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## IMMUNE-MEDIATED HEMOLYTIC ANEMIA

Immune-mediated hematologic disease including hemolytic anemia (IMHA) and/or thrombocytopenia is being reported with increasing frequency in animals and humans. In dogs and occasionally in cats, this disorder can be associated with bone marrow failure (nonregenerative anemia, erythroid dysgenesis, red cell aplasia). Affected animals have one or more of the following signs: lethargy, anorexia, pale mucous membranes, weakness, exercise intolerance, tachycardia, tachypnea, icterus, hemoglobinuria and fever. Prognosis is guarded to poor with reported mortality rates between 28-70%. Laboratory abnormalities may include: red cell autoagglutination, positive Coombs' test, spherocytosis, thrombocytopenia, and neutrophilia. Anemia may be regenerative or nonregenerative depending on the duration of illness and immunological targeting of red cell precursors in the bone marrow. Some dogs may also have other autoimmune diseases. While many cases may be classified as idiopathic, a recent stress event such as vaccination, drug, chemical or toxic exposure, surgery, hormonal change, infection, or injury within the previous 30-45 days may be identified as a potential trigger. Many breeds are reported to have an increased risk for IMHA, and mixed breed dogs can also be affected.

Four recent retrospective studies have addressed the clinical and laboratory findings and compared treatment outcomes of dogs with IMHA. In one study of 70 cases, Cocker Spaniels, English Springer Spaniels, Poodles, Miniature Schnauzers, and Collies were at increased risk. Only 3 dogs had been vaccinated within 2 weeks of the diagnosis. Regenerative anemia was present in 83% and 79% had spherocytosis. Only 37% of the dogs had positive Coombs' test. Thrombocytopenia was also found in 29 dogs. Elevated serum bilirubin concentrations, present in 68% of cases, was significantly associated with decreased survival. A significant difference in survival was found between treatment groups (see Table).

The overall mortality was 70%. While 29 dogs died or were euthanized during hospitalization, 41 were discharged but 15 died, most within 3 months

Treatment	# Dogs	Median Survival Days	Mortality Rate (%)
Prednisone only	16	57	62.5
Prednisone + Cyclophosphamide	28	28	67.8
Prednisone + Azathioprine	5	974	80.0
Prednisone + Cyclophosphamide + Azathioprine	16	15	68.7

of discharge. Dogs with IMHA were four times more likely to die than dogs in the general hospital population.

The second study involved 60 cases. Cocker Spaniels had a 3.3 times increased relative risk for IMHA. Unlike an earlier study, no seasonal incidence, or correlation between vaccination and onset of disease or survival times was found. Positive Coombs' test and autoagglutination were seen in 89% of cases, and 75% had spherocytosis. The anemia was regenerative in 42% and nonregenerative in 58%. Increased bilirubin concentrations were present in 80% of cases, but hyperbilirubinemia was not associated with higher mortality. The median survival time was only 21 days. Dogs receiving prednisone, cyclophosphamide, and azathioprine had a median survival time of 370 days as compared to only 9 days for those given only prednisone and cyclophosphamide. Of the dogs given compatible transfusions, no adverse effects were recorded and the median survival time was better (21 days) versus 2 days for dogs that were not transfused. Overall mortality was 52%. Thirty-three dogs were discharged and followed for at least 2 years; 8 dogs relapsed and in 7 of these, relapse occurred within 21 days of discharge.

The third study included 88 dogs. Twenty-six dogs received only prednisone. Of these, 15 (58%) survived to be discharged, and the mortality rate was 30%. The relative risk of death for dogs treated

## IMMUNE-MEDIATED HEMOLYTIC ANEMIA (CONT'D.)

with prednisone and azathioprine (n=27), prednisone and danazol (n=16), prednisone and cyclosporine (n=24) or prednisone and intravenous gamma globulin (n=7) was not different from dogs treated only with prednisone. With cyclophosphamide, however, there was a significant increased risk of mortality. Although dogs with autoagglutination were twice as likely to be treated with cyclophosphamide, there was no significant relationship between autoagglutination and mortality. The mean PCV of dogs that were treated with cyclophosphamide was not significantly different from dogs not receiving this drug. The 3 dogs receiving bovine hemoglobin solution did not survive. Overall mortality rate in this study was 50%, but dogs were followed only until discharge.

The last study involved 43 dogs with severe idiopathic nonregenerative anemia. Labrador Retrievers were overrepresented here. While 54% of cases had spherocytosis and 57% had positive Coombs tests, only 5% had autoagglutination. Seven of 31 dogs tested (23%) had positive antinuclear antibody titers. Leukocyte counts were normal, but 22% of the dogs had some degree of thrombocytopenia. All dogs had bone marrow biopsies. Bone marrow aspirates were difficult to obtain in 27 dogs, and core marrow biopsies were performed in 16 of them. Fifty-five percent of dogs had erythroid hyperplasia, 14% had normal erythropoiesis and 26% had erythroid hypoplasia,

37% had erythroid maturation arrest, and 2 dogs had pure red cell aplasia with no red blood cell precursors found. All 16 core biopsies revealed myelofibrosis. Iron stores were moderate in 23% and large in 72% of the dogs. Treatment outcomes varied with responses seen in 1-10 weeks (see Table).

Follow-up bone marrow biopsy on 2 dogs showed resolution of myelofibrosis. Overall mortality was 28%.

**Conclusion:** Prognosis for dogs with IMHA is guarded to poor. The various combination drug protocols may not work better than corticosteroids alone. Use of cyclophosphamide to treat dogs with the regenerative form of IMHA may be associated with increased mortality. Dogs with the non-regenerative form of IMHA do not have a worse prognosis than dogs with the classic regenerative form. Myelofibrosis can occur secondary to immune-mediated destruction of red cell precursors and may respond to immunosuppressive therapy.

Treatment	# Dogs	Outcome Response (%)			Relapse (%)
		Complete	Partial	None	
Prednisone only	5	25	50	25	62.5
Prednisone + Cyclophosphamide	12	73	9	18	67.8
Prednisone + Azathioprine	26	52	16	32	80.0

**References:** Dodds, Can Vet J 37 (3): 133, 1996; Reimer et al, JAAHA 35: 384-391, 1999; Burgess et al, JVIM 14: 456-462, 2000; Grundy and Barton, JAVMA 218: 543-546, 2001; Stokol et al, JAVMA 216: 1429-1436, 2001.

## ANATOMIC PATHOLOGISTS JOIN WEST COAST ANTECH STAFF

Antech Diagnostics welcomes the following pathologists:

### DR. L. RACHEL ANOTHAYANONTHA

Received her Doctor of Veterinary Medicine degree at Iowa State University in 1997. A Masters degree in anatomic pathology was attained following a residency at Purdue University, after which she became Board-Certified by the ACVP. Before joining Antech's Phoenix laboratory, she held a position in toxicology at Purdue University.

### DR. CYNTHIA BACMEISTER

Received her Doctor of Veterinary Medicine degree from Cornell University, and then practiced in Detroit and California before relocating to Kansas State University to pursue her doctoral degree and training in anatomical pathology. Upon completing the program, she took a fellowship at the Armed Forces Institute of Pathology where she helped create a data base for dogs deployed to the Persian Gulf during the Desert Storm conflict. She has a special interest in avian and exotics pathology, and will be taking the ACVP Board Examination this fall. Cynthia is located in Antech's Irvine lab.

### DR. KAI-NING TANG

Received his Doctor of Veterinary Medicine from Taiwan, Republic of China, and MS, Ph.D. degrees in anatomic pathology from the University of Georgia. In 1991, he became Board-Certified by ACVP and was an Assistant Professor at the Veterinary Diagnostic and Investigational Laboratory at University of Georgia. Before joining Antech's Irvine laboratory, Kai-ning was Vice President of a commercial laboratory in Dallas. His many interests include surgical and avian pathology, dermatopathology, diagnostic oncology and cytology.

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