound also shows morphology of the cyst, thickness of the wall, extent of communication to biliary tree, the diameter of biliary and vascular channel. Supplemented with Doppler it indicates the status of portal vein, hepatic artery, and retro hepatic venacava. Intra-operative US (IOUS) is very helpful during surgery and can alter operative strategy.

Based on US sign Hassan Gharbi in 1981 classified the liver hydatid cyst into five types [7]. This classification is widely used:

Type I: Pure fluid collection.

Type II: Fluid collection with split wall.

Type III: Fluid collection with septa.

Type IV: Heterogenous appearance.

Type V: Those with reflecting thick wall.

Depending on the cyst characteristic described by Gharbi the WHO—IWGE proposed a new classification based on ultrasound morphology and corelated with activity of the disease that facilitate selection of treatment modalities.

WHO-IWGE classification of hydatid cyst [8]:

CL	Active	USG features—sign not pathognomonic, unilocular, no cyst wall
CE1	Active	Cyst wall, "hydatid sand," rosette Like.
CE2	Active	Multivesicular, cyst wall, rosette Like.
CE3	Transitional	Detachment of laminated Membrane, water lily sign, Less round - decreased intra cystic pressure.
CE4	Inactive	Heterogenous hypo or hyper Echogenic degenerative contents, No daughter cyst.
CE5	Inactive	Thick calcified wall, calcification Partial or complete - not pathognomonic. But highly suggestive of diagnosis

c. CT: CT gives rise to more precise information regarding the number, position and cyst characteristics. It is more useful when complications are suspected (**Figures 2** and **3**). CT has high sensitivity and specificity. Discontinuity of cyst

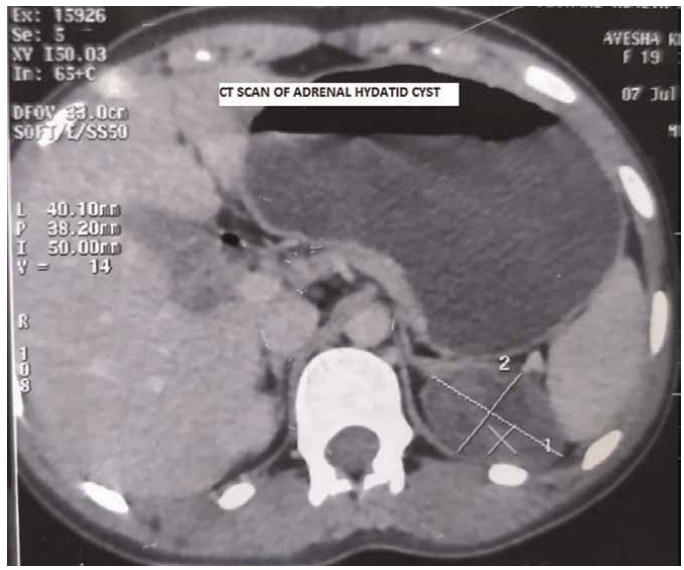


Figure 2.
Adrenal hydatid cyst CT.

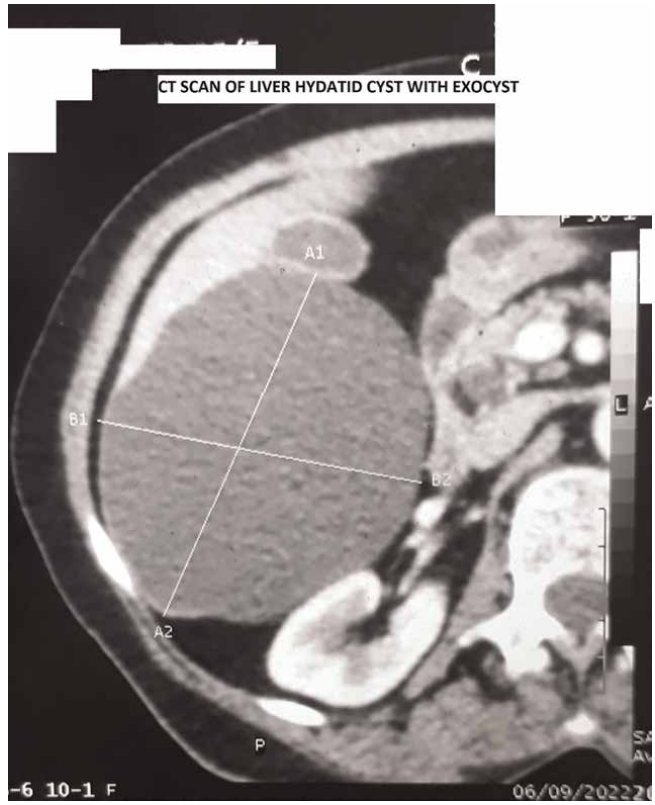


Figure 3.
CT of liver hydatid cyst.

wall near bile ducts is highly suggestive of CBC. Calcification of cyst wall is easily seen on CT. Mother cyst containing daughter cyst are diagnostic of hydatid cyst. CT is also superior in detecting exogenous vesiculation. It also provides information regarding the position and extent of intra-abdominal disease. It is also a very useful investigation in suspected lung or brain hydatid cyst. CT is imperative for operative management specially with a laparoscopic approach (**Figure 4**) [9].

d. MRI: MRI gives rise to excellent image of liver and abdominal hydatidosis. It is most valuable diagnostic tool for skeletal and vertebral disease and cardiac cyst. MR Angiography can be done when large cysts are in close relation to a major vessel. An increase in signal intensity of the cyst content on MR suggest CBC or superinfection [10]. MRCP is considered the investigation of choice for jaundice patients with liver hydatid.

e. ERCP: Routine use of ERCP advocated by some authority to completely delineate bile duct anatomy and to visualize any clinically silent CBC [11]. Pre-operative endoscopic papillotomy is indicated:

i. Imaging showing suspected hydatid material in CBD.

ii. Presenting feature is cholangitis whether CBC is present or not.

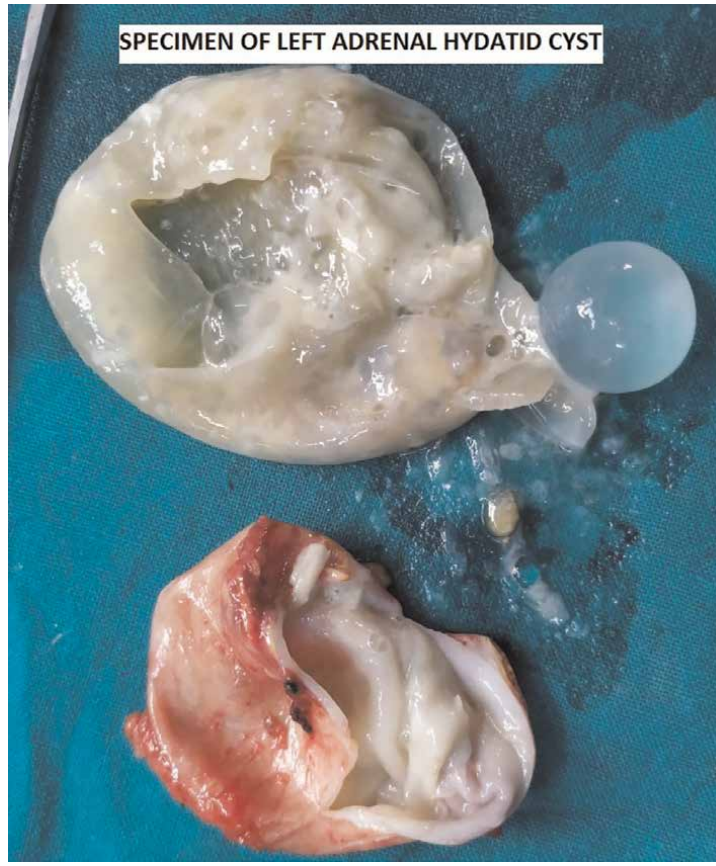


Figure 4.
Adrenal hydatid cyst specimen.

Indication of Post-operative endoscopic papillotomy:

i. Hydatid debris in CBD.

ii. Biliary fistula lasting more than 3 weeks.

iii. High output biliary fistula (more than 1 liter in 24 hours).

iv. Presence of jaundice.

v. Short stricture involving papilla

14.2 Serology

A number of antibodies to the hydatid antigen produced from oncosphere, laminated membrane and cyst fluid. The detection of circulating *Echinococcus granulosus* antigen is less sensitive than the detection of antibodies. Detection of serum antibodies

using specific antigen (8 and 16 KDA) from hydatid fluid are frequently used to support the diagnosis of CE.

14.3 Antibody detection

Test detecting antibody against antigen B are ELISA, Indirect hemagglutination test and indirect immunofluorescence test.

Test detecting antibody against hydatid fluid fraction 5 antigen are CFT and precipitation test. The arc of precipitation (Arc 5) seen on immune electrophoresis is most specific and virtually diagnostic of hydatid disease.

A negative serology does not exclude the diagnosis of hydatid disease in a anechoic liver cyst because of high incidence of false negative result (**Figure 3**).

15. Clinical criteria for diagnosis

According to the WHO-IWGE the diagnostic criteria are:

i. Slowly growing cystic mass or masses diagnosed by imaging

ii. Incidental finding of a cyst in a asymptomatic carrier or detected by screening technique

iii. Anaphylactic reaction due to leaking or ruptured cyst.

The diagnosis is based on:

a. Typical organ lesion detected by imaging

b. High sensitivity and specificity serologic test

c. Macroscopic morphology of hydatid cyst in surgical specimen

d. Histopathology or parasitology typical for hydatid cyst

15.1 Treatment modalities

- Wait and see
- Chemotherapy
- Percutaneous treatment
- Surgery

Based on WHO Classification certain management guidelines suggested:

A. Active cyst: Type CL, CE1, CE2- About one- third of the cyst are sterile. In these patients management options are: wait and see, further differential diagnosis, chemotherapy.

Remaining two-third of the patients having fertile cysts and half of them will have secondary cyst. Management options are: surgery, PAIR, chemotherapy.

B. In Transitional state (Type CE3): Living protoscolices can exist and all treatment options should be considered.

C. Inactive cysts (Type CE4 and CE5): Further differential diagnosis is usually necessary and no treatment is usually required.

15.2 Chemotherapy

It is an integral part of management of hydatid cyst. The main advantage of chemotherapy is that it can be given in out-patient basis and avoid surgical complications. The most commonly used agents are - mebendazole (MBZ) and albendazole (ABZ). Both drugs interfere with glucose absorption through the wall of the parasite leading to glycogen depletion. ABZ is the only drug that is ovicidal, larvicidal, and vermicidal and it is the drug of choice. Praziquantel has been used with albendazole to increase the protoscolicidal effect of albendazole but side effects are significant.

Chemotherapy can be given alone as a primary therapy, pre-interventional administration, or adjuvant therapy after operation.

15.3 Indications of primary chemotherapy

a. Contraindications to surgery

b. Poor surgical risk

c. Inoperable patient with primary liver and lung disease

d. Patient with multiple cyst in two or more organ

e. Multiple small liver cysts

f. Deep seated liver cyst

g. Prevention and management of secondary echinococcosis

h. Recurrent echinococcosis

i. In combination with surgery and PAIR

j. Pulmonary hydatid cyst

Available evidence indicates that chemotherapy alone is not the ideal treatment with high failure rate and recurrence. About 25% of the cyst recurs once medical therapy stopped [12]. Pre-operative chemotherapy is given to sterilize the cyst contents and thereby diminishing the chance of secondary echinococcosis by accidental spillage during surgery. Three to 4 weeks of pre- operative treatment significantly reduce viability of the cyst [13].

Short-course albendazole is ineffective [14]. Post-operative ABZ to be started for about 4 weeks if there is leakage of cyst contents during surgery. According to WHO-IWGE preinterventional administration of ABZ or MBZ should be given 4 days before intervention and continued one month for ABZ and 3 months for MBZ.

15.4 Dosage

ABZ is given orally 10–15 mg/kg/day in divided doses with a fat rich meal for 28 days followed by a gap of 14 days. Three such cycles to be given. Improvement is defined as reduction in cyst size more than 25%, membrane separation or calcification. Now there are emerging evidence that continuous treatment as opposed to gap in between the courses is safe and more effective. Limited data available for use of praziquantel. The dose is 40 mg/kg/week for the management of intraperitoneal spillage during surgery or other interventional procedure. In endemic areas echinococcosis can be prevented by administering Praziquantel to infected dogs. MBZ is given at a dosage of 40–50 mg/kg/day in three divided doses with a fat rich meal for a period of 3–6 months.

15.5 Side effects

Alteration of liver function has been reported. 10 to 20% patients may develop elevation of transaminases which is reversible. Idiopathic bone marrow suppression is also seen with these drugs. Other side effects are jaundice, pyrexia, alopecia and leucopenia.

15.6 Percutaneous treatment

PAIR (Puncture, Aspiration, Injection, Re-aspiration): Previously percutaneous puncture of hydatid cyst was contraindicated for fear of spillage around puncture site as pressure inside the cyst maybe as high 70 cm of water. A new interventional procedure-PAIR emerged in 1990 with high success rate. RCT by Khuru et al. in 1993 [15] and many other studies showed risk of anaphylaxis and risk of recurrence is negligible. The technique is ideal for Gharbi Type I to III cysts. Treatment of ABZ started 10 days before the procedure and continued for 1–2 months after the procedure.

16. Indication of pair

i. Cyst Type CL, CE1, CE3 and some CF2 (Gharbi Type I and II and some patients with Type III and IV with drainable material).

ii. Infected cyst

iii. Inoperable patient

iv. Pregnant women

v. Patient with multiple cysts greater than 5 cm in diameter in different liver segments

vi. Recurrence following surgery

vii. Lack of response to chemotherapy

17. Contraindications to pair

i. TYPE III and IV cysts (Hydatid cyst with heterogenous echo pattern)

ii. Communication with biliary system

iii. Cysts inaccessible to puncture

iv. Multiple septal divisions

v. Lung or bone cyst

vi. Children less than 3 years old.

18. Technique

Classical PAIR procedure is done under USG guidance in the following steps:

1. Percutaneous puncture of the cyst through transhepatic route
2. Aspiration of cyst fluid and assessment for viable protoscolices and bilirubin
3. Injection of a scolicidal agent in the cyst and left for 15 minutes
4. Reaspiration and examination of fluid for viable protoscolices
5. Procedure is repeated until no viable protoscolices found or there is total separation of germinal layer from pericyst
6. A catheter can be left in cavity for drainage if it is more than 6 cm

Recurrence rate vary between 0 and 4% and overall complication rate vary between 15 to 40%. Major complications like anaphylactic shock is rare. Minor complications like urticaria, itching, hypotension, fever, infection, rupture into biliary system ranges from 10 to 30%. 2.8% patients require repeat procedure to achieve satisfactory result [16]. Complicated cysts, cysts with many daughter cysts or large volume cysts are indications of PAIR modification:

1. The PAIR catheterization technique
2. The D-PAI (Double puncture, aspiration and injection technique)
3. PEVAC (percutaneous evacuation of cyst content)
4. MOCAT (modified catheter aspiration technique)

19. Scolicidal agents

In any intervention on hydatid cysts major danger is spillage of viable protoscolices resulting in peritoneal dissemination. To kill the viable elements scolicidal agents are frequently injected into the cysts and also to cover the surrounding liver parenchyma with gauze or mops soaked in scolicidal agents.

Formalin, hypertonic saline 15–20%, chlorhexidine, cetrimide, hydrogen peroxide, polyvinyl pyrrolidone-iodine, silver nitrate, ethyl alcohol are some of the many agents used [17]. Formalin causes sclerosing cholangitis, Hypertonic saline can lead to hypernatremia, Acidosis with chlorhexidine and chemical cholangitis with alcohol has been reported. No agent should be injected pre-evacuation due to high intra cyst pressure. WHO regards use of scolicidal agents for intra operative killing of infectious material questionable because no agent is both safe and effective. According to WHO ethanol 70–95%, hypertonic saline 15–20% and cetrimide solution 0.5% having relatively low risk [18].

19.1 Surgery

Surgery remains the gold standard for hydatid cyst management. Objectives are:

1. Eradicate macroscopic parasite
2. Inactivate the scolices
3. Prevent spillage of cyst content
4. Elimination of all viable materials of the cyst
5. Management of CBC if present
6. Management of residual cavity

19.2 Indications of surgery

i. Large cyst with multiple daughter cysts

ii. Superficially located cysts that may rupture

iii. Infected cysts

iv. Cysts with CBC

v. Large cysts exerting pressure effect on vital structure

vi. Cysts in lung, brain, kidney, bones and other organs

19.3 Contraindications to surgery

i. Extreme of age

ii. Pregnancy 1st and 3rd trimester

iii. Severe comorbid conditions

iv. Numerous cysts

v. Cysts in multiple organs

vi. Difficult to access

vii. Dead cysts

viii. Very small cyst less than 5 cm

19.4 Surgical options

1. Conservative—open/laparoscopic—deroofing and cyst evacuation. It is a tissue sparing procedure which is limited to remove the parasites and other viable elements with most of the pericyst left in situ.

2. Radical surgery:

    i. Cysto pericystectomy

    ii. Liver resection

    iii. Liver transplantation

20. Conservative surgery

20.1 Basic steps

i. Adequate exposure of the cyst

ii. Safe decompression of the cyst

iii. Sterilization of the cyst contents

iv. Evacuation of the cyst contents

v. Identification and management of CBC if present

vi. Management of residual cavity.

21. Open technique

After adequate exposure, the cyst is packed off from rest of the peritoneal cavity using blue or green packs soaked in 15–20% saline (**Figure 2**). Colored packs and drapes ensure better visibility of whitish cyst element. The cyst is aspirated with 16G needle until it is no longer tense taking utmost precaution to avoid spillage. Some special devices have been developed for safe decompression of the cyst. The use of "cone" which adheres to liver surface by vacuum to prevent spillage have been described. Once no further fluid is aspirated a scolicidal agent is injected (provided the cyst fluid is not bile stained) and if it is hypertonic saline it is left for 10 minutes. Cyst is finally aspirated and larger incision is made to introduce large bore suction cannula. The remaining cyst fluid and solid contents are aspirated. Cyst is finally deroofed and remaining daughter cysts and germinal membrane are removed using sponge holding forceps. Cavity is finally inspected cautiously for a bile leak which is best demonstrated by packing the cavity with white colored pack left in place for 5–10 minutes and note any bile staining. If bile-stain appears a meticulous search for orifice of CBC is conducted aided by gentle squeeze of gall bladder if necessary. Intraoperative detection of CBC is essential for adequate management. Many authors have recommended intraoperative (cystic duct) cholangiogram. Cavity may then be irrigated with a scolicidal agent [11].

21.1 Management of CBC

1. Suture: majority of patients with CBC is with a peripheral and small duct and simple suture of the defect is sufficient

2. Drainage only

3. Suture plus T-tube

4. T-tube only

5. Drainage plus decompression of biliary tree- decompression is achieved externally by T-tube or internally by endoscopic papillotomy, trans duodenal sphincteroplasty, biliodigestive bypass

6. CBC with major duct: options are

    - Roux-en-Y cystojejunostomy
    - Roux-en-Y intracysticjejunostomy
    - Roux-en-Y hepaticojejunostomy
    - Intracystic bile duct repair
    - Liver resection

21.2 Management of residual cavity

1. Omentopexy

2. External drainage

3. Pericyst cavity left open

4. Simple closure of cyst cavity

5. Introflexion of the rim of pericyst

6. Capitonnage- spiral suturing from the bottom of the cyst cavity upwards

Most commonly used methods for management of remaining cavity are omentopexy and external drainage. Omentopexy is preferred when cyst is simple without CBC and external drainage is preferred in infected cyst and when CBC is present. Though omentopexy is an easy procedure most serious complication is ischemia of transposed omentum. Detection of recurrence by USG also becomes more difficult after omentopexy. Open cyst evacuation recurrence rate is 10–30% [17]. A RCT by Seyed Reza Mousavi et al. showed lower post operative complications (5.7 v/s 16.6%) and less mean hospital stay (6.5 v/s 15.6 days) in omentopexy group compared to external drainage group [19].

22. Laparoscopy

Laparoscopic surgery follows the same principles as in conventional open approach. Peripherally located Echinococcal liver cyst may safely be managed by laparoscopic cyst evacuation [18]. Excluding criteria for laparoscopic cyst evacuation are- deep intraparenchymal cyst, posteriorly situated cyst, more than three cysts, cysts more than 15 cm, cyst closer to vena cava and cyst with thick and calcified wall. The difficult part of the procedure is initial puncture of the cyst and to aspirate viscous particulate material, daughter cysts, laminated membrane and avoid spillage in the peritoneal cavity. To overcome this problem various techniques and instruments have been described with expected results:

1. Isolated hypobaric technique by Bickel

2. Aspirator grinder apparatus by Acarli

3. Perforator grinder apparatus (PGA) by Saglam

4. Liposuction cannula by Al-Shareef

5. Palanivelu hydatid system

23. Radical surgery

Pericystectomy involves removal of the cyst along with a rim of liver tissue in a non-anatomic plane. This is a major operation and involves major blood loss. Preoperative localization of bile duct and vascular system is imperative. If a bile duct connection is suspected pre-op ERCP should be obtained. IOUS is also helpful.

Pericystectomy decreases the risk of spillage of cyst content and also lower the risk of recurrence.

Sub- adventitial cystectomy—with the concept that pericyst consist of two layers, a plane is dissected between outer adventitial layer and inner avascular exocyst layer and as liver parenchyma is not dissected bleeding and bile leak is expected to be minimum.

Hepatic resection - Non- anatomic liver resection is actually the cystectomy procedure.

Anatomic liver resection - Rarely if the affected liver lobe is irreparably destroyed lobectomy is justified. *E. multilocularis* infection may lead to fulminant hepatic failure from sclerosingcholangitis or Budd-Chiari like syndrome and in these rare cases orthotopic liver transplantation may be necessary.

24. Complications of hydatid cyst surgery

1. Spillage: Spillage during intervention can lead to peritoneal hydatidosis which is to be avoided by any means

2. Recurrence: This is a serious problem in conservative surgery and left over exocyst is responsible for most recurrences. This also explains why recurrence is least with pericystectomy and hepatic resection. To detect exocyst IOUS plays a very important role.

3. Other various complications include wound infection, chest infection, subphrenic abscess, liver abscess, purulent collection residual cavity, residual obstacles in CBD, bile peritonitis, bile leakage and ischaemia of omentum in omentoplasty. Bile leakage is drainage of bile through abdominal drains for not more than 10 days. If it persists more than 10 days it is a biliary fistula. Depending upon the amount it can be low output fistula (less than 300 ml/day) or high output fistula (more than 300 ml/day). Low fistula usually heals spontaneously but high variety requires biliary decompression -ERCP and Papillotomy.

25. Pulmunary hydatid disease

The right lung and lower lobe are slightly more often involved. Uncomplicated cysts present as rounded or oval lesion on chest X-ray. Erosion of the bronchioles results in air being introduced between pericyst and laminated membrane and gives a fine radiolucent crescent “meniscus or crescent sign.” This is often regarded as a sign of impending rupture. When the cyst ruptures the collapsed endocyst floats in the residual fluid- “the water lily sign” on CT scan. Mainstay of treatment is surgery. Medical treatment is less successful and considered when surgery is not possible because of poor general condition or diffuse disease affecting both lungs or recurrent and ruptured cyst. The principle of surgery is to preserve as much viable lung tissue as possible. The exact procedures can vary from cystotomy, capittonage, pericystectomy, segmentectomy or occasionally pneumonectomy (**Figure 5**).

Figure 5.
Pulmunary hyadtid cyst post mortem specimen.

26. Vaccine

A defined antigen vaccine has been developed which can prevent hydatid disease in sheep and thus indirectly reduce the incidence of infection in human [20]. Vaccination of dogs also giving encouraging results. In future it is expected development of effective human vaccine against a parasitic disease.

27. Conclusion

Improvement in imaging supplemented with serology most cases of hydatid diseaae can be diagnosed with certainty. As the complications can be very serious most cases demand some form of treatment. Chemotherapy with albendazole is useful both in preoperative and post operative cases to prevent secondary echinococcosis. Although

surgery is the gold standard, PAIR has emerged as a standard curative treatment with minimal complication. Future hope is the development of an effective human vaccine.

Conflict of interest

The author declare no conflict of interest.

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Chapter 3

New Insight into the Immunity during *Echinococcus granulosus* Infection

Ibrahim Faris Ali

Abstract

Echinococcus granulosus is a causative agent of cystic echinococcosis disease which represents a real challenge of health and economic sectors by threatening human and animal life. In *E. granulosus*-infected intermediate hosts, the local immune responses represent by balance between T helper-1 (Th1)/Th2 responses and involving of IL-10-secreting $CD8^+$ T cells, as well as induction of antigen presentation and production of antibodies were suggested. Spill out of hydatid cyst fluid from ruptured cysts can induce deadly anaphylactic reactions. Although the host promotes effective immune responses against *E. granulosus* infection, the parasite can be survived, suggesting exist of mechanisms of immune evasion that help *E. granulosus* to grow and develop. Several mechanisms of immune evasion have been suggested during *E. granulosus* infection including; antigenic variation that lead to produce useless antibodies, alteration of Th1/Th2 cytokine profile, anti-apoptotic process, molecular mimicry and interfering with Antigen presentation, as well as fibrosis of hydatid cysts can be occurred in chronic cases. Furthermore, as an efficient drug against *E. granulosus* infection still not available, immunization of hosts could be necessary. Interestingly, combination of multiple EG95 proteins of oncospheres from the different isomers could possibly maximize the EG95 vaccine efficacy.

Keywords: *E. granulosus*, hydatid cysts, anaphylactic reactions, immune evasion

1. Introduction

Cystic echinococcosis is a neglected zoonotic disease as recognized by world Health organization. The disease is caused by a parasite tapeworm of the *Echinococcus granulosus* genus in intermediate hosts such as human and other warm-blooded animals. The parasite is transmitted by fecal–oral route. The parasite exploits bile acid and salt in the host duodenum to hatch its eggs into oncospheres. The oncospheres transfer to internal organs in particular liver through portal vein to establish cystic echinococcosis disease. The disease is described by a slow growing of fluid-filled cysts called hydatid cysts (metacestode stage) and this may be accompanied with serious chronic complications including; destruction of liver tissues and anaphylactic reactions [1].

The early stage of *E. granulosus* infection is asymptomatic and with progression in growth of hydatid cysts lead to interaction between host immunity and parasite.

Hydatid cyst fluid of *E. granulosus* contains a complex mosaic group of antigens such as Ag5, a 67-kDa glycoprotein, and antigen B (AgB), a 160-kDa lipoprotein, which represent immune modulator antigens responsible for parasite survival in the intermediate hosts. Additionally, protoscolex tegumental surface antigens (PSTSA) and oncosphere surface antigen can also stimulate protective immune responses in immunized hosts [2]. Based on that, this chapter will cover three related sections of host–parasite interactions including; host anti-parasite immune responses, immune evasion mechanisms of parasite and host immunization.

2. Host immune responses in *E. granulosus* infection

2.1 Innate immune responses

The innate immunity is a part of immune system responsible for generating the early immune responses against non-specific pathogens. Host–parasite interaction complex is the baseline of immune response regulation, where cross-stimulation that mediated by a package of immune cells, receptors and sensors can work together to induce effective immune response against pathogen [3]. The level of Toll-like receptor2 (TLR2) and 4 (TLR4) can increase in the early stage of cystic echinococcosis suggesting a trigger role of them in innate immune responses by activation of myeloid differentiation factor 88 (MyD88) and important transcription factors, such as nuclear factor-κB (NF-κB), interferon regulatory factors) IRFs) and mitogen-activated protein kinase (MAPKs(leading to promote secretion of pro-inflammatory cytokines [4].

Furthermore, during establishment stage of hydatid cysts, induction of the innate immune responses are generated by an increase in the number of monocytes and macrophages with infiltration of neutrophils and macrophages into the site of damaged tissues. Involvement of the innate susceptibility/resistance (s/r) factors in host–parasite interaction include; activation of complement, nonspecific phagocytosis and cytolytic leukocytes. Moreover, feature of leukocytosis as a result of increase in the number of circulating neutrophils, eosinophils, lymphocytes, and macrophages are common indicators during *E. granulosus* infection [5]. The circulating monocytes can migrate and permanently settle in the particular tissues (i.e., the Kupffer cells of the liver and alveolar macrophages), for detection and elimination of invading pathogens or their products and host-belong injured materials [6].

2.2 Adaptive immune responses

Adaptive immune response is another type of immune responses generated against specific pathogen. There are two types of adaptive immunity including; cellular and humoral immunity. Understanding the local liver immune responses may contribute in designing new therapies and blocking immune evasion mechanisms during establishment stage of parasite infection. The second challenge of host by oncospheral antigen after 21 days from primary infection provided high level of protection. This likely due to the role of antibody-dependent cell-mediated cytotoxicity (ADCC) reactions [7]. In CD4 T cells- deficient mice that immunized with protoscoleces (E4+) antigen, production of CD4+ T cell-independent antibodies was determined in the early stage of infection [8]. The term of humoral immunity refers to antibody-mediated immune response that occurs when antigen presenting cells

such as macrophages and DCs engulf antigens and expose them on their surfaces to amplify immune responses against specific pathogen [9]. In early stage of experimental infection of *E. granulosus*, although the activation of B cells has been detected that resulting in production of IgM and IgG2b, the *E. granulosus* can still grow and develop into hydatid cysts [10].

3. Mechanisms of immune evasion of *E. granulosus*

The real challenge for any pathogen is been survival as unwanted visitor in inconvenient environment. Therefore, to avoid effective immune responses of the host, *E. granulosus* developed several techniques called immune evasion strategies. The two main mechanisms are used by *E. granulosus* to equivocate the immune system of host; first is a passive escape by avoiding damaging effects of immune system components in the early stage of infection, and the second is by modulating of immune responses [11].

3.1 Protective role of hydatid cyst wall

In intermediate hosts, the first protective barrier following hydatid cyst (metacestode) formation is cyst wall. The hydatid cyst wall consist of outer membrane called laminated layer (antigenic variant layer) and inner layer called germinal layer responsible for production of protoscoleces. Although the hydatid cyst wall consist of different proteins which they can motivate immune responses against parasite, but it also provides physical protection from immune components [12]. Additionally, some of the host molecules that involve in immune response and protective action can be sequestrated in hydatid cyst fluid suggesting that the host molecules may absorbed by laminated germinal layers during host–parasite interaction [13].

3.2 Control of host complement system

Complement is a part of immune system represented by a serial of soluble proteins, membrane expressed receptors and regulators, where blocking of complement can cause perturbation in defense system of host against pathogens [14]. In the early stage of infection, deactivation of host complement can be occurred during several diseases including cystic echinococcosis. This complement deactivation lead to inhibition of acute inflammatory responses which include; boost of vascular permeability, infiltration of leukocytes, and chemotaxis of immune cells into infection site [15].

In alternative way of complement activation, triggering of complement cascade occurred by cleavage C3 into C3b and iC3b which is essential for producing membrane attack complex (MAC) of complement. The complement activation is regulated by host inhibitor factor H (FH), where FH binds with C3b component of complement leading to complement inhibition to protect host cells from self-attack by complement [16]. Preventing accumulation of complement cascade on the pathogen surface and perturbation in phagocytosis has been described by interaction between complement inhibitor FH and FH-binding proteins of many pathogens including *E. granulosus*, which causes down-regulation of opsonization process and increase phagocytic resistance of pathogens [17]. Furthermore, Sequestration of host complement inhibitor FH by high charged components on the hydatid cyst wall is suggested as a mechanism of complement evasion by *E. granulosus* [18].

3.3 Interference with infiltration of immune cells

Migration of immune cells from circulatory system into the various organs and tissues during normal and inflammatory conditions are common events in host body. In experimental cystic echinococcosis following by ingestion of mice with ovalbumin (OVA) after 3 months post infection to induce asthma model, the histopathological data indicated the ability of *E. granulosus* to reduce eosinophil infiltration and mucus secretion [19]. Furthermore, hydatid cyst fluid has ability to modulate infiltrating monocytes from differentiating into dendritic cells [20]. Although the T lymphocytes are the most frequent infiltrating cells in mice organs infected with of *E. granulosus*, but it is not correlated with the fertility of hydatid cysts [21, 22].

3.4 Manipulation of dendritic cells

Dendritic cells (DCs) are the most efficient antigen presenting cells that uptake the pathogen antigens and exposed them to the Th2 cells to trigger production of antibodies by B lymphocyte cells. It has been found that hydatid cyst fluid can directly modulate predifferentiated DCs and impairing their ability to release interleukin 12 (IL-12), IL-6 and prostaglandin E2 (PGE2) [20]. The effect of purified AgB and sheep hydatid fluid (SHF) of *E. granulosus* were evaluated to their ability in host monocyte maturation and differentiation into DCs, as well as interleukin secretion. The outcome data indicated the ability of AgB and SHF to impair maturation of monocytes to DCs, alternation of DCs differentiation towards nonprotective Th2 cell responses and inhibition of DCs-mediated proinflamatory responses [23] Interfering of Toll like receptors (TLRs) in DCs-mediated immune responses against *E. granulosus* was investigated, where the role of TLRs in trigger of effector DCs that promote MyD88-dependent negative signal for Th2 cell development was suggested [24].

3.5 Molecular mimicry

Molecular mimicry refers to the similarity in sequencing between specific pathogen antigens with some host's self-antigens, where many pathogens have ability to share molecules has sequencing similar to the host antigens. According to the molecular mimicry strategy, the pathogen antigens can be recognized as a "Self" antigen, which helps to protect parasite from host immune responses [25]. The metacestodes of *E. granulosus* and *E. multilocularis* avoid the prospective immune responses in intermediate hosts by molecular mimicry, immunomodulation and alternation of leukocyte functions [26].

3.6 Interference with secretion of cytokines and chemokines

The interaction between *E. granulosus* and host immune system can be occurred including avoid host effective immune responses. *E. granulosus* has ability to induce T-helper 2 (Th2) responses leading to limitation of anti-parasitic immune responses which involves in metacestode parasite survival, rather than T-helper 1 (Th1) responses, that effectively suppress growth and development of hydatid cysts [10]. Induction of immune suppressor cells such as CD8+ T suppressor cells has been suggested as a mechanism of evasion by *E. multilocularis*, where CD8+ T suppressor cells detected in spleen of infected mice [27]. Depletion of CD4+ T cells can promote growth and development of protoscoleces to hydatid cysts in *E. granu*losus infected

mice, indicating the role of CD4+ T cells in suppression and elimination of hydatid cysts in experimental model. However, the balance between CD4+ T cells-mediated cellular immune responses and IL-10-produced CD8+ T cells has a critical role in growth and development of hydatid cysts of *E. granulosus* [28].

In another study, interfering with immune response against protoscoleces in the early stage of infection has been suggested as a mechanism of evasion, where co-culture of protoscoleces with peripheral blood mononuclear cells *in vitro* indicated an increase in protoscoleces survival. This indicator was supported by using IL-10 and IL-4 antibodies which caused reduction of kill percentage of protoscoleces with inhibition of NO production that released by peripheral blood mononuclear cells. Additionally, IL-10 and IL-4 can reduce Th1 responses causing an increase in the probability of parasite survival [29]. AgB of *E. granulosus* metacestode stage that contributes in lipid metabolism in the parasite, also has a key role in host immune modulation by inhibiting inflammation response, where down-regulation of IL-1β and TNF-α secreted from LPS-induced macrophages and monocytes in IL-10-dependent manner were determined [30].

Although, the glycan antigens of *E. granulosus* including; glycoprotein and glycolipid molecules that are expressed in the protoscoleces, hydatid cyst fluid and laminated layer have a high antigenicity features, but parasite can reduce their effects by inhibition the expression of glycan antigens on the surface of laminated layer leading to generate limited immune responses against parasite [31]. Two main antigens including; tegumentary antigen and Antigen B in protoscoleces and metacestode, respectively, has shown a key role in host immune evasion, where tegumentary antigen can inhibit chemotaxis process, induction of IL-4-producing lymphocytes, production of non-complement fixing antibodies like IgG4 and stimulating a nonprotective Th2 cell response [32].

Further *in vivo* investigation was obtained by Rigano *et al*. [33] for evaluating the rule of parasite AgB in escape form the early immune responses mediated by specific immunoglobulin E (IgE) and IgG4 antibodies, where the data showed inhibition of chemotaxis process of polymorphonuclear neutrophils (PMN) and high level production of IL-4 and IL-13, but not IL-12 with significant lower concentration of IFN-**γ** in AgB-induced peripheral blood mononuclear cells.

3.7 Anti-apoptosis strategy

Apoptosis, a first type of programmed cell death is controlled by a serial of proteins and enzymes responsible for cascade of events in unicellular and multicellular organisms during infection and normal conditions. Apoptosis is a route of cell transformation during normal growth, as well as it serves as a protective mechanism by eliminating of damaged cells, infectious agents and malignant cells. There are two ways to promote apoptosis including; extrinsic and intrinsic routes. The protoscoleces of *E. granulosus* can undergo to both ways of apoptotic destruction that mediated by caspase-3 enzyme (**Figure 1**) [34].

Furthermore, it has been shown that some of hydatid cysts can be free of protoscoleces called infertile hydatid cysts and this may be attributed to high expression of apoptotic components. In related to that, high level of DNA fragmentation and caspase-3 were detected in infertile hydrated cysts as compared to fertile cysts suggesting that apoptosis can be involved in hydatid cyst infertility [36]. The study obtained by Amirmajdi *et al*. [37] suggested that apoptosis can serves as a mechanism of survival by help *E. granulosus* to overwhelms host immune defends, where they detected

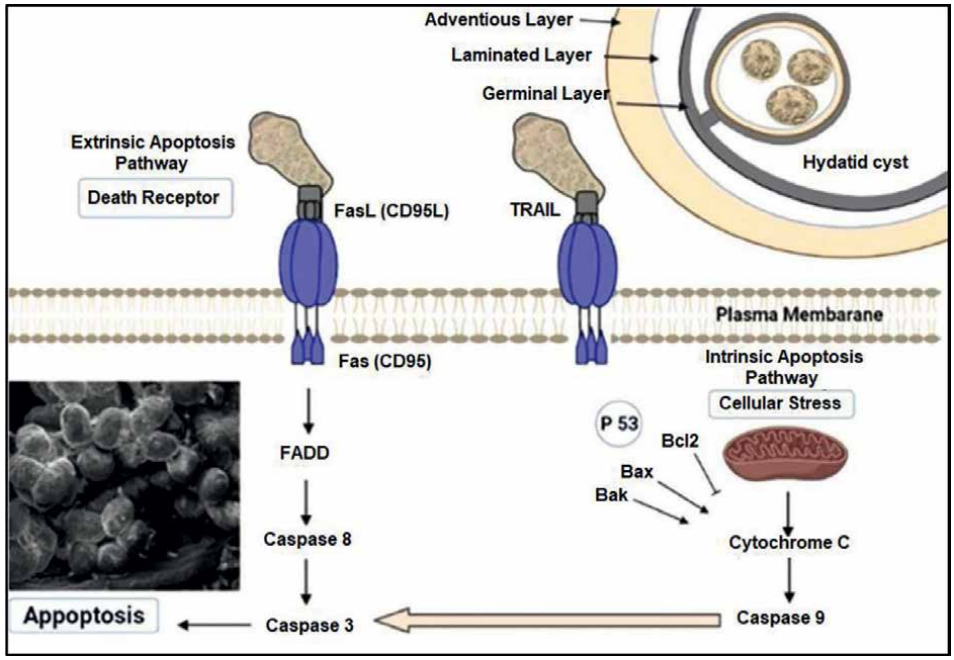

Figure 1.
Host innate immune response (inflammasome and apoptosis) against E. granulosus*—the figure modified from [34]—SEM image of protoscoleces from [35].*

that the expression ratio of pro-apoptotic (Bax)/anti-apoptotic markers (Bcl-2) and activity of caspase-3 are higher in lymphocytes treated with hydatid cyst fluid after 6 hrs exposure in comparison with control group. Additionally, two anti-apoptotic proteins of *E. granulosus* including; apoptotic protein inhibitor (Eg-IAP) and Eg-BIRP can reduce apoptosis in protoscoleces during establishment stage of the *E. granulosus* in intermediated hosts [38].

3.8 Camouflage strategy

According to the previous literatures, using camouflage strategy by invading pathogens allow them to stay survival in their hosts, where pathogens can exploit host components and secretions such as cells, proteins and enzymes to avoid effect of immune responses against them. The outermost layer around hydatid cysts of *E. granulosus* is produced by host tissues such as liver and lung consist of host cells which playing an important role in parasite survival [39]. It has been shown that high level of arginase-1 has an immune suppressive effect during infections. In cystic echinococcosis disease, high level of arginase-1but not arginase-2 that is produced by peritoneal cells helps parasite to be survive in intermediate hosts, where protective effects of arginase-1 by impeding the removal process of *E. granulosus* and cancer cells has been shown in BALB/c mice through down-regulation of T-cell receptor expression [40].

3.9 Antigenic variation

Antigenic variation or antigenic alteration is the ability of pathogens such as parasites, bacteria and viruses to alter the exposed proteins and carbohydrates on their

body surfaces regularly to avoid been recognized by host immune cells. This strategy can help pathogen to dispose the generated effective immune response [41]. It has been shown the ability of *E. granulosus* to avoid host immune responses by modification of its exposed antigens which lead to produce useless antibodies [42].

3.10 Interfering with antigen presentation capability

Antigen presentation refers to expose components of pathogen on the surface of antigen presenting cells including; macrophages, DCs and B cells through the major histocompatibility complex type two (MHC-II) receptors to the specific immune cells. Antigen presentation is a major process of adaptive immune response that includes; recognition, phagocytosis and exposure of pathogen antigens by antigen presenting cells following by recognition of antigens through Th lymphocyte cells [43]. *In vitro* study suggested the role of hydatid cyst fluid *of E. granulosus* in modulation of immune responses by interfering with the function of antigen presenting cells to ensure its continued survival, where, impairment of antigen presentation process by down-regulation of MHC-2 has been determined in Balb/c mice experimentally infected with *E. granulosus* [44]. Excretory–secretory products (ES) and adult worm antigens of *E. granulosus* were caused impairing the development of Th1 cells and inhibition of DCs function which may reduce antigen presentation process and cytokine secretion from DCs [45].

4. Vaccination against *E. granulosus* parasites

At the early stage of *E. granulosus* life cycle, the oncosphere components can be a potent source of host protective antigens in sheep. The new EG95 vaccine was originally described by Lightowlers *et al.* [46] which consists of a single recombinant antigen of *E. granulosus* oncosphere and the Quil A adjuvant has ability to reduce the burden of hydatid cysts and providing protective immune responses by inducing complement-fixing antibodies. Vaccination trails using EG95 were applied in sheep, goats and cattle in New Zealand, Australia, Argentina, Chile and China [47]. Interestingly, combination of multiple EG95 proteins of oncospheres from the different isomers could possibly maximize the EG95 vaccine efficacy [48]. The protection program of sheep from *E. granulosus* infection using EG95 vaccine has been applied as follow; the first dose been offered at 2 months of mice age, following by a booster 1 month later, and yearly vaccination. In experimental study to evaluate the protective immune efficacy of recombinant *E. granulosus* (Chinese strain) glutathione S-transferase (rEgGST) as a new vaccine against protoscoleces development in mice indicated potential reduction of hydatid cyst formation, as well as elevated levels of IgG1, IgG2a, IgG3, IL-2, IL-4, IL-10 and IFN-γ which reflecting an increase in the activity of Th cells [49]. Moreover, antigen B in hydatid cyst fluid is another candidate vaccine that used in vaccination of intermediated hosts against *E. granulosus* infection. DNA vaccines encoding 8-kDa subunit of *E. granulosus* antigen B (HydI) with murine interleukin 12 (IL-12) as a genetic adjuvant was used in BALB/c mice vaccination. The HydI/MIL12-vaccinated group showed high significant levels of IFN-γ and IgG2a antibodies comparing with only HydI-vaccinated and control groups [50].

Another candidate vaccine that has been used to immunize intermediate hosts is protoscolex tegumental surface antigens (PSTSA). The data from PSTSA-immunized sheep showed an increase in the titer of antibodies after single and double

immunization [51]. Furthermore, three recombinant proteins of egM gene family of *E. granulosus* named egM4, egM9 and egM123 were used to immunize dogs against *E. granulosus* infection. The egM gene subcloned in *E. coli* bacteria to express glutathione S-transferase (GST) fusion proteins, where 3 doses of 80 mg/protein/dog provided 97–100% of protection in terms of elimination of worm and reduction of egg production. This can breakdown the parasite life cycle in the dogs which is important for preventing the parasite transmission in intermediated hosts [52].

More recently, it has been shown that multi-epitope combination vaccine of *E. granulosus* tegumental protein (EgTeg) that consist of two CD4 T-cell epitopes, three CD8 T-cell epitopes and four B-cell epitopes has high level of antigenicity and immunogenicity in both *in vivo* and *in vitro* studies. *In vivo* and *in vitro* experiments of effectiveness evaluation of EgTeg vaccine indicated significant increase in the level of IFN-gamma, perforin and granzyme-B that produced by activated CD4+ T cells and CD8+ T cells, respectively. Additionally, the titer of antibodies was higher in immunized group in comparison with control group [53].

5. Conclusions

Overall, the outcome data from previous literatures about *E. granulosus* infection discovered the ability of intermediate hosts to generate effective immune responses against parasite, but growth and development of *E. granulosus* in these hosts with existence effective immune responses suggesting present of immune evasion strategies that enhance the parasite survival and causes successful infection. The suggested mechanisms of immune evasion of *E. granulosus* in intermediate hosts include; antigenic variation, interfering with Th1/Th2 cytokine profile, anti-apoptotic process, molecular mimicry and perturbation of antigen presentation. The vaccination against *E. granulosus* can reduce the destructive effects of parasite in intermediate and definitive hosts. The most common candidate vaccines that can provide protective immune responses against *E. granulosus* infection are EG95 and antigen B with Freund's and Quil A adjuvants.

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Chapter 4

Natural Products as Therapeutic Option for Echinococcossis

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Abstract

Until the 1980s surgery remained the only treatment option for cystic echinococcosis, a neglected tropical disease caused by infection with tapeworms of the genus *Echinococcus*. Following the development of the benzmidazoles, there has been an increase in the use of chemotherapy over the years, especially as an adjunct to surgery or in the management of inoperable cysts. In spite of their usefulness, both surgery and chemotherapy are associated with significant limitations that warrants the search for or consideration of alternative treatment options such natural products. This chapter aims to discuss the scolicidal activity of different species of medicinal plants and their active metabolites in the treatment of echinococcosis. Excerpta Medica Database, Google Scholar, PubMed Central and Scopus were electronic databases used to retrieve the relevant literature. Medicinal plants used commonly and effectively against protoscoleces were *Zataria multiflora*, *Nigella sativa*, *Berberis vulgaris*, *Zingiber officinale*, and *Allium sativum*. Only *Z. multiflora* and *A. sativum* were shown to effective against *Echinococcus granulosus* protoscoleces *in vivo*. In addition, these natural products have not been associated with any significant adverse effect. In animal models Thus, natural products with demonstrated activity against *E. granulosus* may serve as alternative therapy in the management of echinococcosis.

Keywords: cystic echinococcosis, natural products, benzmidazoles, medicinal plants, toxicity

1. Introduction

Helminths are generally classified into two main phyla: Platyhelminthes (cestodes and trematodes) and Nematodes [1]. A third of the 3 billion people living in low socio-economic conditions in the developing countries of the Americas, Asia, and sub-Saharan Africa are infected with one or more helminthes. Helminthic parasitic infections are regarded as neglected tropical diseases because less than 1% of global research funding is allocated to these infections or diseases [2].

The etiological agent of cystic echinococcosis (CE)/hydatid disease, a neglected tropical disease with a global prevalence, is the cestode, *Echinococcus granulosus* sensu lato (s.l) (*E. granulosus*), a tapeworm of the family, Taenidae [3]. Globally, 1 to 3.6 million disability-adjusted life years (DALYs) are caused by human CE infections; with the majority of these cases living in low- and middle-income countries [4]. In China, South America, Europe, Australia, and Africa, CE raises a serious economic and public health concern. Moreover, infestations with CE result in great losses to the livestock industry (about $3 billion every year) through reduced milk supply, lower fertility, increased mortality, weight loss as well as morbidity and mortality in humans [1, 5].

Canids, such as dogs, wolves, foxes, and jackals serve as the infection's primary hosts in the home environment, with a wide range of other herbivores including sheep, goats, water buffalo, and cattle serving as intermediate hosts [5, 6]. Through the consumption of pasture grass contaminated with *E. granulosus* eggs released by infected dogs, intermediate hosts also get infected. The cycle is then completed when definitive hosts consume cysts (metacestodes) found in various organs (such as the liver, lungs, spleen, and heart) of infected intermediate hosts, notably sheep and goats. Ingestion of *E. granulosus* eggs accidentally from contaminated soil, water, and vegetables results in human infection. Humans are therefore regarded as the "accidental intermediate hosts". Humans typically develop fluid-filled hydatid cysts in the liver and lungs, with less frequency occurring in the abdominal cavity, muscle, heart, bone, and nervous system. Due to risky practices including sharing a home with unrestrained dogs, having no regulations governing the killing of animals, and living in unhygienic settings, socio-economic and cultural determinants have a significant influence in the transfer of illnesses to people [7].

Clinical signs only appear when the cyst puts pressure on the nearby tissues or organs or when they rupture, even though the infection may go years without showing any symptoms. Depending on the development and location of the cyst, the infection might constitute a major health risk to people. Ultrasound and, to a lesser extent, serology are the primary imaging methods used to diagnose CE [2, 3]. The size, location, and quantity of hydatid cysts determine the best treatment plan. Currently, anthelmintics, surgery, and percutaneous aspiration are the only treatments available for CE. The chemical medications used to treat human hydatid cysts are albendazole and mebendazole. In order to treat the disease, these medications are frequently used at high doses, which might have negative effects on the liver and other organs [1].

2. Diagnosis of cystic echinococcosis

Currently, diagnosis of CE is mostly performed by means of imaging techniques comprising magnetic resonance imaging (MRI), ultrasonography, computed tomography (CT) scan and/or conventional chest radiography [8]. These methods are indispensable, enabling the easy establishment of the specific stage of the hydatids and also the localization. For instance, the WHO Informal Working Group on Echinococcosis (WHO-IWGE) has issued ultrasonography standardized classification of stage-specific cystic images for the diagnosis and management of CE [9]. Although either of these imaging techniques are useful, MRI is preferred over CT due to better visualization of liquid areas within the matrix [10]. Tumors and infectious lesions are, however, considered for differential diagnosis [8].

As confirmatory test, serological analyses are used to support the findings of the imaging techniques. These tests may also be used as screening or for follow-up monitoring after CE diagnosis [11]. These serological methods are based on the detection of specific IgG antibodies produced against *E. granulosus*. Currently, the main immunological methods for the diagnosis of CE and follow-up in patients with the disease are enzyme-linked immunosorbent assays (ELISAs) and immunoblotting (IB). ELISAs are used as a screening test whereas IB is employed as a confirmatory test due to its higher specificity and sensitivity when compared to other assays [11]. Other serological methods that have been used in the diagnosis of human CE include immunofluorescence assay, indirect hemagglutination assay, immunochromatographic test and dot immunogold filtration assay. However, these tests are associated with lower sensitivity and specificity, thus are used less [12].

Given the pitfalls associated with radiological and immunological techniques, interest in the use of recombinant proteins and synthetic peptides have increased [9]. These molecular diagnosis or DNA-based analysis are very useful in the diagnosis of CE because they offer a wider and complete diagnostic picture of CE patients [8]. DNA probes for Southern hybridization tests and polymerase chain reactions are very helpful in confirming diagnosis of CE. Moreover, PCR has high sensitivity and specificity for the pathogen's DNA, thus allows for precise determination of infection status and identification of genus, species, and genotype [12]. As such, PCR is the foremost molecular analysis in the diagnosis of human CE.

3. Current treatment protocols

Treatment of CE depends on stage of the disease, size and location of the cyst, and complications that may be associated with the cysts. Currently, four treatment modalities are employed for the clinical management of CE. These modalities include surgery, chemotherapy with synthetic drugs and puncture aspiration injection and re-aspiration [2]. However, for clinically silent and inactive cysts, active surveillance is the preferred intervention [13]. In this section, we focus on the strengths and limitations associated with current pharmacological and non-pharmacological management of CE.

3.1 Surgery

Until the 1980s surgery remained the only treatment option for CE [2]. Although other treatment modalities have been made available over the past few decades, surgery remains the treatment of choice for most cases of hydatid hepatic cysts [14]. Surgical intervention enables complete eradication of the parasite, treatment or prevention of complications, and avoidance of relapse. According to WHO-IWGE, treatment strategy of the disease must be based on the cyst stage. Accordingly, surgery is indicated in patients with cysts greater than 10 cm or with stages 2 or 3b CE that is with daughter cysts. Patients with other cysts that do not satisfy these criteria may also require immediate surgical treatment. These include infected cysts, superficial cysts with a higher risk of rupture and cysts communicating with the biliary tree [15].

Owing to its satisfactory outcomes, surgery is considered the preferred treatment modality for CE patients with large and complicated cysts [16]. Nonetheless, benzimidazole must be administered to sterilize cyst content prior to surgical treatment in order to prevent dissemination or anaphylaxis [14]. In addition, scolicidal solutions

must be used to eradicate protoscolices of the parasite that may be present within the content of the cyst. Such scolicidal solutions may include silver nitrate, hypertonic saline, povidone iodine, hydrogen peroxide and the anthelminthic albendazole which can be used alone or in combination.

In surgical management of CE, cysts that lie deep, in close proximity to large vessels, and contain multiple daughter cells or calcified cysts must be treated with open surgery [14]. In contrast, laparoscopic surgery is indicated for superficial cysts located on the anterior side of the liver. If open surgery is indicated, the operative site is scrupulously packed and a variety of conservative and radical operative techniques are employed [14].

3.1.1 Conservative operations

In conservative surgical procedures used in the management of hydatid cyst, only the parasitic cyst contents are removed. Pericystic membranes are retained and procedures such as capitonnage, omentoplasty and external drainage are used to manage the residual cavity. The modified Aydin technique has also been used in the management of giant pulmonary hydatid cyst. This technique is advantageous since it avoids major capitonnage complications [17]. In these conservative procedures, the cyst is exposed safely and the pericystic area and operating field are covered with scolicide-soaked pads. Thus, preventing the spillage of parasite-containing contents into surrounding tissues and peritoneal cavity. Subsequently, the cyst is punctured and as much fluid as possible is aspirated following which the scolicide is instilled into the cyst. This is to prevent dilution of the scolicidal agent after introduction into the cyst [18].

The scolicidal agent is allowed to remain in the cyst cavity for a period of 5–15 min after which it is aspirated, and the cyst is unroofed. In the case of hepatic hydatid cyst, cyst contents including germinative membrane and daughter cysts, are evacuated and the surgeon carefully explores the cavity for any gross communication with the biliary tract. At the same time, the surgeon explores the presence of any exogenous cyst that may be embedded in the wall [18]. Following this, external or internal drainage, capitonnage, omentoplasty, marsupialization, and introflexion can be used to manage the residual cavity [14]. These may give rise to the Mabit procedure where omentoplasty and external drainage is used to extract the parasite from the cavity, or Posadas procedure which employs capitonnage, i.e., the surgical closure of the cyst cavity via the application of sutures so as to cause approximation of the opposition surfaces. In all, conservative surgery is easy, safe, and rapid, but has significant limitations such as high morbidity and recurrence rates that sometimes necessitates the choice of radical operations [14].

3.1.2 Radical surgery

In recent times, the use of conservative surgical procedures has become more acceptable among surgeons [19]. However, invasive surgery is sometimes still needed to eradicate parasitic infection in patients with complicated hepatic cysts and also in patients who do not respond to anthelmintic therapy [16]. In contrast to conservative techniques, radical techniques used in hepatic infections can include cystectomy and may involve removal of the germinative layer by non-anatomical liver resection.

With the aim of eradication or elimination of local relapse or complications due to false orbiting, radical surgeries remove the cyst along with the pericystic membrane

and parasitic contents. The procedure may also involve liver resection if indicated [14]. In the treatment of hepatic cysts with radical surgery, procedures such as partial pericystectomy, subadventitial cystectomy, and hepatic resection may be used. Either procedure is associated with its own advantages and limitations. To illustrate, subadventitial cystectomy is not suitable for patients with cysts located near vital vessels of the liver or bile ducts. Hepatic resection on the other hand is time-intensive, nonetheless associated with a low rate of cyst recurrence. Although, recurrence rate is lower in subadventitial cystectomy and hepatic resection, the former is associated with less injury to healthy liver tissue than hepatic resection. In contrast to hepatic resection, pericystectomy and partial pericystectomy are easy to perform, less time-invasive and associated with little blood loss [14].

Regardless of the choice of procedure, depending on the cyst location, effectiveness and safety, radical surgery aims at a common goal, that is, the residual cavity must always be treated with excellent care [20]. This is crucial in preventing biliary leakage, biliary fistula, and abscess formation. Radical surgical approaches are associated with a low risk of postoperative complications, fewer relapse cases, long postoperative hospitalization, and low mortality rates; they are all operations with a high difficulty level mostly suitable for highly specialized liver surgeons. Owing to its low risk of postoperative complications, relapse and low mortality rates, radical surgery is considered superior to conservative surgery [21].

In spite of the low morbidity and mortality associated with radical surgeries, these procedures might not be applicable in all cases [22]. Thus, influencing the introduction of less harmful and more accurate treatment options such as chemotherapy.

3.2 Chemotherapy

According to the WHO and the World Organization for Animal Health's Manual on Echinococcosis in Humans and Animals, chemotherapy is indicated for inoperable cysts, cysts in multi organs, and for pre-emptive treatment of secondary echinococcosis. In contrast, the use of chemotherapy-alone is contraindicated in early and late pregnancy, and patients with inactive cysts or cysts with a greater risk of rupturing [23]. Although, chemotherapy has been indicated for inoperable cysts, evidence from several studies conducted over the past few decades, mainly case series, suggest that chemotherapy could be an alternative to surgery in patients with uncomplicated cysts [13]. This has resulted in an increased use of chemotherapy over the years.

Given the above, various factors need to be considered prior to the choice of anthelminthic therapy in the treatment of CE. When indicated, patients with inoperable cysts must undergo long-term treatment with benzimidazoles such as albendazole and mebendazole, or the pyrazinoisoquinoline praziquantel [24].

3.2.1 Mebendazole

Mebendazole, chemically known as methyl 5-benzoyl-1H-benzimidazole-2-yl-carbamate, is a broad spectrum anthelmintic used for the treatment of helminth infestations in both humans and animals. Since its development in the 1970s, mebendazole has been useful in the treatment of helminthiasis with varying causative organisms such as CE, ascariasis, trichuriasis and enterobiasis [25]. Recently, the use of mebendazole has largely been replaced with albendazole due to some advantages of the latter. For instance, the poor solubility of mebendazole limits its use in the treatment of CE and other tissue helminthiases. Consequently, the use of mebendazole in

hydatid cyst is obsolete, with albendazole being more preferred due to its better intestinal absorption and lower dosage [26].

3.2.2 Albendazole

Albendazole, a benzimidazole carbamic acid methyl ester, is a broad spectrum anthelmintic used for the treatment of various helminthiases. Since its introduction about four decades ago, the drug has been used for its vermicidal activity in infectious conditions such as CE, toxocariasis, taeniasis, gnathostomiasis, and cysticercosis [27]. By binding to intracellular microtubules, albendazole preferentially inhibits parasite's tubulin polymerization and prevents assembly of microtubules. Consequently, glucose uptake decreases resulting in the depletion of the parasite's glycogen stores [28]. This coupled with degenerative changes in the germinal cell mitochondria and endoplasmic reticulum, and increased lysosomal activity, albendazole decreases production of adenosine triphosphate and induces autolysis. Thus, reduces the survivability of the parasite.

In spite of its use in the medical treatment of CE, albendazole is also a useful adjunctive therapy to percutaneous treatment or surgery in preventing secondary CE. When used as an adjunct, albendazole is initiated at least 4–30 days before surgery, and continued for at least 1 month after surgery or percutaneous procedure [26]. Notwithstanding the usefulness of albendazole in the management of CE, studies have reported some adverse effects associated with its use. In one cohort study involving 35 children with abdominal CE, mild increase in the liver enzymes along with mild leukopenia were observed at daily doses of 10–15 mg/kg for 1 month [29]. Rarely, liver failure, hemolytic anemia and pancytopenia has been reported [25].

3.2.3 Praziquantel

Praziquantel is a broad spectrum anthelmintic that has been in use since 1980. The drug exhibits activity against various helminthic infections of human and veterinary origin. Although the exact mode of vermicidal action is uncertain, praziquantel is believed to cause rapid paralytic muscular contractions by increasing intracellular calcium influx and tegumental disruption. This paralytic action of the drug expels the worms from their primary habitat, after which they undergo degeneration due to tegumental disruption [30].

Although useful in the treatment of CE, praziquantel is not indicated as first-line option. The drug is nonetheless effective in perioperative treatment and in the treatment of bone or disseminated CE [31]. For instance, when used together with albendazole, praziquantel is effective in the preoperative treatment of intra-abdominal hydatidosis [26]. Unlike albendazole, the use of praziquantel is safe in pregnancy.

3.3 Challenges with current treatment protocols

Given the above, current surgical and chemotherapeutic interventions are essential therapeutic tools in the management of CE. However, these treatment strategies may be associated with some challenges that may limit their usefulness in the treatment of CE. For instance, surgical treatment of hepatic hydatid cysts may result in major complications such as cholestatic jaundice. Rupturing of cyst into the biliary tree adjacent structures, or the peritoneum during surgery may also result in secondary

infection, sepsis and anaphylaxis [14]. Postoperative hemorrhage, incisional fistulae, cholangitis, surgical site infection, pneumonia and pulmonary embolism are all major complications that have been reportedly observed following surgery. Moreover, spillage of cyst contents during removal and incomplete removal of the endocyst increases the risk of recurrence of the disease. The risk of local and secondary disease recurrence may also be increased by exophytic cyst development that surgeons fail to notice during surgical interventions [32].

Similarly, the use of benzimidazoles is also associated with significant drawbacks, albeit improves life-expectancy in patients with CE [24]. Specifically, the use of current chemotherapeutic agents can reduce cyst size but months of therapy may be required [23]. This may be explained in part by the poor oral absorption and the reduced oral bioavailability of these drugs. As a result, recent studies have suggested developing new formulations such as nanocrystals and liposome formulations to enhance oral absorption and bioavailability, and reduce duration of therapy [33, 34]. Not only is chemotherapy limited by its long course in the treatment of CE, but this treatment approach is also not effective against all stages of cyst development. Benzimidazoles may get diluted in large cysts with size greater than 10 cm, hence less effective against such large cysts. In addition, treatment failure and disease recurrence are more common when chemotherapeutic agents are used in treatment of CE involving multiple, or complicated cysts surrounded by thickened calcified tissue layers [10, 35].

Albeit the relevance of current treatment protocols cannot be overstated, these treatment approaches are associated with significant limitations that warrants the search for or consideration of alternative treatment options. These alternative options include natural products such as monoterpenes, taxanes, isoflavonoids and plant extracts which have been shown to be effective in the management of CE.

4. Natural products with reported activity against Echinococcus

For contemporary systems of herbal and natural drug development, medicinal plants with dependable therapeutic effects are valuable. The synthesis of more complicated semisynthetic chemical compounds can start with bioactive substances found in plants, which can also be used as a direct source of medicinal or bioactive chemicals [2]. Finally, plants can be utilized as bioactive markers for spectroscopic and chromatographic investigations together with the discovery of new compounds [36]. Isolated chemicals of medicinal plants can lead to the development of new medications. In this chapter, we discuss the medicinal plants, fungi, and isolated chemical compounds shown to have scolicidal activity against the protoscoleces of *E. granulosus*.

4.1 Medicinal plants with reported activity against Echinococcus

In all, 57 species were found to have been employed as echinococcicidal agents in the *in vitro* investigations as a result of our comprehensive review. The most popular extract for killing protoscoleces was *Zataria multiflora*, which was then followed by *Nigella sativa*, *Berberis vulgaris*, *Zingiber officinale*, and *Allium sativum* (**Table 1**).

The *in vitro* research made considerable use of leaves among herbs, methanolic extract among extraction, and herbs among plant forms. In the *in vitro* trials, it was discovered that plants like *Z. multiflora*, *Ferula assafoetida*, and *B. vulgaris* had a better efficiency. At a dosage of 1 mg/mL, *Z. multiflora* eliminated all scoleces in 5 min. At

Botanical name	Extraction method	Part used	Phytochemical component	Concentration (mg/mL)	Exposure time (min)	Scolicidal efficacy (%)	References
Allium noeanum (Reut)	Ethanolic	Leaves	Flavonoid	0.49	0.5	100	[37]
Allium Sativum (Garlic)	Ethanolic/ chloroform	Garlic cloves	Silver nitrate	200	15	17	[38]
Allium sativum (Garlic)	Methanolic	Garlic cloves	Mannitol	50	10	100	[39]
A. sativum (Garlic)	Chloroform extraction	Fresh garlic	N/A	200	1	100	[40]
Artemisia (Wormwood)	Methanolic	NA	N/A	100	15	97.24	[41]
Artemisia sieberi (Wormwood)	Hydrodistillation	Aerial parts	α-Thujone (31.5%)	0.005	120	99.30	[42]
Artemisia sieberi (Wormwood)	Aqueous	As a whole	N/A	50	20	100	[43]
Atriplex halimus (Orache)	Aqueous	Leaves	Phenolic and flavonoids	60	120	99.36	[44]
Berberis vulgaris (Barberry)	Aqueous	Fruit	N/A	4	30	100	[45]
B. vulgaris (Barberry)	Methanolic	Root	Berberine	2	10	100	[46]
Blepharocalyx salicifolius (Kunth)	Aqueous	Leaves	Gallic acid and rutin	200	5	100	[47]
Bunium persicum (Black Caraway)	Hydrodistillation	Seeds	g-terpinene (46.1%), cuminaldehyde (15.5%), r-cymene (6.7%), and limonene (5.9%)	0.0125	10	100	[48]
Cannabis sativa (Hemp)	N/A	Aerial parts	N/A	0.01	10	26.08	[49]
Capparis Spinosa (Caper)	Methanolic	Fruit	Flavonoids, tannins, terpenoids, glycosides and alkaloids	300	20	100	[50]
Cassia fistula (Golden shower)	Ethanolic	Fruits	N/A	100	60	67.74	[51]

Botanical name	Extraction method	Part used	Phytochemical component	Concentration (mg/mL)	Exposure time (min)	Scolicidal efficacy (%)	References
Cinnamomum zeylanicum (Cinnamon)	Hydrodistillation	Bark	Cinnamaldehyde (91.8%), metoxicinamate (1.57%), and _ pinene (1.25%)	0.05	5	100	[52]
Coriandrum sativum (Coriander)	Hydrochloric acid + diethyl ether	Seeds	Phenols	750	10,080	100	[53]
Corylus spp.	Hydro-alcoholic	Seeds	N/A	50	20	98	[54]
Cucurbita moschata (Pumpkin)	Hydroalcoholic	Seeds	N/A	1	60	16	[55]
Curcuma longa (Turmeric)	Ethanolic	As a whole	N/A	30	30	100	[56]
Curcuma longa (Turmeric)	Hydrodistillation	Rhizome	α-turmerone (27.1%), β-turmerone (21.8%), l-phellandrene (8.8%), and ρ-cymene (5.4%)	0.1	5	100	[57]
Curcuma zadoaria (White turmeric)	Hydrodistillation	Rhizome	Pentadecane (29.6%), Delta-3-carene (14.7%), and Cis-cinnamic Acid (8.4%)	0.15	7	100	[58]
Eucalyptus globules (Bluegum)	Aqueous	Leaf	Eucalyptol (79.32%)	10	5760	94	[59]
Eucalyptus globulus (Bluegum)	NA	Leaves	Eucalyptol (79.32%)	5	3	100	[59]
Ferula macrecolea (Koma)	Hydrodistillation	Leaves	Terpinolene (77.72%), n-nonanal (4.47%), and linalool (4.35%)	0.3	10	100	[60]
Lepidium sativum (Garden cress)	Aqueous	Leaves	N/A	100	15	100	
Mallotus philippinensis (Kamala Tree)	Methanolic	Fruit	N/A	20	120	100	[61]
Melaleuca alternifolia (Tea tree)	N/A	Tree oil	Terpinen-4-ol (35.4%), _-terpinene (11%), -terpinene (20.4%) and 1,8-cineole (3.4%)	20	5	90	[62]

Botanical name	Extraction method	Part used	Phytochemical component	Concentration (mg/mL)	Exposure time (min)	Scolicidal efficacy (%)	References
Mentha species (Lamiaceae)	Methanolic	Aerial parts	Phenolic, flavonoid and flavonol	200	10	99.54	[62]
Myrtus communis (True myrtle)	Hydrodistillation	Leaves	α-pinene (24.7%), 1,8-cineole (19.6%), and linalool (12.6%)	0.1	5	100	[63]
Myrtus communis (true myrtle)	Methanolic	Leaves	N/A	100	20	100	[64]
Nectaroscordum tripedale (Sicilian Honey Garlic)	Ethanolic	Leaves	Terpenoids, flavonoids, tannins and fatty acids	50	10	100	[1]
Nigella sativa (Black Cumin)	Hydrodistillation	Seeds	Thymoquinone	10	10	100	[1]
Nigella sativa (Black Cumin)	Methanolic	Seeds	Thymoquinone	50	30	100	[1]
Ocimum bacilicum (Sweet basil)	Methanolic	Leaves	N/A	100	60	24.10	[65]
Olea europaea (Olive)	Aqueous	Leaves	N/A	1	120	96.7	[66]
Olea europaea (Olive)	Ethanolic	Leaves	N/A	150	25	100	[1]
Peganum harmala (Syrian rue)	Ethanolic	Seeds	N/A	62.5	2880	100	[67]
Pelargonium roseum	Hydrodistillation	Leaves	N/A	0.05	60	100	[68]
Pestalotiopsis spp.	Methanolic	Leaves, stems and roots	N/A	30	30	92	[1]
Piper longum (Long pepper)	Methanolic	Fruits	Phenolics, flavonoids, alkaloids, tannins, terpenoids, and glycoside	100	60	100	[1]
Pistacia khinjuk (Khiniuk)	Methanolic	Fruits	Terpenoids, flavonoids, and tannins	100	10	100	[1]

Botanical name	Extraction method	Part used	Phytochemical component	Concentration (mg/mL)	Exposure time (min)	Scolicidal efficacy (%)	References
Poikilacanthus glandulosus (Ariza)	Ethanolic	Branches	Polyphenols and flavonoids	0.01	15	100	[68]
Punica granatum (Pomegranate)	Alcoholic	Stem and root	N/A	9	1440	100	[1]
Rhus coriaria (Sumac)	Methanolic	As a whole	N/A	30	20	98.89	[69]
Ruta graveolens (rue)	Methanolic	Aerial parts	Phenolic (25.53%), flavonoids (6.6%) and tannins (8.0%)	40	720	100	[1]
Salvadora persica (Miswak)	Ethanolic	Root	Indole alkaloids, flavonoids, tropaedoin, triterpenes, phytosterols, and isothiocyanates	50	10	100	[1]
Satureja hortensis (summer savory)	Aqueous	Aerial parts	Carvacrol and -terpinene	1	20	100	[70]
Satureja khuzistanica (Jamzad)	Hydrodistillation	Leaves and flowers	Carvacrol	5	60	100	[71]
Saussurea costus (Costus)	Ethanolic	Root	N/A	250	60	100	[1]
Sideritis perfoliate (Ironwort) 25 60,100	Methanolic	Leaves and flowers	Fumaric acid (260.13 mg/L), syringic acid (27.92 mg/L) and caffeic acid (26.84 mg/L), and a flavonoid, luteolin (11.23 mg/L)	25	60	100	[1]
Silybum marianum (Milk thistle)	Ethanolic	Seeds	Silydianin (14.41%), isosilybin A (10.50%), and silychristin (10.46%)	0.5	60	77	[1]
Taxus baccata (Common yew)	Hydroalcoholic	As a whole	Octane (13.36%), 4-methoxycarbonyl 3,5-diphenyl-1 (8.30%), and 9,12,15-octadecatrienoicacid (10.75%)	150	60	66.60	[72]
Teucrium polium (Felty germander)	Ethanolic	Flowers	N/A	100	50	100	[1]
Thymus vulgaris (Garden thyme)	Hydrodistillation	Leaves	Thymol	0.5	103,680	100	[73]

Botanical name	Extraction method	Part used	Phytochemical component	Concentration (mg/mL)	Exposure time (min)	Scolicidal efficacy (%)	References
Trachyspermum ammi (Ajowan)	Hydrodistillation	Fruits	Thymol	5	10	100	[74]
Zataria multiflora (Shirazi thyme)	Methanolic	Leaves	Carvacrol and thymol	25	1	100	[1]
Zataria multiflora (Shirazi thyme)	Diethyl ether	Essential oil	Thymol (66.9%), carvacrol (15.2%), carvone (7.3%), neo-dihydrocarveol (2%), and 1,8-Cineole (1.6%)	1	5	100	[1]
Zataria multiflora (Shirazi thyme)	Methanolic	Leaves	Carvacrol and thymol	10	10	100	[75]
Zataria multiflora (Shirazi thyme)	Hydrodistillation	Aerial parts	Thymol (41.8%), carvacrol (28.8%), and p-cymene (8.4%)	0.1	10	100	[1]
Zataria spp. (Satar)	Hydrodistillation	Leaves	Carvacrol and thymol	100	1	100	[1]
Zingiber officinale (Ginger)	Methanolic	Rhizome	N/A	100	30	100	[1]
Zingiber officinale (Ginger)	Methanolic	Root	N/A	100	40	100	[1]
Zingiber officinale (Ginger)	Aqueous	As a whole	[6]-gingerol	100	1440	100	[76]
Zingiber officinale (Ginger)	Ethanolic	Rhizomes sheets	N/A	200	30	100	[1]
Ziziphora tenuior (Mint)	Ethanolic	Shoots	Thymol	100	240	40.25	[77]

Table 1.
List of medicinal plants with in vitro activity against protoscoleces of Echinococcus.

dosages of 60 g/mL and 2 mg/mL for 10 min, *F. asafoetida* and *B. vulgaris* were shown to have 100% effectiveness [1, 2].

Two plant species, *Z. multiflora* and *A. sativum*, showed *in vivo* anti-echinococcal activity. In the *in vivo* studies for their validation against *E. granulosus* protoscoleces, the leaf extracts, peels and other parts were tested (**Table 2**) [1].

4.2 Fungi with reported activity against Echinococcus

Characteristic ultrastructural changes were observed when protoscoleces of *E. granulosus* was treated with extract of endophytic fungi *Eupenicillium* and *Pestalotiopsis* sp. isolated from *Azadirachta indica* and *Chaetomium* sp. *Piper longum* plants respectively. *Pestalotiopsis* sp. showed a promising scolicidal activity up to 97% mortality just within 30 min of incubation. In a study comparing commercial chitosan to fungal chitosan isolated from *Penicillium waksmanii* and *Penicillium citrinum*, it was observed that Fungal chitosan was the most bioactive type with higher degree of deacetylation showed stronger scolicidal activity *in vitro* [88].

4.3 Isolated compounds from natural products with reported activity against *E. granulosus*

A total of 8 active chemicals compounds extracted from various medicinal plant are reported to show activity against *E. granulosus*. They are, thymol, carvacrol, menthol, berberine, genistein, thymoquinone, ampelopsin, and gallic acid (**Figure 1**). In an *in vitro* study, thymol, berberine, and thymoquinone showed substantial *in vitro* scolicidal action at concentrations of 0.1, 0.5, and 1 mg/ml after exposure for 5, 10, and 1 min. *In vivo* tests with thymol and carvacrol also showed promising scolicidal efficacy [89, 90].

5. Toxicity and safety profile of the natural products with reported activity against *E. granulosus*

With increased advocacy for the use of natural products in the management of conditions such CE comes the heightened interest in the safety of these natural products. Obviously, alternatives to synthetic protoscolicidal agents are being sought not only because of associated reduced efficacy, increased recurrence rates and increased drug resistance, but also to the incidence of adverse effects [10]. Thus, successful integration of natural products in the treatment of CE will require the establishment of the toxic profile of these natural products. It is to be noted that, the idea that 'natural product' always implies 'safe' is deceptive since these products contain pharmacologically active compounds which may exert detrimental effects at high doses or in specific conditions [91].

Given the above, toxicity assessments have been conducted on some plants and active metabolites with reported activity against *E. granulosus*. For instance, *Z. multiflora* was associated with no significant toxicity in mice [92]. Similarly, essential oil obtained from *C. longa* was not shown in toxicological studies to exert any significant toxicity in NIH mice [93]. *In vivo* toxicity assessments of thymol in mice and golden hamsters also showed no overt toxicity or changes in serum biomarkers such as uric acid and bilirubin [94, 95]. Similarly, berberine at the tested clinical doses was not identified to exert cytotoxic and mutagenic effects [96]. Thymoquinone when

Botanical name (common name)	Extraction method	Part used	Phytochemical component	Experimental animal	Concentration (mg/mL)	Exposure time (min)	Scolicidal efficacy (%)	Ref
Algerian propolis (Propolis)	Ethanolic	N/A	Polyphenol, flavonoid	Mice	25	10	100	[1]
Allium sativum (Garlic)	Methanolic	N/A	N/A	Mice	50	10	100	[78]
A. sativum (Garlic) Mice	Methanolic	Garlic cloves	1% Alliin	Mice	80	43,200	Significant	[79]
Annona squamosa (Sugar apple)	Alcoholic	Leaves	N/A	Rats	100	2880	100	[1]
Artemisia Herba-alba (Wormwood)	Ethanolic	Leaves and flowers	Alkaloids, phenols	Mice	0.28	1440	55.17	[1]
Nigella sativa (Black cumin)	Ionotropic gelation technique	Seed	N/A	Mice	1.14	86,400	100	[1]
Pistacia vera (Pistachio)	Hydrodistillation	Branch	Essential oil	Mice	200	10	100	[80]
Punica granatum (Pomegranate)	Aqueous	Peels	N/A	Mice	16	2880	100	[81]
P. granatum (Pomegranate)	Aqueous	N/A	Peel	Mice	0.65	86,400	66.7	[82]
Sophora moorcroftiana	N/A	seeds	N/A	Mice	0.25	60,480	76.1	[83]
Zataria multiflora	Essential oil and oleic acid	Essential oil	N/A	Mice	20	10	100	[84]
Zataria multiflora (Shirazi thyme)	Diethyl ether	Aerial parts	Gallic acid (1.1618 mg/g), catechin (2.808 mg/g), caffeic acid (5.531 mg/g), and quercetin (9.961 mg/g)	Mice	0.04	43,200	Significant	[85]

Botanical name (common name)	Extraction method	Part used	Phytochemical component	Experimental animal	Concentration (mg/mL)	Exposure time (min)	Scolicidal efficacy (%)	Ref
Zataria multiflora (Shirazi thyme)	Methanolic	Leaves	Thymol (66.9%), carvacrol (15.2%), and carvone (7.3%)	Mice	8	43,200	100	[86]
Zataria multiflora (Shirazi thyme)	Hydrodistillation	Essential oil	Thymol	Mice	2	10	100	[87]
Zingiber officinale (Ginger)	Ethanolic	As a whole	N/A	Mice	150	60	100	[1]

Table 2.
List of medicinal plants with in vivo activity against protoscoleces of Echinococcus granulosus.

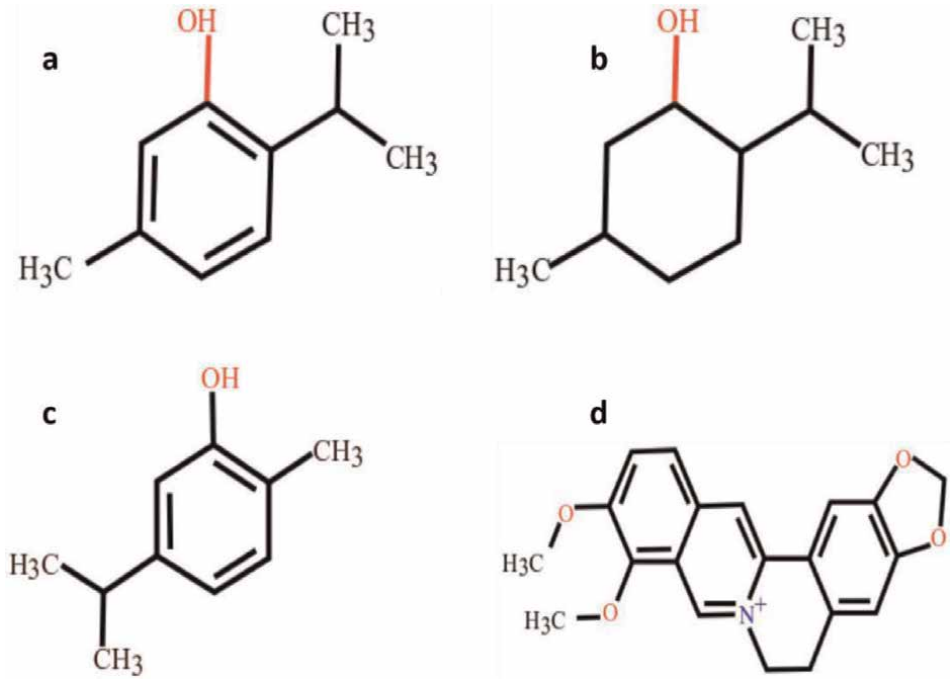

Figure 1.
Active chemicals compounds extracted from various medicinal plant are reported to be active against Echinococcus granulosus*. a: thymol; b: menthol; c: carvacrol; d: berberine.*

assessed for mortality and toxicity in mice, at doses of 0.1, 0.2, 0.3 mg/ml for a period of 3 months was proved to be safe [97].

Albeit toxicity data may not be available on all medicinal plants shown to be effective against *E. granulosus*, available evidence on numerous other plants shows that these natural products may be safely used in the treatment of CE [98, 99].

6. Discussion

Medicinal plants with dependable therapeutic effects are valuable sources of bioactive substances that can be developed into potential lead compounds in the development of drugs for treatment of CE, a neglected tropical disease [2]. Due to the rise in the emergence of resistant species associated with infectious diseases, developing novel and effective drugs is imperative for the continuous survival of the human race. Owing to this, there has been resurgence in the search of natural products that can serve as alternative synthetic agents in the management of diseases. These natural products contain a large variety of secondary metabolites that possess several biological effects including anthelminthic activity [100]. As such, large numbers of natural products have been screened particularly against *E. granulosus* protoscolices with the hope of identifying natural products with prominent scolicidal potential.

One such natural agent with prominent scolicidal activity is *Zataria multiflora*, the most reputable member of the family Lamiaceae [100]. It has been shown that, the essential oils of *Z. multiflora* exert powerful anti-hydatid effect even with short exposure times [101]. This remarkable activity of *Z. multiflora* essential oils has been

attributed to the presence of significant phenolic monoterpenes which contains a hydroxyl group and possess an innate hydrophobic nature. The presence of a hydroxyl group and the hydrophobic nature of phenolic compounds enable *Z. multiflora* essential oils to penetrate cell membranes resulting in the death of the helminth [102].

In eukaryotic cells, phenolic monoterpenoids primarily decrease the integrity of plasma and mitochondrial membranes, resulting in cell death. However, the exact mechanism of action of phenolic monoterpenes in protoscoleces has yet to be determined, albeit it has been shown to penetrate the cell membrane, damage the lipid bilayer and, alter cell permeability. This results in leakage of intracellular components, which lowers the membrane electric potential. This change in the plasma membrane electric potential probably causes leakage of ATP, proteins, potassium and calcium, resulting in membrane damage and cell death [103].

Other natural products such as the medicinal plants *Ferula assafoetida* and *A. sativum*, fungal chitosan, and extracts of endophytic fungi *Eupenicillium* and *Pestalotiopsis* sp. isolated from *Azadirachta indica* and *Piper longum*, respectively have also shown significant scolicidal activity. Essential oils obtained from *Ferula assafoetida* contain disulfide compounds which have been shown to be responsible for their scolicidal action [104].

In vitro and *in vivo* tests have both been used in investigating the pharmacokinetic characteristics and pharmacodynamic effects of target extracts, as well as host immune reaction to these natural products. However, majority of studies that evaluated the protoscolicidal activity of different medicinal plants during the past two decades have utilized *in vitro* assays. Only a few studies involved *in vivo* animal models [1]. More *in vivo* screening of these natural products with effect against CE are needed to develop a complete picture of their efficacy and toxicity in whole organisms. Considering currently available protoscolicidal agents are associated with serious adverse effects, close attention must be paid to the toxicity of these natural products in other to identify suitable alternatives to current management [10]. A good protoscolicidal agent is one that is steady in the cystic contents and possesses the least toxicity [105].

Moreover, owing to the multiplicity of active metabolites found in natural products, the risk of development of drug resistance may also be low. Data from toxicity studies available on these medicinal plants also shows the reduced risk of adverse effects associated with their use. However, additional studies will be desired to prove these outcomes by establishing the toxicity profile for all the other species of plants identified to possess activity against *E. granulosus.* In addition, the exact mechanism by which the extracts and their isolated compounds exert scolicidal activity, and their pharmacokinetic profiles must be well established. Knowledge obtained from these suggested studies should be well synthesized and used to appropriately design randomized controlled trials in human subjects in order to bridge the gap between the bench and the bedside for CE treatment.

7. Conclusion

Cystic echinococcosis is a public health menace, affecting humans and livestock worldwide. Although drug treatment is available for its management, in many cases, existing drugs are insufficiently efficacious, ineffective due to resistance, relative toxic or contraindicated in some populations. Thus, hindering global efforts to eliminate this neglected tropical disease. Interestingly, natural products have demonstrated

significant activity against *E. granulosus*, indicating their potential for use in the treatment of CE. Medicinal plants such as *Zataria multiflora* and *Allium sativum* have been shown to be effective in both *in vitro* and *in vivo* models. In light of the slow development of new anthelminthics over the past few decades due to lack of commercial attractiveness, natural products may serve as alternatives or adjuncts to current treatment approaches. Also, these medicinal plants are rich pools of active metabolites that may serve as drug leads in the development of scolicidal drugs.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 5

Perspective Chapter: Prospects for Pharmacological Therapy of Hepatic Alveolar Echinococcosis

Asher John Mohan, Bhaskar Kumar Gupta and Silviya Sarah Lal

Abstract

Often misdiagnosed as liver cancer at first, the Alveolar hydatid disease or hepatic alveolar echinococcosis is an uncommon but potentially harmful variant of the disease also synonymously known as *Echinococcus multilocularis* (*E. multilocularis*). The major area being drastically affected is the liver, from where its later advances into the lung and brain, typically fatal if left untreated. Even if surgery is still the recommended course of treatment for the condition, drug therapy cannot be thwarted off and remains essential and vital for individuals with disease extremity. This chapter therefore aims to present a framework through which FDA-approved drugs and nano drug delivery technologies collaborate to manage progressive hepatic alveolar echinococcosis.

Keywords: alveolar hydatid disease, hepatic alveolar echinococcosis, *Echinococcus multilocularis*, FDA-approved medications, nano drug delivery

1. Introduction

Echinococcosis is amongst those neglected diseases that the World Health Organisation (WHO) intends to manage or mitigate by the year 2050. Significant inclinations toward overhauling the treatment, management and control of Echinococossis originate from limitations of current diagnostic techniques, toxicity and low efficacy of medication options, usually suboptimal surgical procedures and other factors [1]. As the name implies, this chapter seeks to outline the latest clinical findings regarding the management of Hepatic Alveolar Echinococcosis (HAE) also just known as Alveolar Echinococcosis (AE).

2. Physiology of transmission

During its life cycle, the parasitic worm primarily picks out a carnivore like dogs and their prey (rodents) to act as its definitive and intermediate hosts. Despite not being actively engaged in the propagation of the illness, humans can nonetheless

serve as intermediate hosts in certain situations. The maturation of adult worms and the release of eggs in the faeces of the definitive host as mentioned above are the variables that are involved in the transmission phenomena. After being consumed by a person (through food or water), the eggs later hatch and reach the liver via the lymphatic channels. This locus is significant in terms of the eggs developing into larvae and later metastasizing into other organs of the host [1].

3. Prevalence

Alveoli echinococcosis has been a significant problem in northern Japan, China, Tibet and other parts of Central Asia [2–7]. In much of Europe, both definite and intermediate hosts have now been reported to be significantly more vulnerable to the infection [8, 9]. Until recent findings from parts of Mexico, AE was not regarded as a major human hazard in North America [10]. Nonetheless, over the past 10 years, human infections have been identified in North America and other parts of Canada [11, 12].

4. Clinical indications

The liver is where a high proportion of the disease's primary lesions are sited, out of which many may differ to manifest for up to 15 years. Trauma to the hepatic blood vessels or bile ducts emerges as disease symptomatology [13]. The delay in disease identification was caused by both false imaging results and acute clinical symptoms, pointing to a problem (incorrect therapeutic management) that could not be easily overlooked [14]. It has been determined that elevated levels of biological response modifiers such as interleukins and genetic variations in antigen presenting cells such as the human leukocyte antigen are positively correlated with the onset or progression of the disease in humans [15, 16]. The occurrence of AE and its rapid progression have also been linked to acquiring therapeutic immunosuppression, which results from immunosuppressant administration necessary during a liver transplant [17].

5. Diagnosis

Visual tests (CT scans), imaging techniques and serology are amongst the most widely employed methodologies for the confirmation of the parasite. Other than these prominent ones, southern blotting and polymerase chain reactions (PCR) are the molecular techniques involved in the diagnosis of the disease. Discussed below are the most widely employed diagnostic methods for AE.

5.1 Imaging techniques

In order to offer physicians a trustworthy source of information when making a clinical judgement, the WHO has classified the disease lesions into a variety of forms solely based on imaging data obtained in the US [18]. The effectiveness of these imaging data as a screening and follow-up aid is gaining significant attention in centres of both Asia and Europe [19, 20]. Lesions from an abscess or tumour can now

be differentiated by these techniques such as Contrast-enhanced ultrasonography (CEUS) [21]. In addition to the above technique, the methodology involved in an imaging technique named FDG-positron emission tomography (FDG-PET) is used to prevent inaccurate tumour interpretations [22].

5.2 Serology

Drawbacks of imaging techniques described above such as the inability to distinguish between an abscess and a neoplasm, difficulty in data interpretation and unreliability with respect to early diagnosis cause a shift in preference toward blood serum analysis known as serology. Furthermore, serology is more accurate as an affirmatory and reliable tool for AE cases. This is largely prevalent in developing nations where these techniques are absent [23]. Apart from these decisive advantages, patient follow up post medical or surgical treatment is also made simpler [24, 25].

5.2.1 Specific serological diagnosis of AE

This section covers the involvement of specific serological markers pertaining to the diagnosis of AE.

Excretory/secretory proteins (ESPs), also termed as parasitic antigens, are responsible for triggering the host's immune response [26]. A member of the *E. multilocularis* specific ESPs, Em2, also referred to as Em2a and Em18, allows for precise discrimination between an AE and Cystic echinococcosis patient [27, 28]. Recent findings also render the role of a varied antigen named Em492 in the diagnosis of AE [29]. Similarly, showing high diagnostic performance for confirmation of AE is EM10 and its derivatives (another Echinococcus antigen) [30]. Based on molecular research done on mice, lipoprotein antigen B is the last of the few ESPs that is expressed in the disease condition [31].

5.2.2 Importance of serology both in pre and post therapy of AE

The method of Elisa to detect specific antibodies relating to AE with high sensitivities of up to 95% is employed at various laboratories. Addition of an immunoblotting technique to this ELISA maximised the diagnostic sensitivity [32]. A follow up usually done as relapses can prevail even after surgery of chronic administration of medications. This is where serology reappears back into the confirmation process where the antibody detection can be directly linked to the degree or extent of disease. A challenging situation that arises in this method occurs in the case of an immunosuppressed patient as less information is available to quantify or qualitatively analyse the antibody response. Based on a study to optimise the role of serology both for diagnosis and monitoring of pre or post therapies of AE have brought about the following results

a. Serology can help in distinguishing between an active and inactive lesion. This holds true both in the diagnosis or pretreatment phases thus unnecessary advice for a surgery or medication can be avoided

b. Serological methods as a follow up study post-surgery or therapy can aid in prediction of disease relapse [33].

6. Treatment

6.1 Invasive modus operandi

Profound resection of liver lesions constitutes the basis for the adoption of a treatment decision [34]. Even though hepatic surgery is the best course of action, significant cases of morbidity and mortality cannot be addressed even under expert supervision. This therefore exemplifies the fact as to why only one-third of the patient population develops positive outcomes from the procedure alone. Also note that the majority of geographical regions where this occurs have delayed diagnoses [35]. These drawbacks may also be attributed to the evidence that an intrusive procedure alone is unsafe for disease treatment because of its close association with complications as mentioned above [36].

In light of this, the treatment goals, and regimen for AE have now been tailored as follows.

a. Complete occlusion of the parasitic lesion, followed by 2 years of anti-infective medication (examples discussed later).

b. If the initial strategy fails to diminish disease burden, the period of anti-infective drugs needs an extension (upto 10 years to prevent recurrence).

c. Lingering underlying difficulties can be tackled in aspects of reducing inflammation or obstruction in the bile duct [37]

With respect to the above-laid objectives let us dive deep into some of the pros and cons of the treatment.

An advanced parasite infection is indicated by lesions around the hepatic veins and progress into the inferior Vena cava. Such situations are resolved with the liver transplant procedure. Negative compliance with this strategic approach may be brought on by the lack of an appropriate matching donor and prolonged use of immunosuppressants [17].

As an alternative to a full transplant, the procedure known as *Ex vivo* liver resection can be used, in which the patient's liver is physically removed, cleared of lesions post which it is reinserted. In cases of irresectable livers or late stages of the illness, this is favoured and produces favourable results without requiring long-term immunosuppressive treatment [38].

The other types of disease burden are hepatobiliary complications, which signify an unpleasant shift in the disease progression [39]. Ameliorative techniques used up until the turn of the century involved the percutaneous dilatation of the blocked bile ducts [40]. The contribution of such an invasive technique (termed as Perendoscopic bile duct stenting) for treating biliary obstruction is irreplaceable and is at widely being used. The desired result for individuals hospitalised for this procedure is an improvement in the quality of life [41].

6.2 Medication

Breakthroughs in AE have been made possible by faster detection, the introduction of drug therapy, and the gradual abandonment of resective procedures [42]. End-stage

diagnoses, a lack of medical resources, and the failure of a specific drug or the severity of their side effects can unnerve nations going through such suffering [43].

7. Negative consequences in the current treatments of AE

Foretelling the outcome of AE is daunting as resection is often accompanied by chemotherapy using benzimidazoles for unquestionable periods of time [44]. Hepatotoxicity of the lot is amongst the major concerns. Along with this distress, although significantly increasing the survival rate of patients; they are capable only in reduction (static effect) but not destruction (cidal effect) of the parasite. In short, recurrence after drug withdrawal cannot be avoided [1].

This presents a clear conundrum regarding the need for additional AE treatment options. Therefore, selectivity, a sizable therapeutic window and a cidal rather than a static effect should be given priority when choosing a conventional drug for treatment of AE.

8. Pharmacological prospects for AE treatment

There is a plethora of preclinical research (both *In vitro* and *In vivo*) containing data on potential treatments for AE, such as usage of anti-infectives, anti-cancer drugs etc. However, these could not be completely depended upon due to the absence of thorough and reliable screening methods [45].

With respect to *In vitro* studies, the development of extensive means for specific species culture of AE larvae have brought about a change in the aforementioned conclusion, thereby opening doors for whole or reliable drug screening assays against the parasite [46, 47].

8.1 Anti-infective agents

These agents find place in AE as this condition is not restrictively a parasitic burden but also infectious in nature.

In vivo data revealed that chemotherapeutic drugs and anthelmintics, in addition to benzimidazoles, all had parasitostatic effects [48]. When used both alone (*In vitro*) and in conjunction with a benzimidazole (*In vivo*), nitazoxanide demonstrated promising outcomes against AE [49, 50]. Monotherapy and combination therapies on the contrary failed to treat AE in humans, despite the mentioned claims [51].

Tricloabendazole had the strongest *In vitro* antiparasitic activity of all the benzimidazole compounds evaluated. When evaluated *In vitro* and on additional mice models, drugs like fenbendazole, oxfendazole, and febantel were highly efficacious against the disease [52, 53].

8.2 Anti-malarial compounds

The Mefloquine compound used in treating malaria showed promising albendazole-like features when looking at an In vivo activity alone. Higher rates of reduction in the parasite burden were seen with an increase in dose of the said drug candidates. However, the latter's incomplete pharmacokinetic data and the presence

of neurotoxicity following prolonged mefloquine treatment could be a hazard to therapeutic regimens involving them [54].

8.3 Antibiotics

Clarithromycin, an antibiotic macrolide, significantly reduced the proliferation and morphological traits of *E. multilocularis* in vitro. Similar abnormalities were also translated on to the adult forms of the parasite. However, no suitable in vivo tests were carried out to further investigate these promising findings [55].

8.4 Other methods for assessment of potential targets

Affinity chromatography followed by MS-based sequencing can now be used to validate novel targets or other significant proteins expressed during the host–parasite encounter [56]. When it became necessary to assess the degree of harm brought on by pharmacological therapy, a technique of drug screening based on the release of the enzyme phosphoglucose isomerase was devised. This is now mostly used to anticipate how well different anti-parasitic medications can improve disease burden [57].

8.5 Cancer cell proliferation inhibitors

Reoccurring and indistinguishable characteristics between the parasitic condition and malignancies such as ongoing cell proliferation, ability to alter immune response, production of proteolytic enzymes, angiogenesis stimulation, over-expression of certain proteins, and the capability to create metastases, may find their application in usage of anti-cancer medications as a possible form of treatment [58].

One of the earliest anti-cancer compounds investigated for the potential use against AE was doxorubicin in the form of nanoparticles. Mostly because of the serious side effects that were accompanied to this moiety, this concept of therapy was dropped [59].

Later, genistein, an isoflavonoids-class of anti-tumour drug which demonstrated anti-parasitic properties, was introduced. Although highly effective, its negative impact on long-term treatment deprived it from being implemented or approved for the world scenario [60].

Another occurrence involved the research findings from the endogenous oestrogen metabolite, 2-methoxyestradiol, which caused substantial in vitro harm to the parasite. This however revealed no statistically significant differences from the conventional albendazole medication [61].

At very low concentrations, the mitogen-activated protein kinase and tyrosine-kinase inhibitors pyridinyl imidazoles and imatinib, respectively, caused parasite cell death [62, 63].

A possible therapeutic target that requires careful examination is the role glutathione-S-transferase plays in AE and other malignancies where it promotes cell proliferation. In other words, medications inhibiting cell proliferation could make way into pharmaceutical care for AE [64].

Investigation of other enzyme inhibitors, such as the proteasome inhibitor bortezomib, showed that this enzyme is a viable pharmacological target that should be pursued further [65].

With the help of early findings that require further analyses, cytostatic compounds can also be helpful moieties in AE prevention [66].

9. Recent lab findings

This section emphasises on the recent developments found in the research areas regarding AE.

9.1 Anti-cancer drugs

Alterations to a proto-oncogene (a gene involved in normal cell growth) may lead to the formation of oncogenes, which aids in cancer development. RAF is an example of such a proto-oncogene that regulates a variety of cellular functions, bringing about a gain in malignant properties of a normal cell. The anticancer drug, Sorafenib inhibits tumour cell proliferation and formation of new blood vessels (angiogenesis) by targeting RAF in Raf signalling pathway. The drug in question was found to exhibit strong inhibitions in conditions of multilocular echinococcosis [67].

9.2 Immune checkpoint inhibitor

After invasion the parasite has the capability to escape an encounter with the host immune system [68]. This immunosuppressive setting is highly influential for the viability and proliferation of the parasite [69].

It was found that Programmed Cell Death Ligand 1 abbreviated as PD-L1 plays a negative role in cancers by attenuating immune responses [70]. Studies that focused on this transmembrane protein reached the conclusion that the development of HAE was in close association with high expressions PD-L1. This could be a probable mechanism by which the parasite achieves immune escape [71].

Other supporting research was found to be in agreement with the above inference. Confirmation of this hypothesis was brought about by a control in the infection utilising immunotherapy which acted on PD-L1 pathway blockage [72, 73].

Alongside the above mechanism, an additional blocking activity on TIGIT, an inhibitory receptor led to tumour rejection. This was an indication that TIGIT and PD-1/PD-L1 blockade enhanced or synergised the anti-tumour effects of lymphocytes [74]. When In vivo studies on mice and humans were based on these mechanisms, TIGIT highlighted its potential as an immunomodulatory strategy for the treatment of AE [75, 76].

9.3 Nano drug delivery system

The rate of cure in a conventional anti-infective such as albendazole was found to be low. Poor bioavailability was found to be the reason behind the unfavourable effect. The need to alleviate this drug disadvantage led to the shift in focus for designing new formulations of the drug being discussed.

Liposomes that help in delivering active molecules to the site of action were the answer to this research problem [77, 78]. These treatments significantly reduced parasite burden in patients by increasing the mortality rate against larvae of the parasites when compared with traditional albendazole [79].

Other than liposomes, a valid suggestion for the employment of nanocrystals resulted in an increase in bioavailability of the same medication [80].

The preventive efficacies of these nanotechnology-based preparations were also found to be enhanced [81]. All these findings contribute to the fact that nanomedicinal forms of an anti-infective have developmental potential in improving anti-AE drug therapy.

10. Conclusions

Alveolar Echinococossis, although rare and neglected, is fatal if left untreated. The profound mode of treatment involves the resection of liver. However, we have discussed that this alone wasn't sufficient and that supportive therapy using medications was a necessity. The severe adverse effects of traditional drugs also caused a decline in quality of life of patients. The above stated reasons brought about the need to seek further advanced treatment options for the disease such as new drug targets, elucidation of novel mechanisms involved in disease progression, various drug delivery technologies etc. The authors hence have highlighted the clinical indications and the need for specific diagnostic approaches of the disease such as imaging techniques and serology. Along with invasive modes of treatment, the additional employment of various medicaments including anthelmintics, anti-malarials, antibiotics, inhibitors of cancer proliferation, immune checkpoint inhibitors and nano drug delivery system that were found to be promising for the treatment of AE without exhibition of the adverse effects of traditional drugs were briefed. This chapter was approached with the sole purpose of exploring the various novel trends and those that are presently in action to tackle this slowly rising, yet worrisome endemic.

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Conflict of interest

We, the authors, would like to declare that there is no conflict of interest based on the information produced.

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Chapter 6

Current Concepts in Curative Surgery for Cystic Echinococcosis of Liver

Daniela Kniepeiss and Peter Schemmer

Abstract

Cystic echinococcosis (CE) may cause unspecific symptoms like abdominal discomfort in the right upper quadrant of the abdomen due to capsule tension pain of the liver related to an increased expansion of the cyst. Further, a growing cyst may put pressure on intrahepatic bile ducts or can get direct access to the biliary system with complications like obstruction, cholangitis and fistulas. Large or rapid growing cysts may cause compression of blood vessels with thrombosis or Budd-Chiari syndrome. However, the vast majority of patients with CE of the liver is asymptomatic. CE of the liver can be cured surgically in many cases. In the past, cystectomy with resection of the pericyst components was performed as a standard. The today's parenchymal sparing state-of-the-art surgery is endocystectomy combined with partial cystectomy. This procedure includes (i) evacuation of paracyte-derived cyst content, (ii) sterilization of the cyst wall (host) and (iii) deroofing of the cyst (partial cystectomy). Here the advantages, risks and outcomes of the surgical approaches are discussed, and the need for an interdisciplinary treatment of these patients is outlined.

Keywords: partial cystectomy, endocystectomy, 20% sodium chloride, recurrence, interdisciplinarity, surgical approach

1. Introduction

Echinococcosis in humans is mainly caused by *Echinococcus granulosus* (*E. granulosus*) or *Echinococcus multilocularis* (*E. multilocularis*), which cause cystic echinococcosis (CE) or alveolar echinococcosis (AE), respectively [1]. It is an important parasitic disease of humans, which represents a considerable endemic health problem in some areas of the world. CE affects the liver in up to 70%, less frequently the lung, the spleen, the kidney, the bones and the brain can be involved [2–4]. CE of the liver is asymptomatic in most cases; however, both biliary and vascular complications like cholestasis, cholangitis, biliary fistula and thrombosis or Budd-Chiari syndrome, respectively, are observed. In some cases, CE can become even a life-threatening disease. *E. granulosus* is endemic in South America, Eastern Europe, the Middle East and China with incidence rates of up to 50 per 100.000 persons per year [5, 6]. A prevalence of up to 95% was described in some slaughter houses in South America [7].

On the other hand, there are zones without hydatid cysts like Tanzania, Cyprus, Malta or New Zealand [8], which can be attributed to the health policy of these countries. Although the mortality rate of CE is low with 2.2%, morbidity is high [9].

An acute course of the infection has never been described in humans [10], and the development of a cavity and of the germinal and laminated layer of the cyst wall occurs 10–14 days after the infection at earliest [11]. The growth of the cysts is only partially understood, and the growth rate is variable [12]. The behaviour of cysts in different stages is often unpredictable and varies greatly [13, 14].

Diagnosis of CE is often coincidentally in patients presenting with unspecific abdominal symptoms, pain or poor appetite [15]. Imaging techniques like ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are essential for diagnosis and clinical management [16–18].

Treatment options have been discussed by the "Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans" and are published by the WHO-Informal Working Group on Echinococcosis [19]. In contrast to the watch and wait strategy, therapeutic options include conservative treatment with benzimidazoles, interventional sterilization techniques and surgical approaches. While surgery can provide curative treatment in selected patients, the overall treatment strategy depends on various disease dependent factors (size, number and location of cysts), individual contraindications for surgery, intolerance to benzimidazoles and on CE-derived complications.

2. The hydatid cyst structure and its progress

In order to understand the different surgical approaches, the structure and progress of a cyst in the liver should be known. The cyst in the liver consists of three layers. Outside there is the adventitia or pericyst. It consists of compressed liver parenchyma and fibrotic tissue and results from the expanding parasitic cyst. Further inside is a laminated membrane or ectocyst, which is easy to separate from the pericyst. The innermost layer is called germinal epithelium or endocyst. It is a single layer of cells, and it is the only living component. The cyst is filled with hydatid fluid, solices and sometimes brood cysts or daughter cysts [20].

The history of a hydatid cyst in the liver consists of two phases. First the cyst growths and could rupture due to a high pressure inside. This might lead to complications like acute allergic reaction, infection or jaundice. During the second phase of the hydatid cyst, it is full of solices and daughter cysts, which replace the hydatid fluid. In this phase, calcifications occur in the pericyst. The growth of the cysts may cause pressure on the surrounding tissue with symptoms like upper abdominal pain, discomfort or obstructive jaundice [21].

3. Complications of CE of the liver

In about 40% of hepatic CE complications occur. The most common complication is infection, which can be asymptomatic or clinically noticeable with pain and fever. Another common event is the intrabiliary rupture of the hydatid cyst, which can happen in two ways: the occult rupture is marked by the drainage of cystic fluid into the biliary tree. Its incidence is up to 37%. The frank rupture is characterized

by an overt passage of intracystic material to the biliary tract. It occurs in 3–17% of the patients. The incidence of intrabiliary rupture into the right hepatic duct is indicated with 55–60%, into the left hepatic duct with 8–11% and into the gallbladder with 5–6%. The intrabiliary rupture causes further biliary complications like cholangitis or hydatid biliary lithiasis [22–24]. In a few cases, rupture into the thorax or into the peritoneum is possible. Intrathoracic rupture can cause lesions of the pleura, the lungs and bronchi, which can lead to coughs and dyspnea [25]. The rupture into the peritoneal cavity is rare and occurs spontaneously in most cases. It leads to abdominal pain, allergic reactions, vomiting and nausea [26]. Very rare complications of hepatic CE are fistulization to the skin, portal hypertension or vascular erosions [27].

4. Diagnosis

4.1 Clinical symptoms

After the infection, patients are mostly asymptomatic. Symptoms depend on the size and number of the arisen cysts and on the effect within the affected organ. Especially non-complicated cysts are often asymptomatically and diagnosed incidentally. Vague symptoms comprise abdominal pain in the right upper quadrant or epigastric pain due to an enlarged liver. Symptoms of complicated cysts range from anaphylaxis and infections to jaundice due to biliary complications [28].

The diagnosis of hepatic CE requires both imaging and serologic and immunologic investigations. Routine laboratory values might show eosinophilia in some cases. Serum alkaline phosphatase levels are elevated in about 30% of patients.

4.2 Serology and immunological tests

Serological tests are used to detect antibodies against the parasite. Immunglobuline (Ig) G antibodies are elevated after exposure to the parasite, and in cases of active infection, specific IgM and IgG antibodies are high. Circulating hydatid antigen can be detected in the serum with ELISA-tests and can be used for monitoring after therapy. The sensitivity of ELISA-tests is up to 90% and therefore preferred. In patients with hepatic CE, the indirect immunofluorescence assay (IFA) is the most sensitive test (95% sensitivity) [29].

4.3 Imaging techniques

The screening method of choice is ultrasonography (US). CT scan provides information concerning lesion size, location and relations to intrahepatic structures and therefore plays an important role in preoperative diagnostics to evaluate vascular, biliary or extrahepatic extension of the cyst.

4.3.1 Ultrasonography

It is the primary radiological technique with an accuracy of 90%. Solitary or multiple cysts, daughter cysts, separation of membranes, but also complications can be diagnosed. Doppler US provides information on the interference with vascular

structures. US features are classified by Gharbi et al. [30] as follows: type I shows a pure fluid collection, in type II there is a split wall additionally. Type III presents septa and/or daughter cysts. Type IV cysts show a heterogeneous echo pattern, and type V cysts are calcified. Another classification was introduced by the World Health Organization (WHO) [31]: they range from CL (single cyst), CE 1 to CE 5. The type depends on the disease status and morphological type of the cyst.

4.3.2 CT scan

The highest sensitivity for detecting hydatid cysts with number, size and location is given by a multi-detector row CT scan. Additionally, intrabiliary ruptures or the presence of other complications can be diagnosed. CT scan is important for the planning of surgical intervention.

MRI adds little information and is therefore rarely indicated. In cases of intrabiliary rupture, endoscopic retrograde cholangiopancreatography (ERCP) is an important tool for diagnosis or intervention [32].

5. Surgical treatment

Surgery is the gold standard treatment for hepatic CE and aims to remove the CE. Cure can be achieved with various surgical approaches including pericystectomy, liver resection and parenchymal sparing endocystectomy with partial cystectomy. The choice depends on the number and size of cysts as well as on the condition of the patient. One important point and challenge is avoiding the spillage of cyst content and thus to decrease the risk of recurrence [33]. In the following the standard surgical procedures for CE of the liver are described, and advantages and disadvantages of such are summarized (**Table 1**).

5.1 Endocystectomy with partial cystectomy

Endocystectomy with partial cystectomy is a novel parenchymal sparing surgical technique for CE of the liver [34]. After laparotomy, the liver is dissected free from its ligaments. Intraoperative ultrasound verifies the location of CE. Subsequently, a layer of cloths soaked with normal saline solution is placed in the abdomen to protect tissue surrounding the liver. These cloths are covered by a second layer of cloths that are soaked with 20% saline solution (**Figure 1**). This hyperosmolar saline prevents a spread of CE even in the case of contamination with hydatid fluid.

A 12 mm safety trocar is inserted into the cyst (**Figure 2**), and the parasite-derived cyst content is sucked out completely (**Figure 3**). After removal of the trocar, a white test is performed [35] to exclude access from the cyst to the biliary system. Bile fistulas are closed with stitches, and the cyst is filled with hyperosmolar saline for 15 minutes to devitalize remnant protoscoleces (**Figure 4**). Finally, the cyst is deroofed (**Figure 5**) and filled with omentum (**Figure 6a** and **b**).

A great advantage of this procedure is the excellent view and control of the parasite-derived material during surgery. Complications, i.e. bleeding, postoperative bilioma or fluid collection, have not been reported. Most importantly, endocystectomy with partial cystectomy as described here prevents from recurrence of CE [34].

The following surgical procedures for treatment of CE are described considering their disadvantages:

Surgical technique	Advantages	Disadvantages	Potential complications	Outcome
Parenchymal sparing approach	• Excellent view • Good control of the parasite-derived material • Less complications • Less recurrence	• Open approach	• Biliary lesions	• Low risk for complications • Recurrence-free up to 48 months
Pericystectomy without liver resection	• Less invasive than liver resection	• Risk for sclerosing cholangitis	• Biliary fistula • Cavity infection	• Complication rate up to 24% • Recurrence rate up to 25%
Pericystectomy with liver resection	• Radical removal of the cyst and all components • Opening of the cyst can be avoided • No risk for cavity infection and lower risk for biliary fistula	• More complex and difficult procedure compared to the conservative approach	• Bile leakage • Postoperativ bleeding • Liver failure • Wound infection • Incisional hernia	• Complication rate 3–30% • Recurrence rate up to 4%
Laparoscopic approach	• Less hospital stay • Less pain • Less wound healing complications	• Posterior and superior segments of the liver are difficult to reach • Difficulties with aspiration of the cyst content • Risk for spreading of the cyst content	• Bile leakage • Cavity infection • Port-side infection and/or contamination with CE	• Complication rate up to 15% • Recurrence rate up to 11%

Table 1.
Advantages, disadvantages and outcome of different surgical procedures.

5.2 Pericystectomy

Pericystectomy of the CE includes total cystectomy with removal of the parasite-derived cyst components together with the entire pericyst. It can be performed with the resection of the surrounding liver tissue or without liver resection to preserve healthy liver parenchyma. Pericystectomy combined with liver resection can be indicated for large or multiple or complicated cysts, if the future liver remnant is large enough for excellent hepatic function.

Disadvantages of pericystectomy without liver resection are the risk for sclerosing cholangitis, biliary fistula and cavity infection. There is a complication rate of up to 24% and a recurrence rate of up to 25% [36]. Pericystectomy with liver resection is a radical removal of the cyst, all components and surrounding liver tissue. The procedure

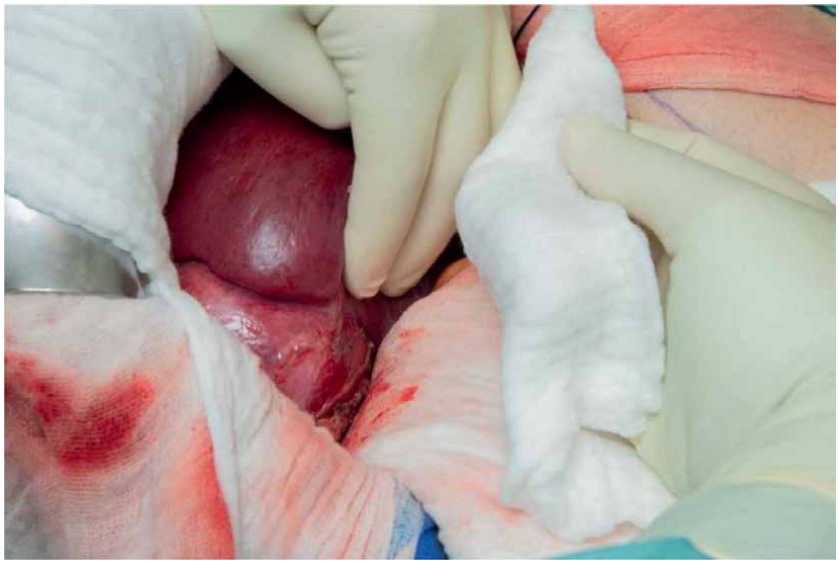

Figure 1.
Layer of cloths soaked with normal saline solution and a second layer of cloths soaked with 20% saline solution is placed in the abdomen to protect the tissue surrounding the liver.

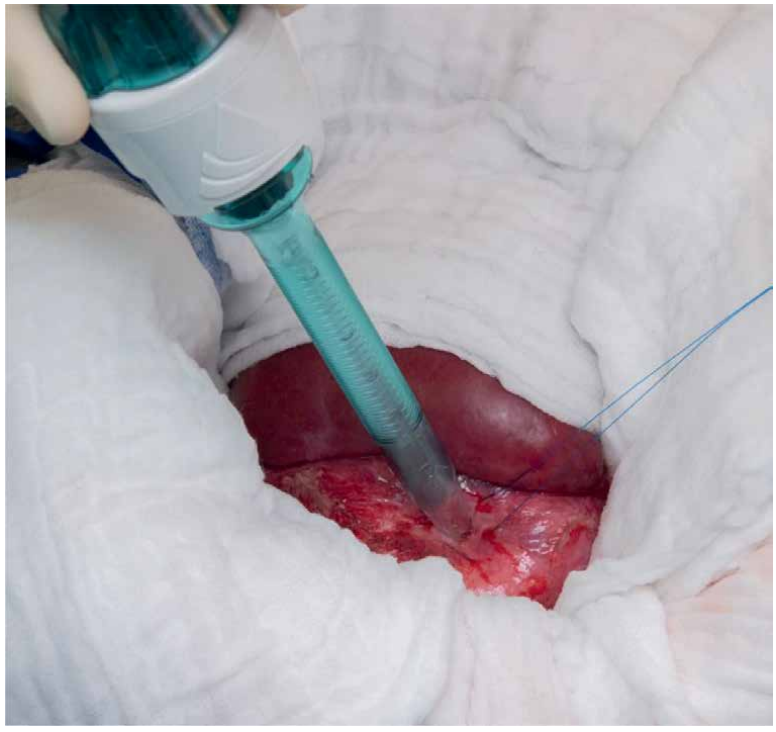

Figure 2.
Noncutting twelve-millimeter trocar is inserted into the cyst.

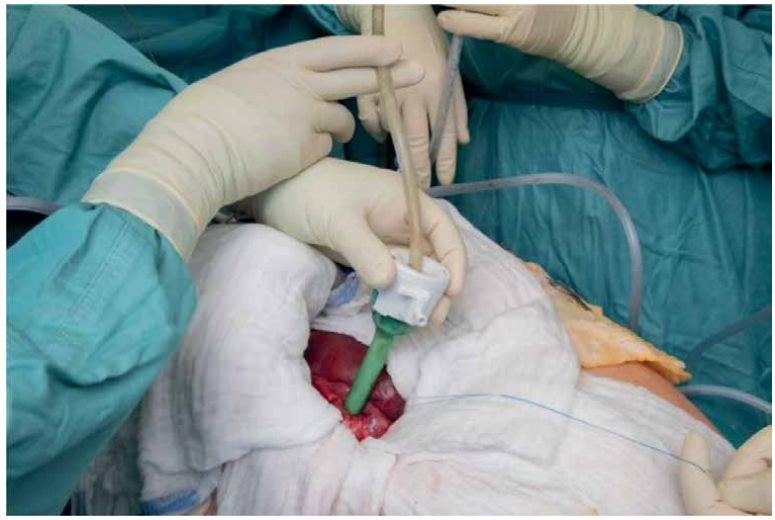

Figure 3.
Parasite-derived cyst content is sucked out completely via the trocar.

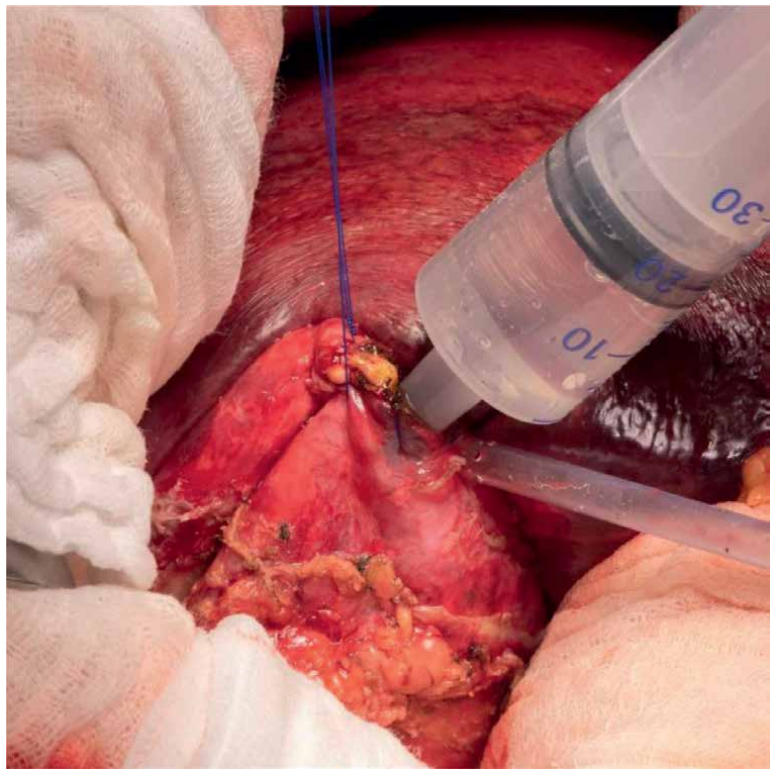

Figure 4.
Hyperosmolar saline fills the cyst for 15 minutes.

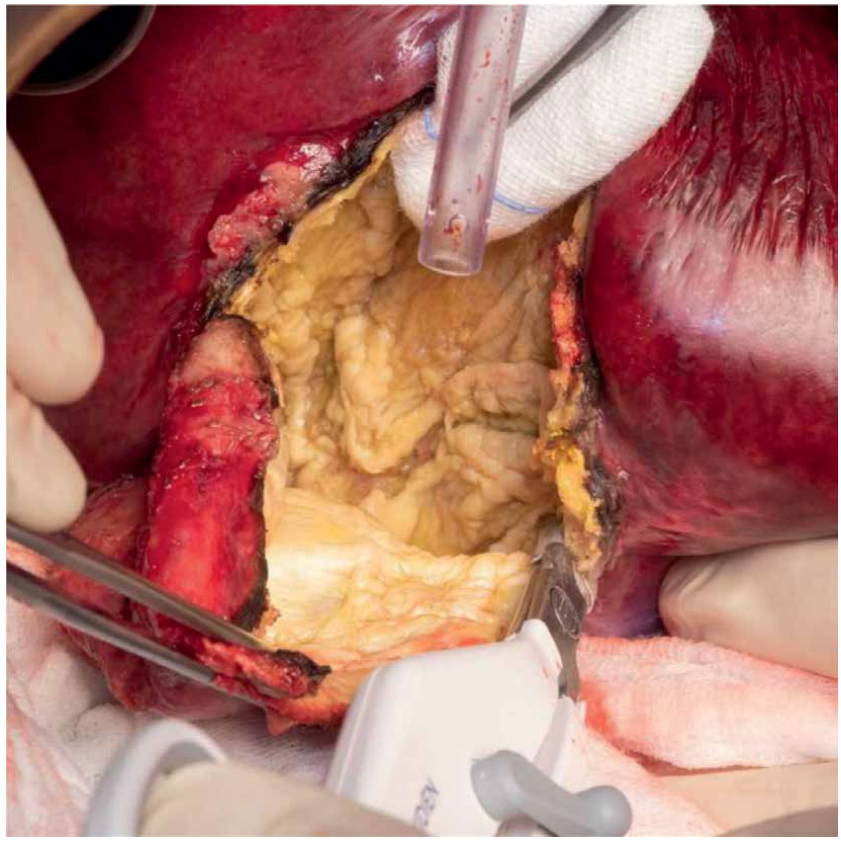

Figure 5.
Deroofed cyst.

is more complex and difficult compared to less invasive approaches. Disadvantages are the risk for bile leakages, postoperative bleeding, liver failure, wound infection or incisional hernia. There are higher complication rates with 3–30% depending on the extent of resection. The recurrence rate is reported in up to 4% of cases [37, 38].

5.3 Laparoscopic approach

The laparoscopic approach for surgical treatment of liver CE has been considered as treatment option [39]; however, it is a challenge to reach cysts located in the posterior and superior segments of the liver. Furthermore, there are some exclusion criteria for a laparoscopic approach like intrabiliary rupture, central localization of the cyst, size of the cyst of more than 15 cm, multiple cysts or calcified walls. Further, it is almost impossible to avoid spilling cyst content during the evacuation process. Thus, recurrence of CE is described in 11% of cases [40, 41]. Another disadvantage of the spillage is the higher risk for allergic reactions.

5.4 Interdisciplinary treatment

Interdisciplinary treatment of these patients is recommended. For the diagnosis the cooperation with experienced radiologists is important. Surgery should

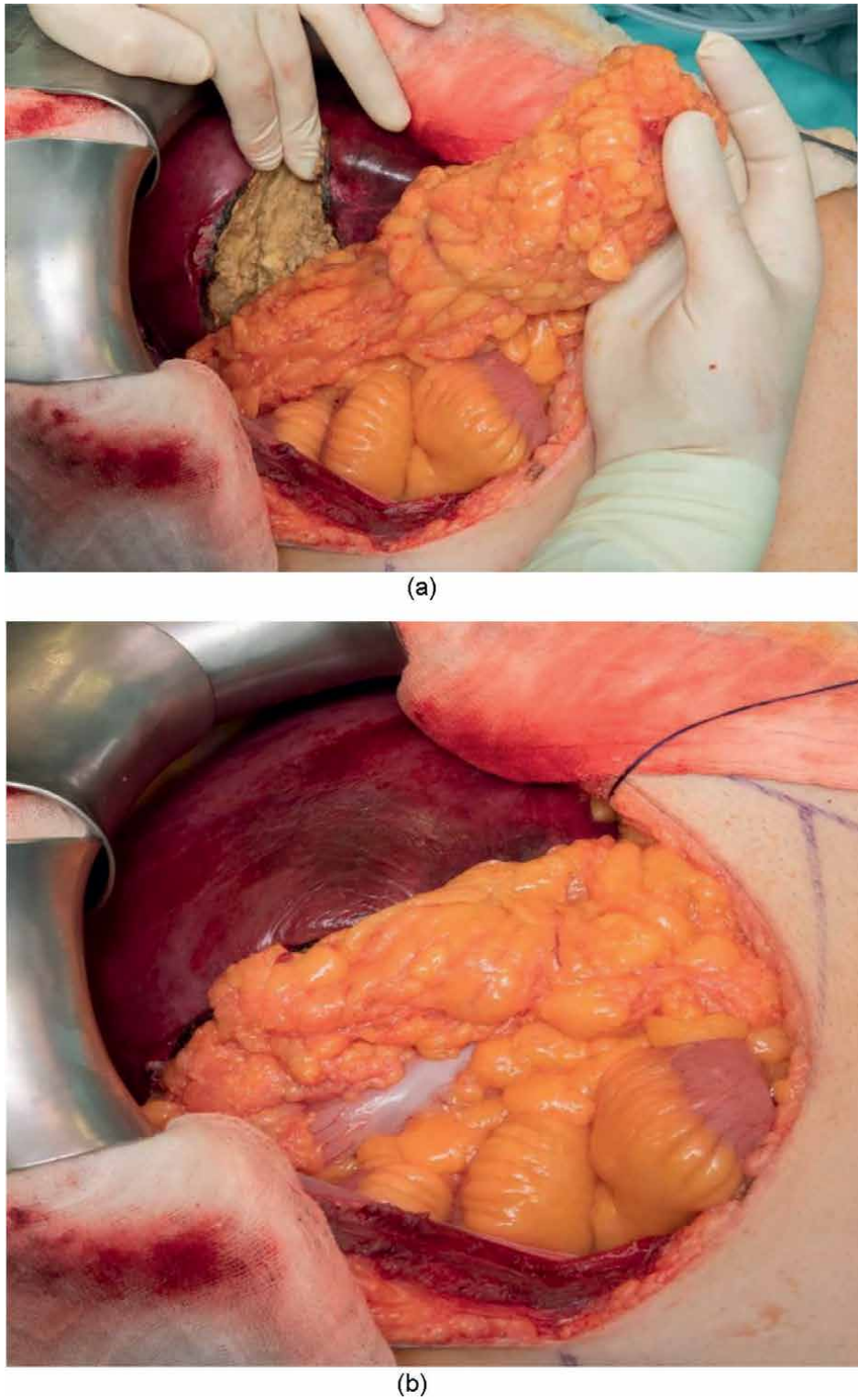

Figure 6.
a. Omentum for omentoplasty. b. Cyst filled with omentum.

be performed in a specialized centre for hepatobiliary surgery. Perioperative Albendazole is recommended to prevent recurrence. A dose of 10 mg/kg/day shall be given for 6 months after surgery. Since regular blood tests are indicated, there should be an interdisciplinary treatment of these patients. Side effects of Albendazole therapy are mild abdominal pain, nausea, vomiting, pruritis or headaches. Leucopenia, eosinophilia, icterus or mild elevation in transaminase levels can occur.

6. Discussion

The high variability of hepatic CE requires individual treatment depending on factors like cyst characteristics, but also on available resources and the preference of the treating physician. Due to a lack of randomized clinical trials, there is a low level of evidence especially in comparing different therapy modalities with each other. However, surgery has been considered the best option, even after implementation of medical treatment or percutaneous procedures.

7. Conclusion

Hydatid disease is a public health problem in some areas of the world. The liver is affected mostly with up to 75% of patients. However, CE can be cured with surgery combined with medical treatment with Albendazole. There is no recurrence of CE reported after novel parenchymal sparing endocystectomy with partial cystectomy which is associated with very low postoperative morbidity [34]. However, there is still a controversial discussed on the best surgical treatment for hepatic CE.

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Conflict of interest

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Chapter 7

New Energy Devices in the Treatment of Cystic Echinococcosis

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Abstract

Treatment of cystic echinococcosis of the liver still remains a debatable subject. The method of choice should aim for the total elimination of the parasite with minimum morbidity and mortality. Different approaches have been proposed. Medical treatment as a monotherapy has been abandoned due to the high chances of recurrence and is mostly used as an adjuvant to surgery or minimally invasive methods. Surgical methods are divided into conservative ones, which include cystectomy and partial pericystectomy, and radical ones, total pericystectomy and hepatectomy. Radical procedures are correlated with lower complication and recurrence rates and, therefore, should be attempted when indications are present. On the other hand, conservative surgery can be the first option in endemic areas, performed by non-specialized general surgeons. The development of laparoscopic techniques made their use a possible alternative approach in selected cases. The use of percutaneous treatments is also quite widespread due to their minimally invasive nature. New energy devices seem to play a significant role in the treatment of cystic echinococcosis, although more studies are needed to establish their efficacy. Observation without intervention is an option for inactive uncomplicated cysts.

Keywords: cystic echinococcosis surgical treatment, percutaneous treatment of cystic echinococcosis, radiofrequency ablation, high-intensity focused ultrasound

1. Introduction

When the question of how we are going to treat the echinococcus cyst exists, there is no specific answer. Once cystic echinococcosis is diagnosed it requires an immediate treatment, as the cysts usually grow and cause complications. The treatment of choice should aim for the total elimination of the parasite and prevention of recurrences, with minimum morbidity and mortality.

Treatment options of Cystic echinococcosis of the liver include: (1) surgical treatment (open or laparoscopic), (2) minimally invasive approaches, (3) endoscopic/interventional treatment, (4) medical treatment, or (5) observation without intervention ("watch-and-wait") [1].

The appropriate treatment is determined by the characteristics of the disease, regarding the cyst number, size and location, the patient's current health state and

the availability of medical staff. An algorithm for the possible treatment according to the stage of cysts is shown in **Table 1**. The stage of the cyst is defined by the US classification that WHO-IWGE suggests, that takes into account the size, location and presence/absence of complications and classifies the cysts into three relevant groups: active (CE1 and 2), transitional (CE3) and inactive (CE4 and 5) (**Table 2**). Percutaneous treatments (PT) and antiparasitic treatment with benzimidazoles (BMZ), such as Albendazole, represent alternatives to surgery [1, 2].

Type	Description	First Option Treatment	Alternative
CE1 Active	Simple cyst often full of hydatid sand. Visible cyst wall. Fertile.	Only ABZ(6 m) Surgical treatment +ABZ(1–6 m) Surgical treatment +ABZ(1–6 m)	PAIR+ABZ(1 m) PAIR+ABZ(1 m) MoCaT+ABZ (1 m)
CE2 Active	Multiple or multi-loculated cysts. May appear honeycomb like with daughter cysts. Fertile.	Only ABZ(6 m) Surgical treatment +ABZ(1–6 m) Surgical treatment +ABZ(1–6 m)	MoCaT+ABZ (1 m) MoCaT+ABZ (1 m) MoCaT+ABZ (1 m)
CE3 Transition	Degenerating cyst but still contain viable protoscolices. Often see floating membranes in fluid filled cysts.	Only ABZ(6 m) Surgical treatment +ABZ(1–6 m) Surgical treatment+ABZ (1–6 m)	MoCaT+ABZ (1 m) MoCaT+ABZ (1 m) MoCaT+ABZ (1 m)
CE4 Inactive	Degeneration is advanced. Cysts may be calcified. Not likely to be fertile. Heterogeneous appearance with few or no daughter cysts.	Watch and wait	Watch and wait
CE5 Inactive	Often calcified. Usually infertile.	Watch and wait	Watch and wait
Complicated cyst	Any diameter. Complicated, no matter what stage	Surgical Treatment(+/– interventional endoscopy in case of rupture into the biliary tract) + ABZ(6 m)	Surgical Treatment in case of rupture. Percutaneous drainage in case of infection+ ABZ(1 m)

Table 1.
Therapy protocol for cystic echinococcosis by WHO [2].

Type	Description
I	Pure fluid collection (the cyst is similar to simple liver cysts) (CE1)
II	Fluid collection with a detached membrane, "honeycomb"(CE2)
III	Fluid collection with multiple septa and/or daughter cysts (CE3)
IV	Hyperechoic with high internal echoes (CE4)
V	Cyst with reflecting, calcified, thick wall(CE5)

Table 2.
Classification of cystic echinococcosis by Gharbi et al. [3] and WHO [2].

2. Surgical treatment

Surgery is the first choice for large CE2-CE3b cysts with multiple daughter cysts, single superficial cysts, complicated or infected cysts and cysts communicating with the biliary tree. Some contraindications for surgery are the inactive asymptomatic cysts or the very small cysts, difficult to access cysts because of their location and the general condition of the patient that does not allow them to undergo surgery. The classic types of surgery procedures differ in the approach of pericyst, i.e. the capsule that surrounds the cyst. In simple cystectomy, the pericyst is not resected by the surgeons and is dealt with in second time. The procedures that include resection of the pericyst are the partial pericystectomy, total pericystectomy and hepatectomy. Cystectomy and partial pericystectomy have been introduced as conservative surgery options, whereas total pericystectomy and hepatectomy are considered radical operations [4].

Simple cystectomy is a conservative safe and fast procedure but has high rates of postoperative morbidity and recurrence. In this procedure, only the cyst's content is removed and the pericyst is retained. The remaining cavity is then treated with methods such as external drainage with a drain tube, bipolar drainage of the cavity and the main bile duct, padding, omentoplasty, drainage of the cavity by anastomosis with the stomach/jejunum or pericysto-biliar drainage. Omentoplasty seems to be the best possible surgical alternative for the radical treatment of hepatic cystic echinococcosis, due to reduced complications compared to external drainage. The method of external tube drainage is recommended for infected cysts. Biliary drainage procedure can also be added when the cysts are accompanied with intrabiliary rupture [5].

Partial pericystectomy, in which the cyst is opened, sterilized and its content is removed, with partial resection of the pericyst, is a procedure especially suited for endemic areas where the operations are performed by general surgeons and no special equipment is required. Subtotal pericystectomy is an approach similar to partial pericystectomy, with the difference that the surgeon leaves the pericystic areas closed to vessels and bile ducts untouched, to avoid complications such as biliary leakage and hemorrhage [6].

In total pericystectomy, where the whole pericyst is resected, two methods can be used; the closed total pericystectomy, in which the cyst is removed without opening, and the open total pericystectomy, where sterilization with protoscolicidal agents take place first, evacuation the contents of the cyst and then removal of the pericystic tissue. The open method is preferred when the cyst has a thin wall and there is a risk of rupture a major vascular structure with the closed cyst method. Consequently, in total pericystectomy, where the opening of the cyst is avoided, the recurrence of the disease is minimized [7].

Liver resections that have been proposed for the treatment of cystic echinococcosis are segmentectomy and left or right lobe hepatectomy. Remnant liver tissue's function is a thing to take under consideration, as it has been proven that in cases where a large hepatic parenchymal part needs to be removed or echinococcosis-related hepatic cirrhosis occurs as a complication, liver transplantation is then necessary [1]. Nevertheless, hepatectomy may be performed when conservative methods have failed, the cyst compresses the healthy liver tissue and impair a lobe or segment, and interrupt with the biliary tree or cystobiliary fistulas in draining zones are present [6].

In hepatectomy and total pericystectomy, the complete resection of the closed cysts with a fairly wide safety margin is achieved. However, these radical

interventions involve an increased risk of postoperative complications, such as rupture into the bile ducts and the creation of biliary fistulas, which are quite important given the benign nature of the disease. The question of whether is preferable to perform these approaches rather than conservative surgery stays controversial nowadays. A recent meta-analysis showed that overall postoperative complications are lower compared to conservative surgery and no statistically significant differences were detected in terms of mortality risk and the duration of hospital stay between the two methods [8].

Inactivation of the parasite must precede the opening of the cyst cavity regardless the type of surgery that is going to follow. At present, 20% hypertonic saline is recommended, which should be in contact with the germinal layer for at least 15 minutes. Alternative options are ethyl alcohol, hydrogen peroxide or Albendazole, but these agents are accompanied with a higher risk of complications. The isolation of the cyst from the rest of the peritoneal cavity must also be ensured. This can happen by wrapping the adjacent areas with dressings soaked in anthelmintic substances or by applying adherent cones to the cyst using the icing technique or suction. Benzimidazole (BMZ) agent is usually used after surgery to reduce the risk of anaphylaxis and secondary CE [4].

2.1 Surgical treatment of complicated cystic echinococcosis

The most common complication of hepatic cystic echinococcosis is rupture into the biliary tree and it appears in 10–25% of patients. The clinical symptoms of cystobiliary communications are obstructive jaundice, abdominal pain, fever, nausea and vomiting. If an intrabiliary rupture is found perioperatively, cholangiography and endoscopic removal of any residual debris in the common bile duct can be performed. Alternatively, if cystobiliary communications are suspected after the operation, common bile duct can be explored with a T-tube drainage or a following choledochoduodenostomy. Cystobiliary fistulas are defined whenever bile leakage is continued up to 10 days. Treatment essentials for fistulas are endoscopic intervention with sphincterotomy, stent insertion, or nasobiliary tube drainage.

Peritoneal perforation can occur in approximately 10–16% of patients after surgery or percutaneous treatment. It presents with similar symptoms as intrabiliary rupture, including allergic reactions and anaphylactic shock. A confirmed diagnosis with U/S or CT is necessary to build the treatment strategy, which can be radical or conservative surgery [1, 4].

2.2 Laparoscopic technique

Laparoscopic surgery, which is also a minimally invasive technique, can reach well results in the treatment of cystic echinococcosis. Especially, cysts located peripherally and anteriorly can be resected successfully with a laparoscopic operation in uncomplicated patients. However, posterior, deep or calcified cysts, and cysts located close to the inferior vena cava cannot be selected for this procedure. Specifically, the contraindications for laparoscopic surgery are patients CE5 without clinical symptoms, those who have liver function grade C in Child–Pugh classification with no potential aspect to downstage, intolerance of laparoscopic surgery based on patient's current health state, deep intraparenchymal or inaccessible cysts and relapsed CE, multiple cysts with diffuse distribution in liver, extrahepatic metastasis, dense adhesions

surrounding the CE cysts difficult to separate and cysts with thickness of external capsule wall less than 3 mm [9].

The benefits of laparoscopic surgery include reduced post-operative pain, faster exit of the hospital and great cosmetic results. During the procedure, visualization of the surgical field on the monitor allows detailed exploration of the cystic cavity in a larger image and makes possible the detection and removal of germinal layer's remnants [10].

Both conservative and radical surgery approaches can be performed with laparoscopic technique. Considering the fact that laparoscopic partial pericystectomy has higher rates of recurrence and postoperative complications, this approach is advised when a history of multiple surgeries is present or the space between external layer and liver parenchyma is limited. Total pericystectomy seems to be a great option in selected patients, as it can succeed the total elimination of the disease leaving a small wound. Therefore, total pericystectomy can be considered as the treatment of choice when laparoscopic surgery is about to be performed [11].

With laparoscopic surgery, short-term recurrence rates are 0–9%, while the recurrence of the disease after an open surgery is 0–30%. Postoperative morbidity rates in laparoscopic procedures are 8–25% and mortality 0%, whereas morbidity and mortality with open methods are 12–63% and 0–3% each. On the other hand, the risk of complications, especially leakage to the biliary tree, is more common to occur in laparoscopic surgeries due to peritoneal spillage that is less predictable with this technique [6].

3. Minimally invasive/interventional treatment

Percutaneous treatments of hepatic CE can aim at the destruction of the germinal layer (PAIR) or the evacuation of the entire endocyst (Modified Catheterization Techniques).

PAIR (Puncture, Aspiration, Injection, Re-aspiration) is a relatively recent and minimally invasive therapeutic option that consists of four steps: percutaneous puncture of the cyst using U/S guidance, aspiration of the cyst fluid, injection of a protoscolicidal agent (e.g., 95% ethanol or 20% NaCl) and re-aspiration of the fluid. This method has reduced risk compared with surgery, improved efficacy of chemotherapy given before and after the procedure (probably because of an increased penetration of antihelminthic drugs into cysts re-filling with hydatid fluid), reduced hospitalization time and less cost.

Indications for PAIR include non-echoic lesion ≥5 cm in diameter (CE1m and l), cysts with daughter cysts (CE2), and/or with detachment of membranes (CE3), multiple or infected cysts and patients who refuse surgery. Contraindications for PAIR are non-cooperative patients and inaccessible location of the cyst, inactive or calcified lesion and cysts communicating with the biliary tree. The most serious risks of PAIR involve allergic reactions, secondary echinococcosis and chemical cholangitis. The possibility of secondary echinococcosis can be minimized by concurrent treatment with benzimidazole [12].

It is good to be noticed that PAIR procedure is showing a higher cure rate, lower complication rate, and lower mortality compared with laparoscopic surgery. Superiority of the laparoscopic approach is visible only in terms of recurrence rates [13].

If PAIR cannot be used, as in cases of rupture to the biliary tree or the presence of a giant cyst, then the modified catheterization technique (MoCat) is suggested. In this procedure, a catheter is inserted into the cystic cavity and is followed by continuous injections and aspirations of isotonic saline solution, until the total removal of endocyst and daughter cysts is achieved and the daily output falls down to 10–15 ml/24 hours [1].

A modified PAIR method, that is suitable for patients with multivesicular cysts containing non-drainable content, is percutaneous evacuation (PEVAC). This technique is characterized by U/S guided cyst puncture, injection and re-aspiration of isotonic saline due to a large bore catheter, use of scolecidals if no cystobiliary communication is present or external drainage of cystobiliary fistulas combined with endoprosthesis or sphincterotomy and catheter removal when and the daily output is less than 10 ml. In case of a univesicular cyst with a cystobiliary fistula, PEVAC is more safe compared to PAIR because a possible damage to the biliary tree or blood vessels by scolecidals can be avoided [14].

4. New energy devices

4.1 Radiofrequency ablation

Radiofrequency ablation (RFA) was first introduced to the field of hepatobiliary as an alternative, more innovative technique that can be used as percutaneous treatment of solid liver tumors. In this method, a needle conducting high-frequency electrical energy is inserted into the cyst's cavity and cause heat-mediated necrosis of the surrounding tissue. The heat inside the cyst leads to denaturation of the proteins and can succeed the distraction of its germinal layer [15].

There have been described series of attempts to use RFA as a scolidial agent in the ablation setting in percutaneous treatment approaches for cystic echinococcosis or intraoperatively as a surgery tool. Thermal ablation of the germinal layer was first introduced by Brunetti et al. [16]; the scientists reported that U/S guided RFA in a percutaneous ablation setting for the treatment of complex cysts is safer and simpler than large-bore catheters and the need to use some additional methods did not came up. Later on, more surgical teams managed to achieve good short-term results including RFA to their percutaneous procedures [17, 18]. However, at that time, the lack of sufficient data on the subsequent course of the patients does not allow safe conclusions regarding the effectiveness of the method in preventing recurrences of the cystic echinococcosis. Intraoperative use of U/S-guided RFA appears to be a safe and very promising approach that can be performed in liver resections. This technique is related with minimal blood loss and allows maximum liver parenchyma preservation. U/S guided RF pericystectomy is indicated especially in cases of cysts located away from the liver hilum [19].

Great advantages are associated with this method, such as the fact that the use of scolidial agents with injections and aspirations, large catheters or other evacuations steps is not necessary. However, this technique comes with limitations, due to the high costs of the equipment that is required and the need for high skilled surgeons. Also, RFA cannot be used in cases of superficial or peritoneal cysts and cysts attached to hollow and vascular structures [15]. While the recurrence rates seems to be low, prospective studies are initial to show if RFA has a critical superiority in cystic echinococcosis treatment compared to other approaches [20].

4.2 High-intensity focused ultrasound

High-intensity focused ultrasound (HIFU) is a non-invasive, image guided method that can be provably used in urology cases and certain tumors [21]. This procedure is characterized by the application of high-energy waves to a specific area causing cell death, cavitation and necrosis of a small part of tissue. The damage to protoscolices, that requires the presence of high temperatures, is achieved due to conversion of acoustic beams into heat and cavitation effects that are gained with gaseous micro-bubbles formation. Therefore, HIFU is effective in both inhibition of the growth of protoscolices and their development to germinal layer [22].

Effectiveness of HIFU has been proven to be enhanced with use of a superabsorbent polymer and ultrasound contrast agent, especially when they are used in combination [23].

The advantages of HIFU lie in its non-invasiveness type, which means that possible complications of invasive methods such as infections, allergic reactions and rupture to surrounding tissues can be avoided. Some significant constraints are the expense of the equipment, the need for general anesthesia and the weakness of its use on all cyst stages. Nevertheless, there is a need of further evaluation of HIFU for the treatment of cystic echinococcosis [15].

5. Medical treatment

Chemotherapy with antiparasitic drugs for the treatment of echinococcal cyst of the liver was initially used in patients who had contraindications for surgical treatment. Through the bibliographic review of this method's results the last decades and the introduction of new surgical techniques the exclusive use of chemotherapy has been limited. Given the fact that is not possible to ensure the complete disappearance of daughter cysts through medication and, therefore, the cyst with regenerate, this approach has a low chance of cure and high rates of recurrence (3–30%) [4].

Nowadays, medical treatment is primary used as an adjuvant therapy to surgery or minimally invasive techniques. Anthelminthic drugs that can be used are the benzimidazoles (BMZ) albendazole and mebendazole, and praziquantel. is used to prevent recurrence and secondary hydatidosis. Albendazole (ABZ) is the drug of choice for the treatment of hepatic CE at the average dose of 10–15 mg/kg/day. Praziquantel is used with ABZ for combined treatment that reaches more efficacy than ABZ alone [24]. Mebendazole can be used alternatively when albendazole is not tolerated by the patient, in the dose of 40–50 mg/kg per day, higher than ABZ due to its poor absorption but with a comparable efficiency. The duration of medical treatment with these agents is indicated to be 4–30 days prior to the surgical operation and continued for at least 1 month with albendazole or 3 months with mebendazole [25]. Pre- and postoperative use of albendazole decreases the viability of cysts at the time of surgery and reduces the rates of recurrence and secondary hydatosis [26].

Medical treatment with a BMZ can be used alone in patients who have disseminated disease, in those who have comorbid disease, and who have small (<5 cm) CE1 and CE3 cysts in the liver and lungs. The recommended duration of therapy is 6 months with ABZ, while MBZ treatment requires a longer period of time [25].

Most common side effects of BMZ are nausea, hepatotoxicity, neutropenia and occasionally alopecia. Therefore, patients should be regularly checked with liver

function tests and leukocyte counts. Medical treatment with BMZ must not be encouraged in cases of pregnancy, chronic hepatic diseases and bone marrow depression [12].

6. Watch-and-wait

Uncomplicated cysts do not require any treatment. CE4 and CE5 cysts should not be treated, until their parasitic nature has been proven. In these cases, long-term follow-up of patients with U/S imaging maybe is enough until a change in the behavior of the cyst is observed. A 5-year follow-up in cysts that inactivated naturally is recommended, while cysts that became inactive due to interventions require closer observation due to higher recurrence rates (50% in 18 months) and reconsideration of the best approach after a 5-year follow-up [27].

7. Future directions

New energy devices such as RFA and HIFU have significantly enhanced surgical outcomes in certain patients. The great results of the reported evidence prove the necessity of turning attention to these emerging technologies and the need to implement them in treatment strategies and real-life clinical practice. More studies are expected to validate the mentioned results and reveal their superiority to classic approaches.

8. Conclusion

Cystic echinococcosis of the liver is a condition that can easily become complicated and, therefore, careful treatment is necessary. Among the various treatment options, surgical methods seem to have prevailed over the years, due to the definitive cure they can provide. However, the surgical approach is not free of complications and requires an experienced coordinated medical staff. The evolution of percutaneous methods has made their use a good alternative option, but also includes several risks. There is strong evidence that new energy devices can clear the field of treatment choices. Radiofrequency ablation and high-intensity focused ultrasound are both very promising techniques and the results of more studies are expected in order to demonstrate their efficacy in the treatment of cystic echinococcosis.

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Chapter 8

Perspective Chapter: Primary Cystic Echinococcosis of the Pancreas

Azize Saroglu and Alexander Julianov

Abstract

Primary cystic echinococcosis of the pancreas is rare, even in endemic regions. The clinical presentation depends on the affected part of the pancreas and the presence of local complications, but there are no specific symptoms, which can be a clue to diagnosis. Imaging studies usually reveal avascular lesions in the pancreas that are most frequently misdiagnosed as pseudocysts or neoplastic cystic tumors. The treatment options vary from evacuation and drainage to formal resection of the pancreas, with no evidence of the best treatment strategy. This chapter provides a comprehensive review of the current knowledge of the clinical presentation, diagnosis, and treatment of primary cystic echinococcosis of the pancreas. Acute thrombosis of the splenic artery which leads to massive splenic infarction and abscess, a previously unreported initial manifestation of cystic echinococcosis of the pancreas is also presented, as well as the first use of intraoperative pancreaticoscopy to clear the mean pancreatic duct from membranes of the parasite.

Keywords: cystic echinococcosis, pancreas, diagnosis, treatment, pancreaticoscopy

1. Introduction

Cystic echinococcosis is a zoonotic disease caused by the larval stage of the *Echinococcus granulosus* parasite, representing an endemic problem in many regions of the world such as the Mediterranean countries, Australia, New Zealand, South America, South East and Far East Asia, and Middle Eastern countries [1]. The parasite was named in 1801 by Rudolphi who wrote: "*Echinococcus*, that's what I call the granular bladderworms..." (**Figure 1**) [2].

The prevalence of isolated pancreatic cystic echinococcosis (PCE) is very low, ranging from 0.14 to 2% of total systemic echinococcosis [3–5]. Pancreatic cystic echinococcosis (PCE) may develop as a primary isolated disease involving the pancreas only, or as a secondary disease with multiple organ involvement (**Figure 2**), and can masquerade as more common lesions of the pancreas such as pseudocysts or cystic pancreatic neoplasms.

The lack of specific clinical manifestations of PCE is clearly demonstrated by the majority of cases published in the literature, thus explaining why preoperative diagnosis is challenging [5–8]. In symptomatic cases, clinical findings may be similar to

Echinococcus, ſo nenne ich die körnigen Blaſenwürmer. Goeze *) unterſchied die geſelligen Blaſenwürmer in ſolche, wo viele Würmer auf einer gemeinſchaftlichen Blaſe ſitzen, ohne eine weitere Außenblaſe oder Decke zu haben, und in ſolche, wo viele Würmer in einer gemeinſchaftlichen Blaſe befindlich ſind, die noch eine kallöſe Außenblaſe haben, jene nannte er Taenia vesicularis; cerebrina; multiceps, dieſe aber Taenia visceralis socialis granulosa. Zeder **) macht hieraus

Figure 1.
The original text of Rudolphi introduces the name "Echinococcus" .

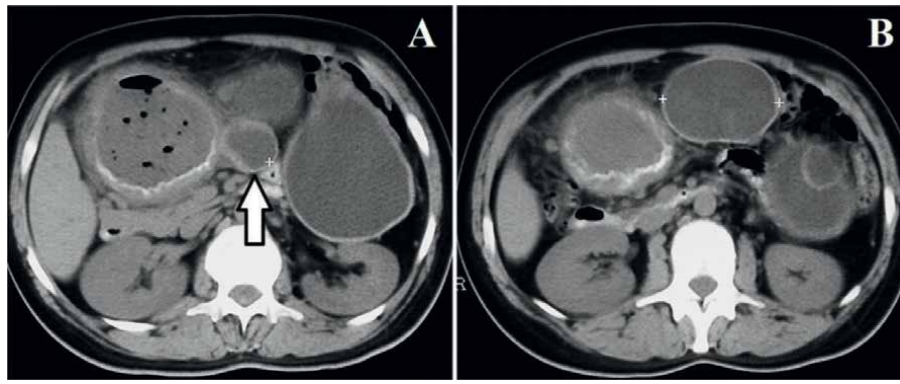

Figure 2.
(A, B) axial computed tomography scans of a patient with abdominal cystic echinococcosis with multiple locations including body of the pancreas (arrow, a).

those of other pancreatic diseases. However, the imaging features of PCE are almost identical to those of other cystic diseases of the pancreas, and given the rarity of the problem, isolated primary pancreatic cystic echinococcosis is often misdiagnosed even in endemic areas of the world.

2. Clinical presentation

The clinical presentation of PCE is a result of: 1) the pressure generated by the cyst on the pancreatic tissue and adjacent structures, which depends on the size and anatomic location of the cyst; 2) the local inflammatory reaction to the parasite involving neighboring anatomical structures, and; 3) the presence of local/systemic complications.

According to data from the literature, 50–58% of pancreatic echinococcosis is found in the pancreatic head, 24–34% in the pancreatic body, and 16–19% in the

pancreatic tail [8–10]. It is considered that the embryos of hydatid cysts end up in the pancreas mainly by hematogenous dissemination [11]. The rich vascular network on the head of the pancreas explains the more frequent involvement of this part of the gland by the parasite. Other possible mechanisms for the involvement of the pancreas include local spread by passage of cystic elements via the bile duct into the pancreatic duct, direct passage of cystic components through the intestinal mucosa into the peripancreatic lymphatic plexus, and retroperitoneal spread [11–13].

Pancreatic echinococcosis is considered to be asymptomatic for a long period, due to its slow growth rate of 0.3–2.0 cm per year [14]. All data for the clinical symptoms of cystic echinococcosis of the pancreas come from a small published series or case reports in the literature. An abdominal mass, epigastric pain, weight loss, discomfort, and vomiting are the main nonspecific clinical symptoms [5, 9, 10, 14–22]. PCE located in the pancreatic head most commonly causes cholangitis, obstructive jaundice, or acute pancreatitis [3, 12, 13, 16, 21–28]. Cysts of the parasite located in the body or tail of the pancreas can be asymptomatic and usually present as an abdominal lump when they enlarge [3, 19, 22, 29–31]. Infrequently, PCE located in the pancreatic tail can result in splenomegaly and segmental portal hypertension owing to splenic vein compression/thrombosis [32]. Other reported uncommon complications include mesenteric/portal vein thrombosis, upper gastrointestinal bleeding with splenic artery pseudoaneurysm, intracystic bleeding, and rupture into the biliary system or peritoneal cavity, pancreatic fistula, recurrent pancreatitis, and pancreatic abscess [6, 7, 32, 33].

As primary PCE can mimic any other pancreatic disease, it is still frequently a clinical surprise rather than a preoperatively established diagnosis. We observed a previously unreported initial manifestation of PCE in a patient who presents with splenic infarction and abscess secondary to acute splenic artery thrombosis due to isolated cystic echinococcosis located in the body of the pancreas (**Figure 3**). The patient was erroneously diagnosed preoperatively as having a complicated malignant pancreatic tumor with splenic artery involvement, and a correct diagnosis was made during laparotomy.

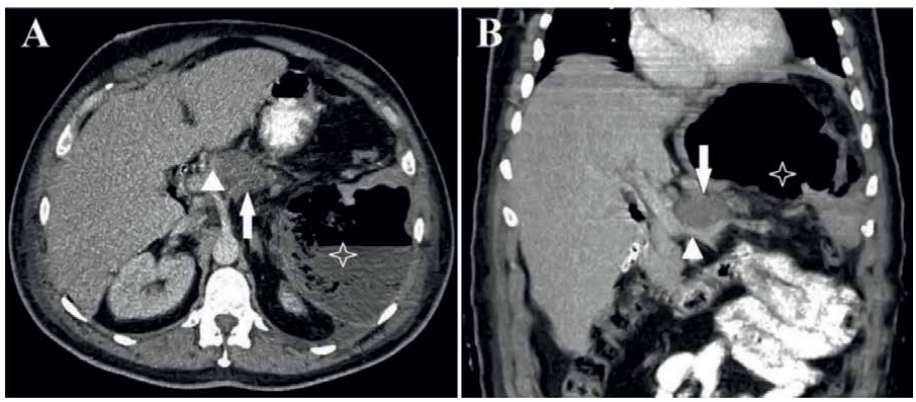

Figure 3.
Computed tomography in a patient with primary PCE. (A) Axial image demonstrating pancreatic cystic lesion (arrow), thrombosis of splenic artery at its origin (arrowhead), and splenic abscess (asterisk). (B) Coronal image demonstrating patent splenic vein (arrowhead) along with the pancreatic cyst (arrow) and splenic abscess (asterisk).

3. Diagnosis

The first and probably most important step in the diagnosis of PCE is clinical suspicion, particularly in endemic regions. The diagnosis is much easier when associated with other localization(s) (**Figure 4**).

Characteristic imaging findings of echinococcosis are often missing in isolated PCE, with considerable imaging overlap between other cystic lesions of the pancreas and peripancreatic regions (**Figure 5**), such as pseudocysts, choledochal cysts, serous or mucinous cystadenomas, and cystadenocarcinomas, which complicates the diagnostic process. The higher prevalence of mucinous cystadenomas of the pancreas and, on the other hand, the rare occurrence of pancreatic echinococcosis leads to the fact that it is rarely taken into account in the differential diagnosis [34, 35], and pancreatic echinococcosis is, as a result, often misdiagnosed [20, 36–38]. According to data from the literature, the vast majority of PCE patients are not diagnosed preoperatively [7, 37].

In daily clinical practice, blood tests for detecting specific serum antibodies and circulating echinococcal antigens usually include indirect hemagglutination assay, immunoelectrophoresis, enzyme-linked immunosorbent assay, complement fixation test, and immunofluorescence assay [3, 7, 22]. According to a systematic review by Dziri et al. [3], hydatid serology has a low sensitivity (62%). In another literature review by Akbulut et al. [7], the sensitivity of hydatid serology was even lower (54%).

The most commonly performed imaging modalities for the diagnosis of pancreatic cysts are transabdominal ultrasound (US), contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI). Cases that require further workup are examined using invasive diagnostic tools such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS); the latter has emerged rapidly as an effective technique to gain diagnostic information and access to retroperitoneal organs such as the pancreas.

Transabdominal ultrasound is a widespread, cost-effective, and sensitive method for detecting internal cyst structures, including membranes, septa, hydatid sand, and daughter cysts. It can show a well-defined anechoic lesion with a hyperechoic thick double-lined wall and internal echogenic material, although the sensitivity is decreased in cases of PCE due to the retroperitoneal location and superponing bowel gas [37, 39].

Localization and size of the pancreatic cyst can be detected accurately on CT, that moreover, may provide information about the relationship between the cyst and bile

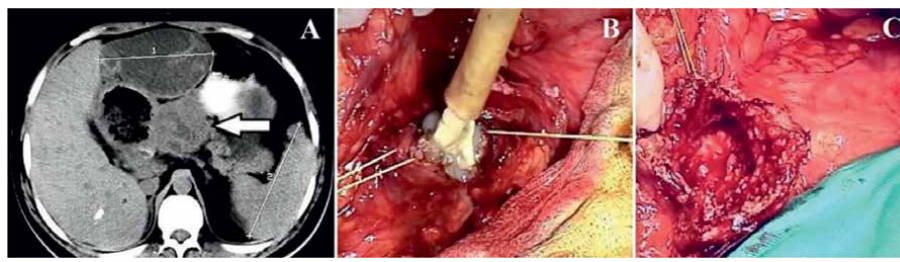

Figure 4.
Abdominal cystic echinococcosis. (A) Axial computed tomography demonstrating cystic lesion in the head of the pancreas (arrow) and ventrally located cyst in the left liver with typical appearance of cystic echinococcosis. (B, C) intraoperative photograph shows removal of the parasite and remaining defect in pancreatic head.

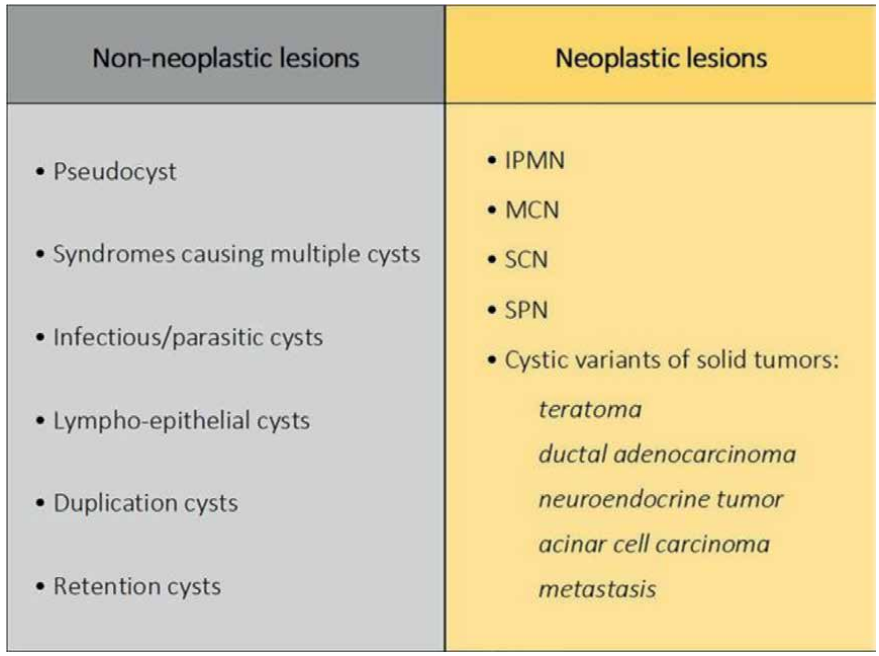

Figure 5.
Differential diagnosis of pancreatic cystic lesions.

ducts and wall calcification, and CT angiography can show significant displacement of vascular compression in the arterial and venous phases [7, 8, 19–22, 32–34, 37].

In the PCE case series of Li et al. [22], MRI provided a better depiction of the fluid content of cystic lesions and communication with the pancreatic duct due to its higher soft-tissue contrast and capability of multiplanar imaging. Pancreatic cystic echinococcosis showed a hypointense signal on T1-weighted MRI images, a hyperintense signal on T2-weighted images, and a hyperintense signal.

EUS is another diagnostic tool that is commonly used in the evaluation of cystic pancreatic lesions. Nowadays some authors recommended a fine-needle aspiration biopsy to differentiate a hydatid cyst from other common cystic lesions [40, 41].

According to data from the literature, accurate diagnosis cannot be established based on radiological findings alone, and this is especially true for pancreatic cystic lesions demonstrating particular imaging features such as multilocular cysts, presence of internal septations, calcifications, and wall enhancement as they are encountered in both benign and malignant pancreatic cystic lesions [22, 36]. Blood tests may be helpful for diagnosis in some cases, but according to the published experience with PCE, the sensitivity of the routinely used tests is still low [3, 7].

4. Surgical treatment

Surgery remains the main treatment option for patients with PCE as most cases are correctly diagnosed intraoperatively. However, due to a lack of evidence, it is not clear which is the best treatment strategy for patients with isolated PCE. However, Dziri et al. in their review reported that surgery is the main treatment of PCE and the open approach is performed in 95% of the cases [3]. Furthermore, depending on the cyst's

location, several procedures have been suggested, including cyst fenestration, internal derivation, central or distal pancreatectomy with or without splenectomy [3, 6, 7], and presently, available treatment options include formal resection, internal capsule stripping and external capsule removal (subadventitial total exocystectomy) [42].

Regarding the available surgical options to treat PCE, it is clear that formal pancreatic resection is not necessary to treat such benign diseases and should be avoided when possible to spare the patient from complications associated with resection of the pancreas. Superficially located cysts that do not communicate with the pancreatic ductal system can be excised, opened, or drained without substantial complications. On the other hand, the main question to the surgeon after parasite removal (**Figure 6**) is whether the remaining cavity in the pancreas communicates with the ductal system. In cases with ductal communication, the surgical option is to perform a drainage procedure on a Roux-en-Y jejunal limb or to proceed with formal resection. However, the latter is justified only in cases where resection of the body/tail may be sufficient, and formal pancreaticoduodenectomy does not seem justified to treat PCE.

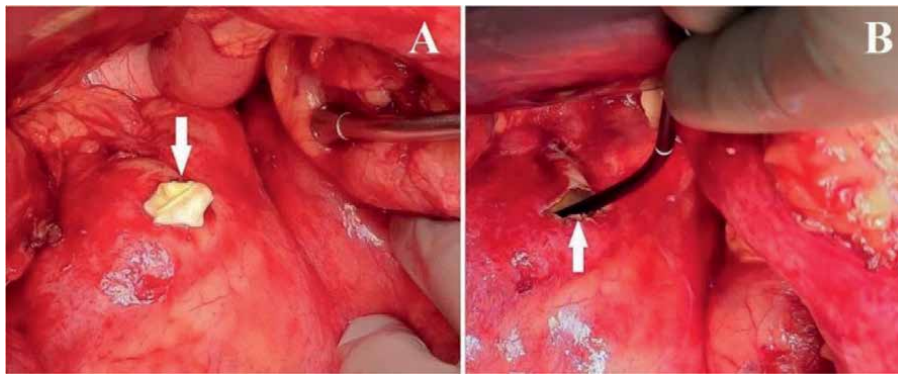

Figure 6.
*Intraoperative photographs of a patient corresponding to **Figure 3**. (A) Protrusion of parasitic membrane (arrow) through the cystotomy. (B) Pancreaticoscope (arrow) is inserted in the main pancreatic duct toward the head of the pancreas.*

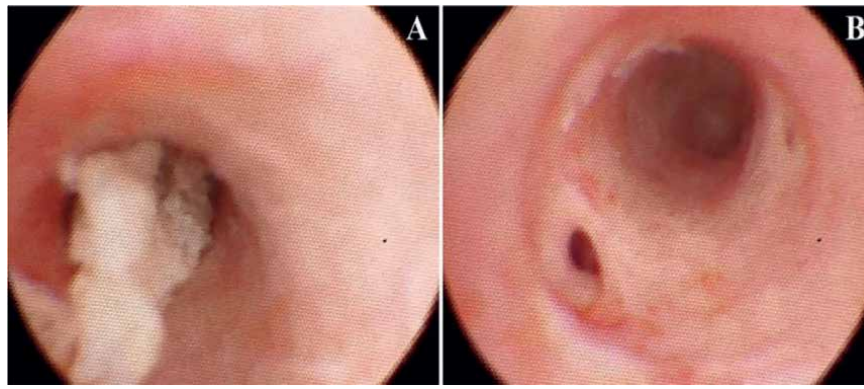

Figure 7.
*Intraoperative pancreaticoscopy in a patient corresponding to **Figure 5**. (A) Hydatid membrane impacted the main pancreatic duct. (B) the pancreatic duct is cleared from the parts of the parasite.*

Intraoperative management of the main pancreatic duct has not yet been resolved. We consider this a topic of concern as parts of the parasite may migrate to the main pancreatic duct in the case of ductal communication of the PCE, causing ductal obstruction, further symptoms, and even disease recurrence. To resolve these problems, the use of intraoperative pancreaticoscopy seems to be a good solution, similar to its use in surgery for chronic pancreatitis [43].

Direct endoscopic inspection of the main pancreatic duct through communication with the residual cavity is simple, securely detects intraductal pathology, and can be easily used to clear the duct (**Figure 7**). Any available flexible endoscope that fits the pancreatic duct can be used for this purpose. Other options to evaluate the involvement of the pancreatic ductal system include intraoperative ultrasonography of the pancreas and intraoperative pancreatography. However, both of them cannot manage the duct in cases of involvement, and the diagnostic accuracy of pancreaticoscopy is unmatched.

5. Conclusion

Primary cystic echinococcosis of the pancreas is rare even in endemic areas. Despite radiological imaging, including transabdominal ultrasound, CT, MRI, EUS, ERCP, laboratory tests, and hydatid serology, the preoperative diagnosis of pancreatic cystic echinococcosis remains difficult, and the correct diagnosis is most often intraoperative.

Clinicians may still encounter undescribed clinical presentations of pancreatic echinococcosis, as presented in this chapter. PCE should be considered in the differential diagnosis of pancreatic cystic lesions, particularly in endemic geographic regions. Surgical treatment combined with albendazole can reduce the recurrence rate and morbidity of pancreatic cystic echinococcosis. As the intraoperative management of the main pancreatic duct in the case of communication with the parasite is not resolved, the use of intraoperative pancreaticoscopy may play an important role as a valuable adjunct to the operative strategy and contribute to more precise surgery.

Primary cystic echinococcosis of the pancreas remains a diagnostic challenge, and it seems that only high clinical suspicion and awareness of the disease can improve the preoperative diagnosis rate.

Conflict of interest

The authors declare no conflict of interest.

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Echinococcosis is a neglected parasitic disease caused by *Echinococcus* spp. of the family Taeniidae. The prevalence of the disease is increasing worldwide due to industrialization and climate change. This book provides a comprehensive overview of echinococcosis, including information on epidemiology, geographic distribution, diagnosis, management, and prevention.

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