Patching the petechiae: Highlights of the Consensus statement on the treatment of immune thrombocytopenia in dogs and cats

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Keywords: ITP, immunosuppressive therapy, vincristine, intravenous immunoglobulin, splenectomy, cyclosporine, mycophenolate, azathioprine, transfusion, platelets, glucocorticoids, romiplostim, relapse

Since immune thrombocytopenia (ITP) is a heterogenous disease with varied pathogenesis, the clinical presentation is also variable. Patients may have no clinical signs or may have severe mucocutaneous bleeding. Therapy should, therefore, be individualized based on the clinical presentation. Treatment strategies should aim to restore adequate platelet count to prevent bleeding, but should not necessarily target a normal platelet count. Frontline therapy involves immunosuppressive glucocorticoids combined with adjunctive immunosuppressive therapy as needed. Here we review treatment strategies for ITP based on disease severity as guided by the recent American College of Veterinary Internal Medicine Consensus Statement on the Treatment of ITP in dogs and cats. As for ITP diagnosis, a focus is placed on dogs simply because the disease is rare in cats and thus literature-based evidence for ITP treatment in cats is lacking.

As part of the ITP Consensus, the panel investigated 20 clinical questions using a Population Intervention Comparison Outcome (PICO) approach. Questions investigated whether, in dogs and cats with primary ITP (P), treatment with a specific intervention (I), compared to a stated alternative intervention (C), improved the patient-centered outcomes survival to discharge, duration of hospitalization, blood product usage, time to platelet recovery, response to first line treatment, and relapse (O). Nineteen other questions that could not be readily use the PICO approach were also queried to help guide clinical practice.[1] Answers to PICO and non-PICO questions resulted in development of algorithms for initial management of ITP (Figure 1) and drug withdrawal, remission, and relapse (Figure 2).

Fig 1. Scan to access ACVIM Consensus Initial Treatment Algorithm for ITP in Dogs and Cats with ITP. BUN, blood urea nitrogen; DOGiBAT, daily canine bleeding assessment tool; EACA, epsilon aminocaproic acid; FWB, fresh whole blood; GI, gastrointestinal; hIVIg, human IV immunoglobulin; PC, platelet concentrate; Plts, platelet count; PRP, platelet-rich plasma; TDM, therapeutic drug monitoring; TXA, tranexamic acid.

Fig 2. Scan to access ACVIM Consensus Treatment Algorithm for Remission, Relapse, and Drug Withdrawal ITP in Dogs and Cats with ITP. Dx, diagnosis; hIVIg, human IV immunoglobulin; Plts, platelet count; Rx, treatment; TDM, therapeutic drug monitoring.

1. **Treating the Stable ITP Patient**

The lack of correlation between platelet count and bleeding severity provides a treatment dilemma. Platelet counts of 30,000/µl are generally considered a threshold for spontaneous hemorrhage, yet some patients with higher platelet counts require extensive transfusion support and many with platelet counts below 10,000/µl have minor petechiae as their only clinical sign. The question then becomes, which patients require aggressive therapy? Much of the overall disease burden of ITP is due to the lack of prognostic criteria and resultant uniform administration of high intensity and long-term immunosuppressive therapy. At least in human patients with severe ITP, mortality results equally from refractory hemorrhage and secondary infections in immunosuppressed patients.[2] Very few outcome predictors in ITP have been identified, and more research needs to be performed in this area to help guide individualized therapy so that only higher risk patients are aggressively immunosuppressed. In dogs, elevated BUN and melena are the only markers that have thus far been associated with reduced ITP survival.[3] Bleeding scores like the canine bleeding assessment tool or "DOGiBAT," may also reflect disease severity and help to guide treatment.[1, 4]

The mainstay of ITP treatment remains immunosuppression, with glucocorticoid therapy being the frontline treatment. Prednisone (prednisolone in cats) is started at 2 mg/kg/day, or 50-60 mg/m^2 for dogs over 25 kg. Doxycycline therapy should be started pending infectious disease screening results in regions with tick-borne disease.

Relevant PICO questions for the stable ITP patient that were addressed by the consensus are highlighted below.

1.1 In dogs and cats with pITP (P), is treatment with glucocorticoids combined with a second immunosuppressive drug (I) compared with use of glucocorticoids alone (C) associated with different primary or secondary outcomes (O)?

1.2 In dogs and cats with pITP (P), is a maintenance treatment with glucocorticoids and a 2nd immunosuppressive drug (I) superior to glucocorticoids alone (C) to prevent relapse (O)?

1.3 In dogs and cats with pITP (P), is treatment with glucocorticoids and any 2nd drug (I) compared with treatment with glucocorticoids and any other 2nd drug (C) associated with different primary or secondary outcomes (O)?

Overall, the consensus found insufficient evidence to determine if combining glucocorticoids with a 2nd immunosuppressive drug is associated with a different outcome or is superior in relapse prevention than use of glucocorticoids alone.[1] There are no prospective controlled studies that address the impact of second agents on ITP outcomes and the identified retrospective studies were all likely underpowered or did not directly compare treatment groups and outcomes. Similarly, there are insufficient data to allow comparison of any of the available 2nd immunosuppressive drugs in improving outcome in dogs and cats with ITP.[1]

Based on these results, the guidelines the consensus panel generated for treating a stable patient are summarized below:[1]

1. An adjunctive immunosuppressive agent should be considered if:
    a. The patient does not respond within 5-7 days of starting glucocorticoids.
    b. The patient develops or is expected to develop severe adverse effects related to the use of glucocorticoids. This includes dogs >25 kg.
    c. If the patient relapses during glucocorticoid taper.
    d. The patient has severe bleeding.
2. If a second immunosuppressive agent is to be used in dogs, reasonable options for adjunctive immunosuppressive agents include azathioprine, modified cyclosporine, leflunomide, and mycophenolate mofetil.
    a. It should be noted, especially for those practicing in warmer regions, that cyclosporine has the disadvantage of being associated with increased risk of opportunistic invasive cutaneous fungal infections.[5]
3. If a second immunosuppressive agent is to be used in cats, reasonable options for adjunctive immunosuppressive agents include modified cyclosporine and chlorambucil.
    a. Azathioprine should not be used in cats as they can develop severe, even fatal, drug-induced myelosuppression due to their low concentrations of thiopurine methyltransferase.[6]
4. If remission is not obtained with two immunosuppressive drugs, the panel recommended further diagnostic workup for an underlying cause that might have been missed, performing therapeutic drug monitoring, or switching adjunctive immunosuppressant agents. Triple immunosuppressant therapy should be avoided, as this has been associated with poor outcome in one study.[3] (Figure 2)

The treatment goal in a stable ITP patient should be considered. Does platelet count need to be normalized or should our target be a safe platelet count, as is human medical practice? The American Society of Hematology 2019 ITP guidelines recommend observation only for ITP patients with platelet counts over 30,000 platelets/µl and absence of clinical bleeding.[7] Since it would be unrealistic to ask our veterinary patients with ITP to maintain a quiet lifestyle chronically, a higher platelet count goal than 30,000/µl is likely necessary. The consensus panel's treatment goal recommendation is $\geq$ 100,000 platelets/µl with no active bleeding.

2. **Treating the Scary ITP Patient**

The approach to the bleeding ITP patient should be more aggressive. Our approach changes when a patient is bleeding into the gastrointestinal tract or when respiratory or central nervous system bleeding is suspected. There are two medical rescue options:

2.1 Vincristine

Vincristine is speculated to increase platelet count by preventing microtubule polymerization and thereby accelerating megakaryocyte fragmentation and platelet release from bone marrow.[8] Studies have demonstrated more rapid resolution of thrombocytopenia and shorter hospitalization duration in ITP dogs treated with vincristine (0.02 mg/kg) intravenously once in combination with prednisone compared to prednisone alone.[9] Some have questioned the hemostatic capacity of vincristine-induced platelets, but one recent study determined by a flow-cytometric assay that vincristine-induced reticulated (young) platelets are functional.[10] Evidence for the efficacy of vincristine in feline ITP is less convincing.

2.2 Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) is a human plasma product primarily composed IgG. One of IVIg's main mechanisms of action in ITP is blocking antibody-mediated platelet clearance by saturating macrophage Fc receptors.[11] There are other proposed mechanisms of action such as immunomodulation by increasing regulatory T cells and reduction in autoantibody production.[11] A similar study to the vincristine trial demonstrated that treatment of dogs with severe ITP with IVIg combined with prednisone also shortened platelet recovery time and hospitalization duration compared to prednisone alone.[12]

Several PICO questions were investigated by the consensus panel relating to vincristine and IVIG, but the most critical one is:

2.3 In dogs and cats with pITP (P), is treatment with combined glucocorticoids and IVIg (I) compared with use of glucocorticoids and vincristine (C) associated with different primary or secondary outcomes (O)?

One study demonstrated that vincristine and IVIg are equally as effective in reducing time to platelet count recovery and hospital duration in dogs with ITP.[8] Given that vincristine is less costly, more available than IVIg, and easy to administer, the consensus panel recommended that vincristine be used as a first line adjunctive emergency therapy in preference to IVIg in dogs with ITP and clinically relevant bleeding.[1] Caution, however, should be used in breeds with a high incidence of the ABCB1 gene mutation.

Limited data from case reports/series favors IVIg over vincristine as an adjunctive emergency treatment option in cats with ITP.[1] However, apparent lack of responsiveness to vincristine in the feline case reports may have been due to use of vincristine in late course refractory disease.[13-15]

3. **Novel Therapies**

In people with ITP, frontline treatments include short courses of corticosteroids and IVIg, while second-line therapies include an anti-CD20 antibody (rituximab), splenectomy, and TPO receptor agonists.[16]

3.1 TPO receptor agonists

Since the identification of inappropriately low to normal TPO levels in human ITP, treatment with TPO receptor agonists has become a standard second-line therapy for patients who do not respond to steroids or IVIg alone. TPO agonists have greatly improved outcomes and reduced side effects in human ITP patients. One such agent, romiplostim (Nplate®) is a peptide fusion protein that works at a conserved region of the canine TPO receptor with homology to the human protein. Romiplostim was used successfully in a pilot study of 5 dogs with ITP.[17] Since this study was not controlled, further studies of romiplostim in canine ITP are needed. A recent study confirmed that TPO is unexpectedly normal in canine ITP patients, giving further indication for exploration of this treatment option in dogs.[18] The consensus panel recommended considering romiplostim use in patients with refractory disease, or where glucocorticoids or immunosuppressants are contraindicated.[1] However, the high cost of romiplostim currently limits its routine usage.

3.2 Splenectomy

Splenectomy, another second line therapy in human ITP has a reported response rate of 60% life-long remission.[19] Another consensus PICO explored the evidence for splenectomy efficacy in dogs and cats with ITP and determined that splenectomy may lead to increased platelet counts in some animals refractory to medical treatment and lead to sustained remission in some individuals.[20] However, data is only from case series and not controlled studies, and relapse after splenectomy was commonly reported. Therefore, the panel concluded that splenectomy can neither be recommended nor not recommended and can be considered when patients are refractory to treatment or when they experience adverse drug effects of immunosuppressive therapy.[1] Screening for infectious disease should always be performed prior to splenectomy. There is a complete lack of data regarding splenectomy in cats with ITP, thus, routine splenectomy is not recommended in cats with ITP but can be considered in refractory feline ITP patients.[1]

3.3 Rituximab

The final second line therapy in human medicine, rituximab, is not currently an option for our patients. Rituximab is an anti-human CD20 antibody that effectively reduces antibody production by depleting B cells. Its response rate is similar to that of splenectomy in people, though with less sustained remissions.[19] However, rituximab does not bind canine or feline B cells and there are currently no available anti-CD20 antibodies for use in veterinary patients.[21]

4. **Platelet Transfusion Therapy**

Platelets transfused to ITP patients will likely have short half-lives and not impact platelet count significantly. However, they may provide essential hemostasis at sites of critical bleeding like the central nervous system or respiratory tract while allowing other treatments time to take effect. Human ITP guidelines recommend that platelet transfusions be reserved for those patients experiencing hemorrhagic bleeding or requiring invasive surgery.[16] When these conditions are not present, a recent study determined that platelet

transfusions were not associated with improved clinical outcomes in human ITP patients.[22] Platelet containing transfusion products include fresh whole blood, fresh platelet-rich plasma, fresh platelet concentrate, cryopreserved platelets, and a lyophilized canine platelet product, StablePlateRx™ (See Hemostatic Hurdles notes).

PICO questions related to platelet transfusions included:

4.1 In dogs and cats with pITP (P), does treatment with any platelet-containing transfusion product (I), compared with no platelet-containing products (C), improve any outcomes (O)?

4.2 In dogs and cats with pITP (P), does treatment with 1 platelet-containing product (I), compared with any other platelet-containing products (C), improve any outcomes (O)?

Overall assessment of these questions was similar to human guidelines in that platelet transfusion should be reserved for those patients with severe or life-threatening bleeding. While fresh platelet concentrate is the standard blood product used in human medicine and is routinely available due to an advanced blood banking infrastructure, fresh platelet concentrate is not often an accessible option for our patients. Insufficient numbers of studies have investigated the ideal platelet product in veterinary medicine;[23, 24] thus there is not enough evidence to determine if one platelet-containing product is superior to another for treatment of dogs/cats with ITP. Product availability, volume, safety and platelet concentration in the available products should factor into transfusion production selection.

5. **Prognosis**

The overall prognosis of canine and feline ITP is good with reported survival rates ranging from 70 to 90%.[13, 25-27] When patients are in remission, the consensus recommends tapering patients off glucocorticoids by dose reduction by 25% every 2-4 weeks after confirming a stable platelet count. If a patient is receiving an adjunctive immunosuppressant, the choice to taper glucocorticoids versus the second agent depends on the patient's tolerance of glucocorticoid side effects and owner finances. If the patient is tolerating steroids and cost is an issue, the second agent may be tapered first. However, usually glucocorticoid side effects motivate prednisone taper as the first step. Some patients relapse during taper, with published canine relapse rates ranging from 9 to 47%.[3, 25, 28] Approach to a patient experiencing relapse is outlined in Figure 2. Patients that relapse can be maintained on an adjunctive immunosuppressant long term or, alternatively, splenectomy or romiplostim can be considered.

6. **Summary**

Due to the complex disease pathogenesis, ITP patients present with variable disease severity and bleeding phenotypes. Therapy should be individualized to the patient's disease severity as best as possible to balance bleeding risk relative to the risks of immunosuppression. Identification of bleeding predictors will facilitate this approach in the future. Glucocorticoids remain the mainstay of therapy, with second-line immunosuppressants being utilized as needed along with vincristine and/or IVIg in critically

bleeding patients. Clinicians should consider a treatment goal of a safe, but not necessarily normal, platelet count. Pathogenesis of human and canine ITP is an area of active research. Improved understanding of the disease pathogenesis will result in more targeted immunotherapies.

Acknowledgment: Some sections of these notes are extracted from LeVine DN, Brooks MB. Immune thrombocytopenia in *Schalm's Veterinary Hematology*, 7th edition. Eds. Weiss DJ, Wardrop J, Harr K, Seelig D, Brooks MB. 2022.

References

1. LeVine DN, Goggs R, Kohn B et al. ACVIM consensus statement on the treatment of immune thrombocytopenia in dogs and cats. *J Vet Intern Med* 2024;38:1982-2007.
2. Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. *Blood* 2001;97:2549-2554.
3. O'Marra SK, Delaforcade AM, Shaw SP. Treatment and predictors of outcome in dogs with immune-mediated thrombocytopenia. *Journal of the American Veterinary Medical Association* 2011;238:346-352.
4. Makielski KM, Brooks MB, Wang C et al. Development and implementation of a novel immune thrombocytopenia bleeding score for dogs. *J Vet Intern Med* 2018;32:1041-1050.
5. McAtee BB, Cummings KJ, Cook AK et al. Opportunistic Invasive Cutaneous Fungal Infections Associated with Administration of Cyclosporine to Dogs with Immune-mediated Disease. *J Vet Intern Med* 2017;31:1724-1729.
6. Salavaggione OE, Yang C, Kidd LB et al. Cat red blood cell thiopurine S-methyltransferase: companion animal pharmacogenetics. *J Pharmacol Exp Ther* 2004;308:617-626.
7. Neunert C, Terrell DR, Arnold DM et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv* 2019;3:3829-3866.
8. Balog K, Huang AA, Sum SO et al. A prospective randomized clinical trial of vincristine versus human intravenous immunoglobulin for acute adjunctive management of presumptive primary immune-mediated thrombocytopenia in dogs. *J Vet Intern Med* 2013;27:536-541.
9. Rozanski EA, Callan MB, Hughes D, Sanders N, Giger U. Comparison of platelet count recovery with use of vincristine and prednisone or prednisone alone for treatment for severe immune-mediated thrombocytopenia in dogs. *J Am Vet Med Assoc* 2002;220:477-481.
10. Allen EC, Tarigo JL, LeVine DN, Barber JP, Brainard BM. Platelet number and function in response to a single intravenous dose of vincristine. *J Vet Intern Med* 2021;35:1754-1762.
11. Zufferey A, Kapur R, Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). *J Clin Med* 2017;6.
12. Bianco D, Armstrong PJ, Washabau RJ. A prospective, randomized, double-blinded, placebo-controlled study of human intravenous immunoglobulin for the acute management of presumptive primary immune-mediated thrombocytopenia in dogs. *J Vet Intern Med* 2009;23:1071-1078.
13. Bianco D, Armstrong PJ, Washabau RJ. Presumed primary immune-mediated thrombocytopenia in four cats. *J Feline Med Surg* 2008;10:495-500.
14. Tasker S, Mackin AJ, Day MJ. Primary immune-mediated thrombocytopenia in a cat. *J Small Anim Pract* 1999;40:127-131.
15. Zini E, Hauser B, Meli ML, Glaus TM. Immune-mediated erythroid and megakaryocytic aplasia in a cat. *J Am Vet Med Assoc* 2007;230:1024-1027.
16. Neunert C, Lim W, Crowther M et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011;117:4190-4207.
17. Kohn B, Bal G, Chirek A, Rehbein S, Salama A. Treatment of 5 dogs with immune-mediated thrombocytopenia using Romiplostim. *BMC Vet Res* 2016;12:96.

18. Brooks MB, Brooks JC, Catalfamo J et al. Plasma concentration of thrombopoietin in dogs with immune thrombocytopenia. *J Vet Intern Med* 2024;38:2507-2517.
19. Cooper N. State of the art - how I manage immune thrombocytopenia. *Br J Haematol* 2017;177:39-54.
20. Bestwick JP, Skelly BJ, Swann JW et al. Splenectomy in the management of primary immune-mediated hemolytic anemia and primary immune-mediated thrombocytopenia in dogs. *J Vet Intern Med* 2022;36:1267-1280.
21. Impellizeri JA, Howell K, McKeever KP, Crow SE. The role of rituximab in the treatment of canine lymphoma: an ex vivo evaluation. *Vet J* 2006;171:556-558.
22. Goel R, Chopra S, Tobian AAR et al. Platelet transfusion practices in immune thrombocytopenia related hospitalizations. *Transfusion* 2019;59:169-176.
23. Goggs R, Brainard BM, LeVine DN et al. Lyophilized platelets versus cryopreserved platelets for management of bleeding in thrombocytopenic dogs: A multicenter randomized clinical trial. *J Vet Intern Med* 2020;34:2384-2397.
24. Davidow EB, Brainard B, Martin LG et al. Use of fresh platelet concentrate or lyophilized platelets in thrombocytopenic dogs with clinical signs of hemorrhage: a preliminary trial in 37 dogs. *J Vet Emerg Crit Care (San Antonio)* 2012;22:116-125.
25. Putsche JC, Kohn B. Primary immune-mediated thrombocytopenia in 30 dogs (1997-2003). *J Am Anim Hosp Assoc* 2008;44:250-257.
26. Lewis DC, Meyers KM. Canine idiopathic thrombocytopenic purpura. *J Vet Intern Med* 1996;10:207-218.
27. Wondratschek C, Weingart C, Kohn B. Primary immune-mediated thrombocytopenia in cats. *J Am Anim Hosp Assoc* 2010;46:12-19.
28. Williams DA, Maggio-Price L. Canine idiopathic thrombocytopenia: clinical observations and long-term follow-up in 54 cases. *J Am Vet Med Assoc* 1984;185:660-663.