8 *Echinococcus* spp.

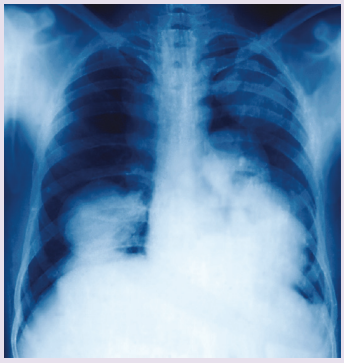

Figure 8.1 Pulmonary hydatid cysts. Chest X-ray showing hydatid cysts (opaque areas at center right and center left) in a patient's lungs. The cysts are caused by the parasitic tapeworm *Echinococcus* spp. Humans are not a natural host for the parasite but may become infected from ingesting eggs shed in the feces of an infected dog or other canids. Cysts may be formed in the liver, lungs or any other organ in the body. Large pulmonary cysts may cause symptoms, including shortness of breath, chest discomfort and sometimes wheeze. Treatment involves giving anti-parasitic drugs and careful surgical resection when possible. *From Zephyr / Science Photo Library, with permission.*

A 28-year-old Kurdish refugee complained of upper abdominal pain for 4 months. He had recently noticed some pain on the right side of his chest. He had not noticed any fever and his weight was stable. His doctor requested a chest X-ray. This showed a mass lesion in the right lung. He was referred to the Thoracic Surgical Department at the local hospital. A **CT scan** of his chest and abdomen was requested. This demonstrated a cystic structure in his liver, with other **cysts** in his chest (**Figure 8.1**). The surgeons excised the right lung lesion. The histopathologists reported that it was a **hydatid cyst**. The patient was referred to the Infectious Diseases Department. A serologic test was positive for *Echinococcus*. He was given treatment with albendazole and his remaining cysts were initially monitored serially on scans.

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

CAUSATIVE AGENT

Echinococcus species are tapeworms, also known as cestodes. Adults are only 2–7 mm in length. Two species are responsible for the majority of human infections. *Echinococcus granulosus* arises from dogs and other canids and has been described worldwide. It causes cystic echinococcosis. *Echinococcus multilocularis* arises from arctic or red foxes and is restricted to the Northern Hemisphere. It causes alveolar echinococcosis. Infection with the latter seems to be spreading as red-fox populations have been growing. Adult tapeworms, numbering in the thousands, live in the intestines of the dog or wild canid hosts. They attach to the mucosa with suckers and hooks. There are different parts to the structure of the tapeworm, and these are shown in **Figure 8.2**. The adult tapeworms lay eggs, which pass out in the feces and contaminate the soil. Unless dessicated, eggs may survive in the soil for one year. These may be swallowed by an intermediate host such as sheep for *E. granulosus* and small mammals for *E. multilocularis*.

ENTRY AND SPREAD WITHIN THE BODY

Humans are infected if they accidentally swallow eggs present in soil, water or food. The eggs have a tough shell that breaks down and releases a larval form called the oncosphere. The oncosphere burrows into the intestinal wall and then spreads to other parts of the body along blood vessels or lymphatics. The liver is the commonest site of infection as most of the intestinal drainage of blood is along the portal vein to the liver. However, infection could arise anywhere in the body.

When the oncosphere lodges in an organ it develops into a vesicle. This progressively grows into a cyst. The cyst wall includes an inner germinal layer. From this buds a stage called a protoscolex within brood capsules. Around the germinal layer is an acellular, laminated layer. For *E. granulosus* this cyst is unilocular and known as a hydatid cyst. For *E. multilocularis*, the cyst is multilocular or referred to as alveolar. Occasionally,

Figure 8.2 An adult tapeworm of *Echinococcus granulosus*. *(From www.healthatoz.com/healthatoz/Atoz/images/)*

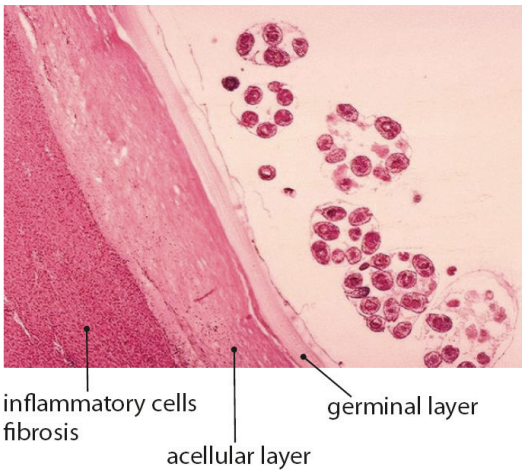

Figure 8.3 Histopathology of the structure of a hydatid cyst. Round protoscoleces are seen on the right. They arise from a thin germinal layer, which is surrounded by an acellular layer; the host inflammatory cells can be seen to the left of this. *Courtesy of the Centers for Disease Control, Atlanta, Georgia. Image is found in the Public Health Image Library #910. Additional photographic credit is given to Dr Peter Schantz who took the photo in 1975.*

cysts can rupture giving rise to secondary, "daughter" cysts. The structure of a hydatid cyst due to *E. granulosus* is shown in **Figure 8.3**.

PERSON-TO-PERSON SPREAD

Humans do not spread *Echinococcus* spp. from person to person. Humans are an end host, with occasional exceptions.

INTERMEDIATE HOSTS

Animals such as sheep or cattle may ingest *E. granulosus* eggs shed in dog feces. They can act as intermediate hosts. When sheep or cattle are killed, dogs may eat their meat or offal. When the dogs swallow cysts within infected tissues the protoscoleces are released. They attach to the dogs' intestinal mucosa to mature into the adult tapeworms. Thus, the life cycle is completed (**Figure 8.4**). Dogs are the definitive hosts. This life cycle for *E. granulosus* occurs on farms but for *E. multilocularis* there is a rural, or **sylvatic**, life cycle with small mammals serving as the intermediate host and arctic or red foxes as the definitive host.

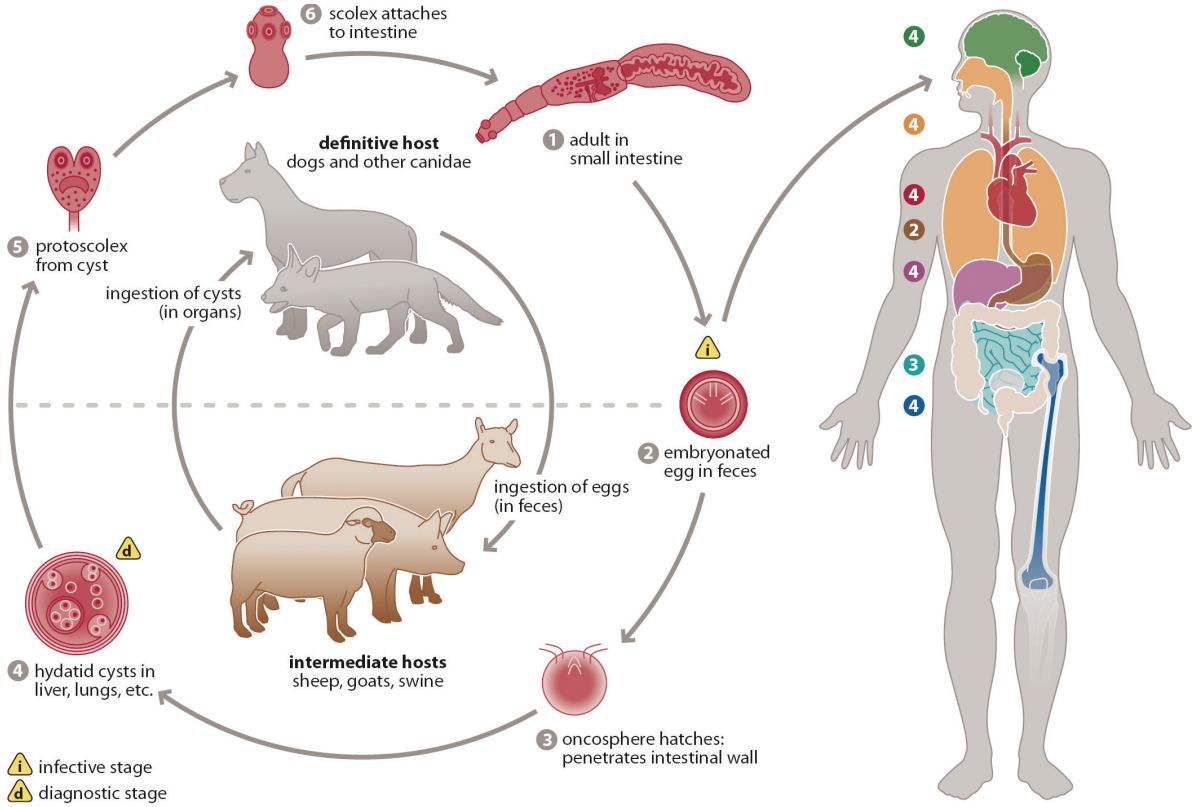

Figure 8.4 Life cycle of *Echinococcus granulosus*. Adult worms living in the dog intestine shed eggs in dog feces. These contaminate the environment and may be ingested by intermediate hosts such as sheep. In the intestine, oncospheres hatch from the eggs and penetrate the intestinal wall. The oncosphere spreads to other organs and eventually matures into a cyst. Within the cyst, protoscolices develop. When a cyst is ingested by a dog the protoscolices are released, attach to the intestinal mucosa as a scolex, and mature into adult worms. *Courtesy of the Centers for Disease Control, Atlanta, Georgia. Image is found in the Laboratory Identification of Parasites of Public Health Concern.*

EPIDEMIOLOGY

Given the life cycle, hydatid disease is most common where dogs and animals such as sheep and cattle mix. For *E. granulosus*, worldwide rates are highest in South America, Africa, Asia, and parts of Europe. In some rural regions close to 10% of the population may be infected. *E. multilocularis* is found in northern regions of China, Mongolia, Russia, Europe, and North America, with geographic spread relating to growing fox populations.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

Potentially, the host may mount a response to the oncospheres, after they have entered the intestine, or against the cysts, which become surrounded by the acellular, laminated layer. There may also be a host response to fluid that leaks from a ruptured cyst.

Little is known of the host response to the oncospheres. A single or small number of oncospheres may not pose a sufficient antigenic stimulus to trigger an adaptive immune response. The innate immune response, utilizing phagocytic cells or complement, may attack them after invasion of the intestinal mucosa. Once a hydatid cyst has developed, an antibody response occurs that is initially **IgM** followed by an **IgG** and **IgE** response. If these antibodies also recognize the oncospheres, they could play a part in preventing further ingested oncospheres from causing additional infection.

An inflammatory response occurs around the maturing cyst. This is triggered by complement activation. There is an infiltration of macrophages and lymphocytes and these include both **CD4**+ and **CD8**+ T lymphocytes. Both **Th1**- and **Th2**-type **cytokines** are found, such as **interferon (IFN)-γ**, **interleukin** (IL)-4, and interleukin-10. Eventually, a host-derived, fibrous layer forms around the cyst. Complement activation and inflammation subside as the acellular layer accumulates. It is thought that there is local immunomodulation with impaired macrophage responses, impaired **dendritic cell** differentiation, and T-regulatory cells. Cyst-derived antigens, including an antigen B, affect the maturation and function of dendritic cells, such that when they present antigen to lymphocytes the immune response skews to a Th2 pattern. The latter is characterized by IL-4 production and increased IgG and IgE levels.

PATHOGENESIS

Large cysts cause pressure and may cause pain or dysfunction of the organ affected. If a hydatid cyst ruptures its proteinaceous contents leak, with a sudden, large antigenic stimulus. This can cause an anaphylactic reaction if IgE antibodies trigger the activation of mast cells and the systemic release of histamine and other mediators (**type 1 hypersensitivity**).

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

Hydatid cysts grow gradually. They may not cause any physical problems and may remain asymptomatic. Just over half of infected individuals are asymptomatic. When the cyst is large, pressure effects may cause pain or dysfunction of the organ affected. If a cyst ruptures, daughter cysts may cause additional problems and cystic fluid can trigger life-threatening **anaphylaxis**.

Hydatid cysts may be found in any part of the body but about 90% occur in the liver or lung or both. Large cysts in the liver can cause upper abdominal pain. The pain may localize more to the right side of the abdomen, as the right lobe of the liver is most frequently affected. The liver can enlarge and become palpable. The cyst may become secondarily infected with bacteria. If the cyst presses on the biliary tree, obstructive **jaundice** can develop. Rupture into the biliary tree may lead to daughter cysts in the common bile duct. Again, these can cause an obstructive jaundice. In the lung, large cysts may cause pain. This may be felt as a central chest ache. When cysts abut the chest wall, they cause localized pain at these sites. Very large cysts may make individuals short of breath and cause a cough.

Hydatid disease due to *E. granulosus* has a case fatality rate of about 2%. Infection due to *E. multilocularis* has a higher mortality rate. It can cause any of the clinical features associated with hydatid disease but can have a progressive course with growing cysts that enlarge the liver and compromise its function.

If cysts rupture, an abrupt antigenic challenge may trigger anaphylaxis. A classical anaphylactic reaction comprises swelling of lips, tongue, vocal chords, and bronchial airway mucosa; urticarial reactions in the skin; and a fall in blood pressure. **Eosinophilia** may be observed if there is cyst leakage but is not uniformly present with intact cysts.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

The case history illustrates that sometimes the diagnosis is made after surgical removal of a lesion and histopathologic examination. However, it is preferable to make a diagnosis before surgery as accidental incision of a cyst and leakage of its contents may trigger anaphylaxis.

Either ultrasound of the liver or a CT scan of thorax or abdomen may reveal a cystic structure. Some features are highly suggestive of a hydatid cyst. There is a thick cyst wall. Septa may be seen within the cyst. If the germinal layer detaches from the cyst wall, the inner septa may float in the fluid like a "water lily". Mature, degenerating cysts may become calcified. Cystic appearances determine treatment strategies.

Serologic tests are available for *Echinococcus* antibodies. Methods used include **enzyme-linked immunosorbent assay** (**ELISA**), indirect hemagglutination assays, and latex agglutination assays. The antigens used in assays are derived from hydatid cyst fluid. There may be cross-reactions with other tapeworm infections affecting specificity. Initial serology may be followed by immunoblotting for more specific results. Sensitivity may be as low as 60% for infection in the lung, but more than 80% for liver.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is from other causes of cystic structures. The range of possibilities is larger for the lung than for the liver. In the liver, benign cysts with thin walls can occur. A liver abscess may cause a different overall clinical picture and aspiration may yield pus. Liver tumors may have the same shape but are more solid structures. The more extensive liver changes in *E. multilocularis* infection may appear like nodular cirrhosis.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

MANAGEMENT

Treatment options depend on the size of the cyst (a viable cyst <5 cm may be treated with chemotherapy alone), whether there is a single or multiple compartments (a viable cyst >5 cm with a single compartment may be aspirated alongside chemotherapy) and whether there are features of viability (an inactive cyst may be observed alone). Surgical removal may be required for troublesome cysts, if technically feasible.

Albendazole is the chemotherapeutic agent of choice and may be used continuously for months. Cysts reduce in size in about 70% of cases. The addition of praziquantel to albendazole may help prevent the development of daughter cysts if there is cyst rupture. Chemotherapy is used as an adjunct to surgery and aspiration. Albendazole may be used one week to one month prior to surgery and for at least one month afterward, reducing cyst viability and making surgery safer. At surgery, 20% hypertonic saline may also be injected into a cyst to reduce viability prior to excision.

Another approach to the management of some cases of cystic echinococcosis has been aspiration of accessible cysts with a needle and injection of an agent such as 95% ethanol to kill the protoscoleces inside the cyst. The ethanol is then aspirated back after 20 minutes. Microscopy of the aspirate shows free protoscoleces, which are sometimes referred to as "hydatid sand". This method is referred to as **PAIR**, which stands for **P**uncture, **A**spiration, **I**njection, **R**easpiration. The key risk is anaphylaxis if cyst fluid leaks out but is rare in experienced hands.

PREVENTION

Humans need to maintain high standards of washing hands and fresh food to avoid swallowing eggs. Prevention of *Echinococcus* infection requires breaking the natural life cycle. Dogs have been treated with arecoline or praziquantel. Praziquantel baiting has been used to treat red foxes. On farms, dogs are kept away from offal.

Vaccines have been trialed in sheep and dogs. A recombinant DNA vaccine containing the gene for an oncosphere antigen, and designated EG95, has shown >90% protective efficacy in sheep.

Despite efforts, *Echinococcus* infection continues to be a problem in many countries.

SUMMARY

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY, AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

- The causative agent is *Echinococcus granulosus* or *Echinococcus multilocularis*. These are tapeworms, or cestodes.
- Adult Echinococcus tapeworms live in the intestine of dogs or foxes and shed eggs in the feces. Dogs and foxes are the definitive hosts.
- The eggs are accidentally swallowed by other species. Once swallowed, oncospheres emerge from the eggs, penetrate the intestinal wall, and spread to other parts of the body where they form cysts.
- Dogs are infected when they eat meat or offal containing cysts. This happens for instance on farms, where they might eat offal from sheep or cattle.
- Species such as sheep or cows are therefore referred to as intermediate hosts. Humans are usually an end host.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

- Little is known about the host response to the oncospheres when they penetrate the intestinal wall.
- Once the oncospheres develop into cysts in tissues, there is a surrounding inflammatory response triggered by complement activation, involving macrophages and then a CD4+ and CD8+ T-lymphocyte response.
- Eventually, an acellular and fibrous layer develops around the cyst with down-regulation of the immune and inflammatory response.
- The pathogenesis of disease depends on the size of cysts. Large cysts can pose a physical problem in the infected organ.
- If cysts rupture and leak, an IgE-mediated response can be triggered.

Continued...

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3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

- Small cysts may remain asymptomatic.
- Hydatid cysts due to *E. granulosus* are mostly found in the liver or lung or both. The cysts of *E. multilocularis* are primarily found in the liver.
- Large hydatid cysts in the liver can cause pain, may obstruct the flow of bile, and may rupture into the biliary tree.
- Disease due to *E. multilocularis* can be steadily progressive.
- Cyst rupture and leakage of proteinaceous contents can trigger an anaphylactic reaction.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

- Diagnosis is based on imaging such as ultrasound or CT scan. Typical radiologic features may be present to diagnose hydatid disease.
- Additional tests include serology.
- Cross-reactions with other tapeworm infections affect the specificity of serology. Sensitivity ranges from 60% to 80%.
- The differential diagnosis is from other causes of cystic lesions.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

- Treatment options depend on cyst size, cyst compartmentalization, and features of cyst viability.
- The main chemotherapeutic agent is albendazole.
- Surgical resection may be performed if necessary and if feasible.
- Some experienced centers also undertake a procedure called PAIR, which involves percutaneous puncture of cysts, aspiration of contents, injection of ethanol, and then reaspiration.
- Prevention requires breaking the life cycle by treating dogs and preventing the consumption of offal by dogs. To avoid accidental infection, humans must maintain high standards of hand hygiene.

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Students can test their knowledge of this case study by visiting the Instructor and Student Resources: [www.routledge.com/cw/lydyard] where several multiple choice questions can be found.