

The use and misuse of glucocorticoids in veterinary practice

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KEY POINTS

- Glucocorticoids (GCs) are potent hormones that affect all body tissues.
- These hormones are produced in the adrenal cortex in the minute amounts required for survival.
- Nonproduction of GCs results in Addison's disease or hypoadrenocorticism – a life-threatening but treatable illness.
- When GCs are produced in increased quantities, either due to adrenal neoplasia or hyperplasia, the resultant constellation of clinical signs is known as Cushing's disease or hyperadrenocorticism.
- GCs are among the most frequently used drugs in veterinary medicine.
- Overuse or misuse of GCs can cause iatrogenic hyperadrenocorticism or hypoadrenocorticism and may cause death due to bacterial, fungal, or protozoal infections.
- The therapeutic use of GCs should be reserved for the patient diagnosed with a specific disease in which GCs have been shown to be of benefit.

INTRODUCTION

Glucocorticoids (GCs) are steroid hormones produced in the adrenal cortex. These hormones affect virtually every tissue in the body. Although necessary for the maintenance of homeostasis, these powerful drugs produce significant side effects when given in pharmacological dosages. Use of these agents should be restricted to those cases in which a specific diagnosis of a disease routinely treated with GCs has been made. Cases 1 and 2 illustrate the consequences of the inappropriate use of GCs, and **Table 1** illustrates the typical changes seen on the blood profile.

PHYSIOLOGICAL EFFECTS OF GLUCOCORTICIDS

The body tightly regulates the production of GCs in the adrenal glands (**Figure 1**). Corticotropin-releasing hormone (CRH) is produced in the hypothalamus and stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. The ACTH stimulates the production and release of cortisol from the adrenal cortex. Cortisol then feeds back negatively on the hypothalamus and pituitary to reduce CRH and ACTH production respectively, thereby decreasing the production of cortisol. This feedback mechanism is termed the hypothalamic–pituitary–adrenal axis (HPAA).

Glucocorticoids are the 'fight or flight' hormones. They prepare the body physiologically to deal with stress. Information gained from laboratory animals and *in vitro* studies of human T lymphocytes has shown that the effects of GCs are mediated through stimulating

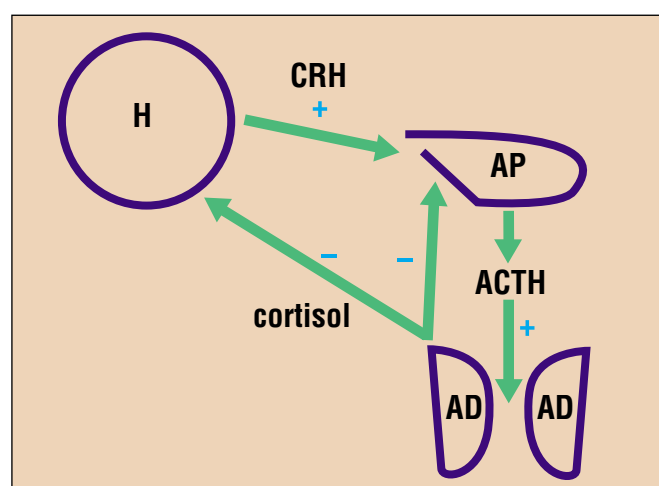


Figure 1 Hypothalamic–pituitary–adrenal axis. H = Hypothalamus, AP = Anterior pituitary, AD = Adrenal glands, CRH = Corticotropin, ACTH = Adrenocorticotropic.

Table 1
Taffy's laboratory results

Parameter	Result	Normal
Hematology		
PCV (%)	38	37–55
Hb (g/dl)	13.4	12–18
WBC ($\times 10^3/\mu\text{l}$)	18.7	6–17
Neutrophils ($\times 10^3/\mu\text{l}$)	16.0	3–11.5
Bands ($\times 10^3/\mu\text{l}$)	0.3	0–0.3
Lymphocytes ($\times 10^3/\mu\text{l}$)	1.8	1.0–4.8
Monocytes ($\times 10^3/\mu\text{l}$)	0.4	0.2–1.4
Eosinophils ($\times 10^3/\mu\text{l}$)	0.2	0.1–1.2
Basophils ($\times 10^3/\mu\text{l}$)	0	rare
Biochemistry		
Glucose (mg/dl)	135	65–122
ALP(IU/l)	3200	18–141
ALT (IU/l)	453	10–120
AST(IU/l)	0.2	0–0.4
Cholesterol (mg/dl)	385	130–300
Total protein (g/dl)	7.2	5.4–7.4
Albumin (g/dl)	4.0	2.7–4.5
Globulin (g/dl)	3.2	1.9–3.4
BUN (mg/dl)	16	7–28
Creatinine (mg/dl)	1.0	0.6–1.5
Calcium (mg/dl)	10.3	9–11.2
Phosphorus (mg/dl)	4.5	2.8–6.1
Sodium (meq/l)	145	145–158
Potassium (meq/l)	4.6	4.1–5.5
Chloride (meq/l)	107	106–127
HCO ₃ (meq/l)	18.2	14–27
Urinalysis		
Color	Pale yellow	
Specific gravity	1.015	
pH	7	
Protein	2+	
Glucose	Negative	
Ketones	Negative	
Blood	Negative	
Bilirubin	1+	
RBC/hpf*	0–1	
WBC/hpf*	0–1	
Crystals	Occasional triple phosphate	
Bacteria	None	

Values in bold are consistent with, although not pathognomonic for, hyperadrenocorticism. Hpf* = high-power field.

Table 2
Relative potency and activity of glucocorticoid preparations (3, 11)

Preparation	Glucocorticoid activity	Mineralocorticoid activity	Duration of action
Short-acting			
Cortisol	1	1	8–12 hours
Aldosterone	0.3	3000	
Intermediate-acting			
Methylprednisolone	5	0	12–36 hours
Prednisone	4	0.8	12–36 hours
Prednisolone	4	0.8	12–36 hours
Triamcinolone	3	0	12–36 hours
Fludrocortisone	10	125	12–36 hours
Long-acting			
Dexamethasone	25	0	35–54 hours
Betamethasone	30	0	35–54 hours
Deoxycortisone			28 days

DNA-dependent synthesis of messenger RNA in the nucleus of target cells (1). This leads to the production of proteins that alter cell function. For instance, when GCs enter the white blood cell, they bind to an intracytoplasmic receptor. This receptor–ligand complex then moves into the nucleus and binds to regulatory sequences of genes causing either an increase or decrease in their expression. In the lymphocyte, down regulation of Interleukin 2 production occurs, stopping the amplification of the immune response. Glucocorticoids can also exert their effect posttranscriptionally by altering the secretion of a protein or increasing degradation of messenger RNA (1).

The main effects of GCs are on the metabolism of carbohydrates, proteins, and lipids (2). In general, GCs stimulate protein catabolism, which results in increased serum concentrations of amino acids. Increased hepatic uptake and metabolism of amino acids results in increased gluconeogenesis and glycogenesis. Reduced peripheral utilization of glucose causes an increase in blood glucose concentration. Inhibition of hepatic lipogenesis and stimulation of lipolysis in adipose tissue by GCs results in increased concentrations of free fatty acids in the peripheral blood. All these effects provide the energy source for dealing with stress.

Glucocorticoids have a permissive effect on a number of other metabolic reactions. In other words, GCs are not responsible for the effects but are necessary for other hormones to exert their effect. For instance, GCs need to be present for catecholamines to produce pressor responses and bronchodilation.

Without GCs, skeletal muscle becomes weak and fatigues easily. Glucocorticoids indirectly affect the central nervous system by maintaining normal blood glucose concentrations and maintaining normal fluid and electrolyte concentrations.

PHARMACOLOGICAL EFFECTS OF GLUCOCORTICIDS

Glucocorticoids vary with respect to potency, mineralocorticoid effect, antiinflammatory effect, onset of action, plasma half-life, and duration of biological effect. Potency usually refers to the glucocorticoid (antiinflammatory) effects of these drugs.

Hydrocortisone (cortisol) is the standard against which other GCs are compared. Cortisol, for comparative purposes, is said to have antiinflammatory and mineralocorticoid activity equal to 1. The potency of other GCs is calculated as factors of this (Table 2). Prednisone and prednisolone have intermediate antiinflammatory activity but somewhat less mineralocorticoid activity than cortisol, while fluorinated compounds, such as dexamethasone, betamethasone, and triamcinolone, have potent antiinflammatory activity but essentially no mineralocorticoid effect (3).

The onset and duration of action vary, depending on the GCs' formulation, the route of administration, serum protein concentration, and metabolic capabilities of the patient (3). Binding GCs to water insoluble esters prolongs the onset and duration of action by slowing absorption (4). Glucocorticoids are released over days to weeks from moderately soluble esters (acetate, diacetate) and over weeks to months from poorly soluble esters such as acetone, pivalate, and dipropionate. Esterification may also increase the antiinflammatory potency in some cases. Water soluble salts (succinate, phosphate, hemisuccinate, and polyethylene glycol) of GCs have a relatively short onset of effect.

Protein binding affinity varies for different GCs. Hydrocortisone and prednisone are highly bound to transcortin and albumin. Thus, because the free drug is active, dosages should be adjusted in animals with hypoproteinemia. The biological half-life of GCs is the duration of effects on various body systems, specifically the suppression of the HPA. The biological half-life is longer than the



plasma half-life (5). For instance, prednisolone has a plasma half-life of less than 1 hour, although suppression of the HPA axis continues for 12 to 36 hours.

The effects on the immune system depend on the dosage used. At lower doses, antiinflammatory effects predominate. Much of the inflammatory response is generated by neutrophils. Normally, neutrophils marginate and leave the blood vessels at sites of trauma or infection. Their migration is directed towards a target (chemotaxis). Upon reaching the site of inflammation, neutrophils ingest and kill bacteria and remove debris. Bacterial killing is mediated by the generation of toxic oxygen metabolites by the neutrophil. In addition, neutrophils and other leukocytes produce inflammatory mediators, leukotrienes, and prostaglandins which amplify the inflammatory response and recruit more cells to fight off the offending agent. Leukocyte kinetics are altered by GCs so that although neutrophils are released from the marrow at an increased rate, they fail to marginate and egress into the tissues (6). These changes result in the mature neutrophilia seen in the peripheral blood of patients receiving GCs. Without neutrophils at the site of tissue trauma, there is less inflammation because there is reduced recruitment of more immune cells and reduced production of toxic oxygen radicals.

Glucocorticoids alter gene transcription such that a potent inhibitor of phospholipase A2 is produced, blocking synthesis of prostaglandins and leukotrienes (6). Myeloproliferation of fibroblasts and collagen synthesis is also suppressed by GCs (6).

At higher doses, GCs are actually immunosuppressive. Cell-mediated immunity normally involves a complex series of interactions between antigen-presenting cells and lymphocytes, resulting in the generation of antigen-specific effector cells. Glucocorticoids inhibit the production of interleukins (1, 2, 6), which greatly reduces the proliferation and differentiation of lymphocytes. The role of the monocyte/macrophage is more complex than that of the neutrophil in maintaining host defenses. They not only phagocytose foreign particles, but also present antigens to T lymphocytes to initiate the antigen-specific arm of the immune response. Macrophages normally respond to and produce cytokines that up-regulate the immune response. Antigen presentation by macrophages is inhibited by GCs (6).

Humoral (antibody-mediated) immunity is also affected by GCs, mostly due to alterations in T helper cell function. Most antigens are T cell-dependent, meaning that T cell help is required for B cells to proliferate and produce antibodies. Redistribution of lymphocytes and the antiinflammatory effects of GCs result in decreased antigen presentation (6). The catabolic state induced by GCs' administration may also directly reduce antibody production to some degree.

CLINICOPATHOLOGICAL CHANGES ASSOCIATED WITH ADMINISTRATION OF GCs

The complete blood count alterations associated with GCs therapy include neutrophilia, lymphopenia, and eosinopenia, the classic 'stress leukogram' (7). In cats, a lymphocytosis may occur (7). In addition, GCs can increase the number of nucleated red blood cells and platelets seen in the peripheral blood (8).

The changes in the serum chemistry panel reflect the induction of alkaline phosphatase isoenzyme production by hepatocytes in dogs. Cats have no steroid induced isoenzyme (9, 10). Alanine transaminase is often increased moderately in dogs. Blood glucose concentration is increased to just above the normal range (11). Serum cholesterol may be increased (see Table 1).

Urine specific gravity is usually in the isosthenuric range. There may be mild proteinuria, especially if urinary tract infection or hypertension secondary to GCs is present. Occult urinary tract



Figure 2 Myopathy, hyperextension of the legs, secondary to spontaneous hyperadrenocorticism.

infections are common in animals on GCs, therefore, a urine sediment exam should be performed on patients on long-term therapy. There may be few clinical signs due to the antiinflammatory properties of GCs, and pyuria may be absent. Bacteriuria without pyuria should warrant a urine culture.

ADVERSE SIDE EFFECTS OF GLUCOCORTICOIDs

When GCs are administered exogenously, the same negative feedback cycle occurs as when they are secreted by the adrenal gland. The exogenously administered GCs shut off the production of CRH and ACTH, eventually resulting in atrophy of the adrenal cortex. Abruptly stopping GCs after this atrophy has occurred can result in a hypoadrenal crisis (5). If appropriate treatment is not given, the animal may die.

At pharmacological doses, GCs alter the health of most cells in the body, based on their physiological effect. For instance, canine hepatocytes are induced to produce more alkaline phosphatase and to store glycogen (11). They become swollen, and the liver increases in size. Although hepatic function is usually unaffected, hepatomegaly can result in abdominal discomfort and tachypnea or dyspnea. Cats seem to be resistant to these hepatic effects (10).

Skeletal muscle weakness can result from potassium depletion and from actual loss of muscle tissue through prolonged catabolism. In some cases the muscles may stiffen because of steroid myopathy (Figure 2) (12). This has not been reported in cats. Weakening of the abdominal muscles contributes to a pendulous abdomen in dogs and cats. Additionally, weakened intercostal muscles are in part responsible for the panting or tachypnea that results from steroid administration.

In the gastrointestinal tract, GCs cause reduction in gastric mucus production and decreased gastric epithelial cell turnover, resulting in a tendency toward gastric ulceration (13). Reduction in the aqueous portion of pancreatic secretions and pancreatic duct cell proliferation may predispose to pancreatitis when GCs are used at high doses (14). The effects of GCs on the small and large intestine are variable. In the case of dogs with severe spinal cord disease, their administration has been associated with fatal colonic perforation (15). Alterations in local immune function in the small intestine may result in bacterial diarrhea.

Cutaneous changes associated with long-term use of GCs include decreased cell turnover, resulting in thin skin, and an increase in bacterial infections (15). A symmetrical loss of hair and poor regrowth of hair following clipping is also noted. As a consequence of reduced fibroblastic activity, wound healing is poor and the walls of blood vessels weaken, so promoting bruising.

Calcinosis cutis, a dystrophic calcification of the dermis, may also occur in animals on chronic GC therapy (Figure 3) (15).

In cats with naturally occurring hyperadrenocorticism, cutaneous changes predominate. Thin, fragile skin, and alopecia are common (10). The author has also seen sterile subcutaneous abscesses or granulomas secondary to the injection of repositol



Figures 3a and 3b Calcinosis cutis in an English bulldog treated with oral glucocorticoids. Note the erythema and alopecia on the dorsum.

products in a cat.

The immunosuppressive and antiinflammatory effects of GCs cause an increase in bacterial infections in animals. Most commonly, infections of the skin, urinary and gastrointestinal tracts are noted. About 50% of dogs on chronic GCs therapy have lower urinary tract infections (15, 16). Opportunistic systemic fungal infections can also occur.

Long-term GC therapy has detrimental effects on the bones. Increased calcium resorption from the bones due to increased parathyroid hormone, inhibition of osteoblast activity, and reduced intestinal absorption of calcium can result in osteoporosis (5, 15).

Glucocorticoids are contraindicated in animals with diabetes mellitus due to their effects on carbohydrate, lipid, and protein metabolism (5, 15). They are referred to as diabetogenic and have even induced diabetes in normal animals.

Thyroid hormone synthesis is reduced by GC therapy (17). This fact makes it difficult to determine if hypothyroidism is present. Measurement of endogenous TSH concentration is necessary to accurately diagnose hypothyroidism.

In the intact bitch, chronic GC administration can suppress the ovarian cycle, resulting in prolonged anestrus and infertility (15).

The effects of GCs on the central nervous system are varied. Polyphagia and panting are common side effects (5, 15). Although not as common in dogs and cats as in humans treated with GCs, mental changes can also occur. These include euphoria, hyperactivity, and depression.

IATROGENIC HYPER- AND HYPOADRENOCORTICISM

The long-term administration of GCs, even at low dosages, can result in all the outward signs of Cushing's disease (hyperadrenocorticism) (18). Symmetrical alopecia, thin skin, *Calcinosis cutis*, pendulous abdomen, recurrent skin and urinary tract infections, polyuria, polydipsia, and elevated serum alkaline phosphatase can all occur. However, exogenous administration of GCs reduces ACTH and CRH secretion via negative feedback mechanisms, resulting in atrophy of the adrenal glands. Therefore, if an animal on chronic GCs therapy is tested for hyperadrenocorticism, the results of the test actually support the diagnosis of hypoadrenocorticism (19). Fortunately, the atrophy is reversible. If the animal is carefully weaned off the GCs and then placed on alternate day therapy for 2–4 weeks, the adrenal glands will gradually regain their ability to secrete cortisol.

The prevention of iatrogenic hyperadrenocorticism is simple if the physiology of GC secretion is kept in mind (5). When high doses of a GC are required for long periods of time to treat a disease, then it is wise to slowly reduce the dose over time to the lowest dose that will still control the clinical signs. The author reduces the dose by 50% every three weeks as long as the disease stays in remission. When the animal is receiving 0.25–0.5 mg/kg daily, alternate-day therapy can be instituted as long as remission is maintained. If higher doses are needed to maintain remissions, alternative immunosuppressive therapies are indicated.

Ideally, most diseases that require chronic glucocorticoid administration can be maintained in remission with long-term, low-dose, alternate-day medication. Short-acting GCs such as cortisone or prednisolone are ideal for this type of treatment because of the intermediate duration of their HPA axis suppression. When given on alternate days, the HPA axis is allowed to recover on the days that the drug is not given. Without the negative feedback, the adrenal glands are then stimulated by ACTH to again secrete GCs.

When iatrogenic hyperadrenocorticism has been diagnosed, physiological doses (0.2 mg/kg once daily) are required until the animal regains its own GCs production. Two to three weeks of daily supplementation followed by six to eight weeks of alternate-day supplementation will usually allow the patient to regain a normal HPA axis. Occasionally, longer therapy is necessary.

INDICATIONS FOR THE USE OF GLUCOCORTICOIDS

The use of GCs should be reserved for animals in which a diagnosis of a specific disease routinely treated with GCs has been made and the dosage required will vary with indication (**Table 3**). Five types of disease categories exist (20–23):

- Physiological replacement
- Management of allergic disease
- Immunosuppressive treatment of immune-mediated disease
- Adjunctive treatment in neoplastic diseases, e.g., mast cell neoplasia
- As part of an antishock protocol

In physiological replacement therapy for animals with hypoadrenocorticism (5), the animal will not survive without supplemental GCs, sometimes requiring mineralocorticoid replacement. The goal is to replace the cortisone that is not being made by the adrenal glands with a product that has adequate GC effects lasting approximately 24 hours. Hydrocortisone, prednisone, prednisolone, and methylprednisone are reasonable choices for this



Figure 4
(a) Taffy, a nine-year-old mixed breed dog with iatrogenic hyperadrenocorticism.
(b) Alopecia and hyperpigmentation on the bridge of the nose.
(c) Thin skin and bruising on the ventral abdomen. Note the prominent subcutaneous veins.



purpose. Dosages are listed in **Table 3**. Glucocorticoid indication in the management of neoplastic disease (22) and the treatment of shock (23) are beyond the scope of this article.

The potent antiinflammatory effects of GCs are useful in the therapy of a variety of inflammatory diseases (20). Allergic reactions are a classic example (21). In a type 1 hypersensitivity reaction, the dose can be reduced fairly quickly until the dose is <0.5 mg/kg/day; then it should be given every other day or every third day. In those individuals refractory to other means of control, such as immunotherapy for example, long-term GC therapy may be necessary and low-dose alternate day protocols are essential.

For immune-mediated diseases, the protocol listed in **Table 4** has worked well in the author's experience. The idea is to reduce the dose so slowly that the aberrant immune response is kept controlled. However, this protocol is meant to be used as 'a' guideline. Each patient must be treated as an individual, and the decision to lower

Table 3
Recommended dosages of glucocorticoid preparations

Preparation	Maintenance	Anti-inflammatory	Immuno-suppressive	Shock
Cortisol	0.2–1.0	*	*	*
Prednisone	0.1–0.2	0.5–1.0	2–4	11–33
Prednisolone	as prednisone			
Methylprednisone	*	0.4–1.0	2–4	8–26
Dexamethasone	*	0.05–0.15	0.3–0.9	4–11
Betamethasone	*	0.05–0.15	0.3–0.9	4–10

* – not used for this purpose

Table 4
Guide to reducing the dose of GCs in patients with immune-mediated disease

Examination date	Dose*
Day 1	2–4 mg/kg/day divided BID
Days 2–7	Same dose and monitor clinical improvement (rising PCV, rising platelet count, etc), depending on the disease:
Days 8–28†	1–2 mg/kg/day
Day 29	0.5–1 mg/kg/day
Day 50	0.25–0.5 mg/kg/day
Day 71	0.2 5 mg/kg every other day
Day 112	Discontinue if possible

*The dose is written for prednisone, prednisolone, methylprednisolone orally.

†This day is variable depending on the response of the patient – i.e., if a good clinical response does not occur until days 7–14, then the next dose reduction is on day 35.

the dose of GCs is based on reevaluation of the patient. At each point when the dose is reduced, the owner needs to be aware that relapse can occur. If caught early, a relapse may be dealt with easily by increasing the dose to the next step up, rather than starting all over again at the highest dose. Relapses can be more difficult to treat than the original occurrence of the disease – i.e., a second remission can be difficult or impossible to achieve once a relapse occurs. Therefore, in the long term it is better to err on the side of a slow reduction in dose rather than to attempt to stop the GCs too quickly. Although the owners may not like the side effects of GCs in their pet, they should be persuaded that the end result will be much better and less expensive.

SUMMARY

When used properly, GCs can be lifesaving. However, the detrimental effects have a high price, including possible death, when they are used inappropriately. Wise selection of the type of GC and the dose in cases of diagnosed illness will usually prevent problems.

Case 1

Taffy was a nine-year-old spayed female terrier cross that had been plagued with allergies her whole life. She was owned by an elderly man who just wanted his dog to be comfortable. His regular veterinarian had prescribed a topical spray containing gentamicin and betamethasone – a highly potent GC. The owner sprayed the dog with this solution daily to control Taffy's pruritus and renewed the prescription frequently. Taffy was receiving no oral GC preparations.

She was presented to me because of hair loss, weight gain, lethargy, and polyuria/polydipsia. On physical examination, Taffy had a symmetrical truncal alopecia and a generalized thin hair coat (Figure 4). The bridge of her nose was hairless and hyperpigmented. Additionally, she had a pendulous abdomen and an enlarged liver. Results of laboratory evaluation are listed in Table 1.

Taffy had classic clinical signs and biochemical changes (highlighted in Table 1) associated with hyperadrenocorticism. Therefore, an ACTH stimulation test was performed to determine the status of her adrenal function. Results of the ACTH stimulation test revealed that Taffy had iatrogenic hyperadrenocorticism. Her pre- and post-ACTH serum cortisol concentrations were nondetectable, indicating that her adrenal glands were shut down by the negative feedback of the topical betamethasone. If her GC administration had been stopped abruptly, Taffy may have suffered from a hypoadrenal crisis.

We placed Taffy on a physiological dose of prednisone and gradually weaned her off GCs. She later returned for skin testing and eventually her atopy was controlled by hyposensitization. Although the use of GCs was indicated in the initial management of pruritus due to atopy in this dog, alternatives to chronic GC administration were indicated. Inappropriate use of GCs resulted in a potentially life-threatening situation. Any topical preparation, including solutions for the ear and eye, can result in iatrogenic hyperadrenocorticism so it is important to monitor patients that receive these medications.

Case 2

Chelsea was a four-year-old spayed female Irish Setter that presented with a history of lethargy and anorexia of two days' duration. The physical examination revealed a body temperature of 39.5°C, tachycardia, tachypnea, a grade II/IV holosystolic heart murmur, icterus, and hepatosplenomegaly. When a blood sample was obtained from the dog, strong autoagglutination in saline was noted. A regenerative anemia with spherocytosis and microscopic agglutination was evident on the complete blood count. Hyperbilirubinemia and mild increases in liver enzymes were noted on the serum chemistry profile. All findings were compatible with immune-mediated hemolytic anemia (IMHA), and Chelsea was treated with immunosuppressive doses of prednisone.

After initial improvement, her status deteriorated, and she died within 48 hours of hospitalization. A necropsy showed that Chelsea had bacterial endocarditis. She died of sepsis brought about by suppression of her immune system with GCs. Although primary IMHA is treated routinely with GCs, this dog had IMHA secondary to bacterial endocarditis. The use of GCs in this situation is controversial, however. Initial treatment with antibiotics and possibly a blood transfusion may have saved this dog's life.

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