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# Current Research Advance on Echinococcosis

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## Abstract

Echinococcosis is caused by infection with larva (metacestode) of the tapeworms of the genus *Echinococcus*. Within genus *Echinococcus*, two species are known as public health concern worldwide: *Echinococcus granulosus* causing cystic echinococcosis (CE) and *Echinococcus multilocularis* causing alveolar echinococcosis (AE). The co-evaluation due to the interaction between parasites and their hosts has been well known to be able to allow tolerating to maintain parasitism as long as possible. With many research advanced findings, scientists have been much interested in using either those molecules from parasites producing due to invading and surviving or those cytokines from hosts responding due to defenses to carry out immunotherapeutic practice that is not only against parasitic infection but also for cancer or other immunological related disorders. Taken advance of knowledge on *Echinococcus* genome research outcomes, recent attentions regarding the discoveries of targeting antiparasitic drug and/or vaccine were extensively discussed in this review.

**Keywords:** *Echinococcus* species, parasitism, interactions between parasites and hosts, immunotherapy agents, drug and vaccine discoveries

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## 1. Introduction

The echinococcosis in human occurs as a result of infection by the larval stages of taeniid cestodes of the genus *Echinococcus*. Originally, four species have been recognized as the public health concern: *Echinococcus granulosus* [agent of cystic echinococcosis (CE)], *Echinococcus multilocularis* [agent of alveolar echinococcosis (AE)], and *Echinococcus vogeli* and *Echinococcus oligarthrus* [both are the agents of polycystic echinococcosis (PE)] [1]. Recently, two new species have been identified: *Echinococcus shiquicus* [2] in small mammals from the Tibetan plateau and *Echinococcus felidis* [3] in African lions though these two new species infective to

human are still unknown [4]. A couple of studies have provided augments that these diseases are an increasing public health concern and showing emerging or re-emerging diseases [4, 5].

Among recognized four public health concerned species, *E. multilocularis* and *E. granulosus* are important for human health and economic welfare [4]. The disease occurs in most areas of the world, and currently about 4 million people are infected and another 40 million people are at risk [4, 6, 7]. The economic cost of the disease is estimated to be around 3 billion USD a year. It is classified as a neglected tropical disease [4].

The knowledge on the geographical distribution of the environmental factors for the persistence of the lifecycle is scarce [8, 9]. Studies to improve the knowledge on epidemiological risk factors should be encouraged to enable risk-based sampling. *Echinococcus* notification should always be done at species level in order to discriminate between the more severe alveolar and the cystic echinococcosis [10, 11]. Updated knowledge on the *Echinococcus* parasitism was also discussed for the potential application in immunotherapeutic against parasites and other immune disorders.

## 2. Transmission

The life cycle of *Echinococcus* species requires a predator-prey relationship between the definitive and intermediate hosts.

*E. granulosus* is adapted to an environment in which livestock farming plays a central role, completing its cycle through dogs or wild carnivorous animals (as definitive host) and a variety of livestock species, mainly sheep, cattle, pigs, horses, goats, and camels as well as the several wild ungulate species serve as intermediate hosts for the different lineages of the *E. granulosus* species complex [12]. In contrast, several wild rodent species (typically rodents of the families *Arvicolidae* and *Cricetidae*) are the natural intermediate host for *E. multilocularis* [12, 13].

The intermediate hosts become infected through ingestion of eggs in contaminated food or water [12]. The host digestive enzymes dissolve the egg's shell, releasing the oncosphere, which burrows through the host's gut wall and is transported via blood or lymph to the target organ of liver for AE, but mainly liver and lungs, as well other organs for CE [14]. While the life cycle of *E. multilocularis* is completed after a fox or canine consumes a rodent infected with alveolar echinococcosis [8]. Once again adults begin to release a new gravid proglottid, which usually carries some 1500 eggs [15], to be passed to the outside environment with their feces. The adult worms are hermaphroditic. *E. granulosus* becomes prepatent in 32–80 days in the definitive hosts [16], this period varies with the species or strain. While *E. multilocularis* usually becomes prepatent in foxes or dogs in 28–35 days [17], the life cycle of *E. multilocularis* is predominantly sylvatic [18].

Humans can serve as an aberrant intermediate host, acquiring the infection by accidental ingestion of eggs, due to handling of infected animals or ingesting contaminated food, vegetable, and water. Except in rare cases, where infected humans are eaten by canines [19], humans are a deadend for *Echinococcus* species, which means that this kind of intermediate host does not allow transmission to the definitive host [20].

Briefly, the disease is spreading when food or water contains the eggs of the parasite, which may be eaten by intermediate animals (such as sheep for *E. granulosus* and rodents for *E. multilocularis*),

or due to close contact with an infected definitive animal (carnivorous animals, e.g., dogs, foxes), while the definitive animals, to become infectious, they must eat the organs of an intermediate animal that contains the valid cysts.

### 3. The parasitism establishment

Generally, selective pressure between host and parasite (parasitism relationship) provides chance for coevolution [21, 22]. A constant adaptation occurs in both populations due to an accumulation of the genetic changes that results in the development of new parasitic strategies and new host defenses [21].

Parasites with complex life cycles often behave differently in their intermediate and definitive hosts [1, 23]. *Echinococcus* species presents strongly affected its intermediate hosts (moose or and small mammals, and rodents) due to high virulence but low virulence in the definitive hosts (such as wolf, fox, or dog). The strong effect makes the intermediate hosts to be more severe sick and easily be captured/hunted by the carnivorous animals [9, 18], thus, benefit parasitic life-cycle and increase transmission dynamics.

The relationship between *Echinococcus* species and their intermediate hosts leads to the necessity for the pathogen to have the virulent alleles to infect the organism and for the host to have the resistant alleles to survive parasitism. Variation in the pathogenicity of strains/species of *Echinococcus* is well known to influence the prognosis in patients with echinococcosis [23]. Increasing epidemiological evidence suggests that certain strains of *E. granulosus* (such as those adapted to horses and pigs) may not be commonly infective to humans [1], and the transmission of parasite strain differs (genetically) geographically and host-adaptively [24]. Therefore, estimates of gene flow between populations in different intermediate hosts or geographic areas can have valuable epidemiological applications [1, 11]. In the genomes of cestodes, considerable gene gain and gene loss associated with the adaptation to parasitism has been found in recent genome parasitic programs [21, 22]. Although, the different morphologies of their metacestode stages caused by *E. multilocularis* and *E. granulosus* are clinically often regarded as “distinctly different entities” [25], they are highly similar concerning gene structure and gene content [22]. Salient differences were so far only observed in the *Echinococcus*-specific apomucin gene family [21]. This is presumably associated with one of the few clear morphological differences between two species of *E. multilocularis* and *E. granulosus*, the thickness of the laminated layer, since the apomucin gene family encodes important components of this structure [26].

### 4. Interaction between *Echinococcal* parasites and their hosts

During echinococcosis infections (including AE and CE), the distinguishing feature of the host-parasite interaction is that chronic infection coexists with detectable humoral and cellular responses against the parasite [27]. It is well known that the *Echinococcus* species can actively interact with host's both innate and acquired immune systems to maintain their survival

with successful evasion from host's immune attacks [28]. The disease spectrum is clearly dependent on the genetic background of the host, as well as on the acquired disturbances of Th1-related immunity [29], such as pregnancy [30], malnutrition [4], severe stress due to work or life [4], coinfection (e.g., HIV) [31, 32], or using immune-suppressing drugs [4, 28]; thus, this kind of circumstances can provide an opportunity to allow the pathogen invading. Human AE appears to be an example of "opportunistic infection", when you make your immunity capability weakness [28, 30]. The genetic constitution of both hosts and pathogens is involved, host genes controlling resistance or susceptibility to infection, genes of the pathogen determining characters such as virulence [23].

In order to establish a successful infection, parasite releases molecules that directly modulate the host immune responses favoring and perpetuating parasite survival in the host [33]. Recent experimental evidence suggests that parasites can not only evade immune responses actively but also exploit the hormonal microenvironment within the host to favor their establishment and growth [34]. Hormonal host parasite cross communication facilitated by the relatively close phylogenetic relationship between *E. multilocularis* and its mammalian hosts, thus appears to be important in the pathology of AE [35]. *E. multilocularis* metacestode metabolic pathway cascades can be activated by host's cell signaling [13, 36], resulting in the larvae development [37]. Conversely, the larval *Echinococcus* can also influence their host immunity response and metabolic signaling mechanisms through the secretion of various molecules [24]. Therefore, immunomodulatory activities of *Echinococcus* and pathological consequences on the host's tissues were attracted by many research concerns for decades [38].

The laminated layer could also play a role similar to that of the placenta at the materno-fetal interface [39]: ensuring parasite growth and infected tissue cell homeostasis while ensuring proper immune tolerance. Tolerance is essential to ensure growth and development of the larval stages of *Echinococcus* species in their hosts [27]. It has been recognized that a series of host-adapted species in the genus *Echinococcus* fits in nicely with observations on host range [1], life cycle, and transmission patterns in areas where echinococcosis is endemic [23]. The ability of hosts to regulate parasites through innate and adaptive immune responses is one of the most important determinants affecting levels of infection, both in the individual and the population [1]. Immunomodulation and, to some extents, immune tolerogenic role have been a great interest of researchers during echinococcosis infection both in human and in animal studies. Many reports have described the worms achieve to switch in the host's response by releasing molecules that share epitopes (and possibly functional activity) with host cytokines [40]. The high relevance for host parasite interaction mechanisms is also found that the presence of evolutionarily conserved signaling systems in *Echinococcus*, such as components of the epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor  $\beta$  (TGF- $\beta$ ), and insulin signal transduction cascades [40, 41], though the signaling systems in animals are also known to be primarily influenced by both factors of the genetic heritage and living environments [42].

The host-derived EGF is known to induce the *Echinococcus* mitogen-activated protein kinase (MAPK) cascade, probably through direct interaction with parasite EGF-receptors [13]. Parasitic components, and not only factors from host origin, were actually acting on hepatocyte



metabolic pathways. Recent report indicated that host insulin acts as a stimulant for parasite development within the host liver and that *E. multilocularis* senses the host hormone through an evolutionarily conserved insulin signaling pathway [13, 35].

Although both parasites and hosts benefit from the dynamic balance that grants parasite-induced damage to hosts at a reasonable level and in turn [42], to some extent, provide parasites nutrients, in some cases of human echinococcosis, spontaneous healing of the disease was observed [20, 27]. Such abortive cases are characterized by calcified parasite lesions suggesting the generation of immune responses which are able to limit parasite growth in humans [27].

## 5. Disease in animal hosts

A carnivore animal is the definitive host—where the adult worms live in the intestines; and almost any mammal, including humans, can be the intermediate host—where the worms form cysts in various organs for CE but mainly in liver for AE.

### 5.1. Infection in definitive hosts (mainly implication for dogs)

It is much more difficult to tell when a dog is infected with *Echinococcus* compared to other tapeworms such as *Taenia* or *Dipylidium* [16, 17]. An adult *Echinococcus* species is tiny—only a few millimeters long. Dog infection generally does not show any signs of illness at all even though the hundreds or thousands of tapeworms live in its intestine. Despite the difficult differentiation of the eggs between *Echinococcus* and *Taenia* species under microscopy through fecal examinations [16, 17], the diagnosis of dog infection is an important and useful through dog-copro-DNA assays [16, 17, 43]. So, dog fecal examinations should be performed regularly.

### 5.2. Infections in intermediate animal hosts

**For AE:** the primary metacestodes are found in rodent's liver. The germinal membrane of *E. multilocularis* proliferates externally, rather than internally, to form a multilocular structure with many small cysts. These vesicles are usually 1–10 mm in diameter. Hundreds to thousands of protoscolices develop from the germinal membrane in some animal intermediate hosts (small mammals). These multilocular cysts have semisolid matrix and resemble malignant tumors. The center of lesion may be necrotic. The lesion can completely infiltrate an organ, and spread to other organs and tissues nearby. The cysts can also metastasize to distant sites. Although, the tumor-like cysts can kill rodents within a few weeks of infection, this parasite has recently evolved into an experimental model system by use of rodent species to study larval cestode development and associated host-parasite interaction mechanisms.

**For CE:** the intermediate hosts include a large number of domesticated and wild animals, particularly herbivores. The rate of development varies with the intermediate host and species of parasite, but the cysts usually grow slowly. Their diameter generally increases from less than 1 to 5 cm every year. The parasitic cyst comprises of two walls of an outer laminated membrane and an inner membrane called the germinal layer. All the brood capsules can be

produced from the germinal membrane. If the cyst contains protoscolices, it will be named as fertility cyst. Some cysts are sterile, since protoscolices are not produced or killed by bacterial infection. The percentage of sterile cysts varies with the different intermediate host and its susceptibility to a particular strain/species of parasite. The cysts in livestock also seem to be asymptomatic, probably due to the relatively short lifespan of these animals. Because the cyst grows slowly and the symptoms can only appear until its size can effect on adjacent tissues and organs. Occasionally, symptoms have been reported in sheep [5]. But mostly the infected livestock shows poor growth, weakness, and lameness. Therefore, the economic loss assessment modeling due to livestock infections (mainly in sheep) has attracted some extensive attentions in endemic regions and countries worldwide.

## 6. Disease in humans

Epidemiological studies have demonstrated that the majority of human individuals exposed to infection with *Echinococcus* spp. eggs exhibit resistance to disease as shown by either seroconversion to parasite specific antigens or the presence of “dying out” or “aborted metacystodes” [4]. Seroconversion proving infection, but lack of any lesion indicating the failure of the parasite to establish and further develop within human tissues (mainly in liver) or resistance as shown by the presence of fully calcified lesion [44]; while the developing parasite can be partially controlled by host immunity in those susceptibility individuals where infection leads to disease, as found in the AE and CE patients who experience clinical signs and symptoms approximately 5–15 years after infection [20, 30].

If untreated or uncontrolled, the hyper proliferation of the metacystode due to an impaired immune response could be resulted by immune modulation of host immunity toward energy that can be triggered by parasite metabolites [38], and/or be resulted by additional clinical conditions, such as AIDS or any other reason to induce the immune deficiencies [20, 27, 30]. The disease often starts without symptoms, and this may last for years. The symptoms and signs can occur depend on the lesion location and size for CE. While, AE usually begins in the liver but can spread to other parts of the body.

Cystic echinococcosis (CE) can cause very severe symptoms, if the cyst bursts (e.g., from sudden trauma) or even fatal. The released protoscolices can spread the parasite to other parts of the body to form many new cysts [20].

Alveolar echinococcosis (AE) ranges in size from a sesame seed to a large melon [45]. Although, the mass lesions grow slowly, the tumor-like growth manner tends to invade neighbor organs or tissues, making treatment very difficult [30].

Fibrosis is an important component of the pathophysiology of each disease caused by *Echinococcus* species. However, this role differs markedly in CE and AE. In CE, the rapidly established periparasitic fibrosis surrounding the laminated layer contributes to the unicystic feature of the disease and to limit cyst growth [46]. In AE, the slow fibrogenesis in an extensive and partially unsuccessful periparasitic granuloma does not prevent germinal layer budding.

In the long term, it eventually leads to a dense and irreversible fibrosis, responsible for the main complications of the diseases, such as bile duct, vessel obstruction, and secondary biliary cirrhosis [47–49].

## 7. Human disease diagnosis

*Echinococcal* lesions may grow for years, depending on their location, without causing any signs of illness in people [4]. The signs of illness do occur in late stages of diseases, such as abdominal pain and jaundice due to obstruction of bile ducts (in liver), chest pain and difficulty in breathing (in lungs) [4], neurological signs, and seizures (in brain) [30]. Cysts/lesions are sometimes found occasionally when tests are performed for other reasons [4]. Generally, the clinical symptoms and image presentations, e.g., radiographs, ultrasound, CT, or MRI, need to combine the evidences from a blood test for antibodies to the parasite or biopsy for histopathological examination or PCR assay to confirm the diagnosis [4]. Screening individuals living in high-risk areas by ultrasound and serological investigation [44] can catch the infection early and can make treatment much easier and more effective [44].

Therefore, diagnosis requires a combination of tools that involve imaging, histopathology, or nucleic acid detection, and serology. The ultrasound though computer tomography (CT) or magnetic resonance imaging (MRI) may be used commonly. Serology methods for antibodies against the parasite detection can be some certain supplemental tool for imaging/clinical diagnosis. The histopathology or nucleic acid using biopsy after invading methods could provide the final confirmation [4, 20].

## 8. Management of echinococcosis in human

The growth of larva of *Echinococcus* spp. and the proliferation of the larva are similar to a slow-growing tumor. If the lesion occurs in liver, it can damage liver function. Sometimes, it is difficult to differentiate it from liver cancer because of invasion to biliary and vascular tissue of the liver [50]. Early diagnosis and radical surgery provide the best chance for treatment and cure. Although, treatment of AE is less effective than treatment of CE, the general approach for both types of echinococcosis treatment remains to be surgery with the purpose of complete resection of infected parts of involved organs [4]. Antiparasitic drugs cannot kill cysts if the lesions have already established. However, if untreated, patient survival time is very limited. Therefore, early detection and treatment are important ways to improve patients' survival [4, 20].

Although treatment of cystic echinococcosis by surgery to remove the hydatid cyst was always a risk that the cyst would burst during the procedure, resulting in a very severe, even fatal reaction in the patient to the spilled fluid, drug therapy alone is usually not enough to eliminate cysts, but it can help reduce lesion size and operation risks. More recently, treatment with antiparasitic drugs and drainage of the fluid from the cyst using a needle has been used to treat the disease in certain cases without surgery. Briefly, with proper care, 96–98% of CE patients survive [20].



## 9. *Echinococcus* species infective risk to humans

The risk of infection with *E. granulosus* or *E. multilocularis* to humans from most pets is very low, but it is higher risks for those residents living in endemic areas. Their work or recreational activities involve direct contact with contaminated water, soil, and their dogs for a long time or life time [10]. Those dogs may allow to roam, hunt, and eat raw tissues from potentially infected animals (e.g., rodents, rabbits, sheep, moose) [8].

The risks for the susceptible of infection with *Echinococcus* spp. can occur in those peoples with immune-compromised conditions (e.g., HIV/AIDS patients, transplant recipients, cancer patients) or with other complications because their immune systems cannot fight infections efficiently [20]. Mostly, ingestion of *Echinococcal* eggs occurred in early ages, if they have chance to contact with contaminated environments, but the disease may appear until they are adults [44].

## 10. Prevention and control program

Dogs if allowed to enter *Echinococcus*-free areas from potential endemic areas need to be treated with anthelmintic agents (e.g., Praziquantel). Routine inspection of the potential parasitic intermediate host animals before permitting for importing could also prevent the parasite into a country [15].

In endemic areas, dogs should not be allowed to eat the carcasses, particularly the viscera of potential intermediate hosts. Dogs should also be kept from hunting wild rodents and small mammals [6]. Regular examination and treatment of dogs [8] can decrease echinococcosis in domesticated livestock [14].

Prevention of *Echinococcus* species spreading is by treating dogs that may carry the disease and vaccination of sheep. Health education programs focused on echinococcosis and its agents, and improvement of the water sanitation attempt to target poor economic living condition and poor drinking water sources. Educational material should include information about proper disposal of sheep viscera in abattoirs and proximity to dogs and sources of transmission [15].

## 11. Parasitism perspective applications

### 11.1. Treatment parasitic infections

In the absence of fully effective antiparasitic chemotherapy for AE and CE, modulation of the host's immune response could be envisaged to fight against the parasite and to prevent the disease and/or its complications such as using IFN- $\alpha$ 2a immunological treatment [28] and some parasitic antigens as potential vaccination to prevent disease occurrence such as

using Em14-3-3, Em 95, EMY162, and EmTetraspanin [24]. Additionally, current picture on *Echinococcus* signaling systems will be given and the potential to exploit these pathways as targets for antiparasitic chemotherapy [51].

### 11.2. Using parasite productions for cancer treatment

The presence of Tn antigen in larval and adult tissues of *E. granulosus* was reported [52], this finding is interested in cancer-associated mucin-type because this parasite produced peptides can act on the nonspecific natural killer cell to express cytokines that are effective agents against tumor growth; therefore, the family of Tn antigens might be useful targets for antitumor immunotherapy [41, 53, 54]. These evidences may contribute to the design of tumor vaccines and open new horizons in the use of parasite-derived molecules that can fight against cancer [55, 56].

Cancer vaccination is an important and promising approach in cancer immunotherapy. Obstacles for clinical success may include immune tolerance to TAAs [57], the weak antigenic nature of TAAs, and active immune evasion mechanisms employed by progressing tumors [58]. Vaccination with TAAs coming from evolutionary distant organisms (such as *E. granulosus*) should be useful to override tolerance problems encountered with human TAA-based cancer therapeutic approaches [58].

### 11.3. Echinococcosis diagnosis

Additionally, the high level of the O-glycosylated Tn antigens generated from larvae of *E. granulosus* are found in the sera of the patients with cystic echinococcosis (CE), providing a pathway that a series of Tn antigens might be sort as a biomarker for this parasitic disease diagnosis, but the hypothesis needs more work to verify the clinical values regarding those antigens [59].

## 12. Conclusions

Overall, genus *Echinococcus* can be thought an example of successful adaptation to their hosts extensively. Taken advance of recent research outcomes, the parasite immunotherapy for human echinococcosis has been discussed widely by scientific literatures, but importantly, the advanced outcomes may also be interested in terms of using parasites' productions for treatment of other diseases, including cancer.

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