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# *Echinococcus granulosus sensu lato* and *Echinococcus multilocularis*: A review

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ABSTRACT

*Echinococcus* spp. have a global distribution and are found on every continent except Antarctica. Infections with these parasites are considered extremely serious, contributing to significant morbidity and mortality in addition to substantial economic losses to the livestock industry. *Echinococcus granulosus* sensu lato *(s.l.)* and *Echinococcus multilocularis*, causing cystic echinococcosis (CE) and alveolar echinococcosis (AE) respectively, are the two main species of interest from a human and veterinary perspective. This review collates the current state-of-the-art understanding of these two parasites within four key areas of relevance to human and veterinary professionals: transmission and epidemiology, clinical signs and pathogenesis, diagnosis, and treatment and prevention. This review should serve as a broad introduction to the most important *Echinococcus* spp. The reader is advised to seek out specific literature on individual diseases and their causative parasites for a deeper understanding.

## 1. Introduction

*Echinococcus* spp. are Taeniidae cestode parasites with the genus *Echinococcus* comprising of eight currently recognised species and one genotypic cluster (*E. canadensis*). These parasites utilise a predator-prey relationship in their transmission and the genus has a cosmopolitan distribution, found on every continent except Antarctica. Some *Echinococcus* spp. are transmitted via predator-prey cycles that involve domestic animals, others utilise lifecycles involving wildlife species although domestic animals can contribute to transmission (Romig et al., 2017). All species in the genus have been reported or are suspected to be zoonotic but one species complex *E. granulosus sensu lato (s.l.)* and one species, *E. multilocularis,* represent a significant public health concern: with the former causing cystic echinococcosis (CE) and the latter alveolar echinococcosis (AE) (Deplazes et al., 2017).

These parasites cause disease in both humans and animals, responsible for serious health and economic problems and are two of the most widespread zoonoses of medical importance (Deplazes et al., 2017)). *E. granulosus s.l.* was previously considered to be a single species but is now recognised as an assemblage of cryptic species with differing host specificity which includes pathogenicity and infectivity to humans. *E. granulosus s.l.* is currently subdivided into *E. granulosus sensu stricto* (*s. s.*) (with the genotypic variants G1-G3), *Echinococcus felidis, Echinococcus equinus, Echinococcus ortleppi* and *Echinococcus canadensis* (genotypic variants: G6/G7, G8 and G10) (Romig et al., 2015; Vuitton et al., 2020). Although *E. granulosus s.s.* appears to be the most important in humans and livestock (Andresiuk et al., 2013; Tamarozzi et al., 2020), in this review we will consider all variants in the *E. granulosus s.l. complex*. *E. granulosus s.l.* does not typically cause evident disease in animals while alive and as such is not prioritised from an agropastoral perspective; however, it can cause economic losses through condemned carcasses and reduced carcass weights (Cardona and Carmena, 2013). *E. granulosus s.l.* is predominantly transmitted between dogs and various intermediate hosts but, rarely, involves a predator-prey wildlife cycle without anthropogenic involvement (Tamarozzi et al., 2020).

*Echinococcus multilocularis* (the small fox tapeworm) is widely distributed within but restricted to the Northern Hemisphere. Although phylogenetic studies have identified the species as a separate entity from the *E. granulosus* complex, the genus is complex leading to difficulties in interpreting its taxonomy (Knapp et al., 2015). The parasite is predominantly transmitted via a wildlife cycle involving canids (typically foxes) as definitive hosts and various species of rodent serving as intermediate hosts. However, dogs and cats can also serve as competent definitive hosts (Kapel et al., 2006).

AE is an extremely serious disease, with considerable human cost in Asia, particularly the autonomous region of Tibet, mainly attributable to the lack of curative treatment options (Lundström-Stadelmann et al., 2020). Although not as pathogenic to human patients, CE is responsible

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for a substantial public health burden in addition to significant economic costs, and its endemicity is more widely distributed (Budke et al., 2006; Battelli, 2009).

In a recent assessment aimed at prioritising important foodborne parasites in Europe based on numerous criteria including the economic impact in poor communities, risk of introduction, and occurrence of illnesses attributable to the parasite and morbidity severity, AE was listed as most important with CE fourth out of 93 species under consideration (Bouwknegt et al., 2018). *E. granulosus* (whether this refers to *s.s. or s.l.* is not specified in Bouwknegt et al., 2018 but it is likely to be predominantly *s.s.* e.g. (Umhang et al., 2020)) was however listed as the most important foodborne parasite in South-Western and South-Eastern Europe with *E. multilocularis* listed second in these regions (Bouwknegt et al., 2018).

In Africa, studies have shown that there is active transmission of *E. granulosis s.l.* between humans and animals (including wildlife) in countries previously not considered to be endemic (Rojas et al., 2014; Deplazes et al., 2017) including hyperendemic areas in Libya, Tunisia, Algeria and Morocco and *E. multilocularis* appears sporadically in Tunisia and Morocco (Dakkak, 2010). CE constitutes a severe threat in the Mediterranean countries with high prevalence in Spain, certain areas in Italy, Greece and Turkey (Dakkak, 2010). In South America, five thousand cases of CE are diagnosed annually from Argentina, Brazil, Chile, Peru and Uruguay (Pavletic et al., 2017). In central Asia, for both species combined, 270 million people live with the risk of becoming infected and the parasite is re-emerging in a number of countries, including Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan (Casulli, 2020).

Due to the significant morbidity associated with *E. granulosus s.l.* and *E. multilocularis* and the substantial economic impacts resulting from *E. granulosus s.l.*. infection in livestock, this review will focus on these two species, exploring the latest research in their transmission and epidemiology, clinical signs and pathogenesis, their diagnosis and finally prospects for treatment, control and prevention. However, certain compromises and generalisations need to be made in a review paper seeking to combine two separate species with different life-histories. Therefore, this review should be viewed as a broad introduction for the two parasites in the *Echinococcus* genus most significant to human and animal health. The reader is advised to seek out specific literature on the individual species for greater detail.

## 2. Transmission and epidemiology

The lifecycles for all *Echinococcus* spp. are indirect with the definitive and intermediate hosts as predator and prey species respectively. The adult worm is found in the small intestine of the definitive host and sheds eggs into the environment with faeces. The eggs are ingested by the intermediate host and develop into a metacestode. Metacestodes are considered fertile after the development of protoscoleces, and the cycle is completed when the infected organs of the intermediate host are ingested by a definitive host (Romig et al., 2017).

The distribution of *E. multilocularis* and *E. granulosus s.l.* in both animal and human hosts has been extensively reviewed in recent literature, see (Davidson et al., 2016; Cardona and Carmena, 2013; Carmena and Cardona, 2013, 2014). *E. granulosus s.l.* has a worldwide distribution with endemic areas on six continents (Deplazes et al., 2017).

*E. multilocularis* is restricted to the Northern hemisphere, with no known endemic areas further south than Tibet and the Sichuan province in China (Deplazes et al., 2017; Feng et al., 2015). The true distribution of *Echinococcus* spp. in both humans and animals is likely underestimated. Logistical constraints, such as costs associated in diagnosis and difficulty in obtaining and safely analysing samples with respect to public health, limit studies in animal hosts. Human cases are likely underdiagnosed due to limited knowledge of these parasites and a wide differential diagnosis and misdiagnosis with other similar-looking but more common disorders (e.g. hepatocellular carcinoma and other forms of liver cancer and cirrhosis) and limited availability of advanced diagnostic techniques (Vuitton et al., 2015). Patients with low economic status, who incidentally could have a higher risk of parasite exposure due to, for example, a pastoral lifestyle, may not have the opportunity to seek medical help (Deplazes et al., 2017). Furthermore, there is a lack of mandatory and coordinated reporting, even within the developed countries of Europe (Rossi et al., 2016) making estimates of disease burden and incidence difficult to determine. However, the European Centre for Disease Prevention and Control (ECDC) has compiled all information available on incidence rates (of CE and AE combined) for the majority of EU/EEA countries from 2012 to 2016 (ECDC, 2016) and recent coordinated initiatives such as the HERACLES project (Human Echinococcosis Research in Central Eastern Societies) have attempted to more comprehensively understand the burden of disease e.g. (Tamarozzi et al., 2018).

Occurrence of *Echinococcus* spp. in recent decades has remained relatively stable, but with some fluctuations noted in limited areas or specific countries (Deplazes et al., 2017). *E. multilocularis* is considered an emerging disease in Europe with the endemic area now expanding as far north as Sweden (Davidson et al., 2012, 2016). Increased reports in animals and humans may be due to increased awareness but also unintended introductions via movement of animals and goods (Davidson et al., 2012). In Switzerland, a country with reliable medical records dating back to the 1950s, annual incidence of AE in humans was reported to have nearly doubled in the early 2000s (Schweiger et al., 2007). An increase in the fox population after the successful rabies campaign in the 1980s and the increasing occurrence of foxes in urban areas probably contributed to this upturn in human cases (Schweiger et al., 2007; Liccioli et al., 2015).

Although these lifecycles exist in both domestic and sylvatic environments, *E. granulosus s.l.* is best known as a parasite of concern in domestic animal systems and *E. multilocularis* as a parasite of wildlife. The most common definitive host for *E. granulosus s.l.* worldwide is the domestic dog with domesticated sheep, goats, camels, pigs and equids as intermediate hosts (Romig et al., 2017). There are also reports of wild canids (wolves, coyotes) and felids acting as definitive hosts and wild ungulate species acting as intermediate hosts with the subspecies of the *E. granulosus s.L.* complex determining proclivity to their intermediate host (Romig et al., 2017; Laurimäe et al., 2018; Romig et al., 2015). The most common definitive host for *E. multilocularis* worldwide is the red fox (*Vulpes vulpes*); however, other canid species, such as wolves, raccoon dogs (*Nyctereutes procyonoides*) and domestic dogs, and to some extent felid species can also host the tapeworm (Romig et al., 2017). Intermediate hosts are small mammals, namely rodents, such as vole and pika species (Romig et al., 2017).

Infection of the definitive hosts is facilitated through the predator-prey relationship. This is particularly true in the case of *E. multilocularis* and the sylvatic lifecycles for *E. granulosus s.l.*. In the case of *E. granulosus s.l.*, transmission in domestic animal production systems is augmented by uncontrolled slaughter practices whereby dogs (or other wild canids) can access contaminated offal (Romig et al., 2017). Infection of intermediate hosts is somewhat unclear but is reliant upon the host ingesting parasite eggs. While some animals, particularly rodents, may eat infected faeces, eggs are more likely dispersed into soil and onto plants via rain, insect fomites and wind, then taken up as intermediate hosts graze or ingest soil (Tamarozzi et al., 2020). The limited movements of both the intermediate hosts, particularly in the case of rodents, as well as the propensity for the host species to optimize foraging by targeting concentrated areas of prey species, leads to the formation of micro-foci of parasite transmission in the environment (Giraudoux et al., 2002).

Although *Echinococcus* spp. appear to occur in a variety of host species, metacestode development and fertility as well as adult worm development and fecundity are optimized in certain host species. This may be due to ecological and morphological adaptations (Romig et al., 2017), but also host immunity (Gottstein et al., 2017). Fertile *E. multilocularis* metacestodes were found to develop within 95% of

experimentally infected common voles (*Microtus arvalis*) and 89% of field voles (*Microtus agrestis*) within 10 weeks, whereas only 4% of experimentally infected bank voles (*Myodes glareolus*) developed fertile metacestodes within this same time period (Woolsey et al., 2015a; Woolsey et al., 2015b, 2016). It is noteworthy that the red fox, the most common definitive host for *E. multilocularis*, has a dietary preference for the *Microtus* spp. in Europe (Guislain et al., 2008; Raoul et al., 2010), a preference which would optimize completion of the parasite lifecycle.

Humans infected by *Echinococcus* spp. are considered dead-end hosts and therefore do not contribute to the perpetuation of the parasite lifecycle. Human infection occurs faecal-orally by ingestion of viable eggs with potential routes for infection including close contact with definitive hosts which produce infected faeces, ingestion of contaminated food, water or soil, and interaction with contaminated fomites (Tamarozzi et al., 2020). AE in dogs (canine AE) is a rare disease, however, can occur due these definitive hosts ingesting eggs from contaminated vegetation or autoinfection after primary infection of adult worms (Haller et al., 1998; Corsini et al., 2015; Peregrine, 2015). Dog ownership has been cited one of the highest risk factors for both *E. multilocularis* and *E. granulosus s.l.* (Rojas et al., 2018). Infected dogs (and other definitive hosts) shed eggs in faeces and eggs from infected faeces can be retained in their fur (Torgerson and Heath, 2003). More recent investigations suggest that, at least for *E. granulosus s.l.*, interaction with concentrated areas of contaminated soil may provide the greatest risk for infection (Tamarozzi et al., 2020). Although presence of taeniid eggs and *Echinococcus* DNA has been documented in food (e.g. (Malkamäki et al., 2019; Federer et al., 2016)), the significance of transmission via food and water sources remains unclear (Rojas et al., 2018; EFSA, 2018).

Median incidence per 100,000 inhabitants was calculated at 0.6 (95% UI 0.4–5) for CE and 0.1 (95% UI 0.01–0.2) for AE with the highest median incidence in the European and South-East Asian Regions for CE followed closely by the African and Eastern Mediterranean regions (WHO, 2015; Torgerson et al., 2015). Median incidence per 100,000 inhabitants for AE was highest in the European and Western Pacific Regions (Torgerson et al., 2015). China is estimated to be responsible for over 90% of AE cases worldwide (Torgerson et al., 2010). In 2015 the human burden for both species combined was 871,000 disability adjusted life-years (DALYs). Individually, CE accounted for 184,000 DALYs (95% UI 88,100–1.59 million) with AE 688,000 (95% UI 409,000–1.1 million) (WHO, 2015; Torgerson et al., 2015).

## 3. Clinical signs and pathogenesis

Both CE and AE are chronic, severe diseases in which the juvenile metacestode stage of the parasite grows, in most cases, as intrahepatic lesions. After ingestion of viable eggs, oncospheres (early stage larvae) of the parasite migrate to the liver where they establish a germinal layer (GL) in the form of a small cyst. After 7–10 days the parasite has developed a laminated layer that appears crucial for parasite protection from host immunity. With *E. multilocularis,* initial cysts remain small and begin to generate external buds that typically remain attached but occasionally detach from the parent cyst forming a 'multilocular' metacestode. Multiplication of the metacestode is continuous with the speed of growth dependent on the localised host immune response. *E. granulosus s.l.* is not capable of external budding like *E. multilocularis* and thus this metacestode increases in size concentrically forming a single hydatid cyst. For both parasites, the GL has the potential to produce 'brood-capsules' which in turn produce protoscoleces (Gottstein et al., 2017).

Although the incubation period of CE infection is variable, *E. granulosus s.l.* metacestodes will cause clinical symptoms once they reach a certain size and begin to exert pressure on host tissue manifesting in a range of pathologies (Ammann and Eckert, 1996; Kern et al., 2017). Still, most infections are asymptomatic unless complications occur. Clinical signs for CE are usually not pathognomonic but systemic immunological reactions may manifest such as asthma and anaphylaxis (Eckert et al., 2001).

The asymptomatic phase is undefined but may persist for many years (Eckert et al., 2001). While most CE infections exhibit single organ infection with a single metacestode, 20% of infections have multiple organ involvement (Eckert et al., 2001). Primary organ involvement can include a range of other organs and although secondary infections occur this is typically due to invasive treatment causing traumatic rupture of the cyst, thereby releasing protoscoleces. The course of CE infections and the subsequent prognoses are dependent on the primary infection location; hepatic and pulmonary locations are by far the most common, with approximately 70% of cases occurring in the liver and 20% causing pulmonary echinococcosis (Ammann and Eckert, 1996; Eckert et al. 2001; Budke et al., 2013; Pham et al., 2019).

With hepatic infections, the right lobe of the liver is affected most often. Disease progression is typically slow and does not involve identifiable clinical symptoms, but complications can occur through septic, toxic or mechanical issues in 21% of patients. Symptoms can involve abdominal pain, fever, and a rash indicating an allergic reaction (Kern et al., 2017). 13–37% of hepatic infections present with a cysto-biliary fistula (Demircan et al., 2006). For pulmonary infections, cysts are usually acquired during childhood and cases involving multiple cysts usually make up 30% of cases (Kern et al., 2017). Seldomly, lung metacestodes can develop secondarily due to hepatic cyst rupture. Nonspecific symptoms of pulmonary CE can include chest pain, haemoptysis and chronic cough (Santivanez and Garcia, 2010). Atelectasis or pneumonia may result from cyst bronchi compression and the presentation of an urticarial rash with or without fever may result from ruptured cysts. Other commonly reported infection localities include the spleen, peritoneum, kidneys, bone and the brain and spinal cord. Renal cysts (comprising 1–4% of CE cases) result in nonspecific pathology but can include pain in the lumbar region (Kern et al., 2017). Bone CE, although very rare (<1% of cases), causes severe pathology with mortality rates >50% (Zlitni et al., 2001).

The establishment of *E. multilocularis* larvae is always asymptomatic and can take years before lesions become apparent (Kern et al., 2017). Except for immunosuppressed patients, the incubation period is estimated to last 10–15 years for most cases (Ammann and Eckert, 1996); however, the parasite can proliferate for decades before the infection is noticeable (Kern et al., 2017).

In Western Europe, most infected individuals present symptoms at 50–60 years, cases in children are very rarely reported, and there has not been any observed gender skew in infection. This is not reflected in Asian countries where infections are diagnosed at 40–50 years with a greater proportion of cases in young adults and females. Abdominal pain, jaundice and cholestasis are the most predominant initial symptoms (Kern et al., 2017). To a lesser extent than for CE, the location of the lesions in the liver is a greater determinant of disease severity with lesion size of secondary importance (Bresson-Hadni et al., 2000). If the parasite is located centrally, infection typically manifests with less severe symptoms, but lesions situated close to the hepatic veins or inferior vena cava can result in a Budd-Chiari- like presentation. Metastasis is more likely when the parasite is located close to these vessels, leading to secondary lesions in other organs (i.e. lungs and heart) and a more severe prognosis. Infections in the periphery of the liver are the least severe and remain asymptomatic for longer with symptoms appearing after lesions have attained a significant size. Death usually results from complications arising from major liver resection, septic shock, liver failure, biliary cirrhosis leading to gastrointestinal bleeding or cerebral AE (Kern et al., 2017).

## 4. Diagnosis

In livestock CE detection typically occurs at slaughter. Slaughterhouse surveys are often conducted to assess the prevalence of CE in cattle, sheep and pigs e.g. (Chihai et al., 2016) although it is possible to

detect the parasite in livestock through serological investigations (Bulashev et al., 2017; Golassa et al., 2011). Canine echinococcosis can be diagnosed either post-mortem or purged from the intestines; however, neither of these methods are appropriate for mass screenings (Abbasi et al., 2003). Typically, *E. granulosus s.l.* in dogs is diagnosed via faecal examination followed by a range of molecular confirmation techniques including enzyme-immunoassay (EIA) (Moro et al., 1999) or PCR (Abbasi et al., 2003).

In the intermediate host, *E. multilocularis* detection is identified via trapping/euthanasia followed by necropsy with identifiable lesions in the liver confirmed via PCR targeting the mitochondrial gene of 12S rRNA (Stieger et al., 2002) or the NADH dehydrogenase subunit 1 (Trachsel et al., 2007) e.g. (Miller et al., 2016; Avcioglu et al. 2017). In definitive hosts the prevalence of the parasite is often determined in screening studies testing faecal samples from, typically fox, but also dogs and cats collected from the environment and copro-DNA and antigens identified via PCR (e.g. Poulle et al., 2017) and ELISA (e.g. Buishi et al., 2005) respectively. Infected definitive hosts can be examined directly, using carcasses obtained from road-killed animals or through hunting or trapping. The post-mortem analysis of intestinal content e.g. the sedimentation and counting technique (SCT) is considered the "gold standard" diagnosis, as it allows the visualisation and morphological identification of adult *E. multilocularis* worms (Tackmann et al., 2006; Umhang et al., 2011).

In humans, CE diagnosis is performed via abdominal ultrasound (US) examinations both at individual and population level. This technique is also capable of imaging parasitic cysts when located peripherally in the lungs. Other imaging techniques include computed tomography (CT), magnetic resonance imaging (MRI) and microscopic detection of protoscoleces in aspirated cyst fluid and conventional X-Ray for detection of pulmonary cysts (Eckert et al., 2001; Brunetti et al., 2010). A standard cyst classification scheme was put in place by the World Health Organisation Informal Working Group on Echinococcosis (WHO-IWGE) in 1995 which organised cysts into three main groupings: active (CE1 and 2), transitional (CE3) and aborted (CE4 and 5). This classification scheme is used as the basis for present diagnostic guidelines (Brunetti et al., 2010). Immunodiagnostics are viewed as a supportive tool in CE diagnosis due to limitations in sensitivity and specificity but may be particularly useful in cases where cysts are not clearly definable on imaging.

Similar imaging methods, in particular US, are used for diagnosis of AE. In 70% of AE cases, lesions appear in one of two forms: 1) a lesion characterised by irregular liver borders due to the invasive growth of the metacestode 2) a large hepatic lesion containing a central necrotic area surrounded by a ring of parasitic fibrous tissue. In the remaining 30% of cases, small fibrous nodules are visualized and represent early AE infections. These can often be misdiagnosed as haemangioma (Kern et al., 2017; Bartholomot et al., 2002; Bhutani and Kajal, 2018).

Post-imaging, confirmation should be conducted via serologic tests and histopathology, which forms the basis of a 'case definition and likelihood of AE diagnosis'. Cases are thus split into possible, probable or confirmed cases. Possible cases are defined as any patient with imaging *or* serology suggesting AE combined with an epidemiological or clinical history. Probable cases are defined as imaging *and* serology with clinical and epidemiological history and confirmed cases consist of all the above with either histopathology consistent with AE and detection of a specific molecular target or sequence confirmation of the parasite (Kern et al., 2017).

## 5. Treatment, control and prevention

Interruption of *E. granulosus s.l.* transmission between dogs and domestic livestock is the predominant form of intervention; however, the burden of CE in humans may be reduced by measures aimed at avoiding the consumption of *E. granulosus s.l.* eggs. Most human cases are caused by *E. granulosus s.s.* and are mainly observed in rural areas (Tamarozzi et al., 2020).

As the disease does not cause overt pathology in animals, there have been difficulties in the intersectoral collaboration required for successful control strategies (Craig and Larrieu, 2006; Tamarozzi et al., 2020), and successful control strategies have thus far only been achieved in isolated settings e.g. Tasmania (Tamarozzi et al., 2020). These relied on long-term interventions including dog population control and deworming, but new control strategies e.g. sheep vaccination are coming online and have proven effective in controlled experiments and field trials (Tamarozzi et al., 2020; Craig et al., 2017). Mathematical models suggest that a combined approach, integrating sheep vaccination, dog deworming, and culling of older sheep could help in successful implementation of control strategies. These new measures are needed as CE control is not on target for the schedule implemented by the WHO for the elimination of targeted NTDs (Torgerson and Macpherson, 2011; Tamarozzi et al., 2020).

Primary prevention of AE in humans involves de-worming of dogs with praziquantel to prevent *E. multilocularis* egg contamination in the domestic environment. Control in wildlife is difficult and various methods, including hunting and poisoning hosts have been used with varying success (Hegglin and Deplazes, 2013). One successful technique is the use of praziquantel-laced baits placed in the environment to deworm definitive hosts; however, the success of this technique is limited by the baiting design, definitive and intermediate host abundance and presence of other species competing for the bait (Hegglin and Deplazes, 2013). This is also expensive and time-consuming, as treatment is not life-long and the baiting regime must continue months to years to see an effect (Hegglin and Deplazes, 2013). Still, this technique may have merit in isolated areas or where the infection pressure in wildlife is a significant public health concern. Because it has been shown that intermediate host populations can fluctuate in relation to certain land management practices (e.g. (Viel et al., 1999; Wang et al., 2006)), reduction of intermediate host numbers through manipulation of these practices has also been suggested (Hegglin and Deplazes, 2013).

For CE, surgery is considered the gold standard treatment, but alternative forms of treatment are being considered as primary treatment options. These include percutaneous therapy, drug therapy with benzimidazoles and observation with no intervention. Resource and expertise availability, stage, size and location of the metacestode in addition to presentation of symptoms are key elements considered for determining appropriate treatment options (Pham et al., 2019). As there is no test to demonstrate a cure and serology may remain positive for years after treatment, follow-up imaging is required to monitor for cyst reoccurrence (Pham et al., 2019). Benzimidazole has been the sole therapeutic drug available to treat CE and, unlike with AE, can be parasiticidal; however, questions, such as optimal treatment duration, remain (Pham et al., 2019; Vuitton, 2009). Although compounds such as metformin have been shown to work synergistically with benzimidazoles (Loos and Cumino, 2015), there is an urgent need to apply research efforts in this area (Pham et al., 2019).

The only curative treatment for AE available currently is invasive surgical resection; however success is limited by the ability to completely remove the parasite cyst with a safe margin of healthy tissue (He et al., 2015; Hillenbrand et al., 2017). Although nearby lymph nodes are also often affected by the parasite, a recent study found that reoccurrence was not dependent on lymph node removal, but rather on complete liver cyst resection, further emphasizing the importance of a safe tissue margin (Hillenbrand et al., 2018). Although differences in physical and mental quality of life between patients treated surgically and those only receiving drug therapy was not shown to be significant, there was a positive trend for an overall improved quality of life (particularly physical life) after surgery for patients within the surgery group (Schmidberger et al., 2019). Grüner et al demonstrated that drug therapy combined with surgical resection (both partial and complete) resulted in more favourable outcomes, defined by reduced progression or relapses of cysts (Grüner et al., 2017). Unfortunately, surgery is only

available to 20–50% of patients, as it is not possible to remove all parasite biomass in the later stages of infection when the parasite has metastasised to other organs (Kern et al., 2017). Factors associated with favourable outcomes with AE for drug treatment and surgery and drug treatment alone were the early commencement of treatment, early detection of the disease (particularly the absence of metastasis) and no chronic inflammatory diseases (Grüner et al., 2017).

Surgical intervention is accompanied by benzimidazole (BMZ) treatment and drug therapy is the only treatment if surgery is not possible. BMZ mode of action involves binding to beta-tubulins resulting in the inhibition of tubulin polymerization and all associated cellular processes. However, this target is expressed in *E. multilocularis* germinative cells, which have a low affinity to BMZ binding due to the presence of a β- tubulin isoform (tub-2) with amino acid motifs insensitive to BMZ binding (Schubert et al., 2014; Brehm and Koziol, 2014; Lundström-Stadelmann et al., 2020). This low affinity combined with the short half-life and limited uptake of BMZs results in a parasitostatic rather than parasitocidal drug choice for AE. BMZ treatment also has the disadvantage of potentially severe toxicity in the patient. As treatment options for AE rely exclusively on BMZs, patients are often left with no recourse to alternative treatment (Lundström-Stadelmann et al., 2020). A recent study aimed at assessing a variety of licensed drugs via an *in vitro/in vivo* screening cascade found that the anti-malarial compound mefloquine was active against the metacestode. Although not parasiticidal, the drug demonstrated a significant reduction in metacestode growth and treated mice exhibited similar serum concentrations that are present in humans after malaria prophylaxis. As such, this drug could be used as a salvage treatment in humans and encourages other anti-malarial compounds with similar modes of action to be investigated (Lundström-Stadelmann et al., 2020).

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