CHAPTER 1
Body water physiology

C. Langdon Fielding
Loomis Basin Equine Medical Center, Penryn, CA, USA

Introduction

The topic of fluid therapy usually focuses on the ideal fluid type and rate that should be administered to equine patients for specific clinical conditions. While the remainder of this textbook addresses these important questions, a brief introduction to the distribution of administered fluids is needed as a basis from which to interpret subsequent chapters. Specifically, concepts including the physiologic fluid spaces, effective osmolality, and oncotic pressure are important foundations to understand prior to important foundations to understand prior to formulating a fluid therapy plan.

Physiologic fluid spaces

The physiologic fluid spaces are typically divided into total body water (TBW), extracellular fluid volume (ECFV), and intracellular fluid volume (ICFV) as shown in Figure 1.1. It is important to remember that these fluid spaces are both physiologic (not anatomic) and dynamic. They represent a volume estimate at a point in time and therefore are constantly changing based on a number of physiological principles. Much of the attention in clinical medicine is focused on the ECFV; blood sampling for laboratory testing comes from this fluid space.

Total body water (TBW)

Total body water represents the total volume of water within the animal. Values in adult horses have ranged from 0.55 to 0.77 L/kg depending on the measurement technique used (Dugdale et al., 2011; Fielding et al., 2004; Latman et al., 2011). A consensus from most of the research would suggest that a typical horse has a volume of TBW between 60 and 70% of its weight. A value of 2/3 is often used by many textbooks and is easy to remember. The majority of studies determining TBW have used deuterium oxide dilution, but this is not practical in a clinical setting. Acute changes in body weight are likely the best determination of changes in TBW in sick horses and foals. Monitoring of weight change should be done frequently (1–2 times per day if possible), in order to recognize acute loss or gain of body water.

Extracellular fluid volume (ECFV)

Extracellular fluid volume represents the volume of TBW that is not contained within the cells. This includes the plasma volume (PV), interstitial volume (IV), and transcellular compartments (gastrointestinal tract, joint fluid, etc.). The ECFV has also been measured using a number of different dilution techniques and reported values in adult horses have ranged from 0.21 to 0.29 L/kg (Dugdale et al., 2011; Fielding et al., 2004; Forro et al., 2000). A good approximation of the ECFV is about 1/3 of TBW.

In addition to evaluating fluid balance, monitoring the size of the ECFV is clinically useful in determining the dosage of some medications. In disease states, the ECFV is the space from which fluid losses often occur (e.g. sodium-rich fluid loss in diarrhea); it is also the space where fluids are administered and often remain (i.e. intravenous isotonic crystalloids). Three techniques that have been used clinically to monitor changes in the ECFV are bioelectrical impedance analysis (BIA), sodium dilution, and volume kinetics (Fielding et al., 2008; Forro et al., 2000; Zdolsek et al., 2012).

Equine Fluid Therapy, First Edition. Edited by C. Langdon Fielding and K. Gary Magdesian.

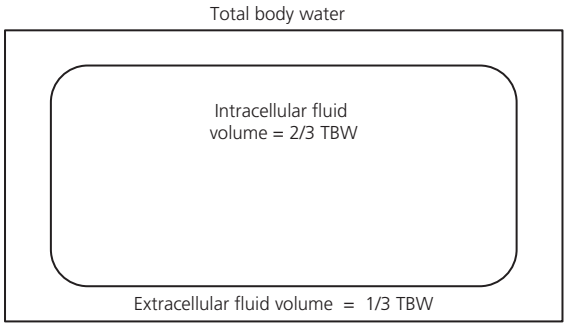

Figure 1.1 Relationship between total body water (TBW), extracellular fluid volume (ECFV), and intracellular fluid volume (ICFV) in a normal horse. Diagram represents a simplified "single cell" model.

Plasma volume is easier to estimate as compared to the other fluid spaces and has been reported as 0.052 to 0.063 L/kg in healthy adult horses (Marcilese et al., 1964). Clinical monitoring of the PV is essential as excessive expansion or contraction can lead to clinical derangements such as edema and shock, respectively. Changes in packed cell volume (PCV) over time may give an indication of PV alterations, but the role of splenic contraction makes the use of this measurement somewhat complicated in horses. Total plasma protein concentration may be a more useful tool for monitoring PV; however, abnormal protein losses can make interpretation problematic.

Intracellular fluid volume (ICFV)

Intracellular fluid volume is the volume of fluid contained within the cells. It is usually estimated as the difference between TBW and the ECFV. Bioimpedance technology has been used to make estimates of this fluid space in horses, but dilution techniques cannot be easily applied to the ICFV. Reported values for ICFV are between 0.356 and 0.458 L/kg in horses (Dugdale et al., 2011; Fielding et al., 2004; Forro et al., 2000). Monitoring of the ICFV is typically not performed in clinical practice, but BIA may offer the best assessment available at this time.

Physiologic fluid spaces in foals

Physiologic fluid spaces in newborn foals have been described (Table 1.1). In general, there is an increased size of the ECFV and TBW as compared to adults (Fielding et al., 2011; Spensley et al., 1987). Values of TBW in newborn foals appear to be larger (0.74 L/kg) as compared to adults, which is consistent with other species (Fielding et al., 2011). Estimations of ECFV in foals are also significantly larger than in adults and have been reported to be between 0.36 and 0.40 L/kg in newborn foals; this decreases to 0.290 L/kg in foals at 24 weeks of age (Fielding et al., 2011; Spensley et al., 1987). The PV was estimated to be 0.090 L/kg (Fielding et al., 2011; Spensley et al., 1987), which represents an increase as compared to adults. Interestingly, the ICFV of foals is approximately 0.38 L/kg, which is similar to that in adult horses (Fielding et al., 2011). The ratio of ICFV to ECFV is approximately 1:1 in newborn foals as compared to adults with a ratio of approximately 2:1 (Figure 1.2).

Table 1.1 Physiologic fluid spaces in horses and foals.

Fluid space	Adult horse (L/kg)	Neonatal foal (L/kg)
Total body water	0.55–0.77	0.74
Extracellular fluid volume	0.21–0.29	0.36–0.40
Intracellular fluid volume	0.36–0.46	0.38
Plasma volume	0.052–0.063	0.09

These differences in physiologic fluid spaces in foals alter the volume of distribution for common medications that have a high degree of water solubility (i.e. aminoglycoside antibiotics). This is one reason why the dosing of some medications differs in neonates as compared to adult horses. Fluid therapy plans must also take into consideration the different fluid physiology of the neonate.

Concepts in fluid balance

Perhaps the two most important physiologic concepts in water balance and fluid therapy are:

1. *Effective osmolality* (*tonicity*) – this guides the intracellular to extracellular fluid balance.
2. *Starling's law of net filtration* – this guides the intravascular to interstitial fluid balance.

Osmolality

Osmolality refers to the number of osmoles per kilogram of solvent (or water). The osmotic effect exerted by solutes is based on the total number of particles regardless

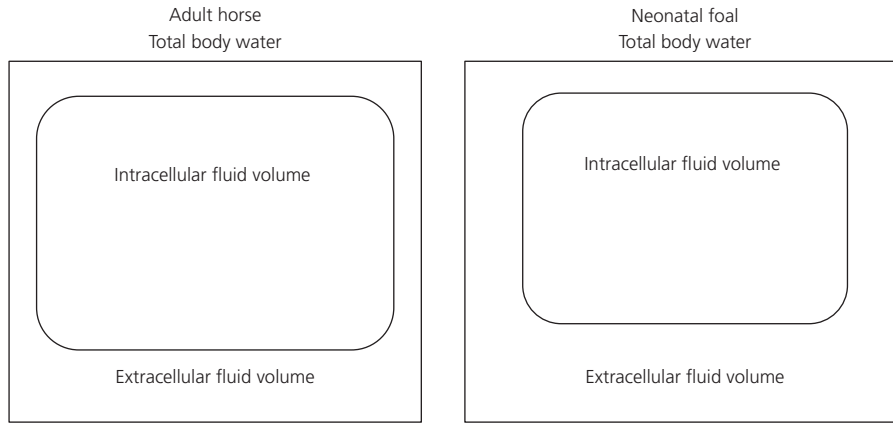

Figure 1.2 The relative sizes of the intracellular fluid volume, extracellular fluid volume and total body water in adults and foals.

of the size or weight of those particles. Osmolality is measured in serum by the method of freezing-point depression. Serum osmolality in adult horses was reported to range from 271 ± 8 to 281 ± 9 mOsm/kg H_2O (Carlson et al., 1979; Carlson & Rumbaugh, 1983; Pritchard et al., 2006). Serum osmolality in foals has been reported as 245 ± 19 to 267 mOsm/kg H_2O (Brewer et al., 1991; Buchanan et al., 2005).

Osmolality in serum can also be estimated with a calculation that is based on the use of the primary osmotically active substances in serum. One of the available equations for calculation is:

$$\text{ECF osmolality (mOsm/kg)} = 2\times([Na^+]+[K^+])+[\text{glucose}]/18+[\text{BUN}]/2.8 \quad (1.1)$$

The values for sodium and potassium are doubled to estimate the contributions of the anions (given that positive and negative charges are always balanced). Glucose and body urea nitrogen (BUN) are divided by their molecular weights in order to convert milligrams per deciliter to millimoles per liter. While not extensively reported, normal values for calculated osmolality in horses would likely range from 295 to 300 mOsm/kg H_2O based on reported ranges for these ion concentrations in horses.

The osmolal gap is the difference between measured and calculated osmolality. Reference ranges for the osmolal gap in horses have not been reported; based on available information, it is anticipated that the calculated osmolality may be greater than the measured osmolality. This same observation has been reported in cats and has been attributed to laboratory error (Wellman et al., 2012). A wide osmolal gap represents the presence of unidentified osmoles. The clinical usefulness of this test in horses may be more limited than in small animal medicine, as ethylene glycol toxicity is not commonly reported in horses. Other unidentified osmoles could be suspected using this calculation, however.

Effective osmolality (tonicity)

Effective osmoles are those that do not freely move across a membrane, and therefore exert tonicity. When considering horses (or other animals), the cellular membrane dividing the ECF from the ICF determines whether an osmole is effective. For example, sodium, potassium, and glucose that are distributed into the extracellular fluid space (e.g. by intravenous infusion) cannot freely move across the cell membrane into the cell (they all have specific mechanisms of transport). These are examples of effective osmoles. By contrast, urea (BUN) can freely move across the cell membrane and is therefore considered an ineffective osmole.

Tonicity refers to the effective osmolality of a solution. If the tonicity of an administered solution is the same as that of plasma, it is referred to as an isotonic solution. Conversely, a solution with an increased tonicity (i.e. 7.2% saline) as compared to plasma is referred to as hypertonic, and a solution with a decreased tonicity (i.e. 0.45% saline) is referred to as hypotonic.

Understanding the tonicity (effective osmolality) of different intravenous fluids as compared to plasma is critical to understanding fluid therapy. Many fluids

(e.g. 0.9% saline) are referred to as "isotonic" even though they are slightly hypertonic (osmolality = 308 mOsm/kg H_2O) as compared to normal equine plasma (approximately 280 mOsm/kg H_2O). This mild hypertonicity of some supposedly "isotonic" intravenous fluids can lead to movement of water out of the cells and resulting cellular dehydration, as shown in Figure 1.3 (Fielding et al., 2008). This cellular "dehydrating" effect will be more significant when horses do not have access to free water.

Fluids that are hypotonic compared to normal plasma can result in movement of water into cells (Figure 1.4). This may be an important part of treatment in animals that have lost water from both the ECFV and ICFV. However, in cases of chronic hypernatremia, this movement of water into cells (when water is administered to the patient) can be life-threatening (see Chapter 2). These important concepts are further outlined in the discussion of transcellular fluid shifts below.

Effective osmolality is the main determinant of fluid balance between the ECFV and ICFV. All fluids that are lost must come from one or both of these spaces. In order to effectively provide fluid therapy, the clinician must recognize or estimate the source of fluid deficits (ECFV vs ICFV) and attempt to replace them from the respective location. Similarly, all fluids that are administered (intravenously, orally, etc.) will distribute to one or both of these spaces. Effective fluid therapy results when fluids are targeted to replace the missing fluid volume

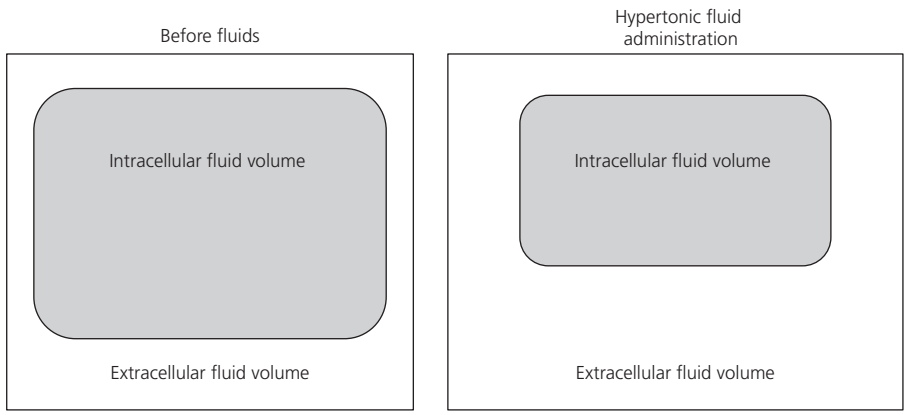

Figure 1.3 The effect of administering hypertonic fluids to the extracellular fluid volume (ECFV). There is an expansion of the ECFV and a shrinking of the intracellular fluid volume (ICFV).

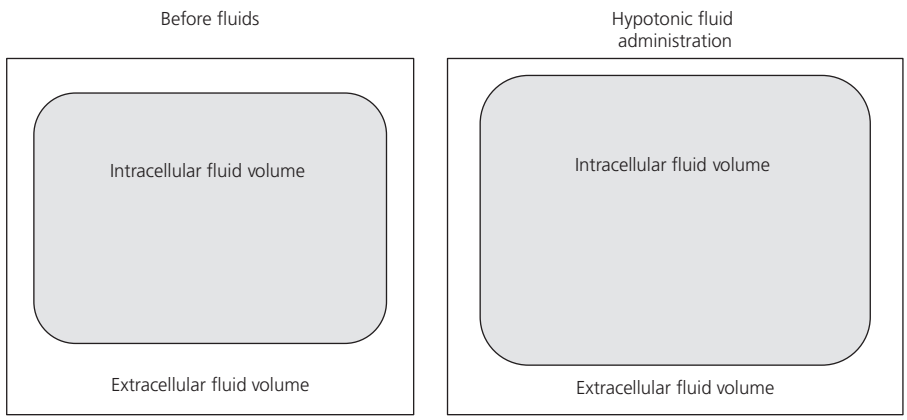

Figure 1.4 The effect of administering hypotonic fluids to the extracellular fluid volume (ECFV). There is an expansion of the ECFV and an expansion of the intracellular fluid volume (ICFV).

(e.g. a sodium-rich fluid is used to treat a hypovolemic horse with severe diarrhea that has ECFV deficits). However, ineffective fluid therapy results when fluids are misdirected to the inappropriate fluid space (e.g. a sodium-poor fluid such as 5% dextrose is used to treat the same hypovolemic horse with diarrhea).

In conclusion, the effective osmolality (tonicity) of a given fluid is extremely important for selecting the composition of a fluid to be administered to the patient. In general:

1 Administration of hypertonic fluids tends to expand the ECFV by an amount greater than the administered volume by drawing fluid from the ICFV.
2 Administration of hypotonic fluids tends to expand the ECFV by an amount less than the administered volume, as some fluid volume is lost to the ICFV.

Colloid osmotic pressure

Colloid osmotic pressure (COP) is the osmotic pressure generated by proteins within a fluid (typically plasma). It is also referred to as "oncotic pressure". The COP is one of the determinants (hydrostatic pressure also plays a role) of fluid balance between the vascular and interstitial spaces. Administered fluids that have COPs below plasma values will tend to move out of the vascular space and into the interstitial space. Conversely, fluids with COPs that are similar to or greater than plasma values will tend to "hold" fluid within the vascular space.

When fluids rich in protein are lost from a patient (i.e. severe blood loss), these fluids may be more effectively replaced with a fluid that has a normal to supranormal COP (i.e. whole blood). However, loss of fluids that are low in protein (e.g. prolonged, large-volume nasogastric reflux) can typically be replaced with fluids having a low oncotic pressure (i.e. an isotonic crystalloid).

Starling's law

The complex relationship described by Starling's law helps to govern the movement of fluid out of the vascular space into the interstitium. Figure 1.5 shows a simple model of Starling forces moving fluid out of the vascular space into the interstitial space.

$$\text{Net filtration} = K_f[(P_{cap} - P_{int}) - (\pi_{plasma} - \pi_{int})] \qquad (1.2)$$

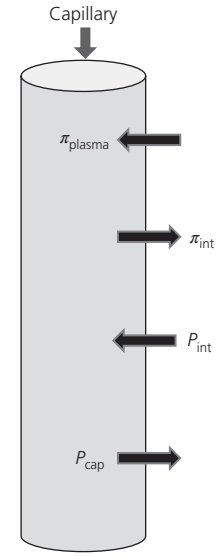

Figure 1.5 Starling factors affecting the fluid movement out of the vascular space into the interstitial space. P_{cap} refers to the hydrostatic pressure within the vascular space. P_{int} refers to the hydrostatic pressure within the interstitial space. π_{plasma} represents plasma oncotic pressure. π_{int} refers to the oncotic pressure within the interstitial space.

The term K_f represents the permeability of the capillary wall. In states of inflammatory disease, it is presumed that permeability significantly increases and results in movement of fluid and protein out of the vascular space (Levick & Michel, 2010). This fluid would then accumulate within the interstitial space resulting in edema that is observed clinically. Recent research has questioned the role of other factors, such as decreases in interstitial hydrostatic pressure, in addition to changes in K_f in the formation of edema (Reed & Rubin, 2010). Treatments designed to decrease K_f (i.e. some colloid solutions) aim to reduce the amount of fluid moving from the vascular space to the interstitial space.

The term P_{cap} refers to the hydrostatic pressure within the vascular space. Under normal circumstances, this pressure is generated by the heart. In experimental conditions, it can be increased by ligation of veins, with local increases in hydrostatic pressure. In heart failure or fluid overload, the P_{cap} increases thereby raising the pressure pushing fluid out of the capillary into the interstitial space. The role of P_{cap}, when designing a fluid therapy plan, should not be underestimated. Patients suspected of having an increased P_{cap} (sometimes in specific organs or local tissue regions) may need more

moderate volume replacement (if any at all). Likewise, administering fluids with an increased oncotic pressure to volume overloaded patients can be particularly risky.

The term P_{int} refers to the hydrostatic pressure within the interstitial space. This can be considered the pressure that is "pushing back" against the inevitable flow of fluid out of the vascular space into the interstitium. The role of P_{int} was ignored for many years, but recent research has focused on its importance in the role of edema formation. Changes that occur in the structure (matrix) of the interstitium can cause a decrease in P_{int} (sometimes highly negative values) thereby "pulling" more fluid out of the vascular space and into the interstitium. A normal, healthy interstitium will hold a limited amount of fluid and as the volume increases, the hydrostatic pressure increases and resists further fluid movement out of the capillary. However, a diseased interstitium (i.e. as a result of inflammatory disease) may allow marked fluid expansion without creating significant pressure to resist further fluid entry. Under inflammatory conditions sometimes a negative pressure within the interstitial space can be generated, which may contribute to edema formation (Reed et al., 2010).

The term π_{plasma} represents plasma oncotic pressure and is described above. The normal plasma oncotic pressure has been reported as 22 to 25 mmHg (Boscan et al., 2007; Jones et al., 1997) in healthy horses. Horses that are sick and/or undergoing anesthesia may have plasma oncotic pressures as low as 12 mmHg (Boscan et al., 2007). Equations have been developed to estimate plasma oncotic pressure based on the value of total plasma protein, but these can have unacceptable accuracy (Magdesian et al., 2004; Runk et al., 2000). Plasma oncotic pressure was estimated to be approximately 19 mmHg in healthy neonatal foals (Runk et al., 2000). The oncotic pressures of the fluids commonly used in equine practice are discussed in Chapter 24. Rapid administration of a fluid with a low oncotic pressure (as compared to plasma) is likely to further drop the plasma oncotic pressure.

The term π_{int} refers to the oncotic pressure generated by the proteins and mucopolysaccharides within the interstitium. It is important to remember that the majority of protein is located within the interstitium (not the vascular space). Albumin, the primary determinant of plasma oncotic pressure, has an interstitial concentration lower than the plasma concentration. However, given the much larger size of the interstitial space, the absolute amount of protein within the interstitium is much greater than that within the vascular space.

Protein can move from the vascular space into the interstitium and then return through the lymphatic system. For this reason, administration of protein (in the form of plasma transfusion) into the vascular space will result in a distribution of some of the administered protein throughout much of the ECFV (i.e. into the interstitial space). This means that plasma administration is essentially ineffective at reducing fluid accumulation within the interstitial space (edema) and is unlikely to significantly change plasma oncotic pressure unless large amounts are administered. Interstitial colloid osmotic pressure is difficult to measure, but some estimates are in the range 12–15 mmHg in other species under experimental conditions (Wiig et al., 2003).

Changes in any of the terms of the Starling equation will likely affect other parameters as well. For example, when capillary hydrostatic pressure is increased experimentally, there is a subsequent drop in the interstitial oncotic pressure (Fadnes, 1976). This results from increased fluid moving into the interstitium, thereby lowering its oncotic pressure.

In a more expanded version of the Starling formula, the capillary reflection coefficient (σ) is included:

$$\text{Net filtration} = K_f[(P_{cap} - P_{int}) - \sigma\,(\pi_{plasma} - \pi_{int})] \qquad (1.3)$$

The reflection coefficient acts as a correction factor for the effective oncotic pressure given that some capillaries are more permeable to proteins than others. For example, capillaries in the glomerulus may be quite impermeable and have values close to 1. Conversely, capillaries in the pulmonary system are relatively more permeable to protein and have a reflection coefficient close to 0.5. The other variables are described above.

Fluid movement out of the vascular space

In a simplistic model, fluid should be considered to move continuously out of the vascular space (according to the Starling factors described above), then into the interstitial space, and finally into the lymphatic system. The fluid is returned to the vascular space by way of lymphatic flow (e.g. thoracic duct draining into left subclavian vein). A certain amount of protein is taken with this fluid and also moves continuously through the system.

Fluid accumulation within the interstitial space (interstitial edema) results when there is dysfunction of this continuous system (of fluid movement from the vascular space to the interstitium and to the lymphatics). Causes of edema in equine practice include the following:

1 Decreased plasma colloid osmotic pressure (hypoproteinemia).
2 Increased capillary hydrostatic pressure.
3 Increased capillary permeability.
4 Lymphatic obstruction.

However, it is likely that any type of systemic inflammation will result in changes to the interstitial hydrostatic pressure (as well as causing changes in capillary permeability) and that this also may contribute to edema formation. A single abnormality (e.g. hypoproteinemia) may have to be very severe in order to cause edema. However, when multiple derangements are present (e.g. hypoproteinemia, increased intravascular pressure due to excessive fluid administration or cardiac dysfunction, and decreased interstitial pressure due to inflammation), edema formation will be more likely to manifest, and will do so sooner than with an individual abnormality (Figure 1.6).

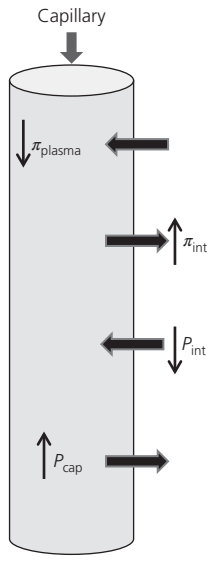

Figure 1.6 Starling factors affecting increased fluid movement out of the vascular space into the interstitial space and resulting in interstitial edema. P_{cap} refers to the hydrostatic pressure within the vascular space. P_{int} refers to the hydrostatic pressure within the interstitial space. π_{plasma} represents plasma oncotic pressure. π_{int} refers to the oncotic pressure in the interstitial space.

Starling's law and fluid therapy

The practical implications of Starling's law underlie many of the basic concepts for fluid therapy. In choosing a fluid therapy plan, the clinician can influence the capillary hydrostatic pressure and the plasma oncotic pressure most directly. The two main concepts are:

1 Fluids with a high oncotic pressure relative to plasma are likely to raise both plasma oncotic pressure and capillary hydrostatic pressure.
2 Fluids with low oncotic pressure relative to plasma are likely to lower plasma oncotic pressure and raise capillary hydrostatic pressure.

Over time, administered fluids may also have an effect on the interstitial oncotic pressure, but likely play a minor role in changing the interstitial hydrostatic pressure. While the role of capillary permeability remains unclear, most intravenous fluid choices do not strongly influence this variable. Some synthetic colloids (depending on the size of the molecules) may have the potential to "plug" capillary walls that are more permeable. More information on this topic can be found in Chapter 24.

Optimal fluid therapy considers all of the components of Starling's law. For example, a newborn foal with bacteremia may be undergoing a severe systemic inflammatory response (SIRS), and would be expected to have reduced interstitial hydrostatic pressure and possibly increased capillary permeability and reduced oncotic pressure. This patient is a prime candidate for edema formation. Conversely, a severely dehydrated endurance horse is likely to have a high plasma protein concentration and a normal interstitial hydrostatic pressure. This horse is likely to tolerate aggressive fluid therapy well.

Summary of tonicity and colloid osmotic pressure

Based on the information above, potential fluids can be described as either hyper- or hypotonic and either hyper- or hypo-oncotic as compared to the patient's plasma. A fluid that is both hypertonic and hyperoncotic has the potential to shift fluid from the ICFV into the ECFV and expand the intravascular volume. This would potentially make a good resuscitation fluid as it expands the vascular space quickly; however, it would make a very poor maintenance fluid as it is likely to dehydrate

the cells. A hypotonic and hypo-oncotic fluid such as 0.45% saline would be very poor at expanding the vascular volume, but might make a better long-term fluid (especially with some additives) for maintenance of hydration of cells, interstitium, and vascular space.

References

Boscan P, Watson Z, Steffey EP. (2007) Plasma colloid osmotic pressure and total protein trends in horses during anesthesia. *Vet Anaesth Analg* **34**:275–83.

Brewer BD, Clement SF, Lotz WS, et al. (1991) Renal clearance, urinary excretion of endogenous substances, and urinary diagnostic indices in healthy neonatal foals. *J Vet Intern Med* **5**:28–33.

Buchanan BR, Sommardahl CS, Rohrbach BW, et al. (2005) Effect of a 24-hour infusion of an isotonic electrolyte replacement fluid on the renal clearance of electrolytes in healthy neonatal foals. *J Am Vet Med Assoc* **227**:1123–9.

Carlson GP, Rumbaugh GE. (1983) Response to saline solution of normally fed horses and horses dehydrated by fasting. *Am J Vet Res* **44**:964–8.

Carlson GP, Rumbaugh GE, Harrold D. (1979) Physiologic alterations in the horse produced by food and water deprivation during periods of high environmental temperatures. *Am J Vet Res* **40**:982–5.

Dugdale AH, Curtis GC, Milne E, et al. (2011) Assessment of body fat in the pony: part II. Validation of the deuterium oxide dilution technique for the measurement of body fat. *Equine Vet J* **43**:562–70.

Fadnes HO. (1976) Effect of increased venous pressure on the hydrostatic and colloid osmotic pressure in subcutaneous interstitial fluid in rats: edema-preventing mechanisms. *Scand J Clin Lab Invest* **36**:371–7.

Fielding CL, Magdesian KG, Elliott DA, et al. (2004) Use of multifrequency bioelectrical impedance analysis for estimation of total body water and extracellular and intracellular fluid volumes in horses. *Am J Vet Res* **65**:320–6.

Fielding CL, Magdesian KG, Carlson GP, et al. (2008) Application of the sodium dilution principle to calculate extracellular fluid volume changes in horses during dehydration and rehydration. *Am J Vet Res* **69**:1506–11.

Fielding CL, Magdesian KG, Edman JE. (2011) Determination of body water compartments in neonatal foals by use of indicator dilution techniques and multifrequency bioelectrical impedance analysis. *Am J Vet Res* **72**:1390–6.

Forro M, Cieslar S, Ecker GL, et al. (2000) Total body water and ECFV measured using bioelectrical impedance analysis and indicator dilution in horses. *J Appl Physiol* **89**:663–671.

Jones PA, Tomasic M, Gentry PA. (1997) Oncotic, hemodilutional, and hemostatic effects of isotonic saline and hydroxyethyl starch solutions in clinically normal ponies. *Am J Vet Res* **58**:541–8.

Latman NS, Keith N, Nicholson A, et al. (2011) Bioelectrical impedance analysis determination of water content and distribution in the horse. *Res Vet Sci* **90**:516–20.

Levick JR, Michel CC. (2010) Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res* **87**:198–210.

Magdesian KG, Fielding CL, Madigan JE. (2004) Measurement of plasma colloid osmotic pressure in neonatal foals under intensive care: comparison of direct and indirect methods and the association of COP with selected clinical and clinicopathologic variables. *J Vet Emerg Crit Care* **14**:108–14.

Marcilese NA, Valsecchi RM, Figueras HD, et al. (1964) Normal blood volumes in the horse. *Am J Physiol* **207**:223–7.

Pritchard JC, Barr AR, Whay HR. (2006) Validity of a behavioural measure of heat stress and a skin tent test for dehydration in working horses and donkeys. *Equine Vet J* **38**:433–8.

Reed RK, Rubin K. (2010) Transcapillary exchange: role and importance of the interstitial fluid pressure and the extracellular matrix. *Cardiovasc Res* **87**:211–17.

Runk DT, Madigan JE, Rahal CJ, et al. (2000) Measurement of plasma colloid osmotic pressure in normal thoroughbred neonatal foals. *J Vet Intern Med* **14**:475–8.

Spensley MS, Carlson GP, Harrold D. (1987) Plasma, red blood cell, total blood, and extracellular fluid volumes in healthy horse foals during growth. *Am J Vet Res* **48**:1703–7.

Wellman ML, DiBartola SP, Kohn CW. (2012) Applied physiology of body fluid in dogs and cats. In: DiBartola SP (ed.) *Fluid, Electrolyte, and Acid–Base Disorders in Small Animal Practice*. St Louis, MO: Saunders, pp. 2–25.

Wiig H, Rubin K, Reed RK. (2003) New and active role of the interstitium in control of interstitial fluid pressure: potential therapeutic consequences. *Acta Anaesthesiol Scand* **47**:111–21.

Zdolsek J, Li Y, Hahn RG. Detection of dehydration by using volume kinetics. *Anesth Analg* 2012;**115**:814–22.