Treatment of diarrheic calves

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Clinical evaluation of hydration status and estimating prognosis

The most accurate methods for assessing hydration status are the extent of eyeball recession into the orbit and skin tent duration in the neck region. All other methods of assessment are inferior to these two validated methods. Eye recession is measured by rolling the lower eyelid out to its normal position and measuring the distance between the cornea and lower eyelid. The recommended formula to estimate hydration status is: % dehydration = 1.7 x (eyeball recession in mm). Eyeball recession is less accurate in calves with chronic weight loss than in calves that have been on a reasonable plane of nutrition because chronic weight leads to loss of the periorbital fat and eye recession. Skin tent duration is measured by pinching a fold of skin, rotating it 90 degrees while pulling gently away from the calf, and then releasing. The skin tent should disappear within 2 seconds of release. Measuring eyelid skin tent duration on the upper or lower eyelid is not recommended because skin is this area is poorly elastic.

Profound acidemia impairs cellular and organ function and consequently should be associated with an increased risk of mortality in critically ill humans and animals. Neonatal diarrhea in calves can result in potentially serious metabolic derangements including profound acidemia due to strong ion (metabolic) acidosis, hyper-D-lactatemia, hyper-L-lactatemia, azotemia, hypoglycemia, hyperkalemia and hyponatremia. In a recent retrospective study, we assessed the prognostic relevance of clinical and laboratory findings in 1,400 critically ill neonatal calves with diarrhea admitted to a veterinary teaching hospital. The overall mortality rate was 22%. Classification tree analysis indicated that mortality was associated with clinical signs of neurologic disease, abdominal emergencies, cachexia, orthopedic problems such as septic arthritis, and profound acidemia (jugular venous blood pH < 6.85). When exclusively considering laboratory parameters, classification tree analysis identified plasma glucose concentrations < 3.2 mmol/L, plasma sodium concentrations > 151 mmol/L, serum GGT activity < 31 U/L (indicative of failure of transfer of passive immunity) and a thrombocyte count < 535 G/L as predictors of mortality. However, multivariable logistic regression models based on these laboratory parameters did not have a sufficiently high enough sensitivity (59%) and specificity (79%) to reliably predict treatment outcome. The sensitivity and specificity of jugular venous blood pH <6.85 were 11% and 97%, respectively, for predicting non-survival in this study population. In conclusion, laboratory values (except jugular venous blood pH <6.85) are of limited value for predicting outcome in critically ill neonatal calves with diarrhea. In contrast, the presence of specific clinical abnormalities (neurologic disease, abdominal disease such as distention, cachexia, and orthopedic diseases such as septic arthritis) are indicative of a poorer prognosis.
Clinicopathological changes in calves with diarrhea

Strong ion (metabolic) acidosis is due mainly to hyponatremia, forestomach/intestinal fermentation of lactose and glucose to D-lactate and volatile fatty acids, and intestinal bicarbonate loss. There are minor contributions from lactic acid production in tissues secondary to tissue hypoxia, and decreased acid secretion by poorly perfused kidneys in calves with dehydration. The result of strong ion acidosis is progressive central nervous system depression, decreased suckle reflex, ataxia, recumbency, coma, and then death, particularly when plasma D-lactate concentrations are elevated.

The degree of strong ion acidosis is not highly correlated with the degree of dehydration. In general, strong ion acidosis is more severe in calves >7 days old than calves <7 days old with the same degree of dehydration, and is particularly common in calves aged 14-21 days old. The most likely reason for this effect of age on the severity of acidemia may be that increased D-lactate concentration (a strong anion) becomes much more common as calves become older; this has been attributed to fermentation of ingested milk by Gram-positive bacteria to D-lactate because of decrease lactase activity and damaged intestinal epithelium. The gold standard method for detecting and quantifying strong ion acidosis is blood gas analysis (pH, base deficit). Venous blood should be used for blood gas analysis unless concurrent respiratory disease is suspected.

If access to laboratory equipment is not available, then the degree of strong ion acidosis can be estimated on the basis of clinical signs and age (unfortunately this is often wrong). Base Deficit = 15 to 20 mmol/L for calves >1 week old requiring IV fluids; 10 to 15 mmol/L for calves <1 week old requiring IV fluids. In the absence of laboratory data, the cattle veterinarian should assume that the dumbest kidney is smarter than the smartest clinician; accordingly, calves requiring intravenous fluids should receive at least 2 liters of 1.3% sodium bicarbonate solution with additional glucose in sufficient volume to restore extracellular fluid volume. This will ensure adequate glomerular filtration rate and in the unlikely event that the calf does not have acidemia and a strong ion (metabolic) acidosis, the renal system will still be able to alter urinary excretion so that a normal acid-base balance is maintained.

Intestinal electrolyte loss and decreased milk intake results in a total body deficit of Na⁺, Cl⁻, and K⁺. Serum Na⁺ is almost always decreased in calves with diarrhea. Serum K⁺ concentration is variable in diarrheic calves and does not reflect body stores, because K⁺ is primarily an intracellular ion. The assessment of serum electrolyte abnormalities really requires laboratory evaluation, and the Horiba Na and K ion-selective electrodes are extremely helpful in this regard. If unavailable, total body electrolyte deficits of sodium and potassium should always be assumed in calves with diarrhea. Bradycardia, cardiac arrhythmias, and clinical signs of profound weakness are suggestive of hyperkalemia, although these clinical signs are not observed in the majority of calves with hyperkalemia.

The method used for fluid administration in calves with diarrhoea should be based on the degree of dehydration, presence or absence of a suckle reflex, and ability to stand (hence the
focus on three aspects, **hydration, suckle, strength**). Calves that are able to suckle and are less than 6% dehydrated (eye recessed < 3 mm into the orbit) should be administered an oral electrolyte solution; some of the fluid can be intubated using oro-esophageal intubation if needed. Calves that are not able to suckle or that are 8% or more dehydrated (eye recessed 4 or more mm into the orbit) should receive intravenous fluids. These can be administered by placement of a jugular venous catheter or auricular vein catheter. Calves that are unable to stand should be administered intravenous fluids.

**Oral electrolyte solutions**

Our knowledge of the requirements for the ideal oral electrolyte solution for diarrheic calves continues to evolve. However, much progress has been made over the last 30 years, and the critical issues in formulating the ideal oral electrolyte solution are osmolality, sodium concentration, source of the alkalinizing agent, and the energy content (which is intimately tied to osmolality). An unknown component is whether solutions should contain agents such as glutamine that may facilitate repair of damaged intestinal epithelium.

The osmolality should range from isotonic (300 mOsm/kg) to hypertonic (700 mOsm/kg). The effective osmolality at tip of the intestinal villus is approximately 600 mOsm/kg due to a countercurrent exchange mechanism. Although markedly hypertonic fluids should be avoided in animals having severe villous damage, it is impossible to predict which animals have severe villous damage on the basis of the physical examination findings and measurement of fecal pH or other body parameter. Low osmolality fluids (300 mOsm/kg) have inadequate energy content because they have insufficient glucose. For this reason, if milk is withheld, then hypertonic oral electrolyte solutions (~600 mOsm/kg) should be administered. If milk is fed, then isotonic oral electrolyte solutions (300 mOsm/kg) should be administered, because inadequate energy content is no longer an issue.

The sodium concentration should be between 90 and 130 mmol/L. Adequate sodium absorption is the main determinant of successful expansion of the extracellular space. Sodium concentrations <90 mmol/L provide an inadequate sodium load, whereas sodium concentrations >130 mmol/L can lead to hypernatremia and additional free water loss.

The oral electrolyte solution should also contain glucose and either acetate, propionate, or glycine to facilitate Na absorption and provide energy. There are cotransport mechanisms for Na⁺ and glucose, Na⁺ and volatile fatty acids such as acetate and propionate, and Na⁺ and amino acids in the luminal membrane of villus epithelial cells. Administration of glucose, acetate, propionate, and glycine facilitates Na⁺ absorption. These transport mechanisms are unimpaired in enterotoxigenic *E. coli* and are at least partially functional in malabsorptive/maldigestive diarrhea due to rotaviral infections.

The alkalinizing agent should be acetate or propionate instead of bicarbonate, at a concentration range of 60 to 90 mmol/L. Acetate-containing fluids are as effective as bicarbonate-containing solutions at correcting mild to moderate acidosis. Acetate must be
metabolized to be effective, and metabolism may be impaired in severely dehydrated or acidemic animals. Acetate-containing fluids can be fed with milk as acetate does not raise abomasal pH or inhibit milk clotting. Bicarbonate-containing fluids are more effective at rapidly correcting severe acidemia, since bicarbonate reacts directly with H+ ions. The main disadvantage of bicarbonate-containing oral fluids are that the pH of the abomasum (a natural defense mechanism) is increased. The pH effect has been suspected to interfere with milk clotting in the calf based on in vitro studies. However, we, and others, have demonstrated that the theoretical disadvantage that bicarbonate inhibition of milk clotting in the calf’s abomasum does not occur, at least when low bicarbonate (< 40 mmol/L as fed) oral electrolyte solutions are fed.

The strong ion difference (SID) of the oral electrolyte solution provides an excellent index of the amount of alkalinizing agent available, where three elements are used to calculate SID (which we call SID3), such that SID3 = [Na+] + [K+] – [Cl–]. The European Commission regulation No 1123/2014 emphasizes a minimum SID3 value of 60 mmol/L for oral electrolyte solutions. The oral electrolyte solution SID3, and therefore abomasal luminal SID3, is linearly and positively associated with abomasal pH. Our current understanding indicates that the SID3 of oral electrolyte solutions should be approximately 80-90 mmol/L for improved correction of dehydration and strong ion (metabolic) acidosis, although higher SID3 values, such as 110 mmol/L, may be optimal. One study demonstrated that an oral electrolyte solution SID3 >92 mmol/L increases serum SID3 and thereby created a strong (metabolic) alkalosis, which is desirable when treating neonatal calves with diarrhoea.

In summary, oral electrolyte solutions should have a SID3 >60 mmol/L. Solutions containing acetate or propionate, when fed in water, are preferred over solutions containing high concentrations of bicarbonate (>40 mmol/L), because bicarbonate excessively alkalinizes the abomasum and proximal small intestine, thereby decreasing the effectiveness of the “abomasal sterilizer” in killing ingested enteric pathogens, and promoting enteroxigenic E. coli attachment to epithelial cells and STa enterotoxin production. Moreover, bicarbonate does not inhibit growth of Salmonella in the intestinal lumen, whereas acetate and propionate both inhibit Salmonella growth. The concerns about oral electrolyte solutions containing bicarbonate are decreased when the solution is mixed with milk, when the bicarbonate concentration as fed is <40 mmol/L, and bicarbonate containing oral electrolyte solutions are useful when fed with milk. Whenever possible, and certainly after the first 12 hours of treatment, we should administer oral electrolyte solutions that can be fed with milk or milk replacer, as this provides effective rehydration, alkalinization, and energy to the calf, while facilitating repair of damaged intestinal epithelium.

**Intravenous fluid solutions**

Lactated Ringers solution or Acetated Ringers solution can be used to correct mild to moderate acidosis (venous pH >7.20; base deficit >-10 mmol/L). Lactate and acetate must be metabolized before they have an alkalinizing effect. D-lactate is very slowly metabolized by ruminants (Lactated Ringers solution used to contain both D and L-lactate isomers, but more recent
formulations appear to be totally or predominantly L-lactate). Both lactate and acetate provide energy when metabolized, and it is not clear whether or how much additional glucose should be added to the infused solution when acetate or lactate based solutions are administered. However, glucose should be administered routinely to all calves receiving intravenous 0.9% NaCl or 1.3% sodium bicarbonate, as diarrheic calves are commonly hypoglycemic. Intravenous glucose administration is particularly indicated if it is more than 12 hours since the calf was fed milk or milk replacer, even if high glucose containing oral electrolyte solutions have been administered. Diarrheic calves have decreased concentrations of serum total cholesterol; if whole body cholesterol is decreased this would be expected to be associated with decreased cellular membrane and immunological function.

Bicarbonate should be used to correct severe acidemia (pH <7.20, base excess <-15 mmol/L). Bicarbonate should not be added to solutions containing calcium as a calcium carbonate precipitate forms. Isotonic sodium bicarbonate (1.3-1.4 % solution = 13-14 g of NaHCO3/L) is used to correct severe acidemia. The amount of NaHCO3 required is calculated from the base deficit: base deficit x 0.6 x (body weight in kg) = mmol of HCO3⁻ required. 1 gram of NaHCO3 contains 12 mmol of bicarbonate, so the (mmol of HCO3⁻ required)/12 = grams NaHCO3 required. This means that the total grams NaHCO3 required = (base deficit x 0.6 x body weight in kg)/12. This calculation method assumes that HCO3⁻ distributes in the extracellular fluid space that is equal to 60% of the body weight in the suckling calf. This assumption is probably not correct as the distribution space appears to vary with the severity of the strong ion (metabolic) acidosis.

A revolutionary approach to fluid administration is provided by rapid intravenous administration of small volume hypertonic saline solution (4-5 ml/kg over 4-5 minutes of 7.2% NaCl solution = 2400 mOsm/L) or hyperonic sodium bicarbonate solution (6 ml/kg over 6 minutes of 8.4% NaHCO3 solution = 2000 mOsm/L. These protocols provide the fastest resuscitation of dehydrated calves and should be considered the treatment of choice for resuscitating comatose diarrheic calves.

Profound hyperkalemia can be the specific cause of death in diarrheic calves and consequently needs to be identified and treated with intravenous fluids. Hyperkalemia in diarrheic calves is usually characterized by clinical signs of dehydration and impaired ability to stand. The electrocardiographic effects of hyperkalemia are exacerbated by the presence of hyponatremia, acidemia, and hypocalcemia. Treatment of hyperkalemia should focus in chronological order on antagonizing the effect of increased plasma potassium concentrations on excitable tissues, redistributing extracellular potassium into cells, and finally on enhancing the elimination of potassium from the body. These treatment recommendations can be readily achieved in neonatal diarrheic calves by the rapid IV administration of hypertonic sodium salt solutions such as 8.4% NaHCO3 (preferred) or 7.2% NaCl as those solutions induce rapid plasma volume expansion and have the potential to enhance the redistribution of potassium ions into the cells. More importantly, the resulting sodium load of those infusion solutions is helpful as the cardiotoxic effect effects of hyperkalemia can be rapidly reversed by increasing plasma sodium concentrations. The addition of glucose to the intravenous solution can induce insulin release
and assist in the movement of potassium back into cells, although insulin-induced transcellular potassium movement is suboptimal in calves with severe acidemia (blood pH < 7.10).

**Recommended references (last 10 years)**