Glucocorticoids (Prednisone, Dexamethasone, Budesonide, Fluticasone)

Glucocorticoids are considered first-line therapy for immune-mediated diseases for induction and maintenance of remission, including immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia (IMT), polyarthritis, inflammatory bowel disease (IBD), pure red cell aplasia (PRCA), chronic hepatitis, dermatologic diseases (pemphigus foliaceus, cutaneous vasculitis), SLE, and asthma or allergic bronchitis. Glucocorticoids bind their intracellular glucocorticoid receptor and modify gene expression of glucocorticoids response elements. At immunomodulatory doses glucocorticoids suppress mononuclear-phagocytic activity (immediate effect), remove surface antibodies from target cells (immediate effect), and suppress the production of immunoglobulins (delayed effect). Common side effects of glucocorticoid therapy include HPA axis suppression, iatrogenic hyperadrenocorticism, gastrointestinal ulceration, urinary tract infections, pancreatitis, and diabetes mellitus (cats). Contraindications to steroid therapy include concurrent therapy with NSAIDs, due to the significant risk of gastrointestinal ulceration or perforation. Different types of glucocorticoids are commercially available, including prednisone, dexamethasone, budesonide, fluticasone, methylprednisolone, and long-acting esters.

Prednisolone is the active form of the prodrug prednisone. In cats treated with prednisolone, higher prednisolone plasma concentrations are achieved compared to those treated with prednisone. Cats have lower prednisone absorption and decreased conversion of prednisone to prednisolone, but there is no evidence documenting these differences’ impact on clinical response. The dose of prednisone used determines the pharmacological response. A physiologic response occurs at 0.1–0.2 mg/kg/day, an anti-inflammatory response occurs at 0.5–1.0 mg/kg/day, and an immunosuppressive response occurs at 2.0–4.0 mg/kg/day. Large dogs are especially sensitive to the steroid side effects; therefore, use the low end of dosage range or dose based on body surface area (do not exceed 60 mg/kg/m² or 80 mg/day). Cats have fewer and lower affinity glucocorticoid receptors and less observable clinical side effects; thus they can tolerate dosing at the high end of the dosage range.

Dexamethasone is 7 times the potency of prednisone. Dose calculated based on the targeted prednisone dose and divide by 7 to get the equivalent dexamethasone dose. Dexamethasone has no mineralocorticoid activity and therefore has less sodium retention, making it a good choice in animals with underlying heart disease or a history of congestive heart failure, hypertension, or concurrent hypoalbuminemia (higher risk for effusion formation). Dexamethasone is available as oral tablets and for parenteral administration as a sodium phosphate short-acting ester (dexamethasone SP). Relative to prednisone, dexamethasone is associated with an increased risk GI ulceration and bleeding.

Budesonide is an oral glucocorticoid with a high first pass metabolism but may be a good choice in treating IBD and chronic hepatitis in patients with significant side effects to other systemic steroids like prednisone. Budesonide has the potential due to its significant first pass metabolism for less severe systemic side effects, including PU/PD, polyphagia, weakness, and muscle atrophy, but does result in HPA suppression with chronic use.

Fluticasone (Flovent®) delivers a metered dose of aerosolized steroids for inhaled delivery. Overall it has less severe systemic clinical side effects, but it does suppress the HPA axis. Fluticasone is considered a good choice for treating inflammatory respiratory diseases like feline asthma or canine allergic bronchitis.

Methylprednisolone has no advantage over prednisone. Long-acting, injectable esters (depo-medrol or vetoalg) last weeks and do not allow controlled tapering and cannot be reversed once administered. The longer-acting steroids are best avoided in most cases.

Cyclosporine

Cyclosporine was initially used in veterinary medicine for kidney transplants and atopy but is now used in treating a variety of immune-mediated diseases as either a first- or second-line therapy. Cyclosporine is considered a first-line therapy for immune-mediated diseases like perianal fistulas (with concurrent ketoconazole), pure red cell aplasia, IMHAs with a severe initial presentation, or in many dermatological diseases, including pemphigus foliaceus and erythema multiforme. Cyclosporine inhibits T cell activation by initially binding with cytoplasmic cyclophyltin, forming a cyclosporine-cyclophylin complex that binds and blocks the function of calcineurin (serine/threonine
phosphatase), preventing dephosphorylation of the cytoplasmic component of the nuclear factor. This stops IL-2 production and complete T cell activation. By specifically decreasing IL-2, T cell proliferation is attenuated, including antigen-specific cytotoxic T cell proliferation. Side effects include gastrointestinal distress, hepatotoxicity, gingival hyperplasia, cutaneous fungal infections, neoplasia (~10% of transplant patients), and renal toxicity (humans). There is wide individual variability in GI absorption of cyclosporine that is in part due to oral formulation administered. Formulations available include Neoral® (cyclosporine modified), a microemulsion formulation with higher oral bioavailability, and Sandimmune®, an oil preparation with lower oral bioavailability. Due to the higher oral bioavailability, the microemulsion formulation is more commonly used. To evaluate for toxicity rather than therapeutic goal, trough cyclosporine levels (evaluated right before the next dose of cyclosporine is administered) can be monitored using a HPLC analytical method. The goal is for the patient’s trough cyclosporine levels to not exceed 400 ng/mL; this is based on the therapeutic goal of transplant patients, 200–400 ng/mL. The price of cyclosporine has decreased over the last several years, making it more affordable in small/medium-sized dogs and cats. Concurrent therapy with antifungal medication ketoconazole inhibits hepatic cytochrome P450 enzymes, decreasing cyclosporine metabolism; consequently concurrent cyclosporine and ketoconazole therapy increases cyclosporine blood levels while allowing a 50–75% dose reduction in cyclosporine, making cyclosporine therapy in larger dogs more affordable. Ketoconazole can cause hepatotoxicity, so when using this therapeutic regimen, monitor both cyclosporine levels and liver enzymes.

**Azathioprine (Imuran®)**

Azathioprine is primarily considered a second-line therapy for refractory immune-mediated diseases that are nonresponsive or incompletely responsive to prednisone or other immunosuppressives, or used to maintain remission in cases that are experiencing intolerable side effects of glucocorticoids or cyclosporine. Immune-mediated diseases in small animal veterinary species commonly treated with azathioprine include IMHA, IMT, IBD, and some dermatological disorders. Therapeutic levels require a *minimum* of 7–10 days after medication is started (may even take longer); therefore it may not be all that useful in an emergency situation. Azathioprine is a thiopurine analog that creates nonfunctional DNA and RNA. Azathioprine is metabolized to thiopurine antimetabolites that compete with endogenous purines for incorporation into RNA and DNA, disrupting DNA and RNA synthesis and suppressing T cell-mediated immunity in both humans and dogs. Azathioprine has a narrow therapeutic range, and side effects include gastrointestinal distress (diarrhea), reversible myelosuppression including leukopenia, thrombocytopenia, anemia (macrocytosis), pancreatitis, and hepatitis due to hepatotoxicity. Do not use azathioprine in cats due to severe myelosuppression.

**Vincristine**

Vincristine is used in refractory cases of immune-mediated thrombocytopenia. When used at lower than chemotherapeutic doses, vincristine stimulates megakaryocyte endomitosis, enabling maturation and release of mature platelets from the bone marrow. Significant side effects include gastrointestinal upset (anorexia, vomiting, and diarrhea), myelosuppression, and extravasation injuries when administered perivascularly, ranging from irritation to necrosis and tissue sloughing.

**Leflunomide (Arava®)**

Leflunomide is indicated in the treatment of immune-mediated polyarthritis, rheumatoid arthritis, and other immune-mediated diseases, including ITP, IMHA, and autoimmune/inflammatory skin disease. In human medicine it is also used in transplant medicine. Leflunomide is metabolized to an active metabolite, malononitriloamide, that is a selective pyrimidine synthesis inhibitor and an inhibitor of tyrosine kinase activity. Leflunomide is immunosuppressive and antiproliferative through inhibition of B and T cell proliferation, suppression of immunoglobulin production, augmentation of immunosuppressive cytokines (TGF-β), inhibition of proinflammatory cytokines, and interference with cell adhesion. Side effects include lethargy, GI upset (nausea, vomiting, and diarrhea) that is usually transient and responds to dose reduction, and elevated liver enzymes (a less than twofold increase that responds to dose reduction). The use of leflunomide is not recommended during pregnancy. Reported dosing in dogs is 2–3 mg/kg once a day.

**Human Immunoglobulin (ivHIG)**

Human immunoglobulin is ~90% biologically intact IgG, produced by pooling plasma of healthy human donors. It contains intact IgG (90%) and trace amounts of IgA, IgM, CD4, CD8, HLA molecules. The exact mechanism of action is unknown, but the IgG most likely blocks the Fc receptor on macrophages and effector cells, decreasing B cell auto-antibody production. Other affects may include down-regulation or modulation of antibody
production/response, inhibition of lymphocyte proliferation, and regulation of inflammatory mediators (complement and cytokines). The use of ivHIG allows adjunctive therapy for immune-mediated diseases without the risk of increased immunosuppression. Indications include immune-mediated disorders that are severe or refractory or for patients that develop adverse effects to classic immunosuppressive therapy. Reported efficacy in small animals is limited to severe refractory cases, including IMT and IMHA in dogs, and dermatological diseases, including pemphigus foliaceus, erythema multiforme, or toxic epidermal necrolysis in dogs and cats. Availability is limited (acquire through human pharmacy) and expensive (~$1,000/10g: 10g is enough to treat a 20kg dog at 0.5 g/kg, once). Side effects include allergic reaction secondary to the exposure of foreign proteins. Repeated treatment is not recommended but has been reported without adverse reactions. Other side effects reported in people include vomiting and fever. Reported dosing in dogs and cats is 0.5–1.5 g/kg, given slowly over 6–12 hours.

**Cyclophosphamide (Cytoxan®)**
Cyclophosphamide is a nitrogen mustard, an alkylating chemotherapy agent that alkylates DNA. It suppresses cell-mediated (T cells) and humeral immunity (B cells). The use of cyclophosphamide in treating immune-mediated disease is reserved for refractory cases with an underlying primary immune-mediated etiology and used as adjunctive therapy to other first- or second-line drugs. Side effects include sterile hemorrhagic cystitis, gastrointestinal upset, and myelosuppression.

**Danazol**
Danazol is a synthetic androgen (weak androgenic activity) that is thought to reduce the binding of immunoglobulin and complement red blood cells and platelets and decrease the expression of Fc receptors on macrophages. The details of its mechanism of action are unknown. Danazol is used as adjunctive therapy for refractory cases of immune-mediated anemia and/or thrombocytopenia (type II immune complex diseases). Danazol is considered synergistic with glucocorticoids. Side effects include hepatotoxicity, and virilization in females, and it is considered teratogenic (contraindicated during pregnancy).

**Therapeutic Considerations**
The goal of any immunosuppressive therapy is remission. Therapy begins with induction, followed by maintenance and a slow therapeutic taper. In some cases reinduction is necessary when the patient experiences a clinical relapse during therapeutic taper or once therapy is discontinued. Induction therapy includes first-line therapies, and severe life-threatening cases or those that respond poorly or are refractory to first-line therapy may require multidrug therapies (the addition of second- or third-line therapies).

Glucocorticoids are considered a first-line therapy for most immune-mediated diseases. The type of glucocorticoids chosen is a function of the underlying disease and disease severity. Examples include IBD (prednisone or dexamethasone ± budesonide), IMHA (steroids +/- cyclosporine, azathioprine), ITP (steroids +/- vincristine), polyarthritis (steroids +/- leflunomide), perianal fistula (cyclosporine and ketoconazole). Consider multidrug therapy in conjunction with initial therapy, in patients with severe disease at presentation (IMHA—intravascular hemolysis, slide agglutination, severe anemia with inability to successfully transfuse), patients with poor response or disease refractory to glucocorticoids, patients known to be glucocorticoid intolerant or to have significant side effects, and patients that relapse after drug withdrawal.

Common second-line therapies include cyclosporine and azathioprine. Other second-line therapies that are indicated based on specific underlying disease include budesonide (IBD, chronic hepatitis), vincristine, single dose (IMT), and leflunomide (polyarthritis). Common third-line drugs include ivHIG, cyclophosphamide, and danazol.

Rational choice of therapies is based on type of disease and disease severity, potential side effects, concurrent underlying diseases or organ dysfunctions, and available routes of administration. For patients with IMHA or IMT that are actively bleeding or hemolyzing, consider cyclosporine over azathioprine. Cyclosporine has a faster onset of action relative to azathioprine. For a dog with IBD that responds completely to prednisone, but the owner complains of profound PU/PD on systemic steroids, consider budesonide as a second-line therapy to maintain remission and enable a faster systemic steroid taper. Avoid cyclosporine in dogs with elevated liver enzymes. Consider dexamethasone versus prednisone in animals with a history of congestive heart failure or hypoalbuminemia. In patients that are anorectic, vomiting, or have diarrhea, consider injectable (dex SP); for patients with severe IBD that fail to or only partially respond to oral prednisone therapy, consider trying injectable steroids.
A typical therapeutic protocol is difficult to formulate, as all animals are individuals; therefore, standard therapeutic protocols need to individualize based on the animal’s clinical response. For induction consider an immunosuppressive dose of prednisone (2mg/kg/day) and monitor for positive response of clinical disease. Initially this may be daily or weekly. If no significant therapeutic response occurs within days to weeks, consider adding a second drug. If a good response is observed, maintain it at the initial dose until clinical signs resolve and the disease stabilizes (approximately 2 to 4 weeks). Once clinical signs resolve and disease stables with initial therapy consider tapering the prednisone dose by 25%. Monitor for relapse (clinical signs, quantitative evaluation), q 7 days after tapering. If the disease remains stable, maintain at the new dose for an additional 3 weeks. Reevaluate at 3 weeks, and if remission is maintained, taper further.

Guidelines for therapeutic tapering are as follows. As long as the disease is in remission, continue SLOW taper, tapering by 25 to 50% q 4 weeks; this may take 4 to 6 months. The goal is to treat with the lowest dose that maintains remission; thus some patients can be completely weaned off therapy, while others may require lifelong low-dose therapy. A slow taper is best. In cases with significant steroid side effects, consider adding a second drug to enable a quicker prednisone taper rather than a fast prednisone taper alone. Taper second- or third-line therapies similarly to glucocorticoids: in multidrug protocols taper the drug causing the most significant side effects first, taper the drug most likely NOT contributing to clinical remission next, taper the drug you feel was most responsible for clinical remission later. Do not taper multiple drugs concurrently in the event of a relapse, as you will not know which drug is most likely responsible for the relapse. The recommendation is to taper drugs in serial fashion.

In the case of a relapse during therapeutic taper, return to the dose or therapeutic combination that previously controlled the disease. Consider a slower taper. In multidrug protocols, the drug the most recently tapered is likely important in controlling the disease; therefore the next taper should focus on a different drug. When clinical relapse occurs once all therapies have been discontinued, consider reinduction at immunosuppressive doses and/or combination therapy (especially if significant side effects occur). A slower taper may be necessary. Once a patient has experienced a relapse, consider lifelong therapy at the lowest dose that will control the disease.