Severe, acute hemorrhage can be a life-threatening situation that requires immediate. The practitioner must first identify the source of bleeding, arrest further blood loss if possible, and ensure adequate tissue perfusion. While the causes of acute bleeding are numerous, treatment can be focused with this step-wise plan for resuscitation.

**Pathophysiology of hemorrhagic shock**

Hemorrhagic shock is technically a subset of hypovolemic shock, defined separately from hypovolemia by a loss of oxygen carrying capacity as a result of a loss of red blood cells. As blood volume decreases due to the loss of both plasma and cells, cardiac output and total oxygen delivery to the tissues decreases. In response, cardiac output is increased by autonomic responses that result in tachycardia, vasocostriction, improved cardiac contractility, and redistribution of blood flow to the vital organs. In time, the oxyhemoglobin dissociation curve is shifted to the right, and tissue oxygen extraction increases from the red blood cells that remain. Severe or sustained blood losses eventually overwhelm these compensatory mechanisms and the body can no longer meet the needs of systemic oxygen demand. This stage of hemorrhagic shock is called the critical total oxygen delivery point, and is consistent whether it is caused by anemia, hypoxemia or hypovolemia.1

Clinical signs of dysoxia are related to the organ systems affected and the stage of hemorrhagic shock.2 The respiratory, hepatic and gastrointestinal systems are the first organs affected, due to redistribution of the circulating blood to the heart, brain and kidneys. For the respiratory system, clinical manifestations of lung injury can include tachypnea and signs of pulmonary edema (dyspnea, frothy mucus from the lower airways), due to intrapulmonary shunting and reduced compliance. Hepatic injury may be identified by elevations of both bilirubin and alkaline phosphatase on serum chemistries. In the gastrointestinal tract, ischemia is characterized by signs of abdominal pain. Compromise of blood flow resulting in mucosal ischemia may allow for ulceration, bacterial translocation to the venous circulation and, ultimately, sepsis.

As the compensatory mechanisms for hemorrhagic shock begin to fail subsequent to continued blood loss, the function of the brain, heart and kidneys begins to deteriorate. Clinical signs of hypoxia affecting the central nervous system are seen initially as agitation, followed by a lack of response to simple commands, depression, coma and death. While the cardiovascular system may attempt compensation early in the course of hemorrhage by tachycardia and increasing stroke volume, continued hemorrhage results in hypoperfusion of the myocardium, causing cardiac ischemia and eventually cardiac failure. Cardiac murmurs and arrhythmias may be noted in the late stages of hypovolemic shock. Activation of the renin-angiotensin-aldosterone system by the kidneys provides some support to the cardiovascular system early on. Urine specific gravity is initially increased, but as renal perfusion decreases, oliguria is noted as compensation fails. The goals for treatment of acute hemorrhage are limit further organ damage and prevent multi-organ failure. The method of treatment is to restore an adequate circulating volume and oxygen carrying capacity with fluids, plus or minus cells.

**Treatment of hemorrhagic shock**

The first step in treatment of acute blood loss is to classify the type of hemorrhage involved. Hemorrhage is defined as controlled if it is caused by blood loss from a vessel or organ that can be stopped using physical means. In situations of controlled hemorrhage, the solution is fairly straightforward in the form of applied pressure, bandages, or ligation of the bleeding vessel. In contrast, the source of bleeding in uncontrolled hemorrhage is either difficult to access, or so extensive that continued blood loss is expected. If bleeding is internal, inaccessible, or the source cannot be identified, mitigation is the key.

Medications that have been evaluated in horses to inhibit uncontrolled hemorrhage are aminocaproic acid, formalin, and yunnan baiyao. Aminocaproic acid, a lysine derivative, may reduce clot disruption through inhibition of fibrinolysis. In horses, administration can result in a reduction in partial thromboplastin time (PTT), which is the measure of the efficacy of the intrinsic and common coagulation pathways.3 Due to its short half-life, this medication is currently recommended as a constant rate infusion, and has been shown to provide adequate circulating plasma levels using 3.5 mg/kg/min for 15 minutes, followed by 0.25 mg/kg/min.4 This dose was based on efficacy of this medication in humans, and recent research in horses has identified that this dose may be twenty times too high, based on the sensitivity of the equine clotting system to this medication.5 Further evaluation of the efficacy of this dose in a live animal model will be required, but its use should be cautioned if an underlying coagulopathy is suspected. In a field situation, a bolus dose of 30 mg/kg of aminocaproic acid may provide some benefit if a CRI is not possible. An alternative anti-fibrinolytic medication,
called tranexamic acid, may be substituted for aminocaproic acid, and has been recommended by one manufacturer at an anecdotal dose of 5-25 mg/kg IV.6

Intravenous formalin has also been assessed in the horse to mitigate hemorrhage, due to its ability to activate platelets and enhance primary hemostasis when tested in other species.7 A low dose (0.37% formaldehyde; 37 ml of 10% buffered formalin in 1000 ml balanced electrolyte solution) had no negative effects on bleeding times, PTT, activated partial thromboplastin time (APTT), fibrin degradation products, or activated clotting times in the horse. However, higher doses of formalin (0.74% formaldehyde) resulted in numerous side effects including muscle fasciculations, agitation, tachycardia, and tachypnea.

Finally, the Chinese hemostatic medication Yunnan baiyao (or paizao), purported to contain a mixture of progesterones, saponins, and alkaloids, has been anecdotesly documented to mitigate hemorrhage. The mechanism of action is unknown, but a study in ponies showed a prolongation of template bleeding time, which may indicate stimulation of platelet activation.8 The dosage for Yunnan baiyao is 8 mg/kg 2-4 times daily, per os.9 In all of these studies, the effects of these medications on hemorrhage were not directly assessed, only their effects on measures of clotting times and activation of the clotting cascade in the normal horse. At this time, aminocaproic acid would be the recommended medication for uncontrolled hemorrhage in the horse based on its safety documented in these experimental models.

Once hemorrhage has stopped, or attempts at reducing further blood loss have been made, fluid resuscitation should be instituted to improve tissue perfusion. There are important considerations for fluid therapy based on whether the bleed is classified as controlled or uncontrolled hemorrhage.10 For horses where blood loss has been controlled, the goal of resuscitation is to restore the circulating blood volume to a level that normalizes arterial blood pressure and cardiac output. Objective measures of adequate fluid resuscitation in controlled hemorrhage include normalization of blood pH (7.35-7.4), blood lactate (<2.0 mmol/L), central venous pressure (7.5-12 mmHg), and urine output. To monitor resuscitation clinically, the practitioner should observe the horse for urine production and an improvement in peripheral pulses, temperature of the extremities, and mentation.

Fluid choices include crystalloids (Normasol R, Plasmalyte 148, Plasmalyte A, lactated Ringer’s), colloids (Hetastarch) and 7.5% hypertonic saline. Crystalloids are preferred over colloids and hypertonic saline due to the fact that crystalloids can restore interstitial losses. Approximately 60-75% of the administered volume redistributes to the interstitium within 60 minutes of infusion, leaving approximately 30% in the vasculature. While a potential advantage, it is important to remember that approximately 3 liters of crystalloids will be required to replace each liter of lost blood. Colloids provide an advantage over crystalloids in that they can remain in the vascular space for up to 3 days, and can more rapidly improve cardiac output. Side effects of colloids include the possibility of coagulopathies at high doses (for Hetastarch, >10 ml/kg/day) due to dilution of clotting factors, and the inhibition of clotting factor 8 and von Willibrand’s factor. In addition, colloids must be followed immediately by crystalloids administration to replace interstitial losses. Alternatively, hypertonic saline can be used in controlled hemorrhage to rapidly expand the extracellular fluid volume. While hypertonic has anti-inflammatory, anti-oxidant and anti-apoptotic effects, its effects on arterial pressures are short lived (<45 minutes). Hypertonic saline must be followed by crystalloid replacement to maintain the circulating volume. The dose for hypertonic saline is 2-4 ml/kg (approximately 1-2 liters per 1000 lbs. or 500 kg.). After restoring the intravascular fluid volume with fluid administration, blood products can be administered, if needed, to ensure a circulating hematocrit >12% and a platelet count of greater than 50,000/uL. Clinically, if the horse is still showing signs of tissue hypoxia (lactic acidosis, signs of colic), a transfusion may be required. It is important to remember that cardiac output cannot be significantly increased with blood products alone, due to their viscosity. Therefore crystalloids are still required for the initial volume resuscitation, and may prolong or prevent the need for a transfusion.

In uncontrolled hemorrhage where blood loss cannot be controlled, fluid therapy should be provided to maintain only the minimum circulating volume that will support the vital organs. This treatment, termed permissive hypotensive resuscitation, supports an adequate circulating volume to reduce further organ damage by hypoxemia, but prevents disruption of fragile clots or excessive dilution of clotting factors that could increase blood loss.11 Initial therapy in uncontrolled hemorrhage should be provided by administration of crystalloids at a maintenance fluid rate (2.5 ml/kg/hour). Rapid plasma expanders, such as hypertonic saline and colloids, should be avoided. The goals of hypotensive resuscitation are to maintain a mean arterial blood pressure of 60-70 mmHg, with improvement in the other outcome measures, including a lactate <4 mmol/L, blood pH >7.25 and serum creatinine <3 mmol/L. Clinical parameters can be used to guide resuscitation, including improvement in mentation and peripheral pulses. In these horses, blood products should be administered as soon as practical to improve oxygen carrying capacity if hemorrhage cannot be contained.

**Considerations for transfusion**

Transfusions should be considered in horses that have been estimated to have lost >30% of their circulating blood volume. Estimating blood losses is often a difficult task. Urinary fluid losses, splenic contraction, water intake and fluid resuscitation all can alter packed cell volume by diluting or concentrating the remaining blood cells. Hematocrit, in the absence of iatrogenic fluid...
resuscitation, will not reflect the volume of blood lost until 8-12 hours after hemorrhage has stopped, when fluid from the interstitium and water intake have equilibrated with the circulating blood volume.\textsuperscript{6} Once equilibration has occurred, blood loss can be estimated by the following formula:

\[
\text{liters blood lost} = \frac{\text{(normal PCV-patient PCV)}}{\text{(normal PCV)}} \times 0.08 \times \text{patient’s weight in kg.}
\]

Because of the time it takes for equilibration, clinical findings are often more accurate than calculations early on for estimating blood loss, and can be based subjectively on pulse, respiratory rate, urine output and mental status. The overall clinical picture to estimate blood lost by classifying hemorrhage into one of four groups, to estimate blood lost. (Table 1) More sensitive measures of acute blood loss may be serum lactate and central venous pressure (CVP), which is a measure of the systemic blood volume.\textsuperscript{12}

<table>
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<th>Table 1: Classification of acute hemorrhage (adapted from Gutierrez, 2004)</th>
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<td>Estimated Blood Loss</td>
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<td>&lt;15%</td>
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<td>Classification of Hemorrhage</td>
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<td>Pulse rate (beats/min)</td>
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<td>Respiratory rate (breaths/min)</td>
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To further guide the decisions for therapy, objective guidelines have been suggested for transfusion in the horse, including measurement of hematocrit, lactate and the oxygen extraction ratio. While hematocrit is variable, for the reasons stated previously, a hematocrit of <12%, or hemoglobin between 6-8 g/dl, is usually below the critical oxygen delivery level, and warrants transfusion. Lactic acidosis may result from anaerobic metabolism secondary to perfusion deficits or inadequate hemoglobin after hemorrhage. Lactate measurements are easily obtained using a hand held meter, and are relatively accurate for clinical purposes. Blood lactate levels should improve rapidly with fluid resuscitation if hemoglobin concentrations are adequate. Lactate measurements that persist above 2 mmol/L after fluid resuscitation may indicate the need for transfusion. While often less practical, the oxygen extraction ratio (arterial oxygen saturation minus central venous oxygen saturation, divided by arterial oxygen saturation) can be obtained by blood gas analysis. This calculation determines the oxygen extraction by the tissues, and a ratio >50% indicates tissue hypoxia. Central venous samples are difficult to obtain, therefore jugular sampling for P\textsubscript{v}O\textsubscript{2} levels as an estimate of oxygen extraction may provide some insight into tissue perfusion. The cutoff value indicative of inadequate oxygenation in the normovolemic horse is <31 mmHg, but must be interpreted with caution.\textsuperscript{13} Finally, transfusions are warranted in any horse with uncontrolled hemorrhage with clinical signs of tissue hypoxia.

To select a blood donor, horses should be chosen to minimize the risk of transfusion reactions in the recipient. Geldings are preferred, and donors should be current on their vaccinations, and tested for bloodborne pathogens. Because the blood types Aa, Qa and Ca are the most common to cause transfusion reactions, donors should be blood typed and tested for anti-erythrocyte antibodies (UC Davis VMTH Clinical Diagnostic Laboratory). In an emergency, when testing is not possible, a breed least likely to have these blood types (Standardbred or Quarter horse) should be selected. Fortunately, naturally occurring erythrocyte antibodies are rare, and the immune system takes up to 2 weeks to form antibodies after a transfusion. Up to 18 ml/kg (20% of blood volume) may be harvested from an individual donor, without harm, every 30 days. If clinical signs of hypovolemia are noted in the donor during blood collection, a crystalloid bolus (20-30 ml/kg) may be administered to counter blood loss. Often, the donor may show signs of agitation, and sedation may be administered (ie. detomidine, 0.01 mg/kg, IV) without affecting the recipient.

The blood from the donor should be collected into plastic bags to preserve the platelets. Because equine blood is rarely stored, short term anti-coagulants such as acid citrate dextrose (ACD) are typically used, at a 1:9 dilution with blood (400 ml ACD in a 4 liter bag of whole blood). Heparin should not be used, because it may remain active in the recipient, and can cause platelet activation.\textsuperscript{14} The bag should be gently rocked during collection to mix the blood and anti-coagulant, and the bag can be weighed to determine the appropriate dilution has been met (1 ml blood = 1 mg).

Replacement of the total volume of blood lost is not usually required, due to the initial resuscitation by replacement fluids. The dilution caused by crystalloid administration supports cardiac output and improves microcirculation and tissue oxygenation by decreasing blood viscosity. A persistent anemia also allows the body to respond through an increase in erythropoietin production by the kidneys. The amount of blood required is estimated to be approximately 30% to 40% of blood lost. As an example, for a 1000 lb.
(450 kg.) horse, a transfusion would typically be needed when blood loss reaches >40%. If the total blood volume is normally 36 liters (8-10% of body weight), a transfusion would be required after a loss of 14 liters of blood, and ~6 liters of blood would provide adequate oxygen carrying capacity by replacing 40% of the blood lost.

When administering a blood transfusion, a blood administration set is required to filter out microclots that form in the collected blood, despite the anticoagulant. The initial infusion rate should be slow, approximately 0.1 ml/kg over 15 minutes, which equates to 50 ml of blood for a 1000 pound horse. During the initial infusion, the heart rate, respiratory rate, mentation, and rectal temperature should be noted every 2-5 minutes to monitor for transfusion reactions. Common reactions include urticaria, tachypnea, and agitation, and are seen in approximately 16% of cases. If a reaction is noted, the transfusion should be stopped, and the horse should be administered either a non-steroidal anti-inflammatory (ie. flunixin meglumine 1.1 mg/kg, IV), a steroid (ie. dexamethasone 0.08-0.17 mg/kg, IV) or an antihistamine (ie. hydroxyzine 0.5-0.1 mg/kg, PO). If anaphylaxis is noted, epinephrine (0.01-0.02 mg/kg, IV) and fluid bolus is immediately required to restore blood pressure. The transfusion may be restarted in horses with minor reactions after the reaction has resolved, but if it reoccurs, or anaphylaxis developed, a new donor will be required. If no adverse reaction is noted after the initial slow infusion, the blood may be bolused in controlled hemorrhage (up to 20 ml/kg/hr), or increased to up to 3.75 ml/kg/hr for horses with uncontrolled bleeding. If large volumes of blood are administered, or if you are unsure of your dilution of the anticoagulant, serum ionized calcium should be monitored, due to the risk of citrate toxicity. In addition, crystalloids containing calcium must be stopped during the transfusion. The transfused red blood cells can survive from 4 to 20 days.

**Post-transfusion considerations**

Broad spectrum antibiotics are indicated after severe hemorrhage, due to the risk of sepsis from the translocation of bacteria across the compromised gastrointestinal mucosa. Erosions of the gastrointestinal tract (the stomach specifically) due to hypoxia, can be addressed by the administration of gastroprotectants, including omeprazole.

Vital signs, mental status, and urine production should be reassessed throughout fluid resuscitation and after restoration of the circulating volume. Venous access would be indicated for horse with ongoing losses due to uncontrolled hemorrhage, or if the response to therapy was less than expected. Serum chemistries would ideally be performed daily to assess electrolytes, organ function and evidence of metabolic changes. Finally, tissue oxygenation can be estimated by the oxygen extraction ratio and serum lactate, to assess the response to therapy and if tissue hypoxia is persistent.

**References**