

## Review

# Renal echinococcosis; the parasite, host immune response, diagnosis and management

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### Abstract

Renal echinococcosis is a rare parasite-caused disease of humans and animals; it makes up about 4% of confirmed cases of cystic echinococcosis. It is a zoonotic disease that occurs in the intermediate hosts harboring the larval stage, the hydatid cyst, of *Echinococcus* spp. The renal involvement is often asymptomatic or with unspecific signs. Its diagnosis is mostly based on imaging technique. Immunodiagnostic tests are not applicable. Furthermore, because the disease is not common, our knowledge about its different aspects is scarce. In this review, the parasite, host immune response, diagnosis, and management of renal echinococcosis are described.

**Key words:** renal echinococcosis; hydatid cyst; immune response; cystic echinococcosis.

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### Introduction

Cystic echinococcosis (CE) and alveolar echinococcosis (AE) are two important neglected parasite-caused diseases with medical and public health significance [1]. Echinococcosis is a disease of humans and animals caused by different species of *Echinococcus*. The parasite's life cycle involves carnivorous animals as the definitive hosts and many herbivores and rodents as intermediate hosts. Humans can also be an intermediate host and can harbor hydatid cysts, the larval stage of *Echinococcus* [2,3]. The adults are a few millimeters long and have 3-5 proglottids; they live in the small intestine of canids and causes no or mild symptoms [2,4]. The hydatid cysts, on the other hand, may cause problems in the intermediate hosts, such as economic losses in the livestock industries [5]. In humans, CE can be serious, depending on the location of the cyst and the resulting complications. However, a considerable number of cases are asymptomatic and diagnosed only accidentally [4,6].

CE is highly endemic in central Asia, western China, South America, eastern Africa, and in Mediterranean countries. Contact with canids and raising livestock are said to be the main risk factors for the disease. However, active transmission via wildlife has also been reported [7]. Human CE has been

eliminated from New Zealand and Tasmania was provisionally CE-free [8], but *E. granulosus* is still present on the Australian mainland and is found in wild and rural dogs in Tasmania [9]. The elimination and the reduction in the prevalence of CE have been achieved by long-term efforts towards prevention and control measures, mostly directed to deworming dogs using antihelminth drugs, meat inspection, health education, and surveillance in human and livestock populations. Human CE continues to be a significant but neglected zoonotic disease in numerous countries, especially in resource-poor pastoral areas [8].

The incidence of human alveolar echinococcosis (AE), in contrast, has increased in continental Europe and is considered a major public health issue in some areas of Eurasia [8]. For the past 40 years, AE has been a public health issue in parts of Japan. Studies in China have revealed a considerable incidence of AE on the Tibetan plateau and interestingly showed that AE, especially in children, is more prevalent than CE in some areas [7]. There are an estimated 18,235 new cases of AE per year globally, of which 91% are found in China. The majority of these patients live in regions where treatment is not widely available, and consequently, the disease will be fatal. It is estimated that AE results in a median of 666,434 Disability-

Adjusted Life Years (DALYs) per annum. This makes AE one of the very important diseases in particular populations on the Tibetan plateau [10]. The prevalence of *E. multilocularis* infection in definitive and intermediate hosts in Europe is shown to have increased in the first 15 years of the 21<sup>st</sup> century. Also, the endemicity of fox infections is more expansive than it was. Urban foxes can be important in the transmission of AE [7]. Human AE cases have been reported in European countries which were previously known to be AE-free. Moreover, the incidence of AE has doubled in the endemic regions of Germany, France, Switzerland, and Austria [7,11-13].

The taxonomy of the genus *Echinococcus* was controversial for many years. From the oldest descriptions of *Echinococcus*, the genus exhibits significant variability at the species level with regard to host specificity, antigenicity, morphology, development rate, and transmission cycles. In the latest classification of *Echinococcus* based on the review by Thompson (2017), it is categorized into ten species, which cause different diseases. They are as follows: *E. granulosus* (causes CE), *E. equinus* (causes CE), *E. ortleppi* (causes CE), *E. intermedius* (causes CE), *E. canadensis* (causes CE), *E. felidis* (not defined), *E. multilocularis* (causes AE), *E. shiquicus* (causes AE), *E. vogeli* (causes polycystic echinococcosis, PE) and *E. oligarthra* (causes PE) [4].

In the intermediate animals, the microvilli on the surface of the developing metacestode [14], the size of the oncospheres, and the size of the venules and lacteals in different hosts may determine where hydatid cysts will be located among different organs [4]. In primary CE, hydatid cysts may develop in almost any organ. Nearly 80% of patients with CE have a involvement of a single organ with a solitary cyst localized in the liver or lungs [15]. However, multiple organ involvement is also possible [16]. The liver/lung cyst localization ratio may vary from 2 to 1 in symptomatic patients and up to 9 to 1 in asymptomatic ones. The metacestodes first face the liver, and in some cases, it localizes in there. Larvae that escape the hepatic filter may be carried by the bloodstream to the lungs or less frequently further organs, e.g., to the kidneys, bone, brain [17], heart [18] or muscle tissue [19].

The incidence of human CE is different around the globe, ranging from 0.122 to 15 per 100,000 humans [20]. The incidence of CE in human cases in Iran is estimated at 1.18 to 3 per 100,000 inhabitants (overall incidence: 0.61) [21]. Renal echinococcosis is quite a rare disease compared to the hepatic and pulmonary CE; it makes up about 4% of confirmed cases of hydatid

disease. With regard to the location of the cysts, in 37% of renal cases, the cysts were located in the upper pole, 34% were in the lower pole, and 16 in the mediorenal region. The cyst caused kidney damage in 12% of renal echinococcosis patients. The size of renal hydatid cysts, based on the report from Zmerli *et al.* (2001) [22], ranges from 2 to 22 cm. In 2% of these cases, the cyst was also found in the liver, 1% in the lung, and 0.5% in the spleen. Furthermore, 25% of renal hydatid cysts are reported to have ruptured into the urinary tract [22].

The kidney is frequently prone to cyst formation in the human body; cysts are estimated to occur in 5% of humans. Treatment of simple non-hydatid cysts of the kidney is based on existing complications. Percutaneous aspiration and sclerotherapy are the first-line therapies for these kinds of cysts. Surgical decortication is commonly used for recurring or sizeable symptomatic cysts. Surgery, such as laparoscopy, is highly successful and is linked with minimal morbidity. Retroperitoneal surgery is generally preferred for cysts, especially for renal hydatid cysts, to avoid leakage of hydatid fluid into the peritoneal cavity [23]. Diagnosis of renal echinococcosis can best be achieved by imaging. Serological tests for anti-hydatid cyst antibody are usually give false negative results, although positive reactions have been reported [24].

Most hydatid cysts occur in the right lobe of the liver, perhaps in relation to the anatomy of the liver vein. It may be the same factor affecting renal cysts, which are more often reported from the left kidney than the right one. The latter situation is thought to be influenced by the fact that the left renal artery is shorter [25].

### **Parasite genetics and renal echinococcosis**

The *Echinococcus granulosus* complex includes different species, which have different genotypes, namely *E. granulosus* (G1, G2, and G3 genotypes), *E. equinus*, *E. ortleppi*, *E. intermedius* (G6 and G7 genotypes), *E. canadensis* (G8 and G10), and *E. felidis* [4]. Among these, *E. granulosus* is responsible for most of the human infections [26]. There are speculations about the different genotypes/species which may have a different tendency for different organs. For example, Sadjjadi *et al.* (2013) reported that *E. intermedius* G6 has a high affinity for the human brain. In their report, all of the eight cerebral hydatid cysts they found belonged to *E. intermedius* G6 [27]. Few studies have evaluated the genetic characteristics of human isolates of renal hydatid cysts [26,28,29]. In these studies, the genotypes isolated from the kidney belonged to *E. granulosus* (G1-G3, strain not defined) [28,29], and *E.*

*granulosus* G1 [26]. There have been no comprehensive studies as yet on renal echinococcosis focusing on the parasite genotype, and no evidence has been presented to support the idea that a specific genotype has a high affinity for human kidneys.

## Immunology and immunodiagnosis

### *Humoral immune response and immunodiagnosis*

In CE, an IgG response against hydatid cyst fluid and oncospherical antigens is detectable at two and 11 weeks post-infection, respectively, in the animal model [1,30]. The anti-oncospherical antibodies have a significant role in the parasite killing and are essential to produce protective immunity against *E. granulosus* infections in intermediate hosts [31]. It is also suggested that antibody concentrations are low at the beginning of the infection (early stages), while the parasite-killing mechanisms that exist against hydatid cyst may be attributed to antibody-dependent cell-mediated cytotoxicity [1,32].

In chronic CE, elevated antibody levels are detectable mainly for IgG (predominantly IgG4), and IgE [33,34,35]. This increased antibody production is thought to be critical for the advancement of immunological tests [1]. However, from 15% to nearly 40% of patients with CE are reported to be antibody-negative [36]. In many antibody-negative patients, certain levels of circulating antigens and circulating immune complexes are detectable [30]. This observation suggests that there is activation and proliferation of B lymphocytes, which may be regulated and inhibited by the parasite antigens, but whether the mechanism/s are directly targeting B cells or working through regulatory mechanisms of T cells is not known [1].

It has been suggested that immunoglobulins play a role in false immunological test results for echinococcosis. A false-negative immunodiagnosis could be caused by the inactive status of the hydatid cysts, whereas false positives could be caused by previously ruptured cysts, and by cross-reactions among the antigens. Diagnosis of renal echinococcosis can best be achieved by imaging techniques, because of the unreliability of immunodiagnostic tests [24]. Hydatid cyst fluid, protoscoleces, and laminated layer-derived antigens were investigated for the detection of CE in humans using western blots; a 20 kDa band of the hydatid cyst fluid appeared to be an appropriate antigen for immunodiagnosis of human CE [37].

Antigen B (AgB) [38] and Antigen 5 (Ag5) [36] are hydatid cyst fluid-derived antigens and are among the most studied antigens for immunodiagnosis of CE.

These antigens are not specific to *E. granulosus* and can be found in *E. multilocularis* and *E. vogeli* infections. Also, fairly high concentrations of anti-Ag5 were detected in the sera of *Taenia solium* infected patients [39]. The tumoricidal activity of different antigens of hydatid cyst was also evaluated on a range of tumor cells, and some showed promising effects [40-43]; even some common antigens were described between tumors and hydatid cyst [44-46].

The performances of the available serological tests for human CE are not adequate, and the question of which immunological test is better is still the subject of debate among researchers. Despite the fact that several immunodiagnostic tests have been developed, mostly based on hydatid cyst fluid antigens (AgB and Ag5), they are unsatisfactory for the diagnosis of human CE [36]. The situation is even worse for the serological diagnosis of renal CE, because most patients give false negative results [1,22]. The Casoni skin test for hydatidosis is reported to be positive in only 21.5% of patients. Hemagglutination-inhibition (HI) and immunoelectrophoresis tests may become positive in 60% and 66% of the patients, respectively [47]. The clinical diagnosis of echinococcosis needs a combination of ultrasonography and immunodiagnosis, which is suggested to be the necessary complementary confirmation [48].

### *Cellular immune responses*

In the early post-infection phase (establishment phase) of hydatid cyst, marked activation of cell-mediated immunity, including some cellular responses and pathological changes, can be measured. Cellular infiltration, including eosinophils, macrophages, neutrophils, and fibrocytes, occurs around the newly located larvae in human infections [1,49]. In these early stages of oncosphere establishment, the parasite is very vulnerable to antibody-mediated complement-dependent killing [50,51]. In naturally acquired infections, the antibody-mediated immune response may be supplemented by a considerable cellular inflammatory response consisting of macrophages, neutrophils, eosinophils, and lymphocytes in the early four weeks post-infection in sheep. A similar formation of granuloma has been reported from experimental secondary infections with protoscoleces in mice, where immune response-mediated parasite-killing is also documented [51]. However, this usually does not produce a severe inflammatory response, and as they age, the cysts become surrounded by a host-derived fibrous layer that separates the parasite from host tissue [1].

As the parasite is vulnerable to killing by immunological responses during the early establishment phase, the existence of degenerating or dead cysts at different later stages of its development suggests that later killing, even though possibly less intense, can arise during the established stage. However, the causes of parasite death in the later phases are not clearly known to be immunologically mediated. The strain/genotype/species of the causative *Echinococcus*, the intermediate host, and the involved organ can be factors influencing the different levels of parasite development [51-53]. From studies on experimental infections by *Echinococcus*, it becomes obvious that hydatid cysts from the same genotype of the parasite, developed in the same organ in the same individual host, can display substantial variations in their growth, principally considering their size, viability, and fertility [51].

Two cytokine patterns are described for CD4<sup>+</sup> T helper cells in the mouse model, including type 1 helper T cells (Th1), which release interleukin (IL)-2, tumor necrosis factor-beta (TNF $\beta$ ), and gamma-interferon (IFN $\gamma$ ), and Th2 cells producing IL-6, IL-4, IL-5, and IL10 [54]. Helminth infections are proposed to have immunoregulatory potential, such that Th2-type responses play a central role in chronic helminthiasis [55]. It is also proposed that a Th2-type response favors the establishment of the larvae of *Echinococcus*. The Th1-type immune response is regarded as lethal for the parasite in the intermediate hosts. Nevertheless, the situation is not that simple, because often there is a mixed Th1/Th2-type immune response in infected intermediate hosts. Furthermore, regulatory activities by the parasite possibly aim to control the Th1 and Th2 parasite-killing effector mechanisms [56,57]. It has been suggested that in the early phases of experimental infection with protoscolexes, a mixed Th1/Th2-type cytokine response with elevated concentrations of IL-10 will develop [58]. Elevated levels of IFN $\gamma$  [59] and IL-5 are also reported in mice inoculated with the protoscolexes. The initial production of IL-4 and IL-10 may be influenced by the parasite as a mechanism to facilitate its establishment [58]. A high level of IL-4, a Th2 cytokine, was reported in the pericyst of bovine hepatic hydatid cysts [60]. It is not yet clear why the parasite may induce both Th1 and Th2-type cytokine profiles, considering that they typically downregulate each other [1].

The characteristic Th1/Th2-type cytokine profile is also associated with the antigens and the levels of antigen released from the cyst. The AgB released from *E. granulosus* tilts the cytokine ratios towards an immunopathology-linked Th2 polarization, chiefly in patients with progressive infection. This type of immune modulation may be one of the mechanisms of immune evasion of the parasite from host immune defense [61].

#### *Fibrous layer and immune response*

The initial intensity of host cellular inflammatory reaction varies among hosts and rules the destiny of the developing larvae. A too-intense reaction will cause death and degeneration of the parasite, while in an appropriate intermediate host, the early reaction resolves and leaves a fibrous capsule. The latter circumstance is usual when a steady host-parasite relationship has evolved [4]. The fibrous layer (also called adventitia and pericyst) is a host-derived capsule [51] which encloses hydatid cysts and occurs in the renal cyst as well [62]. It is also important for the local immune response against the parasite [51,63]. In large hydatid cysts, its thickness may reach several millimeters and it is made up of several layers adjacent to the normal parenchyma of the organ harboring the cyst [51,63]. The pericyst acts to isolate the cyst from the surrounding host tissue and is a consequence of granulomas, which have become fibrotic elements containing collagen fibers. The fibrous layer may also encompass several cell populations such as macrophages and eosinophils. In inactive (dead) cysts, the adventitial layer calcifies, a process regulated by TGF-Beta1 [51,64].

#### *Cellular composition of pericyst*

The host reaction site, just behind the fibrous layer of the renal hydatid cyst, is reported to be similar to that of the liver. The palisading macrophages are the first immune cell line after the fibrous elements, and behind them, infiltrations of immune cells appear, mostly T cells (CD3<sup>+</sup>). Among the T cells, CD4<sup>+</sup> T helper cells (Th cells) are predominant in number, followed by CD8<sup>+</sup> cytotoxic T cells (CTL). Regulatory T cells (Tregs) are also present in considerable numbers, yet natural killer cells (NK) are rare in the host reaction site of renal hydatid cysts. B cells are present in large numbers, which may be aggregated as granulomas in different areas of the host reaction site, surrounded by T cells. Eosinophils are also present in large numbers, scattered around the host reaction site [65].

## Signs and symptoms

Most patients with renal echinococcosis are asymptomatic or have nonspecific symptoms, and the cyst/s is discovered during screening for other purposes. Reported symptoms include a constant dull pain in the flank, nausea [66], lumbar or abdominal mass similar to a tumor, subcostal pain, abdominal distension, vomiting, and hydatiduria [22]. The reported prevalence of clinical symptoms is as follows: lumbar pain (80% of patients), a palpable mass (25% of patients), fever (10% of patients), and nausea and vomiting (10% of patients). Eosinophilia (30% of patients), pyuria (25% of the patients), and hematuria (20% of the patients) may also be seen in patients with renal hydatid cyst. Furthermore, hydatiduria is rare but happens in the case of communicating cysts [47].

## Imaging

### *Radiography*

In radiography, a soft-tissue mass or spherical calcifications in the kidney region may represent a renal hydatid cyst [67]. Caliceal distortion is the major finding during excretory urography, followed by caliectasis and kidney function loss [22].

### *Sonography*

The typical ultrasound finding is anechoic lesions with well-distinguished borders. Based on the classification by the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE), the ultrasound features of hepatic CE are sorted as CE1 to CE5. CE1 is characterized by round to oval, unilocular, echo-free cysts, regularly double-walled. Free-floating protoscolices can cause a “snowflake effect” when the patient’s position is shifted. In CE2 category, the daughter cysts are observable as “wheel spokes” or a “honeycomb” pattern surrounded by a mother cyst. CE1 and CE2 are indicative of active cysts. CE3 (CE3a/CE3b) indicates the transitional stage of the cysts, yet activity is also possible. In this stage (CE3), the laminated layer of the cyst’s inner side breaks up, showing a degenerative process, and in this stage, the “water lily” sign can be noticed. CE4 corresponds to heterogeneous structures inside the cysts with the look of a “ball of wool.” In the CE5, a bow-like calcified thick cyst wall results in a conical ultrasound shadow. In the CE5 category, there are no visible protoscolices. In the CE4 and CE5 stages, the cysts are inactive [15,68].

The ultrasound observation of a layer of liquid material between the layers with no posterior echoes inside and a tumor-like mass, called the “spiral sign,”

may help to differentiate inactive cysts from renal tumors [67,69]. Moreover, the existence of daughter cyst/s and echoic layer remains, co-existence of hydatid cysts in other organs [67], and a positive serology test [66] favor renal hydatidosis. In inactive lesions, ring-like calcification also appears in the adventitial layer of the hydatid cysts [67].

### *Computed tomography*

A cyst with a thick or calcified membrane, a multiloculated tumor-like mass with heterogeneous internal density, a unilocular mass with a detached wall, and daughter cyst/s with lower density compared to the maternal matrix are typical findings for renal echinococcosis using standard computed tomography (CT scan). The cyst membrane in CE1 can be defined better using a contrast-enhanced CT scan compared with ultrasound [67,70]. Finding daughter cyst/s on CT scan helps to discriminate hydatid cysts from kidney abscesses. CT scan can also help in the diagnosis of inactive hydatid cysts, which looks similar to pseudotumor. This technique can also reveal other organ involvement for hydatid cysts [67].

## Management

### *Surgery*

The optimal treatment for renal echinococcosis is surgery. Surgical management of kidney hydatid cyst can vary and requires pericystectomy or nephrectomy, depending upon the remaining functional parenchyma. Leakage from the cyst should be avoided, because it can cause recurrence or severe anaphylactic shock. Renal hydatid cyst is rare, but it is a quite dangerous disease if not diagnosed precisely [66]. With the surgical approach, either a conservative or a radical cystectomy can be done, depending on the nature of the cyst and the remaining non-damaged renal tissue. The empty cavity that remains after cystectomy is cup-shaped and can be improved by U-stitches applied to the two kidney valves; for a few days a catheter should be placed between them [22]. Nephrectomy is required for about 25% of renal echinococcosis cases but is suggested only for destroyed kidneys as a result of old, infected, and open cysts. Recently, percutaneous treatment of renal hydatid cyst has been presumed to be safe, but the reported experience is still inadequate [22,71-73]. It is recommended not to treat cyst lesions (CL) until their parasitic nature is confirmed [15]. The heterogeneous appearance of inactive cysts should be distinguished from other lesions like abscesses, infected renal cysts, and tumors [67,73]. Rarely there is operative or

postoperative mortality after cystectomy, and most patients will be cured and will live well [47].

### Chemotherapy

Chemotherapy with albendazole as adjuvant therapy may be used for renal hydatid disease [25,74,75]. The surgical approach is the ultimate treatment with a high cure rate, and most of the patients will be completely cured; however, surgery cannot entirely prevent a recurrence. The prescription of albendazole for six months after cystectomy is suggested for the prevention of recurrence. Moreover, albendazole is recommended for patients with liver or lung CE that are not suitable for surgery, for patients with multiple cysts in different organs, and/or peritoneal hydatid cysts [25].

In hepatic CE, surgery is only suggested for the management of CE2 and CE3, while chemotherapy and percutaneous treatment are suggested for CE1, CE2, and CE3a/CE3b. The cysts in CE4 and CE5 stages are inactive; no treatment is required as long as there are no complications, and the preferred strategy is a “watch and wait” approach [15].

### Concluding remarks

Renal echinococcosis is a rare disease, yet it can be serious. Very little information is available about genotypes of the parasites causing renal CE. More work on the immunology of renal echinococcosis is recommended. Its diagnosis is complicated and cannot be based solely on immunological techniques. However, imaging techniques are very valuable for the diagnosis of the disease. The treatment is mostly based on conservative or radical cystectomy; radical nephrectomy should be avoided if the renal parenchyma is not destroyed.

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