Fluid therapies in Large Animals. Where we came from, where we are going. Breaking old habits.

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Total Body Water

- The total volume of water within an animal.
- Estimated to be 60 – 70% of body weight. So, 300 – 350 Liters in a 500 kg animal. 2/3 of body weight is average estimate.
- Total body water is distributed into two pools – the ICF (intracellular fluid volume within cells) and the extracellular fluid volume (ECF) which is all body water not within cells. These pools are dynamic in continual flux between each other and are not anatomically defined. Sampling and treatment is targeted at the ECF pool.
- Acute changes in body weight typically parallel losses in total body water. Weighing patients several times daily (on accurate scale...!) can give good information on body water gains and losses.

ICF (intracellular fluid volume)

- The volume of body fluid contained within cells of the body
- Typically about 40% (35 46%) of horses body weight or approximately 2/3 of the total body water. So, a 500kg horse would have about 220 L of ICF fluid volume.
- Fluid in the ICF space keeps cellular integrity intact for metabolic and oxidative reactions and may shift out of cells to bolster the ECF until organ failure ensues.
- Monitoring of this fluid compartment is not clinically practical and therapy to hydrate this space is mediated through the ECF manipulation

ECF (extracellular fluid volume/space)

- The clinically important, sampled and manipulated fluid volume/space
- This space includes the plasma volume (6% b.w. adults and 8-9% b.w. in neonates), interstitial fluid volume, plus all the “transcellular” compartments i.e. GI contents, synovial contents, urinary filtrate, peritoneal/thoracic fluids, CSF fluid, etc.
- Volume in this space is approximately 1/3 of the total body water (about 120 - 150 liters for a 500kg horse); about 25 – 29% body weight of the animal (adults) but makes up more like 40% body weight of neonates due to their relative increased ratio of TBW to tissue weight
- This volume is used to calculate dosages of many medications and this space is the pool from which fluid losses originate in electrolyte rich losses like diarrhea. This is the space intravenous fluids are administered into and are distributed throughout so is used for calculating replacement deficits

Neonatal Specifics

- As mentioned prior, neonates have increased ratio of TBW (and hence ECF volume) as compared to adults. Likely a function of bone, muscle mass, etc.
- ICF to ECF ratio of newborns is 1:1 whereas it is more like 2:1 as adults (20+ weeks)
- Plasma volume is 1/3 larger for weight than adults (9% vs 6% in adults)
- Again, this influences the volume of distribution for common medications (i.e. gentamicin, ceftiofur, etc.)

Dehydration

Defined as a loss/decrease in total body water such that it results in derangements in metabolic processes.

If not corrected by fluid shifts from ECF > ICF or ICF > ECF then hypovolemia leading to perfusion deficits can also occur which is a separate condition related to but is not identical to simple dehydration

Ways to clinically assess dehydration aka “hydration status” include measuring the PCV, TP (esp. albumin), electrolyte meq/L, specific gravity of urine (assuming normal renal function), skin tent/turgor, measuring serum osmolality (> 295 mOsm/L), sunken eyes, jugular fill, HR, Cr/BUN serum levels

Perfusion Deficits (likely due to uncompensated hypovolemia)

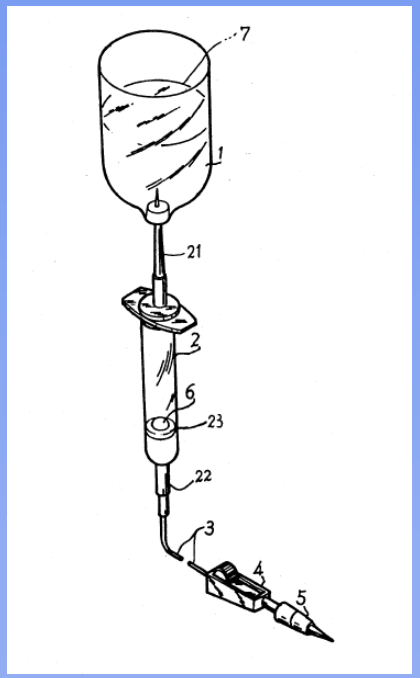
Defined as an actual or functional loss of intravascular fluid volume that lowers blood flow/pressure to tissues resulting in organ dysfunction due to O2 debt and/or metabolic failure

Often a result of moderate to severe dehydration causing subsequent hypovolemia that is uncorrected. Linked to dehydration

Clinically assessed by mucous membrane color/tackiness, CRT, HR, pulse pressure, pulse quality and urine production. Seen on Chemistry analysis as organ dysfunction

History of fluid therapy:

- Rumored that in 1492 Pope Innocent the VIII was failing and blood from a donor was given to the Pope in an attempt to save the Pope.
- 1656 Sir Christopher Wren and Robert Boyle injected wine and ale IV into a dog resulting in a drunk dog. “I have injected Wine and ale in a liveing dog into the Mass of Blood by a Veine, in good Quantities, till I have made him extremely drunk but soon after he Pisseth it out” Dog lived, was stolen from his owner…
- 1831 Thomas Latta studied IV therapies for cholera (Vibrio cholerae). CTX/CT > cAMP > increased H2O, Na, K, HCO3-, and Cl secretion into intestinal lumen.
- 1910 John Murphy developed the Murphy Drip apparatus for the administration of intrarectal fluid administration.
- 1950s IV fluid therapy became more utilized albeit catheters, etc were not commercially available and could be problematic. Some practitioners still don’t trust catheters – maybe with good reason.
- Today, many options for fluid types, methods of administration and composition are available.



Fluid Therapy Overview

Previously, fluids considered a type of “supportive” measure instead of an actual “drug” or “medication”.
Prescribing fluids involves proper choice of route, fluid type and dose.

Concept in the realm of equine medicine or surgery of, if were not sure to do, “give some fluids”... comes back to the old saying when training critical care /ER residents “Don’t just do something, stand there” Sometimes, being accurate is more important than being fast. Remember Wyatt Earp? (“Speed is impressive, but accuracy is final”

Current thinking supports considering fluid therapy (especially IV fluid therapy) as a medication that should be dispensed according to the four D’s – from human literature

- Drug (specific for the disease identified)
- Dose (amount and method administered)
- Duration (how long to be given)
- De-escalation (when and how to discontinue the treatment)

Drug (i.e. fluid type)

Fluid type:

- crystalloid or colloid or mixed
- hypotonic, isotonic, hypertonic or mixed

Fluid composition:

- acidifying, alkalinizing, neutral or mixed
- electrolyte content
- energy content, hormonal manipulation, inflammatory mediation
- cellular or physiologic support (i.e. coagulation, rbcs, gfr, etc.)

Dose

Fluid amount:

- volume administered to achieve desired positive result without negative clinical effects and subsequent increases in patient morbidity

Fluid Administration method:

- Intra-rectal, Intra-gastric (enteral), or Intra-venous (parenteral) in equine
- route chosed is dictated by many influences: disease, cost, availability, practicality, expertise, even patient/owner complicity

Duration

How long to leave therapy ongoing, at which rate, which modality

De-escalation

Decreasing modalities, therapy and/or modifying plan to discontinue all or a portion of the treatment

Dose

Adult horses:

Clinical approach seems to have changed over time...

Judging degree of dehydration based on skin turgor, capillary refill, etc not as reliable as once thought. Current rapid replacement therapy based more on response to bolus replacement crystalloids. Bolus 10 - 20 liters (20 - 40 ml/kg), re-assess lab data and clinical parameters (urine, pcv, tp, etc). Repeat in 10 liter bolus increments until clinically re-hydrated.

Maintenance fluid rate is dependent on whether horse is eating (has gut fill) or is not eating (20+% of ECF is in equine GI lumen). Rates of 2 – 3 ml/kg/hr would be appropriate for horses on feed, rates of 1 – 1.5 ml/kg/hr more appropriate for horses off feed or have no GI fill.

Drug/Dose - Neonate

Fluids:

-Milk has approximately 20 mEq Na and 70 mEq K/L so mare's enteral fluids for neonates are hypotonic. Ingestion of 15-30% bw so hyposthenuric.

- Replacement fluids in neonates are isotonic and if bolus administered, given at 20 ml/kg then reassessed. Often contain glucose due to illness and limited energy stores.

- Maintenance fluid rates are higher than adults and typically are 3 -3.5 ml/kg/hr due to foal's higher total body water, increased metabolic rate, growth and higher surface area to body mass area = increased insensible losses of water. Maintenance can be isotonic but hypotonic may be better in some cases due to electrolyte elevations.

Fluid Administration

Intra-rectal: an area of renewed interest – thought to be at least as effective as the IV route to correct dehydration.

- Has been around a long time (Murphy), paper from 1979 showed that furosamide induced dehydrated horses could be rehydrated with 44 L saline.
- 2018 paper showed naturally dehydrated horses could be rehydrated effectively with 5 L rectal boluses of homemade electrolyte solution. (Astelean P, et al Bull UASVM Vet Med 75:73-7
- 2019 paper found horses tolerated tap water better than isotonic polyionic fluid for rehydration and horses tolerated 5 ml/kg/hr (2X maintenance) continuous gravity flow for 6h (Khan, EVJ 51:767-73).

* Small 24 fr, red rubber, soft enema tube or non cuffed foley catheter placed 10 – 15 cm into rectum and fixed with one suture at edge of anus tolerated. Connected to gravity fluid source at rate

Fluid Administration

Intra-gastric:

- If prodimal GI tract is progressively functional, superior to IV route to increase fecal H_2O content

-reportedly, water emptying from stomach occurs within 15 – 30 min (may be slower if off feed (CO)

- electrolytes or plain water are OK for rehydration however, some electrolyte formulations may cause gastric irritation/colic and adding glucose (Na transport) to replacement is not recommended (vs calves) due to solvent drag into gut and acid/base + electrolyte derangements have been documented with added glucose in horses (Ecke 1998 Vet J). Polymer additives (starches) – buffers?

- Max volume to give IG is 15 – 18L (1000# horse) but must be given slowly, over 15 min. Frequently, use of 8 – 10L q2h is used without issue in adult horses.
- Continuous infusion thru a small indwelling NG feeding tube (20 fr) at 1 – 2L/hr can be utilized as maintenance and for rehydration – not resuscitation

Enteral and Rectal fluids

Formula for enteral and intra rectal electrolytes:

- 5.27 Gm table salt (~1 tsp NaCl), 0.37 Gm lite salt (~1/16 tsp KCl) and 3.78 Gm baking soda ~ 2/3 tsp ($NaHCO_3^-$) in 1 Liter water. Limited data may suggest isotonic fluids better than plain water for right dorsal colon impaction but fluids are definitely absorbed in dehydrated animals and enteral fluids are superior for increasing intestinal water content vs IV.
- Despite this evidence, there is yet a tendency to jump to IV fluid therapy both in human and equine practice based on perceived more rapid response, expectations of clients/patients, and referring veterinarians.
- Bolus volumes as high as 8 – 10L/2hr (Lester used 20 L/q/6hr?) several hrs given via stomach tube (2 - 4L q2-4hr me) and <5L intrarectally tolerated. Continuous intra-rectal or IG rate of 5ml/kg/hr fine.

Crystalloids vs Colloids?

- Traditionally, crystalloid type fluids were considered best to treat dehydration whereas colloidal fluids were used to address perfusion abnormalities
- Not the case any more. There is marked overlap between both of their utilities with discrepancies in the literature as to the advantages of colloids vs crystalloids
- Crystalloids can be utilized to treat both dehydration and perfusion deficits but colloids are not typically used alone to correct dehydration (there are exceptions), only specific perfusion deficits

Crystalloids

Three distinct characterizations:

1. Hypotonic – final electrolyte composition is such that the fluid is hyposmolar compared to plasma (< 270mOsm/Kg adults and < 245 mOsm/kg foals)

2. Hypertonic – fluid composition is greater than 290 mOsm/kg in adults and > 267 mOsm/kg in foals.

3. Isotonic – Fluid composition falls into normal osmolality of plasma (270 – 290 mOsm/kg adults and 245 – 267 mOsm/kg foals)

* Some fluids are termed “isotonic” in bag but functionally hypotonic or hypertonic in vivo (ex. D5W, .45% saline/2.5% dextrose, 0.9% saline, etc.)

Osmolality (vs osmolarity)

Osmolality refers to the amount (1 mole dissolved = 1 osmole) of a fully disassociated element in water. It is expressed as “milli”osmoles/kg (mOsm/kg) 1/1000th of an osmole, in body fluids, due to the dilute nature of these fluids.

*remember a “mole” is a quantity or amount of an element containing Avogadro’s number (6.02 x 10^{23}) of particles i.e. atoms, molecules or ions) using 12 grams of C^{12} to be one mole of carbon. **One mole = molecular weight in grams.**

Osmolarity is nearly the same as osmolality but is by volume (mOsm/L) which can theoretically change with temperature so we use osmolality

Osmolality

Osmolality is what drives fluid shifts between the intracellular (ICF) and extracellular fluid (ECF) spaces. The number of element particles and not their size creates the osmolar effects. In plasma, mainly determined by Na, glucose, urea and sodium"s counter ions which are all termed "effective osmoles". These make up about 95% of osmolar drive in plasma. Albumin makes up ~ 70% of plasma oncotic pressure which pulls fluid into the vascular space esp. with [c] differences across semi-permeable membranes.

"Tonicity" (hypotonic, isotonic, and hypertonic) implies the effective osmolality of a solution. If a solution's osmolality is in the same range as normal plasma then it is considered "isotonic". * <u>This concept is the crux for determining fluid selected...</u>

Calculated tonicity calculated by the formula " 2[NA] + glucose/18 + urea/2.8" is 290 – 300 mOsm/kg for adult horses and 260 - 280 mOsm/kg for neonatal foals. However, the freezing point measured osmolality of plasma may be higher due to unidentified osmolar molecules. The difference is called the "osmolar gap". The *Anion gap different and* is "Na – Cl – HCO_3^-"

Tonicity (osmolality) of fluid administered determines therapeutic effect

- All fluids administered will distribute to one or both of the spaces (ICF and ECF)
- All fluids lost come from the ICF, ECF, or both volume/spaces
- **Hypotonic** fluids generally will distribute more to the **ICF >** ECF due to the movement of free water into cells not retained in ECF by low osmolality. Water, D5W, .45% saline/D2.5W, maintenance fluids go mainly into cells.
    - Can be beneficial if animal has lost ICF volume as well as ECF volume but may cause cellular swelling and be detrimental if it drives edema and organ dysfunction
- **Hypertonic** fluids distribute and remain mainly within the **ECF >** ICF space and can actually shift ICF fluid from cells into ECF.
- Targeting the space/compartment that has been compromised with the appropriate osmolar fluid will cause success or failure to correct deficits

Fluid Chemistry

- Review of the terms written on fluid bags and bottles… really?
- **Mole** – a chemistry amount or measurement like a “teaspoon” but for elements. One mole of an element or molecule (C, Ca, Mg, K, HCO_3^-, etc.) contains the atomic molar mass of that element in grams (is based on the number of atoms/particles in 12 grams of C-12)which is Avogadro”s number 6.022 x 10^{23}).
- A millimole is then 1/1000 of a mole which means 1 millimole (mmol) of an element contains the atomic molar mass in mg.
- So, 1 mmol of Ca (has a molar mass of 40) is 40 mg, 1 mmol of K is 39 mg, 1 mmol of Na 23 mg and so on…
- **Osmole** – is 1 mole of any fully dissociated substance dissolved in water. It is used for fluid concentration vs solids. Takes into account the disassociated ions ie. 1 mole NaCl becomes 1 mole of Na and 1 mole of Cl in water.
- In plasma, [c] of elements (or electrolytes) is low, so it is described in milliosmoles (mOsm) or 1/1000 of an osmole

Fluid Chemistry

Milliequivalent (mEq) – unit of measure for *electro*lytes.

- **It represents binding power or chemical activity of any given element compared to 1 mg of H+.**
- **So, 1 mEq of an element is equal to is millimolar weight x its valence electrons for binding. 1 mEq of H is 1 mg (its molar mass), 1 mEq Na is 23mg (its molar mass) and 1 mEq Ca is 40 mg, and so on…**
- **For monovalent ions, (Na, K, Cl, etc) the mEq will be the same as the mmol value due to just one binding site (charge) on that electrolyte (1 mEq = 1 mmol) but, for bivalent cations, etc, like Ca, Mg, etc there are two charges on each atom so each 1 mmol is 2 mEq.**

*** Many electrolytes are expressed on bottles of electrolyte additives as mEq/ml or mmol/ml which is a much easier method to calculate dosing vs mg, etc.**

SID

H^+	HCO_3^- 24 mmol/L
K 4 mEq/L	
	Proteins
Na 140 mEq/L	Cl 104 mEq/L

- Na + K – (Cl + lactate) = SID not counting in +/- Ca, Mg, and anions that don't contribute substantially given their low [c] or of a crystalloid fluid (SID_{IF})
- SID of plasma then should be ~40
- Anything less than 40 would cause an acidosis, anything below 40 an alkalosis
- This is conceptually only, as there are unidentified or measured strong anions and cations i.e. lactate, ketoacids, etc

Normal gamblegram

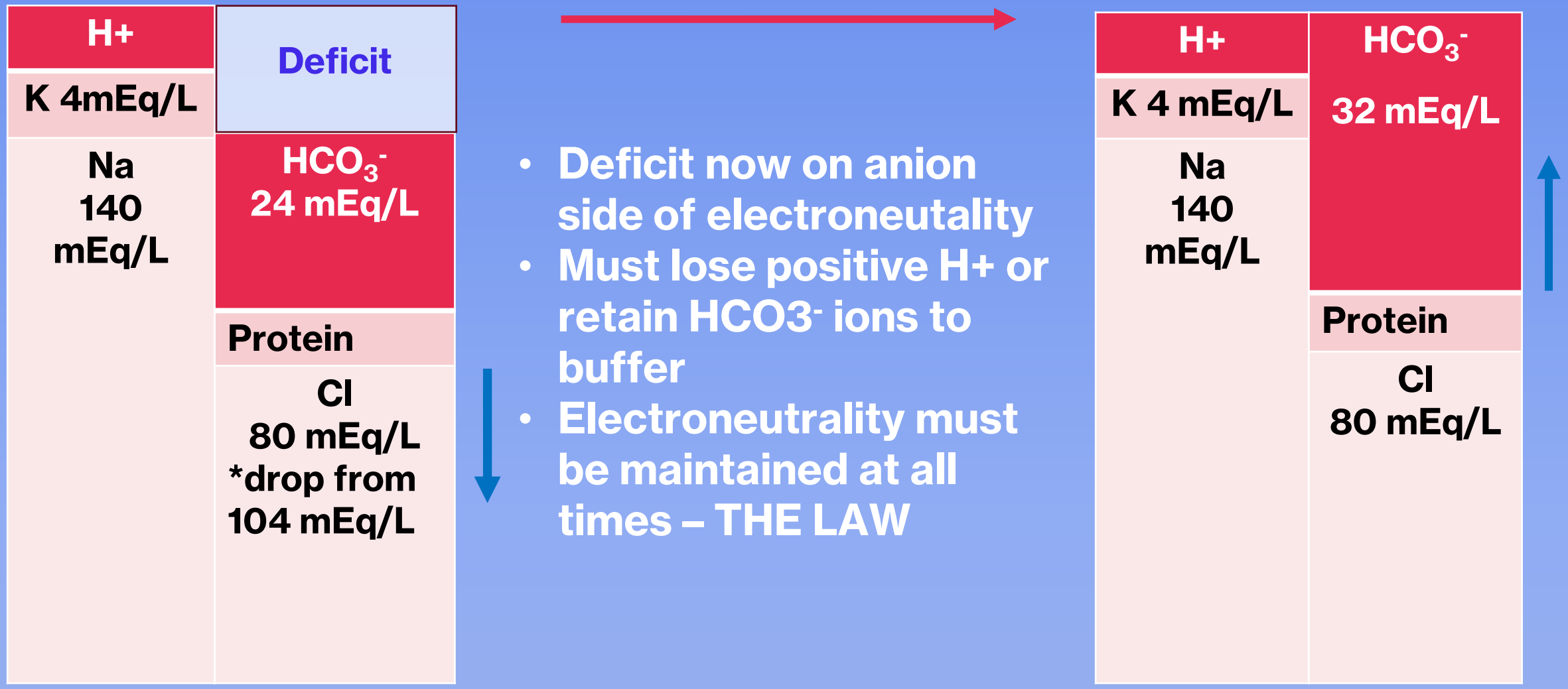
SID (acidosis)

Deficit of cations	HCO_3^- 24 mmol/L
H^+	
K 4 mEq/L	Protein
Na 140 mEq/L	Cl 118 mEq/L * Rise of 16 mEq/l\L

- Theoretically, if the choride rises then, either the Na and K must drop to accommodate the electrical neutrality or… the HCO3- must drop, or…. The H+ must rise to accommodate the “deficit”
- Na and K are hormonally controlled, the protein is ?static, so.. The HCO3- will drop and/or the H+ will rise to achieve chemical neutrality
- The SID would then be 140 Na + 4 K – 118 Cl = 24 = acidosis

H^+	HCO3- 15 mmol/L
K 4mEq/L	Protein
Na 140 MEq/L	Cl 118 mEq/L

SID – (alkalosis)



- Deficit now on anion side of electroneutality
- Must lose positive H+ or retain HCO3- ions to buffer
- Electroneutrality must be maintained at all times – THE LAW

Crystalloids

Two main categories of crystalloid solutions based on their tonicity:

1. **Replacemant**: Can be used to replace fluid deficits rapidly due to isotonic or near isotonic osmolality. Sodium content will closely resemble plasma osmolality (~ 140 mEq/L). Examples are LRS, Plasma-Lytes, Normosol, even isotonic bicarbonate and NaCl 0.0%. These tend to remain within the ECF fluid space. ~ 3:1 distribution.

2. **Maintenance**: Cannot be bolused due to its low sodium content and subsequent hypotonic osmolality. Typically about 25 – 30% of the tonicity of isotonic fluids (i.e. Na 40 mEq/L) Examples would include NaCl of .2%, .3%, .45%, D5W, or Plasmalyte 56 Normosol M w/5% dextrose +/- “poor mans” maintainance. These tend to gravitate to the ICF space > ECF space.

Crystalloids

Maintenance Fluids:

- Not many commercially available for use in equine, mainly come in 500 ml and 1000 ml bags
- Should not be given rapidly, as bolus, due to hypotonic hemolysis potential as well as overexpansion of the ICF (edema) and cell dysfunction (brain, lung,...)
- Normosol M + 5% dextrose (ICU Medical) contains (Na 40 mEq/L, K 13 mEq/L, Mg 3 mEq/L, Cl 40mEq/L, acetate (HCO_3^-) 16 mEq/L, 363 mOsm/L (hypertonic in bag but...)
- Plasmalyte 56 + dextrose 5% (Baxter) exactly like Normosol M
- “Poor man’s maintenance” is typically 1 liter 0.9% NaCl with added 20 mEq/L KCl, +/- Mg, +/- Ca hung with two 1 liter bags of sterile water so they run in at ***maintenance rate only*** (~2 ml/kg/hr)

Crystalloids

0.9% “normal” saline:

- **Has equal amounts of Sodium (154mEq/L) and Chloride (154mEq/L)**
- **Is slightly hypertonic 308 mEq/L (154 Na + 154 Cl) compared to equine plasma (280 – 300mEq/L) so will have mild dehydrating effect on cells (ICF) unless horse is allowed to drink free water**
- **Has a strong ion difference of ZERO (Na + K + Ca + Mg – Cl – lactate)**
- **Normal apparent strong ion difference should be about 40 …. remember the SID concept?**
- **Based on the SID_{IF} of zero, it will have an *acidifying* effect on the plasma pH. pH of solution in bag 5.5**

Crystalloids

LRS (lactated ringer's solution)

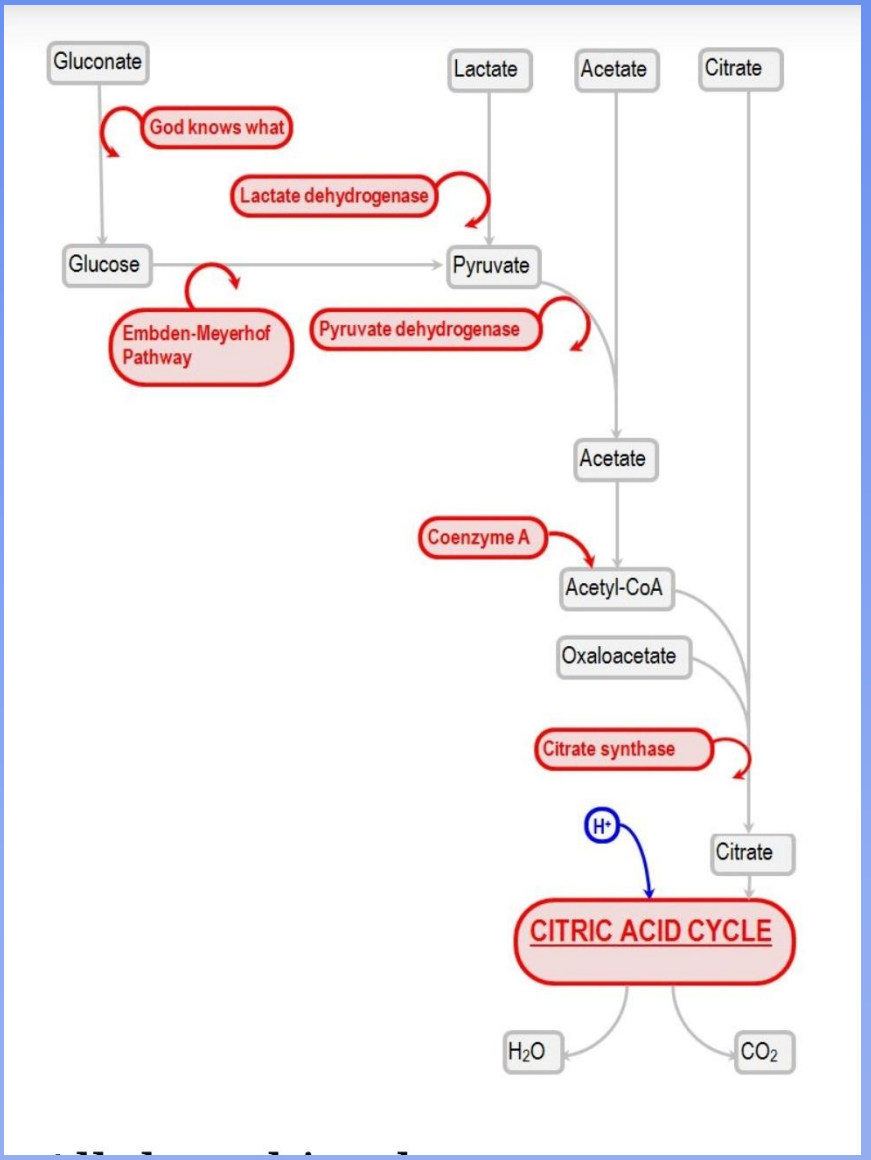
- Developed in the laboratory of Sydney Ringer (Ringer's solution) in the 1880s developing a solution to prolong frog heart beating outside the body... contains sodium chloride, potassium chloride and calcium chloride in water.
- In the 1930s, Dr Alexis Hartmann added lactate as a buffer to the mixture creating 'lactated' Ringers also known as Hartmann's solution.
- LRS is isotonic (272 mEq/L) to slightly hypotonic but has a trend to hyperchloremia (109 mEQ/L) and is *mildly acidifying* due to its SID of 28 (Na 130 + K 4 + Ca 3 – Cl 109) * anything less than 40 will be acidifying, over 40 alkalinizing – remember? pH of solution in bag 6.5

“Bicarbonate precursor”

- Used to loosely describe anion substitute molecules (i.e. for chloride) put into crystalloid solutions to balance electoneutrality so the solutions are more like the plasma electrolyte composition
- Naturally, organic anions and negative charges on proteins (albumin/globulin) allows the chloride to be 40 mEq lower than the Na and K levels
- By adding sodium salts of lactate, acetate, gluconate, citrate, etc to the crystalloid fluid, manufacturers can make the fluid more like ECF fluid with Na levels high enough to remain in the ECF when given (alkalinizing?)
- Bicarbonate would have to be in glass as it will dissasotiate into CO_2 in the bag and accumulate as gas + lowering the pH, organic anions don’t do this

Bicarbonate precursor fates

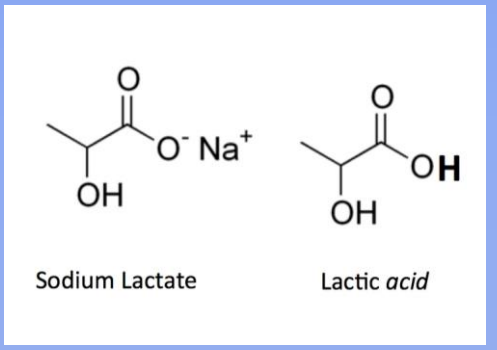
- The fate of bicarbonate precursors is different for each anionic Na salt
- Acetate – metabolized in most all tissues (may be best choice)
- Lactate – 70% of it metabolism requires a functional liver
- Gluconate – not metabolized directly by cells, ~ 80 – 90 % is excreted by kidney unchanged, the remainder likely gets converted to glucose and into energy stores.
- Once sissasociated from Na, the “precursor” is removed from plasma leaving the Na to create a wider SID and thus an alkalosis – remember?



Lactated Ringers Solution

- LRS contains 28 mEq of Na-Lactate, not lactic acid
- Modern formulations contain non-racemic L- Lactate
- D-Lactate is not metabolized and may be toxic to lung, heart and liver cells, likely must be 100x raise (13x)
- Ideally, modern LRS should be L-lactate non-racemic
- Benefits of lactate in LRS:
  - Can act as buffer to accept H^+ ion
  - Can be metabolized back into pyruvate (LDH) for cellular respiration >> CO2 + H2O>> H2CO3>> HCO3- so is considered a “bicarbonate precursor”

Lactate is metabolized mainly by liver (70 %) but can be utilized by many cells throughout the body



LRS

- Electrolyte composition has NA 130, K 4, Ca 3, Cl 109 and lactate 28 mEq/L- 272 mOsm/KG, calories 9 (from lactate metabolism) * no Mg in LRS
- Highly utilized replacement fluid that is not ideal but is preferred still today for resuscitation at many hospitals.
- Due to the calcium in LRS, it should not be administered concurrently with $HCO3^-$, or $MgSO_4$ added to the bag due to precipitation of salts within the solution. CaCO3 = "limestone" and CaSO4 = "gypsum" aka drywall! Plasma and blood infusion should not be thru same line due to citrate
- Is slightly acidifying (SID ~ 28) and slightly hyponatremic, hyperchloremic as compared to plasma
- Lactate cleared poorly in dogs with lymphosarcoma, horses??
- **NOT** contraindicated in lactic acidosis from hypoperfusion or endotoxemia (Na-lac) unless blood lactate is > 9 mmol/L or liver failure
- Fluid of choice for botulism cases due to lack of Mg and subsequent potentiation of neuromuscular blocking
- Perhaps should be avoided in toxicity from cardiac glycoside poisonings (oleander, thevetia, bufo marinus, etc) and CNS injury (trauma, NMS) where Ca may contribute to increased pathology

Hartmann's Solution

- Very similar to LRS with exception of very minor variations of electrolytes i.e. Na 131, K 5, Chloride 111, and lactate 129 mEq/L (LRS has Na 130, K 4, Cl 109, Ca 2.7 and lactate 128 mEq/L)
- Available in 5 L bags
- Care should be taken if treating HYPP horses given the K in solution
- Is an excellent cardiopulmonary resuscitation fluid for rapid volume expansion in hypovolemic shock

Plasma-Lytes 148 and A + Normosol- R

- All are identical in their electrolyte composition and all are most like plasma values of equids (NA 140, K 5, Cl 98, Mg 3 mEq/L)
- All have 27 mEq/L of acetate and 23 mEq/L of gluconate as anion substitute molecules to accommodate the physiologic chloride level once metabolized
- The only differences between the three is the manufacturer and the pH of each solution in the bag
  - Plasma-Lyte 148 has a pH of 5.5 (148 = the cations in the bag…)
  - Plasma-Lyte A has a pH of 7.4 (physiologic – endothelium?)
  - Normosol-R has a pH of 6.6

  These have no Ca so can be administered with blood/plasma and HCO_3^- and are alkalinizing due to SID_{IF} of 140 + 5 + 3 – 98 = 50 so are ideal for animals with metabolic acidosis

  Acetate and gluconate's fates as bicarbonate precursors …..

Crystalloids - replacement

Plasmalyte A, Plasmalyte 148, Normosol – R, Vetivex Phylyte (same composition as Plasmalyte A):

- All three are identical with respect to electrolyte mEq/L composition (140 NA, 5 K, 98 Cl, 3 Mg, 27 acetate, and 23 gluconate.
- All three have osmolality of 295 mOsm/kg
- Only difference is the pH of the solution in bag
  Plasmalyte A is pH 7.4
  Plasmalyte 148 is pH 5.5
  Normosol R is pH 6.6

  There is no calcium in any of these fluids so can be given with blood products and bicarbonate containing fluids. Supplies 1/3 of the Mg needed for daily needs if given at maintainance

  The most physiologic of the common replacement fluids, Plasmalyte A may be least thrombogenic? due to physiologic pH in catheter?

Colloids

- Exert colloid osmotic pressure and “pull” fluid into the vascular space as long as they cannot leave the plasma space through diseased vascular walls, etc.
- Fluids with a COP less than plasma aren’t held within the plasma space and move into the interstitium whereas fluids with COP equal to or greater than the plasma COP will typically remain within the plasma space and increase the COP further.
- Colloids can be protein in nature or sugar in nature (starches) that are large molecules which exert oncotic pressure effects and are less likely to leave the plasma space through normal cellular “leaks”

Colloids

- Used for two main clinical applications:
  1. Hypoproteinemic (protein losing diseases) states that are or are likely to develop edema with or without crystalloid therapy. Goal is to expand the plasma volume without extravasation. The lower the molecular weight, the greater the volume expansion. The route of excretion determines the half life within the plasma space. Data shows use in burn victims may be superior to crystalloids at 8 – 12h post-injury. Cr, BUN, & inc airway pressures lower than LRS treated patients.
  2. Low perfusion states in need of rapid intravascular volume expansion i.e. shock

  * Side effects of colloid administration often carry more risk of side effects than crystalloid choices due to allergic, accumulation of the colloid molecules outside the vascular space in tissues, coagulation inhibition (bleeding) and renal insult (colloid nephropathy)

Colloids

- Colloids are typically natural (plasma, whole blood or concentrated albumin) or synthetic (gelatin, dextran, starches or ? hypertonic saline)
- Albumin and gelatin products are at physiologic pH whereas dextran and starches are acidifying
- [Na] is low in albumin products but similar to isotonic crystalloid solutions in dextrans, gelatins and starches

Colloids

Gelatins:

- not used much any more, originally 100 kdaltons now modified to about 12,000 kd. Can be high in Ca and K so care must be taken if administered with anticoagulants i.e. blood transfusions.
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- Gelofusion®, Plasmagel®, Plasmion® examples of succinylated gelatins
- Polygeline®, Hemaceal® (Hoechst) are urea crosslinked gelatins
- Gelifundol® is an oxypolygelatin

Colloids

Dextrans:

- branched polysaccharides produced by ***Leuconostoc mesenteroids*** bacteria (family Lactobacilli) from sucrose
- not used much if any in veterinary medicine and rarely in humans (bypass) patients, greatly reduce blood viscosity
- excreted by kidneys
- supplied as 6 % high molecular weight dextran (avg molecular wt of 70 kd) and 10 % low molecular wt dextran (avg molecular wt of 40 kd)
- side effects include inhibition of platelets, factor VIII, increased fibrinolysis all of which lead to bleeding abnormalities as well as renal injury. Coat RBCs preventing cross matching.

Colloids

Hydroxyethylstarches (HES):

- highly branched derivatives of amylopectin, starch with structure very close to glycogen
  - first was Hespan® in 1970s
  -labeled as concentration %, avg molecular weight, and the C2 to C6 substitution ratio i.e. 10HES200/0.5 would be 10% hetastarch with 200 kd avg molecular size and the ratio of hydroxyl groups on C2 of the glucose molecules in the starch. Hydroxyl groups on C2 inhibit α amylase in plasma and therefore hydrolysis rate
- these and plasma (fresh frozen) are most used in veterinary medicine
- removed from plasma by renal excretion (70%) and re-distribution (30%)

Colloids

HES:

- In US, hetastarch (0.7 substitution ratio) has a COP of 30, pentastarch (0.5 substitution ratio) with a COP of 40 , and tetrastarch (0.4 sr) with a COP of 36.
- Hetastarch (Hespan®, Hextend®, etc)has 7 hydroxyethyl groups per glucose molecule, tetrastarch 4 HEG/glucose molecule (Volvulen®, VetStarch®) and pentastarch (Pentaspan®) has 5 HEG groups/glucose molecule.
- Human doses are in magnitude of 20 – 50 ml/kg whereas equine (veterinary) doses are much lower 10 – 20 ml/kg. Rare to see any reaction in horses with 10 or 20 ml/kg q 48 hours for two treatments.
- Due to larger molecular weight, HES tends to remain mainly in the IVS until hydrolysis degrades them to < 50 kd where they are excreted by the kidney

Colloids

Albumin (concentrated):

- A 69 kd molecule (small)
- 5 % albumin in 0.9 % saline and fresh frozen plasma are most common colloids utilized in human medicine
- 5 % albumin isotonic elicits 80 % volume expansion whereas 25 % hypertonic solution elicits 200 – 400 % volume expansion in 30 min., duration of effect is 16 – 24 hours
- 5 % elicits similar volume expansion as does Hetastarch
- Negative charged protein that influences acid/base status and anion gap as well as binding plasma sites for cations and some medications
- Expensive, not practical for equine patients

Colloids

Albumin:

- Provides 70% of plasma's oncotic pressure, the other
- 30 % is from the globulin fraction of plasma protein.
- Distributes into the interstitial space as well as IVS where it provides COP. Only 33 % of albumin in contained within the IVS, 66 % resides within the interstitial space where it can act as a reserve "pool" to replenish the plasma albumin if needed.
- Each Gram of albumin can retain 18 ml H_20 within the vascular space. Is physiologic and can expand the plasma volume but is expensive, is small molecule and "leaks" more easily through vascular endothelium with inflammation, and redistributes rapidly out of the IVS. Is associated with renal injury in some cases (colloid nephropathy)
- A drop in this interstitial COP is a large drive for hepatic albumin synthesis so administration of colloids may decrease actual synthesis.

Colloids

Albumin (plasma)

- Equine donor plasma typically contains an average of 30 grams albumin/L
- Administration of 10 – 15 ml of plasma/kg body weight raises the plasma albumin approximately 0.1 gram/dl (1 gram/liter)
- 8 Liters plasma would expand the plasma volume by 4 Liters, so less than synthetic HES.
- Expensive to increase oncotic pressure with plasma and not overly efficient. Using a mixture of plasma and HES may be optimal?
- To bring a 500 kg horses' plasma albumin up from an initial 2.0 g/dl to 3.0 g/dl, would take 10+ liters of plasma at 300 – 400$/liter. Considering ongoing losses, and redistribution, the effect is short.
- Plasma has other components however, that may be beneficial.

Colloids

Hypertonic Saline:

- A crystalloid with colloidal properties due to its concentration and marked osmolality (1232 mEq/liter sodium and chloride – 2464 mEQ/L solution.
- 7.2 – 7.5 % increases plasma volume 3X the amount given by pulling fluid from the interstitial space into the IVS.
- Effect peaks 20 minutes post-infusion and decreases rapidly as the sodium and chloride + fluid is redistributed back into the interstitial space and filtered through kidney. Must follow with 10 – 20 L isotonic...
- Benefits include hemodynamic increases in cardiac output, increased perfusion, and possible down regulation pf adhesin molecules on neutrophils that modulate extravasation in MODS/SIRS (bovine mastitis)
- Given at 3 – 6 ml/kg bw, should not exceed 1/ml/kg/min rate due to induction of hypotension/collapse. Avoid if dehydrated, oliguric/anuric or hypernatremic/chloremic.

Calcium

- Obligatory loss in equine is 1.09 mg/kg/hr.
- Requirement of ~1 mEq/kg/day. Conveniently, 23% Calcium gluconate is one mEq/ml (20 mg/ml) elemental calcium so one ml per kg per day should supply maintenance needs.

Electrolytes

- When deciphering how much of an electrolyte or element to administer to a patient, the dosage must considered in "elemental" format
- Elemental % of an additive defines how much of the element i.e. Ca, Mg, etc that is available to be incorporated into metabolic reactions (free to react)
- Example:

  Calcium borogluconate 23% would imply that 23% translates into 230 mg/ml which is accurate but – only 9.3% of Calborogluconate is elemental Ca which means that each ml of 23% Calgluc only has ~ 21 mg of elemental Ca/ml. 1 mEq of Ca is 20 mg so it is also 1mEq/ml.
  Mg is similar, only 9.86% elemental Mg in 50% $MgSO_4$, so 50% $MgSO_4$ is only 49.3 mg/ml elemental Mg (4 mEq/ml as Mg is 12.1 mg/mEq) – will explain this later... and the list goes on

Acid/Base

- 1831 O'Shaughnessy described that HCO_3^- losses in the blood of Cholera patients in London was responsible for their death
- Thomas Latta furthered O'Shaughnessy's work by treating Cholera patients with HCO_3^- IV improving their survival
- 1907 thereafter, Henderson first coined the term "acid/base"
- Venous pH reflects the metabolism of the tissues drained by the vein sampled whereas arterial pH reflects respiratory compensation
- Acidemia means literally an acid measured blood, alkalemia means an elevated pH of blood
- Acidosis means a condition causing an acidemia whereas, alkalosis refer to a condition causing alkalemia.
- Metabolic or respiratory conditions are the classifications for ...osis

Acid/Base

- **Acidosis** : Metabolic or respiratory?
- Respiratory is under achievement of CO_2 elimination. If CO_2 cannot be eliminated and builds up > carbonic acid accumulation (H2CO3) causes acidemia (⬆$PaCO_2$, ? ⬇ or ⬆ HCO_3^-, normal electrolytes, protein, lactate, base buffer)
- Metabolic is ⬇HCO3-, ⬇PaCO2, abnormal electrolytes, protein, base buffer, lactate SID likely abnormally decreased (< 40)
- **Alkalosis**:
- Respiratory is overachievement of CO_2 elimination – hyperventilation and ⬇ PaCO2, ⬆ HCO3-, normal SID, base buffer, lactate
- Metabolic is ⬇ HCO3-, ⬆ PaCO2, abnormal SID, buffer base, lactate

Acid/Base

- Most acid/base conditions will be “mixed” or a combination of respiratory and metabolic anomalies concurrently (one 1° the other 2°)
- Often, there will be a primary condition with a compensatory response albeit likely not corrective (1° condition dictates blood pH)
- Treatment is typically directed at the primary anomaly and the compensatory condition is monitored as improvement is observed
- Many ways to determine whether an acidemia or alkalemia is driven by a condition one way or another i.e acidosis or alkalosis

    * Arterial/venous blood gas (calculates the base excess + or -)
    * SID (gives strong ion data)
    * Lactate measurement
    * Buffer base alterations (proteins albumin and globulin + PO_4, ? SO_4))

Calcium - additives

- Calcium gluconate/borogluconate 23% contains 9.3% elemental calcium (21.6 mg/ml). Borogluconate is preferred to gluconate due to shelf life and bioavailability.
- Calcium gluconate 10% contains 9.3 mg elemental Ca per milliliter.
- Calcium chloride has **three times** the elemental calcium per ml (27.3 %) and is irritating to vascular endothelium but extremely toxic to perivascular tissue if given extravascularly.
- Calcium chloride 10% contains 27.3 mg/ml elemental calcium (27%).
- Norcalciphos, CMPK, etc usually contain 23% calcium gluconate such as to provide 1 mEq/ml elemental calcium

Magnesium

- NRC suggests an oral requirement of 13 – 15 mg/kg/day.
- Bioavailability of oral magnesium is approximately 70%

Magnesium

- Formulations for supplementation intravenous are MgSO4 and MgCl
- MgSO4 50% solution contains 9.8% elemental Mg per milliliter (49 mg/ml)
- $MgCl_2$ 20% solution contains 12% elemental Mg per milliter (24 mg/ml)