Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 14

Infectious Diseases of Domestic Rabbits

Introduction

Domestic rabbits are susceptible to a number of infectious diseases: parasitic, bacterial and viral. An overview of the commoner infections may be found in Table 14.1.

14.1 Parasites of rabbits

Wild rabbits are host to a variety of parasites that can be transmitted to domestic rabbits. The type and species of parasite varies throughout the world and it is beyond the scope of this book to describe them all. A detailed, illustrated description is given by Hofing and Kraus (1994). The parasites that affect domestic rabbits are described in detail by Owen (1992). This is the major reference source for the parasite section of this chapter.

14.2 Ectoparasites

14.2.1 Fleas

Spilopsyllus cuniculi is a common flea that infests wild rabbits in Europe. It does not occur in the USA (Kraus *et al.*, 1984). The fleas have a predilection for the ears, where they can be found in clusters along the edges of the pinnae. The fleas are mobile and move between the environment and the host. Wild rabbit fleas are not usually found on pet rabbits. *Spilopsyllus cuniculi* is a small flea whose life cycle is influenced by the reproductive status of the host. Egg maturation is dependent on female reproductive hormones. Successful reproduction of the rabbit flea requires contact with a rabbit in late pregnancy or with a newborn nestling. Increased blood corticosteroid concentrations in late pregnancy attract fleas, which attach firmly to the doe to feed. Within a few hours of parturition, fleas move from the doe to the newborn babies to feed, copulate and lay eggs in the nest. The eggs hatch and the larvae feed on flea dirt deposited in the nest by the adult fleas feeding on the pregnant doe. In this way, fleas are spread from one generation to the next and are an important vector of disease, especially myxomatosis.

Ctenocephalides canis or *felis*, the common cat and dog flea, is the usual flea found on pet rabbits. Infestation results from rabbits living in a house inhabited by dogs and cats. Infestation causes intense pruritus and allergic dermatitis can develop. Fleas and flea dirt can be found on the rabbit by combing the coat with a fine-toothed comb.

Control of flea infestation is as for other species. Fipronil should *not* be used on rabbits; however, imidacloprid and selamectin are both safe and effective. All in-contact animals should be treated (including other species), and environmental control should be implemented.

14.2.2 Lice

Haemodipsus ventricosus is a sucking louse that affects wild rabbits and may act as a vector for myxomatosis. It is a large louse 1.5–2.5 mm in length. It is occasionally found on pet rabbits (Owen, 1992).

Table 14.1 Quick reference guide to infectious diseases

Disease	Incubation period	Route of transmission	Clinical signs	Diagnostic tests	Treatment	Comments
Fleas	Life cycle takes 30–35 days for rabbit flea	Direct contact	Pruritus Hair loss Dermatitis	Visualization of fleas. Flea combing	Imidacloprid, selamectin	*Spilopsyllus cuniculi* is the rabbit flea; however, most infestations are *Ctenocephalides* spp.
Lice	Life cycle takes 14–21 days	Direct contact		Visualization of lice or nits	Avermectins	*Haemodipsus ventricosus* may act as a vector for myxomatosis
Mites *Psoroptes cuniculi* (*Leporacarus*, *Cheyletiella*, etc.)	Life cycle 21 days, eggs hatch after 4 days	Direct contact	Intensely painful and pruritic otitis externa (skin flaking/hairloss)	Clinical signs, visualization of mites in exudate/crust	Selamectin, ivermectin, moxidectin are suitable for all mite infestations	May get aberrant infestations on other parts of the body
Warbles *Cuterebra* spp.	28 days to 11 months	Not contagious	Masses around head and over back	Finding the warble within a mass	Mechanical removal of the warble; treat any concurrent infection	USA only, do not occur in UK
Passalurus ambiguus	18 days	Faecal oral contamination	None in adults, possible contribution to enteritis complex of weanlings	Faecal flotation, zinc sulphate flotation	Often not required. Piperazine and fenbendazole are effective	Ivermectin is *not* effective
Obeliscoides cuniculi	16–22 days	Faecal oral contamination	Possibly none	Faecal flotation	May not be required; fenbendazole is effective	Can affect a variety of other species. Rare in the UK

Tapeworms Several species	Rabbits often act as intermediate hosts	Oral intake of eggs from infected pasture	Cysts cause pain and signs related to area in the body in which they are found	Visualization of scolices from cyst fluid		There are tapeworms where rabbit is the primary host
Coccidiosis	7–8 days, complex life cycle	Faecal oral contamination	Diarrhoea, inappetence, weight loss, can be fatal	Faecal flotation, histopathology of gut wall		*Eimeria stiedae* causes hepatic coccidiosis, leading to jaundice, weight loss, ascites, diarrhoea, hepatomegaly
Encephalitozoonosis	30–70 days, variable, may be much longer	Oral intake of spores from infected urine	Vestibular signs, seizures, signs of renal disease. Rarely myocarditis	Serology, PCR of suitable tissue or urine, exclusion of differential diagnoses	Fenbendazole, albendazole, fluoroquinolones, lufenuron(?)	*Encephalitozoon cuniculi* does not fulfill Koch's postulates and it is uncertain whether it can cause disease in and of itself
Toxoplasmosis	7–8 days	Ingestion of infected cat faeces	Sudden anorexia, pyrexia and death, possibly CNS signs	Serology Histopathology	Not reported	The rabbit is not the final host; therefore it is not infectious to other rabbits. No cysts are found in rabbit faeces. Can infect humans eating undercooked rabbit meat

Continued

Table 14.1 Quick reference guide to infectious diseases—cont'd

Disease	Incubation period	Route of transmission	Clinical signs	Diagnostic tests	Treatment	Comments
Pasteurellosis	8–21 days	Direct contact and airborne spread. May be a commensal. Fomite spread possible	Many possible: rhinitis, pneumonia, abscesses, otitis media	Culture and sensitivity, serology	Antibiotics in accordance with sensitivities	Not all manifestations of these clinical signs are due to *Pasteurella*, so culture is mandatory
Bordetella bronchiseptica	3–10 days	Direct contact, airborne spread	Suppurative bronchopneumonia, may be relatively non-pathogenic	Culture and sensitivity	Antibiotics in accordance with sensitivities	Can cause potentially serious disease in guinea pigs housed with rabbits
Tyzzer's disease	3–7 days	Faecal oral contamination, ingestion of spores from environment	Acute diarrhoea, sudden death, intestinal fibrosis	Serology	Reduce stress, increase dietary fibre, antibiosis and supportive care. Generally unrewarding	Usually weanling rabbits 6–12 weeks old
Salmonellosis	6–24 hours	Intake of contaminated food or water	Diarrhoea, emaciation, death. May get asymptomatic carriers	Faecal culture	No successful treatment reported. Questionable whether anything other than supportive care should be employed	Rare
Colibacillosis	12–24 hours	Intake of contaminated food or water, or infected faeces	Enteritis and death, particularly in colony situations	Faecal culture	Antibiosis and supportive care	With some strains mortality can be 25–75%

Clostridial enterotoxaemia	12 hours or more after alterations in bacterial flora	Carbohydrate overload, inappropriate antibiotic treatment	Severe enteric disease	PCR for clostridial toxins on faeces	Supportive care, fluids, cholestyramine resin	Clostridia are present in small numbers in normal rabbit gut flora
Treponematosis	3–6 weeks	Sexually transmitted, or from dam during birthing process	Crusty lesions around, eyes, mouth/nose and on genitalia	Serology, dark field microscopy on material from lesions, histopathology	Penicillin, ×3 doses at 5- to 7-day intervals	Can get clinically normal infected carriers
Listeriosis	3–70 days reported in humans and animals reported to be similar	Intake of contaminated food	Abortion, sudden death	Culture, post-mortem examination and culture	Not reported	Rare, organism appears to have predilection for gravid uterus
Paratuberculosis	Variable, up to several years	Ingestion of contaminated food or water	Intermittent diarrhoea	Histopathology (post-mortem?)	Not reported	Incidence higher in wild rabbits geographically close to farms with a history of Johne's disease.
Pseudotuberculosis (yersiniosis)	15 days or more	Oral intake of infected faeces from wildlife or vermin	Wasting, diarrhoea, dull coat, nodules palpable on the liver	Histopathology (post-mortem)	Not reported clinically. Vermin control required	
Tularemia	1–14 days	Vector (tick) borne	Pyrexia, lethargy	Post-mortem histopathology, serology (not commercially in UK)	Supportive care, antibiosis	Zoonotic

Continued

Table 14.1 Quick reference guide to infectious diseases—cont'd

Disease	Incubation period	Route of transmission	Clinical signs	Diagnostic tests	Treatment	Comments
Lyme disease	Unknown in rabbits, 3–32 days in other species	Tick-borne	Causes polyarthritis in other species, knowledge of recent tick bite	Serology (not available commercially for rabbits)	Not reported	Serological surveys indicate higher prevalence in areas where rabbit-feeding tics are abundant
Myxomatosis	At least 5 days, but varies according to strain	Vector spread, although direct contact possible	Swellings around eyelids/face viraemia and death	Clinical signs	Supportive care, depending on strain is frequently fatal	Rabbits that have been vaccinated previously can get atypical myxomatosis, which presents as subcutanoues plaques/masses. This form is unlikely to be fatal
Viral haemorrhagic disease	3–4 days	Direct contact, fomite spread possible	Severe necrotizing hepatitis, disseminated intravascular coagulation, death	Clinical signs, serology, histopathology	Almost universally fatal. Supportive care	
Shopes fibroma virus	1–5 days	Vector spread (mosquitos)	Fibromatous swellings over body	Clinical signs, histopathology of masses	Swellings usually regress within 3 weeks, so supportive care only if required	Recovery from Shopes fibroma virus confers cross-immunity against myxomatosis
Shopes papilloma virus	7 days	Arthropod vector	Malignant masses resembling squamous cell carcinomas in European rabbits, benign swellings in cotton tails	Histopathology	Supportive care, will likely fail	

Papillomatosis	9–38 days experimentally, natural infection unknown	Direct contact	Small wart-like growths inside the mouth	Clinical signs, histopathology	As the rabbit ages, immunity occurs and the warts regress. Treatment only indicated if lesions are causing problems	Primarily young rabbits 6–9 months of age
Rabbit corona virus	2–5 days for acute, 6–12 days for less acute signs		Pyrexia, pulmonary oedema, enteritis in weanling rabbits. FIP lie syndrome also reported	Histopathology, serology (not available in UK)	None reported, supportive care addresses clinical problems identified	May not be a naturally occurring pathogen. Unlikely to be seen in general practice
Dermatophytosis	1–2 weeks	Direct and fomite spread	Lesions at base of ears and around muzzle	Culture, fluorescence with Wood's lamp	As for other species	May get asymptomatic carriers
Aspergillosis	Variable dependent on dose taken in	From environment or food	Pulmonary granulomas have been reported, rhinitis seen anecdotally	Culture, histopathology	Itraconazole, terbinafine	Reports rare in literature, likely more common clinically

14.2.3 Mites

Psoroptes cuniculi is the common ear mite of rabbits that causes crusting and ulceration of the external ear canal. The mites are large and active and are just visible to the naked eye. They are surface dwellers that cause intense irritation when they are present in large numbers (see Figure 14.1). Occasionally they are found in other areas of the body such as the perineal skin folds (see Section 7.14.3.1).

Cheyletiella parasitovorax is a fur-dwelling mite that can be found in large numbers in pet rabbits (see Section 7.14.3.3). Areas of dense, flaky, encrusted skin are found along the back, especially above the tail base and on the neck. The mites are easily identified by microscopic examination of skin brushings or pluckings (see Figure 14.2). Infestation with *cheyletiella* is often associated with obesity, spinal disorders or dental disease. *Cheyletiella parasitovorax* is zoonotic and can cause erythema and pruritus in man. Pruritic lesions are found on the forearm or neck of humans that have handled infested rabbits. The lesions regress over 24 h.

Figure 14.1 ***Psoroptes cuniculi*.** The rabbit ear mite, *Psoroptes cuniculi*, causes crusting and inflammation of the external ear canal, which often extends up the pinna (see Figure 7.4). Lesions are sometimes found on other parts of the body such as the perineal skin folds. Mites can just be seen with the naked eye in exudate from the lesions. Large numbers of *P. cuniculi* are visible on microscopic examination of the exudate, which can be softened in liquid paraffin before placing on a glass slide. (Image supplied by Dr Sheelagh Lloyd, Division of Animal Pathology, University of Cambridge.)

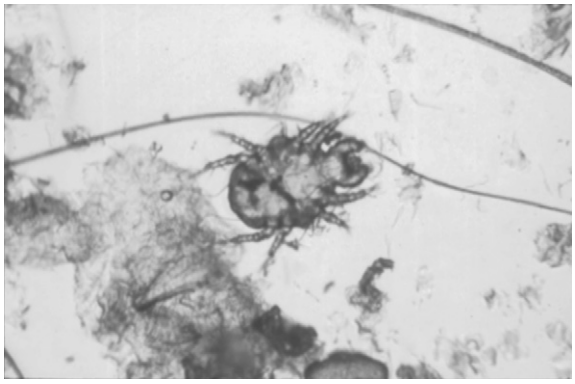

Figure 14.2 ***Cheyletiella parasitovorax*.** This mite can be found in the fur of healthy rabbits. It is not always associated with skin lesions. In large numbers, *C. parasitovorax* mites cause pruritus and areas of white, flaky skin. Heavy infestation is usually linked to some underlying problem with grooming, such as dental disease, obesity or spinal disorders. Mites may be seen moving among skin flakes that are combed out and placed under a bright light. *Cheyletiella parasitovorax* can also be detected by combing out the flakes and applying acetate strips to the exposed underlying skin. The acetate strip is placed on a microscope slide and examined on low power. In heavy infestations a variety of nymphal stages, eggs and adult mites are seen.

Leporacarus gibbus (formerly known as *Listrophorus gibbus*) is the common fur mite of rabbits (see Section 7.14.3.4). Infestation is normally asymptomatic and is not significant, except that large numbers can indicate some underlying disease. The mite is usually found attached to the hair shaft where it feeds on sebaceous gland secretions (see Figure 14.3). The mites are just visible to the naked eye especially on light-coloured rabbits when infestation gives the coat the appearance of being sprinkled with pepper. This effect is more obvious when the coat is wet.

Notoedres and *Sarcoptes* have been described as causes of mange in rabbits.

Mites are susceptible to a range of anti-parasitic medications: selamectin (Stronghold, Pfizer) moxidectin (Advocate, Bayer) and ivermectin (many preparations). However, as many cases of mites, in particular *Leporacarus* and *Cheyletiella*, are due to inability to groom, a robust diagnostic work-up should be undertaken to look for foci of pain or inability to balance.

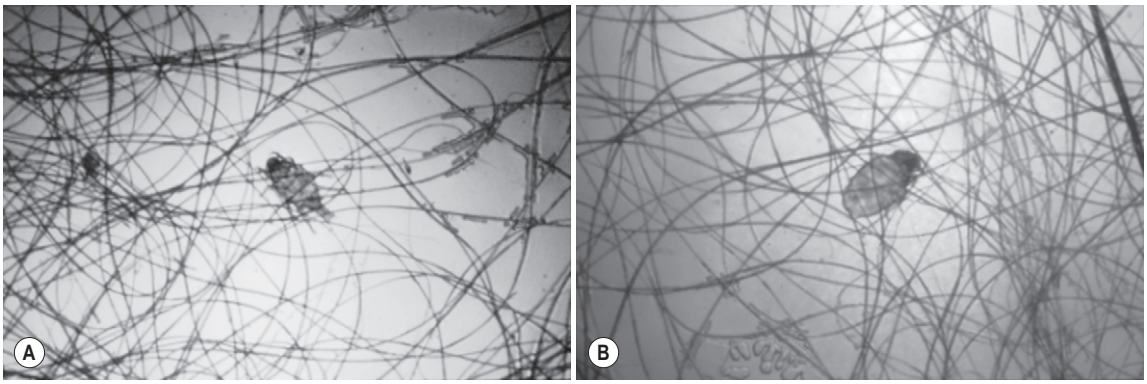

Figure 14.3 ***Leporacarus gibbus*** **(formerly** ***Listrophorus gibbus*****).** *Leporacarus gibbus* can be found in the fur of many pet rabbits. Infestation is usually asymptomatic. Like *C. parasitovorax*, heavy infestation is linked to some underlying problem with grooming, such as dental disease, obesity or spinal disorders. The mite is just visible to the naked eye, especially in light-coloured rabbits. A simple method of detecting *L. gibbus* is to comb through the fur with a fine-toothed flea comb and place the combings in a small, clear plastic bag. The contents of the bag are viewed microscopically under low power and the mites are seen moving along hair shafts. Eggs and empty egg cases can be seen attached to hair shafts. Immature and adult mites are visible. There are morphological differences between male **(A)** and female mites **(B)**.

14.2.4 Warble flies

Cuterebra horripilum and *Cuterebra buccata* are warble flies that affect rabbits in the USA but do not occur in the UK.

14.3 Endoparasites

14.3.1 Intestinal worms

There is a range of nematodes that affect wild rabbits in various parts of the world. With the exception of *Passalurus ambiguus*, infestations in domestic rabbits are rare, especially in pets, and are unlikely to be encountered. *Passalurus ambiguus* is an oxyurid found in the caecum and large intestine. The adult worms measure 5–10 mm and are not pathogenic in the adult animal; indeed, they are thought to have a role in the mechanical function of the caecum. Heavy infestations in young rabbits can be a contributory factor to the enteritis complex of diseases that occur around weaning (see Section 8.2).

The small, thread-like worm is seen in the faeces of affected animals. The life cycle is direct. *Passalurus ambiguus* is susceptible to most anthelmintics, e.g., piperazine and fenbendazole. Ivermectin is ineffective (Morrisey, 1996). It is unlikely that *P. ambiguus* would require treatment in the adult rabbit. Control strategies in the environment should include restricting access to potentially infected faeces, i.e. regular cleaning of hutches, and pasture rotation, particularly where young rabbits are kept.

There are other helminth parasites that principally affect wild rabbits and are not found in the domestic pet. They include *Graphidium strigosum* and *Trichostrongylus retortaeformis* (Allan *et al.*, 1999). *Obeliscoides cuniculi* occurs in wild rabbits in various parts of the world and in domestic rabbits in the USA (Hofing and Kraus, 1994). Clinically it causes haemorrhagic diarrhoea. *Obeliscoides cuniculi* has been used as a laboratory model of *Trichostrongylus* and *Ostertagia* species of ruminants. No species of trematode has been reported in rabbits (Kraus *et al.*, 1984).

14.3.2 Tapeworms

The rabbit is the intermediate host for several tapeworms that affect dogs and cats. Pet rabbits that graze in gardens inhabited by pet dogs or visited by foxes can become infected. The incidence of these parasites is not high, as most pet owners now worm their dogs with preparations that are effective against tapeworms.

Cysticercus pisiformis is the larval stage of *Taenia pisiformis*, which is a tapeworm that affects dogs and foxes, with rabbits acting as the intermediate host. Tapeworm segments packed with eggs are shed in faeces and contaminate pasture. Grazing rabbits ingest eggs that pass into the small intestine where the oncosphere emerges and migrates to the peritoneal cavity via the liver. Multiple oval cysts are found in the mesentery (see Figure 14.4). The cysts contain the inverted scolex of the tapeworm. Heavy infections cause abdominal discomfort and distension. In severe cases, they can cause intestinal obstruction. Migration through the liver results in the development of fibrous tracks and necrotic foci.

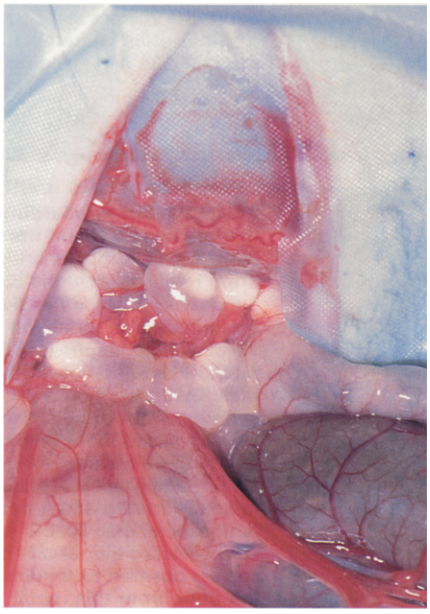

Figure 14.4 ***Cysticercus pisiformis.*** *Cysticercus pisiformis* is the larval stage of *Taenia pisiformis*, which is a tapeworm that affects dogs and foxes, with rabbits acting as the intermediate host. Multiple oval cysts are found in the mesentery. The cysts contain the inverted scolex of the tapeworm. Some of the cysts found during an exploratory laparotomy of an anorexic rabbit showing signs of abdominal discomfort is shown. No faeces had been passed for 48 h. The rabbit was a mature angora male that had recently been adopted by a rescue centre. The cysts were most abundant in the mesentery between the stomach and the distal colon. The cysts had become so large that they had obstructed the large intestine.

Coenurus serialis is the larval stage of *Taenia serialis*, which is a tapeworm that affects dogs and foxes. A variety of mammals can act as intermediate hosts, usually wild rabbits and hares, but primates and even man can host the intermediate stage. Oncospheres from this tapeworm migrate to the subcutaneous tissue where they form cysts that are palpated as soft swellings under the skin. The cyst contains fluid and inverted secondary buds, each containing a scolex. Occasionally a cyst may be found in the orbit where it causes a retrobulbar swelling (Wills, 2001).

Echinococcus granulosus affects dogs and foxes. Most mammalian species, including man and rabbits, can act as intermediate hosts. The adult tapeworm is small in comparison to other tapeworms. It measures 2–9 mm. Oncospheres from ingested eggs migrate to the liver or the lung via the mesenteric blood vessels. The oncosphere then develops into a huge cyst that is able to produce secondary buds, each with an inverted scolex that can produce daughter cysts. The daughter cysts can, in turn, produce daughter cysts, with the result that a huge cyst full of smaller cysts develops. Rupture of the cyst seeds the surrounding tissues with smaller cysts, all of which are capable of developing.

The rabbit can also be a primary host for tapeworms. The cestode species varies in wild rabbits from different parts of the world. An example is *Cittotaenia ctenoides*, which has a free-living mite as its intermediate host.

14.4 Protozoa

14.4.1 Coccidiosis

There are at least 14 species of *Eimeria* which affect rabbits and vary in pathogenicity. Coccidiosis can be a serious problem in rabbit colonies. The disease is described in Section 8.10.1. *Eimeria magna* and *Eimeria irresidua* are the two most pathogenic species that affect the intestine. Other less pathogenic species include *Eimeria perforans*, *Eimeria media*, *Eimeria elongata*, *Eimeria neoloporis*, *Eimeria intestinalis*, *Eimeria caecicola* and *Eimeria piriformis*.

Key points 14.1 Coccidiosis

- Common in colonies of rabbits
- Overcrowding and poor hygiene are significant factors in the development of outbreaks.
- Oral intake of oocysts in contaminated faeces leads to sporozoites infecting duodenal cells, causing damage.
- Clinical signs include inappetence, weight loss, depression and diarrhoea.
- In group situations medication (sulpha drugs) can be given in food or water.
- Recovered rabbits become immune to reinfection.

Key Points 14.2 Principles of infectious disease control

- Infectious and parasitic diseases are more common in groups of rabbits kept in close contact than in individual pet rabbits.
- Diagnosis early in infection is key: a combination of clinical signs and diagnostic testing provides the most reliable information.
- Identify source of infection/routes of transmission and take steps to reduce or eliminate further spread.
- Consider the practicalities of treatment (groups vs individuals).
- Consider public health considerations: is this disease a potential zoonosis?
- Consider concurrent issues such as gut stasis, pain, etc.
- Address external sources of stress, e.g., proximity of potential predators.
- Address environmental issues such as poor ventilation and overcrowding.
- Implement strategies to avoid infectious disease outbreaks in the future.

Eimeria stiedae causes hepatic coccidiosis and has a slightly different life cycle from the intestinal *Eimeria* species. Oocysts can survive for many years in the environment but are susceptible to dry conditions. Recovered rabbits become immune to infection.

14.4.2 *Encephalitozoon cuniculi*

Encephalitozoon cuniculi is a spore-forming obligate intracellular parasite belonging to the phylum Microspora (Wasson and Peper, 2000). The criterion for inclusion in this phylum is possession of a 'polar filament', which extrudes as the spore germinates and is thought to help gain entry into host cells. There are several *Encephalitozoon* species (e.g., *Encephalitozoon intestinalis*, *Encephalitozoon hellem*, *Encephalitozoon bieneusi*, *Encephalitozoon septata*) most of which are opportunist pathogens in immunocompromised human hosts. Diarrhoea, renal disease and keratoconjunctivitis are among the diseases that have been associated with encephalitozoonosis in humans. In animals, *E. cuniculi* is the most important member of the order Microsporidia. *Encephalitozoon cuniculi* primarily affects rabbits but can be found in other species. Microsporidia are unusual in that they lack mitochondria, presumably gaining their nutrition from the host cells (Pakes and Gerrity, 1994). They are characterized by a firm capsule that is strongly Gram-negative (Owen, 1992). A long polar filament is neatly coiled within it. The spore has a polar cap. Infection of the host usually occurs by oral ingestion of food contaminated with infected urine. Once in the alimentary tract, the spore comes in close contact with the mucosa and infects a host cell by extruding the polar filament. Sporoplasm is transferred through the polar filament into a vacuole in the host cell where multiplication takes place. Dividing organisms are lined up along the vacuolar membrane that is thought to be of host origin (Pakes and Gerrity, 1994).

Although *E. cuniculi* is considered to be protozoal, the presence of chitin and trehalose, which are also components of fungi, suggests the relationship to the fungi may be closer than previously thought (Wasson and Peper, 2000). It is a ubiquitous organism, with a wide host distribution, having been isolated from rabbits, shrews mice, rats, hamsters, muskrats, guinea pigs, goats, sheep, pigs, horses,

domestic dogs, domestic cats, both wild and captive foxes, non-human primates and man (Didier *et al.*, 2000; Wasson and Peper, 2000). Three strains of *E. cuniculi* are recognized. Strain I affects rabbits, strain II affects rodents and strain III affects dogs. These strains may be distinguished on a molecular level (Didier *et al.*, 1995).

Infection is by intake of spores. These may be shed in the faeces, mucus and most commonly urine of infected animals. Spores can remain viable in the environment at 22°C for at least 4 weeks (Waller, 1979). Infection of a new host may be by ingestion, inhalation or transplacentally (Baneux and Pognan, 2003). Spores then enter host cells within the gastrointestinal or respiratory system, targeting reticuloendothelial cells in particular. It is unclear whether this is solely by extrusion of the polar tube or if phagocytosis also plays a role. The cells of the reticuloendothelial system are among those invaded and they distribute the parasite around the body. Eventually the organisms develop into mature spores that are oval in shape and measure approximately 2.5 × 1.5 µm with a thick cell wall (Pakes and Gerrity, 1994). The vacuole becomes distended and the cell eventually ruptures, releasing spores that invade new cells. Rupture of the cells is associated with an inflammatory response (Pattison *et al.*, 1971).

Due to the early appearance of the organism in the blood, intradermal testing for *E. cuniculi* becomes positive at 7 days post infection and antibody activity is measurable at 14–28 days post infection (Kunstyr and Naumann, 1985; Pakes *et al.*, 1972).

Once within the bloodstream, the organism is disseminated to areas of high blood flow initially and by 31 days after infection it can be detected in the kidneys, liver and lungs (Percy and Barthold, 2001). Once suitable host cells are penetrated, the parasite proliferates (merogony) and differentiates and matures (sporogony), causing eventual rupture of the host cell and release of spores to complete the life cycle. It is postulated that the rupture of host cells and release of foreign material initiates the granulomatous response commonly associated with this disease. This is why histopathological examination frequently fails to find evidence of organisms within the granulomatous lesions. Chronic granulomatous inflammation in these organs is thought to be responsible for the clinical signs attributed to *E. cuniculi*. The clinical signs commonly believed to be a result of encephalitozoonosis may be grouped into three broad categories: signs of central nervous disease, signs of renal disease and those of ocular disease. Chronic inflammation results in the development of granulomatous lesions in target organs, primarily the kidney and brain, although the liver may be involved (see Figure 10.6 and Figure 14.5). Myocarditis has also been reported (Pakes and Gerrity, 1994). Clinical signs are associated with granulomatous encephalitis or nephritis, notably vestibular disease and chronic renal failure. *Encephalitozoon cuniculi* can also cause lens rupture, pyogranulomatous uveitis and cataracts in rabbits (see Section 9.7.3.1 and Figure 9.4). *In utero* infection of the lens in the developing embryo occurs and causes the lens to rupture in later life (Stiles *et al.*, 1997).

Urinary shedding of spores starts at day 42, by which time the organism has localized within the renal tubular cells, and shedding is at its greatest by day 56. By day 63 the antibody response is at its maximum (Harcourt-Brown and Holloway, 2003). Only after

Figure 14.5 Kidney showing gross lesions associated with *Encephalitozoon cuniculi* infection. The kidney of a 4-year-old male dwarf lop rabbit known to be seropositive for *Encephalitozoon cuniculi* although he showed no obvious clinical symptoms is shown. Both kidneys showed irregular, depressed areas. *Encephalitozoon cuniculi* causes granulomatous interstitial nephritis. Long-standing lesions show interstitial fibrosis and collapse of the parenchyma. Early lesions show focal granulomatous inflammation. Lesions are present in the renal tubule and spores are shed in the urine, which is infective to other rabbits.

63–70 days are the organisms shown to be present and causing lesions in the brain, though compared to the lesions seen in the kidney at this stage, these are relatively mild. From this timeline it is apparent that it is possible to have a positive titre to *E. cuniculi* before the organism is likely to have entered the central nervous system. Any rabbit showing central nervous signs at this time could be wrongly supposed to be showing clinical signs due to this disease. The ability to differentiate IgM and IgG titres may clarify this situation. IgM titres increase early in the course of an infection, then fall, and are absent after day 38. IgG rises more slowly but remains measurable for years (Kunstyr *et al.*, 1986, Sobottka *et al.*, 2001).

Urinary spore shedding ceases by 90 days post infection and by day 98 the organisms are located in the organs of predilection, namely the brain, kidney and heart. Although the heart is named as an area of predilection, heart disease due to *E. cuniculi* is rarely diagnosed.

14.4.2.1 *Encephalitozoon cuniculi* in other species

Encephalitozoon cuniculi can infect a number of mammalian species with predilection sites and disease variation between hosts. Infections have been reported in rabbits, mice, guinea pigs, hamsters, dogs, cats, monkeys and man. There are no morphological or immunological differences between strains of *E. cuniculi* affecting laboratory animals.

Encephalitozoonosis has also been reported in birds (Poonacha and Stamper, 1985). Guinea pigs housed with infected rabbits were found to be at more risk than those housed separately in a survey by Gannon (1980). Nephritis was common but cerebral granulomas were not seen in the guinea pigs. *Encephalitozoon cuniculi* has been described in a wild rabbit in 1955 (Pakes and Gerrity, 1994) but more recent serological surveys have failed to find evidence of infection in wild rabbits, although they can be infected experimentally (Cox and Ross, 1980; Cox *et al.*, 1980). It has been suggested that the natural hygiene habits of wild rabbits significantly decrease post-natal infection.

Serological surveys in dogs in the UK (Hollister *et al.*, 1989) and South Africa (Stewart *et al.*, 1988) demonstrated prevalences of 13 and 2–23%, respectively. The latter prevalences demonstrated the difference between healthy control dogs (2% prevalence), and those with chronic renal disease (23% prevalence). The canine strain (strain III) of *E. cuniculi* has been shown to cause disease in humans (Weitzel *et al.*, 2001).

Two recent studies have looked at the incidence of *E. cuniculi* in wild rodent populations. Hersteinsson *et al.* (1993) found serological evidence of the organism in wild mice in Iceland, and Muller-Doblies *et al.* (2002) isolated *E. cuniculi* from a free-ranging rat (*Rattus norvegicus*). Strain II is typically found in rodents. It has been suggested that carnivores are infected by eating infected prey and that the disease in wild rodent population acts as a reservoir of infection for these species.

In addition to rabbits, *E. cuniculi* can cause severe disease in blue (Arctic) foxes, *Alopex lagopus*, and financial losses to the fur industry. This disease has therefore been extensively studied in this species. Adult blue foxes are asymptomatic carriers but can pass on infection transplacentally and the resultant puppies can have various clinical signs, depending on what body system is primarily involved. These range from acute renal failure to cardiac signs to widespread non-suppurative meningoencephalitis. Akerstedt (2003) demonstrated the humoral response of adult blue foxes in Norway persists for at least one year. Disease in blue foxes has prompted serological surveys of farmed Arctic foxes in Finland (Akerstedt *et al.*, 2002), wild Arctic foxes in Greenland (Akerstedt and Kapel, 2003) and other species of fox, *Dusicyon culpaeus* and *Dusicyon griseus*, in Argentina (Martino *et al.*, 2004). These studies have shown that wild foxes in both Greenland and Argentina demonstrated no evidence of encephalitozoonosis within their populations. However, in farmed foxes the disease is endemic. This mirrors the situation in rabbits in the United Kingdom (Cox and Ross, 1980; Blevins, unpublished data; R. Saunders, personal communication), where exposure is common in rabbit colonies and within the pet population but not in the wild rabbits, but contrasts with the situation in both the United States (Jungherr, 1955) and Australia (Thomas *et al.*, 1997), where exposure has been documented in wild rabbits. In the case of Australian rabbits the seroprevalence in the wild is suggested to have changed in recent

years. A study in 1980 found no evidence of exposure to *E. cuniculi* in wild rabbits in Victoria (Cox *et al.*, 1980), whereas a study in 1997 showed a seroprevalence of 25% in wild rabbits in Western Australia (Thomas *et al.*, 1997). The mechanism for the shift in prevalence in the wild populations in both America and Australia is unknown. In the case of Australia it is possible that *E. cuniculi* was always present in wild rabbits in Western Australia, and is still not present in those in Victoria.

14.4.2.2 Zoonotic potential of *Encephalitozoon cuniculi*

Although *E. cuniculi* can infect a range of hosts, severe systemic disease is rare in other species except in athymic or immunosuppressed mice and neonatal dogs or foxes. Athymic mice do not develop a cellular or humoral response to the parasite and masses of spores are found in the liver and other viscera (Gannon, 1980). Experimental infection of rabbits with *E. cuniculi* cultures administered into the rectum with a catheter after weeks of repeated colonic enemas resulted in *E. cuniculi* infection with hepatic lesions predominating rather than the typical brain and kidney changes (Fuentealba *et al.*, 1992).

In recent years the topic of *E. cuniculi* has received renewed interest due to its potential to cause disease in immunosuppressed humans. Weber *et al.* (1997) described a case of cerebral microsporidiosis in an individual with human immunodeficiency virus (HIV) infection, and two similar cases in children have been described (Didier, 2000). Refractory diarrhoea, bronchitis, pneumonia and sinusitis are other possible manifestations. Hollister *et al.* (1991) found that there was serological evidence of widespread human exposure to *E. cuniculi*. It is interesting to note that in the USA the prevalent strain of *E. cuniculi* found in humans was strain III, which is usually associated with dogs, whereas in Europe strain I (the rabbit strain) was more commonly found (Didier *et al.*, 1995). With the discovery of HIV in the 1980s and the ever-increasing number of people undergoing chemotherapy and organ transplantation the relevance of *E. cuniculi* within the pet population as a potential zoonosis cannot be overstated.

14.4.2.3 Clinical signs associated with *Encephalitozoon cuniculi* infection in rabbits

Encephalitozoon cuniculi was first described by Wright and Craighead in 1922 in rabbits exhibiting hind leg paralysis and other neurological signs. Kimman and Akkermans (1987) described an outbreak in a colony of laboratory rabbits that resulted in heavy losses. Affected animals showed muscular weakness, emaciation, polydipsia, polyuria and occasional neurological signs. Other texts describe encephalitozoonosis as a chronic, latent disease of rabbits that is significant because of its effects on experimental results. Infection with *E. cuniculi* in laboratory rabbits has caused many problems to scientific studies. Subclinical infection has vitiated experimental results and lesions caused by the parasite have been wrongly attributed to a number of other ailments (Wilson, 1979). Encephalitozoonosis can interfere with test results. Blood samples of rabbits with spontaneous encephalitozoonosis have been shown to have significantly lower levels of catecholamines than healthy rabbits (Levkut *et al.*, 1997). Nowadays, laboratory rabbits are screened for *E. cuniculi* and seropositive animals eliminated. In the laboratory setting a 'test and remove' policy in conjunction with strict hygiene is frequently employed because infection with *E. cuniculi* can result in erroneous results during research trials (Ansbacher *et al.*, 1988). This is due to the fact that *E. cuniculi* modifies the way the central nervous system reacts to challenge.

Encephalitozoonosis is widespread in pet rabbits. There is a range of manifestation signs from acute neurological disaster to latent infections that do not exhibit clinical signs of disease. In Germany, a serological survey of 277 pet rabbits showed that 41% were seropositive (Ewringmann and Göbel, 1999). Of the seropositive rabbits, 51 (40.8%) showed clinical signs of encephalitozoonosis. In the UK, a random survey of 30 pet rabbits revealed 8 seropositive individuals (Carmichael, Idexx and Harcourt-Brown, unpublished data). After the animals had been found to be seropositive, the owners were questioned and four reported vague symptoms such as head nodding or swaying at rest, deafness or impaired mental ability. A survey of 97 clinically

healthy UK rabbits in 2006 showed that 52% were seropositive (Keeble and Shaw, 2006). Samples were taken as part of a routine health screen or preanaesthetic screening at veterinary practices in England, Wales and Scotland. Veterinary surgeons completing the survey were asked for information on the animals' husbandry, diet, vaccination, preventive medicine routines and health status. None of these factors were found to be associated with the serological status of the rabbits.

When clinical signs occur, they are usually associated with granulomatous lesions in the brain, kidney or lens, although the liver, heart and other organs can be affected. In the German survey of 277 rabbits, 51 (40% of the seropositive animals) showed signs relating to infection. Twenty-three rabbits suffered from CNS disorders, 16 from renal disease and 7 from uveitis. Two rabbits had both CNS and renal disease and 3 animals had CNS symptoms, renal disease and uveitis (Ewringmann and Göbel, 1999). Renal disease associated with *E. cuniculi* is described in Section 14.5.1 and ocular disease in Section 9.7.3.1.

14.4.2.4 Diagnosis of *Encephalitozoon cuniculi*

Since the first report of *E. cuniculi* as a cause of 'infectious motor paralysis' in young rabbits (Wright and Craighead, 1922) there has always been uncertainty surrounding the diagnosis of *E. cuniculi* as a cause of clinical disease in rabbits. Recent work has shown the seroprevalence of *E. cuniculi* in UK pet rabbits to be 52% (Keeble and Shaw, 2006). The infection is common; however, the rate of disease is unknown. Historically *E. cuniculi* has been found frequently in mammals, but its relevance has been misinterpreted. The use of infected rabbits as models for human disease has led to the clinical and histological signs of *E. cuniculi* being mistaken for syphilis and poliomyelitis (Bull, 1917). It has also been implicated at various times as the causative agent of rabies, scrub typhus, psittacosis and chemical carcinogenesis (Wasson and Peper, 2000).

Because of the significant effects this organism can have on research trials and the need to distinguish infected rabbits from those which are not, reliable serological tests are now available. These are equally suitable for use on pet rabbits as well as in the laboratory setting. The majority of research into this disease has been carried out on laboratory rabbits. With an increase in the popularity of rabbits as pets and the number presented to veterinary surgeons for treatment, it is important to consider this disease from the pet rabbit perspective. In the domestic setting it is often not enough to be able to say a rabbit is infected; it is necessary to decide whether this is relevant to the health status of the individual concerned. A positive titre only reflects exposure but gives no indication of whether the disease is active. This is important in the treatment of the individual animal, but also has relevance to the human owners, since *E. cuniculi* is a potential zoonosis (Deplazes *et al.*, 1996; Weber *et al.*, 1997; Weitzel *et al.*, 2001).

Currently the gold standard for diagnosis of *E. cuniculi* is post-mortem histological examination with immunochemical staining for accurate identification of any organisms found (Franzen *et al.*, 1999; Percy and Barthold, 2001). Changes typically associated with infection are granulomatous lesions, the distribution being defined by the time between exposure and histological examination. Central nervous system lesions are described as 'focal non-suppurative granulomatous meningoencephalomyelitis with astrogliosis and perivascular lymphocytic infiltration' (Percy and Barthold, 2001), and those in the kidneys are 'focal to segmental granulomatous interstitial nephritis' (Percy and Barthold, 2001). In both cases, traces of the organism are not reliably present in the lesions, although they may be found in adjacent cells.

In vivo testing must be compared against histological examination to evaluate the sensitivity and specificity of the results. However, in many cases, certainly those with neurological signs, direct comparison of testing with the gold standard is impossible, since the individuals being tested are still alive. In the pet rabbit, a humoral response to *E. cuniculi* infection cannot be relied upon for accurate diagnosis. In laboratory rabbits, serum antibodies develop after 3 weeks and excretion of the parasite occurs 6 weeks after experimental infection with *E. cuniculi* (Cox *et al.*, 1979). Passive immunity is

transferred from infected dams to their offspring, which can have titres of 1:25 to 1:800 that last until they are about 4 weeks old. After a seronegative period, young rabbits seroconvert at 8–10 weeks of age in response to natural infection (Lyngset, 1980). Therefore the presence of antibodies only indicates exposure to the organism and does not confirm *E. cuniculi* as a cause of disease.

We know that many domesticated rabbits have positive titres; however, this only indicates exposure and indeed absolute titres have no significant relationship to presence of organism in the brain, severity of clinical disease or outcome (Keeble and Shaw, 2006; Kunstyr *et al.*, 1986). Titres may be so variable even between rabbits matched for age, breed and environment (Kunstyr *et al.*, 1986) as to render them uninterpretable. Experimentally, high antibody titres have been found in rabbits showing signs of chronic infection (Pye and Cox, 1977). IgG titres reached a level of 160–2560 after a latent phase of 13–28 days in a study of rabbits experimentally infected with *E. cuniculi* (Kunstyr *et al.*, 1986). Some of the rabbits showed an episodic humoral response and became seronegative after a few weeks. There was wide individual variability in antibody response but the authors suggested that differences in IgM and IgG could distinguish between recent and chronic infection. IgM seroconversion occurs at the beginning of the antibody response and simultaneous IgG and IgM detection suggest recent infection. Jeklova *et al.* (2010) have suggested that finding an IgM titre indicates active infection and warrants treatment.

The situation is made even more complicated by the fact that concurrent disease can affect the host's immune response. Cox (1977) showed that rabbits already infected with *E. cuniculi* exhibited altered immune responses to intercurrent infections, and that IgG levels relating to the new infection may be depressed and IgM levels elevated compared to uninfected animals. This increases the likelihood that concurrent clinical disease may occur (Harcourt-Brown and Holloway, 2003). Similarly, infection with *E. cuniculi* can affect the way the central nervous system reacts to outside challenge. Ansbacher *et al.* (1988) showed that seropositive rabbits displayed an inconsistent inflammatory response both between individual rabbits and between sites within the same rabbit when coated platinum wires were implanted into four sites within the cerebral cortex. The response of each rabbit becomes unpredictable, and renders them unsuitable for many research projects. It is conceivable that response to intercurrent disease may be equally unpredictable.

Various serological tests are available for screening rabbits for *E. cuniculi*, largely due to the fact that the laboratory industry requires negative rabbits for many of its research studies. Boot *et al.* (2000) compared several commercially available test methods for determining their sensitivity and specificity relative to each other. Two indirect immunofluorescence assays (IIF), two enzyme-linked immunosorbent assays (ELISA) and carbon immunoassay were compared. The results suggested that there was no difference between the assays in respect to detecting positive cases, but that quantitative determinations should be performed by IIF and not ELISA. This is proposed to be due to the less quantitative nature of the ELISA assay and not due to any reduction in sensitivity relative to the other methodologies. Intradermal testing (Pakes *et al.*, 1972) is not routinely used for screening at this time, although it proved to be both sensitive and specific in determining rabbits that were positive to the organism.

Encephalitozoon cuniculi organisms can be found in the urine of infected animals (Pye and Cox, 1977). The spores are evident as ovoid, Gram-positive organisms approximately 1.5–2.5 µm in size. Staining procedures using carbol fuchsin will stain the organisms a distinct purple colour (Percy and Barthold, 1993). Theoretically, urine examination is a means of confirming the presence of antigen in the live animal, although it is impractical as a routine diagnostic technique in general practice. Organisms are intermittently excreted and urine collection can be difficult. Normal rabbit urine often contains sediment. PCR testing is now available commercially to identify *E. cuniculi* in urine, faecal and tissue samples.

In the pet rabbit a clinical diagnosis of encephalitozoonosis is reached by a combination of a positive titre with suggestive clinical signs and elimination of alternate causes of these clinical signs where this is possible. The clinical work-up should include a

physical examination, complete blood count and differential, biochemistries, radiography of the axial skeleton and skull, urinalysis and serology as a minimum. This should enable the clinician to rule in or out many of the possible differential diagnoses and will further direct the management of the individual case.

The major differentials for central nervous disease in the pet rabbit are pasteurellosis, neoplasia, trauma, lead poisoning and toxoplasmosis. In the USA cerebral larval migrans caused by *Baylisascaris* is also a differential. As encephalitozoonosis is a disease related to granuloma formation, clinical pathological evidence of this may be used to distinguish it from the possible alternate diagnoses. Of the above list only toxoplasmosis is likely to produce granulomatous lesions at the time of clinical signs becoming relevant. This disease is rarely diagnosed in UK rabbits and its significance can be eliminated by looking at paired titres for this organism. Similarly, the differential diagnoses for chronic renal failure are intrinsic renal failure, benign tumours, such as embryonal nephroma, renal cysts and malignant tumours, such as lymphoma and renal carcinoma. The defining feature of encephalitozoonosis is granulomatous change in the target organs, unlike the alternate causes of similar clinical symptoms. There are two challenges in determining the cause of many of these clinical signs. First is the reliance necessarily placed on invasive or post-mortem testing to achieve definitive diagnoses. Secondly, increases in absolute titres to *E. cuniculi* cannot be used diagnostically due to the difficulties in interpretation. Many workers doubt *E. cuniculi* as a cause of disease by itself (it does not in fact fulfil Koch's postulates), feeling that in many cases, signs attributed to the parasite are in fact caused by one of the differential diagnoses. Successful treatment of the alternative disease can bring about a clinical cure. However, positive diagnosis of one of the differentials for the presenting clinical signs does not rule out active encephalitozoonosis.

Histological examination cannot reasonably be used for ante-mortem diagnosis in rabbits with central nervous disease. Kidney biopsy can be undertaken to establish a diagnosis in those rabbits showing renal signs; however, organisms and histological change may not be continuous throughout the kidney, so lesions can be missed.

Key Points 14.3 *Encephalitozoon cuniculi*

- *Encephalitozoon cuniculi* is a microsporidian parasite that can affect many species of animal.
- *Encephalitozoon cuniculi* spores can be spread in urine and faeces of infected animals.
- Spores can remain viable in the environment for 4–6 weeks.
- Once within a host, spores are taken in the bloodstream to organs of high blood flow (kidney, brain, lungs) but eventually settle in the central nervous system.
- IgM levels rise rapidly after infection, then decrease in chronically infected individuals. IgM signifies recent or active infection.
- IgG levels rise more slowly (they become dominant at around day 17) and can remain high for long periods. Within individual animals, IgG levels can fluctuate over time.
- Diagnostic criteria include compatible clinical signs, exclusion of differential diagnoses and positive IgM and IgG titres.
- Nested PCR can be used to detect microsporidial DNA in urine and faecal samples; however, as individual rabbits can shed spores in urine intermittently, this is not useful diagnostically.
- Treatment should be aimed at controlling the spread of spores within the host, and restricting access to them in the environment. Fenbendazole has been shown experimentally to clear infection in individuals currrently and prevent infection in animals newly exposed to the organism.
- Treatment of the clinical effects of encephalitozoonosis should be undertaken at the same time.

14.4.2.5 Treatment of encephalitozoonosis

There have been no clinical trials examining treatment protocols for clinical encephalitozoonosis in pet rabbits; therefore treatment regimens have been

based on anecdotal reports or extrapolation from the treatment of human microsporidial disease. Suter *et al.* (2001) demonstrated the efficacy of fenbendazole in treating experimentally infected laboratory rabbits. This has led to the licensing of fenbendazole for this use in rabbits in the UK.

A logical approach to treatment should include:

- Reduction of inflammatory response
- Inhibition of spore formation
- Limiting access to infective spores
- Treating concurrent medical issues that are either directly or indirectly caused by the infection: for example, seizures, traumatic damage, renal failure, urine scalding and skin disease.

Individual response to treatment may be very variable, and is thought to be due to differences in immune status, infective strain and dose.

Potential treatments include:

1. Benzimidazoles: this class of drugs (including fenbendazole and albendazole) are microtubule inhibitors. In this instance they stop the host cells becoming infected by preventing the extrusion of the polar filament. Thus, they limit spore formation. Albendazole has been the treatment of choice in human microsporidial infections; however, its use in rabbits is extrapolated from this and therefore anecdotal. Adverse reactions such as bone marrow disease, pyrexia and liver failure have been attributed to albendazole in rabbits. Albendazole is available as an oral preparation for cattle and sheep. It has been used to eliminate the *Encephalitozoon* spp. from human AIDS patients, sometimes with dramatic success (De Groote *et al.*, 1995). Elimination of the parasite is accompanied by relief of clinical symptoms in humans. Eradication of the parasite has been confirmed at autopsy (Joste *et al.*, 1996; Sobottka *et al.*, 1995). Albendazole has also been used to treat clinical cases of *E. cuniculi* in pet rabbits, with no reports of adverse effects and apparent improvement in clinical symptoms. The pharmacokinetic effects of the agent have been tested on rabbits (Li *et al.*, 1995). An empirical course of 3–10 days' treatment appears to be beneficial. In-contact rabbits should be treated as a precaution, although albendazole is potentially teratogenic and is not advisable in breeding females. While it is difficult to support the use of this drug in the face of other proven less toxic compounds, its penetration into ocular tissues and its success in treating ocular manifestations of encephalitozoonosis should not be ignored. Fenbendazole has been tested clinically in experimentally infected rabbits (Suter *et al.*, 2001) and been found to be effective in clearing the parasite from the brain, thereby reducing clinical signs in advanced cases. It is also effective in preventing the establishment of infection in exposed rabbits. Fenbendazole appears to be safer than albendazole in rabbits; however, it has been linked with bone marrow suppression, so rabbits undergoing treatment should be monitored appropriately.
2. Glucocorticoids: the use of glucocorticoids has been advocated in the acute phase of encephalitozoonosis, in order to suppress the inflammatory response. However, rabbits are very sensitive to the immunosuppressive effects of steroids and their use in this species is always controversial. Treated individuals should be monitored closely.
3. Fluoroquinolones: for example, enrofloxacin, an antibiotic known to be safe for and licensed for use in rabbits, has been shown to have some antimicrosporidial action *in vitro*. The use of fluoroquinolones in the vestibular form of encephalitozoonosis is sensible, particularly as they are also effective in treating some of the main differential diagnoses such as pasteurellosis.
4. Other antibiotics: oxytetracyclines and potentiated sulphonamides have also been recommended for use in treating encephalitozoonosis. While potentiated sulphonamides have been shown to be ineffective *in vitro* against *E. cuniculi*, oxytetracyclines do appear to inhibit microsporidial growth *in vitro*.

5. Antifungal drugs: as *E. cuniculi* has been shown to share characteristics with fungi, antifungal medications such as fumagillin have been evaluated as potential treatments. This drug is not well tolerated by rabbits and is not advocated as a treatment at this time.
6. Interferon-gamma: having been shown to be a potentially effective treatment in immunosuppressed humans, in the future interferon-gamma may become a clinically available treatment for rabbits.
7. Chitin synthesis inhibitors: e.g., lufenuron, polyoxin D and nikkomycin Z may also be effective. To date, little information has been gathered about the clinical use of these compounds, either in humans or in rabbits. Some workers in the UK are advocating the use of lufenuron (Program Suspension Cat, Novartis Animal Health), as it has shown to be safe in rabbits. Its efficacy is unproven.

Some cases appear to improve spontaneously without treatment, presumably due to the host's immune response. In the absence of a simple diagnostic test for the presence of the antigen in the live animal, it is difficult to monitor the efficacy of therapeutic agents in eliminating the parasite.

14.4.2.6 Control and prevention of encephalitozoonosis

Encephalitozoon cuniculi infection is widespread in UK rabbits, latently infected asymptomatic individuals occur and it is difficult to definitively diagnose the disease in the live animal. All of these factors make control and prevention of this disease more difficult. Ideally, rabbits should be tested for encephalitozoon exposure before planning housing and management strategies. Even with this strategy, rabbits that have been recently infected will be missed and therefore wrongly categorized. Two tests, 4 weeks apart, would eliminate most of this risk. Negative animals should be housed separately from and without contact with positive animals. If this is impractical, other measures may reduce the likelihood of infection. Regular short prophylactic courses of fenbendazole (with appropriate monitoring) have been shown to prevent infection in exposed rabbits. Strategies to reduce contact with potentially contaminated urine such as regular cleaning and disinfection of the rabbit's environment (including water/food bowls and litter trays), elevation of food and water bowls off the floor to reduce the risk of urine contamination, the use of hay nets rather than blanketing the floor in hay and control of rodent vermin may all be helpful.

Prior to introducing a new animal into a known status group/individual (positive or negative), serological testing is recommended. Any new individuals with negative titres should be tested and found to be negative twice prior to introduction into a negative group. It is difficult to advocate the introduction of a negative individual into a known positive group. In the event that serology is not an option, then a prophylactic 28-day course of fenbendazole has been suggested for any rabbit that may have been exposed, prior to introduction (Keeble, 2011). While this will treat existing infection and prevent acquisition of infection at the time, it will not prevent future infection.

Although *E. cuniculi* spores can persist for up to 4 weeks in the environment, they are very susceptible to disinfectants. Quaternary ammonium disinfectants (Trigene, F10), 1% bleach or 70% ethanol are all effective. As always, thorough cleaning must be undertaken prior to disinfection.

14.4.3 *Toxoplasma gondii*

In common with all mammals, rabbits can be infected with *Toxoplasma gondii*, although infection is usually subclinical. Ingested sporulated oocysts hatch in the duodenum. Sporozoites invade neighbouring cells and are dispersed throughout the body via the blood and lymphatics. Once the host immune responses are established, the organisms can be found as cysts in various tissues where they can remain for years (Owen, 1992). The source of infection for rabbits is feed contaminated by cat faeces and symptoms have been described in rabbits that grazed an area frequented by cats. Clinical signs are

most common in the acute phase in young rabbits. Sudden anorexia, pyrexia and death are the usual signs, although CNS symptoms such as posterior paralysis or seizures can also occur (Leland *et al.*, 1992). Outbreaks have been described in commercial rabbits (Harcourt, 1967; Okerman, 1988). High antibody titres have been found in wild rabbits collected from sewerage farms in Australia (Cox *et al.*, 1981). Ashmawy *et al.* (2011) examined the seroprevalence of exposure to toxoplasmosis in several rabbit farms in Egypt. Eleven per cent of rabbits had been exposed, which presented a public health risk for eating rabbit meat. Positive serology only indicates exposure to infection. Gustaffson *et al.* (1997) compared the difference in susceptibility to toxoplasmosis between two lagomorphs, the mountain hare (*Lepus timidus*) and the domestic rabbit (*Oryctolagus cuniculus*). Domestic rabbits were found to be resistant to toxoplasmosis in comparison with the mountain hare. In the mountain hare, toxoplasmosis is acutely fatal and characterized by necrosis and tissue damage in the small intestine, mesenteric lymph nodes and liver. In the domestic rabbit, lesions are mild, consisting of focal accumulations of mononuclear cells, mainly in the liver and heart. Histopathology is diagnostic. Antibodies are detected early as 7–8 days post-infection (Gustaffson *et al.*, 1997).

Although toxoplasmosis is potentially zoonotic, *Toxoplasma* is only transmissible from rabbits to humans who handle or eat undercooked rabbit meat. Infection is not spread through rabbit faeces.

14.4.4 Other protozoan parasites of rabbits

Cryptosporidium species have been described in rabbits but not as a major cause of disease. *Giardia duodenalis* has also been reported in rabbits, although it does not appear to be pathogenic. A single outbreak of catarrhal enteritis in rabbits has been attributed to giardiasis. There is no evidence of transmission to humans (Pakes and Gerrity, 1994). *Sarcocystis cuniculi* affects rabbits, although it is rarely reported in the European rabbit (*O. cuniculus*). It is more commonly encountered in the cottontail (*Sylvilagus floridanus*). Sarcocystis forms cysts in skeletal and cardiac muscle. The source of infection is believed to be cats.

14.5 Bacterial diseases

14.5.1 Pasteurellosis

Pasteurella multocida is a very small, non-motile, Gram-negative, ovoid, coccoid or short rod that shows bipolar staining. It is aerobic and facultatively anaerobic. The organism forms circular, convex smooth colonies on blood agar after 24 h incubation. The colonies are generally 2–2.5 mm in diameter and slightly iridescent, although variations can occur. The colonies are mucoid in appearance.

There are multiple antigenic strains of *P. multocida* associated with different species of animal. The organism is potentially pathogenic to a variety of animals. It can also be found as a commensal organism; for example, *P. multocida* has been isolated from the tonsils of healthy dogs and from the respiratory tract in humans. In rabbits, *P. multocida* can reside in the nasal cavity without causing disease. In pet rabbits kept individually or in small numbers, *P. multocida* seldom causes primary disease, although the bacterium is often found as a secondary pathogen in any purulent or suppurative condition. In colonies of rabbits kept for breeding, meat and fur production, or for laboratory purposes, pasteurellosis is a serious, infectious disease. Disease occurs when predisposing factors give the bacteria the opportunity to multiply uncontrollably and overwhelm the physiological and immunological defences of the respiratory tract. During these episodes, clones of virulent bacteria increase and are then easily transmitted to neighbouring animals.

The protein pattern of the outer membrane of *P. multocida* shows a relationship between the protein type and the animal host. Bacterial capsular polysaccharides inhibit phagocytosis. Bacterial lipopolysaccharides confer resistance to complement and bactericidal activity of serum (Deeb, 1993). There are several capsular and somatic serotypes of *P. multocida* that are pathogenic for domestic

livestock and poultry, but only a few are pathogenic for rabbits. Serotyping entails the identification of the capsular antigen and serotypes. In rabbits, serotypes 12:A, 3:A and 3:D are the usual types identified (Percy and Barthold, 1993). Snuffles is most frequently associated with 12:A, whereas 3:A and occasionally 3:D are more frequently associated with disease of the lower respiratory tract. Jaglic *et al.* (2008) studied the pathogenicity of serotype F in both immunocompetent and immunosuppressed individuals. Immunocompetent rabbits showed fibrinopurulent pneumonia while immunosuppressed individuals had severe diffuse haemorrhagic pneumonia. A septicaemic syndrome that was eventually fatal occurred in both groups. This indicates that serotype F is a potentially serious pathogen, and could cause serious losses in commercial rabbitries. Virulence of infection varies between serotypes. *Pasteurella multocida* produces an endotoxin that varies with serotype. The role of the endotoxin in clinical disease is unclear, although it may be significant in septicaemic cases. The bacteria also produce adhesins which stick the bacteria to epithelial tissue. Filamentous appendages elaborated by the bacteria may help *P. multocida* colonize mucous membranes (Deeb, 1993). The adhesive properties vary with different serotypes of *P. multocida* and could be important in the pathogenesis of the disease (Manning *et al.*, 1989). Mucosal antibodies (IgA) inhibit growth of bacteria and are produced in response to exposure to *P. multocida*. High humoral (IgG) antibody levels are associated with chronic infection and have been used to identify infected rabbits in laboratory colonies (Deeb, 1993).

14.5.1.1 Epidemiology

When sufficient numbers of *P. multocida* bacteria are transmitted between rabbits, a subclinical infection is established in the upper respiratory tract. Bacteria become abundant in the mucous film covering the mucous membranes but are scarce in the sinuses (Whittaker, 1989). Clinical disease occurs when there is disruption of the balance between mucociliary clearance and bacterial proliferation. Pregnancy, parturition, lactation, poor husbandry, overcrowding, stress, nutritional deficiencies, genetic predisposition and bacterial serotype can affect the course of the disease, which tends to be a greater problem in the colony rabbit than in the adult pet rabbit.

Pasteurella multocida is spread to newborn rabbits shortly after birth from infected does that harbour infection in their nasal cavity. There are many predisposing factors in young rabbits, including the age of weaning, the presence of vaginal infection and the prevalence of infection within the colony. There appears to be genetic susceptibility to pasteurellosis. For example, Chinchilla rabbits appear to be more susceptible than Blue Beverans (Manning *et al.*, 1989). The incidence of disease increases with age up to about 5 months of age. After colonization of the upper respiratory tract, infection extends to the rest of the respiratory tract and tympanic bulla and can cause clinical rhinitis, conjunctivitis, pneumonia, tracheitis, dacryocystitis or otitis media. Some rabbits remain asymptomatic despite the presence of *P. multocida* in the nares. Such individuals are carriers and infective to contact animals. Other animals are negative on nasal culture but harbour *P. multocida* in the tympanic bulla.

Transmission of disease can occur between rabbits by direct contact and by airborne spread. Uninfected rabbits in direct contact with infected rabbits contract pasteurellosis within 8 days to 3 weeks (Manning *et al.*, 1989). Physical separation of rabbits by a distance of a few feet will delay transmission of infection (Lelkes and Corbett, 1983). Fomite spread has been demonstrated and contaminated water supplies have been suggested as a source of infection (Whittaker, 1989).

14.5.1.2 Clinical signs of pasteurellosis

Pasteurella multocida infection can be acute, subacute or chronic. There are several clinical syndromes associated with pasteurellosis. Surveillance of rabbits for pasteurellosis at a laboratory animal facility revealed the following syndromes in a decreasing order of magnitude: rhinitis, conjunctivitis, abscesses and otitis media (DiGiacomo *et al.*, 1983).

14.5.1.3 Rhinitis ('snuffles')

The colloquial term 'snuffles' refers to upper respiratory tract infections manifested by a serous followed by purulent discharge from the nose. Affected rabbits sneeze and cough and may have an audible upper respiratory noise or snuffle. Snuffles is usually associated with *P. multocida* infection, although other infectious agents such as *Staphylococcus aureus* can be involved. In pet rabbits, dental disease and nasal foreign bodies can cause similar signs (see Section 11.2.3). The thick sticky white discharge from the nose is wiped away with the forelegs, leading to a yellow staining and matting of the fur. Poor husbandry, overcrowding, poor ventilation, dust conditions and ammonia build-up exacerbate the disease. Investigations of rhinitis in laboratory rabbits have shown that some rabbits can have rhinitis for up to 2 weeks before *P. multocida* is isolated from nasal swabs. Clinical signs wax and wane but symptoms often persist despite treatment.

14.5.1.4 Pneumonia

Pasteurella multocida is a cause of pneumonia in rabbits. The disease can be acute and rapidly fatal. Chronic or subacute infections also occur in rabbits with no clinical signs. It is not unusual to find incidental pneumonic lesions during post-mortem examination of apparently healthy rabbits. Large abscesses can be present in the thoracic cavity.

14.5.1.5 Genital infection

Pasteurella multocida can be recovered from the vagina in a relatively high percentage of carrier animals (Percy and Barthold, 1993) and the organ can act as a reservoir of infection. *Pasteurella multocida* can be spread during mating. Bucks may harbour infection in their genital tract. Orchitis, pyometra and genital infections can be manifestations of pasteurellosis.

14.5.1.6 Wound infections and abscesses

Pasteurella multocida is often isolated from abscesses and infected bite wounds. The organism is present in the nasal cavity of many rabbits and can contaminate tissues during licking and grooming. It can also be spread haematogenously. *Pasteurella multocida* may be isolated from post-surgical wound breakdowns and can cause osteomyelitis after orthopaedic surgery (Leibenberg and Badger, 1984). *Pasteurella multocida* can be isolated from facial abscesses that result from periapical infection or tissue damage caused by elongated crowns in rabbits with dental disease.

14.5.1.7 Dacryocystitis

Pasteurella multocida can cause dacryocystitis (Petersen-Jones and Carrington, 1988). The organism may be isolated from purulent infections of the nasolacrimal duct, which can result from spread of infection from the nasal cavity or as secondary infections in ducts blocked by elongated tooth roots, especially of the maxillary incisors.

14.5.1.8 Otitis media

Pasteurella multocida can spread from the nasal cavity to the tympanic bulla via the eustachian tube. A common post-mortem and radiographic finding is the presence of inspissated pus in the deeper structures of the ear (see Figure 11.3). Infection can spread along the vestibulocochlear nerve and cause vestibular disease, resulting in neurological signs such as rolling and nystagmus.

14.5.1.9 Detection of pasteurellosis

Confirmation of pasteurellosis in rabbit colonies is required to limit the spread of disease. Clinical signs are indicative of infection but diagnostic tests are required to isolate the organism and detect subclinical carriers. A deep nasal swab is required for bacteriology. It can be difficult to obtain satisfactory swabs in the conscious animal and sedation or anaesthesia is required. Bacterial culture cannot always be relied upon. Infection can be deep within the nasal passages or in the paranasal sinuses and false-negative results can occur. Some rabbits have already been treated with antibiotics. *Pasteurella multocida* does

not survive well in transport media (Sanchez *et al.*, 2000). It survives for less than 24 h at room temperature. Some strains of *P. multocida* grow best at 34–35°C, which is lower than most routine cultures.

Serological tests and a polymerase chain reaction (PCR) test are available in the USA. A rising titre demonstrates exposure to infection. However, the presence of antibodies does not confirm the presence of active infection. Sanchez *et al.* (2000) conducted a study of a combination of bacterial culture, serology and PCR testing in rabbits with clinical signs suggestive of pasteurellosis. They found that the combination of PCR and serology was more useful than culture from nasal swabs. The authors concluded that there are other organisms, such as *Bordetella*, *Pseudomonas* and *Staphylococcus* spp. that cause clinical signs similar to those of pasteurellosis.

14.5.1.10 Control of pasteurellosis in rabbit colonies

Pasteurellosis is a major problem in breeding, laboratory or commercial colonies of rabbits. The disease also presents problems in multi-rabbit households or in sanctuaries and rescue centres that house several rabbits in a small space. Stress, intercurrent disease, overcrowding, and poor air quality can trigger the flare-up of latent infection. As with any infectious disease in an intensive situation, good husbandry is important in the control of the disease. Affected animals should be isolated and treated promptly or even culled, as they are a source of infection to other stock. Keeping the numbers down and minimizing contact between batches of rabbits reduces transmission of disease.

In infected colonies, clinical disease can be minimized by separating newly weaned rabbits from adults and by carefully controlling the environment and reducing stress factors. A clean, dry, well-ventilated environment is required with no draughts. Rabbits can withstand cold but become stressed by high temperatures. Closed stuffy sheds increase the risk of disease, especially if the air quality is poor due to ammonia build-up. Fluctuations of temperature should be avoided, with an optimum temperature maintained at 16–20°C and humidity of 50–70% (Whittaker, 1989). Air quality should be good, with around 20 air changes per hour and preferably a filter system.

14.5.1.11 Prevention of pasteurellosis

Over the years, several control strategies for pasteurellosis have been tried in rabbit colonies with varying degrees of success. Many laboratory colonies are now disease free and are vigilantly barrier-housed to prevent the introduction of infection. *Pasteurella*-free stock is selected by placing rabbits in isolation for 2–4 weeks and repeatedly culturing the nasal passages. Rabbits with positive cultures or signs of rhinitis are culled. Surviving rabbits are bred from, and after 3 years the colony is considered to be disease free. Other methods of producing disease-free rabbits involve Caesarean derivation with hand-rearing (Manning *et al.*, 1989) or the transfer of fertilized ova to *Pasteurella*-free does. Early weaning and the use of antibiotics can increase the number of disease-free individuals. To ensure an uninfected status, periodic serological testing for antibodies to *Pasteurella* is necessary. Recently, a PCR test has been developed that can be used to detect infection (Sanchez *et al.*, 2000).

Antibiotics have also been used prophylactically in an attempt to prevent pasteurellosis by administering them in either the feed or drinking water to pregnant does. There appears to be genetic resistance to *Pasteurella* and attempts have been made to produce disease-free strains of rabbit.

Vaccines against *P. multocida* are used successfully in other species such as sheep and attempts have been made to produce an effective vaccine against pasteurellosis in rabbits. Both live and dead vaccines have been used and found to be effective in reducing mortality and clinical disease caused by a homologous strain of the bacteria. Most pathogenic strains from rabbits carry somatic antigens 3 and 12 and are capsule type A or D. Cross-immunity is higher between strains of the same serotype. However, despite promising results in laboratory rabbits (DiGiacomo *et al.*, 1987), protection against nasal colonization and clinical disease caused by heterologous strains is incomplete and the results of field

trials using an intranasal vaccine against A:12 have been disappointing (DiGiacomo and Deeb, 1989). Suckow *et al.* (2008) demonstrated a successful field trial of a vaccine containing serotype D:3,12,15. Interestingly, the subcutaneous vaccination was more effective than the intranasal. There is a belief among some rabbit breeders that vaccination is feasible with either an autogenous vaccine or a vaccine produced for use against pasteurellosis in other species such as sheep or cattle. Claims of success with these vaccines are difficult to evaluate.

14.5.1.12 Treatment of pasteurellosis

Treatment of pasteurellosis depends on the clinical symptoms and the type and emotional or financial value of the rabbit suffering from the disease. The treatment of abscesses, respiratory tract infections, dacryocystitis and vestibular disease is covered in other chapters.

A logical approach to treatment should include:

- Obtaining a specific diagnosis: culture
- Basing treatment on specificity results
- Reduce stressors such as overcrowding
- Improve environmental factors such as poor ventilation and hygiene.

Key Points 14.4 Pasteurellosis

- Pasteurellosis can be spread by direct contact, aerosol and fomites. It is endemic in many rabbit colonies.
- Clinical disease occurs when there is disruption of the balance between mucociliary clearance and bacterial proliferation.
- Pasteurellosis can cause a variety of clinical signs, but these are not pathognomonic, so culture is recommended.
- Treatment is best planned using sensitivity results on appropriate samples. PCR in combination with serology is the most specific diagnostic test for pasteurellosis.
- Contributory factors such as stress and overcrowding must be addressed.

14.5.2 *Staphylococcus aureus*

Staphylococcus aureus causes suppurative inflammation. The organism is frequently isolated from infected sites in rabbits. It can also cause a fatal septicaemia. Like *P. multocida*, healthy rabbits can carry *S. aureus* in the nasal cavity. It can also be isolated from the conjunctiva and skin of healthy rabbits. *Staphylococcus aureus* may be isolated from cases of mastitis, ulcerative pododermatitis, rhinitis, conjunctivitis, dacryocystitis, abscesses and skin infections. It is often a secondary invader in tissues damaged by trauma or some other predisposing cause. The severity of disease is governed by host resistance and bacterial virulence (Delong and Manning, 1994). In rabbit colonies, staphylococcosis can cause serious losses.

14.5.3 *Bordetella bronchiseptica*

Bordetella bronchiseptica has been isolated from a variety of animal species, including pigs, rats, dogs, cats, guinea pigs and rabbits. In rabbits, *B. bronchiseptica* appears to be relatively non-pathogenic although it has caused localized suppurative bronchopneumonia in laboratory rabbits treated with cortisone prior to nasal inoculation of the organism. *Bordetella bronchiseptica* can cause serious upper respiratory tract infection in guinea pigs. Isolates of *B. bronchiseptica* from different species have been typed according to their bacterial sensitivity and investigations suggest that infected rabbits and guinea pigs can infect each other (Boot *et al.*, 1995). Many texts recommend that the two species should not be housed together because of the risk of cross-infection, although actual reports of this are rare.

14.5.4 Tyzzer's disease

Tyzzer's disease is caused by a large pleomorphic, Gram-negative, spore-forming, obligate intracellular bacterium that is flagellate and therefore motile (Delong and Manning, 1994). The bacterium cannot be grown *in vitro* but can be grown in tissue culture. The bacterial genome is closely related to *Clostridium*

species and, in recent years, the organism has been reclassified as *Clostridium piliforme* rather than *Bacillus piliformis* (Besch-Williford, 1997). Tyzzer's disease can affect a wide range of animals, including rodents, cats and monkeys (Delong and Manning, 1994). The disease affects the caecum, intestine and liver, causing acute diarrhoea and sudden death in the acute stage and intestinal fibrosis, stenosis and liver necrosis in chronic cases. The myocardium can also be affected. The disease usually occurs in weanling rabbits 6–12 weeks old but can occur at any age and is often predisposed by stress. It is a major differential in outbreaks of diarrhoea in rabbit colonies. Recent advances in tissue culture have led to development of diagnostic tests and serological testing is now possible in some countries. A PCR for detecting ribosomal DNA sequences has also been developed; however, the agreement between serology and PCR is not close. The presence of antibody in apparently healthy animals suggests latent infection of the intestinal tract; however, false-positive results can occur due to cross-reaction with non-pathogenic bacteria (Pritt *et al.*, 2010). Stress or immunosuppression can precipitate overt disease (Delong and Manning, 1994). Transmission occurs by ingestion of spores that can survive in the environment for some time after an infected animal has been removed. Overcrowding, stress, low dietary fibre and transport predispose to clinical disease. Supportive treatment and antibiotic therapy are generally unrewarding.

14.5.5 Salmonellosis

Salmonella organisms can be carried by wild rodents that contaminate food and water. The clinical signs can range from asymptomatic carriers to diarrhoea, emaciation and death. No successful treatment has been described.

14.5.6 *Escherichia coli*

Escherichia coli is generally absent from the gut flora in rabbits. However, *E. coli* can cause enteritis, especially in suckling rabbits, and is an important cause of enteritis and death in rabbit colonies. An association has been made between colibacillosis and intestinal coccidiosis, which enhances *E. coli* proliferation. There is variation in pathogenicity between strains of *E. coli* and a large number of strains have been isolated from outbreaks of enteritis. An 'attaching and effacing' strain has been identified in the UK with reported mortality rates of 25–75% (Dannatt *et al.*, 2000). This organism attaches closely to caecal epithelial cells.

14.5.7 Clostridial enterotoxaemia

Clostridia are anaerobic Gram-positive bacilli capable of producing powerful enterotoxins which can produce severe enteric disease. Clostridial enterotoxaemia is usually fatal. Small numbers of *Clostridium* spp. are normal inhabitants of the gut flora of rabbits. *Clostridium spiriforme*, *Clostridium difficile* and *Clostridium perfringens* can cause enterotoxaemia in rabbits (see Section 8.10.2). Weanling rabbits are most commonly affected.

Clostridium spiriforme produces an iota toxin. Glucose is required as a substrate for iota toxin formation. High dietary starch levels are believed to predispose to enterotoxaemia by causing 'carbohydrate overload' of the caecum. Residual starch that reaches the caecum can be broken down to release glucose as a substrate for iota toxin formation. This situation is more likely to occur in juvenile rabbits rather than adults. Immature rabbits do not digest starch efficiently in the small intestine, but in adult animals starch is broken down and absorbed before it reaches the caecum. In adults, enterotoxaemia is usually related to other factors such as stress or antibiotic therapy, which disrupt the caecal microflora and allow *Clostridium* spp. to proliferate.

14.5.8 Other causes of bacterial enteritis

Vibrio and *Campylobacter* have been reported as causes of enteric disease in rabbits. A syndrome known as 'histiocytic enteritis' has been reported in Japan. Adenoviruses, parvoviruses, rotaviruses, coronaviruses and herpes-like viruses have been isolated from outbreaks of enteric diseases in rabbit colonies.

These infections are unlikely to be encountered in the adult pet rabbit. Percy and Barthold (1993) and DiGiacomo and Mare (1994) give detailed accounts of these infections.

14.5.9 Treponematosis

Treponema paraluiscuniculi is a specific pathogen of rabbits. It is a spirochaete that causes crusty, inflammatory lesions on the genitalia and face (see Figure 7.16). It is sexually transmitted (see Section 7.13). Young rabbits can be infected during their passage through the birth canal. The disease is also known as venereal spirochaetosis or 'rabbit syphilis'. Treponematosis is endemic in some breeding colonies and is occasionally encountered in the pet rabbit.

14.5.10 Listeriosis

Listeria monocytogenes infection is uncommon in rabbits. It is characterized by abortion and sudden death. Contaminated feed can cause outbreaks in breeding colonies. *Listeria monocytogenes* has a predilection for the gravid uterus in advanced pregnancy. Infection can cause abortion, stillbirths and death of the doe. Post-mortem signs include straw-coloured fluid in the peritoneal cavity, disseminated pale miliary foci on the liver and visceral congestion. Fibrinous exudate and ecchymosis can be seen on the serosal surface of the uterus.

14.5.11 Paratuberculosis (Johne's disease)

Paratuberculosis, caused by *Mycobacterium avium* subspecies *paratuberculosis* (*M. paratuberculosis*), affects many species, especially ruminants. It is characterized by diarrhoea, emaciation and loss of bodily condition and most animals become infected as neonates through the ingestion of contaminated milk or water. Clinical infection becomes apparent after a prolonged subclinical phase that can last for several years. Although the disease is most often reported in ruminants, monogastric animals have been infected experimentally without evidence of clinical disease. Oral infection of newborn rabbits can produce intermittent diarrhoea and granulomatous enteritis similar to that observed in cattle.

In Scotland, the high incidence of paratuberculosis in wild rabbits has been linked with a high prevalence of infection in cattle. A survey of wild rabbits revealed that 67% were infected with *M. paratuberculosis* (Greig *et al.*, 1997). Epidemiological studies found an association between the infection in wild rabbits and a history of Johne's disease on the farms where the rabbits were caught (Greig *et al.*, 1999). *M. paratuberculosis* was also isolated from foxes and stoats collected from affected farms (Beard *et al.*, 1999). In the wild rabbits affected with paratuberculosis, general body condition was good, although a proportion of them had thickened areas of intestinal mucosa with occasional granuloma. Large numbers of intracellular acid-fast bacilli were present in the lesions.

14.5.12 Pseudotuberculosis

Pseudotuberculosis, caused by *Yersinia pseudotuberculosis*, is a common infection in rodents, especially guinea pigs. In rabbits, the disease is usually encountered in wild animals, although it has been described in captive ones. Affected rabbits suffer from a wasting disease, a dull coat and occasional diarrhoea. Nodular swelling of the liver may be detected on abdominal palpation (Wood, 1978). *Yersinia pseudotuberculosis* can be isolated from faeces or caecal contents. Lesions of pseudotuberculosis include large areas of caseous necrosis in the mesenteric lymph nodes, liver and spleen. Necrosis of Peyer's patches in the small intestine and caecum may be found. The disease may also involve other organs such as the liver and spleen (Delong and Manning, 1994). Yersiniosis is associated with vermin and control of mice and rats is required (Okerman, 1988).

14.5.13 Tularaemia

Tularaemia is an acute septicaemic disease caused by *Francisella tularensis*. It is common in cottontails and hares but is seldom encountered in domestic rabbits. The organism can affect many vertebrate

species and has zoonotic potential. Most human cases that have been linked to rabbits have followed exposure to the cottontail (*S. floridanus*). According to Delong and Manning (1994), there have been no reported human cases of tularaemia acquired from *O. cuniculus*. There are two biovars of *F. tularensis*: type A is generally found in North America, while type B is found in Europe and Asia. Type A is more virulent for both rabbits and humans; it causes an acute febrile disease that is worse in younger individuals. Ticks and possibly other biting insects can spread tularaemia. Treatment includes antibiosis (fluoroquinolones, tetracyclines) and supportive care. A vaccination is available for humans and this has been shown to be effective experimentally in rabbits (Pasetti *et al.*, 2008).

14.5.14 Lyme disease

Lyme disease is an acute, often recurrent polyarthritis of dogs and humans caused by a spirochaete *Borrelia burgdorferi*. It is a tick-borne disease. Cottontail rabbits have been shown to have antibodies to *B. burgdorferi* in areas where rabbit-feeding *Ixodes* are abundant (Telford and Speilman, 1989).

There are many other bacterial infections of rabbits. They are associated with stress, overcowding, injuries, reproduction, poor husbandry and intercurrent disease. Examples include *Pseudomonas*, *Fusiformis* and *Corynebacterium*.

14.6 Viral diseases

14.6.1 Myxomatosis

Myxomatosis is a fatal disease of the European rabbit. It is characterized by subcutaneous swellings that exude a mucoid secretion when sectioned. Lesions occur around body orifices and on the face, especially on the eyelids. Pet rabbits can contract the disease by direct contact with infected wild rabbits or via insect vectors. The disease is mainly spread by arthropods, especially the European rabbit flea, *Spilopsyllus cuniculi*. In wild rabbits, outbreaks of myxomatosis wax and wane according to the virulence of the strain and the immune status of the native rabbit population. Outbreaks also increase when the numbers of rabbit fleas are at their peak (in general when there are pregnant does or young in the nest).

14.6.1.1 History of myxomatosis

Myxoma virus was one of the first viruses to be discovered. It affected a group of laboratory rabbits in Uruguay in 1896 (Fenner and Fantani, 1999). In 1927, Aragao recognized virus particles in stained smears and called attention to its close resemblance with smallpox and fowlpox. Myxoma virus was later classified as a pox virus (Fenner and Ross, 1994). Brazilian workers found that the virus is transmitted mechanically by fleas and mosquitoes.

Myxomatosis is now an endemic disease of wild rabbits throughout Europe. It was first recognized in England in 1953 after it crossed the channel from France, where it was illegally introduced in 1952. Prior to this, in 1952, infected rabbits had been released into the Heisker Islands in the Outer Hebrides as a deliberate experiment in pest control. Two years later, in 1954, the rabbit population was as large as ever despite the considerable mortality that resulted from myxomatosis (Fenner and Fantani, 1999). Although there were efforts to eradicate myxomatosis in the UK, the disease spread rapidly through the wild rabbit population in the summer of 1953 and was endemic by the late 1950s. The attitude to myxomatosis in the UK was different from other parts of the world. Rabbits were frequently kept as pets and there was outcry at the sight of blind, sick rabbits stumbling along roads or on commons and other public places. As a result, in 1954, it became an offence knowingly to use or permit the use of an infected rabbit to spread the disease into an uninfected population. This law was difficult to enforce.

14.6.1.2 Epidemiology of myxomatosis

Myxoma virus causes a trivial infection in its natural host, either *Sylvilagus brasiliensis* (Tapeti, forest rabbit, found in Mexico or Argentina) or *Sylvilagus bachmani* (brush rabbit), which is native to California. In

the European rabbit, myxoma virus causes a serious and life-threatening disease. Myxomatosisis can occur in hares but infection is rare and usually mild.

There are different strains of myxomatosis that affect wild rabbits, e.g., the standard laboratory (Moses) strain and the Lausanne strain, which is more virulent. The standard laboratory strain produces relatively flat skin lesions in contrast to the protuberant lesions produced by the Lausanne strains (Fenner and Ross, 1994). Some variants are associated with fewer and smaller skin lesions but cause massive pulmonary oedema.

Under field conditions, myxomatosis is spread by insect vectors, especially fleas and mosquitoes, although any insect that penetrates the skin will transmit the disease. The disease can also be spread directly between rabbits by contact or inhalation. The virus persists in hutches that have been contaminated with fluid from lesions from infected rabbits and will infect unvaccinated rabbits that are put into them. *Cheyletiella parasitovorax* can act as a vector in the spread of disease (Fenner and Fantani, 1999).

The life cycle of the insect vector affects the pattern of disease outbreaks and epidemiology of myxomatosis. Mosquitoes are the main vectors in many parts of the world. In those countries where myxomatosis is transmitted by mosquitoes, the disease spreads rapidly and is frequently encountered in pet rabbits housed in hutches. There is a high seasonal incidence. In the UK, disease outbreaks tend to remain localized with isolated pockets of infection and the disease is only sporadically encountered in pet rabbits. The difference in epidemiology is attributed to the difference in the life cycle of insect vectors. In the UK, the European rabbit flea, *S. cuniculi*, is the major insect vector rather than mosquito species *Aedes* and *Anopheles* spp. Even in the absence of the host, fleas can maintain infectivity throughout the winter and act as a reservoir of infection for the following year. Fleas are an effective means of transmission due to their life cycle, which is synchronized with the reproductive status of the doe and results in heavy flea infestations of susceptible neonates.

Different strains of the myxoma virus show a variation in virulence. Rabbits infected with highly virulent strains die so quickly that the disease is not transmitted as readily as the less virulent strains. Environmental temperature also has an effect on mortality rates, with the disease being more lethal at low temperatures. There is a genetic resistance to myxomatosis in some individuals.

14.6.1.3 Clinical signs of myxomatosis

The pathogenesis of myxomatosis follows the same pattern as other pox virus infections (Fenner and Ross, 1994). Sequential replication of the virus takes place at the inoculation site and the regional lymph node. It is followed by cell-associated viraemia and generalized infection throughout the body. The disease starts with a skin lesion, which typically develops 4–5 days after inoculation of the virus and enlarges to become about 3 cm in diameter 9–10 days after infection. The rabbit is viraemic, with virus replication taking place throughout the lymphoid system. The eyelids become thickened and eventually the eyes are completely closed by the ninth day with a semipurulent ocular discharge. Secondary lesions develop throughout the body, typically on the nares, lips, eyelids and base of the ears and on the external genitalia and anus. Aerosol infection can result in pneumonic signs, which is a feature of outbreaks in intensive farmed rabbits. This syndrome is characterized by a longer incubation period (1–3 weeks) and accompanied by lacrimation and mucopurulent nasal discharge (Fenner and Fantani, 1999). Myxomatosis is accompanied by sterility and abandonment of litters.

Myxomatosis is usually fatal due to inanition, secondary bacterial infection or, in wild rabbits, predation. In rabbits that recover, inflammation of the testicles renders a buck infertile for up to 12 months (Fenner and Fantani, 1999). Very young rabbits are particularly susceptible to infection and die more rapidly than adult animals unless they have some passive immunity.

Several factors determine whether rabbits survive from myxomatosis and how long they live after infection. Infected rabbits mount an immune response that can be detected by *in vitro* tests about 7 days after infection and reach peak levels by about 28 days

(Fenner and Ross, 1994). Antibodies persist for prolonged periods and give absolute immunity for many months. Maternal transfer of antibodies takes place and immunity lasts for 4–5 weeks in baby rabbits. Some rabbits have a genetic resistance to infection, which has limited mortality rates in outbreaks in wild rabbits. Genetic resistance to infection varies between rabbit populations and countries. British rabbits were slow to develop resistance in comparison with Australian rabbits (Fenner and Ross, 1994). A phenomenon known as 'paternal resistance' is also described. It has been discovered that bucks mating within 7 months of infection sometimes confer partial resistance to progeny born to the mated doe within the following 7 months. Speculation about some immunogenic factor in semen has been made (Fenner and Ross, 1994).

14.6.1.4 Relationship of myxomatosis with Shope fibroma virus

The viruses that cause myxomatosis are members of the *Leporipoxvirus* genus that cause fibromas in their natural hosts. The natural host of myxoma virus is not the European rabbit, but the forest rabbit or brush rabbit that is native to North and South America. Another important member of the *Leporipoxvirus* genus is the rabbit fibroma virus (Shope fibroma virus), which naturally affects the cottontail. In the European rabbit, Shope fibroma virus causes a benign fibroma.

Shope fibroma virus is endemic in cottontails in the eastern USA. It causes fibromas that remain localized but can persist for months. In newborn or immunocompromised individuals, generalized fibromatosis can occur (Fenner and Fantani, 1999). Like myxomatosis, Shope fibroma virus is spread by insect vectors. Transmission by mosquitoes occurs more readily than in the European rabbit. In situations where cottontails and mosquitoes are common, generalized fibromatosis can occur in adults because multiple mosquito bites produce a fibroma at each site (Fenner and Fantani, 1999).

In the European rabbit, fibromas caused by Shope fibroma virus regress within 3 weeks of inoculation. Abundant virus can be found in the superficial layers of fibromas caused by Shope fibroma virus in the natural host, *S. floridanus*, in comparison with fibromas in the European rabbit. Shope fibroma cannot be established as an enzootic disease in European rabbits, but cross-immunity between Shope fibroma virus and myxomatosis occurs and European rabbits that have recovered from infection with Shope fibroma virus are immune to myxomatosis.

14.6.1.5 Immunization

In common with other pox viruses, dead vaccines are unlikely to be effective and so a live vaccine is required to confer resistance to myxomatosis. Live attenuated strains of myxoma virus have been used for vaccination, but problems have occurred with virulence and possible immunosuppression (Fenner and Fantani, 1999). The discovery of Shope fibroma virus and its cross-immunity with myxomatosis led to the development of a live vaccine containing Shope fibroma virus. Until recently the only vaccine available in the UK (Nobivac Myxo, Intervet) was a live, attenuated freeze-dried virus vaccine containing Shope fibroma virus grown in cell-line tissue culture. In 2012 a new vaccine (Nobivac Myxo-RHD) based on an attenuated myxomatosis strain with a rabbit haemorrhagic disease (RHD) capsid protein added was introduced (Spibey *et al.*, 2012). This new vaccine gives one year's duration of immunity.

Key points 14.5 Myxomatosis

- Myxomatosis is characterized by subcutaneous swellings that exude a mucoid secretion when sectioned. Lesions occur around body orifices and on the face, especially the eyelids.
- The disease is mainly spread by arthropods, especially the European rabbit flea, *Spilopsyllus cuniculi.* Mosquitoes are vectors in many parts of the world.
- In wild rabbits, outbreaks of myxomatosis wax and wane according to the virulence of the strain and the immune status of the native rabbit population.

Continued

Key points 14.5 Myxomatosis—cont'd

- Myxomatosisis can occur in hares but is rare and usually mild.
- Environmental temperature has an effect on mortality rates, with the disease being more lethal at low temperatures.
- Myxomatosis starts with a skin lesion at the site of inoculation. The rabbit becomes viraemic, with virus replication taking place throughout the lymphoid system. Secondary lesions develop throughout the body, typically on the nares, lips, eyelids and base of the ears and on the external genitalia and anus.
- Aerosol infection can result in pneumonic signs, which may be a feature of outbreaks in intensive farmed rabbits.
- Myxomatosis is accompanied by sterility and abandonment of litters.
- It is possible, on rare occasions, for rabbits to recover from myxomatosis. Ambient temperature affects the course of the disease, with high environmental temperature increasing recovery rate (85°F).
- Antibiotics, a warm environment, good nursing and non-steroidal analgesics can be used to treat myxomatosis. Corticosteroids are contraindicated due to their immunosuppressive effects. Opioid analgesics are ineffective in ameliorating signs of pain.

14.6.1.6 Recovery from myxomatosis

It is possible for rabbits to recover from myxomatosis. Apart from the virulence of the virus strain, certain environmental factors affect the resistance of the rabbit to myxomatosis, i.e. intercurrent infection and environmental temperature. Ambient temperature affects the course of the disease, with high environmental temperature increasing recovery rate (85°F). Antibiotics, a warm environment and good nursing can be successful and some pet rabbits have survived myxomatosis although their chances are not good. The risk of secondary problems such as gastrointestinal stasis or pasteurellosis is ever-present. Non-steroidal analgesics are useful but the use of corticosteroids is contraindicated due to their immunosuppressive effects. Opioid analgesics do not appear to be effective in ameliorating signs of pain. In a study of the effect of buprenorphine on the course of myxomatosis in laboratory rabbits, there was no difference in survival time. Treated rabbits refused food and water a day earlier than untreated rabbits and had lower rectal temperatures immediately prior to death (Robinson *et al.*, 1999). Rabbits vaccinated against myxomatosis can also be clinically affected, and develop an atypical form of myxomatosis (lumpy bunny syndrome). The severity of the disease is variable and can range from a well rabbit with a single lump to one that is very poorly with multiple skins lesions. The prognosis is less bleak for these individuals, as many of them can recover with appropriate supportive care.

14.6.2 Viral haemorrhagic disease (VHD)

Viral haemorrhagic disease (VHD) is a highly infectious lethal disease of rabbits with a high mortality rate. It is caused by a host-specific calicivirus. VHD only affects the European rabbit.

The disease may be called 'rabbit haemorrhagic disease' (RHD) and the virus known as 'rabbit haemorrhagic disease virus' (RHDV). Sometimes the term 'rabbit calicivirus disease' (RCD) is used. VHD originated in 1984 in the People's Republic of China, which, at that time, was the world's largest exporter of rabbit meat. A disease broke out in a colony of angora rabbits that had recently been imported into Germany (Fenner and Fantani, 1999). Except for the suckling rabbits, all the rabbits died within a week and in less than 9 months the disease had spread over 50,000 km^2 and reached Italy and Europe. By 1988, VHD had been reported in commercial rabbits in many countries worldwide, probably introduced through rabbit meat. In Europe, the disease spread into the wild rabbit population. In 1990, VHD reached Scandinavia. Wild rabbits in the densely populated island of Gotland became nearly extinct within 1 week (Gavier-Widén, 1996). Hundreds of rabbits were seen dead in the fields and many more died in their burrows. Pet rabbits that had been kept indoors and fed on commercial food started dying, indicating that humans can act as vectors for VHD.

Coincidentally, another disease, European brown hare syndrome (EBHS), was sweeping through Europe. EBHS is caused by a distinctly different calicivirus.

In 1996, a non-pathogenic virus was recovered from breeding rabbits in Italy that produced seroconversion and was found to protect rabbits against VHD. The virus has been isolated and identified as a calicivirus. There is evidence that this virus existed before the onset of VHD (Capucci *et al.*, 1997).

14.6.2.1 Pathogenesis of VHD

VHD is caused by a calicivirus that has a predilection for hepatocytes and replicates within the cytoplasm of these cells. Experimentally infected rabbits die 3–4 days after infection.

VHD is essentially a necrotizing hepatitis, often associated with necrosis of the spleen (see Figure 14.6). Disseminated intravascular coagulation produces fibrinous thrombi within small blood vessels in most organs, notably the lungs, heart and kidneys, resulting in haemorrhages. Death is due to disseminated intravascular coagulopathy or to liver failure.

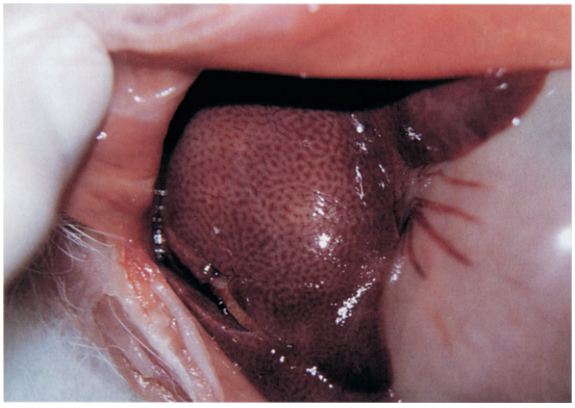

Figure 14.6 The liver of a rabbit that had died from viral haemorrhagic disease (VHD). The typical appearance of the liver of a rabbit that has died from VHD is shown. The liver is enlarged, although not strikingly so, and friable and pale, with a distinct lobular pattern. The liver is always affected in cases of VHD, although the gross appearance may not reflect the severe histopathological changes. The histological appearance of the liver is often diagnostic. It is severely congested, with marked hepatocyte necrosis involving extensive areas of most lobules.

14.6.2.2 Epidemiology of VHD

The calicivirus that causes VHD is antigenically similar to the virus that causes EBHS. Attempts to cross-infect rabbits and hares with heterologous virus have failed to induce disease. VHD only affects the European rabbits, not cottontails or other small mammals such as chinchillas, guinea pigs, rats and mice.

VHD calicivirus can survive for long periods outside the host. Viable virus has been detected for as long as 105 days on a cloth (Fenner and Fantani, 1999). Environmental temperature is an important factor in the survival of the virus, which can remain viable for 22–35 days at 22°C but only for 3–7 days at 37°C. VHD virus is spread by oral, nasal and parenteral transmission and is present in urine and faeces from infected rabbits. Contaminated foods can be a source of infection.

When VHD is introduced into a susceptible population, the mortality rate is high and can be 90–100% in rabbits over 2 months of age. Infected young rabbits survive and become immune, so when the disease becomes endemic the morbidity and mortality rate falls. In wild rabbits, the disease appears to break out every second year. Insects mechanically transmit the virus in viraemic blood from one animal to another. VHD virus can survive for several weeks in carcasses and skin. Fleas, blowflies and mosquitoes are known to spread the disease (Fenner and Fantani, 1999). PCR techniques have shown that virus can be retained in the body of blowflies for up to 9 days and bushflies for 7 days. Fly 'spots' (faeces) are also infective and can contaminate pasture. Flies can travel long distances and be carried along by the wind and spread the disease far and wide. It has also been demonstrated that domestic and wild carnivores can play an important role in the epidemiology of VHD since virulent material can be collected from faecal material after experimental oral inoculation. The virus is very stable in carcasses even after freezing and thawing (Lumeij, 1997). Up until October 1996, VHD was a notifiable disease in Great Britain. It is now endemic and poses a real threat to the pet rabbit due to its resistance and ease of transmission. Deaths have been reported nationwide that have been confirmed at post-mortem to be due to VHD.

14.6.2.3 Clinical signs of viral haemorrhagic disease

VHD has a short incubation period of 3–4 days. The disease can be peracute, with animals being found dead within a few hours of eating and behaving normally. Acute cases are quiet and pyrexic with an increased respiratory rate and usually die within 12 h. A feature of the disease is a dramatic drop in blood pressure that makes it difficult to find a vein to take blood samples or set up intravenous fluids. Dying rabbits are pallid, shocked and collapsed. Haematuria, haemorrhagic vaginal discharges or foamy/bloody exudate from the nostrils may be seen. Vascular infarcts can occur within the brain and occasionally convulsions or other neurological signs are seen just before death. Agonal vocalizing and cyanosis have been described (Donnelly, 1995). The 'classic' picture is a dead rabbit in opisthotonus with a haemorrhagic nasal discharge. The occasional rabbit can recover from the acute phase, only to develop jaundice and die a few days later. Young rabbits less than 4 weeks of age remain unaffected and develop a lifelong immunity if they are exposed to the disease. Unexposed rabbits become increasingly susceptible until 6–10 weeks of age when physiological resistance to the virus disappears. The physiological age immunity of young rabbits has been ascribed to the increase in hepatic transaminase production that occurs after 5 weeks of age (Donnelly, 1995). In adult rabbits, the mortality rate is high. There is no treatment for affected rabbits.

14.6.2.4 Diagnosis of VHD

VHD is suspected in any sudden death, especially if more than one rabbit in the household has died. The post-mortem picture may be of a healthy rabbit with non-impacted food in the stomach and hard faecal pellets in the distal colon, suggesting that death was sudden. The liver is always affected, although the gross appearance may not reflect the severe histopathological changes. The liver is enlarged, friable and pale with a distinct lobular pattern (see Figure 14.6). The spleen is also enlarged. Haemorrhages can be found in any organ but are usually present in the lung. The trachea is often full of a foamy exudate. Haematologically, there are fibrin thrombi, lymphopenia, a reduction in platelets and a failure of other blood-clotting factors that result in multiple-organ failure due to general circulatory dysfunction. Disseminated intravascular coagulation is a characteristic feature of the pathogenesis of VHD (Chasey, 1997). Histopathology confirms acute hepatic necrosis. There may be many other changes such as acute nephropathy or alveolar haemorrhage. Congestion and haemorrhages can occur in any organ due to terminal intravascular coagulation. The typical histopathological changes in the liver are usually diagnostic but there are a number of other tests that confirm the diagnosis, including hamagglutination tests and electron microscopy. Large numbers of characteristic calicivirus can be detected by electron microscopic examination of liver (Chasey *et al.*, 1995). Fresh liver is required by the laboratory. ELISA tests are also available.

14.6.2.5 Vaccination

Due to the devastating effects of VHD in China, a vaccine was quickly developed from inactivated virus obtained from the liver and spleens of infected rabbits. The immunological response to inactivated vaccines is good. VHD virus is difficult to grow in tissue culture, so attenuated strains have not been produced. Virus antigen harvested from experimentally infected rabbits is inactivated with formalin or β-propiolactone to produce effective killed vaccines that are commercially available. Vaccination is advisable for all pet rabbits (see Section 1.8.1). Genetically engineered vaccines that insert the gene for the coat protein of the VHD virus into the attenuated myxoma virus for simultaneous immunization of VHD and myxomatosis are being produced (Barcena *et al.*, 2000; Spibey *et al.*, 2012). This vaccine is now available in the UK and Europe (Nobivac Myxo-RHD, MSD Animal Health). See also Section 1.8.1.

Key points 14.6 Viral haemorrhagic disease

- Viral haemorrhagic disease (VHD) is a highly infectious lethal disease of rabbits with a high mortality rate. It is caused by a host-specific calicivirus. VHD only affects the European rabbit (*Oryctolagus cuniculi*).

Key points 14.6 Viral haemorrhagic disease—cont'd

- The disease may be called 'rabbit haemorrhagic disease' (RHD) and the virus known as 'rabbit haemorrhagic disease virus' (RHDV). Sometimes the term 'rabbit calicivirus disease' (RCD) is used.
- The causative calicivirus of VHD has a predilection for hepatocytes. VHD is essentially a necrotizing hepatitis. Death is usually due to disseminated intravascular coagulopathy.
- VHD calicivirus can survive for long periods outside the host. Viable virus has been detected for as long as 105 days on cloth. Infection does not require direct contact.
- VHD virus is spread by oral, nasal and parenteral transmission and is present in urine and faeces from infected rabbits. Contaminated foods can be a source of infection.
- When VHD is introduced into a susceptible population, the mortality rate is high and can be 90–100% in rabbits over 2 months of age.
- VHD has a short incubation period of 3–4 days. The disease can be peracute, with animals being found dead within a few hours of eating and behaving normally.
- The 'classic' picture is a dead rabbit in opisthotonus with a haemorrhagic nasal discharge.
- Haematuria, haemorrhagic vaginal discharges or foamy exudate from the nostrils may be seen.
- Vascular infarcts can occur within the brain and occasionally convulsions or other neurological signs are seen just before death.
- There is no specific treatment for affected rabbits.
- Young rabbits, less than 4 weeks of age, remain unaffected and develop a lifelong immunity if they are exposed to the disease. Unexposed rabbits become increasingly susceptible until 6–10 weeks of age when physiological resistance to the virus disappears.
- The typical histopathological changes in the liver are usually diagnostic.
- An effective vaccine against VHD is available in the UK.

14.6.3 Papillomatosis

There are descriptions of two papillomaviruses that can affect rabbits. Shope papillomavirus causes a benign disease in cottontails but may cause malignant neoplasms resembling squamous cell carcinomas in the European rabbit. The disease occurs in the wild population of cottontails in the eastern USA and in domestic rabbits in some American commercial units.

Shope papillomavirus is immunologically distinct from the other papillomaviruses, and causes oral papillomatosis. Oral papillomatosis is manifested by wart-like growths on the ventral aspect of the tongue and on other parts of the oral mucosa. The virus is transmitted in oral secretions containing sloughed cells from the warts. Young rabbits are most susceptible and the papillomas grow slowly over a period of 6–9 months. The animals become immune, at which point the base of the papilloma becomes inflamed, causing sloughing of the tumour, ulcer formation and finally re-epithelialization. Oral papillomas of rabbits are not known to undergo carcinomatous transformation (Kraus *et al.*, 1984).

14.6.4 Coronavirus

Coronavirus infection in rabbits was initially described in 1968. Affected rabbits were pyrexic and developed pulmonary oedema and pleural effusion and mortality rates were high. Iridocyclitis has been associated with the disease. An analogy with feline infectious peritonitis has been made. Coronavirus has also been implicated in outbreaks of enteric disease in weanling rabbits.

The virus has not been propagated *in vitro* and it is unclear whether it is a naturally occurring pathogen of rabbits or a virus from another species adapted to rabbits in contaminated treponemal stocks (DiGiacomo and Mare, 1994). The disease was first recognized in the 1960s in rabbits inoculated with suspensions of rabbit testes containing *Treponema pallidum* (human syphilis). Subsequently, the agent has been detected in *T. pallidum*-infected rabbit tissue throughout the world. Coronavirus infection is used experimentally to produce a rabbit model of

cardiomyopathy and has only been described in laboratory rabbits. Antibodies to the virus cross-react with human and other mammalian coronaviruses (DiGiacomo and Mare, 1994).

14.7 Mycotic infections

14.7.1 Dermatophytosis

Dermatophytosis (ringworm) is occasionally encountered in rabbits. *Trichophyton mentagrophytes* and *Microsporum canis* are the species most commonly described (Percy and Barthold, 1993). Lesions are usually found on the base of the ears and muzzle, but can involve other areas of the body such as the paws (see Section 7.15). Asymptomatic carriers can occur. Young rabbits are most likely to be affected (Vangeel *et al.*, 2000). *Dermatophilus congolensis* has been isolated from rabbits.

14.7.2 Aspergillosis

Pulmonary aspergillotic granulomas have been described in laboratory rabbits (Percy and Barthold, 1993). Nasal aspergillosis is an occasional finding in rabbits with chronic rhinitis.

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