

## ***E. cuniculi* Treatment Success Stories**

When I first became involved in the rabbit world twelve years ago, a symptomatic rabbit who was diagnosed with *E. cuniculi* had a very poor prognosis. While there is still no cure, today there are several treatment options that veterinarians have used with success.

Since no single treatment has proven effective in all cases, it is important for all of us, both caretakers and veterinarians, to keep abreast of new treatment options and be open to new ideas. The treatments discussed in this article vary from “widely-used-over-almost-a-decade” to “promising-in-very-limited-testing.” If your veterinarian is open to trying one of the newer treatments, don’t be surprised if she wants to do additional research and/or consult with those veterinarians who have already used these treatments.

### **What is *E. cuniculi*?**

*E. cuniculi* is a protozoan parasite that is spread through spores that are shed in the urine of infected rabbits. A rabbit may contract it at a young age from an infected mother or from cage mates who are shedding spores, or later in life from an infected companion. The parasite attacks the nervous system and major organs, causing a variety of symptoms including head tilt, liver disease, kidney disease, cataracts, incontinence, loss of function in the legs (back, front, or both), nystagmus (eye twitching), and/or other neurological symptoms.

### **Diagnosis**

*E. cuniculi* is diagnosed by a blood test that is not part of routine blood-work. A positive result (often referred to as a positive “titer”) only means that the rabbit has been exposed to *E. cuniculi* resulting in antibody production. *E. cuniculi* is often kept in check by a rabbit’s immune system and many rabbits that test positive for *E. cuniculi* never develop symptoms. However, if the rabbit’s health (mental or physical) is compromised, he may start to develop symptoms.

Some caretakers choose to have all rabbits in their family tested. Knowing whether your rabbit has tested positive can be helpful, especially if he develops symptoms that may (or may not) be caused by *E. cuniculi*, such as head tilt or a wet bottom. However, keep in mind that in a multi-rabbit household, a rabbit that has tested negative **may** test positive at a later date. This is especially important to remember if his companion has tested positive **and** has recently developed symptoms! Spores are thought to be shed only briefly, in the early stages of an active infection.

### **Common Treatments: The -bendazoles**

The most common treatments used for symptomatic *E. cuniculi* today are benzimidazole derivatives used to treat intestinal parasites in various species. While these drugs have been used successfully on many rabbits, there have been some reports of mild to

moderate elevation of liver enzymes. Although values usually return to normal after medication is discontinued, please discuss periodic blood testing with your veterinarian.

The action of benzimidazoles is slow, and the length of a rabbit's gastrointestinal tract further delays absorption by the body. In many rabbits, symptoms return when medication is stopped. Recently, several caretakers who have been treating rabbits long-term with oxibendazole have reported that the treatment gradually seems to stop working over time, **perhaps** indicating that the parasite eventually develops a resistance to it.

### Albendazole

Albendazole, a drug used in humans to treat lesions caused by certain tapeworms, was the first of the benzimidazole derivatives to be used to treat symptomatic *E. cuniculi*. It was first used with some success in the mid-1990's by several veterinarians including Dr. Jeff Jenkins, a well-known rabbit veterinarian in the San Diego area. Albendazole is the only benzimidazole that is quickly absorbed and eliminated by the body, but also may have more side-effects than the others.

### Oxibendazole

In the late 1990's several HRS members and their veterinarians began treating a significant number of symptomatic cases of *E. cuniculi* with oxibendazole, a horse worming paste. For many rabbits, treatment led to remarkable improvement and in many others it stopped progression of the disease. Today oxibendazole is a commonly prescribed treatment for symptomatic *E. cuniculi*. It has been used by hundreds of veterinarians around the world to extend life (with quality) for thousands of rabbits.

Unfortunately, oxibendazole is **not** successful in treating **all** cases of *E. cuniculi*. Despite the large number of rabbits who have been treated with it, there is no compilation and/or analysis of data on rabbits who have been treated and whether treatment was successful (either symptoms improved or rate of progression of symptoms was reduced).

### Fenbendazole

In 2001, a study published in the Veterinary Record (April 14, 2001, pp.478-480) suggested that fenbendazole, a drug used to treat roundworms, might be effective in both preventing and curing *E. cuniculi* infections. This was a major breakthrough, both because there was scientific data to support the findings and because this was the first treatment that was believed to cure (rather than simply control) the condition. In rare cases, **long term** treatment with fenbendazole **may be** associated with the onset of bone marrow failure.

Some veterinarians who had been skeptical of albendazole and oxibendazole because of the lack of scientific data began treating symptomatic cases of *E. cuniculi* with fenbendazole and others switched to prescribing fenbendazole. I have recently heard from several individuals that their veterinarians were going **back** to oxibendazole because they

considered it to be more effective than fenbendazole once symptoms emerge. Again, however, this conclusion is based on each practitioner's individual experience rather than on a pooled scientific data.

### **Baytril**

My veterinarian, Dr. Noella Allan (Lakewood Animal Health Center, Lee's Summit, MO) has had significant success using Baytril, in conjunction with oxibendazole, in the treatment of symptomatic *E. cuniculi*. She frequently prescribes both treatments while waiting for test results in cases where symptoms pointed equally to *E. cuniculi* or a bacterial infection. Over the years, Dr. Allan noticed that in her practice, rabbits with *E. cuniculi* that had been treated with Baytril showed more improvement or slower disease progression than those who were treated with oxibendazole alone. In addition, when symptomatic *E. cuniculi* rabbits on long-term oxibendazole showed progression of symptoms, the addition of Baytril often resulted in overall improvement in their condition.

Although Dr. Allan is not sure of the exact mechanism for this improvement, she suggests the following **possible** modes of action:

- Baytril (or its interaction with oxibendazole) may actually interfere with the protozoan or its replication
- Improvement may be an anti-inflammatory response
- By treating co-existing bacterial infections, Baytril might strengthen the overall immune system

I admit I was skeptical about using Baytril to treat *E. cuniculi*. However, when Henrietta developed head tilt just before Christmas 2001, Dr. Allan started her on both Baytril and oxibendazole while we waited for the results of the *E. cuniculi* test. Henrietta tested positive, but by the time we had the test results her symptoms had significantly improved. We continued both treatments for several months and eventually the only way I could tell which direction her head had tilted was to remember which side of the toilet she would lean against!

### **Pyrimethamine "Cocktail"**

A promising new treatment was suggested by Esther van Praag, Ph.D., a Swiss biologist, in her paper *Can Encephalitozoon cuniculi, a protozoal parasite of the nervous system, be treated with pyrimethamine?* (The complete text of this article is available at [www.medirabbit.com](http://www.medirabbit.com).) Dr. van Praag based her study on the similarities between *E. cuniculi* in rabbits and *Sarcocystis neurona*, an equine protozoal parasite, which lives in the nervous system and spinal cord, and causes equine protozoal myelitis (EMP). According to Dr. van Praag, EMP is routinely treated with the antiprotozoal drug pyrimethamine.

Knowing that pyrimethamine has been safely used in rabbits to treat both toxoplasmosis and hepatic coccidial infections, Dr. van Praag suggested the possibility of using pyrimethamine to treat *E. cuniculi* in rabbits. The protocol, documented in her article, is based on one for treating toxoplasmosis in horses and includes the following drugs:

- Folic acid
- Pyrimethamine
- Sulfadiazine
- A non-steroidal anti-inflammatory (NSAID)

**Note:** Pyrimethamine should not be given by itself!

The drug dosages for use in rabbits were determined by Mark Lennox, DVM (Crossroads Animal Hospital, El Paso, TX), who based them on the treatment of toxoplasmosis in cats. This treatment should be used for a full month, assuming the rabbit is able to safely tolerate the treatment.

According to Dr. van Praag's article, the pyrimethamine both blocks the metabolism of folic acid in the parasite and increases the effectiveness of the sulfadiazine in combating the parasite. It is important to note Dr. van Praag's warning that compounds containing **trimethoprim**, which is combined with sulfadiazine in many sulfa drugs, **should not be used** because trimethoprim may increase the toxicity of pyrimethamine. Her article also points out that the combination of pyrimethamine and sulfadiazine may affect the function of bone marrow, causing a decrease in both red and white blood cell counts. Folic acid is an important part of the protocol because it helps minimize this side effect. However, regular blood work is suggested when using this treatment. The administration of an NSAID (e.g. Banamine or meloxicam) helps reduce the inflammatory response induced by the death of large numbers of parasites at one time.

At this time (February 2006), this treatment has been used on a very small number of rabbits, all of which had previously been treated with one or more of the "-bendazole" treatments and all of which had stopped responding to these treatments. All the rabbits showed a very high titer for *E. cuniculi* and were not suffering from other health issues, except in one case. The results, while very preliminary, seem quite promising.

Heather McMurray's rabbit Sweetie is one of the success stories for this protocol. Sweetie is a 10-year-old rabbit who had one leg amputated several years ago. In 2002 he lost the use of his remaining rear leg and was found to have a very high *E. cuniculi* titer. He was treated first with fenbendazole. When this treatment stopped working after about six weeks, he was switched to oxbendazole for several months, until it, too, stopped being effective. Heather's veterinarian, Dr. Lennox decided to try the pyrimethamine protocol on Sweetie. Heather noticed visible improvement within six days of the start of treatment, and treatment was continued for a full four weeks. Although Sweetie has not regained full use of the leg, the paralysis has not worsened since Thanksgiving when he completed the treatment.

## Lufenuron

For several years, lufenuron, an oral chitin inhibitor, has been used safely in rabbits as a **short-term** flea treatment. Dr. Dean Beyerinck (Irving Street Veterinary Hospital, San Francisco, CA) has treated more than 50 symptomatic cases of *E. cuniculi* with lufenuron and has been pleased with its success rate. The scientific explanation of this treatment is based on information in an article by Elizabeth S. Didier in the July, 1998 issue of **Clinical Infectious Diseases** which suggests that the endospore of the *E. cuniculi* spore is composed of chitin. Thus, while lufenuron probably does not kill the existing organisms, it may be quite effective in keeping them from reproducing!

The **long term** effect of lufenuron on the body of rabbits (and other mammals) has not yet been established. Recently, it has been found that mammals possess chitin-like enzymes, and the interaction of lufenuron with these enzymes has not been studied.

Dr. Beyerinck began treating Susan's rabbit Toby with lufenuron in the spring of 2002. At the time treatment was started, Toby's titer had risen dramatically over a two year period. Although she had been warned that it might be two or three weeks before there was visible improvement, Susan began noticing slight improvement after only three days and significant improvement after eight days. The original plan was to treat Toby every four weeks, but in his case symptoms seemed to return like clockwork after about three weeks. Toby received a lufenuron treatment every three to four weeks until his death (from causes unrelated to his *E. cuniculi*). According to Susan, Toby's overall health and quality of life improved significantly with this treatment.

## Ivermectin

Last fall, while searching online for information on *E. cuniculi*, a friend discovered Barbi Brown's article about her experiences treating (and perhaps preventing the spread of) *E. cuniculi* using Ivermectin. Ms. Brown is a breeder who keeps excellent health records and who believes in regularly treating her rabbits with Ivermectin at three month intervals. She noticed that the rabbits she saw with symptoms of *E. cuniculi* had either never been treated with Ivermectin or had not been treated for at least six months.

Ms. Brown's philosophy of regularly treating her rabbits with Ivermectin is similar to the widely-accepted practice of de-worming horses. Twenty years ago, the preferred horse wormer was fenbendazole; today it is Ivermectin. Given the biological parallels between rabbits and horses, it seems worth pursuing the possibility that Ivermectin **might** help stop the spread of *E. cuniculi*.

Ms. Brown's article states that Ivermectin "paralyzes the parasite and stops the migration to the brain." Her protocol calls for a second treatment seven days after the initial treatment, with follow-up treatments every three months, presumably for the remainder of the rabbit's life.

Despite the current lack of scientific evidence that Ivermectin is effective in treating – and perhaps preventing – attacks of *E. cuniculi*, this may be an option worth discussing with your rabbit’s veterinarian. Ivermectin has an excellent safety profile, having been used to treat fur mites in many rabbits for many years with very few side effects. The major concern Dr. Allan had with Ms. Brown’s protocol is that her dosage is almost four times greater than the upper limit of the (widely accepted) dose range for rabbits. Dr. Allan has agreed to try this treatment with the rabbits who have joined my family at a young age, but at half the dose used by Ms. Brown.

### **Future Directions**

As rabbit caretakers and their veterinarians share their experiences and pool both their data and their scientific and analytic skills, there is reason to hope that some day we will be able to both effectively control symptoms and halt the spread of this disease. To accomplish this, it is important to begin collecting and analyzing clinical data on individual rabbits receiving various treatments, with the understanding that there is as much to be learned from treatment failures as from success.

It is also important to understand that in medicine (both human and veterinary) it is not unusual for a treatment that appeared promising in a controlled, laboratory setting to fail miserably in a real-world clinical setting. Similarly, new indications for existing treatment — or combinations of treatments — are often discovered by observant clinicians who notice trends in their practice.

If you have an idea about a treatment that might be effective against *E. cuniculi*, I urge you to discuss it with your veterinarian, keeping in mind that all ideas — even bad ones — should be explored and discussed. When we were reaching the end of the road treating Goldie in 1998, my husband George and I “brainstormed” possible treatments for her. Dr. Allan quickly vetoed trying quinine because it would be too harsh to use on a rabbit’s delicate system, but agreed it was worth trying George’s suggestion to use the leftover beta-interferon from his MS injections. While this treatment had no noticeable effect, at least we had tried **something!**

The ultimate treatment or cure for *E. cuniculi* will probably not be one of the options discussed in this article. But perhaps it will come from a seed planted by a thought process discussed here, or by a reader daring to toss out an “outlandish” idea for discussion with her veterinarian.