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## Is a cure for IMHA near?

### Veterinarians are making progress in researching the genetic and environmental factors putting dogs at

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By Julie A. Jacob

The image of a straight line neatly sums up the frustration of treating dogs afflicted with immune-mediated hemolytic anemia (IMHA), according to Andrew Mackin, BVMS, DVSc, FANZCVSc, DACVIM, professor and head of the Department of Clinical Sciences at Mississippi State University College of Veterinary Medicine. Dr. Mackin is a member of the American College of Veterinary Internal Medicine's (ACVIM) Small Animal Internal Medicine consensus committee, which will present recommendations for immunosuppressive therapy for treating IMHA at the ACVIM 2018 Forum this month.

A straight line is how a graph charting average mortality from the disease as presented in journal articles over the past four decades would look, said Mackin. The average mortality rate for dogs afflicted with IMHA within three to six months of diagnosis and treatment has stubbornly hovered at about 50 percent, he said, even as veterinary medicine has advanced and outcomes for dogs with many other diseases have dramatically improved.



"Everything we do is chipping away, chipping away," Mackin said. "We're getting a little bit better and a little bit better."

Keith Richter, DVM, DACVIM, chief applied science officer for Ethos Veterinary Health, which runs a network of specialty veterinary hospitals, also thinks that treatment is gradually, perceptibly, improving.

"Our critical care skills are better; our transfusion skills are better," said Dr. Richter.

### The most common autoimmune disease

IMHA is the most common immune-mediated disease to affect dogs, and a busy specialty or emergency veterinary practice may see dozens of cases a year, said Richter.

Yet although it's the most common autoimmune disease, it is still a rare condition, said James W. Swann, VetMB, DACVIM, DECVM, MRCVS, who is researching the effect of system inflammatory disease on hematopoiesis at the University of Oxford's Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences.

At large university-affiliated animal hospitals, dogs with IMHA represent about 1 percent of all dogs brought in for treatment, but that number may be lower for general veterinary practices. Swann recently worked on a project analyzing medical notes from 240,000 visits at veterinary practices in the U.K., which found that about 120 dogs, or 0.05 percent, had IMHA.

"These figures were difficult to verify, which is why this data has never been published, because we were not sure that all these dogs definitely had IMHA," said Dr. Swann, who is also on the ACVIM consensus committee.

The precise interplay of genetics and environmental triggers that cause some dogs to get the disease is still not completely understood, according to IMHA experts.

Genetics likely play a role in the development of IMHA because certain breeds are more likely to be affected than others, said Richter. Cocker spaniels and springer spaniels are among the breeds commonly affected. In fact, the prototypical IMHA patient would be a "middle-aged, female cocker spaniel," he said.

But one of the many mysteries of IMHA is that breeds commonly affected vary geographically, said Mackin. For example, Old English sheepdogs are known in Australia as a breed that commonly develops IMHA, but in Mississippi, where Mackin resides, dachshunds are commonly affected.

"Every time we think we find a genetic trait that puts a dog at risk, another study doesn't confirm it. We know there's a genetic link, but we haven't put our finger on it," he said.

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According to Dr. Friedenberg, preliminary data from the two spaniel studies indicates that genetic predisposition to IMHA may be complex, instead of one "slam dunk" genetic mutation causes the disorder.

Friedenberg is also starting a study to look at gene pathways that are differentially regulated in dogs with IMHA in hopes that it will help veterinarians better understand the IMHA process and possibly lead to more effective therapies.

"This study could potentially get us some quick answers in terms of what's going on and explore the pathogenesis in a new way," he said.

### More research needed on triggers

More research is needed to understand the environmental factors that may trigger IMHA, said Mackin. Sometimes, the trigger is clear, such as reaction to a drug like a sulfonamide, other cases, the cause is unknown or merely suspected, he added. Cancer, tick-borne infections like babesiosis, and bee stings all are associated with IMHA—but association doesn't equal causality, he said.

The limited amount of data on trigger factors makes it challenging to pinpoint them, noted Unity Jeffery, VetMB, Ph.D., DACVP, an assistant professor at Texas A&M University College of Veterinary Medicine and Biomedical Sciences. The many breeds of dogs that develop IMHA, combined with seasonal variations in disease frequency, point to environmental factors, Dr. Jeffery said, but it's still not clear what they may be exactly.

"Identifying these triggers is increasingly becoming a focus of veterinary research, but the limited availability of large epidemiological databases in veterinary medicine makes the environmental practices challenging," said Jeffery.

At the June ACVIM Forum, another consensus committee will review evidence for IMHA trigger factors. It won't provide any groundbreaking information on triggers, "but will give an idea on what has been published so far," Swann said.

### A complex soup

Once a dog is diagnosed with IMHA, the complexity of the disease makes it much more challenging to treat than a disease with a uniform presentation and one standardized treatment, such as transmissible venal tumors, said Mackin.

"IMHA is a complex soup of many different presentations," he said. "Some versions destroy red blood cells by popping them and others eat the red blood cells; some dogs have the disease affecting their platelets and others don't. You can't expect one cookie cutter treatment to work."

The foundation of treatment is steroids often combined with one or more immunosuppressant drugs such as cyclosporine, azathioprine, or mycophenolate.

Because blood clots frequently are a complication of IMHA and thrombosis is associated with higher mortality, aspirin, heparin, or clopidogrel also are often used to reduce the risk of blood clots, said Mackin.

However, there's little evidence on which drug or combination of drugs is most effective, said Richter.

The upcoming consensus statement will provide recommendations for using immunosuppressants, said Mackin, adding that tailoring treatment to individual dogs is crucial and the therapeutic drug monitoring tools are needed.

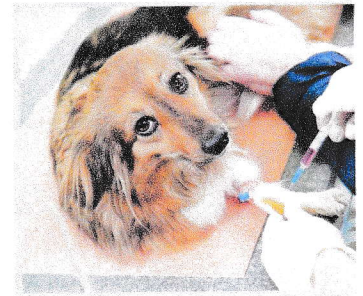
"Dogs have narrow therapeutic windows," he said. "The gaps between effective, ineffective, and dangerous drug doses are really narrow."

One such tool is an assay that was developed at the Pharmacodynamic Laboratory at Mississippi State University College of Veterinary Medicine that can help gauge the immunosuppression activity of cyclosporine and provide dosage guidance to veterinarians who submit blood samples of dogs they are treating. Similar assays will be available soon for other drugs, said Mackin.

Swann is working on a study analyzing blood samples from dogs with IMHA to measure biomarkers such as pro- and anti-inflammatory proteins and the expression of pro- and anti-inflammatory genes that might be able to be used to predict how dogs will respond to treatment, as well as whether they are likely to develop serious side effects.

"Our hypothesis is based on our opinion that there already are effective immunosuppressive drugs available, but that treatment should be individualized for each dog to control the disease while minimizing side effects," said Swann.

They will study whether the biomarkers they measure correlate with treatment outcomes, he added.



### Plasma exchange shows promise

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"We've had success with a few dogs that were dying and were not responsive to even aggressive immunotherapy," he said.

Mackin said that while he, too, is cautiously optimistic that plasmapheresis may become another effective treatment option, it's available only at a few facilities and is expensive and intensive.

### "We'll find the answer"

The experts agree that it's frustrating that not more progress has been made in preventing and treating IMHA in dogs. However, it's being made slowly, they said, and the upcoming statements on trigger factors and the use of immunosuppressants will provide valuable guidance to veterinarians treating dogs with this very serious and complicated disease.

"We are doing a much better job of keeping dogs going long term without intolerable side effects," said Mackin, adding that he is hopeful that someday IMHA might be a easily diagnosed and effectively treated disease.

"I firmly believe that some time in the future we are going to look back at this and recognize that this is a simple disease with a fairly simple diagnosis and a simple treatment," he said these days we are definitely going to find the answer."

"I firmly believe that some time in the future we are going to look back at this and recognize that this is a simple disease with a simple diagnosis and a simple treatment. One of the things we are going to find the answer."—Andrew Mackin, BVMS, DVSc, FANZCVSc, DACVIM, professor and head of the Department of Clinical Sciences at Mississippi State University College of Veterinary Medicine

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