INTRODUCTION

Getting a world consensus on the terminology has been one of the most important initiatives carried out by the World Association of Echinococcosis (WAE) under the coordination of Dominique A. Vuitton with the collaboration of colleagues from all five continents, thus achieving to a standardize approach concepts and definitions to using the same words and expression for the communication between us, scientists and physicians in this field. The list of accepted and rejected terms and expression was published in the international journal “Parasite” (1). Now we can all use the same terminology, thus avoiding language lapses and the wrong use of terms and designations in these particular zoonotic diseases.

ABSTRACT

Human Echinococcosis is a zoonotic infection caused by larval forms (metacestodes) of tapeworms of the genus Echinococcus. Among the different genotypes of Echinococcus described, nine of them – 5 species within E. granulosus sensu lato cluster, E. multilocularis, E. oligarthra, E. vogeli and E. shiquicus – are formally recognized as taxonomically relevant. Echinococcus granulosus sensu lato is responsible for the disease Cystic Echinococcosis, which is endemic in several regions of the world, on the five continents, with a high incidence in the Mediterranean basin including countries in Southern Europe, North Africa and the Near East; in Asia with a high incidence in China; and the Americas, particularly in South America.

The global distribution of this disease involves many experts of all areas of echinococcoses and from different countries, who speak different languages, so it is necessary to use a single terminology so that everyone may understand each other.

Although all of us know the vital cycle of the parasite and the different aspects of the disease, the designations regarding the parasite, its evolution and some therapeutic procedures were not uniform. The World Association of Echinococcosis launched a Formal Consensus process under the coordination of Dominique A. Vuitton, which resulted in the admirable work recently published in the international Journal “Parasite”.

In this article I come to remind and reinforce the idea of respecting terminology, so that we can communicate better among scientists and physicians of different disciplines. I return to this topic because it seems important to me, as a past president of the World Association of Echinococcosis (WAE), that it would be present in the first issue of the International Journal of Echinococcoses, created by the current president of the WAE, Nazmiye Altintas. I will focus on Echinococcus granulosus sensu lato, cystic echinococcosis, the disease due to that species, “cyst” definition, and a few therapeutic aspects.

Keywords: Hydatid; hydatid cyst; cystic echinococcosis; cystectomy; AORC.
Cystic Echinococcosis, the most common disease caused by parasites of the genus Echinococcus, is caused by Echinococcus granulosus sensu lato (E. granulosus s.l.), which includes 5 newly defined and approved species: E. granulosus sensu stricto (s.s.), E. canadensis, E. ortleppi, E. equinus, and E. felidis (in order from the species most likely infect humans to that least). In the life cycle of this parasite, we consider the adult tapeworm, which inhabits the small intestine of some carnivores (called definitive or final hosts), and the larval stage, or “metacestode,” that develops in the herbivores (called intermediate hosts), and accidentally humans.

An important point was stressed in the consensual definition of terms and expressions relating to Echinococcus spp. and echinococcosis (referred to as “Terminology paper”, below), in restricting the use of “hydatid” to the cyst (and its fluid content) of E. granulosus s.l. metacestode. The adjective ‘hydatid’ should no longer be used in reference to qualify any structure of the metacestode of other species (especially E. multilocularis). In addition, the adjective (as in ‘hydatid disease’), as well as the radical ‘hydatid’ (as in ‘hydatidology’, ‘hydatidosis’, etc.) should no longer be used to designate the diseases due to Echinococcus spp. Such a decision had been anticipated at the World Congress of Echinococcosis in Bucharest, in 2015 when the participants voted to change the English name of the “International Association of Hydatidology” into “World Association of Echinococcosis”. It may be expected and recommended, that all national associations will use the same terminology, i.e. “[country] (National) Association of Echinococcosis” According to the World Federation of Parasitologists and the Standardised Nomenclature of Parasitic Diseases (SNOPAD), to designate the diseases due to Echinococcus spp. All terms based on the radical ‘hydatid’ should be systematically replaced by ‘echinococcosis’, preceded by the appropriate adjective. In reference to three names for the main diseases due to Echinococcus spp. metacestodes: “cystic echinococcosis” (due to E. granulosus s.l. cluster of species), “alveolar echinococcosis” (only due to E. multilocularis) E. shiquicus being responsible for a similar disease in animal intermediate hosts, but not known to be responsible for disease in humans), and “neotropical echinococcosis” (due to E. ortleppi or E. oligarthra, in various countries of South America (the New World) tropical areas).

With regards to Cystic Echinococcosis, the intermediate hosts, in which humans are included, are infected by ingestion of eggs within the feces of the definitive hosts. The presentation form of the disease in intermediate hosts is that of lesions known as hydatid cysts, which correspond to the larval stage of E. granulosus s. l. But what is the definition of a ‘hydatid cyst’?

At the beginning of the last century Dévé defined the hydatid cyst as being composed of two parts: the echinococcal parasite (or “hydatid”, used as a noun) and the “adventitia” that surrounds it. The “adventitia” is a layer of inert tissue, of variable thickness, including fibrosis, “which results from the host’s organ reaction against the hydatid considered as a foreign body”. In the description of Dévé (and later, in the ultrasonographic and CT scan definitions of the ‘hydatid cyst’), this layer is an integral part of the cyst. There has been some controversy regarding this definition. Parasitologists around the world argued that the adventitia should not be taken into account when defining the cyst as it is not a part of the parasite. In fact, if the lesion (cyst) corresponds only to the larval stage of the parasite, then its composition cannot (should not) contain other structures that are not of the parasite itself. This is the reason why some authors designated the adventitia as pericystic since, for them, it was not part of the cyst but it surrounded the parasitic cyst.

After discussion between parasitologists and clinicians, the authors of the “International consensus on terminology” eventually considered that the cyst was definitely defined as an anatomical entity produced by the growth of the metacestode of Echinococcus spp. distinct from the surrounding organ parenchyma and filled with fluid. The updated terminology describes the cyst as composed of 3 “layers” (and not membranes), from outside to inside: the adventitial layer (of host origin, even reduced to a few infiltrating cells or to fibrous tissue); the laminated layer and the germinal layer (both of parasite origin); and the cyst fluid (and its content, of both parasite and host origin) (Table 1B of the ‘Terminology’ paper). The hydatid fluid is secreted by the germainal layer of Echinococcus spp. metacestode, and is clean and clear, “as well as the clean water from its natural source”, as nicely evoked by Mazzaacco in 1923.

The germinal layer (20-25 µM of thickness) is composed by various types of cells and gives rise to the different structural elements of the hydatid, including the laminated layer, composed of several concentric layers of polysaccharide material heavily and typically stained by the Periodic Acid Shift (PAS) reagent on histological sections and brood capsules. These contain “protocolecles” (and not protoscolices as often wrongly written) and develop from the germinal layer through a cloning/budding mechanism and defines which ensures the fertility of the cyst. The protoscolices possess invaginated scoleces of the adult stage of Echinococcus spp (not scolices), which develop as the final stage of the “protoscolices”, after contact with the gastric juice and bile of the definitive host’s digestive tract.

The cyst fluid is produced secreted by the germinal layer of Echinococcus spp. metacestode and collects at the centre of the “cyst”, containing secretions from both the
parasite and host.

Brood capsules, protoscoleces and other structures such as calcareous corpuscles often detach from the germinal layer and collect in the cyst fluid as what is referred to as “hydatid sand”

2. Disease transmission, cyst evolution and composition

In primary echinococcosis, the metacestodes (hydatid cysts) develop in various sites from oncospheres after ingestion of *E. granulosus* s.l. eggs. The eggs of these tapeworms excreted by carnivores may infect various species of natural intermediate host animals and humans, and may develop in almost any organ. Most patients (up to 80%) have a single organ involved and harbour a solitary cyst, localized in approximately two-thirds of cases in the liver and in about 20% in the lungs.

In secondary echinococcosis (2), the larval tissue has spread from the primary site and proliferates after spontaneous or trauma-induced cyst rupture or after release of viable parasite material during invasive treatment procedures, which results in secondary cysts (see Table 1C of the ‘Terminology paper’).

During the natural course of infection, the fate of the hydatid cysts is variable. Some cysts may grow (average increase 1 – 30 mm per year) and persist without noticeable change for many years. Others may spontaneously rupture, which often causes an anaphylactic reaction. Spillage of viable protoscoleces after cyst rupture, spontaneous or traumatic, or during interventional procedures, may result in secondary echinococcosis. Others can also spontaneously collapse and can completely disappear. Calcified cysts are not uncommon.

After an undefined and variable incubation period, CE may become symptomatic if active cysts exert pressure on adjacent tissue and induce other pathologic events. Usually, cysts do not induce clinical symptoms until they have reached a particular size. Sudden onset of symptoms may be due to cyst rupture. In the ‘Terminology paper’, a strict definition has been fixed for ‘Complications’, which do not include the size or number of cysts per se, but the possible deleterious consequences of the cyst(s) on the infected organ or tissue (cf. Table 1C).

Through the slow evolution of a cyst several events can occur: the death of the parasite due to dysfunction of the germinal layer (detachment or aging), the “cyst’s wall” fissure due to detachment of membranes or micro traumatisms, the de novo formation of a new cyst from the ‘mother cyst’, i.e. the ‘daughter cyst’, considered to occur when the mother cyst is altered for any reason, or even the transformation of the protoscoleces themselves into new hydatids, locally or in distant sites, when the protoscoleces are released outside the cyst. Both the formation of ‘daughter cysts’ and the formation of newly developed cysts from ‘free’ protoscoleces, which have distinct mechanisms, may represent attempts to preserve the species in the intermediate host when the completeness of the parasite cycle may not be achieved.

The long-term survival of the *Echinococcus* spp. metacestode indicates the existence of protection mechanisms against the immune response of the host. The hydatid fluid and the cells of the germinal layer are the main responsible for the antigenic stimulation, but the laminated layer of the cyst is like a functional barrier against immune competent cells of the host and a stimulus to develop tolerogenic responses from the host. So, any damage in the germinal and laminated layers, like fissures or rupture, will increase antigenic stimulation with subsequent effect or immune response. When this antigenic stimulation occurs, there is a continuous elevation of the various products of the immune response, and especially antibodies, for an indeterminate time. This elevation also happens after cyst manipulation (surgery, puncture etc.).

3. Terminology in therapeutic options in Liver Cystic Echinococcosis (LCE)

The ultimate aim of the treatment in LCE is the death of the parasite and consequently the cure of the disease. It has to be done with minimal risks and discomfort for the patient, and always being aware of causing complications, secondary echinococcosis and relapses (3-8). The methods to achieve the death of the parasite are both the sterilization of the cyst content, using “scolecidal” (and not “scolicidal”, as often written) or more generally anti-*Echinococcus* drugs, or the direct removal of the parasite direct removal, through aspiration or the surgical excision of the entire cyst. There is no “best” treatment option for LCE and no clinical trials have compared all the different treatment modalities, including the “Watch and Wait” attitude which has been recommended for small uncomplicated cysts or degenerating cysts(7, 9, 10).

An important aspect to take into account is the difference between “complicated” and “non-complicated” cysts (7, 8, 11, 12) (see the ‘Terminology paper’ for definition). In non-complicated cysts the choice of the therapeutic method shall have in consideration the cysts characteristics based on the US classification. In its treatment, whether surgical or not, we should consider two options: non-invasive and invasive approach.

The non-invasive treatment corresponds to the oral administration of anti-infective drugs (often called ‘chemotherapy’ in the past, a term which was rejected by the Terminology consensus (1), because of its use in cancer treatment): albendazole, mebendazole or praziquantel.
Nowadays albendazole is the drug chosen for oral treatment of CE. Its metabolite, the albendazole sulfoxide, is the active component that has a half-life of 8.5 hours. Albendazole is orally administered, every 12 hours, in a total dose of 10–15 mg/kg/day. In the past this drug was given during a period that was called therapeutic cycle (4 weeks of treatment followed by 2 weeks of interruption), but according to the “Expert consensus” (3) published in 2010, this so-called “discontinuous administration” of the drug should not be used any longer to treat CE. This has been recalled recently by a group of experts of the WAE (13). The anti- *Echinococcus* effect depends on the stage of development of the cyst and on its germinal membrane integrity too (more effective on young cysts – type CE1 and less on type CE2 cysts with over 50% of failure rate, and more effective on liver cysts than on cysts in other locations, presumably because of a better concentration of the drug in the liver and in the liver cysts). Albendazole is also used associated with surgery to reduce the internal cyst’s tension and prevents secondary echinococcosis. However, the modalities of pre- and post- surgery administration have not been definitively fixed yet (11).

In the invasive approaches we can consider two methods: 1) Non-radical procedures (following both non-surgical and surgical approaches); and 2) Radical procedures (following only surgical approaches).

### Non radical procedures

In non-radical procedures we have two ways to treat the LCE:

- Approaches to sterilizing the cyst content;
- Approaches to removing the parasite layers (part of the cyst).

### Cyst content sterilization

This method is based on the degeneration of the hydatid membranes and destruction of the elements of the hydatid fluid due to the effect of anti-parasite drugs, called also “scolcidal” if they are able to kill protoscoleces whatever injected into the cyst or orally taken. The injection of a scolcidal solution into the cyst cavity is the most ancient method of treatment for the LCE. It was considered the best method for treatment of simple cysts (univesicular cysts), that correspond to the cysts type 1 and 3a in the current WHO ultrasound classification. It achieves the death of the parasite in situ, without its removal, promising the degeneration and solidification of the cyst content, which becomes inactive. In the past this approach was only done by laparotomy, but nowadays we have two additional approaches: laparoscopy (14) and percutaneous puncture (9-15). Percutaneous puncture is known as PAIR (Puncture, Aspiration, Injection (of the scolceide) and Re-aspiration) and it is a minimal invasive technique, less painful for the patient, which has a lower complication rate, is less expensive, with earlier discharge and activity resumption.

### Parasitic layers (hydatid) removal

There are two different ways to remove the parasite: the aspiration of the parasite (hydatid), a procedure called “hydatidectomy”, in the past, or the partial excision of the cyst, which should necessarily remove the parasitic layers. The first must be performed by mini-invasive methods, while the second can only be performed by surgical approach. The removal of the parasite is similar to the puncture method for the sterilization of the cyst except in what concerns the last step (total aspiration), which is done with a high aspiration device, in order to remove the hydatid layers and all the remaining contents, or by using a device that destroys the germinal layer and the cyst content. This method can be performed under laparotomic, laparoscopic or percutaneous approach. There were different methods described for the percutaneous approaches, with different names (16, 17). However, the acronym MoCat (Modified Catheterization) was approved as the single expression to be used for this type of technique, as described by Akhan et al. (16) (Table 1C in the ‘Terminology paper’).

If the patient has surgical indication the complete removal of the cyst should always be considered, but sometimes it is not possible due to the risks. So, if there is a risk of damaging the bilious or vascular structures the alternative is to perform a subtotal or partial cystectomy (figure 1), which is a non-radical procedure.

### Radical procedures

The radical procedures correspond to total cystectomy or organ resection (figure 1). Total cystectomy consists in the excision of the entire cyst (7, 8, 18), which is the ideal surgical procedure, with the lowest rate of relapses and complications. It can be performed through laparotomy or laparoscopy with cyst opening or not. In both options, the dissection is made on the outside of the adventitial layer. The “opened cyst” (OC) method is performed by opening the cyst then aspirating the fluid and finally removing all cyst content, including the entire cyst “wall”. The non-opened cyst (NOC) method, known as Napalkoff’s procedure in the past (8, 11), consists of the entire cyst removal without opening it. In its original description, Napalkoff’s procedure included a dissection in the ‘pericystic’ hepatic tissue (thus called ‘pericystectomy’), to guarantee complete cyst removal, including the adventitial layer. It is now recommended, after the huge experience of Peng Xin Yu and his colleagues (7) in Western China, to perform the dissection in the virtual space between the adventitial layer and the ‘normal’ hepatic tissue, which prevents...
bleeding and is associated with less complications while being as effective to remove all parasitic tissue.

Cystectomy can be performed by video assisted surgery on selected cases, namely small cysts (< 5 cm in diameter) with peripheral localization. Since the total cystectomy is the ideal approach, it should be done by the non-opened cyst method and without using CO\textsubscript{2} to prevent the dissemination risk in case of rupture.

Another option, in very selected cases, is the hepatic resection of the liver parenchyma (segmentectomy or lobectomy), in case of great size cysts in which there is a high risk of ischemia for the remaining hepatic tissue.

With regard to surgical resection of the cyst, a description of the procedures has also been proposed in the ‘Terminology paper’. It consists of using the acronym AORC to describe surgical operations, which means:

- The Approach (“laparotomy”, “laparoscopy” or “robotic”), which corresponds to the letter A;
- The Opening or not of the cyst (“non-opened cyst” (NOP) versus “opened-cyst” (OP), which corresponds to the letter O;
- The type of Resection (“cystectomy”, “hepatectomy”, or “liver transplantation”), which corresponds to the letter R;
- The Completeness of resection (“total”, “subtotal”, and “partial”) which corresponds to the letter C.

**Prevention of complications**

Although nowadays the morbidity and mortality of LCE surgery have diminished, they cannot be overlooked. The prevention of complications starts with an accurate surgical technique and the necessary caution in the removal of the cysts which are very close to the bilious and vascular intra-hepatic structures.

To prevent relapses in 'opened cyst' surgery, it is very important to protect the surgical field with pads soaked with scolecidal solution (7, 8). This precaution will also prevent secondary echinococcosis in case of unexpected spillage of the cyst content if the cyst has to be opened during a priori 'non-opened cyst' surgery.
There is sufficient evidence for the following adjunctive measures to play a useful role:

- Prevention of secondary echinococcosis and relapses
  a) Albendazole – starting 1 week prior to surgery and continuing to up to 3 months after surgery (7, 8, 19) (grade strength of recommendation A, quality of evidence III);
  b) Surgical field protection with pads soaked with scolecidal agents (grade strength of recommendation A, quality of evidence III);
  c) Complete removal of the cyst (if possible) with no residual cavity (grade strength of recommendation A, quality of evidence III).

- Prevention of cholangitis
  a) Direct observation of cysto-biliary fistulas, observation of cyst fluid colour, determination of bilirubin in cyst fluid after aspiration and antegrade cholangiography, where necessary (7, 8). (grade strength of recommendation A, quality of evidence III);
  b) Strictly avoiding injection of scolecidal solution in cyst communicating with the biliary tree (7, 8). (cysto-biliary fistula).

- Management of the residual cavity
  When partial or subtotal cystectomy is performed residual cavities need attention. Simple drainage with suction, filling with epiploon (omentumoplasty) (7, 8, 20). are options to reduce the risk of complications (grade strength of recommendation A, quality of evidence III).

**CONCLUSION**

In addition to the proper use of the appropriate terms in the parasitological nomenclature of *Echinococcus* species, in the description of the various anatomical forms of their metacestodes for veterinarian and clinical practices, and in the description of the disease and their therapeutic procedures, the new terminology thus offers a simple and systematic description of CE surgery so that comparisons may be possible between published studies. Adaptation of the updated international terminology in English to the main languages spoken in echinococcosis endemic areas are currently under way. The Chinese adaptation has been published in 2021 and the French version is already available ‘on line’ in the *Bulletin de l'Académie Nationale de Médecine* (link available until Sept 18, 2021: https://authors.elsevier.com/a/1dUnjkVEePaa; formal publication in October 2021). Spanish, Arabic and Turkish versions are urgently waited for, and should be completed soon.

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