Association of Veterinary Hematology and Transfusion Medicine (AVHTM) transfusion reaction small animal consensus statement (TRACS). Part 3: Diagnosis and treatment

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Abstract

Objective: To systematically review available evidence to develop guidelines for diagnosis and treatment of transfusion associated reactions in dogs and cats.

Design: Standardized and systemic evaluation of the literature (identified through Medline via PubMed and Google Scholar searches) was carried out for identified transfusion reaction types in dogs and cats. The available evidence was evaluated using PICO (Population, Intervention, Comparison, Outcome) questions generated for each reaction type. The evidence was categorized by level of evidence (LOE) and quality (Good, Fair or Poor). Guidelines, diagnostic, and treatment algorithms were generated based on the evaluation of the evidence. Consensus on the final guidelines was achieved through Delphi-style surveys. Draft recommendations were disseminated through veterinary specialty listservs for review and comments, which were evaluated and integrated prior to final publication.

Settings: Academic and referral veterinary medical centers

R**esults:** The Medline via PubMed and Google Scholar databases were searched. There were 14 Population Intervention Comparison Outcome questions identified and corresponding worksheets were developed focusing on the diagnosis and treatment of transfusion associated reactions in dogs and cats. Fourteen guidelines and four algorithms were developed with a high degree of consensus.

Conclusions: This systematic evidence evaluation process yielded recommended diagnostic and treatment algorithms for use in practice. However, significant knowledge gaps were identified, demonstrating the need for additional research in veterinary transfusion medicine.

Keywords: transfusion reactions, corticosteroids, anaphylaxis, fever, hemolysis

Abbreviations:

AABB - American Association of Blood Banks

ACE - Angiotensin-Converting Enzyme

AHTR - Acute Hemolytic Transfusion Reaction

AFAST – Abdominal Focused Assessment with Sonography for Trauma

ARDS - Acute Respiratory Distress Syndrome

AVHTM - Association of Veterinary Hematology and Transfusion Medicine

BCSH – British Committee for Standards in Haematology

BNP - Brain Natriuretic Peptide

CDC - Centers for Disease Control

DAT - Direct Antiglobulin Test

DEA - Dog Erythrocyte Antigen

DHTR - Delayed Hemolytic Transfusion Reaction

DIC - Disseminated Intravascular Coagulation

DSTR - Delayed Serologic Transfusion Reaction

FNHTR - Febrile Non-Hemolytic Transfusion Reactions

Hb – Hemoglobin

HLA - Human Leukocyte Antigen

HNA - Human Neutrophil Antigens

HyTR - Hypotensive Transfusion Reactions

IAT - Indirect Antiglobulin Test

LAH - Left Atrial Hypertension

NHSN - National Healthcare Safety Network

NT-proBNP - N Terminal-proBNP

pRBCs – packed red blood cells

PCR – Polymerase Chain Reaction

PTP - Post-transfusion purpura

SHOT - Serious Hazards of Transfusion

TACO - Transfusion Associated Circulatory Overload

TAD - Transfusion Associated Dyspnea

TA-GVHD - Transfusion Associated Graft Versus Host Disease

TFAST – Thoracic Focused Assessment with Sonography for Trauma/Triage/Tracking

TRALI - Transfusion Related Acute Lung Injury

TTI - Transfusion Transmitted Infection

XM – Crossmatch

Introduction

Transfusions are lifesaving but their administration has risks. Reactions to blood products can either be acute or delayed and can range in severity from minor to life threatening. The prevalence of reactions and complications in veterinary transfusion studies varies from 0-38%,[1–3] depending on the species, reaction definitions, and blood products used. There is limited information on appropriate diagnosis and treatment of transfusion reactions in veterinary medicine.

In 2018, an international committee of veterinary specialists was convened in partnership with the Association of Veterinary Hematology and Transfusion Medicine (AVHTM) to develop consensus definitions and evidence-based recommendations for prevention, monitoring, diagnosis, and treatment of transfusion reactions in veterinary patients.

Methods

The consensus project was initiated through the AVHTM in 2018, as described in part one of this series. The committee decided to limit the project to definitions and guidelines involving transfusion reactions secondary to red blood cell, plasma, and platelet transfusions in canine and feline patients.

Transfusion reactions were defined using evidence review and a consensus process. Those definitions are presented in part one (see companion article). Recommendations for prevention and monitoring were also developed based on evidence review and a consensus process and presented in part two (see second article).

Specific PICO questions were developed by the group around diagnosis and treatment strategies and assigned to transfusion reaction worksheet authors. Comprehensive database searches were then performed including review of both the human and veterinary literature. Each PICO worksheet included search criteria, a review of the relevant veterinary and human literature, and proposed guidelines. Literature was assessed using levels of evidence and quality of evidence as discussed in previous veterinary consensus projects.[4–6]

The proposed guidelines were discussed as a committee with opportunities for changes and suggestions. Delphi style anonymous surveys were then used to tighten and refine the guidelines.[7] These draft guidelines were then presented to the AVHTM, American College of Veterinary Emergency and Critical Care , and American College of Veterinary Internal Medicine discussion boards for comments and suggestions. Guidelines were further refined based on the input received.

Guidelines were characterized as either strong or weak based on four factors:

1) The availability and quality of the evidence

2) Balance of expected beneficial and harmful effects

3) Cost versus benefit

4) Agreement level of the consensus statement members.

Strong recommendations are written as “we recommend.” Weaker recommendations are written as “we suggest.” If we could not find evidence to answer the question, our guidelines start with “No evidence-based recommendation can be made regarding . . .”. Additional recommendations are

listed next. Diagnosis and treatment algorithms for clinical signs associated with transfusion reactions were developed by the group based on these guidelines.

Domain 3: Diagnosis

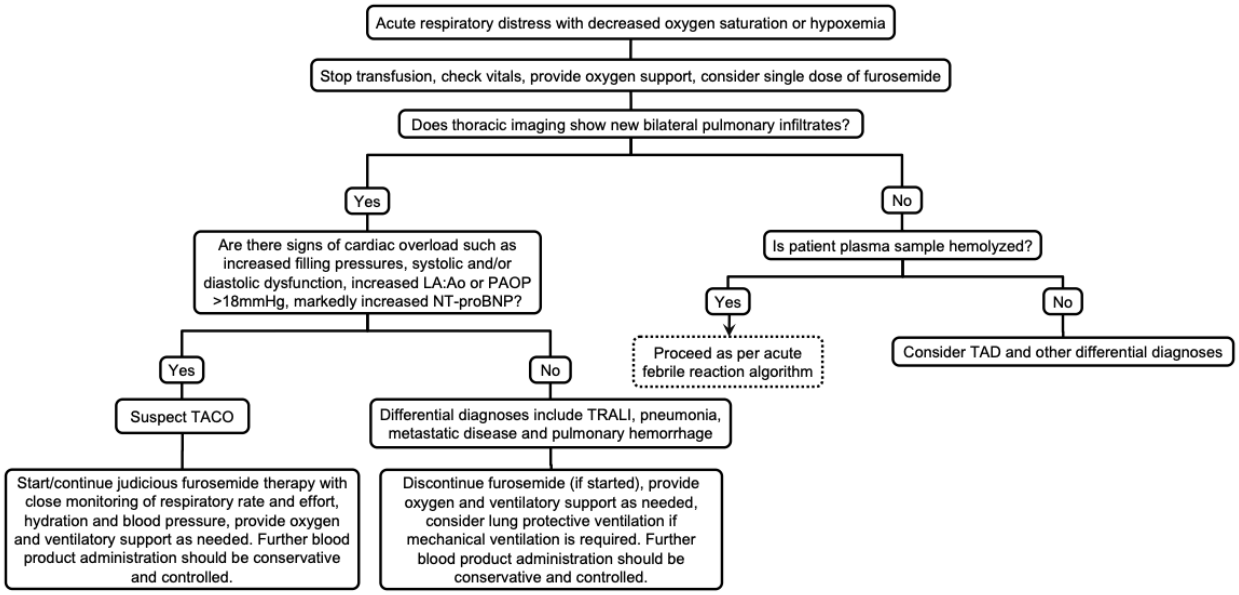
Transfusion reactions are commonly reported in veterinary practice but there is a lack of consensus on how to diagnose specific types of reactions. Systemic review of the current veterinary transfusion reaction literature identifies large knowledge gaps and discordancy in the diagnosis of specific transfusion reactions.[2,3,8,9] Our consensus panel outlined algorithms, based on evidence review, directed at unifying diagnostic criteria for transfusion reactions (Figures One through Four). We also identified three PICO questions focused on specific transfusion reactions in dogs and cats.

Respiratory transfusion reactions

When respiratory signs (tachypnea, increased respiratory effort, cyanosis) develop during or within 6 hours of a blood transfusion, the patient should be evaluated immediately for a possible transfusion reaction (see Figure one). The transfusion should be stopped (if it is still ongoing) and the patient's vitals should be assessed. This should include a pulse oximetry reading, if available.[10] Arterial blood gas analysis may be warranted in ambiguous or more severe cases. Oxygen should also be supplemented in patients that might benefit from it. A point of care ultrasound evaluation of the thorax (thoracic focused assessment with sonography for trauma, triage, tracking-TFAST) may also be performed to identify pleural effusion, pericardial effusion, or ultrasound lung rockets/B-lines (suggestive of pulmonary infiltrates). Clinically significant pleural or pericardial effusion should be removed by centesis as soon as it is identified.

Thoracic radiographs should be obtained as soon as it is safe enough for the patient. Thoracic radiographs may help eliminate non-transfusion related causes of respiratory disease including aspiration pneumonia, metastatic pulmonary disease, pulmonary thromboembolic disease, etc. Animals with transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI)

generally have diffuse bilateral pulmonary infiltrates (TACO and TRALI), and patients with TACO may have cardiomegaly, enlarged pulmonary venous vasculature, or pleural effusion on thoracic radiographs.[11,12] However, it is important to note that radiographic changes are non-specific for both TRALI and TACO.[12] When TRALI or TACO is suspected, point of care ultrasound (TFAST and abdominal focused assessment with sonography for trauma-AFAST) may also be used to try to differentiate between either reaction. Findings on TFAST and AFAST suggestive for TACO can include an abnormal left atrial/aortic (LA/Ao) ratio (> 2), enlarged caudal vena cava or evidence of hepatic venous congestion.[13–16] Other ways of differentiating between TRALI and TACO were systemically reviewed in the following PICO questions.



3.1 In dogs and cats with increased respiratory effort during transfusion (P), is echocardiography (I) compared to physical examination alone (C) useful in differentiating TACO from TRALI (O)?

Guidelines

a. Expected findings in TACO may include evidence of elevated cardiac filling pressures as well as systolic and/or diastolic dysfunction.
b. We suggest that echocardiographic changes may help distinguish between TACO and TRALI in dogs and cats.

Agreement: 13/13

Evidence summary

Echocardiography may provide critical information in the pathogenesis of pulmonary edema after a blood transfusion. It offers a non-invasive structural and functional cardiac assessment and may reveal findings that were not recognized clinically.[17] Echocardiographic changes are expected in patients with TACO due to the pathophysiology of circulatory overload. While this has not been extensively evaluated in a randomized controlled study in human patients, echocardiography is often used to distinguish between TACO and TRALI.

Two studies that evaluated echocardiogram changes in human patients with TACO were identified. In a prospective cohort study in 2009 (LOE 6, poor), Li et al, documented reduced mean ejection fraction in patients with TACO (ejection fraction mean 44%) compared to a group of patients with TRALI (ejection fraction mean 60%).[18] A secondary analysis of another prospective study (LOE 6, poor) suggested that patients with pre-existing left ventricular dysfunction had eight times the risk of developing TACO compared to controls.[19] However, this study did not evaluate or compare echocardiographic changes in patients with TRALI. There are no known studies in dogs and cats evaluating the use of echocardiogram to distinguish between TRALI and TACO, however echocardiogram may still be a useful tool to suggest circulatory overload in dogs and cats, pending its availability on an emergent basis.

There are no known studies in human patients evaluating echocardiographic findings specifically in patients with TRALI. However, anecdotally, the echocardiogram is expected to be normal in patients

with TRALI type I. It is important to note that patients with TRALI type II (TRALI patients with risk factors for Acute Respiratory Distress Syndrome (ARDS), previously called Possible TRALI) may have evidence of cardiac dysfunction and elevated filling pressures, supporting a permeability **and** hydrostatic pressure basis for pulmonary edema.[17]

3.2 In dogs and cats with increased respiratory effort during transfusion (P), is measurement of natriuretic biomarkers such as NT-proBNP (I) compared to physical exam alone (C) useful for differentiating TACO from TRALI (O)?

Guidelines

a. The utility of natriuretic biomarkers in differentiating TACO versus TRALI seems promising in human patients.
b. While there are no studies evaluating the PICO question in dogs and cats, NT-proBNP has been shown to be useful in differentiating other cardiac and non-cardiac causes of respiratory distress in dogs and cats.
c. We suggest that high concentrations of natriuretic peptides in a veterinary patient with acute respiratory distress following a transfusion may be suggestive of TACO.

Agreement: 13/13

Evidence Summary

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT- proBNP) are cardiac neurohormones specifically secreted from the ventricles in response to volume expansion and pressure overload. They may represent an attractive and non-invasive way to diagnose or exclude TACO after a transfusion.[20] TRALI occurs in the absence of volume and pressure overload and is not expected to cause an increase in BNP and NT-proBNP.

There were no studies identified that evaluated the utility of natriuretic peptides in diagnosing TACO or differentiating TACO from TRALI in dogs and cats. Two publications (LOE 6, fair) compared the

use of natriuretic peptides in differentiating TACO from TRALI in human patients. The first was a prospective cohort study, where natriuretic peptides did not reliable distinguish between TACO, type I and type II TRALI.[18] In that study, high levels of BNP and NT-proBNP did not rule out TRALI, especially in patients that were critically ill.[18] The study concluded that natriuretic peptides seem to be unreliable in critically ill patients with concurrent transfusion complications, and therefore should only be considered in cases of mild to moderate severity. However contradictory results were reported in a prospective observational study by Roubinian et al.[21] In that study, there were only very small elevations in BNP levels in patients with TRALI and this mild elevation was not different compared to those of transfused controls without pulmonary edema. BNP had a sensitivity of 88%, specificity of 81% and positive and negative predictive values of 85% in the differential diagnosis of TACO vs. TRALI. For a subset of patients with TRALI type II, BNP levels were elevated relative to controls and patients with TACO. However, a BNP level of more than 1000 pg/mL was useful in differentiating patients with TACO from TRALI type II.

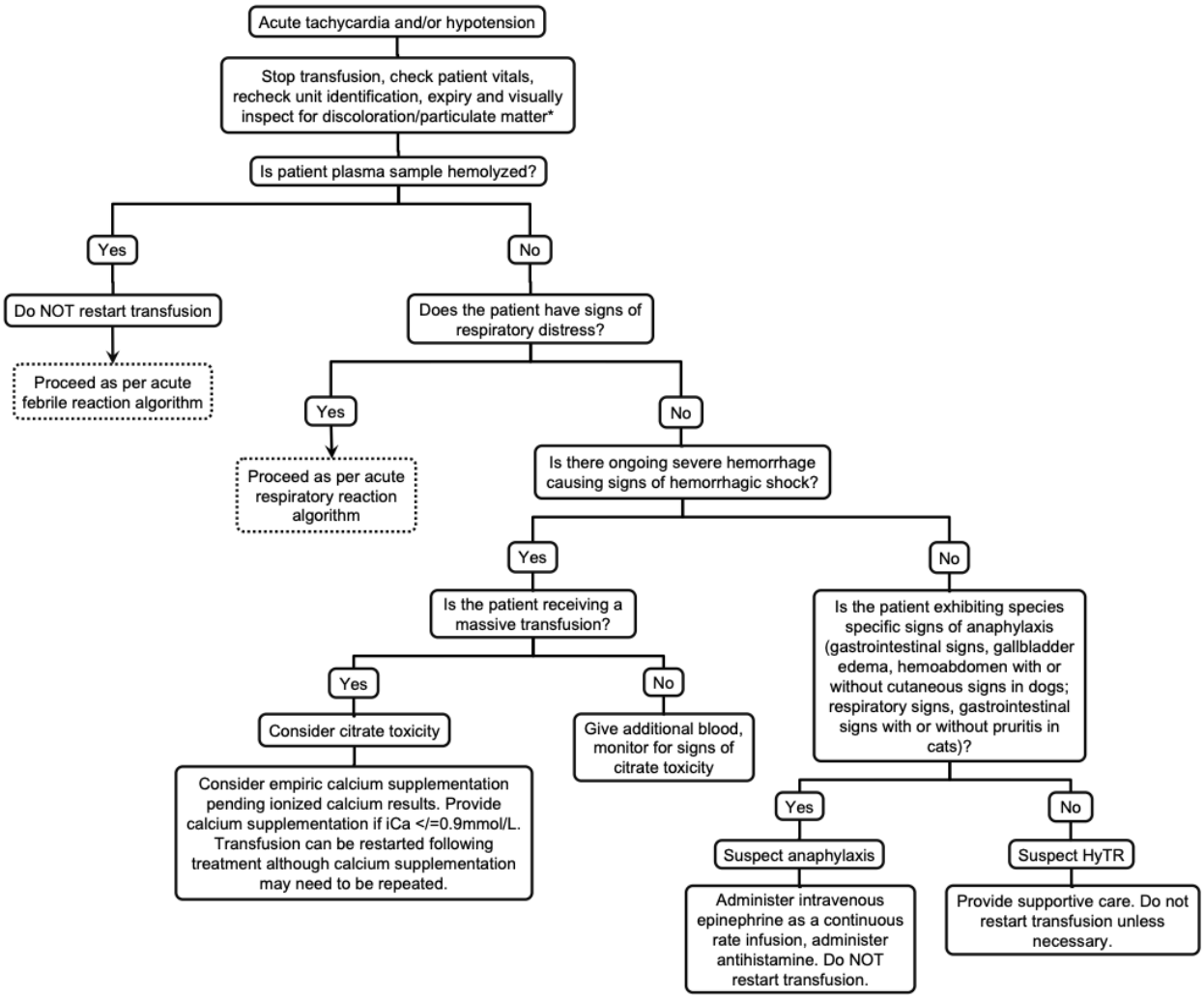
Two additional prospective studies (LOE 6, fair to good) support the use of natriuretic peptides in aiding in the diagnosis of TACO.[20,22] Both studies report high sensitivity and specificity in the use of natriuretic peptides in the diagnosis of TACO. However, neither of these studies enrolled patients with TRALI. To summarize their findings, a post/pre-transfusion NT-proBNP ratio > 1.5 supports the diagnosis of TACO. In blood samples taken within 24 hours after the administration of transfusion, a BNP level of less than 300 pg/mL or a NT-proBNP level less than 2000 pg/mL makes TACO an unlikely diagnosis. [21–23] Cut-off values excluding TACO as a diagnosis are not yet clear.[23]

NT-proBNP has been investigated dogs and cats to differentiate cardiac from non-cardiac causes of respiratory distress.[24–27] Plasma NT-proBNP concentrations > 270 pmol/L in cats with respiratory signs support congestive heart failure as the probable cause with approximately 93% sensitivity and 87% specificity.[27,28] Diagnostic accuracy is improved when NT-proBNP is used in conjunction with point of care ultrasound, as well as the history, physical exam, electrocardiogram, and radiographs.[25,28] A plasma

concentration of <800 pmol/L in dogs with respiratory signs strongly decreases the likelihood of congestive heart failure and suggests a noncardiac cause.[28–30] While there are currently no studies utilizing NT-proBNP in differentiating TACO from TRALI in dogs and cats, it is likely to be a helpful biomarker in the diagnosis of veterinary patients.

Febrile reactions

Fever is one of the most common clinical signs of transfusion reaction seen in dogs and cats.[2,3,9,31–36] While many of these reactions are febrile non hemolytic transfusion reactions (FNHTR), it is crucial to recognize and treat more serious causes of fever including acute hemolytic reactions and sepsis secondary to bacterial contamination of blood products, a type of transfusion transmitted infection (TTI). Figure two presents the panel's recommended approach to a pet who develops a fever during or within four hours of a transfusion. Patients with septic transfusion reactions may also develop other clinical signs prior to or in addition to fever including vomiting, diarrhea, respiratory distress, tachycardia and hypotension.[37,38] A specific algorithm for patients with hypotension and tachycardia was also created (Figure three).



3.3 In a dog or a cat with a suspected septic transfusion reaction due to bacterial blood component contamination (P) is PCR (I) superior to blood culture (C) to determine if the blood unit is the source of the infection (O)?

Guidelines

a. We suggest that blood culture (both aerobic and anaerobic) is superior to PCR in determining if the blood unit is the source of infection in a dog or cat suspected of having a septic transfusion reaction.

b. PCR can be used to confirm the identity of bacterial strains isolated from the patient and the transfused blood unit or to identify an unexpected virus or parasite in the recipient that is suspected to come from the blood unit.

Agreement: 13/13

Evidence Summary

No veterinary studies specifically addressed the relevant PICO question and hence multiple studies and transfusion guidelines from human medicine (LOE 6, good) were extrapolated to generate this guideline.[39–43] Bacterial culture is considered the gold standard for assessing the presence of bacterial contaminants in blood units and blood recipients at most human blood centers and in human transfusion guidelines and hemovigilance system.[41,44] In a survey (LOE 6, good) of representative Canadian human hospitals to determine clinical triggers and general procedures used in the investigation of suspected transfusion-transmitted bacterial contamination, the most frequent laboratory investigations performed were aerobic blood cultures of recipients and of the residual component.[45] Based on review and research articles, human guidelines issued by the Public Health Agency of Canada and the FDA recommend that in order to evaluate bacterial blood contamination, blood from the component and recipient should be inoculated into a set of aerobic and anaerobic blood culture bottles, and a direct slide should also be prepared for Gram staining and microscopic examination.[39,42,43] If the same bacterium is isolated from both the patient and the blood component, the laboratory should attempt to confirm the identity of the strains by using methods such as antibiotic susceptibility, serotyping, or molecular typing.[43,45,46]

The US Centers for Disease Control (CDC)'s National Hemovigilance Module recommends that suspected bacterial, mycobacterial, or fungal pathogen in a blood recipient should be identified by cytology, culture, or other method, while identification of an unexpected virus or parasite in the transfusion recipient should be identified by using culture, direct fluorescent antibody, or PCR.[47]

Visual evaluation of blood in blood units and microscopic examination of a drop of blood from dark or black units for bacteria may be useful in evaluating suspected blood bacterial contamination of a blood unit.[48] It is also recommended that a small amount of blood is saved from every available blood unit so that it could be utilized to investigate any adverse transfusion reactions related to TTI.

Domain 4: Treatment

Therapeutic intervention is an important step in determining the outcome of patients with transfusion reactions. There are many evidence-based guidelines in humans that outline specific recommendations for treating transfusion reactions.[49] The absence of evidence-based treatment recommendations makes treating transfusion reactions in veterinary medicine challenging. Our consensus panel performed systematic based reviews to identify therapeutic recommendations for dogs and cats experiencing transfusion reactions. We identified 12 PICO questions specifically targeted to this goal and used this evidence for construction of our treatment guidelines and algorithms.

Allergic Transfusion Reactions

4.1 In dogs and cats that undergoing an allergic, non-anaphylactic transfusion reaction (P), does treatment with an antihistamine (I) versus no treatment (C) prevent or reduce the severity of the reaction (O)?

Guidelines

We suggest that antihistamine therapy is used to treat canine and feline allergic transfusion reactions.

Agreement: 13/13

Evidence Summary

There are no randomized controlled trials in humans or animals evaluating the efficacy of antihistamines in the treatment of cutaneous allergic transfusion reactions. One experimental canine

study (LOE 3, Fair) suggests cetrazidine may be of use in allergic reactions caused by a non-blood product trigger[50] but another similar study (LOE 3, Fair) found no benefit in the use of diphenhydramine.[51] However, both studies looked solely at the drugs' effects on cutaneous wheal formation and not pruritus.

Similarly, there is evidence in human patients supporting the use of antihistamines in other allergic reactions, e.g. human atopic dermatitis, however, the use of antihistamines in the treatment of allergic transfusion reactions appear to be based on translation from their utility in other allergic diseases. It should be noted that the use of antihistamines is the standard of care for treating allergic transfusion reactions in both human and veterinary medicine.[49,52]

The British Committee for Standards in Haematology (BCSH) guidelines on the investigation and management of acute transfusion reactions state that there are no known trials specifically evaluating the treatment of cutaneous allergic transfusion reactions during a transfusion.[49] However, clinical experience suggests that patients with skin reactions (pruritus or rash) with no other clinical symptoms can continue to receive the transfusion. According to the BCSH guidelines, reducing the transfusion rate and administration of an antihistamine may be helpful in those patients.[49] In patients with anaphylactic reactions, human guidelines suggest that antihistamines may decrease the severity of cutaneous signs but are not rapid in onset and are ineffective in the treatment of cardiovascular and respiratory signs.[53] Therefore, although they may be beneficial, therapy with epinephrine and supportive care should be prioritized for patients with anaphylaxis.

4.2 In dogs and cats experiencing an allergic transfusion reaction (P), does treatment with a corticosteroid (I) compared to no specific treatment (C) prevent or reduce the severity of the reaction (O)?

Guidelines

We suggest that treatment of canine and feline allergic transfusion with corticosteroids should be avoided.

Agreement: 12/13

Evidence Summary

There is a dearth of evidence evaluating the use of corticosteroids for the treatment of allergic and anaphylactic reactions in both humans and veterinary species. There are individual case reports describing the use of corticosteroids in the treatment of dogs with allergic and anaphylactic reactions, and studies examining the efficacy of long-term corticosteroid therapy for atopic dogs, but the former are not controlled and the latter, although studying a type I hypersensitivity reaction, describe a disease that differs markedly in presentation.

A review by Hirayama (2013) suggests that human patients with severe urticarial reaction may require methylprednisolone or prednisolone therapy.[54] However, corticosteroid therapy is not recommended by the BCSH guidelines or the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology guidelines.[49,55,56]

A large 2020 systemic review on anaphylaxis and a Cochrane review investigating the use of corticosteroids to treat anaphylaxis stated that evidence was lacking to support their use.[53,57] While earlier review articles suggest corticosteroids may be of use in decreasing the likelihood of bi-phasic anaphylactic reactions, this is also now no longer supported due to lack of evidence and due to documented adverse effects of corticosteroids.[58] There are no studies evaluating the role of corticosteroids in the treatment of transfusion associated allergic reaction in human and veterinary patients.

4.3 In dogs and cats experiencing an anaphylactic transfusion reaction (P), does treatment with epinephrine (I) versus no treatment (C) prevent or reduce the severity of the reaction (O)?

Guidelines

We recommend the immediate use of epinephrine in the treatment of canine and feline anaphylactic transfusion reactions.

Agreement: 13/13

Evidence Summary

There are no randomized controlled studies examining the use of epinephrine in the treatment of transfusion induced anaphylaxis in humans, cats, or dogs, and, in part, this is due to its rarity. However, studies of experimentally induced anaphylaxis in both dogs and cats suggests that epinephrine is beneficial for the treatment of canine and feline anaphylaxis, by increasing stroke volume, cardiac output and blood pressure as well as decreasing airway constriction.[59–62] Although these non- clinical studies do not involve blood product triggers, it seems reasonable to assume that epinephrine would also be useful in transfusion mediated anaphylaxis. It should be noted that epinephrine's effects are short lasting and that a continuous rate infusion is recommended.[59,63] Epinephrine administration is also recommended for anaphylaxis in human patients.[53] For anaphylaxis in dogs and cats, epinephrine is dosed at a bolus of 0.1 to 0.2 mg/kg IM or IV followed by a constant rate infusion at 0.05 to 0.1 μg/kg/min IV.[64]

4.4 In dogs and cats experiencing a non-anaphylactic allergic transfusion reaction while receiving a blood product transfusion (P), is slowing the transfusion rate (I) versus no change in rate (C) indicated to prevent or reduce the severity of the clinical signs (O)?

Guidelines

a. There is insufficient evidence to recommend for or against slowing the transfusion rate after a mild canine or feline allergic transfusion reaction
b. It should be noted that the transfusion should be stopped, and the patient carefully assessed after detection of an allergic transfusion reaction, to assess the severity of the reaction.

Agreement: 13/13

Evidence Summary

While the practice of slowing down the rate of transfusion is often utilized in managing transfusion reactions in human and veterinary medicine,[49] evidence for this practice after a mild allergic transfusion is lacking. One prospective case controlled study (LOE 6, Fair) in human patients did not demonstrate a difference in the rate of transfusion between patients that experienced an allergic transfusion reaction during platelet transfusions and those that did not.[65] However, this study did not address the specific PICO question of interest.

Therefore, no evidence-based conclusion can be made about whether a transfusion should be stopped or slowed if a dog or cat experiences a mild allergic transfusion reaction. However, human guidelines based on clinical experience suggests that a transfusion may be continued in this situation and that slowing of the transfusion may be considered.[49] If an anaphylactic transfusion reaction occurs, the transfusion should be stopped and not re-started at any rate.

4.5 In dogs and cats experiencing a mild FNHTR while receiving a blood product transfusion (P), is slowing the transfusion rate (I) versus no change in rate (C) indicated to prevent or reduce the severity of the clinical signs (O)?

Guidelines

There is no evidence evaluating the effect of slowing the transfusion compared to any other treatment on outcome for dogs and cats with FNHTR, therefore the practice of slowing the transfusion can neither be recommended or opposed.

Agreement: 13/13

Evidence Summary

There is no evidence from peer reviewed original research in either human or veterinary medicine that slowing the transfusion compared with any other treatment improves outcome, for any transfusion reaction or FNHTR specifically. Four studies were evaluated as part of the systematic review that evaluated associations between transfusion infusion rate and transfusion reactions. Although this did not directly address the PICO question, they were included given the lack of other evidence.

The only veterinary study that loosely addressed the PICO question was a retrospective case series (LOE 5, poor).[9] This manuscript showed that administration rate of pRBCs was slower in patients with febrile transfusion-related complications ($P<0.0001$), and administration duration was longer in animals with any transfusion-related complication (3.1 hours) than in animals without signs of complications (2.6 hours; $p=0.001$). The authors suggest two possible reasons for this observation, either the documentation of a reaction led to slowing of the rate, or slower administration facilitated more thorough identification and documentation of transfusion reactions.

Vomiting

4.6 In a dog or cat that vomits during a transfusion (P), does stopping the transfusion (I) versus not stopping the transfusion (C) improve any outcome (recurrent vomiting, other signs of a transfusion reaction) (O)?

Guidelines

a. In dogs and cats that vomit during a transfusion, we suggest stopping the transfusion temporarily and assessing the patient for evidence of a serious transfusion reaction (fever, hypotension, hemolysis). The transfusion may be restarted at a slower rate if the patient appears to be stable and the reaction is assessed to be mild.

b. In patients with evidence of cardiovascular or respiratory instability accompanied by vomiting, we suggest discontinuing the transfusion, assessing the unit for bacterial contamination as well as assessing both the unit and the patient for evidence of hemolysis.

Agreement: 13/13

Evidence Summary

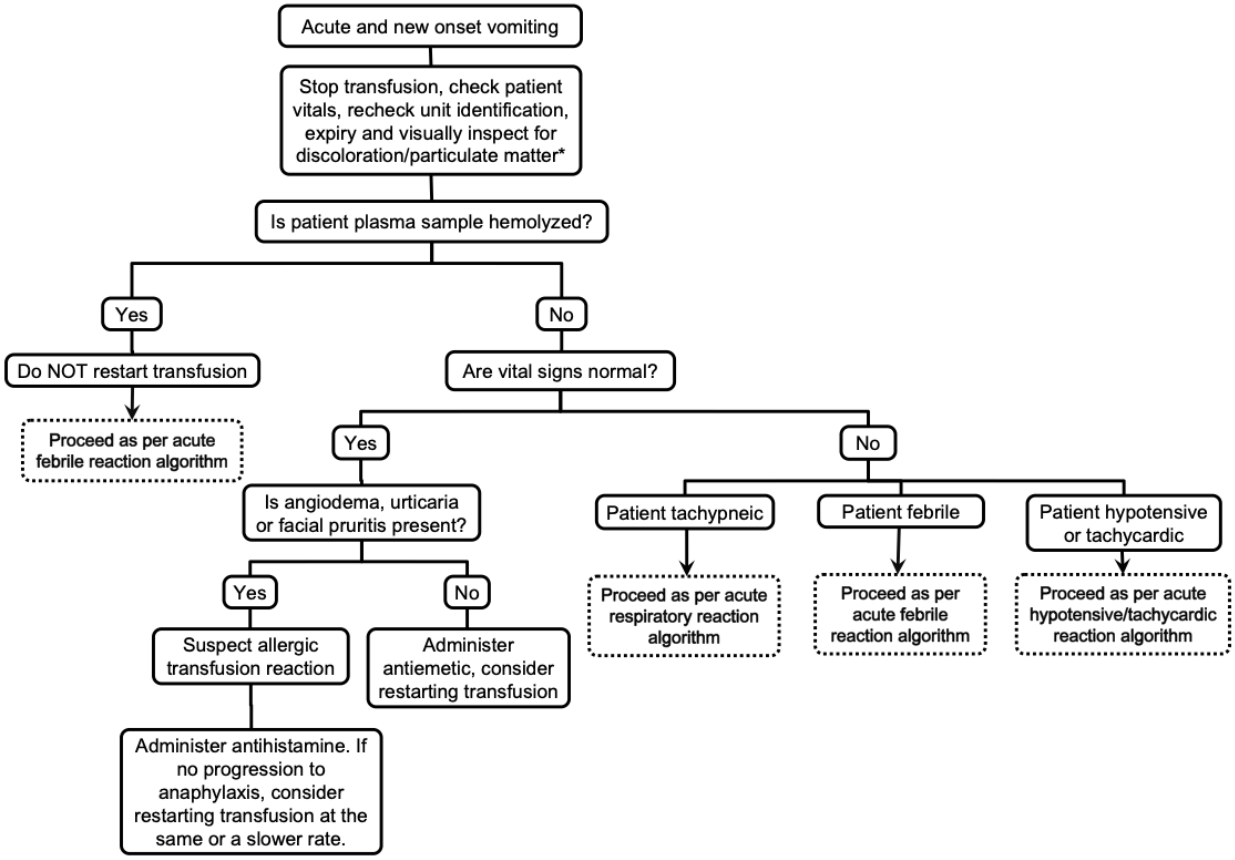
Vomiting is a common clinical sign of a transfusion reaction in dogs and cats[3,66–68] as well as in human patients.[37,69,70] There are no prospective or retrospective studies specifically evaluating the effect of stopping a transfusion in dogs, cats, and humans after vomiting occurs. Although vomiting may occur due to a transfusion reaction, it may also be because of the patient's underlying disease.

In one retrospective veterinary study (LOE 4, Fair), vomiting was considered a standalone transfusion reaction by itself, without associating it as a clinical sign of the more commonly described transfusion reactions (i.e. AHTR, FNHTR or an acute hypersensitivity reaction).[3] However, about one third of the vomiting cases in that study occurred with fever and the authors suggested that the vomiting noted in their study population may represent part of the broader FNHTR syndrome.[3] The effect of stopping or slowing down the transfusion was not evaluated in this study.

In another retrospective study (LOE 4, Fair) evaluating the effect of red blood cell age on acute transfusion-related complications in dogs, vomiting or regurgitation was noted in 9 dogs during the transfusion and in 2 dogs within two hours after completion of the transfusion.[9] Of the 11 dogs with vomiting, eight of them showed signs of another transfusion-related complication including collapse, hyperthermia, and tachycardia. Finally, in a prospective study (LOE 1, Fair) evaluating platelet

transfusions in thrombocytopenic dogs, 2/37 dogs in the study, had an episode of vomiting attributed as a manifestation of a transfusion related adverse reaction.[68] No further investigations into interventions after the vomiting events were reported in either study.

In human patients, the standard of care for all types of transfusion reactions, including the reactions that cause nausea and vomiting, is to stop the transfusion (at least temporarily- depending on the severity of the reaction). While this is a common guideline in practice, there are no studies specifically evaluating the effect of stopping or slowing down the transfusion after clinical symptoms of vomiting. Thus, this recommendation, while widespread, appears to be anecdotal. Once the transfusion has been stopped, venous lines should be maintained with isotonic fluids and supportive care initiated to address the patients cardiac, respiratory, or renal function, as necessary after vitals are obtained (Figure four).[37,49,69] It is also recommended that the blood product labelling and patient identification is rechecked to ensure that the patient received the intended product and the reaction should be reported to the blood transfusion laboratory or blood bank to discuss additional testing.[37,49] The patient and the blood unit should also be evaluated for signs of hemolysis .[49,69] If the reaction is severe or life-threatening, the transfusion should be entirely discontinued, although this decision should be made cautiously in anemic patients where hypotension may be associated with blood loss and continuing the transfusion may be lifesaving.[49]



Febrile Transfusion Reactions

4.7 In dogs and cats with FNHTR (P), are antipyretics (I) compared to no specific treatment (C) effective and safe for treatment of fever (O)?

Guidelines

a. There is no evidence regarding whether antipyretics compared to any other treatment are safe or effective for the treatment of fever in dogs and cats with FNHTR.

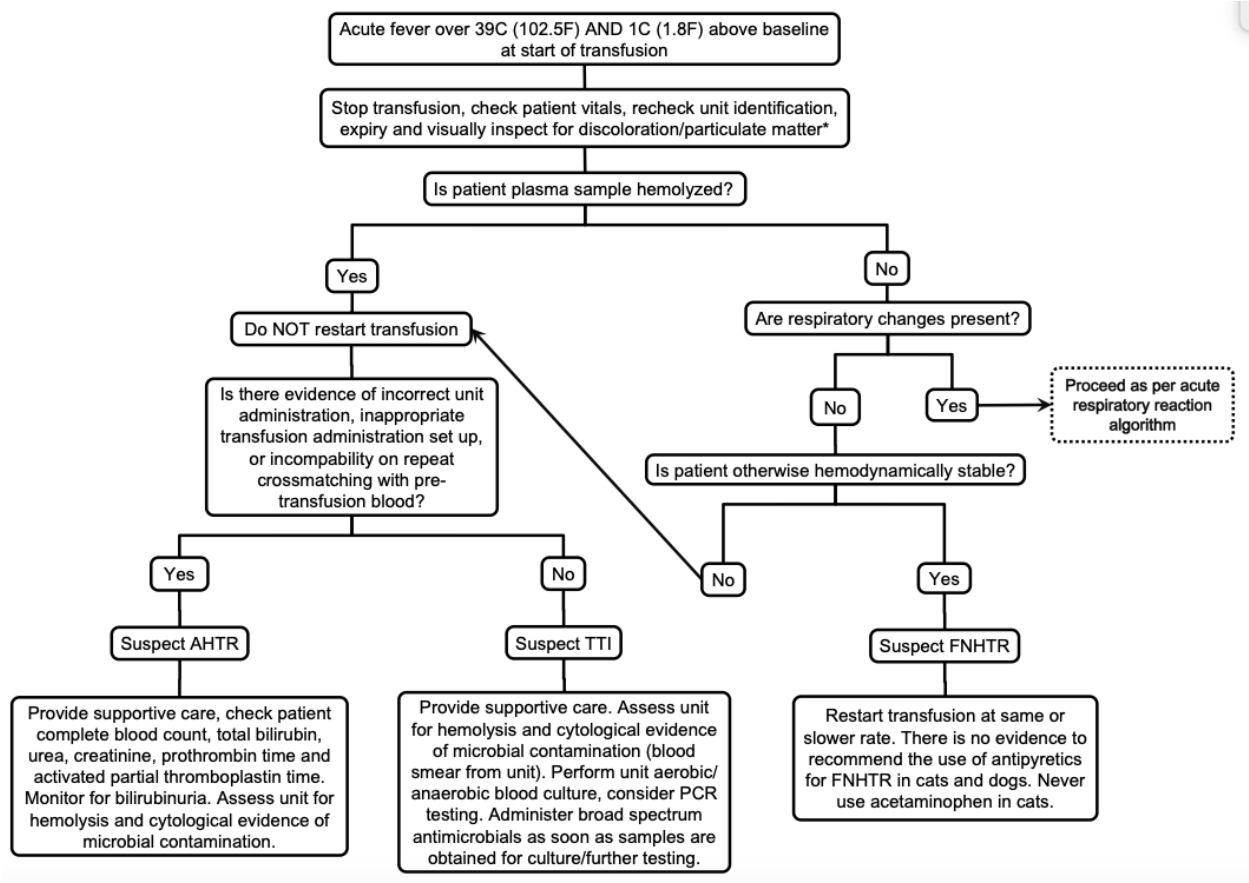
b. We suggest that the fever in dogs and cats with FNHTR is self-limiting and does not require treatment with antipyretics.

c. Acetaminophen should never be given to cats based on evidence of exquisite sensitivity to its hepatotoxic effects, as well as occurrence of methemoglobinemia and Heinz body hemolytic anemia.

Agreement: 13/13

Evidence Summary

There are no peer reviewed original studies that address the impact of antipyretic therapy on outcome with patients with FNHTR. While it has been described that humans with FNHTR commonly respond to acetaminophen administration, there is no evidence supporting that finding.[71] A seminal veterinary review article[72] suggests that acetaminophen is contraindicated in veterinary patients due to hepatotoxicity although recent clinical trials in dogs suggest that safety in this species is less of a concern.[73,74] However, experimental evidence identifies unique risks of acetaminophen toxicity in cats due to impaired hepatic glucuronidation and sulfation and thus cats should never be treated with acetaminophen for any purpose (Figure two).[75]



Respiratory Transfusion Reactions

4.8 In dogs and cats with TACO (P), is furosemide (I) compared to no specific treatment (C) effective in the treatment of respiratory distress (O)?

Guidelines

a. A single dose of furosemide is unlikely to be harmful in veterinary patients with acute respiratory distress after blood transfusion.

b. We suggest that judicious diuretic therapy be considered for the treatment of TACO in dogs and cats.

Agreement: 13/13

Evidence Summary

There are no randomized controlled studies in veterinary medicine that provide evidence recommending the use of diuretic therapy in the treatment of TACO. To date, prospective randomized controlled trials (LOE 6, Good) in humans evaluating pre-transfusion loop diuretic administration in efforts to mitigate TACO have failed to show significant benefit. [76–78] The recommendation for the provision of diuretic therapy in the treatment of TACO seems to be based on consensus reviews of the treatment of hydrostatic pulmonary edema and decompensated heart failure, and is therefore used empirically in cases of TACO.[79] It is suggested that the use of furosemide for TACO should be less aggressive than would be typical for the treatment of congestive heart failure in dogs and cats, and that close monitoring of vital signs (specifically respiratory rate, respiratory effort, hydration, and blood pressure) be performed (Figure one). An initial dose of 1-2mg/kg intravenously could be considered.

4.9 In dogs and cats with respiratory distress where TRALI is a possible diagnosis (P), is furosemide (I) compared to no diuretic (C) likely to improve any outcome (O)?

Guidelines

a. A single dose of furosemide is unlikely to be harmful in veterinary patients with acute respiratory distress after a blood transfusion.
b. We suggest that once TRALI is diagnosed, furosemide treatment should be avoided due to lack of evidence of benefit and potential for harm.

Agreement: 13/13

Evidence Summary

There are no known randomized controlled trials evaluating the use of furosemide for treating TRALI, compared to no diuretics, in human and veterinary patients. A few case reports in human patients were identified in the systematic review (LOE 6, Poor) that describe the use of furosemide in

patients with TRALI. [80,81] In these case reports, furosemide was given while the patient was being evaluated and a diagnosis was still pending. Since patients with TACO look clinically similar to patients with TRALI, it is reasonable to consider administration of furosemide until a diagnosis of TACO or TRALI is made (Figure one). This is because patients with TACO may benefit from furosemide administration since the pulmonary edema in that case is a result of circulatory overload.[82] In a survey of Dutch intensive care fellows, 94.6% (35/37) reported initiating furosemide to treat patients with TACO.[23]

The routine use of furosemide or other diuretics is not recommended in human patients once a diagnosis of TRALI has been made as diuretics may worsen the patient outcome secondary to intravascular volume depletion.[83,84] Supportive care, utilizing oxygen, intravenous fluids, vasopressor support, and mechanical ventilation, if required, is the mainstay of therapy for patients with TRALI. Glucocorticoids are often administered empirically in human patients although there is little evidence to support their use.[84] Since treatment of TRALI is limited to supportive care, the focus in humans is on preventative strategies such as identifying blood products at highest risk for causing TRALI.[84]

4.10 In dogs and cats with TRALI (P), are lung protective ventilation strategies (I) compared to traditional mechanical ventilation (C) associated with improved outcomes (duration of ventilation, improved survival to discharge) (O)?

Guidelines

While there is no evidence on ideal ventilator settings in patients with TRALI, we recommend that lung protective strategies with low tidal volumes should be utilized in dogs and cats with TRALI if mechanical ventilation is required for their care.

Agreement: 13/13

Evidence Summary

There are no randomized controlled trials evaluating ventilation strategies for human and veterinary patients with TRALI. In human patients, many sources recommend that protective lung strategies be utilized for all patients with ARDS or ALI from any cause.[85,86] The ARDS network randomized controlled study concluded that for human patients with acute lung injury, ventilation with lower tidal volumes (6 ml/kg), improves survival compared to ventilation with conventional tidal volumes (12 ml/kg). This guideline is generally used for human patients with TRALI.[86]

In a prospective study performed in mice with induced TRALI (LOE 6, Good), mechanical ventilation with low tidal volumes (7.5 ml/kg) aggravated pulmonary injury as evidenced by increased neutrophil influx, increased pulmonary and systemic levels of cytokines and worse lung histopathological changes compared to unventilated controls. In the same study, the use of high tidal volumes (15 ml/kg) resulted in a further increase in protein leakage and pulmonary edema.[87] The authors of this study concluded that while mechanical ventilation appears to aggravate the course of TRALI, the use of low tidal volumes in patients with ARDS is a rational approach.[87]

Post-Transfusion Purpura

4.11 In dogs with PTP (P), does treatment with corticosteroids and/or intravenous immunoglobulins (IVIG) (I) compared to no treatment (C) improve thrombocytopenia (O)?

Guidelines

Although controlled studies are lacking, we suggest that corticosteroids and/or IVIG be used as treatment for PTP.

Agreement: 13/13

Evidence Summary

There are no original studies comparing the use of corticosteroids or IVIG to placebo in human or veterinary patients. The majority of reported PTP cases in people involve antibodies directed against the human platelet antigen (HPA)-1a.[88,89] Intravenous Immunoglobulins are considered the first line of treatment,[89–91] although corticosteroids alone,[92] or both corticosteroids and IVIG[93,94] have been used.

One case report of PTP in a dog has been documented (LOE 5, poor). The dog developed severe thrombocytopenia (10,000 platelets/uL) 8days after a whole blood transfusion, and platelet-binding IgG was present in the dog's serum. The platelet count increased to 267,000 platelets/uL 6 days after the initiation of prednisone therapy.[95]

Citrate Toxicity

4.12 In dogs and cats receiving massive transfusion (P), does supplementing calcium when the patient becomes hypocalcemic (I) compared to prophylactic calcium supplementation (C) improve any outcome (prevent signs of reaction or improve hospital survival) (O)?

Guidelines

a. In patients receiving massive transfusion, we recommend that calcium supplementation should be provided when the patient's ionized calcium is less than or equal to 0.9 mmol/L. However, based on the patient's clinical status, evidence of clinical signs, and severity of comorbidities, intravenous calcium can be considered when the ionized calcium is greater than 0.9 mmol/L.

b. We suggest that empirical supplementation of calcium can be considered during massive transfusion.

Agreement: 13/13

Evidence Summary

There are no human and veterinary studies that specifically address the PICO question on outcomes when calcium is supplemented prophylactically versus administering only if the patient is

565 hypocalcemic during massive transfusion. Massive transfusion in veterinary medicine is defined as a
566 transfusion of a volume of blood products in excess of half the patient's blood volume in 3 hours or over
567 a full blood volume in 24 hours.[96] There are also no widely accepted published guidelines for the ideal
568 calcium supplementation protocol due to citrate toxicity when patients undergo massive transfusion.[97]
569 In human studies (LOE 6, good), calcium supplementation protocols have been reported both based on
570 severity of hypocalcemia and also based on the volume of blood administered regardless of the severity
571 of hypocalcemia.[98,99] Although a potential complication, hypocalcemia is not consistently reported
572 during massive transfusions in dogs and cats.[96,100,101] Hypocalcemia is not reported during auto-
573 transfusion as long as the blood administered does not contain citrate as an anticoagulant.[102,103]
574 Both intravenous calcium gluconate and calcium chloride (5-15 mg/kg elemental calcium, slowly
575 over 20-30 minutes; may also utilize constant rate infusion of 2.5-3.5 mg/kg/hr of elemental calcium)
576 have been used effectively to supplement calcium during massive transfusions (LOE 3-5, poor to
577 good).[96,104,105] In humans, it is recommended to supplement calcium when the ionized calcium falls
578 below 0.9 mmol/L.[97] In an experimental study (LOE 3, good) using healthy dogs, clinical signs of
579 hypocalcemia were observed in one dog when the ionized calcium was 0.91±0.03 mmol/L.[106] If calcium
580 supplementation is required, a second IV line should be used, and the calcium should not be
581 administered through the same line as the anticoagulated blood product. Depending on the volume of
582 blood products infused, hypocalcemia can be severe and potentially life-threatening. Fortunately,
583 patients appear to respond well to calcium supplementation and, when possible, stopping the
584 transfusion.

585 Conclusions and Future Directions

586 This section of the consensus statement has provided guidelines for treatment of transfusion
587 reactions in dogs and cats. In performing the systematic review utilized to generate these guidelines, it
588 has become is evident that there are large knowledge gaps central to the identification and treatment of

transfusion reactions. Establishment of a central international veterinary transfusion reaction database would be an important first step in collecting information and collaborating for much needed multi-institutional studies. The members of the consensus panel believe that the definitions of transfusion reactions established in the guidelines will provide universal standards for identifying transfusion reactions. Until further studies are performed, treatment recommendations identified in the consensus statement may serve as a reference for treatment of dogs and cats and potentially also serve as a basis for future studies.

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Figure One. Diagnostic and treatment algorithm for respiratory distress developing during or within 6 hours of transfusion.

TACO = transfusion associated circulatory overload. TRALI = transfusion related acute lung injury. TAD = transfusion associated dyspnea.

Figure Two. Diagnostic and treatment algorithm for fever developing during or within 4 hours of transfusion.

AHTR = acute hemolytic transfusion reaction. TTI = transfusion transmitted infection. FNHTR = febrile non-hemolytic transfusion reaction. *If unit is discolored or contains particulate matter, record findings and report reaction to issuing blood bank if commercially acquired units have been used.

Figure Three. Diagnostic and treatment algorithm for tachycardia and/or hypotension developing during or within 1 hour of stopping transfusion. HyTR = hypotensive transfusion reaction. *If unit is discolored or contains particulate matter, record findings and report reaction to issuing blood bank if commercially acquired units have been used.

Figure Four. Diagnostic and treatment algorithm for vomiting occurring during or within 4 hours of transfusion. *If unit is discolored or contains particulate matter, record findings and report reaction to issuing blood bank if commercially acquired units have been used.