Treatment of *Encephalitozoon cuniculi* infection in rabbits

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In the first of this two-part article (VT45.31), the life cycle of encephalitozoonosis was discussed, as well as diagnostic tools to help detect its presence. This article will look at treatment in domestic rabbits.

*Encephalitozoon cuniculi* is a protozoan parasite belonging to the phylum Microsporidia, which comprises more than 1,200 species of ubiquitous, spore forming, obligate intracellular parasites that infect almost all animal phyla (Didier and Weiss, 2006; Keeling and Fast, 2002).

Three different *E cuniculi* strains have been identified (Didier et al, 1995). This parasite is widely distributed among different mammalian species (Canning et al, 1986) and the infection has also been reported in birds (Poonacha et al, 1985).

Encephalitozoonosis is primarily seen and considered a significant disease of captive rabbits and its seroprevalence is internationally recognised (Latney et al, 2014). Farm and laboratory rabbits have been known for a long time as target species, but according to a UK survey (Keeble and Shaw, 2006) healthy domestic rabbits also show specific antibodies against this parasite in their blood, with a prevalence of 52%.

Transmission and pathogenesis
Figure 1. Neurological signs are considered the most common clinical presentation of encephalitozoonosis in pet rabbits. The most frequent neurological signs are often associated with vestibular disease and can include head tilt, ataxia, circling and rolling, nodding or swaying at rest, and nystagmus.

Figure 2. Other neurological signs such as paresis or paralysis of one or both hindlegs, seizures and behavioural changes are also frequently seen.
*E cuniculi* has a direct life cycle, with both horizontal and vertical (transplacental) transmission. In rabbits, the common routes of natural horizontal infection are the small intestine (the spores are shed into the urine of infected rabbits and infection usually occurs via ingestion of urine contaminated food and water) and, less commonly, the respiratory tract (inhalation of spores).

Experimental routes of transmission also include traumatic transmucosal, intravenous, intrathecal and rectal infection (Latney et al, 2014). Tracheal and transplacental routes of infection have also been reported, but appear much less frequent (Harcourt-Brown, 2002). The spore is the infective form of this parasite, resistant to environmental changes and able to survive up to four weeks at 22°C in dry conditions (Keeble, 2014).

Spores have a particular organelle called polar tubule, which is extruded during the infection phase to transfer the infectious sporoplasm into the host cell. Inside the host cells, spores multiply and mature (sporoplasm, meront, sporont, sporoblast), eventually causing rupture of the cell and release of the spores, which can then infect other cells. Rupture of the cells is associated with an inflammatory response.

The cells of the reticuloendothelial system are frequently infected and responsible for the distribution of the parasite throughout the body (Harcourt-Brown and Holloway, 2003).

Target organs are primarily the CNS, kidneys and eyes, but the liver, lung and myocardium may also be involved. In these organs the parasite’s damage can cause chronic inflammation and granulomas (Harcourt-Brown, 2002). When the infection overwhelms the rabbit’s immune system, clinical signs eventually manifest (Figures 1-3).

**Therapy**

Therapy should be aimed at reducing inflammation and blocking spore formation and proliferation, as well as managing associated disease and severe neurological signs. To date, a handful of controlled studies have evaluated the efficacy of treatment in *E cuniculi*-infected rabbits (Ewringmann and Göbel, 1999; Suter et al, 2001; Kunzel et al, 2008; Sieg et al, 2012).

Previous literature suggested the use of anti-inflammatory drugs such as steroids (for example, dexamethasone) in the acute phase of disease to suppress the CNS granulomatous inflammation (Keeble, 2006 and 2014), with careful consideration of the rabbit’s extreme sensibility to their side effects (Rosenthal, 2004).

However, a more recent study provided evidence dexamethasone is not an effective component of the treatment scheme as it showed no effect on neurological scores, on short or long-term survival (Sieg et al, 2012).

Latney et al (2014) discourage the use of dexamethasone to treat *E cuniculi*-mediated inflammation
and in the treatment of head trauma secondary to axial or longitudinal rolling for three major reasons. Firstly, its use in the management of cerebral trauma is no longer recommended for use in humans.

Secondly, dexamethasone has been shown to reduce the efficacy of albendazole in reducing spore migration and host cell rupture (it may therefore also reduce the serum concentration of fenbendazole and its efficacy), and to potentiate disease severity in experimental rodent models of \textit{E cuniculi} infection. It is, in fact, a concern that the immunosuppression induced by dexamethasone may promote persistence and shedding of \textit{E cuniculi}.

Thirdly, it has not been shown to have any therapeutic effect in chronically infected companion rabbits (Sieg et al, 2012). Rabbits are notoriously a corticosteroid-sensitive species and toxic changes have been reported in lymphoid organs, liver and adrenal glands (Borgmann et al, 1976).

Furthermore, immunosuppressive doses of corticosteroids could affect the function of T lymphocytes and the production of T-cell derived cytokines, which is considered the main defence mechanism against \textit{E cuniculi} (Künzel and Joachim, 2010).

\textbf{Figure 3}. A high percentage of cases also show ocular lesions such as cataracts, hypopyon, phacoclastic uveitis or even blindness.

Because even ocular administration of dexamethasone phosphate disodium has been shown to result in systemic absorption in rabbits, extreme caution should be taken before ocular administration of corticosteroids as well (Rosenblum et al, 1967). In case of ocular disease, a topical NSAID may be a safer choice, if renal values are within normal limits (Sieg et al, 2012). Systemic NSAIDs, such as meloxicam, may be safely used as an alternative to treat inflammation.

NSAID therapy should be used cautiously in animals that have concurrent renal disease because the kidney is a target organ for \textit{E cuniculi}-associated inflammation.
In-vitro studies have been carried out on the use of benzimidazole drugs in rabbits (Franssen et al, 1995). These drugs are microtubule inhibitors capable of blocking the extrusion of the polar filament preventing cell infection.

Albendazole, used to treat infections in humans, has been reported to be embriotoxic and teratogenic (Kotler and Orenstein, 1998), and to cause bone marrow suppression and liver failure in rabbits (Mortiz, 2004).

Fenbendazole is, at present, the drug of choice as it has been shown to be effective in reducing clinical signs in an already established infection and to prevent it in exposed animals, when administered at 20mg/kg once daily for 28 days (Suter et al, 2001), coupled with frequent environmental disinfection. In this study, prophylactic administration of fenbendazole prior to experimental infection achieved prevention of *E cuniculi* infection.

Rabbits remained seronegative after 21 days and spores were not recovered in brain tissue on postmortem tissue analysis. Information regarding spore recovery from the kidney and histological analysis for any tissue was not provided.

In the therapeutic trial of fenbendazole orally dosed at 20mg/kg bodyweight daily for four weeks, no spores were noted in the brain based on histological evaluation. Based on these findings, current treatment practices advocate the use of fenbendazole for *E cuniculi* prevention. Some advocate the use of fenbendazole for the treatment of chronic *E cuniculi* infections in rabbits, but no controlled study has truly confirmed the clinical efficacy of this medication in chronic cases that already have advanced CNS inflammation.

Künzel et al (2008) evaluated the therapeutic efficacy of combined treatment with fenbendazole, oxytetracycline or enrofloxacin, and dexamethasone or prednisone, and reported a 54.2% clinical recovery rate (patients with neurological symptoms as compared to 87.5% of those with kidney disease that died or were euthanised). No treatment recommendations were suggested.

More recently, Sieg et al (2012) evaluated the clinical efficacy of fenbendazole, oxytetracycline and steroid therapy. No significant difference was seen in the long-term or short-term survival, or in neurological sign reduction in rabbits receiving the following treatment combinations: oxytetracycline with or without dexamethasone; oxytetracycline and fenbendazole with or without dexamethasone.
Survival analysis performed for those rabbits that received fenbendazole demonstrated they were 1.6 times more likely to survive until day 10 compared with rabbits that did not receive fenbendazole in their treatment protocol. Fenbendazole had a significant effect on long-term survival, but after day 10 no consistency in its efficacy was noted. This demonstrates the need for more controlled studies that histologically demonstrate spore reduction based on the treatment protocol.

Broad-spectrum antibiotics can be prescribed, when necessary, to reduce the risk of secondary infections. Oxytetracycline has been included in many treatment protocols of rabbits with neurological signs from suspected *E cuniculi* infections based on a moderate effect demonstrated in one in-vitro study (Waller et al, 1979). However, controlled in-vivo studies are lacking. Sieg et al (2012) could not evaluate whether oxytetracycline was a necessary adjunct to the therapy against *E cuniculi* infection as all the rabbits were treated with oxytetracycline.

Tetracyclines are effective against rickettsiae, Gram-negative bacteria and Gram-positive bacteria, therefore they may be of use to prevent secondary bacterial co-infections. They may also be useful as an adjunct treatment for CNS inflammation because of their anti-inflammatory and anti-apoptotic properties, and because they act as scavengers of reactive oxygen species (Griffin et al, 2011). Reclassification of microsporidia as fungi rather than protozoa has also been attempted (Keeling et al, 2000).

The microsporidia spores retain fungal elements, including fungal proteins such as tubulins, trehalose, and chitin, and are ancestral relatives of zygomycetes (Bohne et al, 2011). As chitin is a basic component of the microsporidian spore, in-vitro studies have been carried out to evaluate the susceptibility of the parasite to Polyoxin D and Nikkomycin, which are chitin synthetase inhibitors (Sobottka et al, 2002). The author is not aware of any in-vivo studies carried out on rabbits at present.
When ocular disease is present, local and systemic formulations may help in the initial treatment. Phacoemulsification for lens removal (Felche and Sigler, 2002; Figure 4) might be indicated in some cases, but when the disease is advanced and prognosis is poor then enucleation might be the best treatment option.

Fluid therapy and assisted feeding are mandatory to correct dehydration and for appropriate supportive care. Response to treatment may vary depending on whether the infection is acute or chronic and the level of tissue damage sustained. Many rabbits, despite treatment, do not improve clinically because the changes and damage that have already taken place in many organs cannot be reversed.

![Figure 5](image.png)

**Figure 5.** Environmental modifications should be made to provide animals affected by severe central vestibular signs with protection. Soft padding and non-metal cage barriers should be employed to prevent accidental ocular and/or limb trauma.

Anticholinergics, antihistamines and benzodiazepines are used in humans with vestibular problems and may be helpful in the symptomatic treatment of rabbits with vestibular signs. Prochlorperazine is a phenotiazine derivative that has been used to treat vertigo and labyrinthine disorders in humans, and its use has been advocated in rabbits with torticollis (Varga, 2014).

Use of midazolam or diazepam is commonly employed to control seizure activity and act as a mild sedative in animals with severe vestibular disease that is causing falling/rolling.

Environmental modifications should be made to provide animals affected by severe central vestibular signs with protection. Soft padding and non-metal cage barriers should be employed to prevent accidental ocular and/or limb trauma (**Figure 5**). The off-label use of drugs should always be carefully considered.
Prevention

*E. cuniculi,* as with other microsporidia, is widespread among mammals and rabbits in particular. This explains how difficult it is to prevent establishment of infection. Creating *E. cuniculi*-free colonies is possible, but time consuming and expensive. Rabbits should be tested, isolated if positive and treated. Seroconversion usually occurs before renal shedding so in-contact rabbits could be tested to identify infected animals even before the parasite is excreted, in an outbreak. These animals should be isolated and treated as well. This might not be practically possible for pet rabbits, so prophylactic administration of fenbendazole to reduce the likelihood of infection, observing good hygiene practices and performing routine disinfection to reduce urinary contamination, might be of extreme importance.

- Off-label use of drugs may need to be considered where appropriate and written consent obtained from the owner.

References
