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ECHINOCOCCOSIS: A REVIEW

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Abstract

This review covers various aspects of echinococcosis in humans, including the biology, life cycle, etiology, distribution, and transmission of Echinococcus organisms. Additionally, it discusses the epidemiology, clinical features, treatment options, and the impact of improved diagnosis on the diseases they cause. Despite some advances in echinococcosis control, this zoonotic disease remains a significant public health challenge in many countries, including China & Pakistan. Moreover, in several other regions, it is considered both an emerging and re-emerging disease, indicating its persistent threat to human and animal health. No alternative drug to albendazole exists for treating echinococcosis, necessitating urgent development of new compounds. Genomic and proteomic data offer promise for enhancing diagnosis and identifying drug and vaccine targets, which could significantly impact echinococcosis control in the future, addressing its persistent global challenge.

Keywords: Echinococcosis, Cystic Echinococcosis (CE), Alveolar Echinococcosis (AE).

INTRODUCTION

Echinococcosis, also known as hydatid disease, is a parasitic infection stemming from the larval phase of tapeworms found within the Echinococcus genus.(1) The two main species responsible for human echinococcosis are Echinococcus granulosus and Echinococcus multilocularis. (2)Humans typically become infected through the ingestion of parasite eggs shed in the feces of infected dogs or other canids, although transmission can also occur through contact with contaminated soil, water, or food. Once ingested, the eggs release larvae that can migrate and form cysts in various organs of the body, most commonly the liver and lungs. There are six types of Echinococcus granulosus, which are found in different animals like sheep, cattle, horses, camels, pigs, and deer. (3) But, four of these types are important for public health including: Echinococcus granulosus causes a disease called Cystic Echinococcosis. Echinococcus multilocularis causes a disease called alveolar echinococcosis. In 2012, the FAO and WHO ranked Echinococcus

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granulosus as the second most significant foodborne parasite for global public health. (4) Echinococcus vogeli causes a disease called polycystic echinococcosis. Echinococcus oligarthrus causes polycystic echinococcosis. These diseases can be harmful to humans, and it's essential to take measures to prevent and treat them. The annual prevalence of cystic echinococcosis (CE) can range greatly in areas where these illnesses are prevalent, from about 1 to 200 cases per 100,000 persons. (5) The annual incidence of Alveolar Echinococcosis (AE) is less common, usually falling between 0.03 and 1.2 occurrences per 100,000 individuals.(6) Regions with a large sheep-rearing industry tend to have a higher incidence of CE.

The parasite's life cycle involves both sheep and dogs, with dogs being the definitive hosts and sheep acting as intermediate hosts. This close interaction between livestock and dogs contributes to the spread of the parasite in sheep-rearing areas. Echinococcosis is not only a concern for human health but also for livestock. The economic burden it places on governments and agricultural sectors can be significant. In addition to the costs associated with human healthcare, including diagnosis, treatment, and prevention, there are also economic losses related to the impact on livestock production. The annual cost of cystic echinococcosis (CE) in Pakistan is around 26.5 million rupees. Furthermore, the additional money lost as a result of the disease was estimated to be around USD 276.20 and USD 165.72 for every 100 sheep-goats and buffalo cattle, respectively.(7)

Epidemiology

Cystic echinococcosis (CE) is a significant health concern due to its potential severity and wide geographical distribution. The World Health Organization (WHO) recognizes the importance of addressing diseases like CE as part of its efforts to understand and mitigate the global burden of foodborne diseases.(8) By including CE in initiatives aimed at assessing this burden, the WHO can better allocate resources, develop preventive measures, and improve healthcare strategies to combat this disease on a global scale. The World Health Organisation (WHO) lists CE as a neglected zoonotic disease.(9) This categorization highlights the fact that, in comparison to other diseases, it receives relatively little attention and funding, despite having a major global impact on the health of humans and animals. Although CE is found around the world, it is most common in areas like Africa, Asia, Australia, Europe, and some parts of the Americas. In nations like the United Kingdom, the Mediterranean region, Iran, Kuwait, Saudi Arabia, Iraq, Syria, Jordan, and Pakistan, it is particularly noteworthy. In a review study a total of 48 articles covering human cases of cystic echinococcosis (CE) in Pakistan were identified, reporting 1,702 cases in total. All articles were published between 2000 and 2020. Among them, 17 articles (35.4%) were case series, while 31 articles (64.5%) were case reports. None of the studies reported the prevalence of CE infection at the national or regional level. Karachi had the highest number of reported cases, followed by Lahore and Peshawar.(4) An estimated 1.2 million people get the virus annually, and 2.2% of them die from it.(10) Furthermore, it results in 3.6 million DALYs (disability-adjusted life years). Over USD 3 billion is spent annually on treating CE worldwide. The prevalence of numerous parasitic

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infections, including CE, varies significantly. In Pakistan, the infection rates for CE range from 2.44% to 35%.(11-13) In Uzbekistan and Tajikistan, the annual surgical incidence rate has been estimated to be as high as 25–27 cases per 100,000 people, with the highest prevalence reaching 10% (ranging from 0.8% to 11.9%).(14) CE remains a concern in various parts of South America.(15, 16) New Zealand has successfully eliminated CE, and Tasmania in Australia is making progress toward being provisionally free of the disease.(10) This shows that concerted efforts and effective control measures can lead to significant achievements in combating CE.

Alveolar echinococcosis (AE) is caused by the larvae of the tapeworm Echinococcus multilocularis. AE is more commonly found in regions of the northern hemisphere, particularly in Europe and Asia, including China, Russia, and Central Asia, there is limited specific information available about its prevalence in Pakistan.(14) The life cycle of Echinococcus multilocularis primarily revolves around foxes and their rodent prey in habitats distinct from human settlements. However, as fox and coyote populations expand into suburban and urban areas in various regions, there's a notable ecological overlap with human habitats. This increases the risk of transmission to domestic dogs or cats, which could contract the infection by consuming infected wild rodents. Understanding and managing zoonotic diseases in such dynamic ecosystems with heightened human-wildlife interactions become paramount in safeguarding public health. A recent case-control study highlighted a heightened risk of alveolar echinococcosis among individuals who owned dogs engaged in hunting, dogs allowed to roam outdoors unsupervised, individuals involved in farming, and those who owned cats.(17) However, caution is warranted regarding the reported risk associated with owning cats. Recent studies indicate that cats may not play as significant a role in transmitting Echinococcus multilocularis as once believed, as they are less at risk to infection compared to canids.(18) This emphasizes the need for careful interpretation of research findings and a comprehensive understanding of the dynamics of disease transmission in different animal populations.(19)

Different strains or genotypes of E. granulosus can be found in different geographical regions, and they often exhibit variations in their host preferences and life cycles. These geographical distinctions are important for understanding the transmission dynamics of the disease. Molecular studies found G1-G10 genetic types in E. granulosus. Each varies in location, hosts, and harm. Knowing this diversity helps understand echinococcosis spread globally.(20, 21) Each strain is linked to a particular animal species, like sheep, cattle, horses, camels, pigs, and deer, with some strains found in multiple species and others more specific. The discovery of a ninth genotype in swine in Poland and a tenth strain in reindeer in Eurasia indicates ongoing research into their diversity and distribution. The sheep strain (G1) seems to be the most common and often infects humans.(22) Human behavior, like feeding dogs with the viscera of home-butchered sheep, can raise the risk of transmitting the sheep strain to humans as shown in fig 1. This practice exposes humans to the infectious agent in the sheep's viscera, increasing the likelihood of human infection.

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Figure 1: Dogs have Easy Access to Slaughtered Livestock

Etiology and Pathogenesis

Adult tapeworms live in the definitive host's upper small intestine; these hosts include domestic cats, wolves, jackals, and reindeer, but most commonly dogs. Humans, pigs, cattle, and sheep are the intermediate hosts that house the larval stage. By eating eggs released into the environment along with the excrement of sick dogs, these hosts contract the infection. The parasite adheres tightly to the mucosa of the small intestine once it has entered, releasing gravid proglottids that are later ejected in the infected animal's faeces.(23) Once the parasite penetrates through the mucosa, it can spread via the bloodstream to the liver and other sites, initiating the formation of cysts. In humans, most primary infections involve a single cyst. However, in 20-40% of cases, individuals may develop multiple cysts or experience involvement of multiple organs.(24) Handling or consuming meat or organs from infected sheep usually does not result in human infection. Instead, either by coming into close contact with dogs that are carriers of parasite eggs in their faeces or by consuming contaminated water, food, or soil, people end up as unintentional intermediate hosts. In echinococcosis, cysts are usually unilocular and range in diameter from 1 to 15 cm. Cyst growth in cystic echinococcosis (CE) usually varies from 1-2 mm to 10 mm annually. Furthermore, because of the way portal blood flow is designed, they usually impact the right lobe of the liver more often than the left. The cysts consist of two membrane layers: an exterior, acellular, laminated layer and an inner, nucleated, germinal membrane.(25) On imaging tests, the most commonly visible layer is the calcified fibrous capsule formed by the immune system around the cyst in response to it.(26) As the cyst grows, it produces a mixture of daughter cysts and

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protoscolices. The phrase "hydatid sand" refers to the mixture of many protoscolices and cystic fibrosis that appears grain-like on ultrasound imaging. When protoscolices cling firmly to the intestinal wall of their hosts and mature into adult worms with a scolex (head), neck, and proglottids, animals that eat infected organs will become definitive hosts.(26, 27)

Biology and Life Cycle Features

Echinococcus spp., tapeworms, have intricate life cycles with two mammalian hosts.(28) Carnivores like canids (dogs, wolves, foxes) and felids (cats) act as definitive hosts, harboring adult tapeworms in their intestines. These carnivores shed tapeworm eggs in their feces. On the contrary, herbivorous mammals like ungulates (hoofed animals such as sheep, cattle, and deer), rodents, and lagomorphs (rabbits and hares) serve as intermediate hosts. When these hosts ingest tapeworm eggs, the eggs hatch into larvae (metacestodes) within the host's tissues, forming cysts.(29) If a carnivore then consumes the tissues of an infected intermediate host, the life cycle progresses as the larvae develop into adult tapeworms in the carnivore's intestine. Although humans are not the primary hosts in the life cycle of Echinococcus spp., they can become accidental intermediate hosts by ingesting the tapeworm eggs, typically through contaminated food, water, or soil. This can lead to the formation of cysts in human tissues, causing a condition known as echinococcosis or hydatid disease.(30) Within the intestines of their last hosts, hundreds to thousands of adult Echinococcus spp. worms, ranging in length from 3 to 7 millimetres, abound. Finally, the proglottid, or last segment, of each worm matures and produces eggs, which are then released in the excrement of the carnivore and eventually reach the outside world.

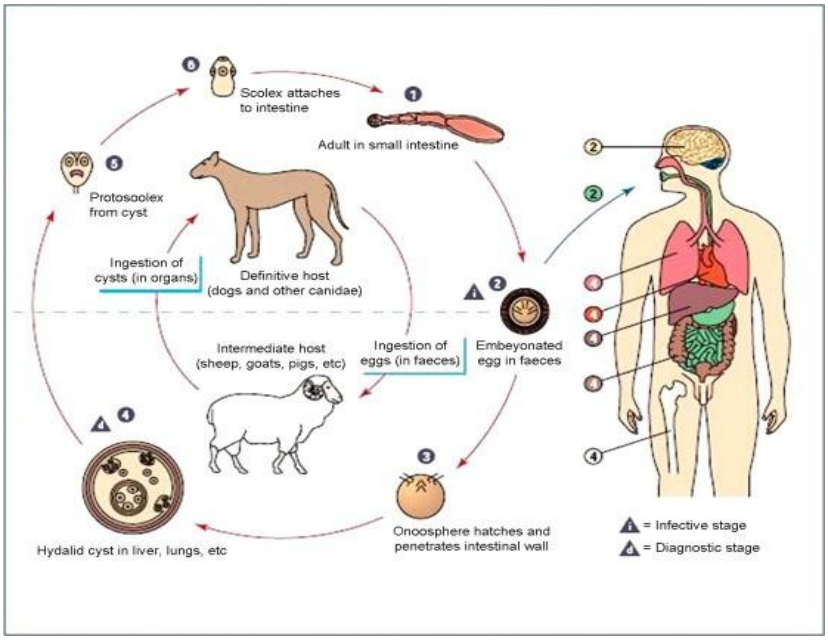

Figure 2: Life cycles of Echinococcus spp.

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Laboratory Finding and Diagnostic Techniques

Depending on the clinical situation and organ involvement, a combination of different techniques is usually used to diagnose echinococcosis. Plans for treatment are based on a detailed examination of serological tests, imaging data, and clinical evaluation. Integrating immunodiagnostic and radiological imaging techniques enables a non-invasive confirmation of the diagnosis. While echinococcal lung cysts can be detected via radiography, visualization in other locations often necessitates calcification for radiographic identification. CT, MRI, and ultrasonography are key for assessing avascular cysts and deep-seated lesions. Abdominal ultrasonography, widely available, is crucial for identifying cysts' number, location, size, and viability in echinococcosis diagnosis.(31-33)

The WHO introduced a standardized classification system for hepatic cysts identified through ultrasonography, comprising the following categories: CE1 (uniform anechoic content with characteristic signs), CE2 (multivesicular, multiseptated cysts), CE3 (anechoic cysts with detached laminated membrane, visible as "water-lily sign"), CE4 (heterogeneous degenerative contents without daughter cysts), and CE5 (cysts with thick calcified walls producing cone-shaped shadows).

Antibody assays play a crucial role in confirming presumptive radiologic diagnoses, particularly in cases of diseases like cystic echinococcosis. However, it's worth noting that not all patients with the condition may show a detectable immune response. This could be due to various factors, including the stage of the infection, individual immune system variability, or the sensitivity of the assay used.(34)

Alveolar echinococcosis often presents symptoms in older individuals, resembling hepatic carcinoma or cirrhosis. Plain radiographs reveal hepatomegaly and scattered radiolucency areas outlined by calcific rings (2–4 mm). Computed tomography typically shows indistinct solid tumors with central necrotic areas and perinecrotic plaque-like calcifications.(35)

Treatment

Treatment of echinococcosis typically involves a combination of medical therapy and surgical intervention. Until the 1980s, surgery stood as the sole treatment option for echinococcal cysts.(36) However, advancements in medical science have introduced alternative treatments. Chemotherapy using benzimidazole compounds emerged as a viable option. A technique known as cyst puncture, aspiration, injection, and re-aspiration (PAIR) has become increasingly popular. These alternatives are often used in conjunction with or instead of surgery for treating echinococcal cysts. This shift reflects both advancements in treatment modalities and a desire to minimize the invasiveness and risks associated with surgical intervention.

Medical Therapy: Medical therapy plays a crucial role in the management of echinococcosis, particularly in cases where surgery is not feasible or as adjuvant therapy to reduce the risk of recurrence. Benzimidazoles remain the cornerstone of

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pharmacological intervention.(31) The effectiveness of benzimidazole drugs in treating echinococcosis is highlighted by achieving a cure in about one-third of patients and significant cyst size reduction and symptom relief in 30-50%. Early detection, prompt treatment, and diligent monitoring are crucial for optimal outcomes. However, treatment can be challenging, requiring prolonged therapy and careful management of adverse effects, with individual responses varying based on factors like cyst size and location.(37, 38)

Albendazole (10-15 mg/kg/day) and mebendazole (40-50 mg/kg/day) are both effective against echinococcosis, but albendazole typically produces superior results due to its enhanced pharmacokinetic properties, aiding in intestinal absorption and cyst penetration. Combining praziquantel with albendazole has shown success in treating hydatid disease.(39-41) in advanced stages, alveolar echinococcosis is frequently misdiagnosed, resulting in irreversible damage. Prolonged therapy, however, occasionally has larvicidal effects. Mebendazole (50 mg/kg/day) or albendazole (15 mg/kg/day) can be used as a long-term treatment to inhibit the growth of larval E. multilocularis, lessen metastases, and improve the quality and length of life.(42)

Mebendazole and albendazole treatment for non-resectable alveolar echinococcosis resulted in an outstanding 80% 10-year survival rate in a Swiss research, compared with 29% for untreated historical controls. In addition, the 16–20-year survival rate increased to about 70%, which is significantly higher than the 0% recorded in historical controls who did not receive treatment.(43)

Surgery: The surgical procedure entails extracting the cyst without rupturing it, as this could result in the cyst contents spilling into the surrounding tissues and potentially induce allergy and infection spread. If the cyst cannot be removed completely, a procedure known as a pericystectomy may be used to remove portion of it. In order to do this, the cyst wall must be removed, leaving any residual parasite material behind. Since it tries to eradicate the parasite entirely while lowering the chance of recurrence, it's frequently the recommended treatment when practical.

Surgery should be avoided for patients who refuse it, are pregnant, have pre-existing high-risk medical conditions, or present with multiple cysts that are difficult to access.

Percutaneous Aspiration, Injection, Re-Aspiration

Percutaneous aspiration, injection, and re-aspiration (PAIR), a minimally invasive procedure, treats echinococcosis, especially for liver or accessible cysts where surgery is risky or impractical.(44) To prevent sclerosing cholangitis, PAIR should not be conducted in patients with cysts showing biliary communication. Echinococcosis can be detected by endoscopic retrograde cholangiopancreatography, intraoperative cholangiogram, or bilirubin detection in cyst fluid. When PAIR and albendazole are combined, the chance of accidental leakage during the treatment resulting in secondary echinococcosis can be reduced. When compared to chemotherapy or PAIR alone, this combined strategy frequently yields better results.(45) Typically, patients undergo a one-

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month course of albendazole after the PAIR procedure. Favorable outcomes have been observed in over 2000 PAIR interventions. A meta-analysis comparing PAIR plus albendazole or mebendazole in 769 patients with hepatic cystic echinococcosis against 952 era-matched surgical control subjects found greater efficacy, lower morbidity and mortality rates, reduced disease recurrence, and shorter hospital stays with the combined treatment.(46)

Prevention and control of Echinococcosis: Prevention and control of echinococcosis in Pakistan require a multi-faceted approach involving various strategies targeting both humans and animals. Educating communities about the transmission, risk factors, and preventive measures of echinococcosis is crucial. This includes promoting hygiene practices, such as handwashing after handling animals, and raising awareness about the importance of proper cooking of meat. Enhancing surveillance systems to monitor the prevalence and distribution of echinococcosis is important for early detection and prompt treatment. Iceland's successful control program, starting 130 years ago, eradicated echinococcosis by the 1950s.(47) It involved a health education campaign and strict control on farm slaughter. Similar initiatives in New Zealand and Tasmania focused on rural education and practice changes, leading to effective control.

In New Zealand, infected dogs were absent by 1985-1986, and hydatid cysts in sheep are now rare. No new human cases in individuals under 19 have been reported since 1977.(48, 49) Cystic echinococcosis has been provisionally eradicated in Tasmania and New Zealand. Cyprus has seen success with aggressive stray dog elimination and strict control of working and pet dogs, using diagnostic purging with arecoline for surveillance and problem farm identification. However, local control programs haven't significantly changed the global distribution or public health impact of hydatid disease. In many endemic regions, effective control hasn't been achieved, leaving much work to be done. Concerns arise regarding the escalation of echinococcosis to hyperendemic levels in areas previously endemic. Evidence indicates increased cystic echinococcosis in newly independent central Asian states (Kazakhstan, Uzbekistan, Kyrgyzstan, Tajikistan, Turkmenistan) following the collapse of the Soviet Union in 1992, linked to disrupted veterinary and public health services.(50)

CONCLUSION

It was concluded that despite certain progress in controlling echinococcosis, this zoonotic illness continues to pose a substantial public health obstacle in numerous countries, Pakistan included. Additionally, in various other areas, it is viewed as both an emerging and re-emerging ailment, underscoring its ongoing threat to human and animal well-being. The absence of an alternative medication to albendazole for echinococcosis treatment underscores the pressing need for the development of new compounds.

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