

Malic Acid & Metabolic Acidosis

BACKGROUND

Ruminants are animals that have multiple stomachs to allow consumption and digestion of fibrous feedstuffs. The key to this digestive process is the bacterial breakdown of the fiber in the first stomach or rumen. The bacterial balance in the rumen can shift, allowing the ruminant to adapt to different diets. Ruminant bacteria convert fiber into lactate and volatile fatty acids (VFA: acetic, propionic, and butyric acids). Lactate and VFA are passively absorbed through the rumen and intestinal epithelium.

METABOLIC ACIDOSIS and ALKALOSIS

Acidosis is defined as a decrease in the alkali (base excess) relative to the acid (hydrogen ion) content of body fluids. Alkalosis is the reverse situation wherein alkali concentration is greater than the acid concentration in body fluids.

The difference in the concentrations of strong ions has been shown to affect the acidity/alkalinity of body fluids. Strong ion difference (SID) is defined as the sum of strong positive ion concentrations minus the sum of the strong anion concentrations. The major strong ions in plasma are sodium and chloride. Potassium and sulfate are two additional strong ions. A decrease in SID below normal results in acidosis (increase in H⁺) and an increase in SID above normal results in alkalosis (decrease in H⁺). Unidentified strong anions such as lactate will decrease the SID leading to acidosis, if present.

Types of Acidosis

Bovine lactic acidosis syndrome is associated with large increases of lactic acid in the rumen, which result from diets that are high in ruminally available carbohydrates, or forage that is low in effective fiber, or both. The syndrome involves two separate anatomical areas, the gastrointestinal tract and body fluids, and is related to the rate and extent of lactic acid production, utilization, and absorption. Clinical manifestations range from loss of appetite to death. Lactic acid accumulates in the rumen when the bacteria that synthesize lactic acid outnumber those that utilize lactic acid.

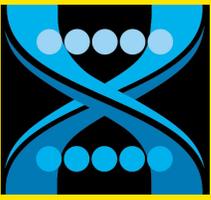
Subacute ruminal acidosis (SARA) is likely to arise when an easily palatable, high-energy diet meets a ruminal environment not adapted to this type of substrate. The increase of volatile fatty acids (VFA) that occur along with the increased production and decreased metabolism of lactate may result in a transient ruminal pH below 5.5.

Lactate accumulates only when the glycolytic flux (hexose units fermented per unit time per microorganism) is high. During dietary adaptation, the glycolytic flux is increased and lactate may accumulate. After adaptation to a certain diet, the number of microorganisms is changed and the glycolytic flux again is normal and lactate is only a minor intermediate in rumen metabolism. It should be noted that the total acid load not lactate alone is responsible for acidosis. The accumulation of VFA also contributes to the total acid load.

Pathogenic Effects

Populations of normally non-competitive lactate producing bacteria, such as *Streptococcus bovis*, can expand rapidly in the presence of excess glucose. The inhibition of *S. Bovis* by thiopeptin can help prevent acidosis.

Under normal conditions lactate does not accumulate in the rumen, however most lactate-using microbes are sensitive to low pH. Consequently, metabolic acidosis can result in bacterial die off lactate-consuming, gram-negative bacteria and release of endotoxins. Though decisive evidence for the pathological role of endotoxins of gram negative bacteria remains scarce, several authors have suggested that these endotoxins play a significant role for the development of diseases such as laminitis, abomasal displacement, sudden death syndrome of feed-lot steers etc. Ruminal acidosis may facilitate the translocation of endotoxins from the intestinal/ruminal contents to the portal vein and eventually the systemic bloodstream.



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The negative impact of organic acids on the ruminal wall may lead to parakeratosis enabling translocation of pathogens into the bloodstream provoking inflammation and abscessation throughout the ruminant body. Acidosis can also result in protozoal rupture and release of large amounts of amylase that accelerates the production of glucose from starch. The rapid glucose release from starch can increase ruminal osmolality inhibiting volatile fatty acid (VFA) absorption and increasing ruminal acidity.

The change in osmolality is much greater than the change in acidity during acidosis. The rapid influx of water into the rumen to neutralize the increased ruminal osmotic pressure, swells the ruminal papillae and can strip the internal surface layers of the rumen wall. In addition osmolytic damage to the ruminal lining, infection of the damaged lining with *Fusobacterium necrophorum* and its translocation to the blood stream and the liver also occurs.

During alkalosis, bone and perhaps renal tissue become unresponsive to increased parathyroid hormone (PTH) concentrations. On the other hand, mild acidosis seems to increase tissue responsiveness to PTH.

DISEASES

The systemic impact of acidosis may have several physiological implications such as laminitis, abomasal displacement, sudden death syndrome of feed-lot steers, poor growth and performance, etc.. Metabolic acidosis one of the prime factors responsible for the death of many diarrheic calves. Nervous system disorders can also be linked to rumen metabolic acidosis. The discussions below are not an exhaustive treatment of the many conditions arising from or aggravated by metabolic acidosis.

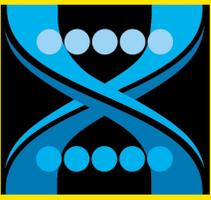
Laminitis

Low-quality hoof horn is a frequent underlying cause of lameness in cattle. The response of the keratinocytes is relatively nonspecific in that lesions often appear the same regardless of cause. Nevertheless metabolic acidosis is frequently a major underlying cause for lameness.

Laminitis is a diffuse aseptic inflammation of the laminae (corium). The severity of laminitis is related to the frequency, intensity, and duration of systemic acidotic insults. Laminitis is also regularly connected to subacute ruminal acidosis (SARA).

The critical link between acidosis and laminitis appears to be associated with a persistent hypoperfusion, which results in ischemia in the digit. Osmolarity, which is intertwined with acidosis, may play a direct role in laminitis. Similarly the endotoxins released due to gram-negative bacterial die-off can contribute to laminitis. In addition the systemic release of metalloproteinases from the ruminal lining and local release of metalloproteinases in the laminae both enhance laminal inflammation leading to lameness.

Since both osmotic imbalance and metalloproteinase release are triggered by acidosis, management of acidosis is critical in preventing laminitis. If pH is chronically acidic, the epithelium releases metalloproteinases that cause tissue degradation. If these metalloproteinases enter the blood-stream, the laminae above the hoof become inflamed, the animal becomes lame, and, in extreme cases the hoof can fall off.



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Developmental Orthopedic Disease

The incidence of developmental orthopedic diseases in other (non-cattle) fast-growing domestic animal species is also a concern. Alkalogenic diets increase dry matter intake and improve both growth in a number of species. High level performance horses and rapidly growing foals are commonly fed high-grain, acidogenic diets. Prolonged acidosis may lead to significant demineralization and skeletal weakening. Correction of the dietary acid-base imbalance may prevent stress fractures in race horses.

Liver Abscesses

Fusobacterium necrophorum, a lactate consuming ruminal anaerobic bacterium, thrives during acidosis. *F. necrophorum* possesses or produces a number of virulence factors that participate in the penetration and colonization of the ruminal epithelium and subsequent entry and establishment of infection in the liver. Approximately 13% of the livers from cattle with subacute acidosis are condemned due to bacterial abscesses.

Fatty Liver and Ketosis

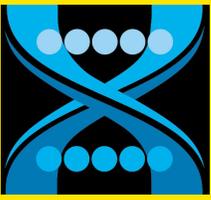
Most metabolic diseases in dairy cows occur during the peripartum period and are suggested to be derived from fatty liver initially developed during the nonlactating stage. Fatty liver is induced by hepatic uptake of nonesterified fatty acids (NEFA) that are released in excess by adipose tissues attributable to negative energy balance when cows go off their feed prior to parturition. Export of newly synthesized triglyceride as very low density lipoprotein occurs slowly in ruminants and is a major factor in the development of fatty liver. This slow release causes liver triglyceride concentration to increase four- to fivefold between d 17 prior to calving and d 1 following calving. Poor feedback control of nonesterified fatty acid release from adipose tissue is a likely cause of ketosis and fatty liver. In this situation hepatic gluconeogenesis is inadequate to supply the needed glucose for body maintenance and lactation.

As discussed above the high forage intake prepartum leads to a metabolic alkalosis due to the high potassium and malic acid present in forage. It is recommended that during the last 3 to 4 weeks prepartum, a diet higher in energy and protein concentration than current NRC guidelines should be fed so that adequate nutrient intake occurs within the limits of the reduced dry matter intake (DMI). This higher grain diet will create a mild acidosis that should be counterbalanced by the addition of malic acid to the subsequent intense energy diet that is known to create severe acidosis and its attendant problems.

Milk Fever or Hypocalcaemia

The hypocalcaemia associated with milk fever is due to a failure of the calcium homeostatic mechanisms in the cow to restore normal blood calcium concentration in a timely manner at the onset of lactation. The defect in calcium homeostasis appears to reside in the sensitivity of bone and kidney tissues to parathyroid hormone (PTH) stimulation. Evidence suggests that metabolic alkalosis is responsible for blunting tissue PTH responsiveness. High cation diets, such as is typical of high-quality forage diets of preparturient period, can cause milk fever in dairy cows as they induce a metabolic alkalosis reducing the ability of the cow to maintain calcium homeostasis at the onset of lactation. Plasma calcium levels can drop in half at the time of parturition in cows that develop milk fever. Hypocalcaemia blunts immune response.

Acidosis on the other hand, increases tissue receptivity to parathyroid hormone (PTH). Improved PTH receptiveness results in increased production of active vitamin D which in turn enhances bone resorption and intestinal absorption of calcium which prevent hypocalcemia and milk-fever.



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Dietary cause

Excessive dietary potassium is very common and is the most important factor causing metabolic alkalosis in dairy cows. Forty-five percent (45%) of dairy operations feed dry cows a "low potassium diet" to reduce milk fever. About 27% of dairy farms feed dry cows a diet with added anions to induce a compensated metabolic acidosis which has proved effective in reducing subclinical hypocalcaemia. These diets are often high in calcium. Hypomagnesaemia can also reduce tissue PTH responsiveness but hypomagnesaemia can be corrected in most rations. There is a very strong association between higher concentration of magnesium in the diet and lower incidence of milk fever.

Improving PTH

Creating a mild acidosis condition to improve PTH at the start of lactation must then be countered quickly since high producing dairy herds, attempting to maximize energy intake, are continually confronted with subclinical acidosis and laminitis. Subacute ruminal acidosis (SARA) manifests as lame cows, thin cows, high herd removals or death loss across all stages of lactation, and milk fat depression

Hypocalcaemia postparturient paresis in dairy cows is caused by the sudden increase of calcium secretion into the colostrum. The manipulation of the dietary cation-anion difference makes it possible to maintain the cows in metabolic acidosis during the critical period that precedes calving, presumably via a mechanism that involves the strong ion difference in the extracellular fluid. As a consequence the mobilization of calcium is enhanced and the incidence of the disorder is decreased. Conversely, a dietary induced metabolic alkalosis leads to a more severe degree of hypocalcaemia and the incidence of the disease is increased.

Displaced Abomasum (DA)

A fundamental advancement in recent years has been recognition of the multifactorial nature of almost all diseases of importance in dairy cattle. A survey of the literature reveals a large number of factors that are associated with abomasum displacement (see table on following page)



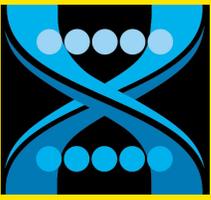
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Factors Associated with Displaced Abomasum

Breed ^a
Gender ^a
Age ^{a, b}
Concurrent diseases ^a
Multiparous cows ^f
Environmental aspects ^a
Springtime ^b
Recent calving ^{b, g, h}
Retained placenta ^g
Metritis (inflamed uterus) ^g
Production levels ^{a, b}
Prepartum depression of intake ^g
Slow postpartum increase in intake ^g
Lower ruminal fill ^g
Decreased ruminal motility from lower ruminal fill ^g
High amount of high-quality roughage in prepartum diet ^f
Excessive amounts of concentrate during the prepartum period ^g
Minimal intake of concentrate during the prepartum period ^g
Reduced forage to concentrate ratio ^g
Failure to increase the absorptive capacity of the ruminal papillae ^g
Failure of the microbial population of the rumen to adapt prior to the intake of high energy postpartum diets ^g
Higher volatile fatty acid concentration ^g
Low ruminal absorption of volatile fatty acids ^g
Gas production in the abomasum ^a
Hypomotility of the abomasum ^a
Subclinical ketosis ^d
Hyperketolactia (High milk ketones) ^c
Uncomplicated ketosis ^g
Serum nonesterified fatty acids (NEFA), in the last week prepartum ^h
Beta-hydroxybutyrate (BHBA) in the first week postpartum. ^h

MATRIX NUTRITION





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Feedlot economics dictate that highly fermentable rations be fed, leaving the ruminant constantly on the edge of lactic acidosis.

Even though ruminal fermentation can be recovered relatively quickly, the transition to high-grain diets often results in acute acidosis due to the overgrowth of rapidly-replicating lactic acid producing bacteria. In contrast lactate-consuming bacteria grow at a relatively slower rate.

Feedlot animals may not die from the immediate effects of a metabolic acidosis, but there are sequelae such as mycotic rumenitis, hepatic abscesses, cauda vena cava thrombosis, and pulmonary arterial thromboembolism that may cause subsequent losses. Approximately 13% of the livers from cattle with subacute acidosis are condemned due to bacterial abscesses.

Feedlot cattle are commonly given the ionophore antibiotic monensin. Monensin is active against Gram-positive bacteria which produce lactic acid, thus reducing the incidence of acidosis during the early stages of adaptation to a high-grain diet. Gram-negative bacteria (lactate consuming bacteria) are resistant to monensin. Monensin reduced daily variation of feed intake and reduced the incidence of digestive deaths in feedlot cattle. The use of prophylactic antibiotics is largely banned in Europe. Public pressure in mounting in the United States, for a similar ban on prophylactic antibiotics. In domestic animals, acid-base balance may be influenced by nutrition. Nutritional interventions to prevent metabolic acidosis would be preferred to pharmaceutical interventions.

DAIRY

Approximately 75% of disease in dairy cows typically happens in the first month after calving. Most of the metabolic diseases of dairy cows-milk fever, ketosis, retained placenta, and displacement of the abomasum-occur within the first 2 wk of lactation. Other metabolic diseases, such as laminitis originate during the first two weeks of lactation but do not become clinically manifest until later. The overwhelming majority of infectious disease, in particular mastitis, become clinically apparent during the first 2 wk of lactation. Adaptation of the rumen to lactation diets that are high in energy density while maintaining normocalcemia, and a strong immune system are critically important during the periparturient period if disease is to be avoided.

Energy requirements increase to 1.3 to 1.5 times maintenance in late pregnancy; therefore, the formulation of rations for dry cows must contain sufficient energy to support fetal growth plus maintenance. Protein requirements during pregnancy increase, particularly during the last 2 mo. In addition milk production in high-yielding dairy cows represents a metabolic stress comparable to fasting or acidosis.

Beef vs. Dairy

The etiology of rumen acidosis in the dairy cow appears to be different from the classical description of rumen acidosis observed in beef feedlot cattle. In feedlot cattle, the rapid production of lactic acid following an abrupt change to a high-starch diet causes rumen pH to fall dramatically, killing many rumen microbes, which then release endotoxins to the blood. As the lactic acid spills over into the blood, it causes severe metabolic acidosis in the animal, which acts with the endotoxemia to cause hypovolemic shock and often death. In the dairy cow, it is the total organic acid load induced by the diet, combined with the inability of the cow to buffer the organic acids with salivary secretions the causes rumen pH to fall. Alkalogenic diets increase dry matter intake and increase milk yield in dairy cows. Heat stress can lead to metabolic acidosis. Alkalizing the diet with buffering agents aids in maintaining dry matter intake (DMI) and milk yield during heat stress.

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Energy Associated Diseases

Milk fever and ketosis are clearly related to the cow's inability to maintain bodily functions in the face of negative calcium or energy balance. Displacement of the abomasum and retained placenta are not as easily categorized as to their cause. However milk fever (hypocalcemia), dystocia, and ketosis each increased the odds of developing left-displaced abomasum. As such it has been recommended that cows be tested for preparturient nonesterified fatty acids (NEFA) and parturient hypocalcemia as indicators of metabolic disease problems in dairy herds. Because subclinical ketosis is a risk factor for displaced abomasum (DA), a number of treatment protocols have been investigated.

Precalving administration of monensin in a controlled release capsule form, resulted in a 40% reduction in both clinical ketosis and abomasal displacement. In addition a 25% reduction in the incidence of retained placenta was observed in monensin-treated cows. Overall the monensin controlled release capsule reduced the incidence of energy associated disease by 30%.

In Summary

Metabolic alkalosis and metabolic acidosis both affect a wide range of bovine physiological functions:

alkalosis	> hypocalcemia > immune disorders > uterine inflammation
alkalosis	> hypocalcemia > muscle weakness > retained placenta
acidosis	> connective tissue breakdown > displaced abomasums

Monensin's affect on the microbial populations of the rumen help prevent metabolic acidosis. This is the likely basis for monensin's benefits in periparturient dairy cattle as well. While monensin is commonly used with feedlot cattle, monensin is not currently approved for lactating dairy cattle in the United States. Therefore other means of controlling acidosis are needed for dairy cattle. The effects of malic acid administration represent a potential nutritional approach to the prevention of displaced abomasum, whose root cause is likely to be a nutritional imbalance during a stressful transition.

MALIC ACID AND MALATE

Fermentation of cracked corn in the presence of 8 or 12 mM DL-malate (disodium salt) resulted in an increase ($P < .05$) in final pH and propionate concentration. Total volatile fatty acids (VFA) tended to increase ($P < .21$), whereas final concentrations of L-lactate numerically decreased. DL-malate treatment also consistently increased final pH values in fermentations of alfalfa hay and Coastal Bermuda grass hay. Fermentation studies show that malate could be used as a feed additive for ruminants fed diets containing medium proportions of forage (i.e. dairy animals) and not only in animals fed high-concentrate diets.



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Lactate Utilization

Dicarboxylic acids such as malate reduce lactic acid concentration by stimulating lactate utilization by the predominant ruminal bacterium, *Selenomonas ruminantium*. It appears that sodium may also be involved in stimulating lactate utilization by *Selenomonas ruminantium*. L-Lactate uptake by *Selenomonas ruminantium* HD4 is stimulated in the presence of 10 mM L-malate at pH values and Na⁺ concentrations commonly found in the rumen.

In contrast the ionophore monensin reduces lactic acid concentration by suppressing lactic acid-producing, monensin-sensitive bacteria (e. g. *Streptococcus bovis*).

In steers, fed a rolled corn-based diet, feed and gain efficiency (gain:feed) improved 8.1% greater (P < .05) for DL-malate than for the control. The average daily gain (ADG) linearly increased (P < .05) with more DL-malate and was 8.6% greater (P = .10) for DL-malate than for the control. Feeding DL-malate to cattle consuming high-grain diets alleviates subclinical acidosis and improved animal performance.

Supplementation With Malic Acid

Supplementation of high-grain finishing diets with malic acid may be beneficial in promoting a higher ruminal pH during periods of peak acid production without detrimental effects on ruminal microbial efficiency or starch, fiber, and protein digestion. Ingestion of malic acid stimulates the expansion of the *Selenomonas ruminantium* and *Megasphaera elsdenii* populations in the rumen. These bacteria provide the secondary metabolism of lactic acid and are critical in the adaptation to a high-grain diet.

As maturity increased, the concentration of malate declined in five alfalfa varieties and three Bermuda grass varieties. Because malate stimulates the utilization of lactate by the predominant ruminal bacterium *Selenomonas ruminantium*, some of the benefits associated with alfalfa in the diets of dairy cattle may be due to the malate in this forage. When five alfalfa varieties and three Bermuda grass hay varieties were surveyed for malate content, the concentration of malate in both plant species declined as maturity increased. However, after 42 d of maturity, the concentration of malate in both forages ranged between 1.9 and 4.5% of the DM. These results suggest that the incorporation of forage varieties that are high in malate may include malate economically into the diet and reduce losses associated with ruminal acidosis.

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