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Neglected Tropical Diseases (A Sanchez, Section Editor)

Human Cystic and Alveolar Echinococcosis

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Opinion statement

Echinococcus granulosus causes human cystic echinococcosis, whereas *Echinococcus multilocularis* produces human alveolar echinococcosis. The latter constitutes a slowly progressive but often fatal disease. Cystic echinococcosis is widely distributed and represents a serious problem in sheep- and cattle-raising areas. Eggs released from gravid proglottids in faeces from definitive hosts may contaminate water, fruits, or weeds, and be eaten by humans or other intermediate hosts where a hydatid cyst develops. Histopathological and microscopic examinations, imaging techniques and serologic tests as well as molecular studies are used in diagnosis. Whenever possible, hydatid cysts should be removed surgically, taking precaution to avoid rupture that could lead to seeding, metastatic proliferation and anaphylactic shock. In cases when surgery is not possible, chemotherapy with albendazole or, alternatively, mebendazole combined with praziquantel is used. The close contact with infected dogs is a risk factor for humans. Prevention includes eliminating infection in definitive hosts—especially domestic dogs—by periodic deworming and preventing them from consuming raw entrails from butchered animals. Introduction of vaccines in sheep has been successful as it remarkably diminishes hydatid cysts, with regard to number and size. However, in spite of the different measures taken, the continuous report of cases in endemic countries shows that those measures are insufficient. Widespread vaccine administration to domestic animals acting as intermediary hosts shows promise in achieving a long-term disease prevention and control. In conclusion, current interventions need to be sustained and combined with effective vaccines.

Introduction

The larval tapeworm of the genus *Echinococcus* causes the disease known as echinococcosis or hydatidosis. *Echinococcus granulosus*, the species responsible for most infections, is universal in distribution. High incidences

of echinococcosis are seen in East Africa, the Mediterranean littoral, South America, the Middle East, Australia, India, and the countries of the former Soviet Union [1]. The geographic distribution of the second most common species, *E. multilocularis*, includes mainly the northern hemisphere especially Canada, central Europe, Turkey, Siberia, northern Japan, China, and Alaska [2, 3]. In some areas of China, the prevalence in humans is very high (4–15%) [4–6]. In central Europe, the annual incidence of human infections is 0.02–1.4/100.000 inhabitants [7]. The infection caused by *E. multilocularis* is called alveolar hydatid disease. The third species, *E. vogeli*, has been known to cause human infections in Latin America since 1979 [8]. The fourth species, *E. oligarthrus*, was first found only in Central and South America [9]. More cases have now been described from Surinam, Brazil, and India [10–12].

Recently, two other species have been identified, namely *E. shiquicus* and *E. felidis*. These have been isolated from small mammals in the Tibetan plateau and from African lions, respectively. However, their pathogenicity remains unknown [13–15].

Most *Echinococcus* spp. previously described genotypes have been classified as new species by mitochondrial phylogenetic analysis [16, 17].

E. granulosus s.*L. complex* groups: *E. granulosus* s.s. (G1/G2/G3), *E. equinus* (G4), *E. ortleppi* (G5), *E. canadensis* (G6/G7/G8/G10), and *E. felidis* ("lion strain) [18••].

Humans contract the infection by the ingestion of infectious *Echinococcus* spp. eggs from the faeces of the definitive host (dogs) in cystic echinococcosis (CE). After reaching the duodenum, the hexacanth embryos contained inside the eggs hatch and penetrate the intestinal wall and reach the portal circulation. The oncospheres can gain access to practically any organ of the intermediate host and develop into a hydatid cysts. Thousands of protoscolices develop inside the cyst. When a definitive host ingests an organ with a hydatid cyst, the protoscolices evaginate and grow into adult worms in the host's intestine [1].

In alveolar echinococcosis (AE), humans contract the infection by the ingestion of eggs of the parasite from the faeces of the definitive host (fox, wolf,). Wild berries, mushrooms and wild weeds contaminated with eggs are possible sources of infection [3].

Humans are the intermediate host carrying the larval tapeworm in infections by both species.

Diagnosis is based on an epidemiological background, clinical examinations, abdominal ecographic and radiographic studies (computed tomography, magnetic resonance imaging), histologic examination, direct examination of hydatid fluid, and serologic tests and polymerase chain reaction (PCR).

The treatment of choice for operable cases of echinococcosis is surgery. Medical treatment should be restrained for patients in whom cyst rupture or spillage has occurred or for those cases not susceptible to surgical treatment [1].

Anthelmintic treatment of dogs is a traditional method of hydatid control, but a prolonged period of treatment is required to achieve a positive outcome.

This review will focus mainly on cystic and alveolar echinococcosis, its diagnosis, treatment and available vaccines, and control methods.

Cystic echinococcosis (CE)

Adult worms of *E. granulosus* measure 3 to 6 mm in length and have a scolex, neck, and strobila with three or four segments. They live in the small intestine of a definitive host. The scolex has four suckers and a rostellum with two rows of 28 to 50 hooklets. The total number and disposition of the hooklets aid in the differentiation of the various strains of *E. granulosus* [19, 20].

The larval form of *E. granulosus* is distinguished by a unilocular cyst, with numerous brood capsules and daughter cysts suspended in the hydatid fluid [9, 21]. The cyst wall is made up of three layers. The outer layer is a rigid, fibrous capsule produced by the host. The middle layer is a laminated, hyaline membrane from the parasite. The inner one is a germinal layer that originates the brood capsules. Inside each brood capsule are 5 to 20 protoscolices. Under certain conditions, daughter cysts are formed by producing a protective layer in

addition to the germinal layer. Daughter cysts can give rise to brood capsules and protoscolices. The ruptured brood capsules, detached protoscolices, and loose hooklets may form a granular deposit at the bottom of the cyst, called the hydatid sand. The most reliable diagnostic structure within the cysts is the protoscolex, which can be identified by the hooklets and suckers on the scolex [1]. In a degenerated cyst, the highly resistant hooklets are the only clue to a reliable diagnosis [22].

The development of clinical signs and symptoms in the infected person depends on the size of the cyst and the organs involved. A hepatic lesion may be asymptomatic for as long as 75 years [23]. As a rule, hydatid cysts in the liver grow about 1–5 cm per year [24–29]. The hepatic form accounts for 60 to 70% of all cases of echinococcosis [1]. In uncomplicated cases, the major clinical manifestations are caused by compression of the neighbouring tissue. These include obstructive jaundice, cholangitis, reactive hepatitis, cirrhosis of the liver, and portal hypertension [21, 30, 31]. A common complication is the rupture of a cyst. When a cyst ruptures into the bile duct or gallbladder, clinical symptoms may mimic those of choledocholitiasis, cholangitis, or cholecystitis. The most dangerous complication is the sudden rupture of a cyst into a blood vessel, which may lead to anaphylactic shock or sudden death [32].

Pulmonary echinococcosis is seen in 25 to 30% of patients with hydatid disease [1]. It can be a primary infection or secondary to hepatic echinococcosis [33–35]. The major clinical symptoms are fever, cough, dyspnea, chest pain, and hemoptysis.

The spleen is the third most commonly involved organ, representing 5.8% of abdominal hydatid disease [36–38]. Clinical symptoms are caused by splenomegaly, secondary infections, or rupture of the cyst.

The frequency of renal echinococcosis is 4% and is close to that of splenic disease [21, 39–41, 42•]. Patients may have a palpable abdominal mass, abdominal pain, hematuria, or albuminuria.

Cerebral echinococcosis is seen in 2 to 3% of patients with cystic hydatidosis. The main neurologic sequelae in these patients are partial and general seizures and temporary paresis [1, 43, 44].

Bone involvement occurs in 0.5 to 2% of cases of cystic hydatidosis. Symptoms include low back pain, sciatica, loss of sphincter tone, and paraparesis [39, 45].

Cardiac hydatidosis is rare but serious [46]. The cyst is most often situated in the myocardium, especially in the left ventricular wall [47, 48]. Clinical symptoms are mainly associated with the obstruction of the atrioventricular valves and the outflow tract of both ventricles and myocardial ischemia.

Ocular echinococcosis accounts for 1% of all published cases of hydatidosis. Almost all reported cases of ocular hydatid disease show only orbital involvement, and the most common symptom is proptosis of the eye [49, 50].

Other unusual sites for hydatid cysts include the pancreas [51•], thyroid gland [52•], adrenal glands [53•], and salivary glands [54•, 55].

Diagnosis

Diagnosis of CE is based on clinical findings, epidemiological history, imaging, serology, microscopic examination of hydatid sand, and/or nucleic acid detection.

Imaging techniques

The most used imaging techniques in the diagnosis of hydatid disease are:

Ultrasonography

This is the method of choice in cystic lesions of abdominal localization. There are many classifications that categorized the lesions taking into account the activity of the cystic lesion; the most used is the one from WHO-Informal Working Group on Echinococcosis (WHO/IWGE). As regards the WHO, the different stages of the cysts are classified into six categories: CL, CE1, CE2, CE3, CE4, and CE5 [29], as follows:CL: cystic lesion without a wall.

CE1: active unilocular lesion with an anechoic and uniform content. The wall of the cyst is visible as a double membrane, occasionally "hydatid sand" is observed. By changing the patient's position, the hydatid sand produces the "snowflake" sign.

CE2: active lesion with multiple daughter vesicles and septa that may adopt different arrangements: "cartwheel", "honeycomb" or "rosette-like" patterns. The content of the lesion presents a mixed echogenicity.

CE3: transitional stage. Unilocular lesion with a detachment of the laminar membrane inside the cyst: the "water-lily" sign.

CE4: inactive stage. Heterogeneous lesion without daughter vesicles. Degenerative content.

CE5: inactive stage. Total or partial calcification of the wall. This may be related to the death of the parasite.

Conventional radiography (X-rays)

It is useful in pulmonary and bone lesions.

Computed tomography (CT) and magnetic resonance (MR)

These are the procedures of choice for subdiaphragmatic lesion, multiple lesions, complicated cysts with fistulae or abscesses, extra-abdominal cysts, and for a pre-surgery evaluation. MR presents a better sensitivity for differentiating liquid areas in the lesion. MR spectroscopy may be used for the determination of viability of the cysts [56].

Microscopic and histological examination

The diagnostic certainty is obtained by the observation of any of the hydatid sand components in the fluid of the cyst. These elements may also be found in sputum, bronchial washings, duodenal sondages, and surgical material, among other fluids. In order to study the viability of the cyst, a methylene-blue staining may be performed. The colouring agent penetrates only the dead protoscolices [57].

The outer layer or cuticle and the inner germinative layer can be studied with the anatomopathological examination. The outer layer is periodic acid-Schiff (PAS) positive [58].

Serodiagnosis

Serology may enable an early treatment and more efficient chemotherapy along with the follow-up of the treatment.

The host produces humoral and cellular responses, and the quantification of these is a necessary condition for elaborating successful serodiagnostic tools [59].

Insensitive and nonspecific assays including the Cassoni intradermal test, the complement fixation test (CFT), the indirect haemagglutination (IHA) test, and the latex agglutination (LA) test have been substituted by better performing including enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence antibody test (IFAT), immunoelectrophorosis (IEP), and immunoblotting (IB) in the routine laboratory [60].

A comparison of the diagnostic sensitivity and specificity of IEP, ELISA, and IB, in detecting IgG antibodies in patient sera to native and recombinant AgB and a hydatid fluid fraction (HFF), showed that HFF-IB gave the highest sensitivity (80%) followed by ELISA (72%) and IEP (31%).

Dipstick assays are regarded as valuable methods for CE serodiagnosis [61]. One dipstick assay exhibited 100% sensitivity and 91.4% specificity [62]. A new 3-min rapid dot immunogold filtration assay (DIGFA) for serodiagnosis of human CE has been designed, and has an overall sensitivity of 80.7%. [63]. Serum antigen detection may be less influenced by hydatid cyst location and provides an aid for serological surveillance of antiparasitic therapy [64]. Circulating antigen (CAg) in CE patient sera can be detected using ELISA directly or indirectly, and against titrated cyst fluid standards, CAg concentrations have been proved to vary from 100 to 700 ng/mL [65].

Sano et al. have developed the immunopolymerase chain reaction (immuno-PCR) for antigen detection. This technique is far more sensitive than conventional ELISA [66].

Treatment

According to WHO guidelines, there are four alternatives for CE treatment: surgery, PAIR (punction, aspiration, injection of chemicals and reaspiration), pharmacological treatment, and "wait and watch". Selecting one of these alternatives as the best option depends on the experience of the medical staff, number and localization of the cysts, associated complications, and the patient preferences [67, 68].

Surgery

It is advisable for big or infected cysts, localized in important organs and with the possibility of rupture; it is also mandatory in pulmonary hydatidosis. Two types of surgery can be performed: radical and conservative. Radical surgery is preferred because its efficacy is 100% when the germinative layer is completely resected. Also, radical procedures seem to result in lower morbidity and mortality rates [69].

Pair

This method consists in the cyst aspiration by percutaneous puncture with a fine needle by using ultrasound guidance and followed by an injection of an

appropriate protoscolicidal (hypertonic 20% NaCl solution or 95% ethanol). Reaspiration of the cyst takes place 15 to 20 min later. It is indicated in stages CE1 and CE2 and in cysts up to 6 cm in diameter [67, 70]. The risk of this technique is anaphylaxis.

Pharmacological treatment

Albendazole (ABZ) is prescribed for patients with CE1 cysts or in symptomatic, uncomplicated patients with contraindications for surgery. The adult dosage is usually 400 mg twice daily orally after a fat-rich meal to enhance absorption. For children, the dose recommended is 10–15 mg/kg/day up to a maximum of 800 mg orally in two doses. For both adult and children, the duration of treatment is from 1 to 6 months.

BZ is also administered 30 days before surgery to inactivate cysts and during the following 60 days after conservative surgery to reduce the possibility of relapses. Other studies refer that a combined treatment with ABZ (10 mg/kg/day) and praziquantel (25 mg/kg/day), administered for a month before surgery produces more non-viable protoscolices than monotherapy with ABZ. More studies are necessary to determine its utility in the prevention of secondary echinococcosis [71].

"Wait and watch"

This approach is indicated in uncomplicated CE4 and CE5 cysts of up to 4 cm in diameter. Imaging techniques (especially ultrasonography) are used to monitor—generally twice a year—cysts progression as they become calcified over time and turn completely inactive [67, 72].

Alveolar echinococcosis (AE)

The adult worms of *E. multilocularis* are 1.2–4.4 mm long and have a scolex, neck, and the strobila with two to six segments. The scolex has four suckers and two rows of 26 to 36 hooklets [73].

Alveolar hydatid disease caused by *E. multilocularis* is characterized by a large multilocular cyst with a jelly-like substance, instead of clear hydatid fluid. As most cases involve the liver, patients may suffer from hepatomegaly and recurrent jaundice. The most severe complication of AE is the lymphatic and hematic dissemination (metastasis) of the cyst to other organs [1].

E. multilocularis proliferates and metastasizes to remote organs mainly lungs [74], brain [75], and lymph nodes [1, 76•]. Metastatic lesions account for 20% of deaths from alveolar hydatidosis [1]. AE has a high mortality rate in untreated or inadequately treated patients [77].

The clinical symptoms in alveolar hydatidosis are analogous to those of cystic hydatidosis. Cysts localize first in the liver, and in the early stages, the infection is generally asymptomatic [77]. As the pattern of growth of the cyst is similar to that of a malignant tumour, the WHO has proposed a clinical classification, similar to the TNM (Tumour, Node, Metastases) classification of tumours. Such classification is a necessary tool when making therapeutic decisions for the treatment of this disease [78].

Diagnosis

Diagnosis of AE is based on clinical findings and epidemiological facts and statistics, imaging tests, serology, histopathology and/or molecular techniques.

Imaging techniques

Ultrasound examination

Similar to CE, ultrasound examination is the essential procedure for AE diagnosis in abdominal regions. Since lesions can be confused with tumours, the value of an experienced radiologist cannot be underrated [79, 80]. Typical findings (70% of cases) include:

- Juxtaposition of hyper- and hypoechogenic areas in a pseudo-tumour with asymmetrical limits and dispersed calcification
- Pseudo-cystic appearances due to a large area of central necrosis surrounded by an irregular hyperechogenic ring.

Less characteristic features (30% of cases) include:

- Haemangioma-like hyperechogenic nodules as the initial lesion
- A small calcified lesion due either to a dead or a small-sized evolving cyst. Ultrasound with colour Doppler is relevant for biliary and vascular involvement [81, 82].

Other imaging techniques

CT provides anatomical and morphological depiction of lesions and best illustrates the typical pattern of calcification [83]. In cases of diagnostic uncertainty, MR imaging may show the multivesicular morphology of the lesions. This fact corroborates the diagnosis and turns it the best method to study expansion to adjacent structures. Magnetic resonance cholangiopancreatography (MRCP) is used to assess the relationship between the AE lesion and the biliary tree [82].

The use of initial X-ray examination to exclude pulmonary and cerebral AE is recommended.

Histopathological examination

This study shows the parasitic vesicles outlined by a PAS-positive laminated layer. The granuloma surrounding the parasite is composed of epithelioid cells, macrophages, fibroblasts, myofibroblasts, giant multinucleated cells, and various cells of the non specific immune response, usually surrounded by lymphocytes. Collagen and other extracellular matrix protein deposits are also present. [84].

Serodiagnosis

ELISA platforms using rEm18 (rEm18 ELISA) or rEm18 plus the native Em2 antigen purified from *E. multilocularis* larvae (Em2-Em18-ELISA) are being used

at present and have a high diagnostic sensitivity of 90–100%, with a specificity of 95–100% [85].

IHA is one of the low-cost screening techniques but it does not perform at par with EIAs; and the Western blot technique, using a whole *E. multilocularis* larval antigen, is the confirmation method for species diagnosis. The quantification of rEm18-specific antibodies can give information on parasite condition after administration of treatment [86].

An immunochromatography test (ICT) was developed using the rEm18 antigen with a sensitivity of 94% and a specificity of 95.4% [87, 88].

DIGFA has also been developed for AE with a sensitivity of 92.9% [63]. Nevertheless, research studies should continue to develop new diagnostic assays for the enhancement of sensitivity and specificity.

Polymerase chain reaction (PCR)

Echinococcus-specific nucleic acids in tissue specimens resected or biopsied from patients can be detected with molecular methods such as the RT-PCR [84, 89]. DNA analysis is a useful complement. However, a negative result does not rule out infection, nor does an RT-PCR negative result indicate complete inactivity of a lesion. Sometimes, it is difficult to detect DNA because of death of the parasite or the samples contain only a minimal amount of parasite DNA [90].

[18F] Fluoro-Deoxyglucose-positron-emission-tomography (FDG-PET)

This method indirectly distinguishes regions of parasitic activity. If combined with CT (PET/CT), or MRI (PET/MRI), it may show active lesions when clinical symptoms are absent and recurring disease is not yet detectable by conventional imaging [91, 92].

WHO classification of AE

The WHO-IWGE PNM classification, based on imaging detections, is the international point of reference for standardized evaluation of diagnostic and therapeutic guidelines [78, 83].

The classification entails the expansion of the parasitic mass in the liver (P), the implication of neighbouring organs (N), and metastases (M). This classification should improve the quality control of treatment strategies at present.

Treatment

Treatment with benzimidazole (BZ) class of drugs such as albendazole (ABZ) is compulsory in all AE patients. These drugs should be administered temporarily after complete resection of lesions, and for life in all other cases.

Radical surgery is mandatory in all cases suitable for total lesion's resection [93]. If lesions are inoperable, long-term pharmacological treatment is mandatory in all inoperable AE patients, as well as after surgical resection of the parasite lesions. Treatment should be administered for at least 2 years after surgery, and patients should be monitored for a minimum of 10 years for possible recurrence [93].

Pre-surgical pharmacological treatment is not recommended except in the case of liver transplantation. Treatment with BZ is contraindicated in pregnant women, chronic hepatic disease, and bone-marrow depression.

ABZ is given orally at a dosage of 10–l5 mg/kg/day, in two divided doses, with fat-rich meals. In practice, a daily dose of 800 mg is given to adults, divided in two doses.

Continuous ABZ treatment of AE is well tolerated and has been used for more than 20 years in some patients.

If ABZ is not available or not well tolerated, mebendazole (MBZ) may be given at daily doses of 40–50 mg/kg/day in three divided doses with fat-rich meals [93].

Prevention and vaccines

One of the main reasons for the endemicity of CE in certain rural cattle-raising areas is the practice of the feeding dogs with unprocessed offal from animals harbouring hydatid cysts. Anthelminthic treatment of dogs is a traditional method of hydatid control but, as mentioned previously, this intervention requires to be long-term to achieve sufficiently good results. Vaccines have become available for immunization of the intermediate host [80]. Evaluating the effects of immunization with the EG95 vaccine revealed a significant 62% decrease in the prevalence of hydatid infection in 6-year-old sheep. Thus, vaccination of animal intermediate hosts with the EG95 vaccine may provide a new opportunity to improve the effectiveness of CE control measures [94, 95••]. Regardless, CE continues to remain prevalent in both human and cattle population in many endemic countries. An in vitro study showed that rBCG-EgG1Y162 vaccine induced a protection in the mice against secondary infection of *E. granulosus*, indicating that rBCG-EgG1Y162 can be a new vaccine candidate for reducing the risk of human infection by *E. granulosus* [96].

With respect to AE, prevention programs have been implemented in various endemic zones. Recently, increases in the urban fox population have been observed in many countries of the Northern hemisphere. This fact suggests that *E. multilocularis* has entered the metropolitan area. Moreover, the proliferation of this parasite has been observed in non-endemic areas [77]. The distribution of baits containing praziquantel is an effective measure for diminishing the infection rate of *E. multilocularis* in wild foxes. Evidence shows that SRf1, a large glycoprotein component from *E. multilocularis*, can lead to an important reduction in the number of worms in experimentally immunized dogs [97].

Compliance with Ethical Standards

Conflict of Interest

Dr. Claudia Menghi declares that she has no conflict of interest. Claudia Gatta declares that she has no conflict of interest. Liliana Arias declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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This article is a substantial addition to the scientific literature. It describes a systematic review of species and genotypes of *Echinococcus granulosus sensu lato* in humans and natural domestic hosts. Only articles where samples were genotyped by sequencing were included. New *E. granulosus s.l.* samples from Argentina and Uruguay obtained by sequencing of cox1 gene are reported

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