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CONSENSUS STATEMENT

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ACVIM consensus statement on the diagnosis of immune thrombocytopenia in dogs and cats

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Abstract

Immune thrombocytopenia (ITP) is the most common acquired primary hemostatic disorder in dogs. Immune thrombocytopenia less commonly affects cats but is an important cause of mortality and treatment-associated morbidity in both species. Immune thrombocytopenia remains a diagnosis of exclusion for which diagnostic guidelines are lacking. Primary, or non-associative, ITP refers to autoimmune platelet destruction. Secondary, or associative, ITP arises in response to an underlying disease trigger. However, evidence for which comorbidities serve as ITP triggers has not been systematically evaluated. To identify key diagnostic steps for ITP and important comorbidities associated with secondary ITP, we developed 12 Population Evaluation/Exposure Comparison Outcome (PECO) format questions. These questions were addressed by evidence evaluators utilizing a literature pool of 287 articles

Abbreviations: AAFP, American Association of Feline Practitioners; EE, evidence evaluator; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; GPs, glycoproteins; IME, integrated measure of evidence; IMHA, immune-mediated hemolytic anemia; IPF, immature platelet fraction; ITP, immune thrombocytopenia; MPV, mean platelet volume; PECO, population evaluation/exposure comparison outcome; PSAIG, platelet surface-associated immunoglobulin; TPO, thrombopoietin.

For affiliations refer to page 1975

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identified by the panelists using a structured search strategy. Evidence evaluators, using panel-designed templates and data extraction tools, summarized evidence and created guideline recommendations that then were integrated by diagnosis and comorbidity domain chairs. The revised PECO responses underwent a Delphi survey process to reach consensus on final guidelines. A combination of panel expertise and PECO responses were employed to develop algorithms for diagnosis of ITP in dogs and cats, which also underwent 4 iterations of Delphi review. Comorbidity evidence evaluators employed an integrated measure of evidence (IME) tool to determine evidence quality for each comorbidity; IME values combined with evidence summaries for each comorbidity were integrated to develop ITP screening recommendations, which also were subjected to Delphi review. Commentary was solicited from multiple relevant professional organizations before finalizing the consensus. The final consensus statement provides clinical guidelines for the diagnosis of, and underlying disease screening for, ITP in dogs and cats. The systematic consensus process identified numerous knowledge gaps that should guide future studies. This statement is a companion manuscript to the ACVIM Consensus Statement on the Treatment of Immune Thrombocytopenia.

KEYWORDS
autoimmune, hemostasis, immune-mediated, platelet, thrombopoietin

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is the most common acquired primary hemostatic disorder in dogs,[1] and although less common, ITP does occur in cats. The mortality rate of ITP in dogs and cats ranges from 10% to 30% and substantial immunosuppressant treatment-related morbidity occurs.[2-5] In severe ITP in humans, mortality results equally from secondary infections associated with immunosuppression and from refractory hemorrhage.[6] Because ITP is potentially fatal and managed with potent immunosuppressants, rapid and accurate disease diagnosis is critical. Presently, ITP in dogs and cats is a diagnosis of exclusion that lacks definitive diagnostic criteria. A similar diagnostic ambiguity exists for ITP in humans, precluding adoption of well-defined human ITP guidelines.

The lack of a diagnostic test for ITP can be attributed to ITP's heterogenous nature, with interpatient variability in pathogenesis, disease course, and response to treatment. In people, the pathogenesis of ITP involves autoantibodies targeting platelet surface glycoproteins (GPs) resulting in Fc gamma receptor (FcγR)-mediated platelet clearance by the mononuclear phagocytic system. In addition, antibody-triggered platelet desialylation may result in Ashwell-Morell receptor-mediated removal by hepatocytes or clearance by hepatic Kupffer cells.[7-10] Complement-mediated platelet destruction also may contribute in some cases.[11] Cytotoxic T cell-mediated platelet destruction may occur in the absence of detectable platelet autoantibodies.[7,12-15] Antibodies and T cells also can target megakaryocytes, inhibiting platelet production.[7] Thrombopoietin (TPO) is the major regulator of platelet production and is necessary for survival, proliferation, and differentiation of megakaryocytes to platelets.[16-18] Inappropriately low TPO concentrations are common in human ITP patients, contributing to decreased platelet production.[16-18] Platelet- and megakaryocyte-associated antibodies have been documented in dogs with ITP using assays that have variable sensitivity and specificity (see Section 4.1.7 below).[19-21] It is likely that antibody-independent mechanisms of immune-mediated destruction occur, as described in humans.[15] Variable mechanisms of platelet destruction contribute to ITP's diagnostic complexity.

Immune thrombocytopenia can be spontaneous (primary, or non-associative) or induced by a putative trigger (secondary, or associative). We chose to use "primary" and "secondary" in keeping with the standard nomenclature in human medicine. Secondary ITP pathogenesis and presentation varies with the underlying cause, resulting in disease heterogeneity. Treatment of secondary ITP aims to eliminate disease triggers, but inciting causes of ITP in dogs and cats have not been systematically reviewed. Guidelines for investigation of potential ITP triggers are needed to improve case management.

The clinical presentation of primary ITP is also variable, with limited association between thrombocytopenia severity and clinical signs of bleeding. Many dogs and cats remain subclinical despite severe thrombocytopenia, whereas others with similar platelet counts experience life-threatening hemorrhage.[22] Biomarkers of disease severity are needed to guide individualized treatment.

We designed a diagnostic algorithm for systematic exclusion of other causes of thrombocytopenia as an essential aid in ITP diagnosis. Informed by systematic review of the available veterinary evidence, we also aimed to develop guidelines on (a) the diagnostic approach to ITP in dogs and cats; (b) comorbidity screening in dogs and cats with ITP; and (c) diagnostic testing to inform prognosis and guide intensity of treatment. Guidelines were developed using a standardized Population Exposure/Evaluation Comparison Outcome (PECO) question

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format. Knowledge gaps in the available evidence were identified to inform future study design.

2 | MATERIALS AND METHODS

An overview of the consensus statement process is shown schematically in Figure 1 and described below. A comprehensive literature search strategy was developed to identify all manuscripts relevant to ITP in dogs and cats (detailed in Supporting Information 1). Clinical diagnostic algorithms for ITP in dogs and cats were developed and used by evidence evaluators in their literature reviews. Draft algorithms were developed (OAG, LK) based on the collective expertise of the consensus panel members and refined by panel members using a Delphi review process. The diagnostic algorithms were reviewed a final time after completion of the PECO question process.

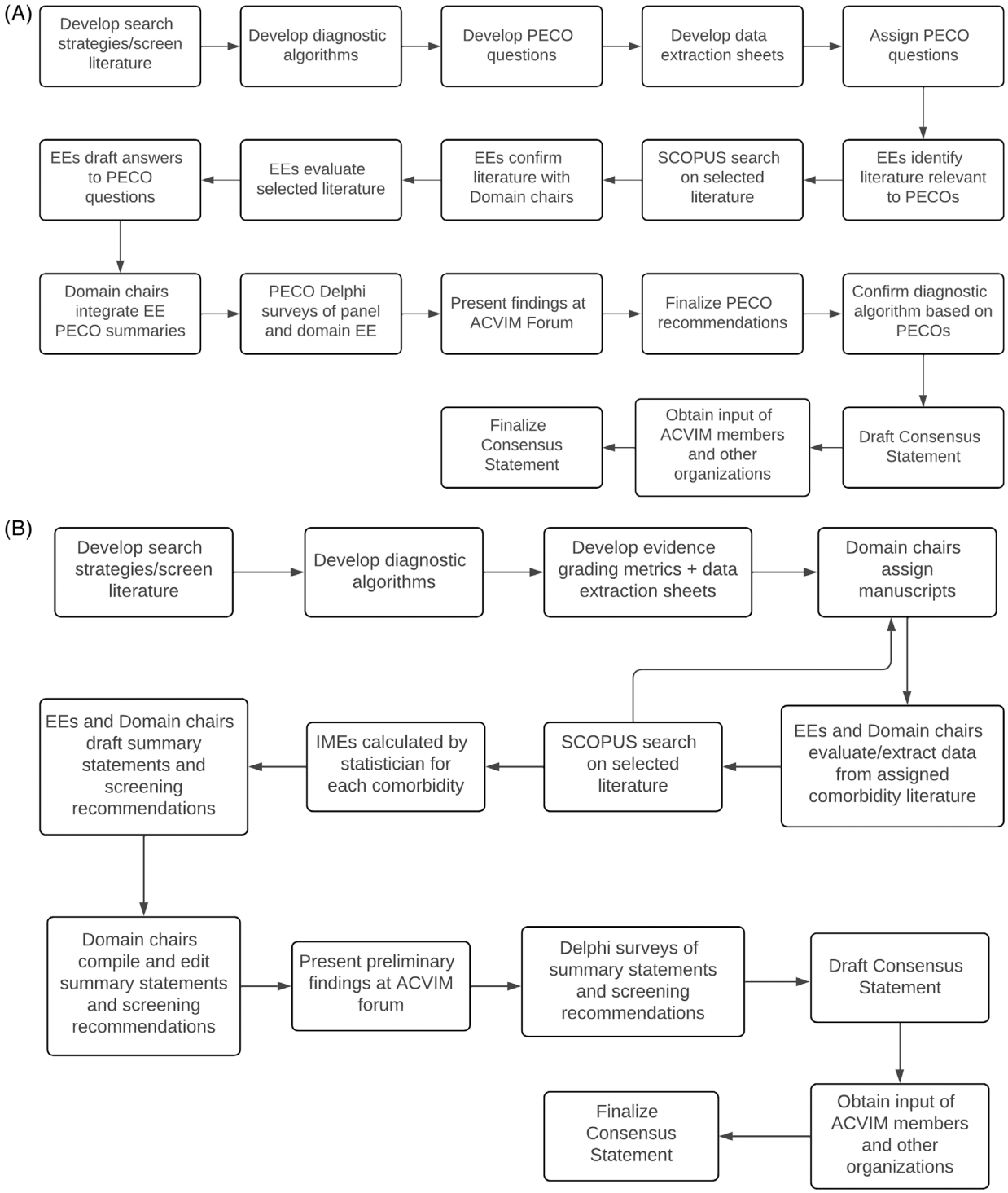

FIGURE 1 (A) Overview of the methodology of the Diagnosis Domain. (B) Overview of the methodology of the Comorbidity Domain. EE, evidence evaluator; IME, integrated metric of evidence; PECO, Population, Exposure/Evaluation, Comparison, Outcome question.

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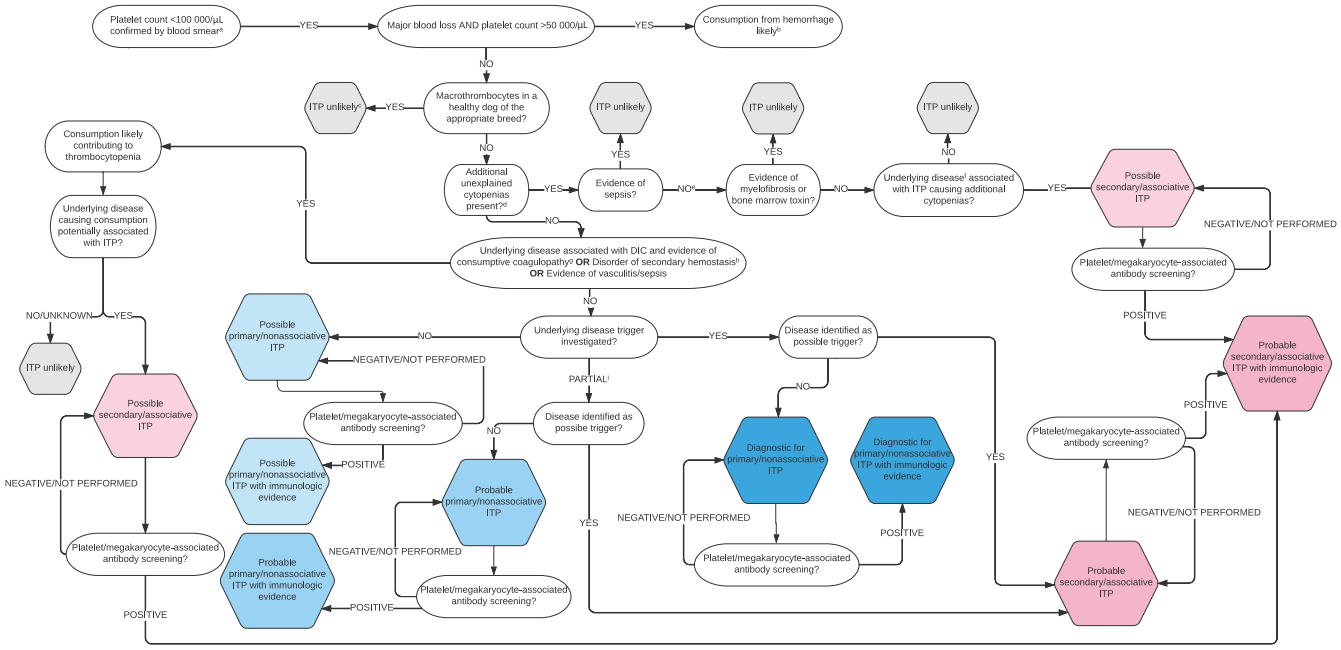

FIGURE 2 An algorithm for the diagnosis of ITP in dogs. [a]Thrombocytopenia should be confirmed with a slide assessment. In brief, to perform a platelet estimate, first assess the slide body and feathered edge under low magnification for clumps, the presence of which suggests that the platelet count is falsely low. Resampling is then warranted, if possible. If there are no clumps, a platelet count is estimated by calculating the mean number of platelets per 10 oil immersion fields (×100) in the body of the smear where erythrocytes are spread in monolayer and multiplying this number by 15 000 to 20 000 to obtain the number of platelets per microliter; [b]the magnitude of thrombocytopenia is consistent with consumption from major hemorrhage. However, it is possible that DIC, vasculitis, sequestration, or ITP may be contributing; [c]consider genetic testing; [d]excludes additional cytopenias with plausible explanations for example, pre-regenerative anemia in the face of acute hemorrhage or hemolysis or lymphopenia in an ill/stressed patient; [e]sampling of bone marrow by aspiration, core biopsy, or both, is undertaken; [f]for example, lymphoreticular neoplasia or ehrlichiosis; [g]at least 2 of 5 parameters abnormal in addition to thrombocytopenia: prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimers > reference interval (RI); antithrombin, fibrinogen < RI; [h]PT or aPTT >25% control value or upper bound of RI; [i]partial screening (ie, not exhaustive) for potential trigger factors undertaken and negative.

The literature review was divided into 2 domains: *Diagnosis* (co-chairs MBB and DNL; evidence evaluators JA, PWC, BG, HM, MCN, LNN, SS, AKV) and *Comorbidity* (co-chairs LK and OAG; evidence evaluators AJB, MAF, ASH, KFL, EL, KFL, KMM, XR, ES). Supporting Information 1 includes extended details of the methods, whereas Supporting Information 2 and 3 includes bibliographies of the manuscripts reviewed by the *Diagnosis* and *Comorbidity* domains, respectively. Supporting Information 4 includes the instruction guide sent to all *Diagnosis* evidence evaluators. Supporting Information 5 includes the instruction guide sent to all *Comorbidity* evidence evaluators.

The *Diagnosis* domain chairs generated clinical questions using a PECO format to investigate whether in dogs and cats with thrombocytopenia (P), evaluation by a diagnostic test (E) compared with platelet count alone (C) improved differentiation of ITP from non-immune thrombocytopenia (O). To investigate disease severity, *population* referred to dogs and cats diagnosed with primary ITP and *outcome* referred to disease severity encompassing bleeding risk, blood product usage, duration of hospitalization, time to platelet recovery, response to first-line treatment, or relapse. Finalized PECO questions were answered by the evidence evaluators using the identified references and structured data extraction and summary templates (Supporting Information 6 and 7). Evaluators' PECO responses (n = 2/PECO) were reviewed by domain chairs and synthesized into a single consensus response to each PECO that subsequently underwent Delphi review. Consensus, or near complete consensus, was reached after 2 Delphi rounds. The remaining disagreements are indicated below.

The comorbidity PECO, "In a population of dogs or cats (P), what is the effect of exposure (E) to comorbidity X compared with a lack of exposure (C) on the development of ITP (O)?" was answered by the evidence evaluators in the *Comorbidity* domain using a quality assessment tool (Integrated Metric of Evidence; IME) and data extraction tool we adapted from the IMHA diagnosis consensus statement (Supporting Information 8 and 9).[23] Threshold IME values were computed to allow comorbidities to be designated as negligible, low, intermediate, or high evidence for a causal relationship with ITP. For the *Comorbidity* domain, manuscripts, not PECOs, were assigned to 2 or 3 evidence evaluators for data extraction, evidence evaluation, and quality assessment. Evidence summaries and screening recommendations were drafted by evidence evaluators for each comorbidity in each manuscript; these summaries and recommendations then were consolidated by LK and subjected to 3 to 4 rounds of Delphi review until 100% consensus was reached.

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3 | ALGORITHM FOR THE DIAGNOSIS OF ITP

Consensus on final versions of the algorithms (Figures 2 and 3) was reached after 4 rounds of revision and review. The first step of the diagnostic algorithms, "Platelet count <100 000/μL confirmed by blood smear examination," warrants further emphasis. The diagnosis of ITP requires determination of platelet count. Although beyond the scope of this discussion, clinicians must consider the biologic, pre-analytic, and analytic variables that influence platelet count.[24-26] Importantly, platelet activation during blood collection or processing can result in spurious thrombocytopenia.[27,28] Pseudothrombocytopenia is especially common in cats because of variable platelet size and relative hyper-reactivity of feline platelets compared with those of other species.[29] Automated hematology analyzers employ different test principles, and all are subject to inherent imprecision.[30] Regardless of instrumentation, low platelet count should be interpreted critically in the context of allowable errors of up to 25%.[26] Confirmation of thrombocytopenia must include slide examination, and replicate platelet count determinations often are warranted. An appropriate diagnosis of ITP is based on persistent thrombocytopenia, and platelet count monitoring over time is best performed using consistent methodology.[30]

The final versions of the algorithm delineate 6 levels of diagnostic certainty for primary ITP: *Possible*, *Possible with immunologic evidence*, *Probable*, *Probable with immunologic evidence*, *Diagnostic*, and *Diagnostic with immunologic evidence*. Although we considered that immunologic evidence such as identification of platelet surface-associated immunoglobulin (PSAIG) or megakaryocyte-associated immunoglobulin strengthened the diagnosis, a confirmatory diagnosis of ITP could be made without such testing. For secondary ITP, diagnostic certainty levels include *Possible*, *Probable*, or *Probable with immunologic evidence*. Coexistence of more than 1 mechanism of thrombocytopenia in secondary ITP precludes definitive diagnosis of ITP in this context.

4 | GUIDELINES FOR DIAGNOSIS OF ITP

The diagnostic guidelines below are presented under their respective PECO questions with their evidence summaries. Guidelines for dogs and cats are presented separately. Guidelines for PECO questions for which minimal or no evidence was identified (common for cats) are included in Supporting Information 11.

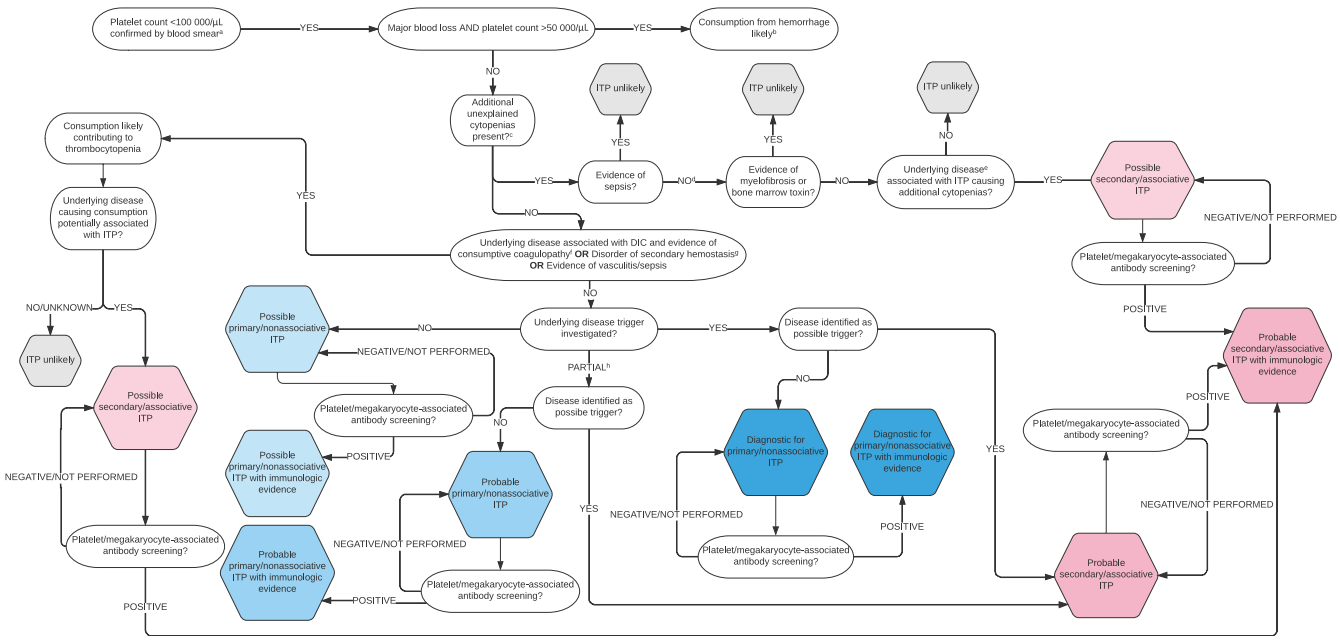

FIGURE 3 An algorithm for the diagnosis of ITP in cats. [a]Thrombocytopenia should be confirmed with a slide assessment. In brief, to perform a manual count first assess the slide's feathered edge under low magnification for clumps, the presence of which suggests that the platelet count is falsely low. Resampling is then warranted, if possible. If there are no clumps, a platelet count is estimated by calculating the mean number of platelets per 10 oil immersion fields (×100) and multiplying this number by 15 000 to 20 000 to obtain the number of platelets per microliter; [b]the magnitude of thrombocytopenia is consistent with consumption from major hemorrhage; this is a rare association in cats. However, it is possible that DIC, vasculitis, sequestration, or ITP may be contributing; [c]excludes additional cytopenias with plausible explanations for example, pre-regenerative anemia in the face of acute hemorrhage or hemolysis or lymphopenia in an ill/stressed patient; [d]sampling of bone marrow by aspiration, core biopsy, or both, is undertaken; [e]for example, lymphoreticular neoplasia or feline immunodeficiency virus infection; [f]at least 2 of 4 parameters abnormal in addition to thrombocytopenia: prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimers > reference interval (RI); fibrinogen < RI; [g]PT or aPTT >25% control value; [h]partial screening (ie, not exhaustive) for potential trigger factors undertaken and negative.

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4.1.1 | In dogs/cats with confirmed thrombocytopenia (P), compared with platelet count alone (C) do platelet indices (eg, mean platelet volume [MPV], immature platelet fraction [IPF], reticulated platelets, plateletcrit) (E) improve differentiation of ITP from non-immune thrombocytopenia (O)?

Guidelines (dogs)

a. There is conflicting evidence regarding changes in MPV in dogs with ITP compared with other causes of thrombocytopenia or healthy dogs.
b. In dogs with thrombocytopenia, increased reticulated platelets may help differentiate ITP from non-immune thrombocytopenia, but not between dogs with primary and secondary ITP.
c. There is insufficient evidence to make recommendations regarding use of plateletcrit and IPF in the diagnosis of ITP in dogs.
d. In thrombocytopenic dogs, use of plateletcrit, IPF, and MPV as routine diagnostic tests for primary ITP are not recommended.
e. In thrombocytopenic dogs, we suggest that increased reticulated platelets (when measurement is available) can be considered to support a diagnosis of primary or secondary ITP.

Level of evidence (dogs): Low. Strength of recommendation: Weak.

Evidence summary (dogs)

Of the 21 observational studies in dogs reviewed for this PECO question, 14 studies with some relevance were identified, and none directly addressed the question.[19,21,31-42]

Reticulated platelets

Of the available platelet indices, most evidence exists for use of reticulated platelets to distinguish primary ITP from non-immune thrombocytopenia, but overall, the evidence is weak. In a prospective cross-sectional study including 17 dogs with probable primary ITP, increased reticulated platelet percentage helped differentiate primary ITP from non-immune thrombocytopenia, whereas platelet count did not.[19] In this study, a reticulated platelet threshold of 8% combined with PSAIG was sensitive (94.1%) but not specific (27.6%) for discriminating primary ITP from other causes of thrombocytopenia.[19] However, neither platelet count nor percentage of reticulated platelets differentiated primary from secondary ITP.[19] In another prospective cross-sectional study 36/45 (80%) thrombocytopenic dogs had increased reticulated platelets. All 6 dogs with ITP had increased reticulated platelets, but so did many other dogs with non-immune thrombocytopenia, and sub-groups were not directly compared.[31] Smaller studies have observed increased reticulated platelets in dogs with ITP[41] and thrombocytopenia in general.[32] Reticulated platelets decrease when platelet counts increase,[33,34] but do not correlate with bone marrow megakaryocyte numbers.[35]

MPV

Seven studies evaluating MPV in ITP were reviewed with conflicting results.[21,36-40,42] In dogs with ITP, both decreased to normal MPV[21,42] and increased MPV have been observed.[37,38] In a retrospective case series of 83 thrombocytopenic dogs, those with ITP (primary and secondary combined, n = 37) and with primary ITP (n = 17) had lower MPV than dogs with non-immune thrombocytopenia.[21] However, the diagnostic algorithm could not be completely applied to this study, decreasing diagnostic certainty.[21] Most studies compared dogs with ITP to healthy controls rather than to dogs with non-immune thrombocytopenia.[38,39] For example, a retrospective case-control study determined that dogs diagnosed with primary ITP (n = 49) have increased MPV compared with healthy control dogs (n = 46),[38] a finding corroborated by a retrospective cross-sectional study.[39] A retrospective case series of dogs with PSAIG showed that MPV was lower in dogs with primary ITP (n = 21) than in dogs with secondary ITP (n = 24).[36] In contrast, another case series described increased MPV in 4/5 dogs with primary ITP and low to normal MPV in dogs with secondary ITP.[37] Finally, a retrospective case series of 60 thrombocytopenic dogs observed that MPV was significantly associated with a bone marrow response, but did not assess the utility of MPV for differentiating the cause of thrombocytopenia.[40]

Plateletcrit

No studies evaluating the use of plateletcrit or IPF for differentiating the cause of thrombocytopenia in dogs were identified. In a retrospective case-control study, plateletcrit was decreased in dogs with primary ITP compared with healthy control dogs, but no dogs with thrombocytopenia of other causes were assessed.[38]

Link to diagnostic algorithm (Figure 2): Although not included in our systematic review, we recommend that identification of macrothrombocytes, particularly in healthy dogs lacking signs of a primary hemostatic defect and breeds, or mixed breeds, with hereditary macrothrombocytopenia, should prompt genetic testing early in the diagnostic evaluation.[43,44]

Guidelines and evidence summary (cats)

See Supporting Information 11.

4.1.2 | In dogs or cats with primary ITP (P), do platelet indices (E) compared with platelet count alone (C) impact predictions of disease severity, including bleeding risk, blood product requirement, hospitalization duration, time to platelet recovery, response to first-line treatment, survival, or relapse (O)?

Guidelines (dogs)

a. In dogs with primary ITP, there is weak evidence to suggest that plateletcrit as opposed to platelet count is more sensitive to platelet recovery.
b. In dogs with primary ITP, there is insufficient evidence to assess the utility of MPV, reticulated platelets, or IPF for prediction of bleeding severity, duration of hospitalization, blood product requirement, or platelet count recovery.
c. In dogs with primary ITP, use of MPV, reticulated platelets, and IPF as routine prognostic tools is not recommended.

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d. We suggest that serial plateletcrits be considered as adjunctive parameters to platelet counts in assessing response to treatment in dogs with ITP.

Level of evidence (dogs): Low. Strength of recommendation: Weak.

Evidence summary (dogs)

No studies were identified that directly assessed platelet indices as severity metrics, but 3 studies provided indirect information.[34,38,45] One retrospective case-control study observed that in dogs with primary ITP (n = 49) plateletcrit increased before platelet count,[38] but did not compare the prognostic value of platelet count and plateletcrit values. Two single case reports suggested that increased reticulated platelet percentage at the time of diagnosis might be associated with treatment response, but confirmatory evidence is lacking.[34,45]

Guidelines and evidence summary (cats)

See Supporting Information 11.

4.2.1 | In dogs/cats with confirmed thrombocytopenia (P), does severe thrombocytopenia (E) compared with mild to moderate thrombocytopenia (C), improve differentiation of ITP from non-immune thrombocytopenia (O)?

Guidelines (dogs)

a. Most evidence suggests that dogs with ITP have more severe thrombocytopenia compared with non-immune causes of thrombocytopenia, but there is overlap between diagnostic groups.
b. In dogs with thrombocytopenia, evaluation of the severity of thrombocytopenia may help differentiate ITP from non-immune thrombocytopenia.
c. We suggest that a platelet count <20 000/μL supports a diagnosis of ITP in dogs but is insufficient to independently make such a diagnosis.

Level of evidence (dogs): Moderate. Strength of recommendation: Moderate.

Evidence summary (dogs)

Five studies were identified that suggest thrombocytopenia severity has diagnostic relevance.[21,22,36,46,47] Two were prospective,[22,46] but did not specifically address the PECO question. In 4 studies, dogs with primary ITP had more severe thrombocytopenia than dogs with non-immune thrombocytopenia.[21,22,46,47] In 3 studies, dogs with primary ITP had more severe thrombocytopenia than dogs with secondary ITP.[21,22,36] In all 5 studies, platelet counts overlapped between groups, precluding use of platelet count alone for primary ITP diagnosis, but suggesting platelet count may aid diagnosis when combined with other data. One retrospective study reported that thrombocytopenia <20 000/μL was consistent with ITP, particularly when accompanied by decreased MPV. However, a cutoff of 40 000 platelets/μL was not discriminating for ITP.[42]

Two opposing studies were identified. In 1 retrospective study, dogs with ITP and disseminated intravascular coagulation (DIC) had lower platelet counts than dogs with thrombocytopenia from other causes, but thrombocytopenia severity was not discriminating.[48] Another retrospective study of dogs with thrombocytopenia observed only mild thrombocytopenia (78 000-125 000/μL) in dogs with ITP,[49] whereas dogs with DIC and other non-immune causes of thrombocytopenia had lower platelet counts. Statistical comparisons were not performed.

Most studies evaluated were retrospective,[21,36,42,47-49] many lacked long-term follow-up, and some were hampered by case selection bias precluding strong recommendations. Overall, the available evidence suggests that severe thrombocytopenia compared with mild or moderate thrombocytopenia may help differentiate ITP from other causes of thrombocytopenia, but platelet count cannot be used as the sole criterion.

Guidelines (cats)

a. There is weak evidence suggesting that cats with ITP have more severe thrombocytopenia compared with those with non-immune causes of thrombocytopenia.
b. In cats with thrombocytopenia, evaluation of the severity of thrombocytopenia may help differentiate ITP from non-immune thrombocytopenia.
c. We suggest that a platelet count <20 000/μL supports a diagnosis of ITP in cats but is insufficient to independently make such a diagnosis.

Level of evidence (cats): Low. Strength of recommendation: Weak.

Evidence summary (cats)

No studies were identified that directly addressed the PECO question, but 4 studies provided indirect and weakly supportive evidence.[4,5,50,51] A retrospective study of 194 cats with thrombocytopenia observed that cats with probable primary ITP had the most severe thrombocytopenia, but platelet counts <50 000/μL also were seen in cats with neoplasia, infection, bone marrow disease, or traumatic hemorrhage.[50] Bone marrow disease was the most common cause of platelet counts <50 000/μL.[50] A retrospective study of thrombocytopenia in 41 cats identified 1 case of primary ITP, but insufficient information was provided to apply the diagnostic algorithm. This cat had 1 of the lowest platelet counts in the study, but the result was similar to those found in infectious causes of thrombocytopenia.[51] In a case series of 4 cats with confirmed primary ITP, all had platelet counts <20 000/μL at diagnosis.[5] Similarly, in 5 cats with confirmed primary ITP, observed platelet counts ranged from 4 to 46 000/μL.[4]

Link to diagnostic algorithms (Figures 2 and 3): Our diagnostic algorithm begins with a confirmed platelet count of <100 000/μL, consistent with ITP definitions in human medicine, and a relevant threshold for likely ITP diagnoses in animals.[52] Some animals with ITP may have higher platelet counts at diagnosis, but this threshold increases the likelihood of an ITP diagnosis. Humans with mild thrombocytopenia (100 000-150 000/μL) have only a 6.9% 10-year probability of developing more severe thrombocytopenia.[53]

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4.2.2 | In dogs/cats with primary ITP (P), does severe thrombocytopenia (E) compared with mild to moderate thrombocytopenia (C) impact prediction of bleeding severity, response to first line treatment, relapse, survival, hospitalization duration, blood product requirement, or time to platelet count recovery (O)?

Guidelines (dogs)

a. In dogs with primary ITP with *moderate to severe* thrombocytopenia (platelet count <50 000/μL), there is moderate evidence to suggest that admission platelet count does not impact disease outcome or response to treatment but may be related to signs of hemorrhage at presentation.
b. In dogs with primary ITP with *moderate to severe* thrombocytopenia (platelet count <50 000/μL), we suggest that admission platelet count alone should not be employed to predict disease outcome or guide treatment.
c. No studies were identified that compared outcomes in dogs with primary ITP with mild (platelet count >75 000/μL) versus moderate to severe thrombocytopenia (platelet count <50 000/μL).

Level of evidence (dogs): Moderate. Strength of recommendation: Moderate.

Evidence summary (dogs)

One prospective observational study was identified that addressed the PECO question, but was considered neutral because all dogs diagnosed with primary ITP had platelet counts <50 000/μL.[22] Platelet count and bleeding severity score (DOGiBAT bleeding assessment tool) were negatively correlated in dogs with primary ITP, suggesting a relationship between these variables, but platelet count was not associated with blood product administration, duration of hospitalization, or survival to discharge.

Five studies indirectly addressed the PECO question and were considered opposed to it.[46,54-57] In a prospective cross-sectional study of 28 dogs with immunologically confirmed ITP and thrombocytopenia ≤60 000/μL, admission platelet count did not predict treatment response.[46] A retrospective cohort study of 73 dogs with probable primary ITP and thrombocytopenia <50 000/μL observed that dogs with melena had decreased survival and higher transfusion requirements than those without melena.[54] Platelet counts were similar between dogs with and without melena, suggesting that platelet count did not impact bleeding severity. Furthermore, the initial platelet count and lowest recorded platelet count were not associated with survival to discharge.[54] A prospective study evaluating the use of vincristine in 24 dogs with probable primary ITP and thrombocytopenia <15 000/μL did not observe a relationship between initial platelet count and time for platelet count recovery.[55] A retrospective case series of 65 dogs with probable primary ITP and thrombocytopenia <40 000/μL determined that platelet count at admission did not differ between dogs that relapsed and those that did not.[56] Likewise, a retrospective case series of 15 dogs with ITP and thrombocytopenia <50 000/μL also found no relationship between initial platelet count and relapse.[57]

Two studies were reviewed that described more bleeding in dogs with severe thrombocytopenia but did not rigorously address patient outcomes related to platelet count. In 1 retrospective case series of 30 dogs with probable primary ITP with immunologic confirmation, thrombocytopenia <30 000/μL was positively correlated with spontaneous bleeding.[3] Most dogs in the study had thrombocytopenia <30 000/μL, but some had platelet counts up to 110 000/μL. All dogs that received transfusions had thrombocytopenia ≤20 000/μL.[3] In another retrospective case series of 54 dogs with possible primary ITP, all dogs with bleeding had platelet counts ≤30 000/μL and 80% of bleeding dogs had platelet counts ≤10 000/μL,[58] but the range of platelet counts was not reported.[58]

Prospective studies with standardized treatment that assess the association between thrombocytopenia severity and outcome are lacking. It is possible that dogs with severe thrombocytopenia were treated more aggressively in the reviewed studies, masking an impact of platelet count on disease outcome.

Guidelines and evidence summary (cats)

See Supporting Information 11.

4.3.1 | In dogs/cats with confirmed thrombocytopenia (P), compared with platelet count alone (C) does the addition of bone marrow examination (E) help differentiate ITP from non-immune thrombocytopenia (O)?

Guidelines (dogs)

a. There is insufficient evidence to determine whether bone marrow examination improves the diagnosis of primary ITP in dogs.
b. Bone marrow examination is not recommended as a routine diagnostic test for primary ITP in dogs.
c. We suggest that bone marrow examination be considered to characterize ill-defined cytopenias, recognizing that there is no bone marrow abnormality diagnostic for primary ITP.

Level of evidence (dogs): Low. Strength of recommendation: Weak.

Evidence summary (dogs)

No studies were identified that directly addressed the PECO question. Several case reports and case series described bone marrow examination in dogs with thrombocytopenia. In a study of 55 dogs with thrombocytopenia that underwent bone marrow examinations, diagnostically relevant cytologic abnormalities were less common in dogs with platelet counts <20 000/μL compared with platelet counts between 20 000 and 200 000/μL.[59] However, causes of thrombocytopenia were not differentiated. Megakaryocytic hyperplasia, hypoplasia, and normal megakaryocyte numbers all are described in dogs with ITP,[21,54,58,60,61] but these studies did not analyze or compare bone

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marrow findings between dogs with ITP and those with non-immune causes of thrombocytopenia.

Guidelines and evidence summary (cats)

See Supporting Information 11.

Link to diagnostic algorithms (Figures 2 and 3): Bone marrow evaluation is only recommended if otherwise unexplained additional cytopenias are present, consistent with current American Society of Hematology guidelines.[62]

4.3.2 | In dogs/cats with primary ITP (P) does bone marrow evaluation (E) compared with platelet count alone (C) improve prediction of bleeding severity, response to first-line therapy, survival, blood product requirement, duration of hospitalization, days to platelet recovery, or ITP relapse (O)?

Guidelines (dogs)

a. Available evidence is contradictory regarding the utility of megakaryocyte hypoplasia for prediction of disease severity in dogs with primary ITP.
b. In dogs with primary ITP, bone marrow examination is not recommended as a routine prognostic tool.

Level of evidence (dogs): Low. Strength of recommendation: Weak.

Evidence summary (dogs)

No studies were identified that directly addressed the PECO question. In a retrospective case series of 34 dogs with primary ITP, anemia, clinical bleeding, transfusion, and poor survival were associated with megakaryocytic hypoplasia or dysplasia (no statistical analysis performed).[63] In 2 case reports, dogs with primary ITP and megakaryocytic hypoplasia had clinical bleeding and delayed responses to treatment.[64,65] In contrast, a retrospective cohort study of 73 dogs with probable primary ITP that included 11 dogs with bone marrow examination found no relationship between megakaryocyte hypoplasia and days to platelet recovery, or survival to discharge.[54] A case series of dogs with thrombocytopenia, including 13 dogs with primary ITP, found that 10 had clinical signs of bleeding, and all 9 dogs with bone marrow evaluation had megakaryocytic hyperplasia but how many of those dogs experienced bleeding was not stated.[21] Finally, all 7 dogs with megakaryocyte hypoplasia survived to discharge in a case series of dogs with thrombocytopenia that included primary ITP cases.[59] Some evidence suggests that megakaryocyte hypoplasia may be related to more severe disease, but contradictory evidence on megakaryocyte response also exists; hence, the prognostic value of bone marrow examination could not be determined.

Guidelines and evidence summary (cats)

See Supporting Information 11.

4.4.1 | In dogs/cats with confirmed thrombocytopenia (P), compared with platelet count alone (C) do platelet/megakaryocyte-associated antibody assays (E) help differentiate ITP from non-immune thrombocytopenia (O)?

Guidelines (dogs)

a. We suggest that in thrombocytopenic dogs, positive platelet/megakaryocyte-associate antibody tests indicate that an immune component is contributing to thrombocytopenia but are not diagnostic for ITP.
b. In dogs with thrombocytopenia, routine measurement of platelet/megakaryocyte-associated antibodies is not recommended.

Level of evidence (dogs): Low. Strength of recommendation: Weak.

Evidence summary (dogs)

Eighteen studies were reviewed that employed platelet or megakaryocyte antibody testing, all neutral to the PECO question.[19-21,32,36,41,46,66-76] In total, the evidence suggests that the presence of PSAIG indicates an immune component to the thrombocytopenia, but is not diagnostic for ITP.

One prospective cross-sectional study describing a direct radioimmunoassay presented sufficient data to allow calculation of assay diagnostic metrics.[20] The PSAIG radioimmunoassay and platelet count <40 000/μL performed similarly for primary ITP diagnosis (Table 1). The PSAIG assay did not reliably differentiate ITP from non-immune causes of thrombocytopenia because 9/17 dogs with non-immune thrombocytopenia had PSAIG concentrations above the cut-off.[20] It was also possible to calculate the positive predictive value (PPV) of PSAIG and platelet count from a retrospective case series,[21] with both PSAIG and platelet count <20 000/μL performing similarly (Table 1). Although 12/13 dogs with ITP were PSAIG-positive, dogs with non-immune causes similarly were positive.[21] Diagnostic data provided were inconsistent, precluding application of the diagnostic algorithm. These studies provide weak evidence suggesting that PSAIG and platelet count perform similarly for differentiating ITP from non-immune thrombocytopenia.

A prospective cross-sectional study provided information regarding the diagnostic utility of a flow cytometric PSAIG assay, but did not compare assay utility with platelet count.[19] The study of 115 dogs, 17 of which had probable primary ITP, reported moderate sensitivities and specificities (Table 1).[19] When dogs with ITP (primary and secondary) were compared with those with non-immune causes, there was no difference in percentage of direct or indirect IgG, direct or indirect IgM, and direct and indirect IgG/IgM combined.[19] However, direct and indirect IgG combined were higher in dogs with ITP compared with dogs with non-immune thrombocytopenia.[19] Another prospective cross-sectional study similarly found no difference in PSAIG between dogs with primary ITP and those with non-immune thrombocytopenia.[71] Several other studies also

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TABLE 1 Diagnostic performance of various assays for platelet surface-associated immunoglobulins (PSAIG).

			Primary ITP vs other causes of thrombocytopenia				ITP (primary and secondary) vs non-immune thrombocytopenia	
Study	PSAIG assay	Metric	Sens	Spec	PPV	NPV	Sens	Spec
Bachman et al[19]	Flow cytometry	Direct IgG	29%	76%	28%	79%		
		Direct/indirect IgM or IgG	77%	66%				
		Direct/indirect IgG					46%	71%
Scott et al[20]	Radioimmunoassay	PSAIG	100%	47%	72%	100%		
		PLT <40 K/μL	96%	76%	85%	93%		
Dircks et al[21]	Flow cytometry	PSAIG			32%			
		PLT <20 K/μL			34%			

Abbreviations: ITP, immune thrombocytopenia; NPV, negative predictive value; PLT, platelet count; PPV, positive predictive value; PSAIG, platelet surface-associated immunoglobulin; Sens, sensitivity; Spec, specificity.

suggest that PSAIG do not reliably differentiate primary from secondary ITP.[41,46,68,71]

Fourteen additional studies were assessed, including 11 observational, cross-sectional studies; 2 retrospective case series; and 1 experimental study (total n = 709 dogs; 275 ITP dogs; 208 primary ITP dogs).[32,41,46,66-70,72-76] None of these studies directly compared PSAIG assays with platelet count for differentiating ITP from non-immune thrombocytopenia. Additionally, in many of these studies, the presence of PSAIG was a criterion for a diagnosis of ITP, limiting assessments of assay diagnostic performance. Regardless, studies that report diagnostic performance data consistently suggest that direct PSAIG assays are sensitive (median, 94%; range, 29.4%-100%), but less specific (median, 75.9%; range, 47%-100%) for differentiating ITP from non-immune thrombocytopenia, with low to moderate PPV (median, 48%; range, 28%-72%) and moderate to very good negative predictive value (NPV; median, 100%; range, 79%-100%) for ITP.

Only 2 studies provided data on megakaryocyte-associated antibody assays for ITP diagnosis, but included no concurrent platelet count data.[67,72] Consequently, there is insufficient information to assess the utility of megakaryocyte-associated antibody assays for ITP diagnosis.

Guidelines and evidence summary (cats)

See Supporting Information 11.

Link to diagnostic algorithms (Figures 2 and 3): The panel considered immunologic testing as supportive evidence for an immune component to platelet destruction but platelet/megakaryocyte antibody testing is not required for a diagnosis of ITP, consistent with current American Society of Hematology guidelines.[62]

Lack of consensus: The 13/14 evidence evaluators agreed with guideline 4.4.1, whereas 1/14 stated that PSAIG assays should be performed if available.

4.4.2 | In dogs/cats with primary ITP (P), do platelet or megakaryocyte-associated antibody determinations (E) compared with platelet count alone (C) impact prediction of bleeding severity, response to first-line treatment, relapse, survival, hospitalization duration, blood product requirement, or time to platelet count recovery (O)?

Guidelines (dogs)

a. In dogs with primary ITP, evaluation of platelet/megakaryocyte-associated antibodies for outcome prediction is not recommended.
b. In dogs with primary ITP, we suggest that serial monitoring of platelet/megakaryocyte-associated antibodies might help identify disease relapse.

Level of evidence (dogs):Low. Strength of recommendation: Weak.

Evidence summary (dogs)

One prospective cross-sectional study was identified that directly assessed the PECO question. The study evaluated whether the magnitude of PSAIG measured using a flow cytometric assay influenced the following disease outcomes: (a) response to initial treatment, (b) survival to hospital discharge, and (c) relapse.[46] The study described 28 dogs with primary ITP and reported that neither the initial percentage of PSAIG-positive platelets nor initial platelet count discriminated for response to initial treatment or survival to hospital discharge.[46] Changes in PSAIG positivity and platelet count for the first 4 weeks of treatment did not predict response to treatment at 6 weeks.[46] These comparisons provide evidence that neither initial magnitude of PSAIG positivity nor initial platelet count predict response to initial treatment or survival to discharge. However, for dogs with primary ITP that entered remission, recurrence of PSAIG positivity was associated with relapse in 2 dogs.[46]

Two studies indirectly assessed bleeding and presence of PSAIG, but not all dogs had primary ITP.[21,72] One retrospective case series

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found more bleeding in dogs with PSAIG, but statistical analyses were only performed for all causes of thrombocytopenia.[21] An additional 4 studies were reviewed: 2 observational, cross-sectional studies and 2 retrospective case series (total n = 252 dogs; 203 ITP dogs; 91 primary ITP dogs). None presented data allowing comparison of autoantibody detection with platelet count for any PECO severity metric.[3,20,36,77]

Overall, weak evidence suggests that platelet/megakaryocyte-associated antibody assays are equally ineffective as initial platelet count for prediction of response to initial treatment and survival to hospital discharge. There is weak evidence that recurrence of PSAIG positivity is associated with ITP relapse. There is insufficient information in the reviewed literature to assess the potential of platelet/megakaryocyte-associated antibody to predict bleeding severity, duration of hospitalization, blood product requirement, and platelet count recovery in dogs with primary ITP.

Guidelines and evidence summary (cats)

See Supporting Information 11.

4.5.1 | In dogs/cats with confirmed thrombocytopenia (P), compared with platelet count alone (C) does the addition of hemostasis testing (eg, coagulation testing, platelet function testing, viscoelastic testing, fibrinolysis testing, D-dimer concentration) (E) help differentiate ITP from non-immune thrombocytopenia (O)?

Guidelines (dogs)

a. In dogs with thrombocytopenia, we recommend performing coagulation testing (activated partial thromboplastin time and prothrombin time) during the routine diagnostic evaluation.
b. In dogs with thrombocytopenia, measurement of fibrinolysis markers (fibrin degradation products [FDP], D-dimer) should be considered.

Level of evidence (dogs): Moderate. Strength of recommendation: Strong.

Evidence summary (dogs)

Five observational studies or retrospective cases series reported coagulation testing in dogs with thrombocytopenia.[49,76,78-80] Overall, these studies support the use of coagulation testing to differentiate patients with consumptive and toxic coagulopathies from patients with primary ITP. Coagulation testing aided identification of dogs with thrombocytopenia associated with disseminated intravascular coagulation (DIC) and anticoagulant rodenticide ingestion.[49,76,78,80] Limited data support the use of fibrinolysis markers (eg, D-dimer) because these markers were inconsistently measured. One study described decreased platelet aggregation in dogs with ITP, but no comparisons were made with non-immune thrombocytopenia, precluding any determination of diagnostic utility.[79]

Guidelines (cats)

a. In thrombocytopenic cats, we recommend performing coagulation testing (activated partial thromboplastin time [aPTT] and prothrombin time [PT]) during the routine diagnostic evaluation.
b. In thrombocytopenic cats, measurement of fibrinolysis markers (eg, FDP, D-dimer) should be considered.

Level of evidence (cats): Moderate. Strength of recommendation: Strong.

Evidence summary (cats)

Five retrospective cases series or case reports describing cats with thrombocytopenia were reviewed.[51,81-84] These reports support the use of coagulation testing to differentiate cats with primary ITP from other systemic disorders associated with thrombocytopenia. In a case series of 85 ill cats, thrombocytopenia was present in 34%, and in 58% of cats with coagulation abnormalities,[84] whereas a second case series of cats with thrombocytopenia identified only 1 cat with primary ITP.[51] Thrombocytopenia was present in 50% of cats with DIC in 1 case series. Prolongation of the aPTT was present in all DIC cats, whereas additional tests (eg, FDP, antithrombin) were useful to further characterize DIC.[81] A case series of 69 cats with at least 1 abnormal hemostasis test result indicated that thrombocytopenia was present in 57% of cats with DIC, with neoplasia, liver failure, and feline infectious peritonitis being the most common inciting diseases.[83] One case report described the use of thrombelastography to characterize a bleeding diathesis in a cat with thrombocytopenia, but the cause was not determined.[82]

Link to diagnostic algorithms (Figures 2 and 3): The panel integrated coagulation testing early in the diagnostic algorithm to rule out consumptive causes of thrombocytopenia before undertaking additional investigation.

Lack of consensus: While 13/14 evidence evaluators agreed with guideline 4.5.1 in dogs, 1/14 suggested that ITP dogs with severe melena can have mildly increased aPTT, D-dimers and FDP. Although 13/14 evidence evaluators agreed with guideline 4.5.1 in cats, 1/14 felt the literature insufficiently supported the recommendation.

4.5.2 | In dogs/cats with primary ITP (P), compared with determination of platelet count alone (C) does determination of bleeding severity score (E) improve prediction of bleeding severity, response to first-line treatment, survival, blood product requirement, duration of hospitalization, days to platelet recovery, or ITP relapse (O)?

Guidelines (dogs)

a. In dogs with primary ITP, we recommend severity scoring be performed to aid assessment of disease severity.

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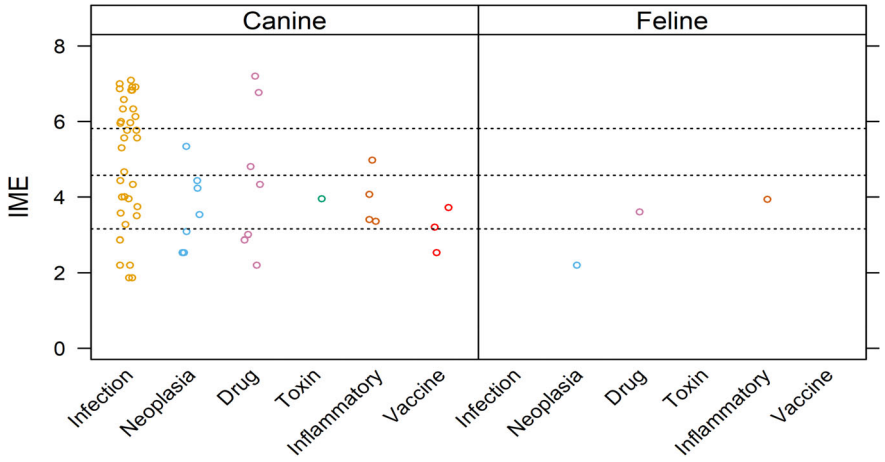

FIGURE 4 Summary of evidence for the causal role of comorbidities as a trigger for ITP in dogs and cats. Level of evidence for a specific comorbidity as a cause of ITP was assessed by means of a published *Integrated Metric of Evidence* (IME) value, which captures information on study design, quality of reporting, confidence of comorbidity diagnosis, likelihood of a causal link between the comorbidity and ITP, confidence of the ITP diagnosis, and the number of patients with a given comorbidity (excluding those patients with more than 1 comorbidity). Horizontal dotted lines indicate threshold IME values between negligible and low (3.15), low and intermediate (4.57), and intermediate and high (5.81) levels of evidence based on predetermined hypothetical thresholds (Supporting Information 8). An IME value of 0 indicates that the study directly demonstrated a lack of evidence that a comorbidity caused ITP.

Level of evidence (dogs): Moderate. Strength of recommendation: Moderate.

Evidence summary (dogs)

Five studies relevant to the PECO question were reviewed.[22,46,54,63,85] Evidence from cohort studies indicates an association between severity score or anatomic site of bleeding with transfusion requirement, duration of hospitalization, or survival. In a cohort study of 34 dogs with primary ITP, a bleeding severity score (DOGiBAT bleeding assessment tool) directly correlated with transfusion requirement and duration of hospitalization, whereas platelet count was not associated with these metrics.[22] In a retrospective study including 73 dogs with probable primary ITP,[54] and a prospective study with 28 primary ITP cases,[46] the presence of melena was associated with poor survival. Gastrointestinal bleeding is a component of the DOGiBAT bleeding assessment tool score.[22]

Guidelines and evidence summary (cats)

See Supporting Information 11.

4.6.1 | In dogs/cats with primary ITP(P), compared with platelet count alone (C) do CBC or biochemistry panel abnormalities (E) improve prediction of bleeding severity, response to first-line treatment, survival, blood product requirement, duration of hospitalization, days to platelet recovery, or ITP relapse (O)?

Guidelines (dogs)

a. In dogs with primary ITP, we recommend that CBC and biochemistry panels be performed to aid assessment of disease severity.

Level of evidence (dogs): Moderate. Strength of recommendation: Moderate.

Evidence summary (dogs)

Nine studies were reviewed, but none directly addressed the PECO question.[3,21,37,54,56,58,63,86,87] Evidence from case reports and case series indicates that biochemistry panel abnormalities (high blood urea nitrogen concentration) and CBC abnormalities (low hematocrit) may be associated with increased disease severity in dogs with primary ITP. A retrospective study of 55 dogs with primary ITP found an association between high blood urea nitrogen concentration and poor survival.[54] An association between low hematocrit and transfusion was reported in 2 case series of dogs with primary ITP, but in 1 of these studies the most anemic dogs had amegakaryocytic thrombocytopenia.[37,63] Other case series identified a variable association or did not evaluate the relationship between these variables and severity metrics.[3,21,86,87] Thrombocytopenia severity was related to transfusion requirements or bleeding in 2 retrospective case series,[3,58] but no assessments of other hematologic variables were described.

Guidelines and evidence summary (cats)

See Supporting Information 11.

5 | GUIDELINES FOR COMORBIDITY SCREENING IN ITP

The first part of this section summarizes the evidence for a causal role of various comorbidities in ITP; the second part presents guidelines for comorbidity screening based on the evidence accrued. Evidence summaries and guideline recommendations are presented for comorbidities

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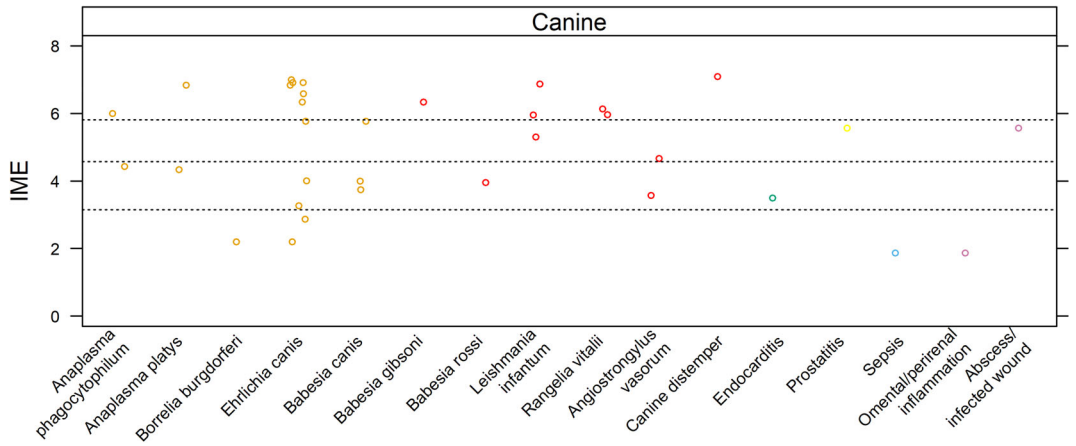

FIGURE 5 Summary of evidence for the causal role of infection as a trigger for ITP in dogs. Level of evidence for infection with a specific pathogen (or location/type of infection) as a cause of ITP was assessed by means of a published *Integrated Metric of Evidence* (IME) value. Horizontal dotted lines indicate threshold IME values between negligible and low (3.15), low and intermediate (4.57), and intermediate and high (5.81) levels of evidence based on predetermined thresholds (Supporting Information 8). An IME value of 0 indicates that the study directly demonstrated a lack of eidence that a comorbidity caused ITP.

represented by ≥1 study with a high level of evidence. The remainder, including all studies in cats, are included in Supporting Information 12.

Overall, 165 manuscripts met inclusion criteria for review (Supporting Information 1 and 3). Integrated metric of evidence values could be calculated for 59 comorbidities from 48 manuscripts (Figure 4, Supporting Information 10).[41,61,70,73,76,78,85,88-128] For the remainder, IME values could not be calculated because the number of animals with ITP or the comorbidity could not be discerned, >1 comorbidity was present, ITP was ultimately deemed "unlikely" or "primary" based on the diagnostic algorithm, the diagnostic algorithm could not be applied, or patient data were already captured in another study.

5.1 | Infections

In humans, several infectious agents are associated with ITP, including *Helicobacter pylori*, *Plasmodium* spp., severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Hepatitis C Virus, and Human Immunodeficiency Virus.[129-135] Evidence suggests that mechanisms of immune-mediated platelet destruction include molecular mimicry, immune-targeting of bound or expressed platelet antigens, and immune-complex binding of platelet FcγRII receptors.[129,132,133,136,137] Genetic and environmental factors that affect the host immune milieu, and genetic and phenotypic differences among strains of microorganisms, also influence whether ITP develops or not.[129,132,136-138] In this study, IME values were calculated for 34 infections as potential causes of ITP in dogs and cats (Figure 5 and Supporting Information 10).

5.1.1 | Canine vector-borne infections

Ehrlichia spp.

Consensus summary statement

Overall, there is a high level of evidence that infection with *E. canis* causes ITP in dogs. Mechanisms in addition to immune-mediated destruction contribute to thrombocytopenia. Further study is needed to determine whether species or strain differences, as well as host or environmental factors, contribute to the development of ITP.

Evidence summary

Twenty-seven studies were evaluated.[3,21,61,70,74,85,93,95,97,100,103,104,107,114,116,117,123,139-148] Integrated metric of evidence values (median, 6.33; range, 2.2-7.0) were calculated for 11 studies.[70,85,93,100,103,104,107,114,116,117,123] Of these 11 studies, evidence was negligible in 18% (2/11),[85,93] low in 18% (2/11),[114,116] intermediate in 9% (1/11),[107] and high in 50% (6/11)[70,100,103,104,117,123] that infection with *E. canis* causes ITP in dogs. Integrated metric of evidence values could not be calculated for the remaining 16 studies.[3,21,61,74,95,97,139-148]

Of the 11 studies with an IME value, 10 specifically studied *E. canis*.[70,85,93,100,103,104,114,116,117,123] One study did not indicate the *Ehrlichia* species involved,[107] but *E. canis* was presumed based on geographic locale.[149] Overall, high level evidence suggests immune-mediated platelet destruction contributes to thrombocytopenia in dogs with ehrlichiosis. In 7 studies (median IME, 6.45; range, 3.27-7.00; n = 50) dogs were experimentally infected.[70,100,103,104,114,117,123] PSAIG was demonstrated using flow cytometry in 4 of these studies.[70,103,117,123] Because PSAIG was demonstrated in some dogs as early as day 7, it has been hypothesized they might represent naturally occurring autoantibodies.[103,140] Of note, experimental infections involved infusing infected canine blood, which presumably contained platelets, into naïve recipients.

Levels of evidence varied for 4 additional studies that involved dogs naturally infected with *E. canis* (median IME, 3.22; range, 2.20-5.77; n = 8),[85,93,107,116] including 2 case reports,[93,116] 1 study comparing platelet transfusion products in which 1 dog was *E. canis*-seroreactive,[85] and 1 study documenting 5 dogs with severe thrombocytopenia and PSAIG.[107] An IME value could not be calculated for 1 additional study that included 7 *E. canis*-seroreactive dogs with thrombocytopenia and PSAIG.[3]

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In addition to PSAIG, splenic sequestration and removal of platelets,[104] vasculitis, hypercoagulability, and myelosuppression all may contribute to thrombocytopenia in ehrlichiosis.[70,150-152]

There were no studies of other species of *Ehrlichia* for which IME values could be calculated. In 1 study, no significant difference was found in mean platelet count for 3 dogs infected with *E. chaffeensis* compared with uninfected controls.[144] This finding contrasted with *E. canis*-infected dogs, in which platelet counts significantly decreased during the study. In a retrospective study of 41 dogs PCR-positive for *E. ewingii*, 16 were thrombocytopenic (range, 5-189 000 platelets/μL) and 2 were reported to have ITP, although the ITP diagnostic criteria were not described.[147]

Leishmania spp.

Consensus summary statement

Overall, high-level evidence suggests that *Leishmania infantum* infection causes ITP in dogs. Mechanisms other than immune-mediated destruction also contribute to thrombocytopenia in dogs with leishmaniosis.

Evidence summary

Seven studies were evaluated.[3,21,96,97,107,121,153] Integrated metric of evidence values of 5.30 to 6.87 (median 5.9) were calculated for 3 studies.[96,97,121] Thirty-three percent (1/3)[97] of the studies demonstrated an intermediate level of evidence and 67% (2/3) demonstrated a high level of evidence that *Leishmania* causes ITP.[96,121] In a study of 33 dogs naturally infected with *L. infantum* (IME, 5.95), platelet surface-associated IgM and IgG were detected by flow cytometry in 64% (21) of dogs.[121] All 21 dogs had platelet surface-associated IgM, and 9 had both IgM and IgG. Platelet surface-associated immunoglobulin was demonstrated in 8 of 9 thrombocytopenic dogs and antibody presence was significantly associated with severity of illness. Three of the 9 thrombocytopenic dogs had platelet counts <100 000/μL. In a prospective case-control study (IME, 6.87) of naturally infected dogs,[96] PSAIG was documented by flow cytometry in 19/20 *Leishmania*-infected dogs with thrombocytopenia, 13/24 *Leishmania*-infected dogs with normal platelet counts, and 0/10 healthy controls. In *Leishmania*-infected dogs, the presence of PSAIG was significantly associated with thrombocytopenia, suggesting that immune-mediated platelet destruction contributes to thrombocytopenia. A third study (IME, 5.30) also suggested that leishmaniosis causes ITP.[97] This study investigated the prevalence of PSAIG in 10 dogs with leishmaniosis, 10 dogs with ehrlichiosis, 10 dogs coinfected with *Ehrlichia* and *Leishmania*, and 10 control dogs.[97] Platelet surface-associated immunoglobulin was documented in 5/10 dogs with leishmaniosis, 6/10 dogs with ehrlichiosis, and 7/10 coinfected dogs. Only 1 *Leishmania*-infected dog had a platelet count <100 000/μL; PSAIG was not detected in this dog (the "n" used in the IME calculation was based on this dog). For 4 additional studies, IME values could not be calculated because of coinfection, inadequate data, reported platelet counts >100 000/μL, and presence of pancytopenia.[3,21,107,153] In addition to immune-mediated destruction, leishmaniosis in dogs may cause thrombocytopenia as a consequence of vasculitis, bleeding diatheses, and bone marrow infection.[154] In a mouse model of visceral leishmaniosis, decreased thrombopoietin, decreased bone marrow megakaryocytic maturation, and increased splenic and hepatic removal of opsonized and desialylated platelets all contributed to thrombocytopenia.[155]

Anaplasma spp.

Consensus summary statement

Overall, there is an intermediate level of evidence that *Anaplasma* spp. cause ITP in dogs. Immunologic mechanisms of platelet destruction were clearly documented only for *A. phagocytophilum*. Whether antibody-mediated platelet destruction occurs during *A. platys* infection is not known. Other mechanisms may contribute to the development of thrombocytopenia in dogs with anaplasmosis. Further study is needed to determine if species and strain differences, or host or environmental factors, affect whether ITP develops during infection.

Evidence summary

Eleven studies were evaluated for evidence that *Anaplasma* spp. cause ITP in dogs.[21,46,88,90,94,100,117,144,148,156,157] Integrated metric of evidence values were calculated for 4 studies (median, 5.2; range, 4.34-6.83; n = 32).[88,90,94,100] Fifty percent (2/4) demonstrated low-level evidence,[88,90] and 50% (2/4) demonstrated high-level evidence[94,100] that *Anaplasma* spp. cause ITP in dogs.

Two studies documented thrombocytopenia associated with *Anaplasma platys* infection.[88,100] In dogs simultaneously or sequentially infected with *Ehrlichia canis* and *A. platys*, or either organism alone, (n = 6 per group), *A. platys* infection resulted in thrombocytopenia, particularly when combined with *E. canis*.[100] The IME value for non-coinfected dogs was 6.83.[100] In a separate study, 3 dogs with thrombocytopenia were documented to be infected with *A. platys* using cytology and PCR (IME, 4.34).[88]

Two additional studies documented thrombocytopenia in dogs infected with *A. phagocytophilum*.[90,94] In a study of 63 dogs (IME, 6.0) PCR-positive for *A. phagocytophilum*, 54 (86%) were thrombocytopenic, including 21 classified as severe (<30 000/μL) and 21 classified as moderate (30 000-100 000/μL).[94] Thirty-six dogs were tested for PSAIG, of which 16 (44%) were positive. The platelet counts in these dogs ranged from 0 to 95 800/μL (median, 16 700/μL). A case report (IME, 4.43) described a dog actively infected with *A. phagocytophilum* with severe thrombocytopenia, PSAIG, IMHA, and polyarthritis.[90]

Seven additional studies for which IME values could not be calculated documented thrombocytopenia in dogs with anaplasmosis.[21,46,117,144,148,156,157] In a study of 18 dogs PCR-positive for *A. phagocytophilum*, 16 were thrombocytopenic.[156] Six of the 9 dogs tested were positive for PSAIG, suggesting an immune-mediated pathogenesis. An IME value could not be calculated for this study because the number of dogs with platelet counts <100 000/μL could not be determined. Another study documented thrombocytopenia after confirmed experimental infection of *A. platys* in 4 dogs and *A. phagocytophilum* in 3 dogs, but an IME value could not be calculated because the number of dogs that became thrombocytopenic after infection was not reported.[144]

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Piroplasms

Babesia spp.

Consensus summary statement

Overall, the evidence that *Babesia* spp. cause ITP is low, although indirect study design affected some IME values. Two studies showed intermediate and high levels of evidence, respectively, that *Babesia* spp. may cause ITP. Further study is required to determine whether there are species differences in the ability of *Babesia* spp. to induce immune-mediated platelet destruction. Mechanisms other than immune-mediated destruction also may contribute to thrombocytopenia in dogs with babesiosis.

Evidence summary

Fifteen studies were evaluated for evidence that *Babesia* spp. cause ITP in dogs.[3,21,41,101,107,109,111,117,145,158-163] Integrated metric of evidence values could be calculated for 5 studies (median, 4.00; range, 3.74-6.33; n = 56).[41,101,107,109,111] Sixty percent (3/5) provided low-level evidence,[101,109,111] 20% (1/5) provided intermediate,[107] and 20% (1/5) provided high-level evidence.[41] For *B. canis*, 3 studies had IME values of 3.74,[111] 4.00,[109] and 5.77[107] (for 1 of these studies, species was presumed based on geographic locale).[107,149] A high level of evidence was provided by a study in which 4 dogs experimentally infected with *B. gibsoni* developed severe thrombocytopenia and PSAIG (IME, 6.33).[41] One study of 24 dogs naturally infected with *B. rossi* provided low-level evidence that *B. rossi* causes ITP (IME, 3.95).[101] This study did not assess whether platelet- or megakaryocyte-associated antibodies were present, but did find that infected dogs had significantly higher levels of platelet-leukocyte aggregates than uninfected dogs, suggesting that innate immunity mediates consumption of platelets during infection. Notably, *B. rossi* can cause DIC,[101] suggesting that multiple mechanisms may contribute to thrombocytopenia in dogs with babesiosis. The 10 studies for which an IME value could not be calculated, and several other studies not captured by the search strategy, documented that thrombocytopenia is common in dogs infected with, or exposed to, many *Babesia* species.[21,41,117,145,158-168]

Rangelia spp.

Consensus summary statement

Two available studies provide high-level evidence that *Rangelia* spp. cause ITP in dogs.

Evidence summary

Two studies were evaluated,[99,112] and provided high-level evidence (IME, 5.97 and 6.13) that *Rangelia* causes ITP in dogs. In a study of dogs with naturally occurring *R. vitalli* infections diagnosed using light microscopy, infected dogs had lower platelet counts than uninfected controls (34 100 ± 27 918/μL versus 259 900 ± 61 050/μL) and more platelets with surface-associated IgM.[99] Another study demonstrated severe thrombocytopenia 10 and 20 days post-experimental infection, but did not test for PSAIG.[112] Mechanisms other than immune-mediated destruction also likely contribute to thrombocytopenia in rangeliosis.[112]

Borrelia burgdorferi

See Supporting Information 12.

Rickettsia rickettsii

See Supporting Information 12.

Angiostrongylus vasorum

See Supporting Information 12.

5.1.2 | Canine viral infections

Canine distemper virus

Consensus summary statement

One study provided high-level evidence that canine distemper virus strain R252 causes ITP, potentially through phagocytosis of platelets with surface-bound virus-antibody immune complexes and decreased platelet production because of megakaryocyte infection with distemper virus. Further study is required to determine the occurrence and clinicopathological course of ITP after natural infections.

Evidence summary

A single study (IME, 7.09) documented ITP in 2 gnotobiotic dogs experimentally infected with canine distemper virus (strain R252).[126] Thrombocytopenia developed on day 1 post-infection and peaked on day 10. Platelet count recovery was observed without immunosuppressive or other treatment until the end of the study on day 15 post-infection. In the same study, 17 additional dogs were inoculated with distemper virus and similarly developed transient thrombocytopenia, albeit with platelet counts >100 000/μL. These dogs were not included in the IME calculation. The study provided mechanistic insights and identified viral antigen and anti-virus IgG on platelet surfaces of infected dogs from day 7 post-infection using immunocytochemistry. Serum anti-virus IgM was detected by ELISA on days 8 and 9. Immune complex-mediated platelet phagocytosis by hepatic reticuloendothelial cells was demonstrated by electron microscopy from day 5. Immunocytochemistry identified viral megakaryocyte infection starting on day 8 post-infection. A second study of 987 dogs with thrombocytopenia described the finding of canine distemper inclusion bodies.[47] The study design did not allow evaluation of the magnitude of platelet counts or the distribution of underlying diseases and an IME value therefore was not calculated.

5.1.3 | Other infections in dogs

See Supporting Information 12

5.1.4 | Vector-borne infections in cats

See Supporting Information 12

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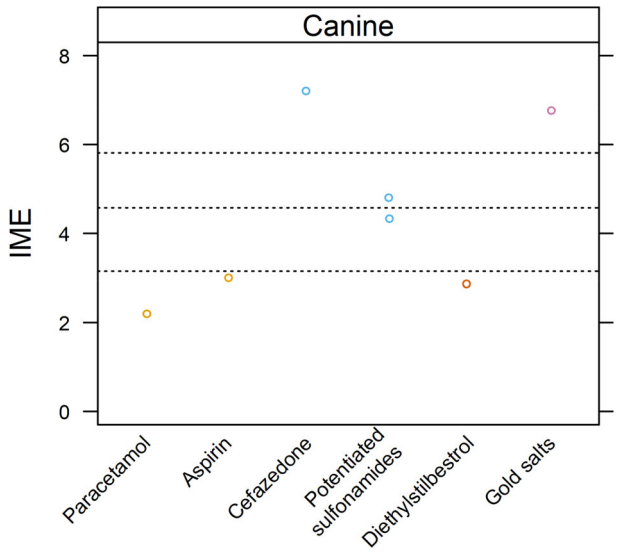

FIGURE 6 Summary of evidence for the causal role of drugs as a trigger for ITP in dogs. Level of evidence for drugs as a cause of ITP was assessed by means of a published *Integrated Metric of Evidence* (IME) value. Horizontal dotted lines indicate threshold IME values between negligible and low (3.15), low and intermediate (4.57), and intermediate and high (5.81) levels of evidence based on predetermined thresholds (Supporting Information 8). An IME value of 0 indicates that a study directly demonstrted a lack of evidence that a comorbidity caused ITP.

5.1.5 | Other infections in cats

See Supporting Information 12

5.2 | Drugs

Mechanisms of drug-induced ITP have been investigated extensively in human medicine.[169-171] Drug-induced immune dysregulation may result in both cellular and humoral immune targeting of platelets.[171] Immune-mediated platelet destruction occurs when antibodies that target drug bound to platelet membranes or drug complexed with surface glycoproteins cause Fc-mediated phagocytosis or complement activation and platelet destruction. Destruction may also occur when drugs bind and cause a conformational change in the complementarity-determining region of specific antibodies allowing the antibody to target platelet glycoproteins.[169,170,172] Drugs also can induce autoantibodies targeting platelets or megakaryocytes directly.[169,172]

5.2.1 | Dogs

Overall, the evidence that drugs cause ITP in dogs is low, but high-level evidence suggests that cefazedone and gold salts, and intermediate-level evidence suggests that sulfonamide drugs, ITP. A lack of evidence for other drugs does not preclude the possibility of a drug-triggering ITP. Drug-induced ITP in dogs may be underreported.

Evidence summary

Twenty-four studies were evaluated.[3,21,38,46,74,91,98,115,120,122,124,128,173-184] Integrated metric of evidence values were calculated for 7 drugs in 7 studies (median, 4.33; range, 2.20-7.20; Figure 6).[91,98,115,120,122,124,128] Forty-three percent (3/7) demonstrated negligible,[98,115,124] 14% (1/7) demonstrated low,[122] 14% (1/7) demonstrated intermediate,[120] and 28% (2/7) demonstrated high[91,128] levels of evidence that a drug caused ITP in dogs.

A high level of evidence for drug-induced ITP was found in 2 studies.[91,128] In an experimental study (IME, 7.20) of high-dose (≥540 mg/kg/day) IV cefazedone given over 6 to 17 weeks, thrombocytopenia developed in 11/14 dogs.[128] Six of the 11 thrombocytopenic dogs had platelet counts <100 000/μL, all of which had PSAIG. Thrombocytopenia resolved after cessation of cefazedone in 1 dog and spontaneously resolved despite continued treatment in 2 dogs. In another experimental study (IME, 6.77) gold salt administration induced thrombocytopenia in 5/28 dogs after administration of PO aurano fin or IM gold sodium thiomalate for 45 to 72 months.[91] PSAIG was documented in 4 thrombocytopenic dogs, and platelet counts were < 100 000/μL in 4 dogs, 3 of which had PSAIG. Thrombocytopenia resolved in 3 dogs after withdrawal of gold salts and in 2 dogs in response to prednisolone. Platelet surface-associated immunoglobulin and platelet count were inversely correlated in 1 dog with relapsing ITP.

One case report yielded an intermediate IME value of 4.80.[120] Thrombocytopenia was documented in a dog treated for 7 days with trimethoprim/sulfadiazine, and thrombocytopenia resolved after the drug was discontinued. An immune-mediated mechanism was proposed since plasma from the treated dog caused fragmentation of healthy canine platelets.[120]

The remaining reported cases were associated with low or negligible evidence supporting drug-induced ITP in dogs.[98,115,122,124] In one case report (IME 4.33), thrombocytopenia, protein-losing nephropathy, lymphadenopathy, and polyarthritis were documented after administration of sulfadimethoxine/ormetoprim that resolved rapidly upon drug discontinuation.[122] In another case report (IME, 3.00), a dog was treated with aspirin at 10 mg/kg PO q8h for 3 weeks, then at 10 mg/kg PO q24h, before developing IMHA with thrombocytopenia.[124] The dog improved with immunosuppression but subsequently was euthanized because of dyspnea. Another case report (IME, 2.87) described a dog that received diethylstilbestrol (2.5 mg/kg weekly) for 3 to 4 years that developed severe thrombocytopenia.[98] In a case report of a dog with IMHA and severe thrombocytopenia after acetaminophen administration (IME, 2.20), the thrombocytopenia resolved rapidly after acetaminophen discontinuation and an unspecified dose of prednisolone.[115]

For 17 studies, IME values could not be calculated because of the administration of multiple drugs, presence of multiple comorbidities, incomplete data reporting, or an inability to apply ITP diagnostic criteria.[3,21,38,46,74,120,173-184] One study explored an immune-mediated mechanism for sulfonamide-induced ITP and documented PSAIG in 19/21 dogs.[179] All 11 thrombocytopenic dogs with clinical bleeding had documented PSAIG. However, thrombocytopenia was defined as <175 000 platelets/μL, and individual values were not reported, precluding calculation of an IME value.

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5.2.2 | Cats

See Supporting Information 12

5.3 | Cancer

See Supporting Information 12

5.4 | Vaccination

See Supporting Information 12

5.5 | Toxins

See Supporting Information 12

5.6 | Inflammatory DIsease

See Supporting Information 12

6 | CONSENSUS SCREENING RECOMMENDATIONS

6.1 | Global screening recommendations for dogs and cats

Testing should be performed according to the diagnostic algorithm (Figures 2 and 3) and the written recommendations presented in the preceding sections to confirm that consumption, sequestration, or bone marrow disease (other than that affecting megakaryocytes because of ITP) are not the sole cause of thrombocytopenia.

To differentiate primary from secondary ITP, a thorough history documenting vaccinations, drugs, toxins, travel, exposure to fleas, ticks and other vectors, flea and tick prevention, and heartworm testing and prevention is recommended. A thorough physical examination including retinal examination and examination of the skin, lymph nodes, joints, bones, digital examination of the rectum, and in male dogs, the prostate gland, should be performed. Laboratory screening should include a CBC with blood film examination by a board-certified clinical pathologist (or equivalently trained hematologist), serum biochemical panel, and routine urinalysis. Urine culture and fecal flotation with centrifugation also should be considered. Imaging and other diagnostic tests to screen for cancer and potential foci of inflammation or infection should be performed at the discretion of the attending clinician based on their likelihood in the individual animal. In intact male dogs, prostatic ultrasound examination should be considered.

6.2 | Specific screening recommendations for dogs

Dogs with suspected ITP should be specifically screened for infection with *Ehrlichia* spp., *Babesia* spp., and *Anaplasma* spp. using combined testing with serology and PCR. Repeat testing by means of PCR or convalescent serologic testing or both should be performed in all dogs originally testing negative but with a high risk of infection based on breed or exposure risk.[144,185-189]

Dogs with suspected ITP and other signs of leishmaniosis living in or with a history of travel to enzootic areas, and at-risk breeds in non-enzootic areas, should be screened for leishmaniosis using microscopy, serology, PCR or some combination of these tests. Dogs with suspected ITP living in or traveling to enzootic areas should be screened for infection with *Rangelia* spp. using combined testing with microscopy and PCR. Repeat testing by means of PCR should be performed in all dogs originally testing negative but with a high risk of infection. In dogs with ITP living in or traveling to enzootic areas, and especially those with concurrent cardiopulmonary disease, screening for *Angiostrongylus vasorum* using fecal sedimentation, antigen assay, or additional testing such as tracheal lavage fluid cytologic examination and PCR can be considered.

Further study to determine how and if other vector-borne disease agents cause ITP is required before definitive screening recommendations can be made for additional organisms. However, screening for additional vector-borne pathogens should be considered in dogs with exposure risk and clinical abnormalities consistent with infection. Screening for canine distemper virus should be considered if dogs are non- or under-vaccinated, living in enzootic areas, and have clinical findings consistent with infection. Evidence of systemic (eg, endocarditis, leptospirosis) or focal infections identified during initial screening should be further investigated, and changes in platelet count in response to treatment monitored.

6.3 | Specific screening recommendations for cats

All sick cats should be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infection, according to American Association of Feline Practitioners (AAFP) retrovirus management guidelines. Although the role of infections in the development of ITP is unclear, identifying infections with a minimum database of CBC, serum biochemical panel, urinalysis, imaging, and specific testing as appropriate for a given case context, is warranted in thrombocytopenic cats with suspected ITP given the implications of immunosuppression and the possible role of infection as a trigger for ITP in an individual cat. In cats with suspected ITP living in enzootic areas or with exposure risk, screening for *A. phagocytophilum*, *Ehrlichia* spp., and *B. felis* should be considered.

7 | LIMITATIONS

A limitation of the literature evaluated for both diagnostic and comorbidity components of this consensus statement is that platelet counts

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were not universally or uniformly verified in the evaluated studies, such that the prevalence and magnitude of thrombocytopenia might have been overestimated. In addition, there was inherent subjectivity and therefore variability in how the diagnostic algorithm was applied by evidence evaluators and, for comorbidities, in evaluating study indirectness by evidence evaluators. For several PECO questions, the level of evidence for the use of a diagnostic test was "low" and the strength of recommendation was "weak." Similarly, evidence that a comorbidity caused ITP was often "negligible" or "low."

For some comorbidities, it is possible that mechanisms other than immune-mediated platelet destruction contributed to the magnitude of thrombocytopenia. For example, infections can cause decreased platelet production by targeting bone marrow or decreasing hepatic TPO production, platelet sequestration from vasculitis or splenomegaly, platelet consumption from DIC, or by causing platelet desialylation and removal.[137,155,190] Applying the algorithm helped to determine whether these processes contributed to the thrombocytopenia, but the extent of their effects could not always be determined. This approach could have affected causation scores and overall IME values.

Many comorbidities were assigned low or negligible IME values because studies did not specifically address whether a comorbidity causes ITP (indirectness). These studies were designated as "Descriptive Association" for the study design (Supporting Information 9). Therefore, low or negligible IME values should not be interpreted as a lack of causation.

Finally, although some studies were designed to determine if a comorbidity caused ITP, IME values could not be calculated because of the way platelet counts were reported or inability to apply the diagnostic algorithm. When identified, these articles were captured in the evidence summaries and are reflected in the evidence summary statements and screening recommendations.

8 | FUTURE DIRECTIONS

Given the lack of available literature to answer many of the PECO questions, appropriately designed outcomes-based studies that directly ask and answer these questions are needed to make more robust guidelines for the diagnosis of ITP in dogs and cats. Additional platelet indices such as immature platelet fraction recently have been introduced to veterinary medicine and may have diagnostic and prognostic utility.[191] Diagnostic guidelines regarding the utility of certain tests may be revised in the future based on the results of studies designed to answer the PECO questions.

Mechanistic studies investigating whether PSAIG causes FcγR dependent or independent clearance, the role of antibody-independent immune-mediated platelet destruction, and whether and how comorbidity or self-antigen is targeted by the immune system may help in the development of tests that definitively diagnose ITP and individualize treatment strategies. Similarly, future research may demonstrate, as it has in murine models and human patients, that the mechanism of platelet clearance varies with the platelet antigen being targeted, which may in turn impact the ideal treatment modality.[192]

AUTHOR CONTRIBUTIONS

Dana N. LeVine, Linda Kidd and Oliver A. Garden are co-chairs on the consensus statement and share corresponding author status. Dana N. LeVine, Linda Kidd, Oliver A. Garden, Marjory B. Brooks, and Robert Goggs share first authorship. Marjory B. Brooks, Robert Goggs, Barbara Kohn, and Andrew J. Mackin are panel members on the consensus statement. Erin Eldermire, Yu-Mei Chang, Julie Allen, Peter W. Christopherson, Barbara Glanemann, Haruhiko Maruyama, Maria C. Naskou, Lise N. Nielsen, Sarah Shropshire, Austin K. Viall, Adam J. Birkenheuer, Marnin A. Forman, Andrew S. Hanzlicek, Kathrin F. Langner, Erin Lashnits, Katharine F. Lunn, Kelly M. Makielski, Xavier Roura, and Eva Spada are advisory task force members on the consensus statement.

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CONFLICT OF INTEREST DECLARATION

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OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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