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Chapter 10

Hydatidosis and Intervention Strategies

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Abstract

Human echinococcosis is a zoonotic infection caused by larval forms (metacestodes) of tapeworms of the genus *Echinococcus*. Among the recognised species, *Echinococcus granulosus* and *E. multilocularis* are of considerable medical importance, causing cystic and alveolar echinococcosis (AE and CE), respectively. The factors of immunology, host-genetic inherits, and *Echinococcus* genetic-diversity and adaption clearly influence infectious establishment and disease progression. However, subtle mechanisms between host and parasite interactions/relationships are still open to study for answers. Despite the global burden, echinococcosis remains a neglected zoonosis. The importance of environmental factors influencing the transmission intensity and distribution of *Echinococcus* species is increasingly being recognised. The intervention strategies for this public health threat have integrated host immune-genetic research, parasite adaptation, and genetic diversity analysis, as well as the transmission dynamic investigations; the limitations of current control programmes are clearly presented in this study that hampers the elimination of *Echinococcus* species worldwide. Continuous efforts by multidiscipline researches are needed.

Keywords: *Echinococcus* species, host immunology and genetics, *Echinococcus* genetic diversity and adaptation, intervention strategies

1. Introduction

The zoonotic disease of echinococcosis (hydatidosis) is one of the most important parasitic helminth diseases, with over three million people infected worldwide. The two major species infecting man are *Echinococcus multilocularis* that causes alveolar echinococcosis (AE) and
*Echinococcus granulosus* that causes cystic echinococcosis (CE). Both CE and AE are life threatening and are associated with severe morbidity. The global burden of human CE exceeds one million disability-adjusted life years (DALYs), resulting in a loss of at least US$760 million per annum. Case series and clinical trials show a mortality rate of 2%-4% for CE, but this increase is marked with poor treatment and care. CE also impacts upon agriculture as *E. granulosus* infects domestic livestock, further adding to economic loss. There are 0.4 million cases of human AE, and survival analysis has shown that, if untreated or if limited treatment is provided, mortality exceeds 90%, 10-15 years post-diagnosis. There are approximately 18,000 new cases of AE annually, with a total annual burden of 666,434 DALYs.

2. Transmission of *Echinococcus* species

All *Echinococcus* species are transmitted to intermediate hosts via the ingestion of eggs and are transmitted to definitive hosts by means of eating infected cyst/lesion containing organs. The life cycle of *E. multilocularis* involves carnivorous definitive hosts (foxes and dogs) and intermediate hosts (predominantly microtine rodents).

For *E. granulosus*, dogs are the major definitive hosts and sheep and other livestock are typical intermediate hosts. In Australia, however, the definitive hosts for *E. granulosus* also include wild dogs and dingoes, while sheep, kangaroos, and wallabies are common intermediate hosts.

Human echinococcosis occurs through the ingestion of *Echinococcus* eggs from environments that have been contaminated by the faeces of infected dogs or foxes. Mostly, following close contact with infected canines carrying *Echinococcus* eggs on their fur; by ingestion of egg-contaminated water or food; or by coprophagic flies serving as mechanical vectors for transmission. Once inside the body, the eggs release oncospheres in the intestine that then migrate through the circulatory system to various organs of the host, notably the liver and lungs. Generally, echinococcosis is associated with poverty, which impacts on sanitation and hygiene, and access to health services, particularly in livestock-raising communities.

3. Epidemiology in Australia and China

Cosmopolitan distribution of *E. granulosus* in a few of countries is completely free from this parasite contamination, while *E. multilocularis* mainly occurs in the northern hemisphere; but it will be an emerging or re-emerging disease in certain countries as a result of ecological alternatives in modern life (Figure 1). AE and CE are of considerable public health concern, particularly in parts of Central and Eastern Europe, and especially Northwest China. While the annual incidence of AE may appear low in many endemic areas (0.03-1.2 per 100,000 inhabitants), it is estimated that many cases are undiagnosed. Human CE is endemic in many pastoral communities. The mortality rate from CE is lower than that from AE (about 2%-4%), but increases considerably if medical treatment is unavailable or inadequate.
Figure 1. The distribution of Echinococcus spp. in Eastern parts of world (Asian and Australia).

3.1. In Australia

*E. granulosus* occurs in Australia and is prevalent in wildlife. The true extent of human CE in Australia is not accurately known. It is estimated that 80–100 new cases of CE are diagnosed annually; however, CE is not a notifiable disease in Australia and has notoriously been under-reported so the true prevalence of CE is likely to be considerably higher than described. Of few data that are available for rural Australian communities, it is apparent that some have an infection index as high as 23.5/100,000. Other data from Western Australia have shown that the incidence in Aboriginal people was 12.2 times higher than in the equivalent non-Aboriginal rural population.

3.2. In China

There are approximately 1.3 million people with echinococcosis in China, where the disease burden is greater than that of any other country. Of the 33 provinces, autonomous regions, and municipalities in China, at least 20 are considered to be endemic for *E. granulosus* and at least five for *E. multilocularis*. The provinces and autonomous regions with the highest risk of echinococcosis include Xinjiang, Qinghai, Sichuan, Gansu, and Ningxia Hui Autonomous Region (NHAR). These provinces/regions are co-endemic for both human CE and AE, with common cases of co-infections. In addition, significant numbers of CE cases occur in Tibet, Shaanxi, as well as Inner Mongolia, Heilongjiang Province. There are now 66 million people at risk of infection.

4. Pathogenesis of human echinococcosis

The initial phase of a primary infection is always asymptomatic for both AE and CE in humans and may remain so for a matter of months up to many (typically more than 10) years.
The metacestodes of *E. multilocularis* develop almost exclusively in the liver as a tumour-like, infiltrative growth. The rapidly growing cysts can grow up to 20 cm or more in diameter, often with a central necrotic cavity. A primary infection of *E. multilocularis* outside of the liver is rare, but the spread of parasitic larvae from the primary site in the liver to other organs by metastatic infiltration is not uncommon. AE is typically identified following the investigation of symptoms such as fatigue and weight loss, hepatomegaly and abnormal US, or through routine laboratory examination.

In CE, *E. granulosus* metacestodes may develop in almost any organ. For the majority of patients, however, a single-organ infection site is generally observed with a solitary cyst localized to the liver or to the lungs. Ultrasound surveys have shown that, while some cysts may grow up to 50 mm per year, others may persist without change for many years. Liver cysts also appear to grow at a lower rate than lung cysts. Most CE cases remain asymptomatic until the cyst compresses or ruptures into neighbouring structures and organs by which time the disease is already advanced.

### 5. Disease diagnosis and severity

Patients with AE and CE are diagnosed based on clinical parameters including assessment of hepatomegaly, jaundice and upper abdominal complaints, as well as by imaging techniques such as ultrasound (US), computed tomography (CT) scans and magnetic resonance imaging (MR). ELISA-based detection of serum *Echinococcus* specific-antibodies and histological examination are also used to confirm diagnosis.

To assess the degree of hepatic involvement of the parasite mass, AE patients are classified according to PNM (P: hepatic localization of parasite; N: extrahepatic involvement of neighbouring organs; M: absence or presence of distant metastases) and staged as P1, P2, P3, or P4 as recommended by WHO guidelines and the European Network for concerted surveillance of alveolar echinococcosis classification. For CE patients, classification of disease is based on liver lesion type (CE1, CE2, CE3, CE4 and CE5) at initial diagnosis, as proposed by the WHO Informal Group on Echinococcosis.

### 6. Susceptibility of human echinococcosis

Despite its public health significance, the susceptibility of human echinococcosis is poorly understood. The general factors that may render an individual more susceptible include malnutrition, co-infection, and immuno-suppression caused by other diseases or through the use of immuno-suppressive drugs. Several reports of children with cystic echinococcosis were predominantly located in the lungs. The reason for lung hydatidosis in children may be explained by either the weaker immune capability in their respiratory system or the faster cyst growth rate (or both) in young ages than that in adults. Pregnancy has also been thought to
increase risk of infection or aggravate the disease due to the impaired cellular immunity frequently observed in pregnant women.

6.1. Host immunology

Immu-suppression is frequently observed in patients with severe AE or CE. High levels of circulating *Echinococcus* antigens can contribute to immune-suppression through polyclonal over-stimulation. The chronicity of *Echinococcus* infection results from persistent antigenic stimulation, polarization of T cell-subset populations and humoral immune responses. Whilst increased Th1 cell activity has been associated with degeneration of CE and AE lesions and successful chemotherapy, high Th2 cell activity is typically associated with active disease and a poor response to chemotherapy. In animals, CE induces local immune-suppression associated with increased IL-10 and TGFβ production. Similarly, in humans, IL-10 production plays a key role in the immune response against *E. multilocularis*. Other studies show, however, a clear immunopathology-associated Th2 polarization in patients with progressive disease related to increased levels of IL-4 and IL-13. Th1/Th2 cytokines have shown association with susceptibility or resistance to both *Em* and *Eg* infection in in vitro studies. Immunological markers have proved useful for monitoring the natural course of echinococcosis. High IgG4/IgE levels are associated with active disease whereas IgG1, IgG2 and IgG3 responses occur when cysts became infiltrated and are destroyed by the host. This highlights the importance of measuring IgG subclasses individually for a more sensitive index of disease activity than total IgG levels. Measurement of both cytokine and antibody levels can provide a more sensitive diagnostic tool for studying the immunological mechanisms involved in echinococcosis.

6.2. Host genetics

Despite the high morbidity and mortality associated with echinococcosis, relatively few studies to date have investigated the genetics underlying human susceptibility to the disease.

The case-control studies of candidate genes that have been previously undertaken have identified a number of associations with susceptibility to human echinococcosis in the HLA region for both AE and CE. Of these, however, many have not been replicated, likely reflecting the complexities and diversities of host susceptibility in different ethnic populations, different environmental conditions, and exposure to different *Echinococcus* genotypes or strains. The majority of candidate gene studies have used small cohorts. Only two genes outside of the HLA loci have been investigated in terms of AE and CE susceptibility. These genes, *TAP1* and *TAP2*, belong to the MDR/TAP subfamily and have been previously implicated in autoimmune diseases such as ankylosing spondylitis, type 1 diabetes, and coeliac disease. As with other complex diseases, it is anticipated that host genetic influences on echinococcosis susceptibility are likely to comprise multiple additive loci. Indeed, a recent study has demonstrated that multiple loci exist that contribute to the susceptibility to echinococcosis in mice. This has been supported by recent evidence that implicated a large number of differentially expressed genes in murine AE. However, the relevant genes that determine susceptibility to human echinococcosis and the clinical outcome from this severe disease remain largely unknown. It is clear
that any gene variations that interfere with these interactions may alter the etiopathogenesis of disease. Given the highly diverse allelic variation within the MHC region observed between different geographic populations and racial groups, it is plausible that the race and origin of an individual can greatly affect their phenotype and the subsequent outcome of infection.

7. **Echinococcus adaptation/genetics**

*Echinococcus* species have developed their signalling systems for the microenvironment, encompassing the host insulin acting as a stimulant for larval *E. multilocularis* development and revealed an important factor in the pathology of alveolar echinococcosis predominantly in the host liver.

The extensive genetic variation of *E. granulosis* comprises a number of strains (G1–G10) that differ in biological features of intermediate host specificity, with diverse viscera involvements, antigenicity, transmission dynamics, and infectivity to humans. An abundant AgB in HCF is involved in the evasion of the immune response of the host due to its ability to inhibit elastase activity and neutrophils recruitment and to elicit an immunopathology-associated Th2 cell response. The significantly different expression levels of 14-3-3 proteins in larval *E. multilocularis* and *E. granulosus* provide different growth behaviours of AE and CE in the intermediate hosts, respectively.

8. **Public health threat**

To date, over five species are recognized in the genus and four species are already revealed to be involved in human diseases. The most common forms are *E. granulosis* and *E. multilocularis* responsible for CE and AE, respectively. Two other forms, namely *E. oligarthrus* and *E. vogeli* cause polycystic echinococcosis; two new species, *E. felidis* and *E. shiquicus* may also contribute to human infection, though little is known.

However, human behavioural changes with economic, technological development, and the spatial expansion of agriculture promoted encroachment into wildlife habitats, driven by increasing human population, leading to ecosystem changes and bringing human, domestic animals into closer proximity to wildlife. Many recently emerged zoonoses originated in wildlife have been reported.

9. **Intervention strategies**

9.1. **Immunological/genetic research**

Many studies of echinococcosis have provided significant information on risk factors of infection, as well as on socio-economic influences and ecological determinants of parasite
transmission. The new immunological/genetic research components for new therapeutic targets, in combination with standard imaging techniques, will enable rapid and efficient evaluation of echinococcosis patients. This will not only greatly assist in monitoring disease progression and treatment efficacy, but also in the development and deployment of new control strategies and disease surveillance fundamental to reducing morbidity caused by long-term chronic infection and at a low cost to the health care systems of areas where echinococcosis is endemic. Further, the genetic study aims that identification of the genes involved in disease susceptibility can provide valuable insight into the protective and pathogenic mechanisms involved in the different clinical outcomes of echinococcosis. Understanding these processes can provide novel therapeutic targets that are essential for the long-term control of the disease worldwide. A significant, but essential challenge will be to develop strategies for translating knowledge of novel susceptibility genes into improved patient outcomes from both AE and CE. Given the considerable inter-individual variation observed in susceptibility to the different clinical phenotypes and their associated clinical outcomes, it is anticipated that subtle manipulation of the host immune response will translate into clinical benefits. Genomics offers a powerful approach to dissect the relevant pathways and may offer novel therapeutic targets for new drugs against both AE and CE, which are urgently needed as the current albendazole treatment is far from satisfactory. Definition of the molecules and pathways that are important in individual patients may eventually lead to a personalised approach to care, with therapy tailored on the basis of an individual’s genetic background.

9.2. Animal host intervention

Various methods for animal host interventions have been employed in echinococcosis endemic regions, for example, the culling of dogs/foxes for CE/AE, culling of rodents for AE, and the anthelminthic treatment (with praziquantel (PZQ)) of dog/foxes for CE/AE. Vaccine development has been ongoing and whilst a vaccine targeting the definitive dog/fox hosts could be a “magic bullet”, all current candidates have low efficacy. A highly efficacious sheep vaccine for *E. granulosus* (Eg95) is currently under investigation but the evidence base, though growing, is not yet established for its incorporation into control programmes to date.

9.3. Comprehensive intervention and limitation

The use of geographic information system (GIS) have become more common as a tool for public health investigations due to the increase in number and quality of satellites used for terrestrial observation. These systems integrate the use of geographic positions sensors (GPS) tool for infectious disease studies, including *Echinococcus*. Spatial analysis provides an improvement in epidemiological analysis and prediction of future events. Using remote sensors for monitoring *Echinococcus* transmission, particularly *E. multilocularis*, have produced information that has showed much importance in designing a control programme. Apart from the detection of animal host assembling linking transmission dynamics due to prey-predatory relations, in terms of geological and ecological environments, prediction mapping provides geographical identification of *Echinococcus* spp. risk areas, allowing for the allocation of resources in reasonable ways/location. Linking with a mathematical model has been done in many other parasitic disease controls. It is believed to be also useful for the determination of the optimal
strategies for control and/or elimination of echinococcosis in specific locations. The optimal intervention strategies can be translated into policy and practice reducing the burden of this disease, leading to improved direct health outcomes. Modelling can also be used for future economic assessments of interventions that reduce the financial impact of the disease.

To date, only five islands (Iceland, New Zealand, Tasmania, Falkland Islands, and Cyprus) have been able to successfully control echinococcosis. Control programmes were predominantly based on health education and control or elimination of home slaughter of sheep, with behaviour change, is central to their success.

Despite the range of intervention strategies, control in endemic regions of the world (especially the poor rural areas) has proved difficult, as demonstrated by the increasing number of cases over the last decade. This failure to effectively control echinococcosis can be attributed to a number of causes: 1) culling of animals has ethical challenges (e.g., use of rodenticides in NHAR resulted in the poisoning of domestic dogs); 2) PZQ is effective in killing adult E. granulosus and E. multilocularis in definitive hosts, but it does not prevent reinfection in the definitive hosts; 3) existing health promotion materials are passive and may not be sufficiently engaging to bring about behaviour change at the population level; and 4) the lack of significant governmental support for control programmes.

10. Conclusion

Hydatid disease is a major cause of morbidity and mortality in many parts of the world. Although immunological research has provided important insight into the mechanisms of immunity in CE and AE, the genetic variants within the host-participating genes may be too subtle or too few to cause much effect on individual risk. The genotypic variation of Echinococcus species reflects phenotypic differences with important consequences in terms of increased host infectivity by local Echinococcus strains. Such adaptations may also result in different sensitivity to drugs or increased virulence for hosts that will impede controls efforts and even affect vaccination strategies against Echinococcus. The environmental factors have been correlated with transmission to humans through changes in animal population, dynamics spatial overlap of competent hosts, and the creation of improved conditions for egg survival. Therefore, echinococcosis is a complex zoonosis with sparse evidence on the effectiveness of control strategies in diverse settings despite many efforts worldwide for decades. Identifying the environmental determinants of the transmission risk to humans will be vital for the design of accurate predictive models to guide preventative public health action against echinococcosis. Mathematical modelling is a useful tool for simulating control packages under locally specific transmission conditions to inform optimal timing and frequency of phased interventions for cost-effective control of echinococcosis.

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