Disorders of Coagulation - Part 3
Secondary Hemostatic Disorders

Introduction

Failure of secondary hemostasis may result from inherited or acquired factor deficiencies. Isolated inherited factor deficiencies are rare, but have been reported. Most commonly these occur in young animals, with minimal or no history of trauma. Blood clotting factor deficiencies are usually acquired. Some of the most common causes are listed below.

- Anticoagulant rodenticide toxicity (prevents production of functional factors II, VII, IX, X)
- Disseminated intravascular coagulopathy
- Liver failure – results in decreased clotting factor production, decreased clearance of fibrin degradation products (FDP’s), and a relative vitamin K deficiency (also seen with cholestasis)
- Hypothermia – slows activity of enzymes involved in the coagulation cascade
- Factor loss – through excessive consumption with thrombocytopenia, or thrombocytopathia
- Dilution of clotting factors – following fluid therapy, diluting total solids to less than 35 g/L

Vitamin K Deficiency and Antagonism

Pathophysiology

- Vitamin K is required for the post-ribosomal carboxylation of glutamyl residues of factors II, VII, IX and X.
- Vitamin K also required for the synthesis of Protein C (Inhibitor of Factor V and Factor VIII)
- Anticoagulant rodenticides inhibit the enzyme vitamin K epoxide reductase, thereby preventing recycling of Vitamin K epoxide to the biologically active vitamin K$_1$. Under normal conditions, vitamin k$_1$ carboxylates clotting factors II, VII, IX and X, which allows them to bind calcium, and participate in the clotting system. Vitamin K$_1$ deficiency therefore reduces the carboxylation of the dependent clotting factors, and results in a secondary coagulopathy
- With Vitamin K$_1$ deficiency or antagonism, the liver produces inactive coagulation proteins, which are antigenically similar to factors II, VII, IX and X.
- The half-life of vitamin k$_1$-dependant clotting factors is as follows
  - Factor II - 41 hrs
  - Factor VII - 7 hrs
  - Factor IX - 14 hrs
  - Factor X - 16.5 hrs
- Peak serum concentration occurs 12 hours after experimental exposure to vitamin K antagonists
Clinical Signs

- Clinical signs are generally related to the presence of bleeding into organs, resulting in organ dysfunction, and the presence of bleeding into body cavities.
- Acute death without previous signs of illness can occur with a sudden hemorrhage into the brain, pericardial sac or thoracic cavity.
- Dyspnea may occur due to anemia, hemorrhage into the lung parenchyma, anemia, intrathoracic bleeding and intra-abdominal hemorrhage.
- Anemia, weakness, pallor, hematemesis, epistaxis, and malena may occur.
- Hematomas may form at sites of trauma and venipuncture.
- Lameness may occur secondary to hemorrhage into joints and muscle tissue.
- ACT, APTT and PT are prolonged.
- The most sensitive early indicator of exposure to a toxic dose of a vitamin K antagonist is the prothrombin time. The reason for this is that the prothrombin time tests activity of factor VII, which has the shortest half-life of all of the vitamin K-dependant factors. Prothrombin time will become prolonged 36 hrs following exposure to vitamin K antagonists. APTT and ACT will become prolonged approximately three days post exposure.

Treatment

- Provide oxygen supplementation if indicated
- Provide ventilatory assistance if the patient is not ventilating adequately. Perform bilateral thoracocentesis to drain pleural fluid if indicated by the presence of expiratory dyspnea, biphasic expiration, and reduced lung sounds.
- Provide circulatory support – patients showing signs of decompensating response to anemia (elevated heart rate at rest, tachycardia, depression, lethargy, recumbency and hypoxia), or patients with a PCV less than 15% should receive transfusion of whole blood.
- Patients with a significant increase in ACT, PT or APTT should receive transfusion of fresh frozen plasma.
- Begin therapy with vitamin K\textsubscript{1} at 2 - 5 mg/kg/day. If the patient will tolerate oral medication with food, begin therapy with oral vitamin K\textsubscript{1}. If the patient will not tolerate oral medication with food, begin with injectable vitamin K\textsubscript{1}. Remember, these patients have a coagulopathy – the fewer injections they get the better! Vitamin K\textsubscript{1} has greatest bioavailability if given orally and fed with a fatty meal. Treatment should continue for 10-35 days, depending on whether a first, second, or third generation vitamin K antagonist has been ingested. A clotting profile (APTT, PT) should be carried out 3 days following cessation of vitamin K\textsubscript{1} therapy to determine if a more prolonged course of treatment is required. It must be noted that vitamin K\textsubscript{1} will take 12-36 hrs to normalize clotting times in dogs and cats. These patients will continue to bleed.
during this lag phase of treatment – they must be kept quiet and preferably under observation, and provided with fresh frozen plasma, cardiovascular and respiratory support if dictated by the patients condition.

Liver Disease

Pathophysiology

- The liver is the site of synthesis of most coagulation factors and their inhibitors
- Patients with liver disease may develop coagulopathies in situations of acute fulminating hepatopathy or acute hepatic necrosis, or with loss of greater than 70% of hepatocellular mass. In both of these situations, a reduction in functional hepatocellular mass reduces production of clotting factors, and reduces clearance of activated clotting factors and fibrin degradation products and availability of vitamin K.
- DIC may occur due to systemic dissemination of the bi-products of hepatic inflammation.
- Increased plasmin generation in liver disease promotes kinin activation, which causes hypotension, shock and end organ damage.
- Reduced synthesis of ATIII and reduced clearance of activated clotting factors provides a stimulus for thrombus formation. Renal or pulmonary thromboses are potential complications.

Disorders of Coagulation – Part 4

Hypercoagulation

Definition

Hypercoagulation is an imbalance in hemostasis, with an increased propensity for thrombus formation. Thrombosis depends of three major risk factors –

1. Changes in the vessel wall (vascular injury)
2. Impairment of blood flow (blood flow stasis)
3. Alterations in blood constituents (hypercoagulability)

This concept is known as Virchow's triad, and is fundamental to the understanding of thromboembolism, hypercoagulation, and its prevention.
• **Vascular injury** - leads to exposure of sub-endothelial collagen, resulting in platelet adhesion, and activation of the contact phase of coagulation. Vascular injury may be caused by the following
  - Trauma (including surgery)
  - Catheterization
  - Inflammatory disease
  - Neoplastic invasion
  - Parasitic damage
  - Plaque deposition (amyloidosis, arteriosclerosis)

• **Vascular stasis** favors thrombosis by retarding local clearance of activated clotting factors, and by causing local tissue hypoxia and vascular injury (through ATP depletion and cellular dysfunction). Vascular stasis may result from the following
  - Hypovolemia
  - Shock
  - Cardiac insufficiency
  - Blood vessel compression (e.g. GDV, neoplasia, organomegaly, etc.)
  - Immobility
  - Hyperviscosity (dehydration, polycythemia, leukemia, hyperglobulinemia, hyperfibrinogenemia)

• **Hypercoagulability** - results from an imbalance between the procoagulants (platelets, coagulation proteins), and the anticoagulants (natural anticoagulants, fibrinolytic system). Hypercoagulability may therefore result from platelet hyper-aggregability, excessive activation or decreased removal of coagulation factors, deficiencies of natural anticoagulants, or defective fibrinolysis.
  - Platelet aggregation - platelet adhesion to damaged vascular endothelium is facilitated by von Willebrand’s Factor (vWF), and glycoproteins (platelet activating factor etc). Following adhesion, platelets produce and release pro-aggregating substances, including thromboxane A₂, ADP, and prostaglandins G₂, and H₂. These induce shape changes in platelets, and the expression of glycoproteins IIb and IIIa receptors on the platelet surface, which allow binding of fibrinogen to platelets. The endothelium releases inhibitors of platelet aggregation including prostacycline (PGI₂), ADPase, nitric oxide (NO) to balance the clotting system.

Increased activation of coagulation factors (by vascular injury or inflammatory mediators) and decreased removal of factors from an area of injury (due to stasis or decreased activity of the reticuloendothelial system) may contribute to thrombosis.
Hypercoagulable States and DIC

Primary hypercoagulable states are inherited disorders that have not been reported in dogs or cats to date. Secondary hypercoagulable states include the following:

- **Nephrotic Syndrome** - Nephrotic syndrome typically leads to a loss of small molecular weight proteins such as albumin, antithrombin III, and macroglobulins into the urine, and retention of larger molecular weight proteins such as procoagulant proteins, and macroglobulins. Glomerular loss of antithrombin III, combined with retention of procoagulant proteins such as factor VIII, fibrinogen, and fibrinectin, leads to a hyper-coagulable state. In addition, loss of albumin results in platelet hyperaggregability. Hypercholesterolemia present in nephrotic syndrome increases blood viscosity and platelet hypersensitivity. The net result is a hyper-coagulable state within the intravascular space. Decreased antithrombin III levels also results in increased hepatic production of alpha-2 macroglobulins, which inhibit hemostasis.

- **Neoplasia** - vascular stasis due to tumor compression and vascular injury, platelet activation by tumor cells, release of tissue thromboplastin by tumor cells and by mononuclear cells stimulated by tumor antigen, elevated fibrinogen, and hypo-fibrinolysis all may induce a hypercoagulable state.

- **Acute pancreatic necrosis** - may cause hypercoagulation through several mechanisms, including increased serum levels of acute phase proteins (esp. fibrinogen), the presence of pancreatic vasculitis, vascular stasis, hypercholesterolemia, and hypo-fibrinolysis.

- **Immune-mediated hemolytic anemia** - The incidence of pulmonary thromboembolism in dogs with IMHA is 11-33%. Mechanisms inducing hypercoagulability in these patients include endothelial-mediated and monocyte-amplified reactions triggered by anti-erythrocyte antibodies, acute phase reactants, vasculitis, indwelling intravenous catheters, and corticosteroid therapy.

- **Hypercortisolemia** - the pathogenesis of hypercoagulation in Hypercortisolemia includes hypofibrinolysis secondary to increased activity of plasminogen activator inhibitor and alpha-2 antiplasmin; and increased levels of coagulation factors (esp. factor VIII)

- **Arteriosclerosis** - rare in dogs; may be found in hypothyroidism

- **Diabetes mellitus** - hypercoagulability in these patients occurs secondary to increased platelet aggregability, due to decreased release of prostacycline, reduced platelet sensitivity to prostacycline, and increased production of thromboxanes.

- **Sepsis and Multiple Organ Dysfunction Syndrome** - activation of coagulation is a normal component of the acute inflammatory response. Inflammatory cytokines alter the endothelium, cause release of tissue factor, and stimulate production of platelet activating factor. The fibrinolytic pathway is also initially activated, but is subsequently inhibited, primarily due to increases the plasminogen activator inhibitor – an
acutephaseprotein. When these processes involve systemic or widespread tissue injury, a hypercoagulable state results.

**Diagnosis of Hypercoagulation**

Diagnosis of hypercoagulation is made based on the following:

- **The clinical setting** – see causes of hypercoagulable states as listed above
- **Routine screening tests** – note that shortened coagulation times does not imply a thrombotic state, as normal individuals may also have shortened coagulation times
- **Fibrin degradation products** – are generated by the dissolution of fibrin by plasmin. Increased levels may be seen with increased thrombus formation, alterations in fibrinolytic activity, and alterations in hepatic clearance
- **Antithrombin III levels** – may indicate thrombotic tendency when levels are decreased. However, few thrombotic states result from primary antithrombin deficiency
- **D-dimer** – is a fibrin degradation product formed when cross-linked fibrin is proteolyzed by plasmin. Since cross-linkage of fibrin implies the production of fibrin, elevations in D-dimer imply the presence of fibrin and circulating plasmin. Sensitivity of the test is 75-93%; specificity of the test is 70-77%

**Clinical Manifestations of Hypercoagulation**

The clinical manifestation of imbalance between pro-thrombotic and anti-thrombotic forces that occurs in patients with predisposing causes of hypercoagulation outlined above is pathologic thrombosis. Pathologic thrombosis can manifest on a macroscopic or microscopic basis.

The clinical manifestation of hypercoagulation may be either overt bleeding, as in disseminated intravascular coagulation, or no bleeding, as occurs with pulmonary thromboembolism. Therefore, even though the manifestations of hypercoagulation are the opposite, the underlying cause is the same – excessive activation of the clotting cascade.

In hypercoagulable states, the production of thrombin may be as much as 100 times greater than the non-injury rate. Production of thrombin is greatest following severe trauma. In addition to the increased circulating thrombin, concentrations of antithrombin III and protein C are significantly reduced. The result is a strongly pro-thrombotic environment in the systemic circulation, resulting in disseminated intravascular coagulation. Once this occurs, the fibrinolytic system is activated to prevent the microcirculation from becoming clogged with microthrombi. As the fibrinolytic system lysed the pathologic thrombi, it also lysed non-pathologic thrombi at sites of vascular injury, causing further activation of the clotting cascade due to exposure of sub-endothelial
Disorders of Coagulation - Secondary and Tertiary Clotting Disorders

collagen and tissue thromboplastin. This causes further clot deposition, and finally, depletion of the pro-
coagulant factors, and the bleeding associated with disseminated intravascular coagulation.

Not all patients with significant tissue injury develop disseminated intravascular coagulation (DIC). The
likelihood of a patient developing DIC is determined by both the volume of tissue thromboplastin released into
the circulatory system, and the patient vascular volume status (i.e. blood flow through capillary beds, and
hence oxygen delivery to tissues).

Hypercoagulable States - The Clinical Approach

Primary Inducers of Hypercoagulation

<table>
<thead>
<tr>
<th>Intravascular Hemolysis</th>
<th>Viremia</th>
<th>Neoplasia</th>
</tr>
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<tbody>
<tr>
<td>Hemolytic transfusion reaction</td>
<td>Infectious canine hepatitis</td>
<td>Massive Tissue Injury</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>CDV</td>
<td>Burns</td>
</tr>
<tr>
<td>Septicemia</td>
<td>Canine herpes virus</td>
<td>Trauma</td>
</tr>
<tr>
<td>Gram-Negative bacteria (endotoxin)</td>
<td>FIP</td>
<td>Surgical procedures</td>
</tr>
<tr>
<td><em>E.coli</em></td>
<td>Feline panleukopenia</td>
<td>Heat stroke</td>
</tr>
<tr>
<td><em>P.Hemolytica &amp; P.multocida</em></td>
<td>Parasitic Infections</td>
<td>Venoms and Toxins</td>
</tr>
<tr>
<td><em>Salmonella spp.</em></td>
<td>Protozoal infection</td>
<td>Snake bite</td>
</tr>
<tr>
<td>Gram-positive bacteria (bacterial coat mucopolysaccharide)</td>
<td>Metazoan infection</td>
<td>Insect stings</td>
</tr>
<tr>
<td><em>Staph spp.</em></td>
<td>Obstetric Complications</td>
<td>Aflatoxin</td>
</tr>
<tr>
<td><em>Strep spp.</em></td>
<td>Miscellaneous</td>
<td>Hepatic Disease</td>
</tr>
<tr>
<td><em>Clostridium spp.</em></td>
<td>Gastric dilatation-volvulus</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td><em>Mycobacterium spp.</em></td>
<td>Diabetes mellitus</td>
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</table>

From the above table, a good rule of thumb is “Expect DIC in patients who have significant hypotensive crisis,
impaired blood flow to a major organ, or release of vasoactive substances into the vasculature”. It might seem
that this approach may lead to a daily expectation of DIC. However, failure to expect hypercoagulation and DIC
will result in increasing patient morbidity and mortality. Hypercoagulation and DIC are much easier to prevent
than they are to treat!
Clinical Signs of Hypercoagulation

The clinical signs of hypercoagulation are usually referable to the underlying disease, the presence of pathological vascular thrombosis, or bleeding. Symptoms may have the following characteristics:

- May be peracute, acute, or chronic depending on whether the underlying illness is acute or chronic.
- Laboratory changes, with no clinical signs may be present with a peracute hypercoagulopathy.
- Acute DIC will be evidenced by oozing from venipuncture sites, mucous membrane hemorrhage, petechiae, ecchymosis, purpura, hematoma formation, and hemarthrosis.
- Physical findings in acute and peracute disease are associated with decreased organ perfusion, and the presence of underlying disease.
- Organ Dysfunction and MODS is a consequence of acute DIC. Any organ can be affected by a coagulation disorder. Hepatic necrosis is common, renal thrombosis or micro-thrombosis may result in renal dysfunction (renal failure). Gastric ulceration and submucosal necrosis result from gastrointestinal thrombi, the clinical signs of which include hematemesis, malena, hematochezia, and occult fecal blood. Impaired pulmonary function may occur due to microvascular thrombosis, the clinical signs of which include tachypnea, hypoxia, and the development of acute respiratory distress syndrome (ARDS). Cerebral microvascular thrombosis may result in altered mentation or consciousness, convulsion or coma.
- Chronic DIC develops with an illness producing low grade or intermittent procoagulant release stimulus. This enables clotting factors, anticoagulant proteins, and platelets to be replenished. Chronic DIC is most commonly associated with neoplasia of the vascular system or soft tissues e.g. hemangiosarcoma, pheochromocytoma, mast cell neoplasia, lymphoma etc.

Diagnosis of Hypercoagulopathy and DIC

The diagnosis of hypercoagulation and DIC is based on clinical suspicion, knowledge of associated diseases and serial laboratory coagulation tests. Early recognition is essential as treatment is more effective when administered early in the disease process. Note – hypercoagulation and DIC occurs in animals with dynamic disease processes - changes in these patients occur rapidly. Repeated patient evaluation is recommended on a regular basis - i.e. every 3-4 hours.

Shistocytes
- Result from mechanical damage to red cell membrane from microvascular fibrin strands. Shistocytes are more commonly found in patients with chronic or compensated DIC.
Thrombocytopenia-Thrombocytopathia
- Platelet counts are variable in DIC. Repeat blood smears essential. Platelet counts in the low-normal interval in patients with severe systemic inflammation are suspected to have DIC, or are expected to develop DIC, particularly if mega-platelets are seen.
- Buccal mucosal bleeding time is usually ineffective in determining thrombocytopathia, due to the variability of platelet counts in patients with hypercoagulation and underlying diseases

Fibrinogen
- DIC results in consumption of fibrinogen when the coagulation cascade is activated and fibrinogen is biotransformed to fibrin.
- Fibrinogen is an acute phase inflammatory protein and will be increased with acute focal or systemic inflammation.
- A low-normal concentration of fibrinogen in patients with systemic inflammation is supportive of DIC.
- A decrease in fibrinogen often precedes a thrombocytopenia
- In the dog, fibrinogen levels below 75 mg/dl will result in prolongation of the APTT and PT.

Prothrombin Time, APTT and ACT
- The Activated Clotting Time is the most useful test for detecting fulminant DIC in clinical practice. The APTT and PT can be used to detect low grade, chronic, or compensated DIC, as they are more sensitive tests than the activated clotting time.

Fibrin Degradation Products (FDP’s)
- Result from plasmin degradation of fibrin and fibrinogen. FDP’s are composed of fibrin fragments X, Y, D, and E. The commercial tests detect E and D.
- Increased levels of FDP’s are associated with an increased bleeding tendency, as they act as anticoagulants preventing biotransformation of fibrinogen to fibrin.
- The presence of FDP’s is not pathognomonic for DIC, as they are also present in diseases such as hepatic failure, major focal vascular thrombosis, dysfibrinogenemia, and excessive fibrinolysis.

**D-Dimer** tests detect the D-dimer of fibrin degradation. The presence of D-Dimer in blood implies fibrinolytic activity secondary to coagulation. D-dimer tests are commercially available as a snap test.

Antithrombin III (AT III)
- ATIII is a alpha-2-macroglobulin acute phase protein manufactured in the liver, that inhibits serine (amino acid) proteases in the coagulation pathways (Factors XII, XI, X, IX, II)
Patients in a hypercoagulable state, that are actively converting prothrombin to thrombin, will have a low AT III concentration. Affinity of AT III for the serine proteases is increased up to 100-fold by heparin. AT III, concentration can be used as a guide for fresh frozen plasma replacement therapy, and heparin therapy for DIC.

- A low AT III concentration is a predictor of DIC.
- An elevated serum concentration of AT III may be found in any inflammatory process.

**Therapy for DIC**

DIC and hypercoagulation represent the result of a complex interaction between many factors. As such, the treatment of hypercoagulation and DIC represents a multi-faceted approach aimed at ensuring adequate oxygen tension in capillary beds, management of the underlying cause, replacement of pro-coagulants and anti-coagulants, and support of the target organs of thrombosis, particularly the liver, gastrointestinal tract, cardiac muscle, pulmonary parenchyma, kidneys, and central nervous tissue. These treatment goals are discussed briefly below

1. Provide adequate blood flow and oxygen delivery to capillary beds - this is usually achieved with appropriate fluid therapy. The fluid therapy of choice varies depending on the clinical setting in which hypercoagulation has occurred.
   - If the patient is in shock; immediate blood volume resuscitation with a combination of lactated Ringer’s solution and a synthetic colloid such as dextran 70; or a combination of hypertonic saline and dextran 70 is preferred, as these fluids will minimize the volume of fluid required for intravascular volume expansion, and will minimize the extravasation of fluid from the intravascular to the extravascular space.
   - If the patient has an active bleeding tendency, as determined by clotting tests, fresh frozen plasma (or whole blood if appropriate) is given at a rate of 10-20 ml/kg/12hrs, following intravascular volume resuscitation, in order to prevent further bleeding into capillary beds.
   - Maintenance of blood flow in capillary beds is achieved with a combination of crystalloids, synthetic colloids, fresh frozen plasma and whole blood. It is essential to monitor parameters such as the PCV, total protein level, albumin, ACT, and electrolytes to ensure the correct fluid is used in each patient.

Despite seemingly adequate fluid resuscitation, some patients appear to remain in a hypotensive state, or appear to respond poorly to fluid therapy i.e. they still show signs of poor tissue perfusion, such as poor pulse quality, and poor organ function - low urine output, vomiting, nausea, mental depression etc. These patients usually have sustained hypotension due to loss of arteriolar vascular tone - a common finding in patients with DIC and conditions of tissue hypoxia. These patients should have their blood pressure monitored, and a urinary catheter inserted, to determine if they are hypotensive or not. If hypotension is persistent despite adequate fluid resuscitation, low doses of dobutamine can be administered at a rate of...
2-5 ug/kg/min in an effort to increase cardiac output, tissue oxygen delivery, and subsequently improve vascular tone. Patients that are hypertensive, but with clinical signs of poor renal perfusion (low urine output) should be treated with furosemide, followed by mannitol, once urination has commenced.

2. Management of the underlying cause is essential to correcting the hypercoagulable state. For example, in sepsis, antibiotic therapy, fluid therapy, colloid therapy, and plasma/blood transfusions are the cornerstones of therapy. Removal of neoplastic lesions or chemotherapy is essential in patients with neoplasia, and immune-suppressive therapy in patients with hemolytic anemia.

3. Replacement of procoagulants and anti-coagulants is achieved with fresh frozen plasma. Prior to fresh frozen plasma administration, incubating the bag of plasma with unfractionated heparin at 100 U/kg for 30 minutes will allow activation of antithrombin III. Without heparin activation of the anti-coagulant antithrombin III, the provision of pro-coagulant clotting factors in the plasma transfusion could potentiate additional intravascular thrombosis. Heparin should be continued for at least 36 hrs at a dose of 80 units/kg sc q 8 hrs.

4. Support of the end organs – the targets of thrombosis – is best achieved by adequate tissue oxygen delivery to tissues. Oxygen therapy, fluid resuscitation, provision of positive inotropic support when indicated, provision of clotting factors, and patient monitoring. In addition, specific therapy for organs such as the gut (ranitidine, metoclopramide, micro-enteral nutrition), kidneys (ensure adequate urine output and systolic blood pressure), lungs (oxygen supplementation, ventilatory support) and cardiovascular system (fluid therapy, positive inotropism, anti-arrhythmic therapy) is used.
Disorders of Coagulation - Part 5
Treatment of Coagulation Disorders

Treatment and potential therapies for patients with bleeding disorders are summarized in the table below.

**Potential Therapies for the Patient with Hypocoagulation**

<table>
<thead>
<tr>
<th><strong>Primary Hemostasis</strong></th>
<th><strong>Secondary Hemostasis</strong></th>
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<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td><strong>Anticoagulant rodenticide toxicity</strong></td>
</tr>
<tr>
<td>• Immune-mediated</td>
<td>• Vitamin K 2.5-5 mg/kg/day</td>
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<tr>
<td></td>
<td>• Plasma – fresh frozen 10-20 ml/kg</td>
</tr>
<tr>
<td>• Infectious</td>
<td><strong>Disseminated intravascular coagulopathy</strong></td>
</tr>
<tr>
<td></td>
<td>• Treat underlying cause</td>
</tr>
<tr>
<td></td>
<td>• Heparin – see later</td>
</tr>
<tr>
<td></td>
<td>• Plasma – fresh frozen 10-15 ml/kg q 12 hrs</td>
</tr>
<tr>
<td><strong>Thrombocytopathia</strong></td>
<td><strong>Liver disease</strong></td>
</tr>
<tr>
<td></td>
<td>• Intravascular fluid support</td>
</tr>
<tr>
<td></td>
<td>• Vitamin K 1-5 mg/kg q 24 hrs</td>
</tr>
<tr>
<td></td>
<td>• Plasma – fresh frozen 10-15 ml/kg</td>
</tr>
<tr>
<td><strong>Secondary Hemostasis</strong></td>
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<tr>
<td><strong>Anticoagulant rodenticide toxicity</strong></td>
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<tr>
<td><strong>Disseminated intravascular coagulopathy</strong></td>
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<td><strong>Liver disease</strong></td>
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