SO THERE'S NO CONFUSION,
It's about Perfusion!

In companion animal practice, fluid therapy is utilized on a daily basis. While fluid therapy is a mainstay in veterinary practice, survey results (Hopper, 2018) support fluid therapy is a complex subject and perplexes many veterinarians:

38% of small animal veterinarians have trouble calculating rate

33% have trouble choosing a fluid type

15% struggle to determine the need for potassium supplementation

Veterinarians often direct their team to administer “maintenance” fluids to hospitalized patients for supportive care, or in some cases 2 or 3 times “maintenance” vs. actually calculating out a patient’s true physiological needs. This could potentially lead to inadequate fluid replacement or even in some cases be harmful to the patient by causing over-hydration. In order to provide appropriate treatment of fluid and/or electrolyte abnormalities, veterinarians need a basic understanding of the physiology of fluid balance. Fluid therapy goals can then be addressed by answering ‘Why?,’ ‘What?,’ and ‘How Much?’ Additionally, veterinarians should have a basic knowledge of the endothelial glycocalyx (EG) and it’s important role in maintaining normal vascular function.

FLUID COMPARTMENTS/ DISTRIBUTION OF BODY FLUIDS

A healthy adult dog or cat’s body weight is made up of approximately 60% water. Neonates have a higher total body water content of ~ 80%, which slowly decreases during the first 6 months of life. Fat has a lower water content than lean tissue, and fluid needs should ideally be estimated on the basis of lean body mass to avoid over-hydration.

The following assumptions are made in order to calculate lean body mass: 1) in normal small animal patients, approximately 20% of body weight is due to fat [normal body weight X 0.8 = lean body mass], 2) morbid obesity increases body fat to approximately 30% of body weight [obese body weight X 0.7 = lean body mass] and, 3) in thin patients, body weight is a reasonable estimate of lean body mass [thin body weight X 1.0 = lean body mass]. (DiBartola, 2012) (Rieser, 2020)

Body water is divided between physically distinct compartments. Body fluids equilibrate with fluids in other compartments by multiple mechanisms to maintain homoeostasis. The largest volume of fluid in the body is found inside cells – **the intracellular fluid compartment (ICF)**. The ICF is roughly 2/3’s of the total body water and approximately 40% of body weight. Any fluid not contained inside a cell is considered to be in the **extracellular fluid compartment (ECF)**. The ECF is approximately 1/3 of the total body water, or 20% of body weight. An easy way to remember distribution of body fluids is to use the 60:40:20 rule: 60% of body weight is water, 40% of body weight is ICF, and 20% of body weight is ECF.

The extracellular fluid compartment (ECF) can be further divided into **interstitial fluid (ISF)**, **intra-vascular fluid**, and **transcellular fluid**. Interstitial fluid (ISF) makes up about ¾’s of ECF and is the fluid surrounding cells but outside the vascular space, and is estimated to be approximately 15% of body weight or 24% of total body water. Intra-vascular fluid, also known as plasma, is the fluid within the vascular space, and it is roughly ¼ of the ECF.

Plasma is approximately 5% of body weight and 8 – 10% of total body water. Transcellular fluid is the fluid produced by specialized cells

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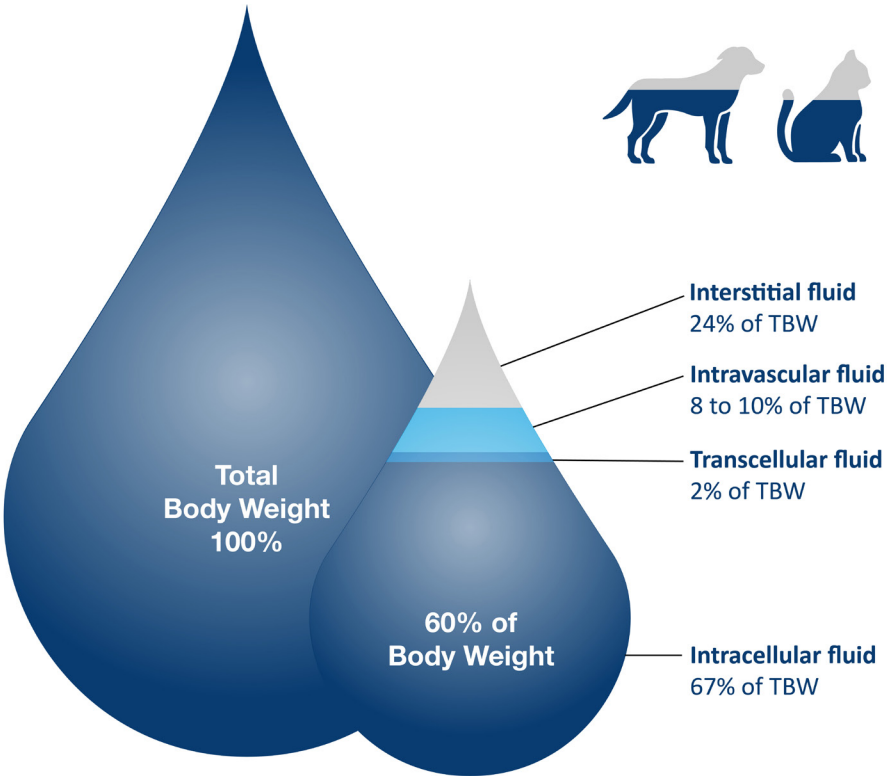
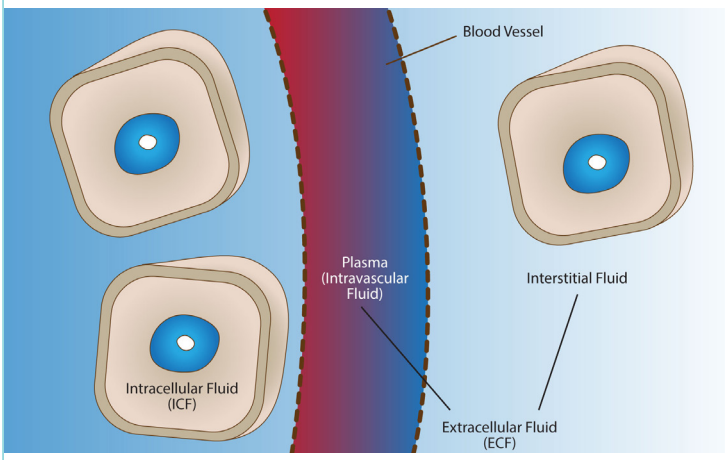
Fluid Compartments



to form cerebrospinal fluid, gastrointestinal fluid, bile, glandular secretions, respiratory secretion and synovial fluid. It is estimated to by 1% of body weight, and 2% of total body water.

While body fluids are traditionally conceptualized within these fluid compartments, it is important to understand water and solutes in these spaces are in a dynamic equilibrium across cell membranes, and across the vascular spaces and interstitial spaces. Under normal circumstances, this allows for exchange of oxygen and carbon dioxide, provision of nourishment, and removal of waste. Fluid movement is constant and remains in its specific compartment due to a combination of physics laws (Starling's Equation), **oncotic pressure** (the force exerted by large, impermanent molecules to hold water within either the capillary or interstitial space), and the endothelial glycocalyx. Additional details on the EG are provided at the end of this document.

In dehydration, fluid shifts that occur can have a marked effect on ECF, and in most disease states, loss of fluids are initially from the ECF fluid compartment. Therefore, it is important to estimate the volume of the ECF compartment and the volume of fluid lost to initiate appropriate fluid replacement and monitor fluid therapy. (DiBartola, 2012)



MEETING THE GOALS OF FLUID THERAPY – THE 'WHY?'

Fluids are an essential part of everyday practice in most veterinary care facilities. Fluids are utilized to help resuscitate patients in shock (intravascular volume depletion) thus improving tissue perfusion, correct fluid deficits/ dehydration (extravascular fluid depletion),

provide daily fluid and electrolyte maintenance in hospitalized patients, and can help maintain tissue perfusion to allow for normal organ and cellular function. Fluids are also often used intraoperatively to support the cardiovascular system and maintain perfusion while patients are under anesthesia, and can help in patients when diuresis is needed.

In order to develop an effective and safe fluid therapy plan, a thorough history and physical examination is performed to determine what testing should be done and asses for changes in fluid volume, change in fluid content and change in fluid distribution in the patient. Clinicians should then answer the following questions:

1) What type of fluid should I use?
2) Via what route should I infuse?
3) What volume should I infuse?

Dehydration and fluid losses in most disease states initially are from the ECF spaces. Measureable (sensible) fluid loss is generally in the form of urine from the urinary tract or vomiting and diarrhea from the gastrointestinal tract. Insensible (cannot be measured) is generally from the respiratory tract from panting and evaporation from the skin.

Dehydration occurs when fluid loss from the body exceeds fluid intake. A deficit of extravascular fluid compartment (interstitial and intracellular) causes dehydration. Dehydration of less than approximately 5% is difficult to detect clinically. A severe deficit may decrease the intravascular compartment and lead to poor perfusion.

Despite a lack of precise objective data, there are many ways to estimate hydration status via several physical examination findings and common laboratory changes. Sticky mucous membranes are usually detected with a 5 – 6% deficit. Dry mucous membranes and a decrease in skin elasticity are noted with a 6 – 8% deficit. By 8 – 10% dehydration, the eyes may be sunken; and over 12% dehydration, corneas are dry, mentation is dull, and perfusion is impaired. Fluid deficits typically lead to decreased urine production/output and elevations in urine specific gravity of greater than 1.030, if renal function is appropriate. A sick animal may lose up to 0.5 – 1% in body weight per day due to anorexia, but changes in excess of this amount are due to changes in fluid status; thus, acute changes in body weight can be helpful in determining hydration status. Many dehydrated patients also have a mild increase is serum sodium concentration and mild rise in serum potassium concentration, but these changes are not universal. Serial measurement of an increasing PCV and total protein may also support evaluation of hydration status; but could also be seen in hypovolemic patients, as could the changes in serum sodium and potassium. (DiBartola, 2012)

FLUID TYPES – THE 'WHAT?'

Fluids can be divided into two general categories: crystalloids and colloids. **Crystalloids** are water-based solutions containing electrolytes and nonelectrolyte solutes (e.g. buffers, +/- dextrose) capable of entering all body fluid compartments. Crystalloids' primary effects are on the interstitial and intracellular compartments. A fluid is considered to be **balanced** if its composition closely resembles that of ECF; examples include Lactated Ringer's solution (LRS) & pHyLyte. If the fluid does not resemble ECF, then it is said to be **unbalanced** (e.g. normal saline). Crystalloids can also be classified as replacement, maintenance, or hypertonic solutions. The composition of **replacement** solutions resembles that of ECF, while **maintenance** solutions contain less sodium and more potassium than replacement fluids. **Hypertonic** solutions contain more sodium than ECF, and most have very high sodium concentrations; therefore, it is important to measure serum sodium levels before and after their administration. In veterinary medicine, hypertonic solutions are most commonly utilized for rapid low volume resuscitation.

Colloids are large-molecular-weight substances that are restricted to the plasma compartment (intravascular space) in patients with an uncompromised intact endothelium. They can be natural substances such as plasma or synthetic such as dextran or hetastarch. Colloids exert their primary effect on the intravascular compartment, and have been used in patients with shock or in those with severe hypoalbuminemia. Synthetic colloids should be used with caution as they are commonly formulated in 0.9% NaCl and primarily result in acidification of plasma. Additionally, concerns regarding the development of coagulopathies, renal injury and pulmonary edema have been associated with use of synthetic colloids. (DiBartola, 2012)

Tonicity refers to the ability of a solution to initiate water movement; it may be thought of as effective osmolality. In reference to fluids, an **isotonic** crystalloid solution approximates the osmolarity of blood and ECF. Because they are essentially equal, there is no movement of water into or out of the red blood cells (RBC). **Hypertonic** solutions have an osmalarity higher than blood and ECF; therefore, water may flow out of RBC's causing RBC shrinkage and may dehydrate intracellular and interstitial fluid spaces as fluid flows from those spaces into the intravascular space. **Hypotonic** solutions have osmolarity lower than blood and ECF, and therefore, fluid flows into RBC's (causing RBC swelling) and may cause edema as water flows from the intravascular space into the interstitial compartment.

Veterinary practitioners can manage most patients requiring fluid therapy with a limited number of crystalloid and additive solutions. (*Please note, when additives are used, clinicians must keep in mind that the final osmolality of the fluid may be higher than anticipated.*) The choice of fluid to administer is dependent on the volume lost, and of the nature of the disease process and the composition of fluid lost. In most disease states, fluid and solutes initially are lost from the ECF. Three basic types of fluid and solute loss may occur: solute in excess of water (loss of hypertonic fluids), isotonic loss (loss of isotonic fluids), or water in excess of solute (loss of hypotonic fluids). (DiBartola, 2012)

Additionally, underlying acid-base and/or electrolyte disturbances should be taken into consideration. Finally, because most of the fluids increase heart rate, diastolic arterial pressure, and central venous pressure, and all of them decrease hematocrit, hemoglobin, and total protein concentration, cardiovascular health and protein balance of the patient should be taken into consideration when developing a fluid therapy plan.

The most commonly utilized solutions in veterinary practice are isotonic, replacement crystalloids, since most disease states initially have fluids and solutes lost from the ECF compartment. This is isotonic fluid loss; therefore, it should be replaced with isotonic fluids. Examples of these fluid types include 0.9% NaCl, Normasol-R, Plasmalyte A, and pHyLyte.

Hypotonic, maintenance crystalloid examples include: 0.45% NaCl (with or without dextrose), 5% dextrose in water (D5W), and Normasol-M. Hypotonic, maintenance crystalloid fluids are utilized less frequently in general companion animal practices, but would be appropriate to consider once replacement fluid therapy goals have been achieved.

Replacement fluid therapy utilizes isotonic crystalloids. Replacement fluids have sodium concentrations similar to plasma, and usually contain one or more buffers to maintain physiologic pH. Common buffers utilized include lactate, which is metabolized by the liver, or a combination of acetate and gluconate. Acetate undergoes metabolism by muscle tissue and most body tissues metabolize gluconate. Acetate and gluconate buffering system is preferred over lactate in animals with severe hepatic dysfunction.

Lactate Ringer's Solution - LRS is widely used in companion animal practices, and it is a balanced electrolyte solution containing lactate that contributes to the correction of acidosis. The pH of LRS is 6.5, which is acidifying initially. Metabolism of lactate is either through gluconeogenesis or by oxidation, and hydrogen ions are consumed by either of these processes, which results in an alkalinizing effect. It can take approximately 30 minutes for this to occur. LRS contains 130 mEq/L of sodium and 109 mEq/L of chloride, but has no magnesium. It does, however, contain calcium, and because blood products generally are stored using a compound that chelates calcium, it should not be administered through the same intravenous line as blood products. Additionally, the calcium in LRS may bind to or cause precipitates to form in the IV line if some drugs are administered through the same line. LRS is often grouped as an isotonic fluid, but technically, it has a osmolality of 272 mOsm/L and with the sodium content of only 130 mEq/L it is actually a hypotonic solution. This hypotonicity could lead to movement of fluid into the intracellular compartment. This may be detrimental in patients with head trauma or cerebral edema. LRS can be a good choice to support perfusion parameters for most anesthetized patients, and does provide a source of free water if used as a maintenance fluid.

Normal Saline – 0.9% NaCl is an isotonic crystalloid solution that has limited use in companion animal practice. The pH of normal saline is 5.5 and the solution does not contain any buffers, therefore it has an acidifying effect on patients. It has a sodium concentration of 154 mEq/L, a chloride concentration of 154 mEq/L, and contains no other electrolytes. In patients with alkalosis (rare), e.g. persistently vomiting patients with an pyloric obstruction, it is the initial fluid of choice. Normal saline is often recommended as the initial fluid choice in salt toxicosis (depending on severity) to bring down serum sodium levels in a more gradual manner, thus preventing rapid shifts of water from the intracellular spaces within the brain. It may also be useful for treating hypercalcemia, and is the fluid of choice when administering blood products.

pHyLyte® - PlasmaLyte A – Normasol-R are all balanced isotonic crystalloids with perhaps the widest profile for replacement fluid therapy in many disease processes in companion animal practice. The pH of these solutions are physiologically normal at 7.4, and contain acetate and gluconate as buffers, which have the advantage over lactate in animals who have specific organ dysfunction such as kidney or liver disease. These fluids are useful for treating both alkalosis and acidosis; in fact, acetate has greater alkalinizing effect than lactate. The sodium concentration of 140 mEq/L closely resembles plasma, and the chloride concentration is 98 mEq/L. Magnesium is also present at 3 mEq/L. Until somewhat recently, magnesium was under appreciated as to its significance. Magnesium plays an important role in maintaining normal homeostasis of important body systems, such as the cardiovascular and neuromuscular systems, and plays a pivotal role in many cellular metabolic processes. For example, magnesium is vital in mitochondria during oxidative phosphorylation and during anaerobic metabolism of glucose, and is important in the synthesis and degradation of DNA and the production of intracellular second messengers such as cyclic AMP. (DiBartola, 2012) While these replacement fluids do not contain enough magnesium to treat hypomagnesemia, supplementation of magnesium is helpful in treating many disease conditions. Finally, because these fluids do not contain any calcium, they may be utilized when administering blood products.

Patient assessment will dictate patient fluid content needs. It is acceptable, and often desirable, to initiate fluid therapy with an isotonic, balanced crystalloid solution until diagnostic tests become available in order to tailor fluid therapy.

Composition of Common Veterinary Fluids (Replacement)

FLUID TYPE	COMPONENT (unit)							BUFFER(S)	PRIMARY USE
	pH	Sodium (mEq/L)	Chloride (mEq/L)	Postassium (mEq/L)	Magnesium (mEq/L)	Calcium (mEq/L)	Osmolarity (mOsm/L)		
Canine Plasma	5.5	145	110	5	3	5	300	HCO_3 (24mEq/L)	
0.9% Saline	7.4	154	154	0	0	0	308	None	Replacement
Plasmalyte A	7.4	140	98	5	3	0	294	Acetate (27 mEq/L) Gluconate (23 mEq/L)	Replacement
Normosol-R	7.4	140	98	5	3	0	294	Acetate (27 mEq/L) Gluconate (23 mEq/L)	Replacement
pHyLyte	7.4	140	98	5	3	0	294	Acetate (27 mEq/L) Gluconate (23 mEq/L)	Replacement
Lacted Ringer's Solution (LRS)	6.5	130	109	4	0	2.7	273	Lacetate (28 mEq/L)	Replacement
Lacted Ringer's Solution (LRS) and 5% Dextrose	5	130	109	5	0	2.7	525	Lacetate (28 mEq/L)	Replacement/ calories (180 kcal/L)

Hyperkalemia is suspected in cases of obvious urinary obstruction, uroabdomen, acute renal injury, diabetic ketoacidosis (DKA), or Addison's disease. Potassium (K) > 6 mmol/L is life-threatening and fluid therapy should begin immediately. There are several benefits associated with administering K-containing balanced electrolyte solutions pending laboratory results, including volume expansion resulting in hemodilution and lowering of serum K concentration and the relative alkalinizing effect of the balanced solution promotes the exchange of K with hydrogen ions as the pH increases toward normal. Additionally, the relief of any urinary obstruction results in kaliuresis that offsets the effects of the administered potassium, and K-containing balanced electrolyte solutions contain lower K concentrations than typically seen in patients with disease processes that result in hyperkalemia. (Davis, et al., 2013)

Patients with **hypokalemia** often need K supplementation of fluids. Charts are available in many texts. It is essential to mix added KCl thoroughly in the IV bag to avoid inadvertent overdoses. Do not exceed an IV administration rate of 0.5 mmol/kg/hr of K. If **hypophosphatemia** exists along with hypokalemia (e.g. DKA), use potassium phosphate instead of KCl. (Davis, et al., 2013)

Hypernatremia can be mild and clinically silent. Causes of hypernatremia include loss of free water (e.g. through water deprivation), and/or iatrogenically through > 24 hour use of replacement crystalloids. Salt toxicity, through oral ingestion of high salt content materials, is another cause of hypernatremia. Provide for ongoing losses and volume deficits with a replacement fluid having Na concentrations close to that of the patient's serum (e.g. 0.9% saline) – ideally within ~ 10 mEq. The cause and duration of clinical hypernatremia will dictate the rate at which Na levels can be reduced without causing cerebral edema -- *do not exceed changes in Na levels of 1 mmol/hr in acute cases or 0.5 mmol/hr in chronic cases*. Once the volume need have been met, replace the free water deficit with a hypotonic solution. Additionally, for anorexic patients, provide maintenance fluid needs with an isotonic balanced electrolyte solution. (Davis, et al., 2013)

Hyponatremia is most commonly seen in DKA and with water intoxication. It is also commonly found in Addisonian patients (along with hyperkalemia). Changes in serum Na levels must occur slowly, as with hypernatremia, and electrolyte levels need to monitored frequently. Use a fluid with Na content similar to the measured plasma Na (ideally within ~ 10 mEq) to keep the rate of change at an appropriate level. (Davis, et al., 2013)

DETERMINING FLUID VOLUME AND RATE – THE 'HOW' AND 'HOW MUCH?'

When developing a fluid therapy plan, there are three components needing consideration – resuscitation (to address hypovolemia), replacement fluids (to correct dehydration and address on-going loss), and daily fluid requirements. The assessment of the volume of fluid required to correct fluid deficits and on-going losses cannot be precisely determined. Thus, therapy is empirical and based on a thorough history, physical examination, and laboratory findings. Clinicians should first determine if the patient is in shock, as this is an emergency situation and requires bolus fluid therapy until corrected. Once evidence of shock has been resolved, additional questions help determine the volume of fluid that should be administered. These questions include: Is the patient dehydrated, and if so, how dehydrated? Can the patient rehydrate on their own? Will the patient continue to lose water? Are the cardiovascular, renal and hepatic systems functioning normally? A clinician's assessment may not be accurate, and therefore the volume of fluid given should be titrated to the patient's needs and the physiologic responses to the fluid administered; therefore, patients should be reassessed frequently and fluid volumes adjusted as necessary.

Physical examination parameters are utilized to assess for hypovolemia and dehydration. Hypovolemia results in inadequate perfusion. In early stage IV fluid deficits (hyperdynamic shock) patients have normal mentation, tachycardia, increased respiratory rate, normal to bounding pulses, and warm extremities. As this progresses to hypodynamic shock (late stage), patients are depressed to obtunded, normal to bradycardic, increased to decreased respiratory rate, weak to non-palpable pulses, and have cold extremities. Cats generally do not show hyperdynamic shock and are generally bradycardic, hypotensive, and hypothermic. (McMichael, 2008)

The presence of altered mental status and cool extremities in association with tachycardia or severe bradycardia are good indicators urgent fluid therapy for volume replacement is needed. Additionally, capillary refill time (CRT) is prolonged and mucous membranes are pale pink to white due to inadequate perfusion, but this can also be seen in patients with anxiety or pain due to effects of epinephrine on alpha-1 receptors. Blood pressure is low in hypovolemic patients, and peripheral pulses may be difficult to detect. Dehydrated patients have a loss of fluid from the interstitial compartment resulting in changes to skin turgor, tacky or dry mucous membranes, and some degree of enophthalmos. To replace or correct fluids lost from the interstitial space, fluids are administered through a constant rate infusion over 6 – 24 hours. Regardless of their underlying disease, severely dehydrated patients can be in shock and require resuscitation phase of fluid therapy. Once this is corrected, the rehydration phase can be initiated. Conversely, not all patients in shock are dehydrated and thus they may not need a rehydration phase.

Fluids can be administered to patients through several routes. Intravenous (IV) fluid administration is used frequently, usually through an intravenous catheter, and is the route of choice when blood volume expansion is desired. It is superior to subcutaneous administration for any critically ill patient with poor perfusion. Intravenous routes are also indicated for administration of total parenteral nutrition, blood products, and intravenous anesthetic agents and drugs. In hypovolemic patients, neonates or very small patients, the intravenous route may not be readily accessed; the intra-osseous (IO) route is an excellent alternative for these patients. It provides access to the vascular space via the capillary beds of the medullary vascular system. This route is best suited for rapid, short-term administration of therapy in emergency situations.

Subcutaneous fluid (SC) administration can be used for patients who do not require vascular access for other purposes. It should be reserved for relatively stable animals,

as peripheral vasoconstriction in illness may limit absorption of fluids from the subcutaneous space. Fluids given via this route need to be nearly isotonic (200 – 400 mOsm) and should not contain dextrose to prevent complications and discomfort. Pain, inflammation and infection can be complications resulting from subcutaneous fluid administration. Additionally, the volume that can be administered at any single site is a limiting factor for this route.

Two other routes of fluid administration include intra-peritoneal (IP) and enteral. Intra-peritoneal administration of fluid is potentially hazardous and offers little to no significant advantages over IV, IO or SC. Enteral administration of fluids is ideal if a patient is stable and has the ability to rehydrate or maintain hydration on their own.

As with fluid volume, fluid rate is also determined by the needs of the patient with regards to addressing hypovolemia, dehydration, on-going losses, and daily fluid requirements. Animals with inadequate perfusion require bolus therapy (dogs 20 – 30 mL/kg & cats 10 – 15 mL/kg) IV as a bolus over 15 – 20 minutes until perfusion parameters are stable. Once patients have normal perfusion, rehydration can be addressed by calculating the volume needed to correct the dehydration and administering the calculated volume over a 6 – 24 hour time frame. On-going losses via the gastrointestinal or urinary tract and daily fluid requirements must also be calculated into the fluid volume and rate to assure adequate hydration is maintained. To help make these calculations simple and convenient, Dechra Veterinary Products has developed the Vetivex® fluids calculator.

Resuscitation is needed for patients with inadequate tissue perfusion, and a crystalloid fluid is delivered as bolus therapy. A total volume of 90 mL/kg for dogs and 50 mL/kg for cats (generally considered to be equal to one blood volume) is calculated then a bolus of one quarter to one third of the calculated total volume is given over a period of 10 – 15 minutes. After a bolus is delivered, the patient's perfusion parameters are reassessed. Bolus therapy continues until acceptable end points of resuscitation (EOR) are achieved. Acceptable EOR's include a return of normal/alert mentation, normalization of CRT & mucous membrane color, as well as heart rate, temperature, and respiratory rates returning to normal. Blood pressure & lactate should stabilize and urine production should be evident. Colloids or hypertonic saline should be considered if there is no improvement in perfusion parameters after 50% of the shock dose volume has been delivered to help avoid volume overload, as only approximately 25% of delivered volume remains in the intra-vascular space by 30 – 60 minutes post-infusion.

Acceptable End Points of Resuscitation

Parameter	Value
Mentation	Alert
Mucous membranes	Pink
Capillary refill time	<2 sec
Temperature	100°F-102.5°F
Heart rate	Cats: 180-220 bpm Small-breed dogs: 100-160 bpm Large-breed dogs: 60-100 bpm
Respiratory rate	20-40 breaths/min
Systolic blood pressure	>100 mm Hg*
Mean blood pressure	>80-100 mm Hg*
Central venous pressure	5-10 cm H_2O
Lactate	<2.5 mmol/L
Urine output	At least 1-2 mL/kg/hr

*Active, noncompressible hemorrhage may be the exception, and achieving a mean arterial pressure (MAP) of 70 mm Hg or a systolic arterial pressure (SAP) of 90 mm Hg with improvement of clinical signs during limited fluid volume resuscitation (LFVR) is acceptable until hemorrhage is definitively controlled.

Once the patient has stabilized, **replacement** fluid therapy can be addressed. Isotonic crystalloid solutions are used to correct fluid deficits due to dehydration and deal with on-going losses. The percentage dehydration is estimated via physical examination parameters and laboratory data; then this figure is multiplied

by body weight in kg and multiplied by 1000 to obtain the volume of fluid in mLs to be delivered to the animal [% dehydration X BW(kg) X 1000 = mLs]. On-going losses are estimated by weighing diarrhea and vomitus and measuring urine output, as well as frequent weight monitoring. The total volume of the dehydration volume and on-going losses are added together and divided over a 6 – 24 hour time frame. Frequent monitoring of the patient during fluid therapy should continue to ensure adequate fluid replacement is achieved while avoiding fluid overloads, and the fluid therapy plan is adjusted after correcting dehydration and with any changes in on-going losses.

Additionally, **daily fluid requirements** for hospitalized patients need to be provided during the replacement phase, and may be needed after volume resuscitation and rehydration if the animal has not recovered to the extent that appetite and ability to consume water have returned to normal. Daily fluid requirements are calculated based on normal animals [30 X BW(kg) + 70 = mL/day or 80 X BW(kg)0.75 = mL/day], but fluid requirements of partially or completely anorexic patients are difficult to predict. Careful observation of urine production may help avoid excessive fluid administration by reducing fluid volumes when patients urinate large volumes of dilute urine frequently. Weighing disposable fluid absorbing pads can be a useful way of determining urine output when urinary catheterization is not used.

Maintenance fluids are designed to meet the ongoing sensible and insensible losses of a patient, and in a normal animal, these needs are met through intake of food and water. When this is not possible or the fluid intake is inadequate, a maintenance fluid can be utilized. While both isotonic and hypotonic fluids may be used for maintenance fluid therapy, ideally, the composition of a maintenance fluid is different from that of a replacement fluid. Generally, maintenance fluids contain a lower sodium concentration, i.e. a hypotonic fluid, (to avoid potentially overloading the patient with sodium), and a higher potassium concentration than replacement fluids.

OVERHYDRATION SIGNS

- Shivering
- Nausea
- Vomiting
- Restlessness
- Polyuria
- Serous nasal discharge
- Tachypnea
- Cough (late)
- Dyspnea (late)
- Diarrhea (late)
- Ascites (late)
- Exophthalmous (late)
- Depresses mentation (late)
- Pulmonary crackles (late)

Maintenance fluid requirements will vary with the size, age, and metabolic needs of the patient, and can be increased in smaller or younger patients and animals with panting and/or pyrexia, but decreased in critically ill or sedentary animals. There are several ways to calculate maintenance fluid requirements, but a commonly used short-cut is 40 – 60 mL/kg/day. (Rieser, 2020)

All patients receiving fluid therapy should be monitored carefully and fluid therapy plans adjusted as needed to ensure adequate tissue perfusion, correction of dehydration, correction of any acid/base or electrolyte disturbances, and to avoid over-hydration.

The Vetivex® Veterinary IV Fluid Calculator app uses parameters that assess hypovolemia, dehydration, ongoing losses, and physiologic requirements. It can be very helpful in allowing for quick and easy reassessment and adjustment of fluid therapy plans for patients. It is iphone/ipad, and android compatible. The formulas are calculations from a dual board-certified small animal emergency and critical care/internal veterinary specialist, Dr. Christopher Byers. (Byers, 2019)

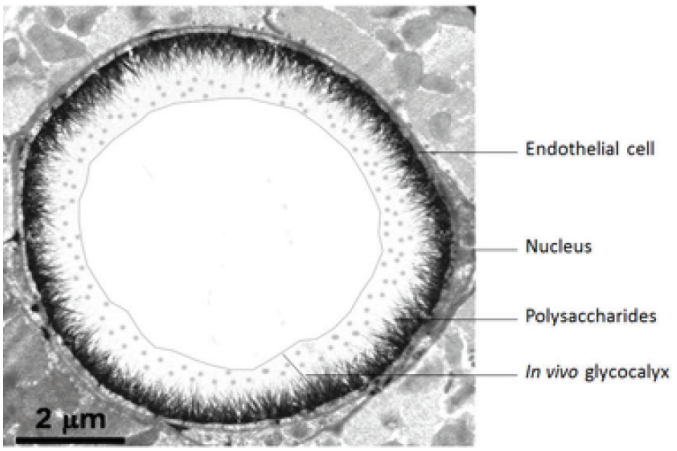
As discussed earlier, patients should be weighed daily to track alterations in fluid balance. Keep in mind that 1 L of water is effectively equivalent to 1 kg of weight. Monitoring body weight for acute changes suggest fluid shifts versus changes in muscle or fat content. Other physiological parameters such as mucous membrane color and moisture, CRT, skin turgor, heart and respiratory rate, blood pressure and urine output give clinicians a good estimate as to the effectiveness of the fluid therapy plan. If signs of over-hydration do occur (e.g. shivering or restlessness, serous nasal discharge, labored breathing or tachypnea, chemosis or exophthalmos, nausea or vomiting, coughing or moist lung sounds, ascites, or depressed mention) fluid therapy should be discontinued and appropriate corrective measures taken.

Intra-operative fluids are used to support tissue perfusion during anesthesia. All anesthetic agents can affect cardiovascular parameters and renal blood flow. Current recommendations are to use isotonic crystalloid solutions starting at a rate of 3 mL/kg/hr for cats and 5 – 10 mL/kg/hr for dogs. Rates greater than 10 mL/kg/hr should be avoided, and fluids rates should be reduced by 25% for every hour under anesthesia if the patient remains stable to help avoid fluid overload, which could result in post-operative complications such as pulmonary edema.

Blood pressure is the main parameter used to estimate tissue perfusion. If hypotension occurs while the patient is under anesthesia, assess patient depth, as excessive anesthetic depth is the most common cause of hypotension. Exercise caution when using fluid therapy as the sole method to correct anesthesia-related hypotension, as high rates of fluids can exacerbate complications rather than prevent them.

If the patient has a relative hypovolemia due to peripheral vasodilation contributing to hypotension in the anesthetized patient, 2013 AAHA fluid therapy guidelines recommend the following steps:

- Decrease anesthetic depth and/or inhalant concentration.
- Provide an IV bolus of isotonic crystalloid such as LRS (3 – 10 mL/kg). Repeat once if needed.
- If response is inadequate, consider IV administration of a colloid such as hetastarch. Slowly administer 5 – 10 mL/kg for dogs and 1 – 5 mL/kg for cats, titrating to effect to minimize the risk of vascular overload (measure BP every 3 – 5 min).
- If response to crystalloid and/or colloid boluses is inadequate and patient is nothypovolemic, techniques such as vasopressors may be needed. (Davis, et al., 2013)

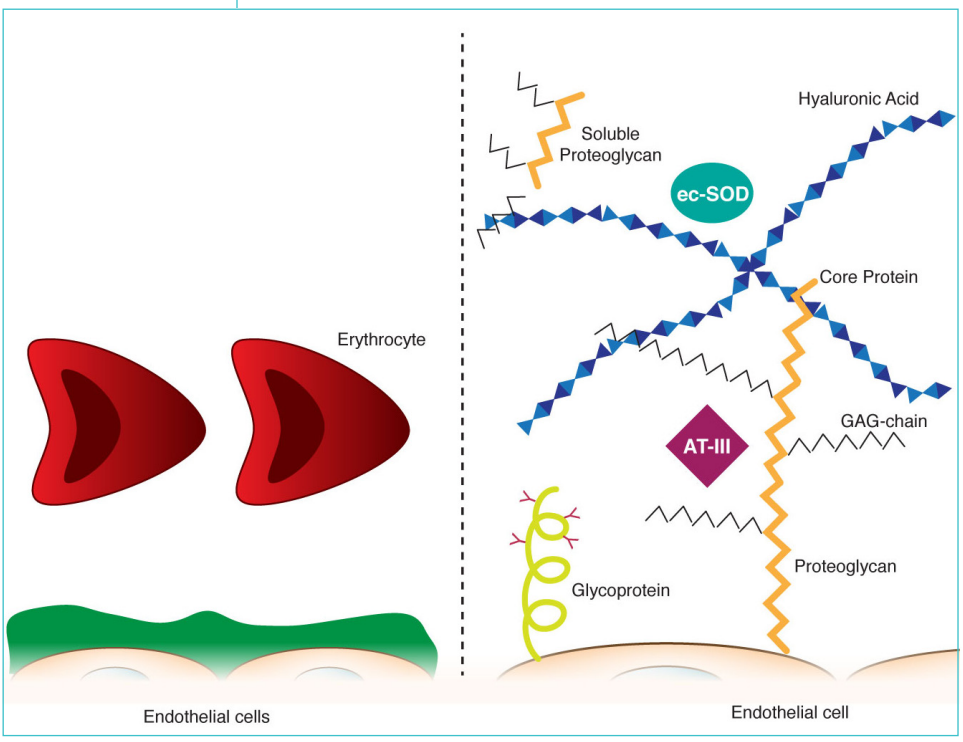


THE ENDOTHELIAL GLYCOCALYX (EG)

Electron microscopy first visualized the existence of glycocalyx structures on the luminal surface of vascular endothelial cells in the 1950's, but it functional significance remained unknown. (Vink, et al., 2012) Over the past decades, research has resulted in a better understanding critical role of the endothelial glycocalyx (EG) in vascular physiology and pathology. EG is essential in regulation of vascular permeability, inflammation, and coagulation and is integral in the pathophysiology of conditions such as sepsis and shock. (Gaudette, Hughes, & Boller, 2020)

The endothelial glycocalyx (EG) is a transparent micro-thin gel-like lining that covers the luminal aspects of all blood vessels and protects the circulatory system. The EG is a complex, filamentous coating composed of a variety of macromolecules, including glycoproteins, polysaccharides, proteoglycans and glycosaminoglycans such as heparin sulfate, chondroitin sulfate and hyaluronic acid. These molecules help repel circulating platelets. The EG also contains constituents of plasma which pass through it or lodges within it such as plasma proteins, enzymes and enzyme inhibitors, growth factors, cytokines, amino acids, cations, and water. In spite of its microscopic thinness, this layer actually occupies about 25% of the total intravascular volume. (Yartsev, n.d.)
In health, the EG is a highly dynamic but stable structure that is maintained via a fine balance between normal degradation and new biosynthesis. However, it is highly fragile and easily disrupted.

Proteoglycans function as "backbone" molecules of the EG. They consist of a core protein (syndecans, glypicans, et al) to which one or more glycosaminoglycan chains are linked. There are five types of glycosaminoglycan chains: heparin sulfate, chondroitin sulfate, dermatan sulfate, keratin sulfate, and hyaluronic acid. The glycosaminoglycan (GAG) chains contain numerous specific binding sites for plasma-derived proteins, and extend off the core protein into the vascular lumen creating the mesh-like structure characteristic of the EG. Sulfate groups attached to the GAG disaccharide units impart a net negative charge to the EG. (Reitsma, Slaaf, Vink, van Zandvoort, & oude Egbrink, 2007) (Gaudette, Hughes, & Boller, 2020) Overall composition of the EG is



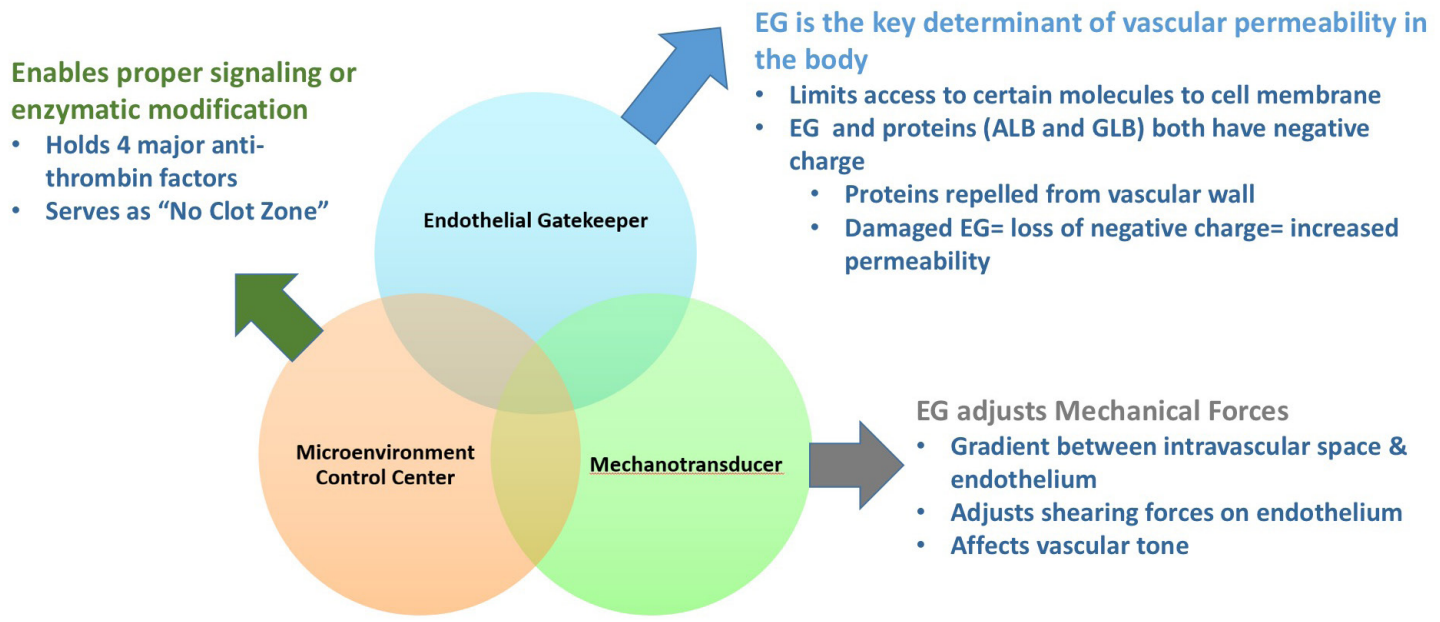
controlled via a fine balance between normal biosynthesis of the EG constituents and the rate of shedding or loss. Shedding of EG constituents occurs adaptively under normal physiological conditions as well as maladaptively during pathological processes. (Gaudette, Hughes, & Boller, 2020)

Soluble plasma components are incorporated into the EG. These various plasma components further enhance the EG by altering its physical properties such as its thickness and permeability. Albumin is one of the key soluble components within the EG and appears to be required to impart normal barrier function. (Gaudette, Hughes, & Boller, 2020)

The EG has both immunological and barrier functions. It forms the interface between the vessel wall and the moving blood, acts as the exclusion zone between blood cells and the endothelium, acts as a barrier against leakage of fluid, proteins and lipids across the vascular wall; and it interacts dynamically with blood constituents. The EG acts as a "molecular sieve" for plasma proteins and acts as the origin of the oncotic forces which control the transcapillary movement of water. Adhesion of inflammatory cells and platelets to the endothelial surface are modulated by the EG. If the porosity of the EG is increased by inflammation, and/or if the capillary pressure and blood flow increase, the net movement of fluid out of the capillary increases dramatically – this underlies the "leaky capillary" phenomenon seen in inflammation and sepsis.

Additionally, the EG functions as a sensor and mechanotransducer of the fluid shear forces to which the endothelium is exposed to; and thus it mediates shear-stress-dependent nitric oxide production which is vital in controlling blood flow and blood pressure. Protective enzymes such as superoxide dismutase are retained with the EG, as well as anticoagulation factors like tissue factor inhibitor, protein C and antithrombin III. (Yartsev, n.d.)

Functions of Endothelian Glycocalyx

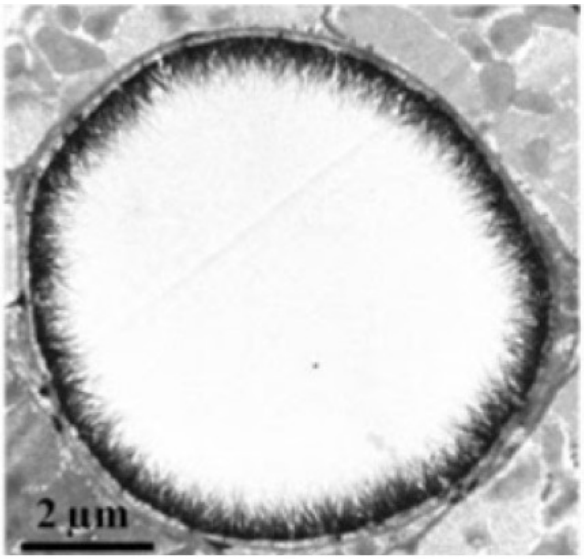


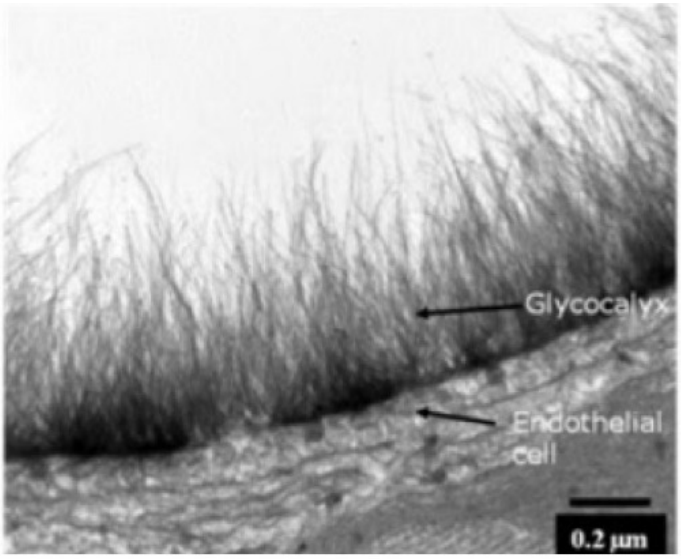
Thinning of the EG layer is caused by hyperglycemia & hyperlipidemia, and shedding of the glycocalyx layer is caused by several factors including:

- Inflammation mediated by TNFα and possibly other mediators of inflammation
- Ischemia-reperfusion injury
    - Halts the endothelial synthesis of glycosaminoglycans.
- Hypervolemia
    - Note: Fluid overload is associated with increased morbidity and mortality; resuscitative fluid therapy is not benign, and a judicious and rational approach must be used.
- Possibly hydroxyethyl starch
- Major vascular or abdominal surgery (even without much sepsis)
- Sepsis
- Trauma and hemmorrhage

(Yartsev, n.d.) (Gaudette, Hughes, & Boller, 2020)

Damage to the EG can happen in a rapid fashion





Damage during disease states leads to serious sequelae such as increased vascular permeability and interstitial edema, development of pro-inflammatory state, alterations in coagulation, and an inability to regulate vascular tone. Each of these consequences of EG degradation can have a profound impact on the critically ill patient. (Gaudette, Hughes, & Boller, 2020)

As previously stated, the EG is a highly dynamic structure that is maintained via a fine balance between normal degradation and new biosynthesis. New biosynthesis usually occurs within minutes to hours as components of the EG can be filtered from the plasma, but at least one study indicated that after acute enzymatic or cytokine-mediated degradation of the EG layer, 5 to 7 days may be required before it is fully restored. (Potter, Jiang, & Damiano, 2009)

Currently there are no commercially available biomarkers of EG damage, but investigators have looked at several components of the glycocalyx (syndecan-1, heparin sulfate, hyaluronic acid), macromolecules which don't belong in the bloodstream. Should these molecules be found in great number, this would be suggestive the glycocalyx has been or is being damaged (i.e. it is sloughing off from the endothelium and floating around in the bloodstream). (Yartsev, n.d.)

There are three well-accepted strategies to protect and repair the EG. These include corticosteroids, maintaining normoglycemia, and avoiding fluid overloads (maintaining normovolemia). Studies investigating how the EG can be modified, preserved, or repaired to aid in the treatment of various critical illnesses are ongoing, but most remain investigative in nature at this time.

Experimental treatments are being investigated. These include:

- The use of antioxidants as a method to reduce EG shedding.
  - For example, pretreatment with N-acetylcysteine reduced EG shedding in acutehyperglycemia.

- Administration of exogenous GAGs to repair the EG.
  - Using a commercially available oral medication called Soludexide may aid in the reformation of the EG

- Use of heparin to reduce EG shedding.
  - In a canine septic shock model, treatment with unfractionated heparinattenuated shedding; the underlying pathophysiology of this 'protective'mechanism remains unknown.

- Treatment with plasma proteins may aid in EG reconstitution.
  - Infusion of 5% human albumin led to reduction in the extravasation of fluids afterischemia-reperfusion injury; albumin appears to be able to penetrate and bind within the EG and restore vascular integrity.

- Animal hemorrhagic shock models have demonstrated that fluid resuscitation with freshfrozen plasma (FFP) compared to crystalloids successfully restores the EG
  - The use of FFP leads to improved microhemodynamics, vascular hemostasis, and reduced leukocyte-endothelium interaction compared to crystalloids or synthetic colloids.

- The use of protease inhibitors, such as antithrombin (AT), is also a promising therapeutic modality.
  - AT is found in FFP and therefore treatment with FP may promote repair of theeG by multiple methods.

- At subantimicrobial doses, doxycycline reduces EG shedding through inhibition of metalloproteinases (MMPs).
  - MMPs have been implicated in EG degradation for various conditions; therefore, use of doxycycline may emerge as a clinically useful treatment to support EG preservation.
- Finally, glucocorticoid administration has reduced EG shedding in the face of various agents known to damage the EG.
  - The mechanisms underlying these protective effects are not completely understood and are likely multifactorial, but mast cell stabilization could be part of the mechanism.
  - Further research is required to determine both how and at what dose glucocorticoids provide their protective effects and to determine their clinical use. (Gaudette, Hughes, & Boller, 2020)

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