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Critically appraised topic / knowledge summary

Is oral low-dose prednisolone (< 2 mg / kg) as effective as high-dose prednisolone (>2 mg/kg) as the sole treatment for canine pemphigus foliaceus?

Clinical scenario

A middle-aged cocker spaniel presented one month ago with a history of crusting skin lesions and pruritus. Cytology of the lesions revealed acantholytic keratinocytes and a marked neutrophilic infiltration, with no microorganisms evident. Histopathology of lesional skin showed large subcorneal pustules, acantholytic keratinocytes and neutrophils, hence a diagnosis of pemphigus foliaceus was made. The dog was treated with glucocorticoids at 2 mg/kg¹. Following two weeks of once daily dosing, the dog became lethargic, polyphagic, polydipsic, polyuric, with inappropriate toileting in the house, behavioural changes and weight-gain. The owners found these side effects to be unacceptable and requested to reduce the dose of prednisolone to hopefully reduce the side-effects.



The question

In [dogs with pemphigus foliaceus] is oral [low-dose prednisolone/prednisone] as effective as [high-dose prednisolone/prednisone] for the [management of the disease]?

Search parameters

The search terms (Dogs/ OR dog* OR canine* OR canid*) AND (exp prednisolone/ OR prednisolone OR exp prednisone/ OR prednisone) AND (pemphigus/ OR pemphigus) were used in CAB and Medline searches, using Ovid®.

Medline

(Dogs/ or dog*.mp. or canine*.mp. or canid*.mp.) and (exp Prednisolone/ or prednisolone.mp or Prednisone/ or prednisone.mp.) and (Pemphigus/ or pemphigus.mp.)
(gave 21 results on 30/10/2019)

CAB Abstracts

(exp dogs/ or dog*.mp. or canine*.mp. or canid*.mp.) and (prednisolone/ or prednisolone.mp. or prednisone/ or prednisone.mp.) and pemphigus.mp.
(gave 40 results on 30/10/2019)

Search outcomes

- Twenty one papers found in Medline search
- Fifteen were excluded because they did not answer the question
- Six total relevant papers from Medline
- Forty papers found in CAB search
- Four were excluded because they were duplicates
- Twenty-nine were excluded because they did not answer the question
- Five papers were unavailable, abstracts were available for two
- Two total relevant papers from CAB
- Three relevant papers found via other method (Google Scholar)

This gave a total of 11 publications. Ten other publications were in other languages, including five for which the full article was not available. Of the ten there was one with no abstract;² in four there was insufficient information in the abstract to include their content;³⁻⁶ in one there was an association between pemphigus foliaceus and nematode infection and the skin condition resolved when the dog was wormed;⁷ in another

publication a dog with pemphigus foliaceus did not respond to various oral therapies and the lesions were surgically excised⁸. An eighth publication was available as a full manuscript but it was not feasible for the authors to assess the response of four cases of pemphigus foliaceus given that it was in German⁹. The ninth non-English publication reported, in the abstract, a good response in one dog to intravenous immunoglobulins, after a poor response to oral prednisolone and azathioprine, eventually going into remission with no therapy¹⁰. Another case report of pemphigus foliaceus (that was found when looking for reference 9 in Google Scholar and not in the Ovid searches) was not treated successfully with prednisone and azathioprine; it responded to intravenous immunoglobulins and went into remission¹¹.

Five single case reports were excluded where co-morbidities were present which may have been causative in the development of pemphigus foliaceus. These included a case that developed pemphigus foliaceus after splenectomy for haemangiosarcoma tumour, the causes may have been a drug reaction or paraneoplastic; the dog recovered completely after a short course of oral prednisolone and mycophenolate mofetil¹². A dog with Leishmaniosis did not respond to treatment for pemphigus with prednisolone and azathioprine¹³. A dog developed pemphigus foliaceus following ingestion of *Echinacea purpurea* plants; treatment included prednisone and mycophenolate-mofetil, the dog went into remission and all therapies were stopped¹⁴. A dog was treated for pemphigus foliaceus and concurrent generalised demodicosis with complete resolution seen in a matter of several months after treatment with oral prednisolone initially using 2 mg / kg then tapered, as well as amitraz and antimicrobial agents¹⁵. A dog was treated for pemphigus following the administration of afoxolaner which was considered to be the likely trigger; oral steroids and ciclosporin therapy were associated with a good response, long term the skin condition was managed with low doses of medication¹⁶.

Summary of evidence see appendix below

Comments

There are mixed reports recorded here of dogs being successfully treated with variable doses of glucocorticoids, with or without additional therapies, and with or without adverse events or side-effects.

While a number of publications were not included in the analysis because it was not possible for the authors to evaluate the content because they were not in English and there were individual case reports with co-morbidities that may have influenced the outcome or unusual therapies were given; there was no compelling evidence that oral steroids (at the doses of around 2 mg / kg per day), even when combined with other therapies, were perceived to be effective in managing the skin disease. There was a suggestion that intravenous immunoglobulins might be a therapy associated with clinical remission, although two single case reports is a limited evidence base.

Higher doses of steroid seem to be more likely associated with clinical remission or improvement; although they also seemed to have higher incidences of side effects and higher mortality rates. There are currently no validated guidelines on how to assess response to treatment of canine pemphigus although clinical remission has been clearly shown to be feasible within a 12 week period and with no lesions present. It may be feasible to manage some cases with minor residual lesions and this may help to manage the side effects of medication, especially when using oral steroids. Consequently, it is unclear if doses of prednisolone less than 2 mg / kg will prove effective, alone or with adjunctive therapy, in some cases of canine pemphigus.

Bottom line

The management of canine pemphigus foliaceus is challenging because the skin condition does not always respond to therapy and this may lead to euthanasia; furthermore, dogs will often show signs of adverse effects to medication. Therapy will usually rely on oral steroids, often in combination with adjunct therapies, although the effectiveness of the latter remains difficult to ascertain.

The use of oral prednisolone at an initial dose of 2 mg / kg / day may prove effective in some cases; long term some cases may require higher doses and some may be satisfactorily managed with lower doses, there is no clear indication from the studies reported herein that dogs must be given higher doses of steroids. There is a need to monitor clinical cases and use ancillary therapies (bathing and antibiotics) and adjunct therapies to balance the therapeutic response to steroids and balance the adverse effects. Large scale clinical trials are required to investigate the optimal dosing schemes and assessment scales for the management of canine pemphigus foliaceus.

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Appendix

Paper 1: Pemphigus foliaceus in dogs: A review of 37 cases¹⁷

Patient group: 37 dogs, with a mean age of 4.2 years, diagnosed with pemphigus foliaceus on histopathology, with or without direct immunofluorescence. There was a higher prevalence for bearded collie, akita, Newfoundland and schipperke, compared to the hospital population.

Study type: Case series.

Outcomes: How efficacy of treatment was measured, and assessment periods and criteria were not recorded.

Key results: 23 dogs were treated with prednisone at 4.4-6.6 mg/kg daily. The doses were tapered to 1.1 mg/kg, which nine dogs were maintained on solely. Side effects included polyuria, polydipsia, weight-gain, lethargy, weakness and pyoderma in dogs treated long term. Five dogs had recurrent bacterial urinary tract infections. Four dogs were given prednisone and cyclophosphamide concurrently and two were given concurrent azathioprine due to inefficacy of prednisone alone. Side effects seen in these cases were iatrogenic Cushing's disease, demodicosis, urinary tract infections, pyoderma and owner discouragement. Eleven dogs were given prednisone with concurrent aurothioglucose (gold salts). Three dogs were maintained solely on gold salts after cessation of prednisone and three with gold salts and alternate day low-dose (1.1 mg/kg) prednisone, though the lesions recurred after stopping the prednisone in these cases. Two dogs presented with oral ulceration possibly due to the gold salts and therapy was unsuccessful in the

remaining cases. All three dogs maintained on gold salts with prednisone had recurrent bacterial urinary tract infections. Only nine cases of the 37 had no side-effects reported. There were 18/34 dogs managed successfully for one year or more (53% survival rate).

Study weaknesses: Though the study was relatively large-scale compared to others, it is difficult to assess efficacy because of the multiple treatment groups. A 53% survival rate is mentioned but it is unclear whether the dogs that did not survive died from the disease or were euthanised due to inefficacy of the treatment, occurrence of side effects or other reasons. A vague timescale of one to seven years survival was given but it was unknown how many dogs survived this long at such high doses of corticosteroids, given that it was not reported when the dose of prednisone was tapered to 1.1 mg/kg .

Paper 2: Pemphigus foliaceus of the footpads of three dogs¹⁷.

Patient group: Three middle-aged dogs (German shepherd dog, Newfoundland and cocker spaniel) with pemphigus foliaceus localised to the footpads, diagnosed with histopathology and direct immunofluorescence. Each dog was treated with high doses of prednisone (2-3.3 mg/kg) which were then tapered to lower alternate day doses.

Study type: Case series.

Outcomes: Assessment periods and criteria were unrecorded.

Key results: Dog one was treated for over two years on alternate day 0.6 mg/kg but it is not known whether this was to remission. Dog two was lost to follow-up due to side effects (lethargy and weight-gain). Dog three was treated with alternate day doses of 0.7 mg/kg for five months but relapsed three months after ceasing therapy. The lesions went back into remission once 0.7 mg/kg prednisone was given daily.

Study weaknesses: This is a small study and the dogs were not assessed at pre-defined points, nor were any lesional scores used to assess treatment efficacy. It is unknown whether the disease was treated to remission. One dog was lost to follow-up due to side effects of steroids. The dogs were treated for different periods of time and one dog had treatment stopped by the owners.

Paper 3: Observations on the Immunopathology and Therapy of Canine Pemphigus and Pemphigoid¹⁹.

Patient group: Twenty-seven dogs with pemphigus or pemphigoid disorders (including seven dogs with pemphigus foliaceus), treated with up to four chemotherapeutic regimens depending on efficacy.

Study type: Uncontrolled clinical trial.

Outcomes: Assessment periods and criteria were unrecorded.

Key results: Seven dogs were administered initially with 1.1 mg/kg prednisolone twice daily. All seven cases were unsuccessfully managed and side effects were reported (polyuria, polydipsia, depression and muscle wastage). Five dogs then received 3.3 mg /kg prednisolone twice daily which was then tapered down to 1.1 mg/kg once lesions were resolving. One of the five was managed successfully on this regimen, the remaining four were unable to be managed on a high enough dose of prednisolone to keep the disease in remission while the dose being low enough as to not cause side-effects. Two dogs were successfully managed on 3.3 mg/kg prednisolone combined with cyclophosphamide but were euthanised four months later for unstated reasons. Three dogs were started on aurothioglucose due to the side-effects of prednisolone which led to successful management.

Study weaknesses: This is a large-scale study, but it included many different pemphigus disorders, not just pemphigus foliaceus. It is difficult to determine the efficacy of each regimen as we do not know which of the seven dogs that started went into each regimen thereafter. The method of determining efficacy was not recorded.

Paper 4: Pemphigus foliaceus in 91 dogs²⁰.

Patient group: Ninety-one dogs of varying ages and breeds, all diagnosed with pemphigus foliaceus based on histopathology or suggestive cytology, clinical signs and response to therapy.

Study type: Retrospective.

Outcomes: Duration until initial improvement and complete remission were recorded. Improvement was defined as one or more small areas of scaling, crusting or erythema without the need for changes in therapy. The follow up period was recorded for each dog.

Key results: Thirty-eight dogs were maintained on prednisone or prednisolone alone on doses varying from 1.5 mg/kg to 5 mg/kg. Other received various therapies including triamcinolone, dexamethasone, azathioprine, doxycycline and niacinamide, tetracycline and niacinamide and topical pimecrolimus, either alone or in combination. Sixteen dogs were managed on prednisone or prednisolone long term with 15 going into remission. Thirteen dogs received other therapies concurrently with prednisone or prednisolone. Side effects, including iatrogenic Cushing's disease, lethargy, polyuria, polydipsia and anorexia, were more common on combination therapies than with just prednisone or prednisolone alone. Of the 15 dogs that went into remission on prednisone or prednisolone alone, five were euthanised for reasons unrelated to the pemphigus foliaceus or the medication side effects.

Study weaknesses: The exact doses used for each dog in this large-scale study are unknown, so it is impossible to compare higher to lower doses in terms of efficacy or incidence of side effects.

The retrospective nature of the study did not allow analysis of lesion scores to aid in determining improvement and remission.

Paper 5: Diabetes mellitus induced in a dog after administration of corticosteroids and methylprednisolone pulse therapy²¹.

Patient group: An eight-year-old female, neutered chow chow with a two month history of facial and footpad erythema and crusting, with secondary pruritus. The diagnosis of pemphigus foliaceus was based on the cutaneous histological findings and immunofluorescence.

Study type: Case report.

Outcomes: Complete blood count and serum biochemistry were measured. Presence of lesions was monitored.

Key results: The dog was treated with 2.2 mg/kg of prednisone and alternate-day azathioprine. Clinical remission was reached in two weeks (azathioprine can take six weeks to take effect), but the dog was re-examined due to anorexia, depression, collapse and hepatomegaly. Steroid hepatopathy was suspected. Prednisone was replaced with low-dose dexamethasone followed by methylprednisolone pulse therapy which led to the dog being diagnosed with diabetes mellitus.

Study weaknesses: It is difficult to attribute each of the side effects to a particular steroid due to the multiple steroids used in this case. This is a small study with a lot of different treatment modalities being used on one case.

Paper 6: Pemphigus foliaceus: a report of two cases in the dog²².

Patient group: A four-year-old female, neutered Labrador retriever with a four-week history of non-pruritic, generalised crusting skin lesions and a 13-year-old entire female Jack Russell terrier with a six-week history of non-pruritic generalised crusting. The diagnosis of pemphigus foliaceus was made on the basis of compatible clinical signs, negative fungal culture and findings with dermatohistopathology and immunofluorescence.

Study type: Case series.

Outcomes: Dogs were assessed at seven days, 17 days and two months, and ten days, six weeks respectively around six months.

Key results: Case one was started on 0.6 mg/kg prednisolone twice daily due to hepatic dysfunction on serum biochemistry. After seven days of no improvement this was increased to 1 mg/kg twice daily which led to all lesions healing after ten days. The prednisolone dose was tapered to 0.6 mg/kg on alternated days. After two months new lesions appeared, so the dose was changed to 1 mg/kg on alternate days. Despite improvement the dog was euthanised six days later due to perceived poor prognosis. Case two was started on 1.5 mg/kg prednisolone twice daily. Marked improvement was seen after ten days hence the dose was tapered. After six weeks all lesions had healed, prednisolone therapy was stopped, and the dog was still in remission around four months later.

Study weaknesses: This small case series used different doses of prednisolone between cases, making assessment of effective doses difficult.

Paper 7: Canine pemphigus foliaceus: a retrospective study of 43 clinical cases and therapy (2000-2005)²³.

Patient group: Forty-three dogs diagnosed with pemphigus foliaceus based on clinical history, clinical examination and cytology of lesions, with histopathology.

Study type: Retrospective.

Outcomes: Cases were re-examined every three to four weeks, complete blood count, serum biochemistry and urinalysis were performed. If azathioprine was added, dogs were examined every two weeks. Owner-assessed improvement was measured in percentages.

Key results: The dogs were started on 1-2 mg/kg prednisone once daily for three to four weeks then the dose was tapered if improvement was seen. If no improvement was seen, azathioprine was added to the treatment regime. Twenty-three dogs responded to prednisone alone, 20 required introduction of azathioprine; 37 had satisfactory control of lesions evaluated by owners between 70-100%. Five dogs were lost to follow up, one was deemed to have unsatisfactory improvement (40%) on combination therapy. No adverse effects were seen.

Study weaknesses: Owner assessment of improvement was used in this large-scale study, rather than veterinary surgeon assessments, which could make measuring less reliable due to inter-personnel variation and lack of veterinary knowledge.

Paper 8: Oral glucocorticoid pulse therapy for induction of treatment of canine pemphigus foliaceus - a comparative study²⁴.

Patient group: Thirty-eight dogs with pemphigus foliaceus based on clinical criteria (including facial involvement) and cutaneous histological changes. One group received high dose pulse therapy with three days of 10 mg / kg once daily of prednisolone/prednisone; followed by a target dose of 2 mg / kg / day; pulses could be repeated at weekly intervals if deemed necessary. The other group received a dose equal or greater than 2 mg / kg / day of prednisolone/prednisone until lesion remission. Ancillary therapies were allowed in both groups for the first 12 weeks. After four weeks of therapy if lesions were present then adjuvant therapies including azathioprine and ciclosporin were allowed in both groups.

Study type: Retrospective

Outcomes: Complete remission (CR) was recorded when no lesions were present;. Incidence and time to CR was recorded for the first 12 weeks, as well as number of dogs receiving ancillary and requiring adjuvant therapies and incidence of severe adverse events.

Key results The continuous therapy group comprised 20 cases; by week 12 three dogs were in clinical remission in two to 12 weeks, 12 needed adjuvant therapies and two had severe adverse events (one dog died suddenly and one developed myelosuppression due to azathioprine therapy). Side effects of polyuria, polydipsia, polyphagia and weight-gain were seen. The pulse therapy group comprised 18 cases; 11 dogs were in clinical remission in two to 12 weeks, two received adjuvant therapies and two had severe adverse events (one was euthanised due to iatrogenic Cushing's disease and one suffered from gastrointestinal bleeding (melena)). Similar side effects were also seen in this group, along with aggression (n=2) and diarrhoea (n=2). There was no statistically significant difference in the time to reach CR, in the number of dogs receiving adjunct therapy or showing adverse effects between the two treatment groups.

Study weaknesses: Small number of cases and the retrospective nature. Given that prednisone needs to be converted to prednisolone it was suggested that the former might not be the optimal steroid for oral dosing. It would have been potentially useful to see individual case records especially in the continuous therapy group to see what dose of steroids was used when cases were in CR – albeit only three.

Paper 9: Outcome and complications associated with treatment of pemphigus foliaceus in dogs: 43 cases (1994–2000)²⁵.

Patient group: Forty-three dogs diagnosed with pemphigus foliaceus based on suggestive clinical signs, cytology and histopathological diagnosis.

Study type: Retrospective.

Outcomes: Case records were analysed to record treatment, duration of treatment and adverse events.

Key results: Of the 43 dogs, 16 were treated with prednisone alone, with the mean dosage being 2 mg/kg daily. The other 27 dogs were treated with prednisone in combination with other therapies or other therapies entirely. Adverse events recorded were polyuria, polydipsia, weight-gain, lethargy, muscle-wastage, recurrent infections, pancreatitis, increased serum liver values, liver failure, disseminated intravascular coagulation, diabetes mellitus, demodicosis and death. Twenty-six dogs died; 18 were euthanised due to complications of the disease, with two owners stating concurrent financial issues, four died unexpectedly and were found to have unrelated causes at postmortem analysis, and four were euthanised due to unrelated reasons.

Study weaknesses: The dogs received various / different treatment modalities and doses. We are unable to elucidate which adverse events correlated with which treatment method and how many of the cases treated with solely prednisone died and for which reason.

Paper 10: Prolonged remission after immunosuppressive therapy in six dogs with pemphigus foliaceus²⁶.

Patient group: All cases were diagnosed with pemphigus foliaceus based on clinical signs and dermatopathological findings; cases were treated with steroids and additional cytotoxic drugs; they were recorded as having no skin lesions for one year after therapeutic interventions were stopped.

Study type: Case series, retrospective.

Outcomes: Remission was based on no skin lesions being observed.

Key results: Five of the six dogs initially received between 1.4 and 2.4 mg / kg of prednisolone daily and given the lack of response to treatment they were then additionally treated with azathioprine before going into remission. One dog was only given prednisone at a dose of 2 mg/kg twice daily. After two weeks, marked improvement was seen so the prednisone dose was decreased to 1.5 mg/kg twice daily for two weeks then 1 mg/kg twice daily for two weeks. Complete clinical remission was seen at which point the dose was again decreased to 1 mg/kg once daily for two months then every other day for six months. No relapse was seen. This study shows the importance of dose reduction when cases are in remission and that in some dogs it may be feasible to stop all therapies.

Study weaknesses: This study was a small case series of six cases and it is unusual for cases to go into remission – so this may be unrepresentative of most dogs with pemphigus foliaceus.

Paper 11 - CTLA4 overexpressing adipose tissue-derived mesenchymal stem cell therapy in a dog with steroid-refractory pemphigus foliaceus²⁷.

Patient group – a dog with pemphigus foliaceus documented on the basis of clinical signs and histopathological findings.

Study type – single open case report.

Outcomes – clinical improvement was not clearly delineated.

Key Results – the dog did not respond to 4.4 mg / kg per day of oral prednisolone over a one month period; additional therapies included ciclosporin and azathioprine were used for several months then stopped. The skin condition seemed to improve with concurrent, repeated injections of adipose tissue mesenchymal stem cells, including a formulation expressing cytotoxic T-lymphocyte antigen- 4; after the injections the dog was managed with 0.25 mg / kg of prednisolone daily and it was suggested that the stem cell therapy had helped to manage the skin disease.

Study weakness – a single case and there was only partial improvement with combined therapies.