Autoimmune dermatologic diseases represent some of the most interesting and challenging problems seen in veterinary dermatology. Current advances in this area have primarily focused on the documentation of a few “newer” diseases, the delineation of the pathomechanism of various diseases (usually compared and contrasted with the disease in man), and the exploration of glucocorticoid alternatives for therapy.

**Therapies for Autoimmune- and Immune-Mediated Diseases**

Glucocorticoids remain the most predictably effective therapies for these diseases. However, the dosages required for long-term management are often associated with significant side effects. Major emphasis is continually being placed on finding adjunctive drugs to lessen steroid dosages or drugs to use as alternates to glucocorticoid therapy.

**Glucocorticoids**

**Canine:** 2–4 mg/kg/day prednisone or prednisolone to initiate therapy. The starting dose is usually dictated by the severity of the problem. We tend to start in the lower end of the range with large breed dogs (even for severe disease). This dosage is divided and given BID to minimize side effects and produce a more constant steroid influence throughout the day. After the first 1–2 weeks (assuming good response), the dose is usually reduced to 1–2 mg/kg for another 1–2 weeks, then to 0.5–1 mg/kg for 1–2 weeks, then this dose given once every other day for 2 weeks, then the dose is gradually decreased to the lowest every other day dose required to control the problem. The goal for maintenance should be < 0.25–0.5 mg/kg every other day. Cases that do not respond adequately to the higher induction dosages can be treated with oral dexamethasone (0.2 mg/kg/day) until significant evidence of improvement has been achieved. At that time, the patient is switched back to prednisone/prednisolone therapy for longer-term treatment. At least 40–50% of dogs receiving chronic glucocorticoids develop urinary tract infections. Urine should be cultured on a routine basis (e.g., once every 6 months while on therapy).

**Feline:** Prednisolone: 2–6 mg/kg/day to start. The goal for long-term, maintenance therapy is less than 1–2 mg/kg q 48 h. Alternatively, one can initiate therapy with methylprednisolone (0.8–1.5 mg/kg BID). Cats who do not respond well to more aggressive dosages of prednisone can be treated with triamcinolone acetonide (4 mg/cat/day or 0.3–0.75 mg/kg/day or 2–3 mg/kg q 12 hrs to start (usually 7–14 days). Once good response is achieved, taper to 0.1–0.2 mg/kg q 48–72 hrs or lowest every other day dose required to control symptomatology. Alternatively, oral dexamethasone can be used at a dosage of 2–4 mg/cat/day or 0.1 to 0.2 mg/kg/day to start. Once remission is achieved, use lowest every other day dose required to control symptomatology.

**Azathioprine**

Azathioprine is the most common steroid-sparing immunosuppressive drug used in the management of canine autoimmuneimmune/immune-mediated diseases in veterinary medicine. Azathioprine is generally used concurrently with glucocorticoids (dosages, as outlined above), with an overall goal of being able to eventually reduce the amount of glucocorticoid required to control the problem. It is uncommon to be able to control dermatologic problems with just azathioprine alone. Therapy is initiated at 2 mg/kg/day (or 50mg/m² per day) for 4–8 weeks until significant clinical improvement is noted. The dosage is then reduced to 2 mg/kg given once every other day. It may take 3–4 months to see the maximal benefit of azathioprine. Major toxicities: hepatotoxicity (usually seen within the first 1–4 weeks of therapy) and myelosuppression (more common when on daily therapy). Liver enzymes are examined pre and 2 and 4 weeks after initiation of therapy. CBCs and platelet counts are done every 2–3 weeks while on daily therapy, then 2 weeks after going to every other day therapy, then 3–4 weeks after this, then in 3 months, then 6 months, then every 6–12 months thereafter. The dose of azathioprine can be decreased by 25% for every 6 months of excellent disease control. However, the dosage is usually not reduced to less than 1 mg/kg every other day for long-term maintenance. Other rare toxicities reported include vomiting, diarrhea, pancreatitis, predisposition to infection, and neoplasia. Azathioprine is not used in cats because of the proven high incidence of myelosuppression with the drug.

**Chlorambucil**

Because of its high cost, chlorambucil has been used most commonly in cats and small dogs. Chlorambucil is often considered as an alternative to azathioprine because it is overall better tolerated. It is a steroid-sparing agent of choice in the cat. Side effects are uncommon and include myelosuppression, anorexia, vomiting, diarrhea, urticarial reactions, and hepatotoxicity. The dosage is 0.1–0.2 mg/kg/day along with prednisone/prednisolone, triamcinolone.
(cats), or dexamethasone (cats) at the glucocorticoid dosages outlined previously. Once approximately 75% remission has been achieved (usually 2–4 weeks), the dosage is reduced to every 48 hours. Monitoring for side effects (CBC, platelet count, and liver enzymes) is done every 2–3 weeks while on daily induction dosages. The frequency of monitoring is then dramatically reduced (e.g., 1–2 months after being on eod therapy; then in 3–4 months, then every 6 months thereafter).

**Cyclosporine**

Cyclosporine (Atopica, Novartis) is generally used at more aggressive dosages for the treatment of autoimmune- and immune-mediated diseases, compared to the standard 5 mg/kg/day that is used in the management of atopy in the dog and the cat. In our clinic, the goal for initiation of therapy is 3–5 mg/kg BID. We gradually work up to this dose over several days to reduce the incidence of gastrointestinal side effects (vomiting). It is also initially given with food to reduce the incidence of GI upsets. Once we are convinced that the drug is being well tolerated, it is given at least 2 hours before or after feeding to enhance absorption. Lower dosages of the drug may be given when individuals are concurrently treated with ketoconazole (i.e., 2.0 to 2.5 mg/kg cyclosporine BID along with 5–7 mg/kg/day of ketoconazole), but this combination may produce a higher incidence of gastrointestinal side effects. Once good control has been achieved on BID therapy, the dosage can be reduced to once daily and then once every other day therapy. Side effects in the canine include a wide variety of gastrointestinal upsets (vomiting, diarrhea, abdominal pain, flatulence, borborygmus), uncommonly gingival hyperplasia, papillomatous, hirsutism, and rarely trembling, hepatopathy, lameness, opportunistic infections (bacterial, fungal), toxoplasmosis (feline), giardiasis, and neoplasia. If there is concern about lack of response or potential toxicity, cyclosporine blood trough levels can be evaluated (blood sample taken just before dosing); goal for immunosuppression is 200–500 ng/ml. Note: When using a specific radioimmunoassay or HPLC, true cyclosporine concentrations are measured. When using TDx fluorescence polarization assays (monoclonal whole blood), multiply the feline concentrations by 0.5 to get the true concentrations, and multiply the canine concentration by 0.6 to get the true concentration.

**Tacrolimus (Protopic, Fugisawa)**

0.1% used topically BID to initiate therapy. 10–100 times as potent as cyclosporine. The product is used sparingly (a little bit goes a long way). Very well tolerated. On occasion, may see some irritation. Once maximal benefit is noted on BID therapy, the frequency is gradually reduced to once daily, then once every other day.

**Gold Salts**

Gold salts are available as an injectable form (sodium aurothiomalate; Myochrysine, Merck) and an oral form (auranofin; Ridaura, SmithKline Beecham). Injectable gold salts are given at a dosage of 1 mg/kg/week IM. Clinical responses are generally noted within 8–12 weeks. If no response is noted by 10–12 weeks, then the dosage is increased to 1.5–2.0 mg/kg. Therapy is continued until the completion of a 20-week trial. Once a good response is noted, the frequency of administration is slowly decreased, with final maintenance injections being given every 2–8 weeks (most commonly monthly). Oral gold salts do not appear to be as effective as the parenteral drug. Oral gold salts are started at a dosage of 0.05–0.2 mg/kg q 12 hr. Because of the significant lag phase to the onset of activity, gold salts are initially used concurrently with glucocorticoids. The goal is to eventually attempt to discontinue glucocorticoid therapy. Side effects are uncommon; they include thrombocytopenia, nephropathy (heralded by the development of a proteinuria), toxic epidermal necrolysis, erythema multiforme, sterile abscesses at injection sites, and eosinophilia. A CBC, serum chemistry panel, and urinalysis are done q 2–3 weeks for the first 2 months of therapy, then monthly for a couple of months, then q 4–6 months thereafter.

**Tetracycline and Niacinamide**

Both drugs are used for their anti-inflammatory effects. The dosage is 500 mg of both tetracycline and niacinamide per dog (250 mg/kg if < 10 kg) given TID for a 3-month trial. TID therapy is maintained until maximal benefit is noted. The dosage is then decreased to BID for 2 months, then once daily. If control remains outstanding on once daily therapy, an attempt is made to stop the niacinamide and treat with tetracycline alone. Side effects of the combination are uncommon. They include anorexia, vomiting, diarrhea, hyperexcitability, depression, seizures, and lameness. Alternatively, tetracycline may be replaced with doxycycline, 5–10 mg BID.

**Pentoxifylline**

Pentoxifylline, a methylxanthine derivative, is noted to lower blood viscosity and improve erythrocyte flexibility. It is also noted to have anti-inflammatory effects. The dosage is 10–25 mg/kg given BID or TID. It is generally given with food. Its major side effect is vomiting. Trial period for therapy is 6–8 weeks.
**Mycophenolate Mofetil (Cellcept, Roche Laboratories)**

Mycophenolate was developed, in part, as a non-myelotoxic replacement for azathioprine in human allograft patients. In dogs, it has been primarily used as a steroid sparing drug, starting at a dosage of 10 mg/kg BID (or 20 mg/kg divided and given 3 times daily) for the first 4 weeks. If response is not significant, the dose can be gradually taken to a total of 40 mg/kg/day (again divided). Once response has been noted, attempts should be made to reduce the dose to 10–20 mg/kg/day (divided) for longer-term control. Although the drug is not expected to produce significant myelosuppression, hepatotoxicity, or pancreatitis, it has been associated with GI hemorrhage, anorexia, and diarrhea, the development of secondary bacterial pyoderma, and Malassezia dermatitis. It is very expensive.

**Leflunamide**

Leflunamide is a synthetic organic isoxazole that the intestinal mucosa metabolizes to an active form. It suppresses lymphocyte function. In dogs, it is given at a dose of 2–4 mg/kg/day (start at 2 mg/kg/day and gradually worked up, if necessary). The dose can be adjusted as needed to obtain a 24-hour serum trough level of 20 microgram/ml (although this is not commonly done in veterinary medicine). Side effects are primarily related to gastrointestinal upsets (lesser incidence at lower dosages).

**Human Intravenous Immunoglobulin (IVIG) Therapy**

High-dose intravenous immunoglobulins have been used in human immune-mediated and autoimmune diseases as an alternative or adjunctive therapy. IVIG is a highly purified IgG preparation made from pooled human plasma and contains more than 95% unmodified IgG. Human IVIG is thought to work by saturating Fc receptors on macrophages and by binding to T and B cells, thereby modulating their function. However, their true mode of action is not known. IVIG (6% solution) is given at a dose of 1 mg/kg (0.5–1.5 mg/kg) IV over a 6–12 hour period once or can be given 2 days consecutively. Although it is possible that it could be repeated monthly as it is used in humans, the safety of this regimen has not been determined in dogs. The therapy appears to be well tolerated in dogs. In humans, side effects include headache, myalgia, flushing, nausea, and tachycardia. It is very expensive.

**Pemphigus Complex**

The pemphigus complex represents several varieties of pemphigus seen in dogs and cats. In humans, the pathogenesis of pemphigus involves the production of antibodies (IgG) directed against desmogleins (transmembrane glycoproteins of desmosomes, which are organelles important in cell to cell adhesion). In dogs it has been shown that IgG binds to the extracellular section of desmosomes, but the identity of the major canine PF antigen(s) remains unknown. The diseases are typified by separation of keratinocytes (acantholysis) and the formation of acantholytic keratinocytes (usually more round than normal keratinocytes). Differentiation of these diseases is often accomplished through both clinical distribution and histologic changes. The region of the epidermis targeted for acantholysis differs with the disease (e.g., subcorneal with pemphigus foliaceus, suprabasilar with pemphigus vulgaris). Because dermatohistopathology is reasonably accurate in defining these problems, direct immunofluorescence or immunoperoxidase staining of tissues to document the deposition of autoantibody or indirect immunofluorescence to determine the presence of auto-antibodies in the serum are not commonly done, even in specialty practice. The improvement and utilization of these techniques have shown variable homology between the diseases seen in humans and dogs and cats. In the past, positive indirect immunofluorescence was thought to be uncommon in dogs. However, with improved techniques, pemphigus foliaceus IgG4 anti-keratinocyte auto-antibodies are commonly detected in the serum. Serum titers correlate with severity of clinical signs and are suppressed with therapy (much as in humans).

**Pemphigus Foliaceus (PF)**

**Canine Pemphigus Foliaceus**

Canine pemphigus foliaceus is a pustular disease that is manifest clinically as pustules (usually transient) or areas of inflammation and crusting (where pustules have been). Mean age of onset has been reported as 4 years and 6 years in various studies. There does not appear to be any sex predisposition. There does appear to be a genetic predisposition to the disease. A high incidence is noted in the akita, chow chow, cocker spaniel, Australian shepherd, bearded collie, Newfoundland, schipperke, doberman pinscher, and Finnish spitz. A small number of cases have been noted to be initiated by drug reactions. There are anecdotal reports of food sensitivity exacerbating the disease. UVB irradiation has been noted to produce acantholysis in the nonlesional skin of an affected individual, which may explain the seasonal waxing and waning of signs (worse in summer) noted in one
PF tends to have one of 4 distributions on clinical presentation: face and ears, pad skin junctions and foot pads, and groin, then becoming more generalized; a generalized form; a chronic facial form (restricted to the face); and a form restricted to the feet (rare) or claws (very rare).\(^7\) Pruritus is noted in one-quarter to one-half of dogs and can be severe (especially in the generalized form). PF can be complicated by secondary bacterial infection. Improved survival time was seen in individuals treated with concurrent antimicrobials during the initiation of immunosuppressive treatment.\(^6\) This was not noted in another retrospective study of a large number of dogs.\(^7\)

The histopathology of PF shows subcorneal, intragranular, and upper spinous cell layer pustules with large numbers of acantholytic keratinocytes, neutrophils, and variable numbers of eosinophils (may be large numbers). It is important to note that a few acantholytic keratinocytes may be seen with any suppurative epidermal process such as bacterial pyoderma, but numbers are few. Trichophyton mentagrophytes infections have rarely been noted to produce significant numbers of acantholytic keratinocytes. For this reason, the author routinely does special stains for dermatophytes and fungal cultures on suspect or confirmed PF cases. In general, the pustules of PF are large and span the length of multiple follicular units, a finding that differentiates these lesions from those of bacterial folliculitis.

Topical therapies for PF have included topical glucocorticoids or topical 0.1% tacrolimus for focal lesions (usually adjunctive therapies). Oral glucocorticoids are the most rapidly and predictably effective therapies. Prednisone or prednisolone are used most commonly (2 to 6.6 mg/kg given once or divided and given twice daily—the author routinely starts at 2–3 mg/kg/day; lesser dosages for larger dogs). More refractory cases are treated with oral dexamethasone or triamcinolone. Emphasis is placed on eventually using the lowest every other day dose to control the problem. In one study, complete remission was achieved with oral glucocorticoid monotherapy in 15 of 39 dogs (38%) within 1.5–12 months (average, 7 months).\(^8\) In another study, glucocorticoid monotherapy produced acceptable long-term control in about 35% of cases.\(^8\) Adjuvant therapies primarily used to reduce glucocorticoid dosages include azathioprine (most commonly used adjunctive therapy; 2–2.5 mg/kg PO once daily; eventually reduce to once every other day therapy) or chlorambucil (0.2 mg/kg every 24–48 hrs). Complete remission was achieved with a glucocorticoid-azathioprine combination in 18 of 33 dogs (55%) within 2–29 months (average, 12 months) of starting therapy. The addition of azathioprine did not lead to a significant difference in the time needed to achieve remission compared to the use of glucocorticoids alone.\(^7\) There are anecdotal reports of azathioprine or chlorambucil being effective when used alone (without glucocorticoids), but this has not been the author's experience. Tetracycline or doxycycline and niacinamide only rarely control patients with the generalized form of the disease.\(^1\) In the author’s experience, they tend to benefit a higher percentage of dogs with the chronic facial form of the disease. These drugs may occasionally be of benefit as adjunctive therapy to reduce other immunosuppressive drug dosages. Oral cyclosporine, to date, has not performed well in managing PF. A recently reported pilot study evaluated the efficacy of oral cyclosporine (5–10 mg/kg once daily) in 5 dogs with PF.\(^9\) Four dogs did not complete the study because of lack of efficacy; one dog had a transient benefit. It is not known whether higher dosages would have been associated with an improved response (+/− use of ketoconazole to achieve these higher dosages). In the author’s experience, higher initial dosages (e.g., 5–10 mg/kg BID), regulated with blood trough evaluations of cyclosporine concentrations, may produce a significantly higher success rate. It is also not known whether cyclosporine can be used as an adjunctive therapy with glucocorticoids to help reduce glucocorticoid dosages. Mycophenolate mofetil has also been used to treat PF, but with only partial responses. Eight dogs with PF were treated with mycophenolate mofetil at 20–40 mg/kg per day divided into 3 daily doses. A reduction in lesional area/severity was seen in 3 dogs. Four dogs did not complete the study. All dogs required concurrent glucocorticoids to control signs.\(^8\) There are anecdotal reports of the successful use of dapsone and sulfasalazine as sole therapies or in combination with glucocorticoids, but their efficacies have not been proven. Human intravenous immunoglobulin has been used in humans to treat pemphigus vulgaris. This therapy has been used in dogs to treat other immune-mediated diseases. There is a report of the successful management of a dog with severe pemphigus foliaceus utilizing intravenous human immunoglobulin.\(^1\)

The prognosis for treated pemphigus foliaceus is guarded. In one study, 17/43 (39%) of cases were alive at the end of 6 years. Of those that died, 92% were dead by 1 year into treatment. Of the dogs that died, 18 of 26 (69%) were euthanized because of intractable disease, poor quality of life, or side effects of therapy. Survival beyond the tenth month of treatment predicted for longer-term survival, suggesting that patience and persistence during the early
months of therapy can be rewarded with an improved outcome. In contrast to these lower survival rates, another study showed a 71% survival rate after one year in 31 dogs. Only 4 dogs were euthanized. In yet another retrospective study of 88 dogs treated for PF, 46 (52%) underwent complete remission, 31 (35%) achieved partial remission, and only 11 (13%) were euthanized due to lack of response, unacceptable side effects of medications, and unrelated reasons.

In some dogs, immunosuppressive therapy can eventually lead to long-term remission, without drugs. In a group of 51 dogs with PF, 6 cases were treated into remission over 1.5 to 5 months with immunosuppressive doses of oral glucocorticoids or glucocorticoids and azathioprine. Dosages were then gradually tapered and discontinued (total duration of therapies being 3 to 22 months). Skin lesions were not noted to recur for 1.5–6 years.

Pemphigus foliaceus is the most common autoimmune disease seen in cats. The age of onset for feline PF ranges from less than 1 year to 9 and 17 years respectively (median, 5 years). The pathomechanism of the disease has not been as well researched and defined as in dogs. Drug-induced/triggered PF has been seen. Although the disease is pustular in nature, pustules are only rarely encountered on a clinical basis (lesions are inflammatory and crusty). Initial and most commonly affected areas are the head/face, ears, paws, nail folds, dorsum and ventrum, legs, chin, and tail (in decreasing order of incidence). Pruritus is mild to severe in 80%. Biopsies show evidence of acantholysis in the majority of cases. Mast cells and eosinophils are a common part of the dermal inflammatory response (at times resulting in the problem being misdiagnosed as allergic disease). Glucocorticoid monotherapy is usually effective for achieving clinical remission. Prednisolone (4–5 mg/kg/day) and triamcinolone (0.6–2 mg/kg/day) are the historically favored glucocorticoids. In one study, complete remission of PF lesions occurred in 15 of 15 cats (100%) using triamcinolone alone and 8/13 (62%) using prednisone alone. Lesser side effects were seen with the triamcinolone-treated cats. In cats whose PF fails to respond to glucocorticoids, chlorambucil (0.2 mg/kg PO once daily) is the immunosuppressive most commonly used. Nine of eleven (82%) PF cats responded to the combination of chlorambucil and glucocorticoid. PF has also been noted to respond to gold salt therapy (aurothioglucose). It would appear that cats with PF more commonly achieve a good response to these various therapies and are better maintained in remission (with fewer side effects), when compared to dogs.

Pemphigus Erythematosus (PE)
PE is an uncommon disease confined to the face and clinically resembling discoid lupus erythematosus. It is considered by some to be a crossover disease because histologic and immunodiagnostics show changes consistent with both PF and lupus. Cases may be ANA positive. It has recently been suggested that there may indeed be insufficient evidence to differentiate what has been described as canine PE from localized facial PF. Therapies are as for DLE (sunscreens, sun restriction, topical glucocorticoids, oral glucocorticoids, glucocorticoids, and azathioprine). More recently, topical tacrolimus (0.1%, Protopic; Fugizawa) has also been noted to be effective in controlling this disease. PE has been reported only rarely in cats.

Panepidermal Pustular Pemphigus (PPP)
PPP is a histologic variant of PF wherein the acantholytic process extends from the subcorneal/intragranular areas to the supra basal area. Lesions may be restricted to the face or may be generalized. It has more recently been suggested that there is little evidence to support the separation of canine PPP from PF.

Drug-Related Pemphigus
In drug-related pemphigus, the pemphigus is caused by the drug administration. In humans, drug-related pemphigus appears to fall into 2 categories. In drug-induced pemphigus, discontinuation of the drug usually results in resolution of the signs. In drug-triggered pemphigus, pemphigus develops in an individual who is genetically more susceptible to the disease. Discontinuation of the drug does not result in resolution, and the disease must be treated as for spontaneous pemphigus. Similar pathomechanisms appear to occur in dogs and cats, although it has been pointed out that the strength of evidence supporting drug causation for rare cases of PF in dogs and cats is weak. Trimethoprim-sulfonamides are the most common drug group noted to produce the problem in dogs; penicillins (amoxicillin, ampicillin) in cats. Although all forms of pemphigus can potentially be triggered in this fashion, PF and PV are most common.
*Pemphigus Vulgaris (PV)*
PV is rarely encountered in both dogs and cats. Most cases begin within the oral cavity, but they can also involve mucocutaneous junctions and can be more generalized. PV tends to be more refractory to immunosuppressive therapy than PF.

*Paraneoplastic Pemphigus (PP)*
This disease has been very rarely encountered in dogs. Cases to date have been associated with thymic lymphoma, cutaneous lymphoma, sertoli cell tumor, and mammary carcinoma. The clinical presentation appears to be a crossover between PV (oral cavity involvement) and erythema multiforme both clinically and histologically.

References