Association of Veterinary Hematology and Transfusion Medicine (AVHTM) Transfusion Reaction Small Animal Consensus Statement (TRACS) Part Two: Prevention and Monitoring

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Abstract

Objective: To systematically review available evidence to develop guidelines for the prevention of transfusion reactions and monitoring of transfusion administration in dogs and cats.

Design: Evidence evaluation of the literature (identified through Medline searches through Pubmed and Google Scholar searches) was carried out for identified transfusion reaction types in dogs and cats. Evidence was evaluated using PICO (Population, Intervention, Comparison, Outcome) questions generated for each reaction type. Evidence was categorized by level of evidence (LOE) and quality (Good, Fair, or Poor). Guidelines for prevention and monitoring were generated based on the synthesis of the evidence. Consensus on the final recommendations and a proposed transfusion administration monitoring form was achieved through Delphi-style surveys. Draft recommendations and the monitoring form were made available through veterinary specialty listservs and comments were incorporated.

Results: Twenty-nine guidelines and a transfusion administration monitoring form were formulated from the evidence review with a high degree of consensus

Conclusions: This systematic evidence evaluation process yielded recommended prevention and monitoring guidelines and a proposed transfusion administration form. However, significant knowledge gaps were identified, demonstrating the need for additional research in veterinary transfusion medicine.

Keywords: transfusion reactions, pre-medication, blood type, crossmatch

Abbreviations:

AHTR - Acute Hemolytic Transfusion Reaction

ARDS - Acute Respiratory Distress Syndrome

AVHTM - Association of Veterinary Hematology and Transfusion Medicine

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

FFP – Fresh Frozen Plasma

fHb – Free Hemoglobin

FNHTR - Febrile Non-Hemolytic Transfusion Reactions

Hb – Hemoglobin

IMHA – Immune Mediated Hemolytic Anemia

LR - Leukoreduction

NHSN - National Healthcare Safety Network

NT-proBNP - N Terminal-pro – Brain Natriuretic Peptide

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

tHb – Total Hemoglobin

TRALI - Transfusion Related Acute Lung Injury

TTI - Transfusion Transmitted Infection

XM – Crossmatch

Introduction

Prevalence of transfusion reactions and complications in veterinary studies varies from 0-38%, depending on the species, reaction definitions, and blood products used.[1–7] While we have consensus recommendations on blood donor screening for prevention of transfusion transmitted infectious disease,[8] there are no publications that systematically examine the evidence for other prevention strategies. In addition, there is limited information on best practices for monitoring transfusions.

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 monitoring transfusions and prevention of reactions secondary to red blood cell, plasma, and platelet transfusions in canine and feline patients. Definitions of transfusion reactions are presented in part one of this series.

Specific PICO questions were developed by the group around prevention and monitoring strategies and assigned to reaction worksheet authors. Comprehensive database searches were 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.[9–11]

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 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 after this.

Guidelines were discussed as a committee for an initial round of changes and suggestions. Delphi style anonymous surveys were then used to tighten and refine the guidelines.[12] These draft guidelines were then presented to the AVHTM, ACVECC, and ACVIM discussion boards for comments and suggestions. Guidelines were further refined based on the input received. A transfusion monitoring form was also created from this process.

Domain One: Prevention Strategies

Donor

Recommendations for screening of blood donors to prevent infectious diseases have been previously published and our committee agrees with those recommendations.[8,13] Due to advances in testing and new publications we opted to look more closely at PCR testing.

1.1 In dog and cat blood donors (P), is the use of PCR in addition to serological tests (I) compared to serological tests alone, (C) useful in preventing selected transfusion transmitted infections (TTI) (O)?

Guideline:

We recommend the use of PCR in addition to serological tests, compared to serological tests alone, for screening blood donors for selected TTI (based on geographic region), to reduce the possibility of transmission of selected TTI from blood donors to blood recipients and to identify serological positive blood donors that do not have active infection.

Agreement: 13/13

Evidence Summary:

Guidelines from both the US[8] on canine and feline blood donor selection and Europe [13] on feline blood donor selection recommend the use of PCR in addition to serological tests for screening blood donors for selected TTI. Four veterinary studies (LOE 3-5, good) demonstrated that PCR in addition to serological tests, or compared to serological tests alone, was useful in identifying selected blood-borne infections in canine and feline blood donors. Screening by PCR should be included in an integrated approach to evaluate potential blood donors for *Leishmania infantum*[14], *Ehrlichia canis*, *Anaplasma platys*, and for *Babesia vogeli* in candidate canine blood donor in the absence of clinical symptoms.[15] PCR was the only test that could identify dogs infected by *Mycoplasma haemocanis*[16], and cats infected by feline haemoplasmas *Mycoplasma haemofelis*, *M. haemominutum* and *M. turicensis*, as serologic assays are not currently commercially available and cytologic evaluation of blood smears has too low sensitivity for these pathogens.[17] PCR is the only test that identifies antigenic serological negative but provirus positive FeLV infected cats.[17] PCR is also useful to identify seroreactive blood donors without an active infection. A positive serological test does not necessarily indicate an active infection and may be a result of a previous exposure to the parasite, especially in endemic regions. In these regions,

identification of seronegative donors may be difficult. Therefore, use of seropositive but PCR negative dogs as donors is considered acceptable. This could be particular useful in areas endemic for *E. canis*, *A. platys*, *B. vogeli*[15] *L. infantum*, *Anaplasma phagocytophilum, Babesia canis*, *Rickettsia conorii* and *R. rickettsii* infections.[18]

Donation

1.2 In cats receiving a blood transfusion (P), does the use of a closed system to collect blood from the donor (I) compared to semi-closed or open feline collection systems (C) reduce the risk of TTI (O)?

Guideline:

a. There is insufficient evidence to make strong recommendations regarding the use of a closed instead of semi-closed or open feline collection systems in feline blood collection to reduce the risk of TTI.
b. We suggest that closed, semi-closed, and open systems can be used for feline blood collection, with appropriate aseptic collection and processing and careful storage to prevent blood contamination.

Agreement: 13/13

Evidence Summary:

Because of the small amount of blood collected, the impracticality of using human closed systems, and the limited availability of commercial closed collection systems for cats, feline blood is usually collected employing a semi-closed system (the collection system is already available in a sterile packaging and the operator only adds anticoagulant before blood is drawn) or an open system (the operator removes syringes from their sterile packaging, manually adds anticoagulant to each syringe, and attaches a butterfly catheter to the syringe).[19–23] This involves a multi-step manipulation of syringes

and other devices by several assistants and each manipulation provides an opportunity for contamination. Therefore, the risk of bacterial contamination of feline blood units might be greater than in standard canine units, precluding storage of these blood products. Veterinary studies[19–22,24–27] have only evaluated bacterial contamination of blood units and not the presence of TTI (sepsis due to bacterial contamination of the blood) in feline recipients. Only one study (LOE 3, good) directly compared closed versus open systems in feline blood collection in terms of bacterial contamination in the blood units.[24] This study did not observe any difference in bacterial contamination between the two collection systems.

Many papers (LOE 3, fair to good) reported bacterial contamination of feline blood units collected both with open, semi-closed, and closed systems. Most studies were not able to demonstrate the source of bacterial contamination.[22,24–26] Only one study found the source of contamination of feline whole blood (WB) units with *Serratia marcescens,* which was alcohol-soaked cotton balls used during skin preparation and a saline solution used during venipuncture of donor cats.[27] Another study evaluated a large number of feline pRBC units collected using a specific feline semi-closed system and no contamination was found. However bacterial cultures in this study were done only at 24 hours after collection, when the bacterial load might be too low to be revealed by culture.[19] Feline pRBC or WB units collected with open and semi-closed system have been negative for bacterial contamination at bacterial culture[20,21,24] and conversely some feline units collected with a closed system have still been contaminated, with *Serratia marcescens*[25], *Pseudomonas fluorescens*[26], *Staphylococcus* spp. and *Ralstonia* spp.[24]

Some hospitals use smaller dogs as donors and use semi-closed systems for donation and storage. Studies have not been done specifically looking at this practice. However, we believe this is likely safe with appropriate aseptic handling, processing, and storage, based on the feline data.

Leukoreduction

1.3 In dogs and cats requiring transfusion (P), does the administration of pre-storage leukoreduced blood (I) compared to non-leukoreduced blood (C) prevent or reduce the risk of any type of transfusion reaction (O)?

Guideline:

a. There is currently insufficient evidence to recommend for or against leukoreduction (LR) to prevent or reduce any type of transfusion reaction in veterinary medicine.

b. Due to evidence in human studies that LR decreases the rate of febrile non-hemolytic transfusion reactions (FNHTR), we suggest that it be considered.

Agreement: 13/13

Evidence Summary:

Leukoreduction can be performed pre- or post-storage. Pre-storage LR is preferred and was the only type included in this review as stored WBC can produce inflammatory cytokines.[28] Thirty five studies, 3 veterinary (LOE 1-3, good) and 32 human (LOE 6, poor to good), were identified. A single prospective clinical veterinary study compared reaction rates in 23 ill dogs receiving LR or non-LR blood products and found no difference in the reaction rates.[29] Similarly, there was no difference in clinical reaction rates in 2 studies, one with 20 healthy dog and another with 13 healthy dogs receiving LR or non LR blood.[30,31]

Many human studies have focused on whether LR, compared to nLR, decreases the incidence of post-operative infections, multi-organ failure, and mortality after surgery. The studies differ in their quality and in their findings and a Cochrane review concluded that there was not enough evidence to make a recommendation.[32–44] Studies have also examined the use of LR to reduce microchimerism as a risk for transfusion associated graft versus host disease (TA-GVHD), also with equivocal findings.[45–47] A

single before and after retrospective observational study found a decrease in TRALI and TACO with universal leukoreduction,[48] but a double-blind randomized study in trauma patients did not confirm this finding.[49] Studies have additionally looked at the role of LR in preventing TTIs. A laboratory study showed a decrease in culture positivity for *Anaplasma phagocytophilum* in blood bags after LR but two case reports demonstrated transmission of *A. phagocytophilum* despite the use of LR.[50–52]

The most consistent finding in people has been a decrease in FNHTR with LR versus nLR platelets and pRBCs.[48,53–58] Six large studies found a significant decrease in the rate of FNHTR with LR while a seventh smaller study found a decrease that did not reach statistical significance.[58] Further research in larger scale studies is needed to see if LR decreases FNHTR and other reactions in veterinary patients.

Storage

1.4 In dogs and cats requiring transfusion (P), does the transfusion of stored (I) compared to fresh RBCs (C) influence the risk of any type of transfusion reaction (O)?

a. There is evidence of increased in vivo hemolysis with transfusion of stored versus fresh RBCs in dogs.
b. We suggest the consideration of fresher RBC transfusion products in dogs with sepsis or hemolytic causes of anemia
c. Further investigation is warranted regarding the influence of RBC age on transfusion reactions in cats

Agreement: 13/13

Evidence Summary:

There were ten veterinary studies evaluating age of RBC transfusion product and association with transfusion reactions. Nine of these studies (LOE 3-5, fair to good) were restricted to the canine

species. A single retrospective study (LOE 5, fair) evaluated feline transfusions.[5] None of the clinical studies included illness severity scores.[1,3,59,60] This deficit in conjunction with small sample sizes, varied patient populations and inconsistency in how transfusion reactions were defined and monitored before and after transfusion all make conclusions challenging. In four of the eight canine veterinary studies, results showed that in vivo hemolysis post-transfusion was increased in dogs receiving older versus fresh RBCs.[1,61–63] Pre-transfusion in vitro hemolysis in the individual blood units was not assessed in these studies. In the clinical canine studies, no association has been found between RBC storage time and survival when considering all dogs regardless of the cause of anemia. In Hann *et al.*, an independent association was found between longer duration of pRBC storage (> 14 days) and decreased survival of dogs with hemolysis. In addition, longer pRBC storage time was associated with development of new or progressive coagulation failure and thromboembolic disease post-transfusion.[59] In the 2013 Solomon *et al* study utilizing a canine experimental model of pneumonia associated sepsis, the authors concluded that the increased in vivo hemolysis with transfusion of pRBC at their expiration date (42 days vs 7 days) resulted in "release of cell-free oxyhemoglobin over days, causing pulmonary hypertension and vascular damage at sites of injury, and gas exchange abnormalities, each contributing to the increased risk of death with older blood."[62] In a follow up study using the same septic dog model, Wang *et al*. confirmed that in dogs with established infection, the in vivo hemolysis associated with 42 day old RBCs worsens outcome.[64] Solomon *et al*'s 2015 study investigating a canine lethal hemorrhage/reperfusion model, did not show that older blood (42 days vs 7 days) was harmful and in fact there was limited data that suggested that older blood may be beneficial in this population.[61]

A 2020 retrospective feline study (LOE 5, fair) exploring risk factors for non-survival and transfusion associated complications showed that older blood was identified as a possible risk factor for developing transfusion-associated complications and for non- survival.[5] Although these findings were statistically significant, the odds ratios were small and clinical significance warrants investigation.

1.5 In dogs and cats requiring transfusion (P), is the use of fresh (I) rather stored blood products (C) useful in preventing hyperammonemia (O)?

Guideline:

a. There is insufficient evidence to make strong recommendations regarding the risk of a hyperammonemia transfusion reaction in dogs with stored blood products and no evidence-based recommendations can be made regarding the use of stored blood products in cats.

b. We suggest that stored blood products appear safe and do not cause hyperammonemia transfusion reactions in dog and cat blood recipients with normal liver function. In patients at increased risk of hyperammonemia, such as those with liver dysfunction or those requiring massive transfusions, we suggest the transfusion of fresh whole blood (< 24 hours) or packed red blood cells that are < 7 days when available rather than older stored blood or components.

Agreement: 13/13

Evidence Summary:

Five studies (LOE 3, good) showed that ammonia increases during storage of canine and feline WB and/or PRBC units and that ammonia concentrations were highly associated with storage duration and markedly increased over time, during standard storage conditions.[21,65–68] In most of these studies, the ammonia increase occurred early in the storage periods, with significant increases in concentrations of ammonia within the first 2 weeks of storage. Only one study (LOE 2, good)[67] directly addressed the question and measured ammonia in stored blood units and in canine blood recipients. Plasma ammonia concentration, measured in blood samples from 5 anemic dogs without primary liver disease immediately before and after transfusion with 5-10 ml/kg of stored pRBC, remained in the normal reference range. The pRBC units used for transfusion had been stored for 18 to 30 days. The lack of a

clinically significant rise in plasma ammonia concentration in the transfused anemic dogs in this study suggests that the ammonia load from a unit of pRBC does not result in hyperammonemia in this patient population. However, the real clinical significance of hyperammonemia in stored blood units transfused to patients with liver failure is yet to be determined and further *in vivo* studies are required to determine the clinical importance of hyperammonemia in stored blood units in these patients. A case report of hyperammonemia after transfusion of two stored pRBC units in human medicine was reported (LOE 6, poor) and highlighted the potential harm from ammonia in stored blood products in patient with liver failure.[69] No veterinary studies specifically address the relevant PICO question in patients at risk of hyperammonemia such as those with liver dysfunction or those requiring massive transfusions, i.e. a transfusion of a volume of blood products in excess of half the patient's blood volume in 3 hours or over a full blood volume in 24 hours.[70] There are no clinical reports of association between increases in concentration of ammonia in canine and feline stored blood products and transfusion reactions. Studies that describe the outcome of dogs and cats receiving massive blood transfusion have not reported hyperammonemia or signs related to hyperammonemia as transfusion complications.[70–74]

Hemolysis

1.6 In dogs and cats receiving packed red blood cells (P), does administering packed red blood cell units with less than 1% hemolysis (I) compared to not checking hemolysis and administering based on expiration date (C) decrease the risk of any transfusion reaction (O)?

Guideline:

a. There is evidence in veterinary medicine that in vitro hemolysis can cause transfusion reactions in recipients.

b. Consistent with human guidelines, we recommend that red blood cell units be checked for hemolysis prior to administration and that those with > 1% not be used. Red blood cell

segments do not accurately reflect hemolysis levels within the unit so assessments should be done directly from the unit or from the administration line. Visual inspection is less accurate than measurement of free hemoglobin.

Agreement: 13/13

Evidence Summary:

Hemolysis in red blood cell products occurs secondary to rupture of the cells with release of hemoglobin. Cells can rupture and release hemoglobin due to issues in processing, issues with the donor's cells, age, bacterial contamination, or related to other storage conditions including type of additive solution, air flow, and temperature.[75–79] Free hemoglobin can cause damage to tissues when infused and can also be a marker of other potentially damaging storage byproducts. Free hemoglobin has specifically been implicated in damage to the proximal tubule of the kidney and redox injury of endothelium.[77] Due to these risks, both the United State and Europe have set standards that human red blood cell products in human should have a mean hemolysis less than 1% and 0.8%, respectively.[77]

While there are no studies that have determined an exact level of acceptable hemolysis, the committee felt that following the human guidelines at 1% is safest. There is a case series with severe clinical signs in dogs thought to be related to storage related hemolysis.[75] In addition, Wang's research on the impact of older blood on dogs with pneumonia suggested negative impacts of free hemoglobin and free iron on mortality.[64]

Four studies in dogs[78–81] (LOE 2-3, good) and three in cats[19,20,25] (LOE 3, good) demonstrate that hemolysis increases in blood products over time. Most of these studies found some units within the normal accepted shelf life with hemolysis over 1% and this was more common after 28 days.[19,20,78,80,81]

Studies in humans have shown that checking the segments for hemolysis is not accurate or reflective of changes in the bag itself. Therefore, the red blood cell unit must be checked directly by sampling from the bag or sampling after running through the administration filter.[82] Measurement of free hemoglobin (fHb) is more accurate than visual assessment in both veterinary and human medicine.[83] Free hemoglobin can be measured with portable devices.[a] The following formula can be used to calculate % hemolysis:

$$\%\text{hemolysis} = (100\text{-HCT}) \times (\text{plasma fHb [g/dL]}/\text{tHb [g/dL]})$$

Typing and Crossing Matching – DOGS

1.7 In dogs requiring transfusion (P), does administering DEA 1 type matched blood (I) compared to non-type matched blood products (C) prevent or reduce AHTRs (O)?

a. No AHTR have been reported following a DEA 1 mismatched transfusion in a transfusion naïve recipient. However, a DEA 1 mismatched transfusion in an already immunized recipient against DEA 1 antigen can result in a severe AHTR.
b. In transfusion naïve dogs, we strongly recommend administering DEA 1 negative blood to DEA 1 negative typed recipients. DEA 1 negative RBCs can be administered to a DEA 1 positive dog. However, we suggest administering DEA 1 positive blood to DEA 1 positive typed recipients to optimize inventory management.

Agreement: 13/13

Evidence Summary:

DEA 1 is considered the most clinically important blood group in dogs due to its strong antigenicity.[84–86] Dogs are either DEA 1 negative or weakly, moderately, or strongly DEA 1 positive.[87,88]

Naturally occurring alloantibodies against DEA 1 antigen have not been described and no AHTR have been reported following a DEA 1 mismatched transfusion in a transfusion naïve recipient. However, there are laboratory (LOE 3, fair) and clinical reports (LOE 5, good) of severe AHTR in previously immunized dogs who receive a further DEA 1 mismatched transfusion.[89,90] Acute hemolytic transfusion reactions (AHTR) are uncommonly reported in dogs, due to the recognition that DEA 1 is the main cause of this reaction in the dog and the widespread acceptance of compatibility testing.[1–3,91,92]

Typing both recipient and donor for DEA 1 before a first transfusion prevents further immunization against DEA 1 antigen. DEA 1 negative dogs should only receive DEA 1 negative blood.[88,93,94] DEA 1 positive recipients can receive either DEA 1 negative or positive blood. Because approximately half of dogs are DEA 1 positive,[86,95,96] the use of DEA 1 positive blood products for DEA 1 positive recipient, is encouraged to make better use of blood resources.

1.8 In dogs requiring transfusion (P), does administering major crossmatch (XM) compatible blood for the first transfusion (I) compared to not crossmatching (C) prevent or reduce the risk of any type of transfusion reaction (O)?

Guideline:

a. While no confirmed AHTR have been reported in dogs at the first transfusion event, firm conclusions concerning the presence and the clinical relevance of naturally occurring alloantibodies cannot be reached.
b. We suggest that major crossmatching may not be necessary in transfusion-naïve dogs. With growing knowledge of naturally occurring alloantibodies, decisions about the need for crossmatching in a clinical case should be balanced with the methodology and cost of crossmatching used, and urgency of the patient's clinical state.

c. Better standardization of pre- and post-transfusion immunohematology testing, including crossmatching, is needed to understand blood type mediated immunologic reactions.

Agreement: 13/13

Evidence Summary:

More than a dozen blood groups have been reported in dogs and some have been classified as Dog Erythrocyte Antigens (DEA).[84–86,97] Other systems and groups, including *Dal*, Kai 1 and Kai 2, have also been described.[97,98] At this time, only DEA 1 can be tested with a patient side test. Studies have conflicting results regarding the presence of naturally occurring alloantibodies against known (e.g., DEA 7) or unknown blood type antigens. Some studies have found no incompatibility in crossmatches performed in naïve-transfusion dogs.[85,93,94] Others report incompatible XM results.[92,99,100] Most studies implicate anti-DEA 7 antibodies.[101–104] While naturally occurring alloantibodies could be present, their clinical relevance has not been clearly shown. Maglaras *et al* (2017) found that transfusion related complications (including hemolysis) were more frequent in transfusions that were not crossmatched prior to administration versus those that were.[1] However, the authors did not document in this study whether or not recipients had been previously transfused. Odunayo *et al* (2017) and Marshall *et al* (2020) showed that immunologic incompatibility can exist between first-time transfusion recipients and potential blood donor dogs.[92,105] Change in HCT after transfusion was significantly higher in dogs that were crossmatched versus dogs that did not undergo crossmatching.[92] This could be due to post-transfusion alloimmunization has been reported against DEA 1,[90,94] DEA 4[106] and a further common antigen.[91] Three recent studies have reported development of alloantibodies other than anti-DEA 1.[93,94,105] It could be hypothesized that even naturally occurring alloantibodies that are of less importance and strength in transfusion-naïve dogs could gain further clinical significance, if enhanced in their expression after multiple incompatible transfusions. The immunogenicity of blood types other than DEA 1, the presence of naturally occurring antibodies against them, the type of antibodies they

generate, and their potential clinical relevance even after first time transfusion, remains largely unknown.

The lack of standardization of XM techniques complicates study comparison. Currently, the reference method of crossmatching, is the laboratory tube agglutination assay.[107,108] However, this technique is labor-intensive, has interobserver variation in interpretation, and requires technical expertise.[109,110]In addition, despite its standardization, this technique is not performed in a standardized way in many clinical situations. Other available methods include slide assay, saline gel column technique, immunochromatography technique, antiglobulin-enhanced gel column test, and commercial gel-tube assay.[85,93,98–100] Not all XM methods are interchangeable and it is difficult to compare results obtained from different techniques.

1.9 In dogs requiring <u>subsequent</u> RBC transfusions (P), does crossmatching and administering major crossmatch compatible blood (I) compared to not crossmatching (C) prevent or reduce acute hemolytic transfusion reactions (O)?

Guideline:

a. We strongly recommend crossmatching in any dog that has been previously transfused more than 4 days prior, independent of initial DEA 1 typing and crossmatching results.

b. The use of the same compatible donor dog will not assure compatibility for a second transfusion even if the original testing was compatible

Agreement: 13/13

Evidence Summary:

There are laboratory studies (LOE 3, fair) and 3 clinical case reports (LOE 5, good) documenting immunologic AHTR occurring after further transfusions in dogs that had previously been transfused and

likely immunized to DEA 1, DEA 4, and an unknown common antigen.[89–91,106] It has been demonstrated in laboratory studies[85,86,93,104] (LOE 3, good) and clinical cases (LOE 5, good)[94] that sensitization to DEA 1, 7, and *Dal* can be recognized with XM techniques. In one of the laboratory studies, 2 *Dal* negative dogs were given *Dal* positive blood. Anti-*Dal* antibodies were identified as early as 4 days after the initial transfusion.[85] Crossmatch incompatibilities against other RBC antigens have also been reported in these and a newer (LOE 3, good) laboratory study.[86,93,105] A retrospective study (LOE 4, good) found that hemolysis was more frequently detected in recipients that that were not crossmatched prior to transfusion.[1] Sensitization can occur to the initial donor used and be recognized with XM techniques.[98] The duration of sensitization has not been fully studied but seems to last several years.[85,90,94]

As mentioned previously, variation in crossmatch technique complicates evaluation of the existence and clinical relevance of those alloantibodies in dogs.[93,98–100,105]

1.10 In dogs requiring plasma transfusion (P), does administration of DEA 1 type specific plasma (I) versus non-type specific plasma (C) decrease the risk of any transfusion reaction (O)?

Guideline:

There is insufficient evidence available to make recommendations regarding the use of DEA 1 type specific versus non type specific plasma in dogs.

Agreement: 13/13

Evidence Summary:

There are no clinical or laboratory studies in dogs that specifically look at the administration of DEA 1 type and non-type specific plasma in dogs. None of the retrospective studies looking at plasma transfusions in dogs include information about blood type of the plasma used.[2,111,112] Risks of hemolytic reactions to plasma transfusion are based on either the presence of clinically significant antibodies

against red blood cells in the donor plasma or on contamination of the plasma with donor red blood cells for which the recipient has antibodies. ABO Type specific plasma is recommended in humans due to naturally occurring alloantibodies.[113] Many countries have set limits on RBC in FFP at less than 6 x 10^9 RBC/liter prior to freezing.[114] Red blood cell contamination is less of a risk when plasma is collected from donors via plasmapheresis. However, there are rare case reports in people of alloimmunization presumably due to red blood cell fragments.[114,115] Dogs do not appear to have clinically significant naturally occurring alloantibodies against DEA 1.[93,97] Thus, administration either DEA 1 positive or negative plasma to a recipient of either blood type should theoretically be safe. However, a study in Italy showed that 38% of DEA 7 negative dogs had naturally occurring alloantibodies against DEA 7 that could lead to delayed hemolytic reaction.[103] In addition, original studies on canine blood transfusions demonstrated that as little as 2-5ml of DEA 1 positive red blood cells could sensitize a recipient and lead to a AHTR if a second DEA 1 transfusion was administered.[89] Thus, if plasma was contaminated with red blood cells during processing, these cells could potentially sensitize a recipient. Research is needed in this area.

1.11 In dogs requiring plasma transfusion (P), does administration of minor crossmatch compatible (I) versus non crossmatched plasma (C) decrease the risk of any transfusion reaction (O)?

Guideline:

There is insufficient evidence available to make recommendations for or against minor crossmatching prior to plasma transfusion to decrease the risk of transfusion reaction in dogs.

Agreement: 13/13

Evidence Summary:

There are no clinical or laboratory studies in dogs that specifically discuss crossmatching plasma prior to transfusion in dogs. None of the retrospective studies looking at plasma transfusions in dogs include information about type or XM.[2,111,112] Risks of acute or delayed hemolytic reactions to plasma transfusion are based on the presence of clinically significant antibodies from the donor against recipient red blood cells. Dogs do not appear to have clinically significant naturally occurring alloantibodies against DEA 1.[93,97] However, as mentioned above, DEA 7 negative dogs can have naturally occurring alloantibodies against DEA 7 that could lead to delayed hemolytic reaction and these antibodies can be identified with a minor XM.[103] Research is needed in this area.

Typing and Crossing Matching – CATS

1.12 In cats requiring transfusion (P), does giving AB type-matched blood (I) compared to non-AB type-matched blood (C) reduce the risk of an AHTR (O)?

Guideline:

a. We strongly recommend giving AB type-matched blood to reduce the risk of AHTRs.

b. Type AB cats can receive type A pRBCs if type AB is unavailable[116].

c. We suggest that AB type-matching alone is insufficient to prevent HTRs in cats.

Agreement: 13/13

Evidence Summary:

There are 3 case reports of AB type-incompatible feline transfusions resulting in severe transfusion reactions including AHTR (LOE 5, good).[117,118] In two of these case reports, administration of non-typed and uncrossmatched blood led to rapid and severe AHTR, and later investigation confirmed a type A donor/type B recipient mismatch. In the third case, a cat originally thought to be type AB (but actually type A) and was given type B blood and had signs of reaction and an inadequate rise in PCV.[116] In another case report (LOE 5, poor), a cat died acutely after receiving only 4ml of untyped blood in what was also suspected to be an AB mismatch.[119] In a laboratory study (LOE 3, poor)[120], cats were given type-compatible or type-incompatible feline blood. No reactions were seen in the type matched

transfusions, a few mild reactions were seen when A cats were given B blood. However, severe acute reactions were seen in 55% of first transfusions when type B cats were given type A blood.

Two prospective studies (LOE 1-5, fair)[109,121] and one retrospective study (LOE 4, good)[122] describe crossmatch incompatibilities and AHTRs between AB type-matched feline donors and recipients. In two of these studies, a suspect AHTR was noted in a cat receiving a unit that was crossmatch compatible. [109,121]Occurrence of a non-immunologic AHTR or previously undiagnosed concurrent hemolytic disease was not excluded.

In an investigative study (LOE 3, fair)[123], an AHTR following a type-matched feline transfusion subsequently revealed a non-AB type incompatibility, leading to donor program compatibility testing involving 70 blood donors of different AB types. The recipient cat plasma was found to be compatible with erythrocytes from only 3 type A cats, suggesting the presence of a different RBC antigen in the rest of the cats. Presence of a previously undescribed but clinically important *Mik* erythrocyte antigen was proposed, with presence of naturally occurring alloantibodies in *Mik* negative cats.

Thus, while blood typing is mandatory prior to transfusion, typing alone is insufficient to prevent all AHTRs in cats. The presence of *Mik* antigen and potentially other unrecognized antigens remain a potential cause of severe transfusion reactions despite AB type-matching. While there are no confirmed reports of non-immunologic AHTR in cats, this also remains a potential in feline type-matched transfusions.

1.13 In transfusion naïve cats (P), does administering major crossmatch compatible blood (I) compared with non-crossmatched blood (C) prevent or reduce the risk of any type of transfusion reaction, including AHTR (O)?

Guideline:

We suggest that major crossmatching be performed alongside type-matching prior to the first transfusion in cats and that crossmatch compatible product be administered to reduce the risk of transfusion reactions.

Agreement: 13/13

Evidence summary:

There are seven studies that evaluate the incidence of XM incompatibility and the incidence of acute transfusion reactions in transfusion-naïve cats (LOE 1-5, fair to good).[4,5,109,121–124] These studies paint a contradictory picture of the utility of XM in predicting rise of PCV after transfusion and predicting the likelihood of feline transfusion reactions.

There are four prospective studies (LOE 1-5, fair-good).[4,109,121,124] . In the first,[4] 101 cats were typed, crossmatched by two methodologies, and given type specific blood. Crossmatch results were not associated with rise in PCV at 12 hours post-transfusion. There were no statistical differences in the occurrence of reactions between XM compatible and incompatible transfusions. In a smaller study,[109] there was a 3.65% incidence of XM incompatibility and there were no statistically significant differences in incidence of transfusion reactions or mean PCV increase between transfusion-naïve cats receiving XM compatible versus non-crossmatched transfusions. Both studies may have been underpowered to detect a difference in reaction rates. In the third study,[121] major crossmatching was only incompatible in one transfusion-naïve cat. Two acute transfusion reactions (1 AHTR, 1 FNHTR) were seen and both occurred with XM compatible blood. This study highlights that major crossmatching could fail to be sensitive in predicting clinically important transfusion reactions. In the last study, no incompatible crossmatches were seen in transfusion-naïve cats and no acute transfusion reactions were observed.[124]

Two retrospective studies[5,122] (LOE 4-5, fair–good) support crossmatching in transfusion-naïve cats. In a study of 450 cats[5], the incidence of acute transfusion reactions did not differ between crossmatched and non-crossmatched groups, but transfusion-naïve cats were not reported separately. However, while post-transfusion PCV increases did not differ between groups at 1-5 hours post-transfusion, PCV was significantly higher in the XM group at 24 hours. In the other retrospective study[122], XM incompatibilities were seen in 23/149 (14.9%) transfusion-naïve cats and an AHTR was suspected in one cat that received a type-matched but not crossmatched transfusion. FNHTRs occurred more often in cats receiving non-crossmatched versus crossmatched transfusions.

The most compelling argument for crossmatching transfusion-naïve cats comes from our knowledge of naturally occurring anti-*Mik* alloantibodies in some cats.[123] Until commercial testing for *Mik* and other alloantibodies are available, major crossmatching remains the only viable means of determining such incompatibilities.

1.14 In cats that have been transfused previously (P), does administering major XM compatible blood (I) compared with non-crossmatched blood (C) prevent or reduce the risk of any type of transfusion reaction (O)?

Guideline:

We suggest major crossmatching cats prior to every transfusion and strongly recommend major crossmatching if previously transfused more than 2 days prior, independent of initial AB blood typing.

Agreement: 13/13

Evidence Summary:

Three retrospective[5,122,125] (LOE 4-5, fair-good) and two prospective[121,124] (LOE 5, fair-good) describe the incidence of transfusion reactions in previously transfused cats receiving type- and crossmatched versus type- but non-crossmatched transfusions. In one retrospective study[5], lack of crossmatching was not associated with increased risk of transfusion-associated complications in previously transfused cats. However, in another retrospective study[122], the incidence of major XM incompatibilities was higher in the previously transfused group compared to the transfusion naïve group. In addition, FNHTR were more common in the cats that received non-crossmatched transfusions. In the third retrospective study[125], post-transfusion PCV was significantly higher following XM compatible transfusions.

In a small prospective descriptive study[121] of type-compatible feline whole blood transfusions, major XM incompatibilities were seen uncommonly and largely in previously transfused cats.

549 Transfusions were given prior to receiving crossmatch results, and 2/8 cats had inadequate rise in HCT
550 following transfusion. No other obvious transfusion reactions were noted for any crossmatch
551 incompatible transfusion. In another small prospective study[124], major and minor crossmatching was
552 repeated every 2 days following administration of crossmatch compatible transfusions. New
553 incompatibility identified by major crossmatch was seen as early as 2 days after the first whole blood
554 transfusion.

555 As mentioned above, an AHTR was seen in a previously transfused cat following a type-matched
556 but not crossmatched transfusion due to a *Mik* antigen-antibody reaction .[123] Crossmatching is needed
557 to identify incompatibility due to anti-*Mik* and other new antigen induced alloantibodies.
558 **1.15** In cats requiring plasma transfusion (P), does administration of AB type specific plasma (I) versus
559 non-AB type specific plasma (C) decrease the risk of any transfusion reaction (O)?

560 *Guideline:*

561 We recommend AB typing cats prior to plasma transfusion and administering AB type specific
562 plasma. Cats with AB blood type can receive type A plasma if AB is unavailable. Type AB plasma
563 can be given to all cats.

564 *Agreement: 13/13*

565 *Evidence Summary:*

566 There are 2 retrospective studies in cats that discuss plasma transfusion and include blood type
567 information (LOE 4, fair-good) and two laboratory studies looking specifically at naturally occurring
568 alloantibodies in cats (LOE 3, good).[6,7,126,127] In one of the retrospective studies, 2 AB cats were given A
569 plasma with no reactions seen. One B cat was inadvertently given 1ml of type A plasma with no reaction
570 seen. There were 9 cats with unknown blood type and it is unclear what type plasma was used.[6] In a

second retrospective, cats were either type A or B and received type specific plasma.[7] In a study of 312 cats in Turkey, all B cats had anti-A antibodies. Most type A cats had low titer anti-B antibody with 12% having no antibody and 4.5% having high titer antibody.[127] The second laboratory study looked at the incidence of antibodies in 49 clinically healthy cats, of type A, B, and AB, using two crossmatch methodologies. The findings were similar. Twelve of 13 B cats had strong anti-A alloantibodies while plasma from the type A cats had weak or no anti-B alloantibodies. The 2 type AB cats had no naturally occurring alloantibodies. The RBC from one of the AB cats reacted to plasma from 7 B cats but none of the plasma from the A cats.[126]

1.16 In cats requiring plasma transfusion (P), does administration of minor XM compatible (I) versus non crossmatched plasma (C) decrease the risk of any transfusion reaction (O)?

a. There is insufficient evidence available to make recommendations regarding the efficacy of minor crossmatching prior to plasma transfusion to decrease the risk of transfusion reaction in cats prior to plasma transfusion.
b. If AB typing is not available, we recommend minor XM prior to plasma transfusion to identify strong alloantibodies

Agreement: 12/13 One panel member felt that minor crossmatch should be considered even if AB typed due to possibility of Mik antibodies

Evidence Summary:

There are studies that look at the influence of major XM on the incidence of red blood cell transfusion reactions in cats.[4,109,122] However, there are no studies that look at the incidence of plasma transfusion reactions with and without minor crossmatch. There are 3 retrospective studies in cats that discuss plasma transfusion (LOE 4, fair-good) and four laboratory studies looking specifically at naturally occurring alloantibodies in cats (LOE 3, good).[6,7,122,123,126–128] None of the retrospectives discuss minor

crossmatching.[6,7,128] Laboratory studies have confirmed the existence of Anti-A and Anti-B naturally occurring alloantibodies that vary in strength and can be identified with XM.[120,126,127] Studies have also identified naturally occurring alloantibodies that exist outside the AB system.[122,123] However, it is unclear if the administration of these other alloantibodies in a plasma transfusion could lead to a clinically significant reaction. Further research is needed in this area.

Additional Issues with Crossmatching

1.17 In dogs and cats requiring transfusion (P), does administration of completely XM compatible blood (I) compared to blood with a minor incompatibility on XM (a small amount of agglutination) (C) prevent or reduce the risk of a delayed or mild hemolytic transfusion reaction (O)?

Guideline:

a. There is insufficient evidence to determine whether administration of completely compatible blood versus blood with mild macroagglutination on crossmatch decreases the risk of acute or delayed hemolytic reactions.
b. We suggest that if XM is performed, that fully compatible red blood cells be used when possible.

Agreement: 13/13

Evidence Summary:

There are no prospective veterinary studies specifically addressing transfusion of blood with mild (1+) macroagglutination on XM. However, there is a laboratory study in dogs documenting transfusion of incompatible blood (LOE 3, fair), as well as two canine case reports (LOE 5, fair) and 3 feline studies (LOE 5, fair) that report transfusion of mild to moderately (trace-3+ agglutination) incompatible blood. The laboratory study looked at blood types and transfusion compatibility in research dogs. The study recognized agglutination on XM with some antigens (termed B, C, D, and F)

but with varying capacity for in vivo red cell destruction. When type B, C, D, and F incompatible cells were transfused into sensitized recipients, no acute hemolytic reactions were seen. However, in vivo sequestration of transfused red blood cells was suspected. The authors concluded that studies are needed with biomarked incompatible cells to understand the in vivo characteristics of these mismatched transfusion.[89] A 1995 case study involved the transfusion of two units of XM incompatible DEA 1- type matched blood to a previously transfused recipient (XM incompatibility grade was not recorded). An acute hemolytic transfusion reaction, and poor response to transfusion (no increase in PCV) was seen to both transfusions that could not be isolated to any known blood type but was considered to be due to the recipient being negative and subsequently sensitized to a common antigen.[129] Another case report involved the transfusion of two units of blood to a recipient that were trace and 1+ macroagglutination XM incompatible. An AHTR was seen to both transfusions and the reaction was discovered to be due to DEA 4 incompatibility.[106]

In a feline retrospective study, 6 cats received transfusion of the least incompatible blood units on XM. Five cats had 1+ major XM incompatibility and 1 cat had 1+ minor XM incompatibility. No AHTR or febrile reactions were seen and PCV change was similar to the rest of the study cats.[122] In another study, 7 cats were transfused with mildly incompatible blood, 5 cases with 2-3+ macroscopic agglutination reaction, and 2 cases with 1-2+ microscopic agglutination. They also reported no obvious transfusion reactions. The PCV increased as expected in 5 but not in the other 2.[121]

Crossmatch Options

There are many XM techniques available. The saline gel column technique has been proven to be highly accurate in human medicine[130] with a sensitivity between 97.58 and 100% and a specificity close to 100%.[131] Studies in dogs[85,86] and cats[94,97,123] showed this technique to be easy to standardize, simple to perform and easy to interpret with a non-operator dependent grading. In dogs, recent studies

639 reported conflicting results with respect to the agreement of the reference laboratory tube method
640 compared to the gel-based techniques[99,100]. Two studies compared XM results of tube and saline gel
641 column methods for detecting naturally occurring alloantibodies in a limited number of cats and found
642 overall agreement between both methods.[122,123]. However, a prospective observational study of 101
643 transfusion-naïve cats showed marked difference in the proportion of XM incompatibility between the
644 laboratory tube method (27%) and a commercial gel tube test (4%).[4]. In cases of IMHA, gel techniques
645 may be preferred as persistent autoagglutination can lead to false incompatible results in tube
646 agglutination assays.[99] On the other hand, gel methods are reliant on the proper centrifuge.[100]

647 Human studies show that the use of XM with specific antiglobulin improves the test's sensitivity
648 for detecting potentially clinically important alloantibodies coating RBCs but may decrease the
649 specificity for identifying clinically significant antibody formation.[132,133] A study in dogs[93] aimed to
650 examine naturally occurring alloantibodies against RBCs and alloimmunization by transfusion using 2
651 antiglobulin-enhanced XM tests (immunochromatographic strip XM and laboratory gel column
652 techniques). The two XM methods gave entirely concordant results. In cats, a study compared a saline
653 gel column test and an antiglobulin-enhanced gel column test in 446 plasma to RBC pairings; both
654 methods showed the same compatibility results for all pairings, except for 15 pairings for which
655 incompatibility was only detected with the antiglobulin-enhanced gel column test (including 14
656 incompatibilities outside the expected AB mismatches).[126] These incompatibilities may demonstrate
657 nonsignificant alloantibody formation due to the enhancement of the test platform. In addition, a recent
658 study in dogs compared a laboratory canine-specific antiglobulin enhanced tube method, a gel tube
659 point-of care test, and a canine-specific immunochromatographic antiglobulin enhanced point-of-care
660 test. Compared to the laboratory method, the gel method and the immunochromatographic tests lacked
661 sensitivity for detecting incompatibilities.[105]

Thus, not all XM methods are interchangeable and it remains difficult to compare results obtained from different techniques. Gel column and tube techniques appear to be highly accurate especially when they are antiglobulin enhanced. They require an appropriate centrifugation procedure, standardization of antiglobulin, and standardization of grade allocation. However, performing a XM remains the most reliable means of avoiding acute and delayed hemolytic transfusion reactions. Crossmatch techniques should be standardized at each clinical site and performed in a validated, repeatable manner by trained personnel to provide reliable results to predict the possibility of transfusion reaction secondary to erythrocyte antigen incompatibilities.

Xenotransfusion

1.18 PICO Question: In a transfusion naive cat that requires an emergency transfusion (P), does the use of a canine blood product (I) compared to a feline blood product with a different or unknown AB blood type (C) improve any outcome (O)?

Guideline:

a. Administration of type A blood to type B cats can cause a fatal reaction.

b. Canine red blood cells transfused to cats have a short lifespan and severe hemolytic reactions can be seen.

c. Before the use of a feline blood product with a different blood type, we strongly recommend crossmatching the donor and recipient, and exhausting all possible means to obtain a compatible feline blood product

d. Canine blood should only be used in cats as a last option and with informed owner consent.

Agreement: 11/13, 2 disagreed with c.

Evidence Summary:

There are 10 veterinary studies addressing xenotransfusion, 4 laboratory (LOE 3, poor to good), 1 prospective (LOE 2, fair) and 5 case series (LOE 5, poor to fair). These studies have shown that xenotransfusion can be lifesaving in an emergency but can cause severe transfusion reactions, including death (LOE 3-5, fair to good). [134–138] In a prospective study of 49 cats that received xenotransfusion, 6 cats had FNHTR and 25 cats had a DHTR with icterus or hemolyzed serum noted at a median of 2 days.[136]A previous laboratory study documented a similar average lifespan of canine erythrocytes in cats of approximately 3 days (LOE 3, fair) and also demonstrated a significant risk of severe anaphylactoid transfusion reaction and death if additional canine blood is administered more than 6 days after the initial xenotransfusion (LOE 5, fair). [139]

Xenotransfusion has been most often considered when no feline blood is available,[140] in a type B cat when type B blood is unavailable, or in an emergency situation when blood typing is not possible.[138] The administration of type A blood to a type B cat can cause an acute life-threatening reaction.[141] Although the transfusion of a different AB blood type can cause an AHTR, plasma from some type A cats have either no or week anti-B antibodies, suggesting that, with a compatible XM, type B blood could be given to a type A in a true emergency situation.[126] Even with a pre-transfusion compatible crossmatch with canine blood, cats can develop a DHTR following the initial transfusion.[134,136,142]

Prior to the transfusion of canine blood, owners should be educated about the risks associated with the transfusion of canine blood and that referral for compatible feline blood products may be more appropriate. If canine blood is given to a cat, informed owner consent should be documented, and the medical record should be prominently marked that canine blood has been administered to the cat and additional transfusions with canine blood cannot be performed.

Pre-Medication

1.19 In dogs and cats requiring transfusion (P), does pre-treatment with an antihistamine (I) versus no pre-treatment (C) prevent or reduce any type of transfusion reaction (O)?

Guideline:

We do not recommend pre-treatment with antihistamine prior to transfusion to decrease the risk of allergic transfusion reaction in dogs and cats due to evidence of lack of efficacy in humans.

Agreement: 13/13

Evidence Summary:

There are conflicts in human and veterinary literature regarding premedication with antihistamine medication prior to blood product transfusion. Repeated large prospective and retrospective human trials have not shown a significantly decreased incidence of allergic transfusion reactions with the use of antihistamine pre-treatment and two metanalyses found no benefit to using diphenhydramine.[143,144] However, the only clinical veterinary study (a large canine retrospective study, LOE 4, good) specifically investigating the use of premedication prior to transfusion, found a decreased rate of allergic cutaneous reactions in patients administered pre-transfusion diphenhydramine.[2] Also, a laboratory study on experimentally induced anaphylaxis in dogs also found that pre-treatment with chlorphenamine decreased the cardiovascular depression caused by anaphylaxis.[145]

The difference between human and veterinary research findings may be due to more robust study methods for human trials, differing standards in human and canine transfusion medicine practice, or due to inherent differences between the species. In humans, cats, and dogs, allergic transfusion reactions are fairly uncommon, with cutaneous allergic reactions noted in only 13/935 transfusions in the Bruce et al (2015) study (1.7% cases transfused with plasma and 1.3% cases transfused with PRBCs).[2]

As anti-histamines can have adverse effects on memory, psychomotor skills and mood, and as the cumulative cost of pre-treatment for every patient would be large, it has been argued that routine pre-treatment should be avoided in humans.[146] However, the distress and discomfort of these reactions should also be considered for those patients in which they are seen. Prospective veterinary studies in this area are needed.

1.20 In dogs and cats with a previous allergic transfusion reaction (P), does pre-treatment with an antihistamine (I) versus no pre-treatment (C) prevent or reduce a further allergic reaction (O)?

Guideline:

a. There is insufficient evidence in dogs and cats with prior allergic transfusion reactions, and evidence of lack of efficacy in humans regarding the benefits of pre-treatment with antihistamines.
b. We do not recommend pre-treatment with an antihistamine prior to transfusion to decrease the risk of allergic transfusion reaction in dogs and cats that have had a previous allergic transfusion reaction.

Agreement: 13/13

Evidence Summary:

There was only one study (LOE 6, fair) considered for this topic; a large retrospective human study which found that premedication did not decrease the risk of allergic transfusion reaction in patients that had previously had an allergic or FNHTR.[146] It should be noted that the study did not separate out the population that had solely previous allergic transfusion reaction when analyzing the likelihood of further allergic reaction. The study also found that a previous allergic transfusion reaction was not associated with an increased risk of an allergic transfusion reaction on repeated transfusion and

751 that the likelihood of allergic transfusion reaction actually decreased with increasing number of
752 transfusions, which has also been reported in another study.[147]

753 Given the decreasing likelihood of allergic transfusion reactions with repeated transfusions and
754 the lack of evidence of efficacy for antihistamine use in decreasing the risk of allergic transfusion
755 reactions in humans that have had a previous allergic transfusion reaction, the practice is unlikely to be
756 useful in dogs and cats.

757 **1.21** In dogs and cats requiring transfusion (P), does pre-treatment with antipyretics (I) versus no pre-
758 treatment (C) prevent or reduce incidence of FNHTRs (O)?

759 *Guideline:*

760 a. There is no evidence regarding whether pretreatment of dogs and cats requiring transfusion with
761 antipyretics prevents or reduces FNHTR.
762 b. We suggest that pretreatment with antipyretics to prevent FNHTR is not indicated in dogs
763 and cats based on the lack of benefit in human studies.
764 c. Acetaminophen should never be given to cats based on evidence of exquisite sensitivity to
765 its hepatotoxic effects, as well as occurrence of methemoglobinemia and Heinz body
766 hemolytic anemia.

767 *Agreement: 13/13*

768 *Evidence Summary:*

769 There is no evidence from peer reviewed original research in veterinary medicine addressing the
770 PICO question. In human medicine, there are 6 relevant studies, 2 of which support pre-treatment with
771 antipyretics and 4 of which do not.

772 A prospective, randomized, double-blind, placebo-controlled trial (LOE 6, good) evaluated the

efficacy of a combination of acetaminophen and diphenhydramine 30 minutes prior to transfusion, for the prevention of non-hemolytic transfusion reactions in hematology/oncology patients. All patients received post-storage leukoreduced RBCs or single-donor apheresis platelet transfusions. In multivariate analysis, the treatment group was associated with a decreased risk of febrile reactions after adjusting for other covariates. However, this was a small trial, and only 21 patients (7 in the active drug group, and 14 in the placebo group) experienced febrile events.[148] The other study supporting the PICO question was a single-center retrospective case series with no control group (LOE 6, poor).[149]

Two randomized placebo controlled trials oppose the PICO question (LOE 6, good), although are confounded by the concurrent use of an antihistamine with an antipyretic in the premedication arms.[150,151] A single center study included 55 hematology/oncology patients, that received 98 leukoreduced, irradiated, single-donor apheresis platelet transfusions.[150] There was no difference in the incidence of NHTRs in the group premedicated with acetaminophen and diphenhydramine (8/52, 15.4%), compared to the placebo group (7/46, 15.2%).[150] A randomized, double-blind placebo controlled clinical trial conducted in children and adolescents also showed no difference between pre-treatment (using acetaminophen and chlorpheniramine) and placebo groups in the development of fever during the first 24 hours after RBC transfusion[151]

Two LOE 6 poor studies also oppose the PICO question. In a prospective observational study of platelet transfusions (LOE 6, poor), institution of a premedication protocol did not decrease the rate of febrile complications.[152] A retrospective case series in pediatric patients receiving pre-storage leukoreduced RBCs and single-donor apheresis platelets (LOE 6, poor) analyzed 7,900 transfusions administered to 385 patients.[153] No premedication was administered prior to 2,521 transfusions (32%), acetaminophen alone prior to 1064 transfusions (13%), diphenhydramine alone prior to 1,271 transfusions (16%), and both prior to 3,044 transfusions (38%). Premedication with acetaminophen or diphenhydramine failed to decrease the risk of febrile or allergic transfusion reactions regardless of

whether patients had a history of reactions.[153]

1.22 In dogs and cats with a previous FNHTR (P), does pre-treatment with anti-pyretics (I) versus no pre-treatment (C) prevent or reduce any type of transfusion reaction (O)?

Guideline:

a. In dogs and cats with a previous FNHTR, there is no evidence regarding whether or not pre-treatment with antipyretics reduces or prevents any type of transfusion reaction.

b. Based on lack of evidence of benefit in humans we suggest that pretreatment with antipyretics is not indicated in dogs or cats with previous FNHTR.

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 is no evidence from peer reviewed original research in veterinary medicine addressing the PICO question. In human medicine, there are 3 relevant studies, 1 of which is neutral (LOE 6, poor), and 2 of which oppose the PICO question (LOE 6, poor to good).

An observational study followed 81 patients with hemoglobinopathies over a 7-year period during which they received a total of 20,668 RBC units. Clinicians were directed to only premedicate patients with acetaminophen if they had at least two episodes of mild or moderate FNHTR within a 24-month period. Twenty-eight FNHTRs were noted in 10 patients during the study period. Five patients

were just observed and had no further reactions. The other five received pre-medication after subsequent reactions and then did not have further FNHTR.[154]

In a prospective, double-blind, placebo-controlled clinical trial,[150] premedication with acetaminophen (650mg PO) and diphenhydramine (25mg IV) was administered prior to 52 transfusions and placebo was given prior to 46. Of patients with a history of FNHTR, 14 received premedication prior to future transfusions while 13 received placebo. There was no difference in the rate of future NHTRs in the premedication group (4/14), vs the placebo group (3/13).[150] This study was small and specifically looked at platelet transfusions so it is difficult to know if it would extrapolate to other patient populations.[150]

A retrospective case series analyzed 7900 pre-storage leukoreduced RBCs and single-donor apheresis platelets administered to 385 patients.[153]. Premedication with acetaminophen or diphenhydramine failed to decrease the risk of febrile or allergic transfusion reactions regardless of whether patients had a history of reactions. Specifically, in those with one previous reaction, 1/134 (0.75%) premedicated with acetaminophen and 1/295 (0.34%) that were not premedicated, had a further NHTR. In patients with two or more previous reactions, 0/82 in the acetaminophen group, and 0/86 in the no premedication group had future reactions.[153]

Transfusion Administration

1.23 In dogs and cats requiring transfusion (P), does starting the transfusion slowly and then increasing the rate if no reaction is seen (I) compared to administration at a set rate for the duration of the transfusion (C) improve any outcome (earlier detection of a reaction or reduced risk or severity of a transfusion reaction) (O)?

Guideline:

a. There is insufficient evidence to make strong recommendations that an initial slow infusion followed by an increasing rate, versus a set infusion rate, results in increasing safety of transfusion.
b. Based on human medical guidelines and when patient condition permits, we suggest a slow rate of transfusion for the first 15 minutes of transfusion with subsequent increase in rate of administration if no adverse effects are noted.

Agreement: 13/13

Evidence Summary:

There are no studies examining the recommended rate of initial blood transfusion in cats, dogs, and humans. Human guidelines from several countries recommend red blood cell transfusions be started slowly for the first 15 minutes, when clinically appropriate, and that the rate is increased after 15 minutes to ensure completion within a 4-hour window.[155–157]

1.24 In dogs and cats requiring transfusion (P), does any specific rate of transfusion administration (I) compared to standard administration (over 4 hours) (C) prevent or reduce the risk of TACO (O)?

a. No evidence-based recommendations can be made regarding an appropriate transfusion rate to mitigate TACO in dogs and cats.
b. We suggest that transfusion rates are selected while considering individual patient signalment, disease process, and comorbidities. We suggest that slower transfusion rates be considered in patients that are euvolemic requiring transfusion, or in those cases with concurrent and significant renal or cardiac disease.

Agreement: 13/13

Evidence Summary:

No veterinary studies to date provide an evidence-based recommendation for optimal transfusion administration rates in minimizing TACO. There are three human studies (LOE 6, fair) that suggest faster blood product infusion rates are a risk factor for TACO.[158–160] Only one, a prospective cohort study, showed a significant difference in ml/hr. rate between transfused patients who developed TACO and those that did not.[160] The optimal transfusion rate of blood components and the efficacy of limiting transfusion rates in the mitigation of TACO in human medicine is currently unknown.

1.25 In cats receiving red blood cell transfusion (P), is administration of the transfusion with a syringe pump and an 18-micron microaggregate filter [b] (I) compared to other administration strategies (C) more efficacious for red blood cell survival in vivo?

Guideline:

a. There is limited evidence available on red blood cell survival using different infusion pumps and blood filters in cats.
b. We suggest that administration of red blood cells to cats using a syringe pump and an 18-micron microaggregate filter leads to acceptable red blood cell survival in vivo.

Agreement: 13/13

Evidence Summary:

There is only one study in cats looking at administration technique (LOE 3, good).[161] In this study, blood was drawn from healthy blood donors, biotinylated, reinfused with either gravity flow and an in-line filter or via a syringe pump and an 18-micron microaggregate filter, and red blood cell life span was tracked. There was no difference in RBC survival at 12 hours or at 6 weeks between the administration methods. This study was performed using whole blood stored for less than 24 hours. Further studies using stored blood would be helpful. Other transfusion studies in cats looking at red blood cell survival

have not listed the administration method.[4,5,122,128] Studies in humans and in dogs have shown increased hemolysis and decreased in vivo survival of red blood cells using certain types of infusion pumps. Rotary and peristaltic infusion pumps appear to be more damaging, especially to stored red blood cells, than other types of infusion pumps.[162,163] Including administration method in future transfusion studies would be helpful for comparison.

1.26 In dogs receiving red blood cell transfusion (P), is administration of the transfusion using an in-line filter and no pump (I) compared to other administration strategies (C) more efficacious for red blood cell survival in vivo (O)?

Guideline:

a. Studies in dogs indicate that use of specific infusion pumps can lead to increased hemolysis, especially with stored red blood cells, and decreased in vivo red blood cell survival.
b. We suggest that red blood cell transfusions in dogs be administered using a standard 170-260 micron in-line blood administration set with gravity flow or using a previously evaluated piston pump[c]. Peristaltic and rotary infusion pumps should be avoided.

Agreement: 13/13

Evidence Summary:

Four studies in dogs (LOE 3, good) have looked at red blood cell viability using different infusion methods.[163-166] Only one (LOE 3, Good) looked at in vivo red blood cell survival. In that study, biotinylated red blood cells were administered by different infusion methods. Red blood cell survival was markedly decreased with pump infusion, either peristaltic with an in-line filter or with a syringe pump and 18-micron microaggregate filter compared to gravity flow.[164] Another study looked at hemolysis after infusion of both fresh and stored red blood cells using in line filters with different pumps

(LOE 3, Good). Significant hemolysis was seen with the use of peristaltic rotary pumps which was worse with stored red blood cells.[165] Subsequent studies in dogs on blood administration with a syringe pump and microaggregate filter have not demonstrated increased hemolysis (LOE 3, good)[163] and also did not find evidence of filter clogging or changes in red blood cell osmotic fragility (LOE 3, good).[166] Previous human research studies (LOE 3, good) also showed increased hemolysis with peristaltic pumps but one study showed acceptable survival using a newer piston pump.[162,167] A recent canine study also showed minimal hemolysis using the same piston pump.[163] Further studies looking at red blood cell in vivo survival of different age products with different pumps are needed. In addition, including administration method in future transfusion studies in dogs looking at improvement in PCV after transfusion would be useful.

Irradiation of Blood Products

1.27 In dogs undergoing transplantation (e.g. bone marrow) and requiring blood transfusion (P) should the use of irradiated red blood cell products (I) rather than non-irradiated red blood cell products (C) be considered to prevent transfusion associated graft versus host disease (O)?

Guideline:

a. Irradiation of blood products prior to transfusion in dogs undergoing transplantation (e.g. bone marrow) might aid in the prevention of TAGVHD.
b. Although controlled studies are lacking, we suggest that irradiated red blood cell products appear safe and can be considered when available for transfusion of canine bone marrow transplant patients.

Agreement: 13/13

Evidence Summary:

Transfusion associated graft versus host disease has been recognized since the 1960s. Shortly after identification of this reaction it was found that reduction of the lymphocyte proliferative capacity in donor blood could avoid TAGVHD. Lymphocyte proliferative capacity is reduced using a variety of mechanisms, most commonly irradiation. Outside of laboratory studies, TAGVHD is not reported in dogs or cats.

There are two canine studies (LOE 3, poor-good) of blood product irradiation. In one, leukocytes were repeatedly transfused to dogs after the dogs underwent total body irradiation and autologous bone marrow transplantation. All dogs administered non-irradiated leukocytes developed signs consistent with TAGVHD. Two parallel groups were transfused on a similar schedule with leukocytes irradiated at low or high doses prior to transfusion. Most dogs receiving low-dose irradiated leukocytes developed TAGVHD while those receiving high-dose irradiated leukocytes did not. The study revealed that certain doses of irradiation prevented the development of TAGVHD.[168]A second study showed that irradiation of canine red cells did not cause significant morphological or biochemical alterations in the blood products.[169]

There are no reported risk factors for TAGVHD in veterinary patients. Press et al speculated that TAGVHD could become a concern with increasing frequency of stem cell transplantation in animals.[169]

Domain Two: Monitoring Transfusions

2.1 Do you agree that this monitoring form (Figure One) is suitable for early detection of the most common types of transfusion reactions

Agreement: 13/13

Summary:

Effective transfusion monitoring is essential to allow for the earliest possible detection of a transfusion reaction. Early detection allows early action, hopefully decreasing the impact of any reaction on the recipient. There have been no previous attempts to standardize transfusion monitoring in veterinary medicine. The production of this monitoring sheet was an iterative process, with feedback from all members of the committee, with several aims which are detailed below.

Our first goal was to produce a simple design suitable for use by all veterinary practices, that could help veterinarians and technicians to track and monitor patient vital parameters. We chose those parameters that are most likely to assist the clinician in determining whether a transfusion reaction is occurring. Blood pressure was included as hypotension has been documented in hypotensive transfusion reactions, anaphylaxis, and septic and hemolytic transfusion reactions.[170-173] Although vital parameter evaluations are hourly after the first hour, it is recommended that recipients are visually monitored much more frequently, and they ideally should not be left unmonitored throughout the transfusion period. The use of a multiparameter monitor with ECG, temperature probe, and oscillometric blood pressure functions can minimize repeated handling. Any patient abnormalities (e.g. hypersalivation, nystagmus, etc.) noted during the monitoring period that do not have a specific column can be numerically listed in the 'other concerns' column with further details described in the comments box. Monitoring is continued after the end of the transfusion period to emphasize that acute transfusion reactions can occur up to 24 hours after transfusion.

It is important to note that a new sheet should be used for each new blood product administered. This allows for the necessary monitoring to be performed prior to each transfusion and also will provide clarity about when each transfusion starts. The monitoring sheet may need to be tailored to an individual case (with more frequent evaluations in a patient receiving a blood product as a bolus or less frequent recording of blood pressure in a fractious or aggressive patient).

Secondly, the form incorporates safety checks that are standard in human medicine to ensure the correct blood product is administered to the correct patient. Human transfusion monitoring guidelines suggest that recipient identification and blood type are confirmed, and blood product blood type and expiry date checked at the patient bedside immediately prior to transfusion.[174] These safety checks, with double signature (as veterinary patients cannot confirm their own identity), have been incorporated into the monitoring sheet.

Third, the form will allow practices to gather information on their transfusion practices. Monitoring transfusion reaction frequency is standard practice in human medicine and is a part of good veterinary clinical governance. The form will also be used to allow standardized data recording between institutions to further multi-center veterinary research in transfusion medicine.

TRANSFUSION MONITORING SHEET

RECIPIENT DETAILS

Name: _____
Signalment: _____
Case no: _____
Blood type: _____
PCV/TS: _____ Serum/plasma colour: _____
Body weight: _____
Previous transfusions: _____
Reason for transfusion: _____
Clinician: _____ Signature: _____

PRODUCT DETAILS

Blood product ID: _____
Date of collection: _____
Expiry date: _____
Blood type: _____
PCV/TS: _____ Serum/plasma colour: _____
Unit volume: _____

(Please circle)	PRBC	FFP	FWB	Other (specify): _____
	Canine Feline	Canine Feline	Canine Feline	Canine Feline

Administration plan (volume & rate): _____
Name: Signature:

Cross-matched? Compatible Incompatible Not evaluated	Method of admin: Gravity Syringe driver Fluid pump

Correct patient (initialled by 2): _____ Correct unit (initialled by 2): _____ IV catheter checked: _____
Start time: _____ Date: _____ Person starting transfusion: _____

	Time	Infusion rate ml/hr	Resp. rate	Pulse rate	MM Colour & CRT	Temp °C	Mentation	S/D/M blood pressure	Serum/ plasma/ urine colour	Angiodema /Erythema/ Pruritis (Y/N)	Vomit or diarrhea (Y/N)	Other concerns
Pre-transfusion												
5 mins												
15 mins.												
30 mins.												
60 mins.												
2 hours												
3 hours												
4 hours												
15 mins post transfusion												
1 hour post transfusion												
24 hour post transfusion												

Finish time: _____ Volume infused: _____ Post-transfusion PCV & time: _____

Comments: _____

FOLLOW TRANSFUSION REACTION GUIDELINES IF YOU SUSPECT A REACTION

2.2 In dogs and cats receiving red blood cell transfusion (P), does checking the post transfusion PCV at 2 hours (I) compared to other time points (C) better reflect the efficacy of transfusion (O)?

We suggest that PCV or HCT can be checked immediately post-transfusion in dogs and cats to determine efficacy.

Agreement: 13/13

Evidence Summary:

In the past, equilibration of hemoglobin concentration after transfusion was expected to take several hours to up to 24 hours.[175] However, studies have been performed in human adults, neonates, and in dogs (LOE 2-6, fair to good) specifically comparing the HCT or PCV at different time points after transfusion.[175-177] These prospective case series have all shown equivalence between initial measurement of PCV and PCV checked several hours later. The studies in human adults and neonates excluded any patient with potential continued bleeding. [175,176] However, the study in dogs showed equivalent values between the PCV measured immediately after transfusion and at 4 hours irrespective of the underlying reason for anemia.[177] There has not been a specific study in cats designed to answer this question. However, a prospective randomized study looking at PCV change after either crossmatch or non-crossmatched blood in cats (LOE 2, good) showed no difference in PCV change immediately, at one hour or at twelve hours post transfusion.[109]

2.3 In dogs and cats receiving massive transfusion (P), does monitoring ionized calcium (I) compared to not monitoring (C) improve any outcome (prevent signs of reaction or improve hospital survival) (O)?

Guideline:

We suggest that dogs and cats that receive massive transfusion or apheresis should have their ionized calcium concentrations monitored regularly.

Agreement: 13/13

Evidence Summary:

In dogs and cats, the development of citrate toxicity usually occurs during massive transfusion or apheresis. Massive transfusion has been defined in veterinary medicine as transfusion of a volume of blood products in excess of half the patient's blood volume in 3 hours or over a full blood volume in 24 hours.[70] There are 10 case series and retrospective studies[70,72,178–185] (LOE 4-5, poor to good) in dogs and cats that discuss the use of specific treatments (massive transfusion, CRRT, therapeutic plasma exchange (TPE), etc.) and report hypocalcemia as a complication due to suspected citrate toxicity. However, plasma citrate levels were not measured. Several complications with citrate toxicity have been reported, including electrolyte abnormalities, acid-base disturbances, ECG changes, vomiting, nausea, and tremors.[186–188]

Conclusions

The use of consistent, evidence-based guidelines in planning, administering, and monitoring transfusions in dogs and cats can improve the safety of these treatments. Many knowledge gaps were identified, and these guidelines will need to be updated as research is performed. The members of the consensus panel believe that identification of these knowledge gaps will help inform future studies. In addition, the members believe that use of a standardized monitoring form will help in collection of data for future transfusion research.

Footnotes:

a. HemoCue Plasma/Low Hb system, HemoCue, Brea, CA.

b. Hemo-Nate 18-micron blood filter, Utah Medical Products, Inc, Midvale, UT.

c. Hospira Plum A+ infusion pump, Hospira Inc, Lake Forest, IL

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