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Progress in diagnosis, treatment and elimination of echinococcosis and cysticercosis

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Abstract

Here I review the current status of geographical occurrence and public health significance of echinococcosis (*Echinococcus* spp. infections) and cysticercosis (*Taenia solium* infection) with special emphasis on the remarkable technologic progress achieved in recent decades that has led to greater understanding of the biology and epidemiology of these cestode infections. The greatest remaining challenges are to apply this knowledge and technology to improved medical management and prevention of these infections.
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Keywords: Cestodes; Tapeworms; Hydatid disease; Echinococcosis; Cysticercosis; Taeniasis

1. Introduction

Thank you for this opportunity to share my experiences and observations for the future in research, treatment and control of echinococcosis and cysticercosis/taeniasis. My experience is shaped by my activities directed toward these cestode parasites in the field and in the laboratory. I first encountered *Taenia solium* taeniasis/cysticercosis as a Fellow in Medical Parasitology at the National University in Mexico and at that time only the most serious of cases of neurocysticercosis were correctly diagnosed, often at autopsy. I first encountered echinococcosis in California when, upon visiting a local slaughterhouse to collect cysticerci of *Taenia hydatigena*, we noted hydatid cysts in the viscera of sheep. This led to the work that formed my PhD thesis at the University of California Davis. Upon completion of graduate study I began a job as Epidemiologist at the Pan American Health Organization's Zoonoses Research Center (CEPANZO) in Buenos Aires, Argentina. A major emphasis of our program was working with scientists at Latin American government institutions in carrying out research and implementing control programs against echinococcosis. In 1974 I had the opportunity to join the U.S. Public Health Service at the Centers for Disease Control and Prevention in Atlanta. In these positions I have had the opportunity to work with scientists from many countries in research and control of parasitic zoonoses with special emphasis on echinococcosis and cysticercosis. It gives me pleasure to reflect upon these experiences and to marvel at just how far we have progressed in the understanding of these zoonotic infections and in development of technology that is effectively applied to diagnosis, treatment and control of these infections.

2. Echinococcosis

Until recently, the genus *Echinococcus* had contained 4 generally accepted species: *Echinococcus granulosus* (Batsch, 1786), *Echinococcus multilocularis* (Leuckart, 1863), *Echinococcus oligarthrus* (Diesing, 1863), and *Echinococcus vogeli* (Rausch and Bernstein, 1972) are morphologically distinct in both adult and larval stages [1,2].

One of these species, *E. granulosus*, is made up of a number of biologically and genetically distinct entities, whose taxonomic positions are in states of flux. These variants are separated ecologically, although not necessarily geographically, by the nature of their respective unique host assemblages. They have been referred to as strains or subspecies [2], however, recent proposals have elevated a number of them to separate species status. Current data, based on genome patterns, generally support previous characterizations based on morphologic and biologic criteria: at least 10 genetically distinct populations exist within the complex until recently denoted *E. granulosus* [2] (Table 1). Probes characterizing the mitochon-

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Table 1
Characteristics of hosts and known geographic distribution of recognized and proposed species and strains in the genus *Echinococcus*

Species strain/isolate (genotype)	Known intermediate hosts	Infective to humans?	Known definitive hosts	Probable geographical distribution	Proposed taxonomic designation
Echinococcus granulosus					
Sheep strain (G1)	Sheep, cattle, pigs, Camels, goats, macropods	Yes	Dog, fox, dingo, jackal and hyena	Australian mainland, Europe, USA, New Zealand, Africa, China, Middle East, South America and Russian Federation	*E. granulosus*
Tasmanian sheep strain (G2)	Sheep, cattle?	Yes	Dog, fox	Tasmania, Argentina	*E. granulosus*
Buffalo strain (G3)	Buffalo, cattle?	?	Dog, fox?	Asia	*E. granulosus*
Horse strain (G4)	Horses and other equines	No	Dog	Europe, Middle East, South Africa	*Echinoccus equinus*
Cattle strain (G5)	Cattle	Yes	Dog	Europe, South Africa, India, Nepal, Russian Federation, South America?	*Echinoccus ortleppi*
Camel strain (G6)	Camels, goats, cattle?	Yes	Dog	Middle East, Africa, China, Argentina	*E. granulosus*?
Pig strain (G7)	Pigs	Yes	Dog	Europe, Russian Federation, South America	*E. intermedius*
Cervid strain (G8)	Moose, caribou, reindeer	Yes	Wolf, coyote, dog	North America, Eurasia	*E. granulosus*
Fennoscandinavian cervid strain (G10)	Reindeer, moose?	?	Wolf, dog	Eurasia	*E. granulosus*?
Lion strain	Zebra, wildebeest warthog, bushpig buffalo, various antelope, giraffe? Hippopotamus?	?	Lion	Africa	*E. granulosus*?
Echinococcus multilocularis					
European isolate	Rodents, domestic and wild pig, dog, monkey	Yes	Fox, dog, cat, wolf raccoon–dog	Europe, China?	*E. multilocularis*
Alaskan isolate	Rodents	Yes	Fox, dog, cat	Alaska	*E. multilocularis*
North American isolate	Rodents	Yes	Fox, dog, cat, coyote	North America	*E. multilocularis*
Hokkaido isolate	Rodents, pig monkey, horse	Yes	Fox, dog, cat raccoon–dog	Japan	*E. multilocularis*
Echinococcus vogeli					
(None reported)	Rodents	Yes	Bush dog	Central and South America	*E. vogeli*
Echinococcus oligarthrus					
(None reported)	Rodents	Yes	Wild felids	Central and South America	*E. oligarthrus*
Echinococcus shiquicus					
(None reported)	Rodents, lagomorphs?		Tibetan fox	Tibetan Plateau (China)	*E. shiquicus*

Modified from Thompson and McManus [1].

drial and genomic DNA of the variant populations provide reliable genetic markers to distinguish them [1–3]. It is likely that the speciation question will be debated for some time and, until it is further clarified, it is important to recognize that important biologic differences exist between populations presently identified in many texts as *E. granulosus*, the causative agent of cystic echinococcosis, and that these may account for local differences in patterns of transmission and clinical and public health significance of the disease.

2.1. Cystic echinococcosis (CE)

In many countries of these endemic regions, national diagnostic incidence rates of CE range from 5 to 20 per 100,000 population [4]. "National" rates are misleading, however, because most urban populations are at low risk; in rural endemic areas diagnostic incidence is manyfold higher. Furthermore, rates based on clinically diagnosed cases underestimate the burden of infection; surveys of populations in endemic populations using ultrasound imaging diagnostic techniques often measure CE prevalences of 2% to 6%, manyfold higher than evident from clinically diagnosed cases [5–7].

Socioeconomic and cultural characteristics are among the best-defined risk factors for human infection with CE throughout its broad global range: uncontrolled dogs living closely with people, uncontrolled slaughter of livestock, and insanitary living conditions [4]. Whether it be among Arabs in Tunisia, Quechua Indians in Peru, Turkana tribesmen in Kenya, or Tibetans in China these common factors are readily discernible. Consistently highest prevalence is found among populations involved with sheep raising, thus emphasizing the predominant public health importance of the sheep genotype *E. granulosus* (G1). In these regions the social and economic impacts of the infection can be highly significant [4,8].

Although mortality rates associated with hydatid disease may appear low in comparison with those for some other infectious diseases, the morbidity associated with each case is considerable. Patients with hydatid disease often require multiple surgical interventions. Extensive secondary hydatid

disease often becomes inoperable, and involvement of the bones usually requires amputation. Economic losses to affected families include surgical and hospital expenses as well as loss of income. Published data on the "burden" of echinococcosis from many countries extensively document the severe impact of these infections in terms of their impact on human health and productivity as well as the monetary losses incurred as a result of infection in livestock hosts [8].

Recent investigations in China have demonstrated that, in addition to direct medical costs, the long-term quality of life in patients treated for CE and AE was permanently affected indicating that morbidity is more subtle and considerably greater than previously appreciated. Budke and others [9] determined that individuals who were previously unaware they had the disease, but diagnosed with CE or AE in a random cross-sectional study using abdominal ultrasound, experienced a significant decrease in the quality of life associated with receiving a positive diagnosis of CE or AE. Their investigation determined that the DALYs (disability adjusted life years) lost due to these infections in terms of medical treatment costs, lost income, and physical and social suffering, was substantial. Such decreases in the quality of life presumably have significant economic effects including impairment in the work place and thus having less highly paid work than would otherwise have been the case, having greater levels of absenteeism from work, or possibly requiring greater levels of long term nursing care.

Imaging technology developed in recent years has revolutionized detection of hydatid cysts and other space-occupying lesions in all parts of the body. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound imaging are all useful for detecting and for defining the extent and condition of avascular fluid-filled cyst(s) in most organs [10]. These noninvasive imaging techniques have proved invaluable for diagnosis and preoperative evaluation by staging the condition of the lesion (intact; unilocular; ruptured; complicated with daughter cysts; and calcified), the extent of the lesion in reference to other organs and vital structures, and identifying the presence of additional, occult lesions. Ultrasonography, because of its relatively low cost and portability, has been used widely for screening, clinical diagnosis, and monitoring of treatment of liver and intra-abdominal cysts [11]. The WHO Informal Working Group on Echinococcosis (WHO-IWGE) proposed a standard ultrasound classification of hydatid cysts based on their ultrasound appearance consistent with the natural history of the disease and response to treatment which is useful for defining the extent and condition of the cyst(s) [12]. The standardized classification scheme is intended to promote uniform standards of diagnosis and treatment and may be applied to clinical management of patients as well as to field diagnostic surveys.

Serologic tests are useful for confirming presumptive imaging diagnoses; however, the limitations of serodiagnosis in cystic echinococcosis must be understood to correctly interpret the findings. Specific confirmation of reactivity can be obtained by demonstrating echinococcal antigens by immunodiffusion (arc 5) procedures or immunoblot assays

(8-, 16-, 21-kDa bands) [13,14]. These latter serodiagnostic markers are the most *E. granulosus*-specific criteria described, but even they may be detected in serum of patients with other forms of echinococcosis and 5% to 10% of patients with *T. solium* cysticercosis [15].

Until recent decades, surgery was the only option for treatment of echinococcal cysts, however, chemotherapy with benzimidazole compounds and, more recently, cyst puncture, and percutaneous aspiration, injection of chemicals, and reaspiration (PAIR) are increasingly seen to supplement or even replace surgery as the preferred treatment. The benefits and limitations of current treatment options have been critically reviewed by consultants for the World Health Organization (WHO) Informal Working Group on Echinococcosis [16].

The development and use of ultrasound imaging technology for clinical diagnosis and population screening has led to significant improvements in clinical management of abdominal forms of echinococcosis and has provided new information on the natural history of the disease; it is now clear that many, if not the majority of cases of CE, have a benign prognosis. This knowledge has led to new, unanswered questions about the necessity for, criteria for, and selection of appropriate treatments. Development of definitive guidelines is still hampered by the lack of a) complete knowledge of the natural history of the disease, b) properly powered clinical trials, and c) adequate long term follow-up. Coordination of effort in long-term multicenter trials will be crucial to significantly improve knowledge and technology of treatment.

E. granulosus has been viewed as highly vulnerable to the implementation of preventive measures, at least in theory. When only synanthropic hosts under human control are involved, the cestode cycle can be interrupted if dogs are prevented from consuming infected viscera from sheep and other domestic ungulates. Indeed, there are now a number of successful examples of echinococcosis control, achieved on a national or regional scale, that confirm that *E. granulosus* is relatively unstable in synanthropic hosts and responds readily to comprehensive and consistently applied measures of intervention [4,17].

Progress in developing effective vaccination against infection with oncospheres and immunotherapy of the metacestode have been reviewed by Lightowlers and others [18]; vaccination may provide an additional tool for control and prevention of this infection.

2.2. Alveolar echinococcosis (AE)

Being largely confined to life cycles involving foxes and arvicolid rodents, in ecosystems generally separate from humans, exposure of humans to *E. multilocularis* is relatively less common than exposure of humans to *E. granulosus*, the cause of cystic echinococcosis. Fox trappers and other persons who work with foxes or their fur would appear to be relatively frequently exposed to eggs of *E. multilocularis*, but these occupations have not been associated with higher rates of infection [19,20]. There is ecological overlap to humans because domestic dogs or cats may become infected when

they eat infected wild rodents and infected pets are an important source of infection for humans [21]. Hyperendemic foci have been described in some Native American villages of the North American tundra (now largely disappeared) and in China [4–6,22] where local dogs regularly feed on infected commensal rodent and lagomorph intermediate hosts. Under these circumstances, indirect or direct contamination from feces of infected dogs appears to be the most important source of infection and human infection prevalence may reach 2–6% [5,6].

E. multilocularis has an extensive geographic range in the Northern Hemisphere, widespread and increasing in Europe, most of northern Eurasia, from Bulgaria and Turkey through most of Russia, and the newly independent nations of the former U.S.S.R., extending eastward to several of the Japanese islands [4]. Recent surveys in Central Europe have extended the known distribution of *E multilocularis* from four countries at the end of the 1980s to at least 11 countries in 1999 [23]. The incidence of diagnosed disease in humans remains low, between 0.02 and 1.4 per 100,000 for entire countries or larger regions of endemicity. Between 1982 and 2000, 559 cases of alveolar echinococcosis in humans were reported voluntarily from nine European countries to the European Echinococcosis Registry [24]. The cestode appears to have spread eastwards in Europe in association with increased populations of foxes and this may herald the emergence of AE in humans in central Eastern Europe. Surveys of foxes in Germany and France carried out in the mid-1990s compared recent data with that collected in the 1970s and 1980s, and documented higher fox densities as well as increased prevalences of *E. multilocularis* infection [25]. New human cases have been reported during the last 10 years in several European countries previously considered non-endemic: i.e. Belgium, Netherlands, Luxembourg, Czech Republic, Slovak Republic, Poland, Italy, Slovenia, Hungary, Bulgaria and Romania [24]. Increasing fox populations, increasing encroachment of foxes into urban areas and spillover of *E. multilocularis* infection from wild carnivores to domestic dogs and cats might presage increased public health risks of AE [26].

The known distribution and prevalence of infection in foxes and coyotes has increased in the United States and now extends from Montana in the West to western Ohio in the East [27,28]. Exposure of humans appears rare. To date only two persons are known to have acquired their infections in the endemic region in central North America—a 54-year-old man from Manitoba, Canada, and a 60-year-old woman from Minnesota; however, the potential exists for a more serious public health problem [4].

Alveolar echinococcosis closely mimics hepatic carcinoma and is a challenge to diagnose, even in endemic regions. CT and MRI imaging diagnostic criteria have been described [16]. Serologic tests are usually positive at high titers [29] and highly specific antigens [30–32] have been identified and synthesized that, when used in serologic assays, are highly sensitive and specific for diagnosis of AE and can distinguish this infection from CE (*E. granulosus*) and other forms of echinococcosis. Antibodies of the IgG1 and IgG4 isotypes are the most

sensitive IgG responses in alveolar echinococcosis and monitoring of these isotypes tended to correlate with active vs. inactive disease and successful treatment [33].

In seronegative patients PCR reactions for detection of echinococcal-specific RNA or DNA, in closed or open biopsy specimens, have been developed and may confirm the diagnosis [34,35].

Clinicians familiar with this disease emphasize that management of alveolar echinococcosis, characterized by a malignant-like proliferating cestode, is extremely difficult and usually requires radical surgery, ideally at an early stage, and long-term to life-long chemotherapy with benzimidazoles [36]. Choosing from the variety of treatment options requires specific clinical experience, therefore, patients should be referred to recognized national or regional alveolar echinococcosis treatment centers [37]. Experience in AE screening programs in Japan and elsewhere have shown that early diagnosis reduces morbidity and mortality.

Active intervention for control of *E. multilocularis* presents special difficulties because the primary cycle is almost always sylvatic. In most regions where *E. multilocularis* is enzootic, controlling the cestode by eliminating its sylvatic hosts would be impractical for economic and logistic reasons or unacceptable for ecological reasons. Where exposure of humans is mainly related to cycles involving synanthropic hosts, that is, dogs, protection might be achieved by regular taeniacidal treatments of dogs. Periodic mass echinococcidal treatments of dogs as an approach to reducing the risk of human infection was evaluated in a 10-year field trial in a village on St. Lawrence Island, Alaska, where *E. multilocularis* was hyperendemic [38]. All dogs in this village were given praziquantel 5 mg/kg body weight at monthly intervals. This was effective in reducing egg contamination as evidenced by an average 83% reduction in infection prevalence in voles during the course of the trial; prevalence in locally captured voles declined from an average of 29% at the beginning of the trial to less than 5% at the end. This control method, which is relatively costly, may be applicable to other regions where synanthropic cycles create a high risk for local human populations; such areas may include recently described endemic foci in Gansu, Qinghai and Sichuan provinces, China, where recent surveys showed high rates of infection in domestic dogs [5–7,22]. The costs and benefits of this approach require further evaluation.

3. Cysticercosis/taeniasis (*T. solium*)

Cysticercosis/taeniasis, caused by the "pork tapeworm", *T. solium*, has emerged just as dramatically as echinococcosis. Although commonly recognized by pathologists and neurosurgeons staffing clinics in endemic regions, international emergence of this zoonotic infection required the development of imaging technology [computerized tomographic (CT) and magnetic resonance (MRI) imaging] which permitted the demonstration of viable cysticerci in the brains of infected persons [39]. Prior to the availability of modern diagnostic imaging technology, antemortem diagnosis of cerebral cysticercosis was mostly limited to patients with calcified cysts that

could be demonstrated in patient's brains by radiographic imaging and, in deceased patients, at autopsy. Today CT and MRI are widely available in hospital settings and the criteria for diagnosis and staging of cysticercosis are described [39,40]. The art and science of immunologic diagnosis of cysticercosis and taeniasis has proceeded rapidly from demonstration of the diagnostically important antigens in larval and adult-stage parasite stages [41,42], assessment of sensitivity and specificity, isolation of the key antigenic components and development of practical diagnostic technology for laboratory and field applications [29,43–46]. Complementing immunologic assays has been development of genetic markers and modification for molecular assays [29,47] These efforts have resulted in a variety of immunologic and molecular diagnostic techniques that can be applied to diagnosis of cysticercosis and taeniasis for clinical and epidemiologic studies.

Deficiencies in diagnostic detection of adult-stage intestinal tapeworm carriers have for long limited epidemiologic studies and control strategies based on detection and treatment of tapeworm carriers. Detection of eggs in feces is insensitive and nonspecific. The development of fecal antigen assays and antibody assays for detection of antibody specific to adult-stage infection provided technology of potential application in epidemiologic surveys and control interventions [29,45–47].

A major factor in improving clinical management of this disease was the development of effective chemotherapy. The efficacy of and strategies for use of praziquantel and albendazole have now been well-described and consensus treatment guidelines have been developed [48–50].

Data obtained from epidemiologic surveys and clinical experiences document that *T. solium* cysticercosis affects millions of people throughout the world and is a major public health problem for most of the developing world [39]. A recent estimate of the prevalence of neurocysticercosis in Latin America indicated that ∼400,000 persons have symptomatic disease and many more are infected but not yet symptomatic [51].

Although *T. solium* is not transmitted in its swine–human life cycle in the United States, it has dramatically emerged as a common cause of seizures among immigrants from Mexico and other endemic areas [39,40]. Diagnoses of neurocysticercosis (NCC) in the United States have followed the movements of migrants in the United States from California north to Oregon and Washington states and west to Texas, the Southeastern and Middle Atlantic states. Although the overwhelming majority of cases of NCC patients have been diagnosed in immigrants who were presumably infected in their countries of origin, foci of autochthonous transmission have been recognized from immigrant *Taenia* carriers to family members and other contacts [39,52]. Similar situations resulting in intrahousehold transmission associated with employment of infected household employees have been documented in Kuwait [53] and Peru [54].

Estimating the global economic impact of cysticercosis is handicapped by inadequate information on the prevalence and public health importance of the disease in most countries. However, the economic losses appear to be highly significant. In Mexico, for example, porcine cysticercosis is responsible for a loss of more than one-half of the national investment in swine production and for more than US$17 million annually in hospitalization and treatment costs for humans with neurocysticercosis [55]. For all of Latin America, porcine cysticercosis accounts for an estimated economic loss of US$164 million. *T. solium* taeniasis/cysticercosis is an important example of an imported infection disease which impacts on the health of the United States' population but requires international coordinated efforts to prevent or limit transmission.

In 1993, the International Task Force For Disease Eradication declared *T. solium* a potentially eradicable infection [56]. The parasite has several characteristics that appear to make it vulnerable to eradication: 1) the life cycle requires humans as definitive hosts, 2) tapeworm infections in humans are the only source of infection for pigs, the natural intermediate hosts, 3) the life span of pigs rarely exceeds 1 year and swineherds can be managed, 4) no reservoirs for infection exist in wildlife, 5) *T. solium* gradually disappeared from most European countries even without control measures targeted specifically at it. Factors credited with the elimination of *T. solium* include improvements in general sanitation and economic status, the introduction of indoor pig husbandry, and rigorous meat inspection. Despite this historical experience and despite the remarkable recent improvements in technology to diagnose and treat this disease, under the conditions that exist currently in countries where *T. solium* infection is endemic, and given available resources, we do not yet know what is required to reduce and ultimately eliminate transmission.

Although a number of intervention trials based on health education and improved sanitation have demonstrated that transmission of *T. solium* can be inhibited temporarily [45], it has become clear that poverty and ignorance combine to thwart changes in behavior and environment sufficient to permanently limit or prevent transmission. Effective elimination of *T. solium* will require sustained pressure on the parasite in both human and swine hosts. A regional program in a highly endemic area of Peru has been initiated to evaluate several intervention strategies: mass or selected taeniacidal treatment of humans; cysticercidal treatment of pigs; and vaccination of pigs and/or humans. The outcome of this experience will inform future intervention programs directed against *T. solium* cysticercosis.

4. Importance of international collaboration

The remarkable progress in development of technology to diagnose, treat and prevent transmission of echinococcosis and cysticercosis has been greatly facilitated by international collaborations that have promoted sharing of ideas and resources. A network of collaborating groups working on echinococcosis was created through the auspices of the World Health Organization (Informal Working Group on Echinococcosis) and has facilitated the production of guidelines on treatment and control [2]. Informal networks of scientists working on cysticercosis such as the Cysticercosis Working Group in Peru and the Cysticercosis Working Group in Asia [57] are leading the way in progress toward improved diagnosis, treatment and elimination of cysticercosis.

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