Seminar

# Echinococcosis

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**Echinococcosis is a near-cosmopolitan zoonosis caused by adult or larval stages of cestodes belonging to the genus *Echinococcus* (family Taeniidae). The two major species of medical and public health importance are *Echinococcus granulosus* and *Echinococcus multilocularis*, which cause cystic echinococcosis and alveolar echinococcosis, respectively. Both are serious and severe diseases, the latter especially so, with high fatality rates and poor prognosis if managed incorrectly. Several reports have shown that both diseases are of increasing public health concern and that both can be regarded as emerging or re-emerging diseases. In this review we discuss aspects of the biology, life cycle, aetiology, distribution, and transmission of the *Echinococcus* organisms, and the epidemiology, clinical features, treatment, and diagnosis of the diseases they cause. We also discuss the countermeasures available for the control and prevention of these diseases. *E granulosus* still has a wide geographical distribution, although effective control against cystic echinococcosis has been achieved in some regions. *E multilocularis* and alveolar echinococcosis are more problematic, since the primary transmission cycle is almost always sylvatic so that efficient and cost-effective methods for control are unavailable.**

Echinococcosis is a near-cosmopolitan zoonosis caused by adult or larval stages of tapeworms (cestodes) belonging to the genus *Echinococcus* (family Taeniidae). Larval infection (hydatid disease, hydatidosis) is characterised by long term growth of metacestode (hydatid) cysts in the intermediate host. The two major species of medical and public health importance are *Echinococcus granulosus* and *Echinococcus multilocularis*, which cause cystic echinococcosis and alveolar echinococcosis, respectively. These are both serious life-threatening diseases, the latter especially so, with a high fatality rate and poor prognosis without careful clinical management. Two other species, *Echinococcus vogeli* and *Echinococcus oligarthrus*, are responsible for polycystic echinococcosis in Central and South America. Few cases of this condition have been reported in man,[1,2] and the real extent of the disease is unknown. A comprehensive account of the biology, life cycle characteristics, and aetiology of *Echinococcus* is available,[3] so only a brief description is presented here. A selection of websites on *Echinococcus* and echinococcosis are presented in panel 1. A special issue of *Acta Tropica* (vol 85, issue 2, February, 2003) entitled: "New Dimensions in Hydatidology in the New Millenium" should also be consulted for recent progress in research on echinococcosis and hydatid disease.

Hydatid cysts of *E granulosus* develop in internal organs (mainly liver and lungs) of humans and other intermediate hosts as unilocular fluid-filled bladders. The life cycles of *E granulosus* and *E multilocularis* are illustrated in figure 1.

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The definitive hosts of *E granulosus* are carnivores such as dogs and wolves, which are infected by ingestion of offal containing hydatid cysts with viable protoscoleces. After ingestion, the protoscoleces evaginate, attach to the canine intestinal mucosa, and develop into adult stages. Sexual maturity (length of 3–6 mm) is reached 4–5 weeks later. Eggs or gravid proglottids are shed in the faeces. Following ingestion by a human or ungulate intermediate host (sheep, goats, pigs, cattle, horses, and camels) an oncosphere larva is released from the egg. The larvae then penetrate into the lamina propria and are transported passively through blood or lymph vessels to the liver, lungs, or other organs, where the oncosphere larvae develop into hydatid cysts (metacestode larvae). These consist of two parasite-derived layers: an inner nucleated germinal layer, and an outer acellular laminated layer surrounded by a host-derived fibrous capsule. Brood capsules and protoscoleces bud from the germinal membrane. The range of intermediate host species depends on the infecting strain of *E granulosus*, regional or local differences in the availability of the various intermediate host species, and other factors.[4] Since the life cycle relies on carnivores eating infected herbivores, humans are usually a "dead-end" for the parasite. This is not always the case. Many transhumant groups (transhumance is the seasonal movement of people and their livestock to regions of different climate) in hyperendemic regions of eastern Africa, such as the Turkana region of northwest Kenya, do not bury their dead. Dogs and wild carnivores are able to scavenge from the human remains; if the cadaver harbours cysts, then under these unique circumstances, human beings can act as intermediate hosts.[5]

Adult worm infections of *E multilocularis* are perpetuated in a sylvatic cycle (figure 1), with wild carnivores—mainly red (*Vulpes vulpes*) and arctic (*Alopex lagopis*) foxes—regarded as the most important definitive hosts. Domestic dogs and cats can also harbour the tapeworm and may be involved in a synanthropic cycle. Small mammals (usually microtine and arvicolid rodents) act as intermediate hosts. The metacestode of *E multilocularis* (figures 1 and 2) is a tumour-like, infiltrating structure consisting of many small vesicles

**Panel 1: Echinococcosis websites of interest**

http://www.dpd.cdc.gov/dpdx/HTML/Echinococcosis.htm
http://www.cdc.gov/ncidod/dpd/parasites/alveolarhydatid/default.htm
http://cal.vet. upenn.edu/dxendopar/parasitepages/cestodes/e_granulosus.html
http://www.biosci.ohio-state.edu/~parasite/echinococcus.html
http://eurechinoreg.org

embedded in stroma of connective tissue. The metacestode mass usually contains a semisolid matrix rather than fluid.[3] Larval growth in the liver remains indefinitely in the proliferative stage, resulting in invasion of the surrounding tissues. The sylvatic cycle accounts for most infections in man, although dogs may also play a role. It is unclear whether cats contribute to transmission to human beings. As with *E granulosus*, it is thought that people become exposed to *E multilocularis* by handling of infected hosts, or by ingestion of food contaminated with eggs. Coprophagic flies and other animals may serve as mechanical vectors of the eggs of both species.

*E granulosus* comprises several intraspecific variants or strains that have substantial variation at the genetic level.[3] By contrast, there seems to be very limited genetic variation within *E multilocularis*,[6-8] and there are no available data to indicate that either *E vogeli* or *E oligarthrus* is variable.

The term strain is used to describe variants that differ from other groups of the same species in gene frequencies or DNA sequences, and in one or more characters of actual or potential importance to the epidemiology and control of echinococcosis.[9,10] The extensive intraspecific variation in nominal *E granulosus* may affect life-cycle patterns, host specificity, development rate, antigenicity, transmission dynamics, sensitivity to chemotherapeutic agents, and pathology.[3,11,12] This may have important implications for the design and development of vaccines, diagnostic reagents and drugs impacting on the epidemiology and control of echinococcosis. For example, the adult parasite of the cattle strain shows a precocious development in the definitive host with a short prepatent period (onset of egg production) of only 33–35 days, nearly a week earlier than that of the common sheep strain.[12] This feature complicates control efforts where drug treatment of definitive hosts is used to break the cycle of transmission, as it necessitates an increase in frequency of adult cestocidal treatment.

A number of well-characterised strains are now recognised that all seem to be adapted to particular life cycle patterns and host assemblages.[3] To date, molecular studies, mainly with mitochondrial DNA (mtDNA) sequences, have identified 9 distinct genetic types (genotypes G1-9) within *E granulosus*.[13] This categorisation follows very closely the pattern of strain variation emerging based on biological characteristics. A reassessment of the taxonomy of *E granulosus* has been recently advocated.[14] Based on a range of different biological, epidemiological, biochemical and molecular-genetic criteria, the case for separate species status for several of these strains, in particular, the horse-dog (G4 genotype) and sheep-dog (G1 genotype) strains, is now overwhelming.[14] Indeed, a recent comparison of the complete mtDNA sequences for these two strains of *E granulosus* relative to the mtDNA sequence of *E multilocularis*[15] has shown them to be almost as distinct from each other as either is from *E multilocularis*.[16]

## Distribution

*E granulosus* has a worldwide geographical distribution (figure 3). It is found on all continents, with highest prevalence in parts of Eurasia (especially Mediterranean countries, the Russian Federation and adjacent independent states, and China), north and east Africa, Australia, and South America.[17] There is clear evidence for the emergence or re-emergence of human cystic echinococcosis in parts of China, central Asia, eastern Europe, and Israel.[17,18] Communities involved in sheep farming harbour the highest rates of infection, showing the

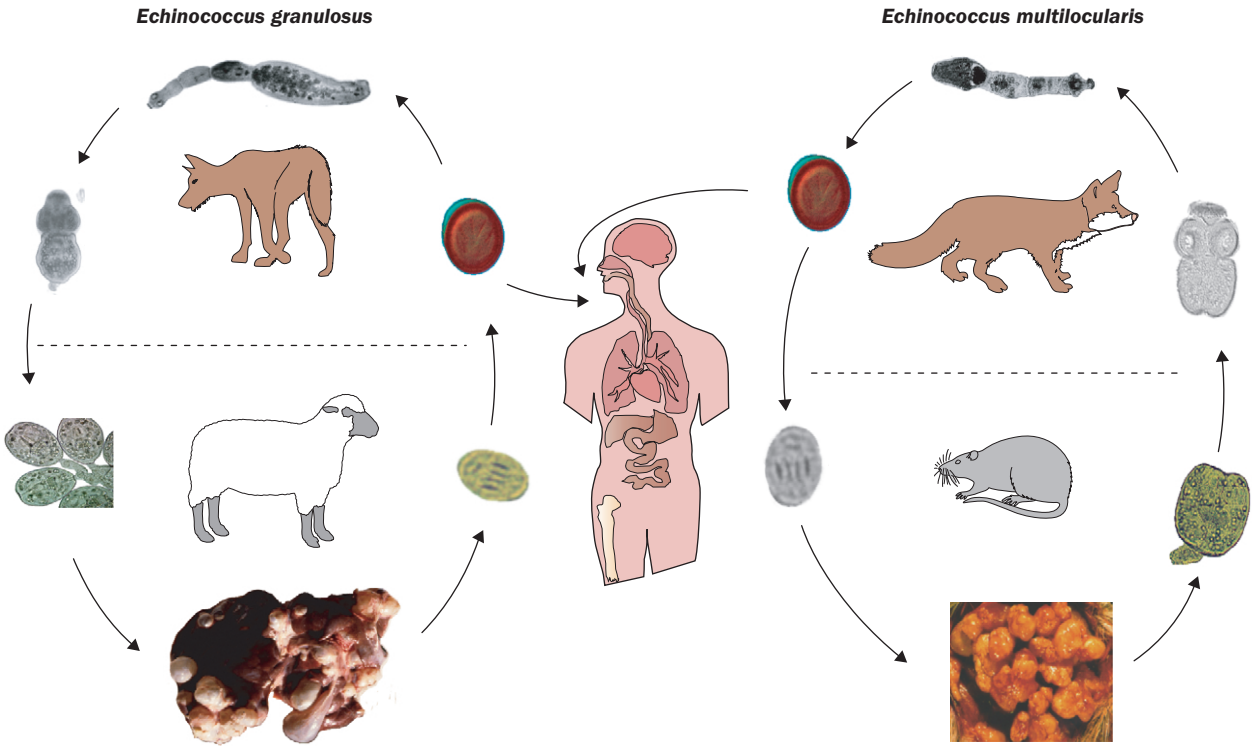


Figure 1: **Life cycles of *E granulosus* and *E multilocularis***

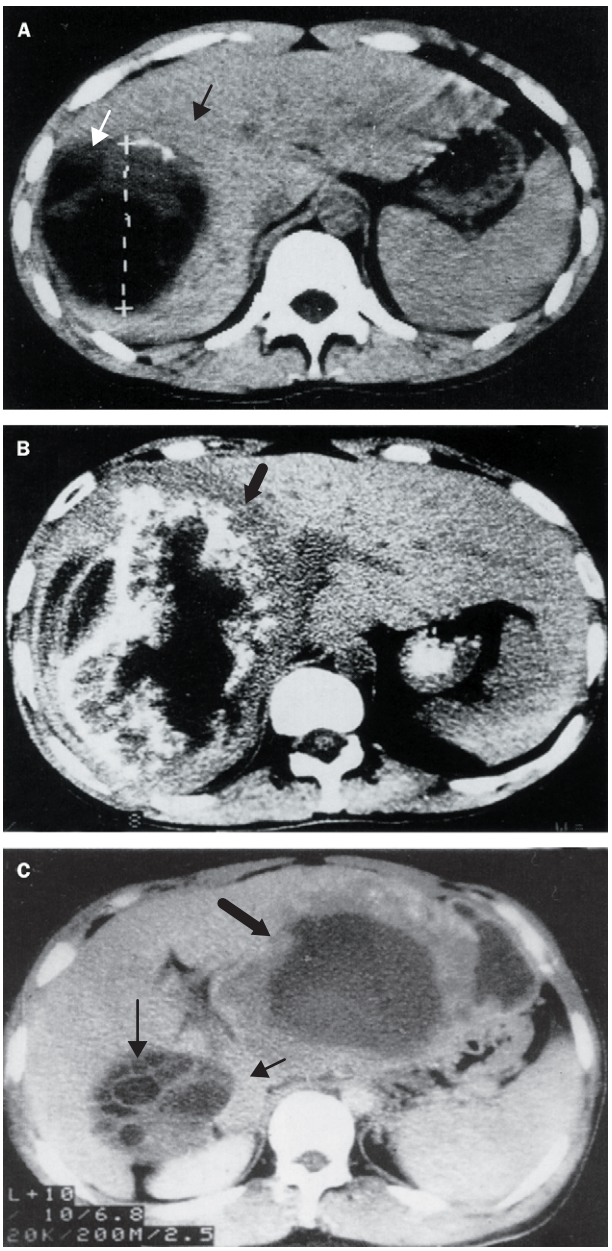


Figure 2: **Abdominal CT scans of patients with hepatic echinococcosis**

(A) Cystic echinococcosis due to *E granulosis*—daughter cysts are marked with an arrowhead. (B) Alveolar echinococcosis from *E multilocularis* infection (arrowhead). (C) A patient with mixed cystic echinococcosis (small arrowhead) and alveolar echinococcosis (large arrowhead) of the liver.

public health importance of the sheep-dog cycle and the sheep strain of *E granulosus* in transmission to people.[3,13] However, other life-cycle patterns involving ungulates and domestic dogs are also important. Wild animals are also involved in sylvatic cycles in different parts of the world although, generally, their zoonotic importance is small compared with the domestic cycles.[3] A substantial sylvatic cycle involving the common sheep strain operates on the mainland of Australia between dingoes (and feral dogs) and macropod marsupials (such as kangaroos and wallabies). This cycle overlaps and interacts with the domestic sheep-dog cycle, complicating control efforts.[3]

Another sylvatic life cycle, involving wolves or sled dogs and cervids, such as moose and reindeer, occurs in the higher latitudes in northern North America and Eurasia. The first two documented human infections with *E granulosus* in Alaska with accompanying severe sequelae in the liver were recently reported.[19] The results of molecular genetic analysis of the cyst material of one of the patients supported identification of the parasite as the sylvatic (cervid) strain and not the domestic (common sheep) strain, which was initially thought to be implicated in these unusually severe Alaskan cases.[20] The adverse outcomes could have been rare complications that are part of the clinical range of diseases caused by sylvatic cystic echinococcosis, an indication that the sylvatic form of *E granulosus*, especially when affecting the liver, has potential for severe clinical consequences.

*E multilocularis* has recently been discovered to have a much wider geographical distribution than was previously thought.[21] The parasite is endemic in the northern hemisphere (figure 3) where its extensive range includes the central part of western Europe, parts of the near East, Russia, and the central Asian Republics, China, northern Japan, and Alaska.[17,18,22] Increasing fox populations, the increasing encroachment of foxes into urban areas, and other factors such as spillover of *E multilocularis* infection from wild carnivores to domestic dogs and cats, might point to a new public health hazard associated with alveolar echinococcosis.[17,21]

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, although the annual incidence of disease in man remains low.[21] It is not known whether these findings show a recent extension of the range of *E multilocularis* or just improved case finding in previously unnoticed endemic areas.[21] There is evidence of parasites spreading from endemic to previously non-endemic areas in North America and North Island, Hokkaido, Japan, due principally to the movement or relocation of foxes. A similar situation may prevail in Hungary, where *E multilocularis* was recently reported for the first time in red foxes.[23] The parasite might be spreading eastwards because the population of foxes has increased as a consequence of human interventions, and this spread could result in the emergence of alveolar echinococcosis in central eastern Europe. Furthermore, recent observations of cases in people in China indicate widespread infection. Indeed, alarming increases in reported cases from rural areas in the western and central parts of China, particularly southern Gansu, southern Ningxia Autonomous Region, eastern Qinghai, and northern Sichuan[17,21,24] point to serious consequences for public health in these communities.

## Epidemiology and transmission

Exposure to *Echinococcus* eggs may be affected by occupational and behavioural factors. In the case of *E multilocularis*, hunters, trappers, and mushroom pickers would be expected to be more highly exposed than the general population, but there is little evidence that these groups are at increased risk of infection.[25-27] The wide distribution and generally high frequency of *E multilocularis* in foxes is not reflected in rates of infection in man which, for reasons not fully understood, are low in most endemic areas. Immunogenetic factors might play a part in this situation.[28-32]

The dynamics of *E multilocularis* transmission are complex, being affected by many factors that include seasonal fluctuations in the size of fox populations, the dispersal of foxes, involvement of other wild carnivores in the life cycle, the susceptibility and immunity of definitive hosts, worm burdens, prepatent period and egg

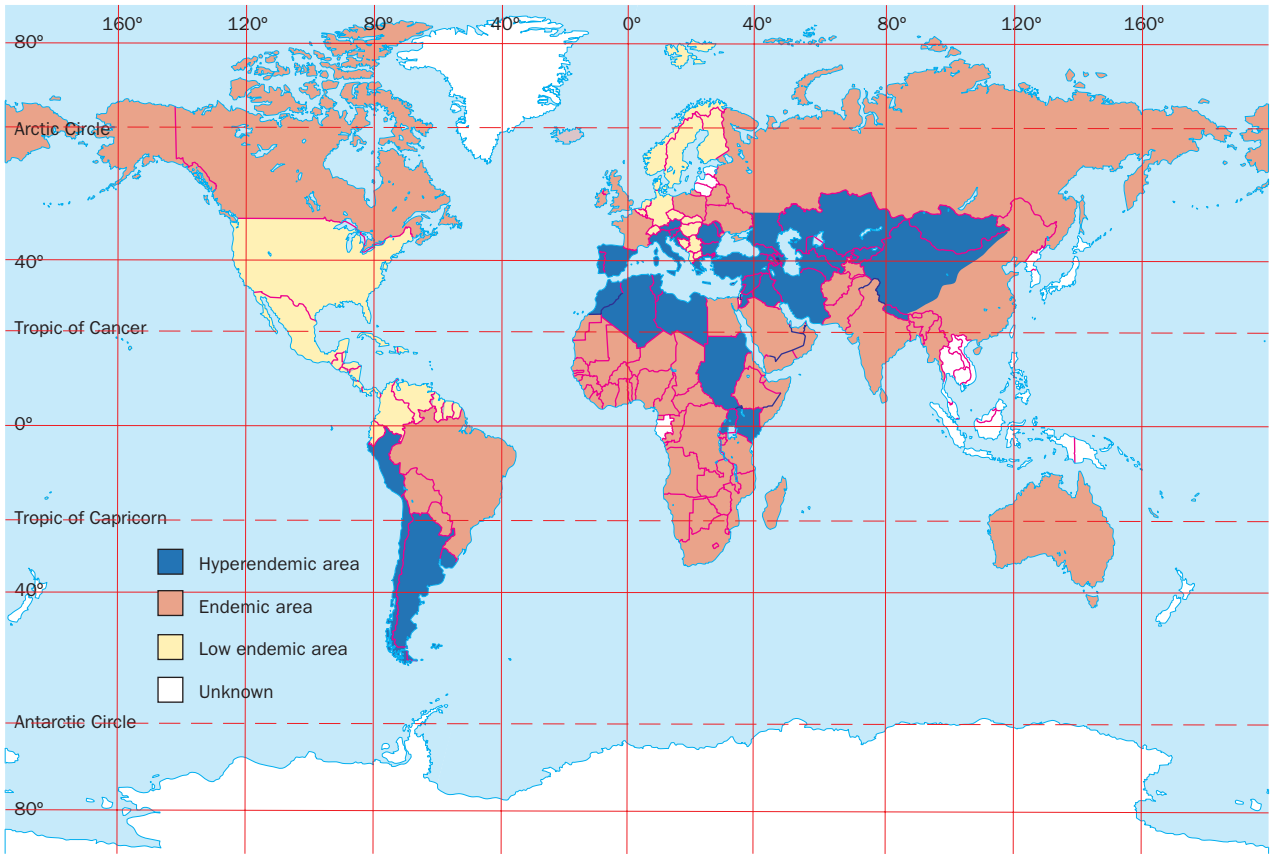


Figure 3: **Worldwide distribution of cystic echinococcosis**
Modified from Schantz P, Gottstein B. Echinococcosis (hydatidosis). Orlando: Academic Press, 1986.

production of *E multilocularis* infections in different definitive hosts, dispersal of eggs, and resistance of eggs to environmental factors. The contributions of intermediate hosts and the ecology of small mammalian hosts[32] to the transmission dynamics of *E multilocularis* are also likely to be very important but are less well defined.[26] The sylvatic cycle can persist with low (<2%) or high (>80%) rates of *E multilocularis* in foxes and with variable infection rates (<1% to >80%) in rodents.[26]

With *E granulosus*, acquired immunity in intermediate hosts represents an important density-dependent constraint for transmission, but parasite-induced mortality in livestock does not seem to play a role in the regulation of the cycle.[33] In *E multilocularis*, the natural intermediate rodent hosts are short-lived, the parasite evades the host immune responses and, generally, but not always, large numbers of protoscoleces are produced in a short period after infection. By contrast, the intermediate hosts of *E granulosus* are long-lived and infection by eggs provokes a high degree of protective immunity, a characteristic that has been used for the development of a highly effective vaccine.

Although knowledge of the epidemiology of *E multilocularis* and the life histories of its hosts are limited, mathematical models of the life cycles of both *E multilocularis* and *E granulosus* have been formulated,[33-35] but not yet rigorously tested and verified. The recent application of satellite remote sensing, geographical information systems, and landscape approaches in mammalian ecology to the study of *E multilocularis* provides a new approach for exploring spatial relationships between landscape composition and transmission that will allow predictive models of alveolar echinococcosis risk to be formulated.[36,37]

## Clinical features

The initial phase of primary infection is always asymptomatic. Small cysts not inducing major disease may remain asymptomatic for many years, if not permanently. The incubation period of cystic echinococcosis is unclear but probably lasts for many months to years. The infection may become symptomatic if the cysts either rupture or exert a mass-effect. Recurrence may arise following surgery on primary cysts. Cystic echinococcosis has been reported to present for medical attention in people aged from younger than 1 year to older than 75 years. In two large published series, most patients presenting with symptomatic disease were between the ages of 4 and 15 years. Rates are fairly similar in both sexes.[38,39] In north Africa, most cases are in adults aged 21–40 years.[40] Up to 60% of all cystic echinococcosis cases may be asymptomatic, although an unknown proportion may become symptomatic. The mortality rate is estimated to be 0·2 per 100 000 population, with a case fatality rate of 2·2%. As referred to earlier, certain occupations such as farm labourers and animal herders are, not surprisingly, associated with an increased risk of the disease.[39] More than 90% of cysts occur in the liver, lungs, or both. Symptomatic cysts have been reported occasionally (2–3% each) in the kidney, spleen, peritoneal cavity, and the skin and muscles; and rarely in the heart, brain, vertebral column, and ovaries (1% or less each).[39] Presenting symptoms of cystic echinococcosis are highly variable.[41] Presenting features depend not only on the organ involved, but also on the size of the cysts and their position within the organ, the mass effect within the organ and upon surrounding structures, and complications relating to cyst rupture and secondary

| | Active | Fertile | Cyst wall | Remarks |
|---|---|---|---|---|
| **Type** | | | | |
| CL* | Yes | No | Not visible | If cysts are due to cystic echinococcosis—early stage of development |
| CE1 | Yes | Yes | Visible | Unilocular, anechoic or "snowflake sign" |
| CE2 | Yes | Yes | Visible | Multiseptate and multivesicular, daughter cysts present- |
| CE3 | Transitional | Yes | Visible | Anechoic content with detached laminated membrane ("waterlily sign"). Decreased intracystic pressure. Cyst starting to degenerate. |
| CE4* | Inactive | No | Not visible | Heterogeneous hyperechoic or hypoechoic contents. No visible daughter cysts. "Ball of wool" sign due to degenerate membranes. Usually no viable protoscolices. |
| CE5* | Inactive | No | Calcified | Thick, variably calcified wall producing a cone-shaped shadow. Usually no viable protoscolices. |

Cysts subclassified according to size: small <5 cm; medium 5–10 cm; large >10 cm. *Further tests required to ascertain a diagnosis of cystic echinococcosis.

Table 1: **Classification of hepatic cystic echinococcosis lesions based on ultrasound examination[44]**

infection (table 1). Manifestations of systemic immunological responses may be evident in response to cyst leakage or rupture. Common complications include rupture into the biliary tree with secondary cholangitis, biliary obstruction by daughter cysts or extrinsic compression, intracystic or subphrenic abscess formation, intraperitoneal rupture (with or without anaphylaxis), rupture into the bronchial tree, and development of a bronchobiliary fistula. In one series,[42] anaphylaxis complicated 10% of all intraperitoneal ruptures; the remaining patients developed multiple intraperitoneal cysts, and anaphylaxis accounted for two of the 221 (0·9%) reported complications of cystic echinococcosis.

Alveolar echinococcosis typically presents later than the cystic form. Cases of alveolar echinococcosis are characterised by an initial asymptomatic incubation period of 5–15 years, and a subsequent chronic course. Untreated or inadequately managed cases have high fatality rates. The peak age group for infection is from 50 to 70 years in Europe and Japan. The sex distribution is fairly equal. The metacestode develops almost exclusively in the liver (99% of cases). The right lobe is involved most frequently, with involvement of the porta hepatis or multiple lobes being less frequent. Parasitic lesions in the liver can vary from small foci a few millimetres in size to large (15–20 cm in diameter) areas of infiltration. Extrahepatic primary disease is very rare (1% of cases).[42,43] 13% of cases present as multiorgan disease where metacestodes involve the lungs, spleen, or brain in addition to the liver (panel 2, table 2). One-third of cases present with cholestatic jaundice, one-third present with epigastric pain, and the remainder present with vague symptoms like weight loss or fatigue, or are noted to have incidental hepatomegaly.[42]

## Diagnosis

Early diagnosis of cystic and alveolar echinococcosis can provide substantial improvements in the quality of the management and treatment of both diseases. In most cases, the early stages of infection are asymptomatic, so methods that are cheap and quite easy to use are needed for large-scale screening of populations at high risk. The definitive diagnosis for most cases of cystic and alveolar echinococcosis in man is by physical imaging methods, such as radiology, ultrasonography, computed axial tomography (CT scanning), and magnetic resonance imaging,[44] although such procedures are often not readily available in isolated communities. Radiological criteria intended to standardise reporting for clinical trials have been described, and are detailed in tables 1 and 2 and panel 2.[44]

Immunodiagnosis is useful not only in primary diagnosis but also for follow-up of patients after surgical or pharmacological treatment.[45-49] Detection of circulating *E granulosus* antigens in serum is less sensitive than antibody detection, which remains the method of choice. ELISA, indirect haemagglutination antibody assay, latex agglutination test, and immunoblot test are the most commonly used immunological methods. The immunofluorescence antibody test and arc-5 immunoelectrophoresis are also used.[50] Hydatid cyst fluid antigens are the usual source of antigenic material for immunodiagnosis.[48] Additionally, the lipoproteins antigen B and antigen 5, the major components of hydatid cyst fluid, are widely used in assays for immunodiagnosis of cystic echinococcosis.[50] The gene encoding antigen 5 has been cloned and was shown to be closely related to proteases of the trypsin family.[51] The use of both antigens is predominantly restricted to scientific applications, and neither is available for general use. Furthermore, there are difficulties related to their lack of sensitivity and specificity and problems with the standardisation of their use.[52] Cross-reactivity with antigens from other parasites, notably other taeniid cestodes, is a major problem. Overall, cystic echinococcosis serology may be improved by combining several defined antigens (including synthetic peptides), and the design of new *E granulosus*-specific peptides that react with otherwise false-negative sera. Currently, however, there is no standard, highly sensitive, and specific test available for antibody detection in cases of the disease.

Interleukin-4 detection may be useful in the follow up of patients with cystic echinococcosis. Furthermore, this test can be combined with RT-PCR to determine mRNA expression of cytokines in peripheral blood mononuclear cells to complement the biological assays in follow-up.[53] Detection of circulating antigens is also relevant as a method for postsurgical follow-up of patients, and for monitoring the growth dynamics and activity of cysts.[44,54,55]

The diagnosis of alveolar echinococcosis is based on similar findings and criteria as cystic echinococcosis, including case history, clinical findings, morphological lesions identified by imaging techniques, PCR or immunohistochemistry, and immunodiagnosis. The area has been comprehensively reviewed.[44] Like cystic echinococcosis, serodiagnosis of alveolar disease provides a complementary role to other procedures in early detection of the infection. The methods are similar to those used for cystic echinococcosis, with serological tests for antibody detection being generally more reliable for alveolar echinococcosis than cystic. Alveolar echinococcosis is a very serious disease with a high fatality rate, so early detection is paramount in order that successful management and treatment can commence.[56] Tests using Em2, a species-specific native antigen isolated from the metacestode of *E multilocularis*[57] and the Em2$^{plus}$ ELISA, a combination of Em2 with a recombinant protein designated II/3-10, have proved especially valuable. The Em2$^{plus}$ ELISA has been commercialised for clinical diagnosis of alveolar echinococcosis[58] and for population screening.[59] Other useful diagnostic molecules applicable in immunoblot, ELISA, or both, include an 18-kDa antigen (Em18) that can differentiate active from inactive alveolar echinococcosis,[18,60] recombinant Em13 and

### Panel 2: **PNM system for classification of human alveolar echinococcosis**[44]

**P: Hepatic localisation of the metacestode**
PX: Primary lesion unable to be assessed
PO: No detectable hepatic lesion
PI: Peripheral lesions without biliary or proximal vascular involvement
P2: Central lesions with biliary or proximal vascular involvement of one lobe
P3: Central lesions with biliary or proximal vascular involvement of both lobes or two hepatic veins, or both
P4: Any lesion with extension along the portal vein, inferior vena cava, or hepatic arteries

**N: Extrahepatic involvement of neighbouring organs**
NX: Not evaluable
NO: No regional involvement
N1: Involvement of adjacent organs or tissues

**M: Presence or absence of distant metastases**
MX: Not completely assessed
MO: No metastases on chest radiograph and CT brain scan
MI: Metastasis present

Em10,[61] and a purified alkaline phosphatase (pAP) from *E multilocularis* metacestodes.[62] Both Em2$^{plus}$ ELISA and Em18 in an immunoblot format have been used for long-term monitoring of patients after pharmacological treatment.[63] Recent work indicates that Em18 is a fragment of Em10, being the product of its degradation by cysteine protease.[64] Recombinant Em18 shows promise in immunoblotting assays and ELISA for detection of alveolar echinococcosis, and may prove especially useful for epidemiological surveys.[65,66]

In comparison with investigations in humans, little research has been directed toward the development of immunodiagnostic techniques for *E granulosus* infection in domesticated animals such as sheep and cattle. Currently, diagnosis of cystic echinococcosis in intermediate hosts is based mainly on necropsy procedures. Accurate serological diagnosis of infection in livestock is difficult due to serological cross-reactions with several other species of taeniid cestodes, including *Taenia hydatigena* and *Taenia ovis*.[67] Furthermore, natural intermediate host animals produce very poor antibody responses to infection compared with the relatively high levels of specific antibody seen in human infection.[47] In sheep, the principal intermediate host of *E granulosus* in most endemic regions of the world, antibodies to various antigens including antigen 5 are detectable in the serum of some, but not all infected sheep ("non-responders").[47] As in human beings, detection of circulating antigen does not seem to be useful for diagnostic purposes.[68] An extensive study incorporating three ELISA-based assays showed that a crude *E granulosus* protoscolex preparation was the most effective for detection of infection in sheep.[69] The test should be useful for the detection of the presence of infected sheep on a flock basis, but it is not sensitive enough to be used reliably for identification of individual animals infected with *E granulosus*.[4]

| | P | N | M |
|---|---|---|---|
| Stage I | P1 | NO | MO |
| Stage II | P2 | NO | MO |
| Stage IIIa | P3 | NO | MO |
| Stage IIIb | P1–3 | N1 | MO |
| | P4 | NO | MO |
| Stage IV | P4 | N1 | MO |
| | Any P | Any N | MI |

Table 2: **Staging of alveolar echinococcosis on the basis of PNM classification**

Two major diagnostic methods have been extensively used in dogs: purgation with arecoline compounds and necropsy of the small intestine. Necropsy is the method of choice for foxes and other final hosts. Two main immunodiagnostic approaches have been developed for diagnosis of *E granulosus* and *E multilocularis* infection in definitive hosts: ELISA-based assays for specific serum antibody,[4,70-72] and detection of parasite products (coproantigens) in faeces.[73,74] Overall, the available ELISA-based methods have variable sensitivities, although there is some broad correlation with high worm burdens in both types of test, especially coproantigen detection. In addition, coproantigen and antibody specificities are reasonably high[75-77] so the usefulness of these tests, especially in population-based studies of canine hosts, should be further explored.

A PCR-based assay has been developed for detection of *E multilocularis* DNA in faecal samples from foxes after isolation of the parasite eggs by a sieving procedure.[78] A similar test for *E granulosus* is being developed.[79] For field application, the coproantigen ELISA has the potential for replacing necropsy examinations, and the PCR test is a valuable method for confirmation of positive coproantigen results and for diagnosis in individual animals.[71]

## Treatment of cystic echinococcosis

Asymptomatic hepatic cystic echinococcosis is common in endemic regions and up to 75% of infected people may remain symptom free for more than 10 years.[80] Cysts may be seen to expand, become septate, or calcify when patients are monitored with serial ultrasound. Community studies with screening ultrasound have identified an increased frequency of this condition compared to similar studies of patients presenting for medical attention.[81] Treatment should be reserved for symptomatic lesions or those affecting vital anatomical structures. There have been no well-designed clinical trials for any treatment modality in either form of echinococcosis.

### Surgery

Surgery has been the mainstay of therapy for large cysts, those that are superficial and likely to rupture, infected cysts, and those in vital anatomical locations or exerting substantial mass effect. Surgery may be impractical in patients with multiple cysts in several organs, or in places where technical expertise or facilities are inadequate. Surgical options include: pericystectomy, partial hepatectomy or lobectomy, open cystectomy (with or without omentoplasty), or (palliative) tube drainage of infected cysts. Cyst extrusion (Barrett's technique) is also a surgical option for pulmonary disease. More radical surgery is associated with a higher complication rate but also a lower relapse rate. Recurrence is usually due to either inadequate cyst removal or previously undetected cysts. Reported recurrence rates range from 2% to 25%.[42] The advent of effective pre-operative chemotherapy has reduced the requirement for aggressive surgical procedures. The intraoperative use of protoscolicidal compounds is questionable. There is no ideal agent that is both effective and safe. For optimum efficacy, compounds require a 15 min "dwell time" within the cavity. Compounds that seem to be fairly safe and effective include 70–95% ethanol, 15–20% saline, and 0·5% cetrimide solution. Formalin should never be used. Chemical cholangitis (with frequently fatal secondary sclerosing cholangitis) can result if there is communication between the biliary tree and the cyst.[82]

### PAIR

The Puncture, Aspiration, Injection, Reaspiration (PAIR) technique was introduced in the mid-1980s.[83,84] The cyst is punctured under ultrasound guidance, as much cyst fluid is aspirated as possible, a protoscolicide (eg, 95% ethanol) is injected, and cyst contents are reaspirated 15–20 min later. Only skilled practitioners should undertake this technique, with intensive-care support in the event of anaphylaxis. Cyst aspirates should be assessed for the presence of protoscolices and bilirubin. PAIR should only be used in patients with chemotherapeutic cover to minimise the risk of secondary cystic echinococcosis. There is no experience of this technique in children and pregnant women. PAIR is best used for liver cysts of 5 cm or greater diameter that are anechoic, multiseptate, or multiple. PAIR has been used in patients who have relapsed after surgery. It is contraindicated for superficial or inaccessible cysts, and for cysts that are calcified, solid, or have communication with bile ducts.[85] Complication rates for PAIR range from 28% in the absence of albendazole[86] to 5–10% with concomitant chemotherapy.[87,88] A multicentre survey on PAIR by the WHO informal working group on echinococcosis[89] reported a 1% major complication (anaphylaxis or spillage) rate and a 13·7% minor (fever, rash, cyst infection, or haemorrhage) complication rate from the 765 cysts included in the survey. Early recurrence rates seem to be low (1·6%) but the follow-up duration is brief and its nature unclear. PAIR with albendazole chemotherapy has been shown to be as effective as pericystectomy for hepatic cystic echinococcosis in one randomised prospective trial[90] with lower post-procedure morbidity and shorter hospital stay. Further well-designed prospective trials comparing PAIR with surgery (especially with concurrent chemotherapy) are needed. A complementary technique derived from PAIR has been developed that allows percutaneous treatment of complicated cases with large cysts, numerous daughter cysts, or both.[91,92]

### Chemotherapy

The benzimidazole compounds—albendazole and mebendazole—have been the cornerstone of chemotherapy for cystic echinococcosis. Treatment with albendazole (10 mg/kg in divided doses—usually 400 mg—twice daily) results in the disappearance of up to 48% of cysts and a substantial reduction in size of a further 24%.[93] Mebendazole (40–50 mg/kg per day in three divided doses) is less efficacious than albendazole.[93] Because of limited toxicological data, albendazole was originally administered in three to six 4-week cycles with intervals of 14 days. However, more recent data suggest that continuous treatment achieves equivalent or improved efficacy with no increased adverse effect.[94,95] Cyst non-viability increases with duration of treatment—from 72% of cysts non-viable after 1 month to 94% of cysts non-viable after 3 months of treatment.[96] Usual adverse effects include nausea, hepatotoxicity, neutropenia (which may not be reversible), and occasionally alopecia. All patients should have regular monitoring of leucocyte counts and liver function tests. Albendazole sulfoxide is the protoscolicidal metabolite of albendazole. Praziquantel has been used (25 mg/kg per day) with albendazole for combined treatment of cystic echinococcosis, and an early trial in man shows improved efficacy over albendazole alone.[97] Praziquantel increases serum concentrations of albendazole sulfoxide fourfold. It remains to be seen if this treatment potentiates albendazole toxicity.

Teratogenicity has been reported when albendozole is administered to laboratory animals in early gestation. Albendazole and mebendazole are listed as category C drugs in pregnancy in the USA[98] and category D and B3 respectively in Australia.[99] Neither drug is absolutely contraindicated in pregnancy. Specialist advice should be sought if treatment during pregnancy is likely.

## Treatment of alveolar echinococcosis

Radical surgery—as for hepatic malignancy—has been the historical cornerstone of treatment for alveolar echinococcosis.[59] Early diagnosis is crucial, and results in a reduced rate of unresectable lesions and reduces the need for radical surgery.[100] Perioperative and long-term adjuvant chemotherapy with albendazole (doses up to 20 mg/kg per day) has been associated with 10-year survival of approximately 80%, compared with less than 25% in historical controls.[42,101] Albendazole is only parasitostatic against the *E multilocularis* metacestode. Chemotherapy should be continued for 2 years after surgery. The role of life-long chemosuppression is being explored. Liver transplantation has been undertaken in some patients with alveolar echinococcosis.[59,102] The therapeutic immunosuppression may allow proliferation of metacestode remnants or proliferation of previously inapparent metastases elsewhere (eg, the brain).[59,102]

## Prevention and control

Preventive measures that have been used to control *Echinococcus* infections include avoidance of contact with dog or fox faeces, handwashing and improved sanitation, reducing dog or fox populations, treatment of dogs with arecoline hydrobromide or praziquantel or use of praziquantel-impregnated baits, incineration of infected organs, and health education. Despite ongoing control efforts, few countries have been able to substantially reduce or eradicate alveolar or cystic echinococcosis. However, there has been notable success in Iceland (eradication, 1950s), New Zealand (control programme instigated in 1959), Tasmania (1965), the provinces of Neuquen (1970) and Rio Negro (1979) in Argentina, Cyprus (1970), and Chile (1978) where highly effective and sustained cystic echinococcosis control programmes have been undertaken.[103,104] The arecoline-based dog-testing programmes adopted by New Zealand and Tasmania resulted in near elimination of *E granulosus* within 20–25 years, and in both campaigns, transmission to humans almost ceased within about 10–12 years.[94]

Control of *E multilocularis* is especially problematic, since the primary cycle is almost always sylvatic and transmission is complicated by the epidemiological features discussed earlier. Some progress has been made in recent years, and praziquantel baits for control of *E multilocularis* infections in foxes may prove of value.[105] However, the Japanese island of Rebun is the only known instance where *E multilocularis* has been eradicated from an area where it was previously endemic, by elimination of the fox and dog population on the island.[106] Such an approach cannot be used in larger areas for ethical and ecological reasons. The successful control programmes show that prevention of transmission to either host can reduce or even eliminate the infection in human and livestock populations. So, if either or both hosts could be vaccinated, the effect would be to improve and more rapidly expedite control.[107] The generally sylvatic nature of the lifecycle of *E multilocularis* makes a vaccination approach to control unlikely.

Vaccination of the animal intermediate hosts of *Echinococcus* represents a burgeoning area that has moved

forward following the development of a recombinant vaccine against *Taenia ovis* infection in sheep.[108] A similar approach has been applied successfully to develop a recombinant vaccine, designated EG95, against *E granulosus* in sheep.[109] The vaccine has been shown to confer a high degree of protection against challenge with different geographical isolates of *E granulosus*[109] indicating that it could have wide applicability as a new method for use in hydatid control campaigns. The vaccine therefore provides a valuable way to aid in control of transmission of this important human pathogen, and it also has the potential to prevent hydatid disease directly through vaccination of humans. A recombinant parapoxvirus expressing EG95 has been constructed, and might prove useful for assessing the potential of recombinant orf viruses to deliver vaccine antigens to sheep.[110] Another protein (designated EM95), closely related to EG95, has been identified in *E multilocularis* that can induce protection against challenge infection with *E multilocularis* eggs in mice.[111]

Compared with the major advances in vaccinating sheep against *E granulosus*, attempts to vaccinate canine definitive hosts have yet to achieve similar success. Nevertheless, a series of experiments to induce immunity in dogs through vaccination with various components has been undertaken, with some encouraging results.[48] There is some evidence for the development of acquired immunity to *E multilocularis* in foxes, although detailed knowledge is unavailable.[26]

## Conclusions

Despite the establishment of extensive and successful control programmes in some countries or regions, *E granulosus* still has a very wide geographic distribution. Worryingly, recent evidence points to cystic echinococcosis being a public health problem of increasing concern in a number of countries where control programmes have been reduced due to economic problems and lack of resources, or have yet to be fully instigated.[21] It is likely that, unless government health authorities prioritise the disease and instigate appropriate control methods, *E granulosus* will persist or re-emerge in many endemic areas worldwide, causing severe disease and considerable economic loss.[112] A similar but even more alarming situation prevails with *E multilocularis* as indicated by the increasing prevalence of alveolar echinococcosis,[113] its wider than previously thought distribution, and the clear evidence that the parasite can readily spread from endemic to non-endemic areas. Additionally, unlike *E granulosus*, effective methods for control of *E multilocularis* are not available, which adds support to the argument for more effective prevention measures and early diagnosis of alveolar echinicoccosis. For both cystic and alveolar forms, chemotherapy has facilitated less invasive surgical management. However there is a clear need for new advances in the prevention and chemotherapy of both these neglected diseases.

*Conflict of interest statement*

None declared.

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