Treatment of Sulfonamide-Hypersensitivity Associated Thrombocytopenia with Human Intravenous Immunoglobulin in a Dog: A Case Report.

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ABSTRACT

Sulfonamide-associated hypersensitivity is an established, yet uncommon, complication of sulfa drugs derivatives in both humans and dogs. Severe, immune-mediated, thrombocytopenia can occur in both species. A four-year-old, spayed female dog was diagnosed with presumed sulfonamide-associated hypersensitivity resulting in severe thrombocytopenia and bleeding. Human intravenous immunoglobulin infusion was administered twice after the dog was refractory to conventional treatment and concern for endocarditis limited further use of immunosuppressive drugs. Improvement in platelet count was evident three days from the second infusion and the dog made full a recovery. This article provides new and unique information in that human intravenous immunoglobulin infusion was successfully used as part of the management of a case of sulfonamide-associated hypersensitivity with severe thrombocytopenia.

Key words: Trimethoprim-sulfamethoxazole; Idiosyncratic; Immune Mediated Thrombocytopenia; Immunomodulation.

INTRODUCTION

Drugs of the Diaminopyrimidines- Sulfonamides family exert their antibacterial action through sequential and synergistic inhibition of the enzymes involved in synthesis of folic acid from para-aminobenzoic acid (1,2). Tetrahydrofolic acid, the metabolically active form of folic acid is an essential co-factor in the synthesis of purines and pyrimidines, and thus to DNA synthesis. It is also required for synthesis of other amino acids such as serine and methionine (2). Mammals, unlike micro-organisms, acquire most folic acid from the diet, which explains the selective action of sulfonamides against microbes (2). Trimethoprim-sulfamethoxazole (TMS) is considered a first line treatment for urinary tract infections, as well as other types of infections such as prostatitis and respiratory tract infections (1,3).

Idiosyncratic reactions, or drug-related delayed hypersensitivity reactions, leading to a wide spectrum of clinical manifestations are associated with the use of sulfonamides and potentiated sulfonamides (i.e. sulfonamides compounded with trimethoprim or ormetoprim). In humans, these reactions are categorized as dermatological reactions, blood dyscrasias, and hepatic necrosis (2,4). Sulfonamide-associated hypersensitivity (SAHS) also occurs in dogs (5). Fever, thrombocytopenia and hepatopathy are the most common findings in dogs treated with potentiated sulfonamides, followed by neutropenia, hemolysis, arthropathy, uveitis, skin eruption, proteinuria, facial palsy, meningitis, pancreatitis, facial edema and pneumonitis (5).

Despite the rather low incidence of sulfonamide-associated thrombocytopenia in humans(2,4,6), it is relatively

common among dogs (5). The pathogenesis of SAHS is incompletely understood, but an immune-mediated reaction is considered the most likely mechanism (7,8). And indeed, the presence of anti-platelets antibodies have been demonstrated (9–12). Drug discontinuation might resolve the thrombocytopenia, but can be insufficient as a sole measure, especially if the patient is actively bleeding.

Due to its immune-mediated nature, treatment of sulfonamide associated thrombocytopenia includes immunosuppression, with corticosteroids being the first line of treatment in humans (13–21). Treatment recommendations for SAHS in veterinary patients are lacking, but immunosuppression with glucocorticoids is suggested (22). Other treatments that are aimed to increase the platelet count or treat the immune-mediated reaction are described in humans with sulfonamide-associated thrombocytopenia, these include: platelet transfusions (14,16,18,20,21), vincristine (13), Rituximab (a B-cell antigen CD20 antibody) (13), plasmapheresis (13) and Human intravenous immunoglobulin (hIVIg) (11,13–18,21).

hIVIg is as an immunomodulator commonly used in veterinary patients with primary immune-mediated thrombocytopenia (IMT) (23). Therapy with hIVIg results in effective, but transient, immunomodulation. It may be incorporated in a multidrug strategy when treating IMT. Especially in patients in which the use of conventional immunosuppression is limited (e.g. concurrent infection) or is not effective.

In this report we present the successful use of hIVIg as part of the management of SAHS, including severe IMT in a dog.

CASE REPORT AND SUMMARY

A-4 years old female, spayed, 29 kg, mixed breed dog was referred to the veterinary teaching hospital (Koret School of Veterinary Medicine, The Hebrew University of Jerusalem) due to hematemesis, anorexia and lethargy. The dog had a previous history of recurrent cystitis, with an episode occurring 7 months prior to presentation, and was treated with TMS (brand name, dosage and duration of treatment unknown). Fourteen days before presentation to the VTH the dog was pollakiuric and stranguric and treatment with TMS (Diseptyl Forte, REKAH pharmaceutical industry, LTD., Hamelacha St., Holon, Israel) was initiated by the primary care veterinarian based on a previous urine culture and antibiogram results. TMS was prescribed for 3 weeks at a dose of 13.9 mg/kg, PO, twice daily. On the 10th day of treatment, the dog was presented to the primary care veterinarian due to hematemesis and melena. Treatment with metronidazole (brand name, dosage and duration of treatment unknown) and famotidine (brand name, dosage and duration of treatment unknown) was prescribed. Clinical signs did not improve, the dog became anorexic, developed petechial hemorrhages and was referred to the VTH.

On physical examination the dog was quite, alert and responsive, had a fever of 39.6^{O}C, was tachycardic (160 bpm), and panting. Ecchymotic hemorrhage was evident near the right axillary region, petechiae were present in the oral mucosa and inguinal area. Complete blood count (Advia 120 or 2120i, Siemens, Medical solutions diagnostics GmbH, Erlagen, Germany; Abacus Junior Vet, Diatron, Wein, Austria) showed severe leukopenia with severe neutropenia, monocytopenia and lymphopenia, mild normocytic-normochromic anemia and severe thrombocytopenia with an increased mean platelet volume (Table 1). Blood smear evaluation confirmed the leukopenia and thrombocytopenia, with 30% band neutrophils. Marked spherocytosis (80%-90%) was evident. Serum biochemistry (Cobas 6000, Roche, Mannheim, Germany; at 37° C) showed an increased activity of the muscle enzymes creatine kinase, aspartate aminotransferase, and alanine aminotransferase. Mild hyperbilirubinemia and mild total hypocalcemia were also evident (Table 2). Activity of 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester (DGGR) lipase was moderately increased (Cobas 6000, Roche, Mannheim, Germany; at 37° C) (Table 2). Clotting times (Werfen; ACL top 300; 180 Hartwell Road, Bedford, USA) were within normal limits (Table 2).

According to the recent history of exposure to TMS and compatible clinical and clinicopathological findings, the presumptive diagnosis was SAHS resulting in leukopenia, IMT, polymyositis, and pancreatitis, and due to the severe spherocytosis, immune mediated hemolytic anemia (IMHA) was also suspected (24).

In light of the presumptive diagnosis, TMS treatment was discontinued. The dog was hospitalized and treated with IV fluids (lactated ringer solution, Teva Medical, Ashdod, Israel; at 2.7 ml/hr), Metoclopramide (CRI at 1 mg/ kg/24hr, S.A.L.F S.p. A, Cenate Sotto, Italy) and Maropitant (1 mg/ kg, SIV, SID, Zoetis Inc., Kalamazoo, Michigan, United

Table 1. Hematology results for a 4 years old dog with severe SAHS reaction to Trimethoprim-Sulfamethoxazole at presentation and post hIVIg treatment.

Hematology	Reference interval	At Presentation	4 days post initial dose of hIVIg	1 day post 2nd dose of hIVIg	7 days post 2nd dose of hIVIg	14 days post 2nd dose of hIVIg	35 days post 2nd dose of hIVIg
WBC	5.2-13.9 (10.e3/uL)	1.4	19.6	18.8	25.7	14.6	10.1
Neutrophiles abs.	3.9-8 (10.e3/uL)	0.3	15.6	N/A	21.7	9.3	7.7
Monocytes abs.	0.1-1.1 (10.e3/uL)	0.1	1.0	N/A	1.2	0.4	0.4
Lymphocytes abs.	1.3-4.1 (10.e3/uL)	0.9	2.7	N/A	2.4	3.5	1.5
Hematocrit	37.1-57 (%)	33.8	19.0	15.7	34.6	44.4	49.1
MCV	58.8-71.2 (fL)	67.3	68.6	73.0	77.5	71.5	62.8
MCHC	31-36.2 (g/dL)	34.8	33.8	29.4	29.7	30.1	32.7
Platelets	143-400 (10.e3/uL)	4.0	7.0	22.0	315.0	616.0	312.0
MPV	7-11 (fL)	14.3	15.5	8.0	15.4	10.9	9.8
Packed cell volume	30-55%	31.0	16.0	15.0	33	N/A	46.0
Total solids	5.5-7.5	6.8	7.0	7.0	8.0	N/A	7.5

Abbreviations: WBC, white blood cells; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume.

States) to correct the hydration status and control vomiting, respectively. Antioxidants were given due to the possibility of acute hepathopathy reported as part of the syndrome (5,22) these included: WePatic® (1 tablet for medium to large dogs, PO, SID, Wepharm® S.A., Porto de Mos, Portugal), Vitamin C (30 mg/kg, SIV, QID, brand and manufacturer unknown) and N- acetyl- cysteine (69 mg/kg, SIV, TID, Aurum Pharmaceuticals Ltd., Essex, UK). Prophylactic antibiotic treatment including Enrofloxacin (Baytril, Bayer Animal Health, Leverkusen, Germany;10 mg/kg, SIV, SID,) and Clindamycin (12 mg/kg, IV, BID, Rafa laboratories Ltd., Jerusalem, Israel) was initiated to reduce the chance of opportunistic infections secondary to the severe leukopenia. Anti-histamine (Diphenhydramine, 3.4 mg/kg, SC, TID, compounded), and Tranexamic acid (10.3 mg/kg, SIV, TID, Italian Medicinal Bioindustrial Laboratories, Novi Ligure, Italy) were also prescribed.

To manage the immune mediated components of the syndrome, treatment with corticosteroids (dexamethasone 0.2 mg/kg, IV, once, WEST-WARD, New Jersey, United States, followed by prednisone (0.86 mg/kg, PO, BID, Rekah Pharmaceutical Industry Ltd., Israel)) and hIVIg infusion (0.34 gr/kg, SIV over 6 hours, Kiovig, Takeda Ltd., Petach Tikva, Israel) were initiated. In addition, granulocyte colony stimulating factor was administered for the severe neutropenia (Filgrastim 5 mcg/kg, SC, SID for 3 consecutive days, NEUPOGEN®, Amgen Manufacturing Limited, Puerto Rico, United States).

On the second day of hospitalization the dog had a normal temperature, was actively bleeding with newly apparent petechial hemorrhages, presence of epistaxis and hematuria, with concurrent decrease in the hematocrit and total protein and worsening of hyperbilirubinemia. These changes were assessed to be the result of the bleeding, hemolysis and pancreatitis. On the fifth day of hospitalization melanotic diarrhea was evident. CBC showed resolution of the leukopenia with rebound neutrophilia, anemia remained unchanged and the severe thrombocytopenia persisted (Table 1.). On the 8th day additional immunosuppression treatments were initiated: Cyclosporine (2.7mg/kg, PO, BID, ATOPICA®, Elanco US Inc., Indiana, United States) was initiated due to the unresolved thrombocytopenia and the active bleeding. Ondansetron (0.1 mg/kg, SIV, TID, Kleva S.A., Athens, Greece) and Mirtazapine (0.52 mg/kg, PO, SID, Unipharm Ltd., Tel Aviv) were also administered to enhanced control the nausea and improve the appetite, respectively.

The next day, the dog became lethargic and tachypneic. Worsening of the anemia was ruled out as the cause for

Table 2. Biochemistry and coagulation panel results of a 4 years old dog with severe SAHS reaction to Trimethoprim- Sulfamethoxazole at presentation.

Biochemistry	Reference interval	At Presentation
CPK	51-399 (IU/L)	7477.0
AST	19-42 (IU/L)	372.0
ALT	19-67 (IU/L)	147.0
ALP	21-170 (IU/L)	71.0
GGT	0-6 (IU/L)	<3.0
Triglyceride	19-133 (mg/dL)	60.0
Cholesterol	135-361 (mg/dL)	136.0
Total bilirubin	0-0.2 (mg/dL)	0.6
Glucose	64-123 (mg/dL)	125.0
Albumin	3-4.4 (mg/dL)	3.0
Total protein	5.4-7.6 (mg/dL)	5.9
Urea	10.7-53.5 (mg/dL)	51.8
Creatinine	0.3-1.3 (mg/dL)	0.9
Phosphate	3-6.2 (mg/dL)	3.1
Total calcium	9.7-11.5 (mg/dL)	9.2
Sodium	140-154 (mmol/L)	151.0
Potassium	3.6-5.3 (mmol/L)	4.2
Chloride	104-118 (mmol/L)	114.3
Lipase DGGR	5-107 (IU/L)	780.0
Prothrombin time	(sec)	8.9
Activated partial thromboplastin time	(sec)	11.3

Abbreviations: CK, creatine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

the deterioration. On physical examination, a newly recognized heart murmur was evident, characterized as 4/6, crescendo-decrescendo, at the heart base. The anemia might have caused a physiological murmur, yet, infectious endocarditis was considered likely due to the dog's initial immune-compromised state and tendency for recurrent infections, combined with the immunosuppressive treatment. No structural changes compatible with valvular vegetations were evident on echocardiography and blood culture was negative for bacterial growth. Despite the lack of definitive diagnosis of infectious endocarditis, cyclosporine was discontinued and prednisone treatment was tapered. The lack of improvement in platelet count, along with the risks involved with conventional immunosuppressive therapy led to the decision to give a second dose of hIVIg (0.57 gr/kg, SIV over 44 hours). The day following completion of hIVIg infusion, the platelet counts markedly improved (Table 1.). At this time, the dog was consistently brighter and alert and there was no evidence of bleeding. The dog was discharged with instructions to feed a fat restricted diet, WePatic® (as above), Vitamin C (as above), Clindamycin (17.3 mg/kg, PO, BID, for 1 month, Pfizer PFE Pharmaceuticals Ltd., Herzliya, Israel), Mirtazapine (as above), Oflodex (9.6 mg/kg, PO, SID, for 1 month, Dexcel LTD, Israel), Cephalexin (28.8 mg/kg, PO, TID, for 1 month, Therios®, Ceva Animal Health Ltd., Buckinghamshire, United Kingdom), and prednisone was completely tapered off.

The dog presented for re-evaluation four days after discharge, at which time the owners reported an overall improvement except for a newly developed mild shifting lameness. On physical exam the dog had effusion of both elbow joints. CBC showed leukocytosis with neutrophilia and monocytosis, improvement of the anemia and normal platelet count (Table-1, day-7 post 2nd hIVIg dose). Doxycycline (9.8 mg/kg, PO, SID, Dexcel Ltd., Or Akiva, Israel) and Gabapentin (11.7mg/kg, BID, PO, Inovamed Ltd., Farmaprojects S.A.U., Spain) were added to the ongoing treatment as infective polyarthritis was considered the most likely cause.

During the following 7 weeks (35 days post 2nd hIVIg dose) the dog continued improving clinically and hematologicaly with an initial thrombocytosis and then normalization of platelet count (Table 1). Also, the lameness was resolved.

DISCUSSION

The dog presented herein showed a complex of clinical and clinicopathological abnormalities compatible with SAHS. Reports describing SAHS and its management are limited in both human and veterinary medicine. A retrospective study from 2003, reported the clinical and clinicopathological abnormalities in 40 dogs with SAHS (5). In that study, the mean time from exposure to potentiated sulfonamides to onset of clinical signs was 12.1 ±5.9 days and females were overrepresented, which is compatible with the time to presentation and the sex of the dog in our report. Fever, thrombocytopenia and hepatopathy are the most common abnormalities reported in dogs with SAHS, and are also present in humans (4,5,25). The dog in this case report was

febrile upon presentation, which could have been a direct result of the hypersensitivity reaction or secondary to other causes such as pancreatitis.

Thrombocytopenia is uncommon in humans with SAHS, when present, it is considered a component of 'blood dyskaryosis' syndrome, and recently recognized as the result of drug-related immune-mediated destruction of platelets (6,17). In most reports describing SAHS in humans, thrombocytopenia developed days after the initial exposure or after repeated exposure to the same drug (22). Immune-mediated destruction is thought to be the primary mechanism and drug-dependent antibodies, targeted either against platelets epitopes, or drug metabolites, have been demonstrated (10–12). Other mechanisms such as vasculitis leading to platelet consumption (13), or bone marrow suppression are also possible. Treatment of severe thrombocytopenia in humans with SAHS is described in several reports. In all, drug administration was immediately discontinued (11,13–17,20,21,26). Additional treatments included: high dose corticosteroids, repeated hIVIg transfusions and platelet transfusions (13–17,19–21,26). Those are in accordance with the consensus guidelines for the initial treatment of IMT in adult humans (27). Thrombocytopenia is present in about 50% of dogs with SAHS, and its presence is considered a negative outcome predictor (5). In dogs and cats with IMT, corticosteroids are the mainstay of treatment due to their effectivity, availability and low cost, while other immunosuppressive drugs are considered 2nd line treatments (23). In the current case, immunosuppression with corticosteroids, and later on, cyclosporin, were administered, yet, due to the new heart murmur, raising the possibility for infectious endocarditis, these were discontinued. Despite the lack of improvement after the initial hIVIg dose, a second dose was assessed to be the best course of treatment due to its relative safety in situations where concurrent infection is suspected. Moreover, the dose of the first hIVIg infusion, was relatively low and could have been insufficient (28). hIVIg has the advantage of treating immune-mediated diseases by immunomodulation, without causing immunosuppression (23). The mechanisms behind these are not entirely understood, but it is postulated that its efficacy is related to Fc receptor blockade, autoantibody elimination, cytokine modulation, complement inhibition, and Fas–Fas ligand blockade (28,29). In dogs with IMT, hIVIg is considered safe, while reducing the time for platelet count recovery and hospitalization duration (30–32). Nevertheless, evidence to support the use of hIVIg in dogs with thrombocytopenia related to SAHS is lacking. The decision to treat the dog in this case was based on the assumed immune-mediated mechanism and extrapolation from humans. Improvement in platelet count was evident one day after the second hIVIg infusion, resulting in complete normalization on the re-examination, 7 days later.

The improvement of the anemia was mainly attributed to the cession of the bleeding when the platelet counts increased. However, it might also have been due to attenuation of red blood cells destruction induced by hIVIg, even though hIVIg showed no benefit in treatment of IMHA and is considered a salvage drug when conventional immunosuppression fails (23). The leukopenia and neutropenia improved rapidly. The mechanism leading to myelosuppression in SAHS is unknown. It was suggested in previous reports that the neutropenia is transient and resolves spontaneously (22). Yet, the administration of corticosteroid and G-CSF could have also contributed to the improvement in the neutrophils count as well as the hIVIg.

The reason for the increased muscle enzymes activity in this dog is unknown. Rhabdomyolysis or myositis are not reported to be part of SAHS. Further tests including muscle biopsy or electromyography were not performed due to the improvement with treatment. It is possible that an immune-mediated polymyositis was present in this dog, explaining the improvement with immunosuppressive treatment. However, the dog also received antibiotics and thus infectious polymyositis cannot be excluded as well as other causes such as poor muscle prefusion due to dehydration or anemia.

Thirty-one days from TMS exposure the dog presented with a shifting lameness and joint swelling. Immune-mediated polyarthritis is a known component of SAHS, although it is not typically delayed. A late manifestation of septic polyarthritis acquired during the period of immunosuppression and suspected endocarditis could not be excluded. Due to the overall improvement in the dog's condition, and the difficulty in differentiating septic from immune-mediated polyarthritis an antibiotic treatment was chosen as the best course of treatment. 36 days later, the lameness resolved.

In conclusion, incorporation of hIVIg in the management of SAHS associated thrombocytopenia potentially contributed to the full recovery of the dog presented herein. Firm conclusions cannot be drawn based on a single case

report; however, the improved platelet count immedi-

ately after the hIVIg administration, indicates its potential contribution the resolution of thrombocytopenia. Therefore, hIVIg should be considered in dogs with SAHS associated thrombocytopenia, especially if concurrent risk for infections (e.g. neutropenia) is present.

REFERENCES

1. Skyes, J.E. and Papich, M.G.: Antibacterial Drugs. In: Little, S.E., Rankin, S.C., Papich, M.G., Weese, Skyes, J.E. and Papich, M.G.: Antibacterial Drugs. In: Little, S.E., Rankin, S.C., Papich, M.G., Weese, J.S: Green's Infectious Diseases of The Dog and Cat 5th ed. Riverport Lane St. Louis, Missouri, pp. 113–4, 2003.
2. Rubin, R.H. and Swartz, M.N.: Trimethoprim-sulfamethoxazole. N. Engl. J. Med. 21;303(8):426–432, 1980.
3. Weese, J.S., Blondeau, J., Boothe, D., Guardabassi, L.G., Gumley, N., Papich, M., Jessen, L.R., Lappin, M., Rankin, S., Westropp and J.L. and Skyes, J.: International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats. Vet. J. Lond. Engl. 1997. May;247:8–25, 2019.
4. Lawson, D.H. and Paice, B.J: Adverse reactions to trimethoprim-sulfamethoxazole. Rev. Infect. Dis. 4(2):429–433, 1982.
5. Trepanier, L.A., Danhof, R., Toll, J. and Watrous, D.: Clinical findings in 40 dogs with hypersensitivity associated with administration of potentiated sulfonamides. J. Vet. Intern. Med. 17(5):647–652, 2003.
6. Kaufman, D.W., Kelly, J.P., Johannes, C.B., Sandler, A., Harmon, D., Stolley, P.D. and Shapiro, S.: Acute thrombocytopenic purpura in relation to the use of drugs. Blood. Nov 1;82(9):2714–2718, 1993.
7. Van den Bemt, PMLA., Meyboom, R.H.B. and Egberts, A.C.G.: Drug-induced immune thrombocytopenia. Drug Saf.27(15):1243–1252, 2004.
8. Kam, T. and Alexander, M.: Drug-induced immune thrombocytopenia. J. Pharm. Pract. Oct;27(5):430–439, 2014.
9. Vayne, C., Guéry, E.A., Rollin, J., Baglo, T., Petermann, R. and Gruel, Y.: Pathophysiology and Diagnosis of Drug-Induced Immune Thrombocytopenia. J. Clin. Med. 13;9(7):2212, 2020.
10. Curtis, B.R., McFarland, J.G., Wu, G.G., Visentin, G.P. and Aster, R.H.: Antibodies in sulfonamide-induced immune thrombocytopenia recognize calcium-dependent epitopes on the glycoprotein IIb/IIIa complex. Blood. Jul 1;84(1):176–183, 1994.
11. Nixon, C.P., Cheves, T.A. and Sweeney, J.D.: Sulfamethoxazole-induced thrombocytopenia masquerading as posttransfusion purpura: a case report. Transfusion (Paris). 55(11):2738–2741, 2015.
12. Kiefel, V., Santoso, S., Schmidt, S., Salama, A. and Mueller-Eckhardt, C.: Metabolite-specific (IgG) and drug-specific antibodies (IgG, IgM) in two cases of trimethoprim-sulfamethoxazole-induced immune thrombocytopenia. Transfusion (Paris). 27(3):262–265, 1987.
13. Martin, M.G., Whitlatch, N.L., Shah, B. and Arepally, G.M.: Thrombotic thrombocytopenic purpura induced by trimethoprim-sulfamethoxazole in a Jehovah's Witness. Am. J. Hematol. 82(7):679–681, 2007.
14. Chute, J.P., Frame, J.N., Ganey, J.T., Phares, J.C. and Shakir, K.M.: Intravenous immunoglobulin followed by platelet transfusion in the acute treatment of trimethoprim/sulfamethoxazole-induced immune thrombocytopenia. Am. J. Hematol. 43(4):329–30, 1993.
15. Herrington, A., Mahmood, A. and Berger, R.: Treatment options in sulfamethoxazole-trimethoprim-induced thrombocytopenic purpura. South Med. J. 87(9):948–950, 1994.
16. Yamreudeewong, W., Fosnocht, B.J. and Weixelman, J.M.: Severe thrombocytopenia possibly associated with TMP/SMX therapy. Ann. Pharmacother. 36(1):78–82, 2002.
17. Papaioannides, D., Bouropoulos, C. and Korantzopoulos, P.: Co-trimoxazole induced acute thrombocytopenic purpura. Emerg. Med J. 20(3):e3–e3, 2003.
18. Aster, R.H., Curtis, B.R., McFarland, J.G. and Bougie, D.W.: Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J. Thromb. Haemost. JTH. 7(6):911–9118, 2009.
19. Tisdale, W.A.: Focal Hepatitis, Fever and Skin Rash Following Therapy with Sulfamethoxypyridazine, a Long-Acting Sulfonamide. N. Engl. J. Med. 258(14):687–690, 1958.
20. Caluwé, R., Van Laecke, S., Emonds, M.P., Peeters, P. and Vanholder, R.: Immediate posttransplantation cotrimoxazole-induced immune thrombocytopenia. Am. J. Transplant. 10(4):943–946, 2010.
21. Gaudel, P., Qavi, A.H. and Basak, P.: Life-Threatening Thrombocytopenia Secondary to Trimethoprim/Sulfamethoxazole. Cureus. 19;9(12):e1963, 2017.
22. Trepanier, L.A.: Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. J Vet. Pharmacol. Ther. 27(3):129–138, 2004.
23. LeVine, D.N., Goggs, R., Kohn, B., Mackin, A.J., Kidd, L., Garden, O.A., Brooks, M.B., Eldermire, R.B., Abrams-Ogg, A., Appleman, E.H., Archer, T.M., Bianco, D., Blois, S.L., Brainard, B.M., Callan, M,B., Fellman, C.L., Haines, J.M., Hale, A.S., Huang, A.A., Lucy, J.M., O'Marra, S.K., Rozanski, E.A., Thomason, J.M., Walton, J.E. and Wilson, H.E.: ACVIM consensus statement on the treatment of immune thrombocytopenia in dogs and cats. J. Vet. Intern. Med. 38(4):1982–2007, 2024.
24. Garden, O.A., Kidd, L., Mexas, A.M., Chang, Y-M., Jeffery, U., Blois, S.L. Fogle, J.E., A. MacNeill, A.L., Lubas, G. Birkenheuer, A., Buoncompagni, S., Dandrieux, J.R.S., Di Loria, A., Fellman, C.L., Glanemann, B., Goggs, R., Granick, J.L., LeVine, D.N., Sharp, C.R., Smith-Carr, S., Swann, J.W. and Szladovits, B.: ACVIM consensus statement on the diagnosis of immune-mediated hemolytic anemia in dogs and cats. J. Vet. Intern. Med. 33(2):313–334, 2019.
25. Malnick, S.D., Atali, M., Israeli, E., Abend, Y. and Geltner, D.: Trimethoprim/sulfamethoxazole-induced rash, fever, abnormal liver function tests, leukopenia, and thrombocytopenia. Ann. Pharmacother. 27(9):1139–1140, 1993.
26. Barr, A.L. and Whineray, M.: Immune thrombocytopenia induced by cotrimoxazole. Aust. N Z J. Med.10(1):54–55, 1980.
27. Gonzalez-Lopez, T.J., Provan, D., Barez, A., Bernardo-Gutierrez, A., Bernat, S., Martinez-Carballeira, D., Jarque-Ramos, I., Soto, I., Jimenez-Barcenas, R. and Fernandez-Fuertes, F.: Primary and

secondary immune thrombocytopenia (ITP): Time for a rethink. Blood Rev. Sep;61:101112, 2023.
28. Viviano, K.R.: Update on immununosuppressive therapies for dogs and cats. Vet. Clin. North Am. Small Anim. Pract. 43(5):1149–1170, 2013.
29. Spurlock, N.K. and Prittie, J.E.: A review of current indications, adverse effects, and administration recommendations for intravenous immunoglobulin. J. Vet. Emerg. Crit. Care San Antonio Tex. 21(5):471–483, 2001.
30. Bianco, D., Armstrong, P.J. and Washabau, R.J.: Treatment of Severe Immune-Mediated Thrombocytopenia with Human IV Immunoglobulin in 5 Dogs. J. Vet. Intern. Med.21(4):694–699, 2007.
31. Bianco, D., Armstrong, P.J. and Washabau, R.J.: 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.23(5):1071–1078, 2009.
32. Balog, K., Huang, A.A., Sum, S.O., Moore, G.E., Thompson, C. and Scott-Moncrieff, J.C.: 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. 27(3):536–5641, 2013.