Pemphigus: current therapy

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Abstract Pemphigus is an autoimmune skin disease that can present in a variety of forms and can be a challenging disease to manage and treat. An overview of the different forms of pemphigus and diagnostics are discussed including pemphigus foliaceus (PF), pemphigus erythematosus (PE), panepidermal pustular pemphigus (PPP), pemphigus vulgaris (PV) and paraneoplastic pemphigus (PNP). Emphasis on therapy is presented. Included are the most current commonly used therapeutics (glucocorticoids, azathioprine, chlorambucil and tetracycline and niacinamide); current alternative therapeutics (cyclosporin and tacrolimus and mycophenolate mofetil) and additional alternative therapeutics (cyclophosphamide, chrysotherapy, dapsone, sulfasalazine and intravenous immunoglobulin (IVIG) therapy).

Keywords: azathioprine, chlorambucil, chrysotherapy, cyclosporin, dapsone, glucocorticoids, mycophenolate mofetil, pemphigus, tacrolimus, tetracycline and niacinamide.

OVERVIEW OF DISEASE

Pemphigus is an autoimmune vesicobullous to pustular skin disease that is characterized by acantholysis or loss of adhesion between keratinocytes. In dogs and cats five forms are recognized: pemphigus foliaceus (PF), pemphigus erythematosus (PE), panepidermal pustular pemphigus (PPP), pemphigus vulgaris (PV) and paraneoplastic pemphigus (PNP). Pemphigus foliaceus (PF) is the most common form in dogs and cats (Fig. 1). It is seen at the author's practices at an incidence of 2% of referral cases. Clinical lesions are variable and include pustules, crusts, erosions, ulcers and alopecia. However, clinical presentations may vary depending on the breed, triggering factors and the cyclical nature of the disease itself. Lesions include pustules, crusts, erosions, ulcers and alopecia. Some cases may remain localized to the head, face and pinnae, while others may generalize and develop additional systemic symptoms. The foot pads can become involved and in some situations lesions can be limited to the footpads. An idiopathic form is most commonly seen in chow chows, and akitas. It tends to present with more generalized lesions often starting on the face, nasal planum, pinnae and can spread to involve the entire body. When generalized, limb oedema, fever and lethargy are common. Pruritus is also more common in the generalized form. Some cases can be triggered by drug reactions or as a result of other chronic diseases such as allergic dermatitis. The drug-induced form is more common in the Doberman pinscher and Labrador retriever. Many cases of PF attributed to chronic disease have often been treated with long-term drugs and may in reality reflect drug-induced cases. Pemphigus erythematosus (PE) is considered to be a variant of PF is limited to the face and does not generalize. PE can look similar to PF histologically but may also show an interface dermatitis. This feature coupled with a combination of immunopathology of both PF and lupus erythematosus as well as a positive ANA (antinuclear antibody) test in some cases, make this form a possible cross over syndrome. However, this is controversial and may simply represent a localized form of PF. Collies and German shepherds may be predisposed. Photoaggravation may be a factor in PE. Pemphigus vulgaris (PV) is a very rare form of pemphigus accounting for less than 0.1% of the referral
cases in a dermatology specialty practice. It is the most severe form of pemphigus and is characterized by vesicles or blisters that usually ulcerate. The most common location of lesions is the oral cavity, axilla, groin, flank, mucocutaneous junctions (lips, nostrils, eyelids, nail beds, genitals and anus) and foot pads. These cases may present with marked salivation and halitosis and are often depressed and anorectic. This form requires the most aggressive forms of combination therapy.

Panepidermal pustular pemphigus (PPP) has been described based on the presence of pustules found at all levels within the epidermis and follicle epithelium. PPP may simply represent a variant of PF, PE or pemphigus vegetans (Hallopeau type) a variant of PV. Clinically there is predominance for facial lesions but generalized disease can occur. Lesions are short-lived pustules that rupture and leave a thick adherent crust.

Paraneoplastic pemphigus (PNP) is a very rare form of pemphigus that has been associated in a limited numbers of dogs with lymphoma and in one case a Sertoli cell tumour. Histopathologically, these lesions appear to be a mixture of PV and erythema multiforme (EM).

AETIOLOGY – PATHOGENESIS

The aetiology of pemphigus is not known in most cases. The development of autoantibodies may result from an abnormal immune regulation or abnormal antigen stimulation. There is a strong genetic predisposition in both humans and dogs. In humans certain HLA types and ethnic groups seem to be predisposed to PF. Certainly the akita and the chow chow appear to fall into this category, having PF more frequently than other breeds. Infectious agents, such as viruses have been suspected in certain regionalized outbreaks. Of specific interest is the PF seen in humans in South America (fogo selvagem) where an insect vector (black flies), virus or local heat, humidity and tannin decomposition are suspected as predisposing factors.

It is interesting to compare this form of PF in humans with what is seen in the dog. There are many similarities between the two when the clinical lesions are compared. Drug induced or association with chronic skin disease has also been reported in humans and dogs. The possibility of ultraviolet light irradiation exacerbating acantholysis also exists.

The exact mechanism for the development of acantholysis is not completely understood. The patient's autoantibodies bind to one of two members of the cadherin group (cell to cell adhesion molecules). In PF the binding is to Dsg 1 and to Dsg 3 in PV. Calcium has been shown to be very important for the adhesion of cadherins. The binding of the autoantibody to the cadherins results in activation of intracellular pathways, which in turn leads to the disruption of intracellular adhesion. This results in the acantholysis. There are many different possible causes for this disruption. The release of the protease, urokinase plasminogen activator (uPA) is thought to convert plasminogen to plasmin which damages the intercellular adhesion. Complement may be involved in some cases, but may just be an enhancing factor as lesions can occur in its absence. One of the most current thoughts is a disruption in the regulation of the assembly and disassembly of the desmosomes by the binding of the autoantibodies.

OVERVIEW OF DIAGNOSTIC METHODS

The hallmark of the pemphigus complex is the histological presence of acantholysis. In PF either intraepidermal or intrafollicular acantholytic pustules are present. These pustules are most common in the corneal, granular or upper spinous cell layers. In PE subcorneal to intrasinuous acantholytic pustules are also present, but a lichenoid-interface dermatitis is usually present. In PV the acantholysis is at the suprabasalar level which can occur in the oral mucosa, epidermis or follicular outer root sheath. In PPP intraepidermal pustules can be seen at all levels of the epidermis and follicular outer root sheath down to the level of the suprabasal layer. Eosinophils may be more abundant in this form. In PNP there are similar changes as seen with PV, but in addition to the suprabasal cleft formation, apoptotic cells and vascular degeneration is present.

Immunopathology, both direct and indirect immunofluorescence, has improved tremendously and has not only aided in the diagnosis of pemphigus but the pathogenesis of the disease. In many cases, antikeratinocyte autoantibodies can be demonstrated. However, immunopathology should always be correlated with the clinical and routine histopathology findings. In PF the pattern of immunofluorescence is 'chicken-wire' involving all of the suprabasal layers. The autoantibodies are usually of the IgG type with some cases having IgA and IgM. Complement may sometimes be present. In the dog, desmoglein 1 (Dsg 1) 150 kDa is the autoantigen that is targeted. In PE, the antikeratinocyte fluorescence is the same as in PF, however, there is a linear deposition of immunoglobulins and/or complement similar to what is seen in lupus erythematosus. A positive ANA can also be detected in 50% of cases. In PV there is also membrane fluorescence of the keratinocytes of all suprabasal epidermal layers, which may extend to the basal cell membranes. The major PV antigen in the dog is desmoglein 3 (Dsg 3) 130 kDa. The immunopathology of PPP is identical to that of PF and PNP is the same as PV.

Other clinicopathology includes the presence of acantholytic cells on routine cytology and variable changes on complete blood counts and chemistry laboratory screens. Many pemphigus cases can have moderate to marked leukocytosis and neutrophilia, mild nonregenerative anaemia, mild hypoalbuminemia and mild elevations in globulins.
CURRENT TREATMENTS

Therapy for all forms of pemphigus requires immunosuppressive or immunomodulating drugs. There are variable responses to treatment with the different forms of pemphigus recognized. As a result it is essential that a diagnosis be made.

Even with a specific diagnosis there appears to be some controversy regarding the treatment success and the ultimate long-term prognosis of canine pemphigus. In general, PV tends to be a more aggressive disease and more difficult to treat and manage. Despite treatment many cases may still die. PF tends to warrant a better prognosis but in a recent report only 17/43 cases (39.5%) were alive at the end of a 6-year study. Of the dogs that had died, 92% were dead by 1 year into treatment. Of these cases, 87% were euthanized because of drug side effects.22 These results are different from what is seen at the author’s practices. Currently, a large-scale retrospective PF study is being conducted at the author’s practices. An initial review of 31 cases with follow-up ranges from 1 to 5 years and a mean of 2.7 years, showed a survival rate of 22/31 (71%). Of the 9 cases (29%) that had died, 4/9 (44%) were euthanized at the end of 1 year because of either poor response to therapy (2/4) or discontinuation of medications and subsequent relapse after the owners discontinued drugs (2/4). The remaining 5/9 cases died because of unrelated problems; heart disease (2), renal disease (1), arthritis (1), old age (1). Many specialists and researchers consider PE, PEP and P vegetans benign variations unrelated problems; heart disease (2), renal disease (1), arthritis (1), old age (1). Many specialists and researchers consider PE, PEP and P vegetans benign variations of pemphigus that usually respond well to treatment and have less overall systemic manifestations.1,8

The author divides therapy into three categories: common therapeutics, current alternative therapeutics and additional alternative therapeutics.

COMMON THERAPEUTICS

Glucocorticoids

More localized forms of PF and PE can be treated with topical glucocorticoids. Occasionally, the author uses topical therapy in conjunction with systemic therapy on more persistent focal areas that remain active despite systemic treatment. When utilized a potent glucocorticoid is often needed initially and then if adequate response is seen switching to a less potent topical glucocorticoid is recommended. The author likes 0.1% amcinonide cream (Cyclocort, Lederle), fluocinonide 0.05% cream (Lidex, Dermik) or 0.015% triamcinolone acetonide solution (GENESIS, Virbac) used daily for 7 days then EOD for 7 days and if an adequate response is seen switching to a 1–2% hydrocortisone cream or ointment (Hytong, Dermik and other generics) on an as-needed basis is recommended. Some 1% hydrocortisone gels and sprays may also be helpful in long-term management (Corticalm, Cortispray DVM Pharmaceuticals, Resicort, Virbac). Persistent use (daily for 14 days or longer) of more potent topical glucocorticoids can create atrophy, alopecia and localized pyoderma. Systemic absorption by percutaneous absorption or ingestion via licking is also a major concern. Iatrogenic hyperadrenocorticism has been well documented with potent glucocorticoids.23,24 The most common form of therapy used in pemphigus management is systemic glucocorticoids. In the author’s specialty referral practices, 35% of the PF cases are adequately controlled with only glucocorticoid therapy. There are unlimited mechanisms as to why glucocorticoids are effective but it primarily relates to their profound effects on the humoral and cell-mediated immunity, phagocytic defences, and inhibition of inflammatory mediators and suppression of autoimmune body levels.25,26 Which form of oral glucocorticoid therapy is selected depends on the individual case response and the side effects seen in that particular patient. Most commonly, prednisone or prednisolone is utilized at immunosuppressive dosages. Initial dosages at 2.2–4.4 mg kg−1 every 24 h can be used. If a response is seen within 10–14 days this dosage is reduced gradually on a daily basis over 30–40 days and then lowered to an alternate day basis with the ultimate goal of dosing at 1 mg kg−1 every 48 h or less. The author prefers methylprednisolone (Medrol, Pfizer) to prednisone or prednisolone due to the reduced mineralocorticoid effects resulting in less polyuria and polydipsia. In addition, there are some cases that will respond more favourably to methylprednisolone than prednisone or prednisolone. The dosing and tapering regime is the same as for prednisone or prednisolone. Oral triamcinolone (Vetalog, Fort Dodge) or oral dexamethasone (Azium, Schering-Plough and generics) are alternative glucocorticoids that can be utilized in more refractory cases or in cases that have profound polyuria and polydipsia or other behaviour or personality changes. These glucocorticoids are considered to be 6–10 times more potent than prednisone or prednisolone. Starting immunosuppressive dosages for these drugs range from 0.2 to 0.6 mg kg−1 every 24 h for triamcinolone and 0.2–0.4 mg kg−1 every 24 h for dexamethasone. As with prednisone therapy these dosages need to be reduced gradually and eventually tapered to an every 48–72 h basis. As these glucocorticoids suppress the hypothalamic–pituitary–adrenal axis for 24–48 h, it is optimal to give these drugs every 72 h for maintenance. However, the author has had many cases do very well long-term on an every 48 h basis as maintenance. Maintenance dosages range from 0.1 to 0.2 mg kg−1 every 48–72 h for triamcinolone and 0.05–0.1 mg kg−1 every 48–72 h for dexamethasone.

In severe cases of pemphigus foliaceus or vulgaris, the author has, on occasion, given shock dosages of prednisolone sodium succinate (10 mg kg−1 IV) or dexamethasone (1 mg kg−1 IV).2 This can be performed as a one time treatment or given two days consecutively. This can be followed with a modification of other oral glucocorticoid therapy. This form of therapy has a higher incidence of gastrointestinal ulceration, in particular gastric haemorrhage. Concurrent use of gastric...
protectants is usually recommended when this form of therapy is utilized.

Side effects are common with long-term oral glucocorticoid therapy. The most common seen include: poor dull scaly hair coats, muscle atrophy, polyuria, polydipsia, polyphagia, weight gain, behavioural changes, panting and increased risk of infection. Secondary bacterial skin and bladder infections are common. Demodicosis and dermatophytosis are also more frequent in dogs on chronic glucocorticoid therapy. Ongoing cases that flare during their course of management should always be rechecked and screened for these secondary opportunistic infections. Other skin changes include atrophic skin, calcinosis cutis, atrophic scars, comedones and 'milia' follicular cysts. Less common side effects include: gastrointestinal ulcerations, diarrhoea, and pancreatitis. Steroid hepatopathy is a major concern and is one of the most important organs to monitor in long-term cases. Other endocrine concerns include the development of diabetes mellitus, adrenal gland suppression and reduced thyroid hormone production.

Monitoring should include semi-annual complete blood counts, chemistry profiles, urinalysis and urine cultures. If cases are nonresponsive to glucocorticoids, fail to control on safe alternative day to every 72 h dosing or have undesirable side effects, alternative or concurrent immunosuppressive drugs are indicated.

**Azathioprine therapy**

Azathioprine (Imuran, Glaxo Wellcome and generics) is the author’s favourite and first choice immunosuppressive to use in canine pemphigus cases. The author has not seen any differences with brand name or generic therapy. It can be used as a glucocorticoid-sparing agent in cases when glucocorticoids cannot be reduced to safe long-term levels, used in combination with glucocorticoids or other immunosuppressives in more refractory cases, or as a sole therapy (Figs 2, 3). It is generally contraindicated in cats due to its more profound myelosuppression and potential for fatal reactions in cats. It is dosed at 1.5–2.5 mg kg\(^{-1}\) every 24–48 h. It is available is a 50 mg scored tablet. It is an antimetabolite that interferes with the synthesis of nucleic acids and is cytotoxic to T cells. It has its greatest effect on T-cell-dependent antibody synthesis. It has a slow onset of action and usually takes 4–8 weeks to see clinical effects. Adverse reactions primarily include myelosuppression (lymphopenia, anaemia and leukopenia) diarrhoea and increased susceptibility to opportunistic infections when used long-term (pyoderma, demodicosis and dermatophytosis) (Fig. 4). The diarrhoea that can be seen usually responds to dosage reduction, although it can be severe (haemorrhagic) and require drug discontinuation. Less common complications include vomiting, hepatotoxicity and possible pancreatitis. A rare azathioprine induced hepatotoxicity can be seen that usually responds to drug withdrawal.\(^2\) Dosage adjustments can be made based on the results of lab monitoring and clinical improvement. Starting at the lower end of the dosage range is generally recommended. Increasing the dosage after subsequent rechecks and lab monitoring can be performed as the case progresses. Complete blood counts with platelet counts are recommended every
2–3 weeks for the first 3 months of therapy. Initially periodic (every 2–3 months) monitoring of chemistry profiles is also recommended. Once cases are in remission monitoring can be reduced to every 6 months.

**Chlorambucil**
Chlorambucil (Leukeran, Glaxo Wellcome) is an alkylating agent that functions by affecting the cross-linking of DNA. It is considered less toxic and slower acting than other alkylating agents. It is dosed at 0.1–0.2 mg kg\(^{-1}\) every 24–48 h. It is available in a 2 mg scored coated tablet, making dosing in small dogs and cats easier. Myelosuppression is a concern and similar monitoring as listed with azathioprine should be performed. Other side effects include vomiting, diarrhoea and anorexia.\(^5\)\(^7\) The author uses chlorambucil in the canine as a glucocorticoid-sparing drug, as an alternative to azathioprine, in combination with glucocorticoids and azathioprine in more refractory cases or as a sole therapy in cases not tolerating other therapies. It is also the author’s drug of choice in feline pemphigus when glucocorticoids do not work or are not tolerated.

**Tetracycline and niacinamide**
The combination of tetracycline and niacinamide has been used with variable success in dogs and humans with pemphigus.\(^2\)\(^8\)\(^2\)\(^9\) The author commonly uses this therapy but usually finds it an adjunctive therapy at best for the pemphigus complex. It may be more successful in localized cases such as pemphigus foliaceus limited to the face or pemphigus erythematosus. Tetracycline has anti-inflammatory properties affecting complement activation, antibody production, chemotaxis, prostaglandin synthesis, lipases and collagenases. Niacinamide inhibits mast-cell degranulation and phosphodiesterase. Adverse reactions include vomiting, diarrhoea, anorexia and increased liver enzymes. When gastrointestinal complications occur, discontinuing the niacinamide may reduce or eliminate these problems. In rare cases the tetracycline may still produce beneficial results. The dosage recommendations are 500 mg of each drug every 8 h for dogs weighing > 10 kg and 250 mg every 8 h for dogs weighing < 10 kg. Clinical response may take 1–2 months. If clinical response is seen the frequency can be reduced to twice or even once daily.

**CURRENT ALTERNATIVE THERAPEUTICS**

**Cyclosporine and tacrolimus**
Cyclosporine (Atopica and Neoral, Novartis) and tacrolimus (Prograf oral formulation and 0.03 and 0.1% Protopic topical preparation, Fujisawa USA, Inc.) are immunosuppressant agents that have been used extensively in human medicine, primarily to prevent organ transplant rejection.\(^3\)\(^0\)\(^3\)\(^1\) However, these drugs have also been evaluated for the treatment of autoimmune diseases. Both of these drugs work similarly, however, tacrolimus is much more potent and the oral formulations appear toxic in the canine. Currently, due to the much greater potency and potential toxicity of tacrolimus and lack of adequate dosing regimes, systemic administration is not recommended in canine clinical cases. Both drugs become activated by binding to specific intracellular receptors, called immunophilins. Cyclosporine binds to cycophilin and tacrolimus binds to FK506-binding proteins. Both drugs inhibit calcium-dependent pathways, particularly affecting the enzymatic actions of calcineurin, a calmodulin-dependent protein phosphatase. This results in blocking of regulatory proteins that up-regulate activation genes of T-helper inducer and cytotoxic cells. Of the cytokines affected interleukin-2 (IL-2) is most notably affected, although many other cytokines are affected.\(^3\)\(^2\)\(^3\)\(^3\) The initial studies of cyclosporin in the treatment of pemphigus and other cutaneous autoimmune diseases has not been impressive and only limited responses have been seen.\(^3\)\(^4\) However, these early studies utilized older formulations of cyclosporin. The author has seen some more recent responses utilizing the microencapsulated formulation (Atopica and Neoral, Novartis). It is dosed at 5–10 mg kg\(^{-1}\) every 24 h with ketoconazole 5 mg kg\(^{-1}\) every 24 h. It is also common to use cyclosporin in conjunction with oral glucocorticoids. However, it may be used as a sole agent or as a glucocorticoid-sparing agent (Figs 5, 6). Cyclosporine is also available as a topical 0.2% ointment (Optimmune, Schering-Plough). The author and his associates have seen some adjunctive effects utilizing this ointment for localized forms of pemphigus. Even more impressive are the responses seen from the topical administration of 0.1% tacrolimus. In a recent study at the author’s practice 10 cases of discoid lupus erythematosus (DLE) and 2 cases of PE were treated. Eight of the 10 dogs of DLE and both PE cases improved with therapy. In 6/8 cases no other medications were used except the topical tacrolimus. No adverse reactions were noted in any of the cases.\(^3\)\(^5\)

![Figure 5. Pre-cyclosporin therapy in a case of pemphigus erythematous.](image-url)
Side effects seen with cyclosporin most commonly include anorexia, vomiting or diarrhoea. More serious side effects are rarely seen. Other side effects reported in limited cases include weight loss, nephrotoxicity, gingival hyperplasia, papillomatosis, hirsutism and involuntary shaking. Drugs which inhibit the hepatic microsomal isoenzyme P450 system, increase blood cyclosporin levels thus ketoconazole is commonly used concurrently with cyclosporin. It allows for a lower cyclosporin dosage and thus cost, making cyclosporin more cost effective. Severe side effects have been seen in dogs with oral tacrolimus as a sole or combined therapy. These side effects include anorexia, vomiting, diarrhoea, weight loss, impaired glucose metabolism, marked hepatotoxicity and infections. Other side effects seen in humans include nephrotoxicity, neurotoxicity and hypertension. The topical preparation appears very safe in the cases treated the author’s practice and no side effects have been seen. Monitoring serum levels of both cyclosporin and tacrolimus have been evaluated. In the author’s experience the serum levels of cyclosporin generally do not correlate with clinical responses. However, there may be some limited value to monitor these levels when clinical responses are not seen. If levels are still in the low therapeutic range dosages could be increased in an attempt to obtain a response. When topical tacrolimus therapy was utilized in the author’s practice, there was no correlation with serum or whole blood tacrolimus levels and clinical improvement or adverse clinical effects or laboratory abnormalities.

Mycophenolate mofetil
Mycophenolate mofetil (CellCept, Roche Pharmaceuticals) is a new drug that inhibits de novo purine (guanine) synthesis. B and T lymphocytes are dependent upon guanosine synthesis because they are unable to use the salvage guanosine synthesis pathway. This unique aspect of lymphocytes allows mycophenolate mofetil to inhibit the proliferation of lymphocytes and the production of antibodies relatively selectively with minimal effects on other tissues. In humans it has been used in a variety of autoimmune skin diseases. The main side effects include bone marrow suppression, nausea, vomiting, diarrhoea and an increased incidence of infections. It does not have significant renal or hepatic toxicity. Canine studies show success rates of ≈ 50% with some dogs weaned off prednisone completely, whereas others have relapsed when the glucocorticoids were dropped too low. Dosages ranged from 22 to 39 mg kg⁻¹ every 24 h divided every 8 h. Side effects were minimal but the most common included pyoderma and malassezia, diarrhoea and leukocytosis. Expense is a limiting factor as a 23 kg dog will require therapy costing US$10 per day.

ADDITIONAL ALTERNATIVE THERAPY

Cyclophosphamide
Cyclophosphamide (Cytoxan, Bristol Myers) is another alkylating agent. It is considered very potent and can be used individually or in conjunction with glucocorticoids and chlorambucil. It is available in 25 or 50 mg tablets. The dosage is 1.5 mg kg⁻¹ every 48 h. The author does not routinely use this drug due to the potential for haemorrhagic cystitis and because of the effectiveness of other therapies.

Chrysotherapy
Chrysotherapy is the use of gold as a sole or adjunctive therapy. It has immune-modulating and anti-inflammatory effects but its exact mechanism of action is not known. Gold is available in two forms, an oral formulation auranofin (Ridaura, SmithKline Beecham) and an injectable form. Only one of the injectable forms is still commercially available sodium aurothiomalate (Myochrysine, Merck). The older form of injectable gold, aurothioglucose (Solganal, Schering) is no longer available. It is this form that most specialists had experience with. The author found aurothioglucose to be quite effective in feline pemphigus as a sole or combination therapy with glucocorticoids. The author considered success in canine pemphigus poor. When utilized it was dosed at 1 mg kg⁻¹ intramuscularly once a week. It had a long lag phase and some cases would not respond for 10–16 weeks. Once remission was obtained the dosage could be reduced to monthly or in some cases of feline pemphigus, discontinued completely with remission maintained. The author has not used the alternative injectable gold, sodium aurothiomalate and no published reports exist on its effectiveness in canine or feline pemphigus. The author has limited experience using the oral formulation, auranofin, however, others have reported some success using 0.05–0.2 mg kg⁻¹ every 12 h. The toxic effects in humans are a concern with one-third of the patients having some type of reaction, although the majority are minor. The most common include skin

Figure 6. Twelve weeks post cyclosporin therapy in a case of pemphigus erythematosus.
It is dosed at 1 mg kg$^{-1}$ every 8 h and should only be used in dogs. Cats have increased sensitivity to dapsone with higher incidence of haemolytic anaemia and neurotoxicity. Side effects include anaemia, neutropenia, thrombocytopenia, hepatotoxicity, gastrointestinal signs, neuropathies and cutaneous drug eruptions. It has a lag phase of 4–8 weeks. Monitoring complete blood and platelet counts, chemistry profiles and urinalyses should also be performed initially every 4–6 weeks during the first 4 months of therapy and then every 6 months thereafter.

**Dapsone and sulfasalazine**

Dapsone (Dapsone, Jacobus) and sulfasalazine (Azulfidine, Pharmacia) have been used either as sole therapies or in combination with glucocorticoids in cases of canine pemphigus.$^{57,45}$ Dapsone decreases complement activation, antibody production, lysosomal enzyme synthesis and neutrophil chemotaxis. It is dosed at 1 mg kg$^{-1}$ every 8 h and should only be used in dogs. Cats have increased sensitivity to dapsone with higher incidence of haemolytic anaemia and neurotoxicity. Side effects include anaemia, neutropenia, thrombocytopenia, hepatotoxicity, gastrointestinal signs, neuropathies and cutaneous drug eruptions. It has a lag phase of 4–8 weeks. Monitoring complete blood and platelet counts, chemistry profiles and urinalyses every 2–3 weeks for the first 4 months is recommended. After 4 months monitoring can be reduced to every 3–4 months. Sulfasalazine is converted in the colon to sulfapyridine 5-aminosalicylate which has anti-inflammatory properties. It is dosed at 10–40 mg kg$^{-1}$ every 8 h. It may be more effective in cases of pemphigus that are more neutrophilic. A severe side effect is the development of keratoconjunctivitis sicca. Tear production should be monitored every 2–4 weeks. Blood counts and chemistry profiles should be checked initially every 2 weeks for the first 6 weeks and then tapered to every 2–4 months.

**Human Intravenous Immunoglobulin (IV Ig) Therapy**

High dose intravenous immunoglobulins (IVIgs) have been used in human immune-mediated and autoimmune diseases as an alternative or adjuvant therapy. They have also been used in canine primary immune-mediated haemolytic anaemia (IMHA). In a study of 10 dogs with primary IMHA that had failed to respond to conventional immunosuppressive therapy, 5 of the 10 dogs had clinically significant responses. However long-term survival was not improved compared with conventional therapy.$^{34}$ More detailed reviews of IVIgs exist for human autoimmune diseases showing the treatment to generally be safe and without many of the drug-related adverse effects including immunosuppression.$^{45}$ One report showed sustained remissions in 21 human patients with pemphigus vulgaris who previously had not responded to prolonged oral prednisone and multiple other forms of immunosuppressive therapy.$^{46}$ IVIg is a sterile, high purified IgG preparation made from pooled human plasma and typically contains more than 95% unmodified IgG. It has a functionally intact Fc-dependent effector function and only contains trace amounts of IgA and IgM. There are numerous immunomodulatory properties, most are mediated by the Fc portion of the IgG. Some of the postulated mechanisms include: functional blockade of Fc receptors, elimination of circulating immune complexes, anti-idiotypic suppression of autoantibodies, inhibition of complement mediated damage, modulation of cytokines, regulatory effects on cellular immune response and blockade of cell surface death receptor Fas and its specific ligand.$^{45}$

IVIg should be given at 1 g/kg intravenously during a 6–12 hour period once or can be given two days consecutively. It is possible that this therapy could be repeated monthly as it is used in humans but this has not been fully evaluated in the canine. Since there is no commercial canine immunoglobulin available human products are used. There are many products commercially available but the author is only familiar with Sandoglobulin® (Sandoz, East Hanover, NJ, USA) a 6% solution. The safety of this form of therapy is not completely evaluated in the canine but it appears to be safe in the limited number of cases treated and is very safe in humans. Mild side effects reported in humans include: headache, myalgia, flushing, nausea, blood pressure changes and tachycardia usually in the first hour of administration. Severe anaphylactic reactions may occur in patients with IgA deficiency. Sugar additives such as sucrose, maltose and glucose are often added to stabilize the immunoglobulin preparations and there are rare reports of acute renal failure related to these sugars.$^{45,46}$

**Relapsing or Refractory Cases**

A small number of cases will present as a therapeutic challenge. Often these have been on traditional modes of therapy, and have either failed to respond or have had adverse reactions to these forms of therapy. When dealing with such cases, switching the type of glucocorticoid therapy can also be of value. This is often combined with a different immunosuppressive or alternative therapy as listed above. If these treatment options fail trying some of the additional alternative therapies should be discussed with the owner. Unfortunately there will be a number of cases that will be euthanized due to limited response, side effects from drugs or simply financial restraints.

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34. Rosenkrantz, W.S., Griffin, C.E., Barr, R.J. Clinical evaluation of cyclosporine in animal models with cutaneous immune-mediated disease and epitheliotrophic lym-


**Résumé** Les pemphigus sont des dermatoses auto-immunes qui peuvent se présenter sous des formes cliniques multiples et représenter un challenge diagnostique et thérapeutique. Cet article présente une revue des différentes formes de pemphigus, notamment le pemphigus foliaceus (PF), le pemphigus erythematosus (PE), le pemphigus panépidermique pustuleux (PPP), le pemphigus vulgaris (PV) et le pemphigus paranéoplasique (PNP). Le traitement est décrit en détail en insistant sur les thérapeutiques les plus souvent utilisées (glucocorticoides, azathioprine, chlorambucil et tétracycline et niacinamide); les alternatives actuelles (cyclosporine et tacrolimus et mycophenolate mofetil) et d’autres alternatives comme la cyclophosphamide, la cryothérapie, la dapsone et la sulfasalazine.

**Resumen** El pénfigo es una enfermedad cutánea autoinmune que puede presentarse con una variedad de formas y puede presentar dificultades de tratamiento. Se discuten los diferentes tipos y el diagnóstico de pénfigo foliáceo (PF), pénfigo eritematoso (PE), pénfigo panépidermico pustular (PPP), pénfigo vulgar (PV) y pénfigo paraneoplásico (PNP). Se hace un especial hincapié en el tratamiento: se incluyen las terapias más frecuentemente empleadas en la actualidad (glucocorticoides, azatioprina, chlorambucil y tetraciclina y niacinamida); terapias alternativas actuales (ciclosporina y tacrolimus y mofetil micofenolato) y terapias adicionales alternativas (ciclofosfamida, crisoterapia, dapsone y sulfasalazina).

**Zusammenfassung** Pemphigus ist eine autoimmune Hauterkrankung, die in einer Vielzahl von Formen vorhanden sein kann und schwierig zu handhaben und behandeln ist. Es wird ein Überblick über die verschiedenen Formen von Pemphigus, wie Pemphigus foliaceus (PF), Pemphigus erythematoses (PE), panepidermaler pustulärer Pemphigus (PPP) Pemphigus vulgaris (PV) und paraneoplastischer Pemphigus (PNP) und deren Diagnose gegeben. Dabei wurde ein besonderer Schwerpunkt auf die Therapie gesetzt. Miteinbezogen wurden die gebräuchlichsten Therapeutika (Glukokortikoide, Azathioprin, Chlorambucil, und Tetracyclin und Niacinamid), gängige alternative Therapeutika (Cyclosporin, Tacrolimus und Mycophenolat mofetil) und andere alternative Therapeutika (Cyclophosphamid, Cryotherapie, Dapson und Sulfasalazin).