

# Dairy Session

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## Fresh cow metabolic diseases: Old myths and new data

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### Abstract

Hypocalcemia, hypophosphatemia, hypomagnesemia, hyperketonemia (ketosis), and hypokalemia are important metabolic diseases of fresh dairy cows. Many dairy practitioners and dairy producers need to update their approaches to these diseases because of new findings about these disorders. Hypocalcemia in standing cows is best treated orally; intravenous calcium causes a rebound hypocalcemia and should be reserved for recumbent cases of milk fever. Glucose or additional electrolytes should not be administered intravenously to cows with hypocalcemia. The strategic use of oral calcium helps manage subclinical hypocalcemia. Hypophosphatemia is less common and is usually secondary to hypocalcemia. Mild to moderate cases of hypophosphatemia are best treated with oral phosphorus; intravenous phosphorus is best reserved for severe cases. Hypomagnesemia may be a clinical problem in grazing herds or a subclinical problem in cows fed stored feeds. Clinical cases may be treated intravenously or via rectal enema; subclinical cases are best managed by oral magnesium supplementation. Ketosis (hyperketonemia) is a very common problem in early lactation cows. Early detection and early treatment of hyperketonemia is key. Hypokalemia may follow prolonged periods of anorexia in early lactation cows. Oral potassium supplementation is the best means of treating and preventing hypokalemia.

**Key words:** fresh cow metabolic disease, treatment protocols, hypocalcemia, hypophosphatemia, hypomagnesemia, hyperketonemia, hypokalemia

### Résumé

L'hypocalcémie, l'hypophosphatémie, l'hypomagnésémie, l'hyperacétonémie (cétose) et l'hypokaliémie sont des désordres métaboliques importants chez les vaches vèlées récemment. Plusieurs praticiens bovins et producteurs laitiers doivent mettre à jour leurs approches concernant ces maladies en raison de nouvelles percées sur ces désordres. Le traitement par voie orale est le meilleur moyen de traiter l'hypocalcémie chez les vaches debout. Le calcium intraveineux engendre un effet de rebond de l'hypocalcémie et devrait être restreint aux cas de fièvre vitulaire avec décubitus. L'administration intraveineuse de glucose ou d'autres

électrolytes devrait être évitée chez les vaches en hypocalcémie. L'utilisation stratégique de calcium par voie orale permet de gérer l'hypocalcémie subclinique. L'hypophosphatémie est moins courante et accompagne souvent l'hypocalcémie. L'administration orale de phosphore est le meilleur moyen de traiter les cas légers ou modérés d'hypophosphatémie. L'administration intraveineuse de phosphore devrait être restreinte aux cas plus sévères. L'hypomagnésémie peut être un problème clinique dans les troupeaux au pâturage ou un problème subclinique chez les vaches alimentées avec de l'ensilage. Les cas cliniques peuvent se traiter par voie intraveineuse ou par un lavement rectal alors que la supplémentation orale de magnésium est le meilleur moyen de traiter les cas subcliniques. La cétose (hyperacétonémie) est un problème très courant chez les vaches tôt en lactation. La détection et le traitement précoce de l'hyperacétonémie sont de grande importance. L'hypokaliémie peut apparaître après une longue période d'anorexie chez les vaches tôt en lactation. La supplémentation orale de potassium est le meilleur moyen de traiter et de prévenir l'hypokaliémie.

### Introduction

Dairy practitioners have a unique role in guiding the diagnostic and treatment protocols used by dairy producers. Protocols recommended by dairy veterinarians should reflect the best available science and clinical experience. Unfortunately, some treatments for metabolic diseases recommended by veterinarians are inappropriate and likely ineffective. Of particular concern is the excessive use of intravenous (IV) metabolites that interfere with the cow's own attempts to regulate these metabolites. Other key concerns are the use of IV multiple electrolyte solutions that contain ineffective ingredients, disregard for oral treatments that are more effective than IV treatments, and diagnostic protocols that are inadequate to diagnose key metabolic diseases.

The therapeutic philosophy that "what doesn't kill the cow will cure her" is not valid. A strong science-based approach to treatment protocols will strengthen the influence that a veterinarian has in determining diagnostic and treatment protocols.

This paper will review the current science and clinical reasoning for appropriate diagnostic and treatment protocols for hypocalcemia, hypophosphatemia, hypomagnesemia, hy-

perketonemia (ketosis), and hypokalemia in fresh dairy cows.

## Diagnosis and Treatment for Hypocalcemia

**Pathophysiology of hypocalcemia.** Dairy cows experience a sudden and extraordinary calcium loss at the start of lactation. They go from excreting about 10 grams of daily calcium into the fetal skeleton<sup>22</sup> to excreting about 30 grams of daily calcium into colostrum.<sup>48</sup> On the day before calving the cow faces demands for both fetal and colostrum calcium. Colostrum is about twice as calcium dense as milk (1.7 to 2.3 g calcium per kg of colostrum vs. 1.1 g/kg calcium in milk).<sup>15,48</sup> The risk for hypocalcemia is greatest soon after calving because of the suddenness and severity of calcium outflow.

Calcium demands steadily increase after calving as milk production increases. Daily calcium requirements increase from about 21 grams per day before calving to about 76 grams per day at 100 lb (45.5 kg) of milk production per day.<sup>38</sup> Cows must go into negative calcium balance in order to accommodate this massive outflow of calcium. Dietary calcium intake does not catch up to calcium excretion until about 2 to 11 weeks after calving – this depends somewhat on dietary calcium intake.<sup>51</sup> During negative calcium balance cows develop lactational osteoporosis and lose about 9 to 13% of their skeletal calcium.<sup>11</sup> Despite the challenge to maintain calcium balance throughout early lactation, overt hypocalcemia is not as likely once the cow is more than about 2 days post-calving.

Given the calcium challenges of early lactation, it is not surprising that about half or more of all second and greater lactation cows will develop subclinical hypocalcemia (SCH) and that about 2 to 6% of second and greater lactation cows develop clinical milk fever. The 2002 dairy study of the US National Animal Health Monitoring System (NAHMS) sampled 1008 second and greater lactation dairy cows; 6.2% of these cows had clinical milk fever (as reported by the producer). The incidence of clinical milk fever appears to be declining; the 2007 NAHMS survey reported 4.9% clinical milk fever. A reasonable goal for clinical milk fever cases in second and greater lactation cows is <2% of calvings.<sup>41</sup>

The 2002 NAHMS dairy study reported that 47% of second and greater lactation cows had SCH. The definition of SCH used in this study was serum total calcium <2.0 mmol/L (8.0 mg/dL) but without clinical signs of milk fever. In contrast to clinical milk fever, the incidence of SCH does not appear to be declining in dairy herds. Recent studies that evaluated SCH<sup>5,28,45</sup> have reported higher rates of SCH – up to 88% of cows tested. Unfortunately, it is difficult to compare risks for SCH across studies because of differences in herd selection criteria, parities of cows sampled, and cutpoints used for SCH.

**Standing vs recumbent cases of hypocalcemia.** Keen dairy producers often recognize very early signs of clinical milk fever while cows are still standing. This is termed Stage 1 clinical milk fever. Key clinical signs during this stage are

wobbliness, weight-shifting, dull appearance, cold extremities, hypothermia, reduced ruminal contractions, and mild tachycardia.<sup>39</sup>

Oral calcium is the preferred supplementation approach for cows in Stage 1 clinical milk fever. Oral calcium supplementation results in peak blood calcium concentrations within about 30 minutes of administration.<sup>12</sup> The increase in blood calcium concentration following oral calcium chloride administration is equivalent to administering about 4 grams of calcium IV.<sup>12</sup> This equals about half the amount of calcium in an IV dose and should be sufficient for treatment of Stage 1 clinical milk fever.

Intravenous calcium is not recommended for treating cows in Stage 1 clinical milk fever. Oral calcium supplementation is much safer for the cow. Treatment with IV calcium rapidly increases blood calcium concentrations to extremely high and potentially dangerous concentrations.<sup>13</sup> In a small proportion of cases, administration of IV calcium may lead to fatal cardiac complications. Hypercalcemia may induce a fatal arrhythmia starting at blood concentrations of about 7.0 to 8.0 mmol/L (28 to 32 mg/dL).<sup>26</sup> Administration of a single dose of IV calcium increases average blood calcium to about 4.8 mmol/L (19 mg/dL).<sup>4</sup> Individual cows may exceed 5.5 mmol/L (22 mg/dL)<sup>13</sup> and thus are dangerously close to fatal arrhythmia.

The exact risk for fatal arrhythmia following IV calcium administration has not been documented. It would be difficult to study because a very low percentage of cows are affected, which makes it extremely difficult to generate adequate sample size. Nonetheless, the theoretical risks of giving IV calcium are sufficient to preclude their use in standing cows.

A more common and clinically relevant problem with IV calcium administration is that it quickly and directly impairs parathyroid hormone (PTH) secretion. Increased PTH secretion is the cow's primary response to hypocalcemia. It enhances renal reabsorption of calcium from proximal renal tubular fluids, enhances osteoclastic bone resorption, and stimulates the production of the hormonal form of vitamin D.<sup>15</sup> All of these are normal adaptations to hypocalcemia and are necessary for the cow to survive the period of negative calcium balance that occurs during early lactation.

Blood concentrations of PTH are very high in cows suffering from clinical milk fever (about 2,000 pg/mL),<sup>4</sup> but within 10 minutes of IV calcium administration blood PTH decreases to about 100 pg/mL.<sup>4</sup> This effectively ends the cow's own efforts to mobilize calcium at this critical time. The induced hypercalcemia also stimulates the release of calcitonin (CT), which is even more damaging because it actively inhibits renal calcium resorption and bone resorption. This can in part be measured by urinary calcium loss, which unfortunately is about 1 to 2 grams of calcium within 30 minutes of IV calcium treatment.<sup>13</sup>

The result of impaired PTH secretion and increased CT secretion following IV calcium administration is a rebound hypocalcemia. Cows given IV calcium return to hypocalcemia

within about 8 hours and remain hypocalcemic until 24 to 48 hours after IV treatment.<sup>4,13</sup> If no preventive measures are taken, about 30 to 35% of cows treated successfully with IV calcium suffer a hypocalcemic relapse and become recumbent again. Relapses into recumbency typically occur about 12 to 18 hours after the initial IV treatment.<sup>9</sup>

Intravenous calcium is necessary for cows with Stage 2 or Stage 3 (recumbent) hypocalcemia. Downer cows can quickly suffer irreversible musculoskeletal damage. About 4 to 30% of cows with clinical milk fever become alert downer cows, and about 20 to 67% of alert downer cows die.<sup>50</sup> The most urgent need for a recumbent cow is to get up; this need overshadows potential complications from IV calcium administration.

**Proper intravenous dose of IV calcium.** Whenever IV calcium treatment is necessary, the goal should be to provide as little calcium as possible in order to get the cow up. Any IV calcium beyond this exposes the cow to additional risk for fatal cardiac complications, inhibits the cow's own attempts at calcium homeostasis, and increases the risk for a hypocalcemic relapse.

The optimal dose of IV calcium for recumbent cases of hypocalcemia cannot be determined definitively and likely varies from cow to cow. However, physiological calculations give us a good starting point. The entire extracellular pool of calcium in a dairy cow is about 11 grams (3.5 grams dissolved in the bloodstream and 7.5 grams in the interstitial fluid).<sup>15</sup> A cow in Stage 2 clinical hypocalcemia typically has a blood calcium concentration around 4.5 mg/dL, or about half the normal concentration. Assuming that blood and interstitial fluid have equal calcium concentrations, the total calcium deficit for this cow is 6.5 grams. A severe case of Stage 3 clinical milk fever could have a blood calcium concentration of about 2.0 mg/dL; this represents a loss of about 88% of the extracellular calcium, or about 9.7 grams. Thus, a single bottle of IV calcium (8 to 11 grams of calcium) usually replaces more than the cow's entire body deficit of calcium. Because calcium continues to be lost in the colostrum, providing some calcium beyond the deficit is reasonable. However, excessive amounts of IV calcium (2 or more 500 mL bottles) is not reasonable.

Some empirical studies further help to define an optimal dose of calcium for IV treatment. One study reported that a low dose of IV Ca (6.2 grams) was not as effective as 8.0 grams in treating clinical cases of milk fever.<sup>37</sup> Another study reported that administering an unnecessarily high dose of IV calcium (12.4 grams of calcium) was no more effective in correcting clinical milk fever than a lower dose (7.4 grams of calcium).<sup>10</sup> These results suggest an optimal IV calcium dose is between about 7 and 10 grams of calcium.

Standard IV calcium treatment in the US is 500 mL of 23% calcium gluconate, which provides 10.7 grams of elemental calcium. Thus, 1 bottle (500 mL) should be more than enough. However, many veterinarians and producers routinely administer 2 or more bottles of IV calcium solutions

to cows with clinical milk fever. For example, 1 field study of clinical milk fever cases reported that 2 bottles (1000 mL total) of calcium-containing solutions were administered to all cases of clinical milk fever.<sup>34</sup> The initial dose of IV calcium from the treatments reported in this study could have been as high as 21.6 grams, depending on the products used. As discussed above, this is physiologically unwarranted and potentially harmful. No studies have quantified the negative aspects of such a high dose of IV calcium; however, it is reasonable to expect higher risks for iatrogenic death, hypocalcemic relapse, and alert downer cows.

Along with risks for sudden death and hypocalcemic relapse, high doses of intravenous calcium may cause excessive acidification. Acidification occurs because boric acid is added to calcium gluconate preparations to solubilize the calcium gluconate and stabilize the solution.<sup>13</sup> In the US, IV calcium solutions are typically labeled calcium gluconate, even though boric acid has been added and the solution is now technically calcium borogluconate. If no boric acid was added, precipitation of calcium gluconate would occur at room temperature for solutions containing more than about 10% calcium gluconate.<sup>2</sup> The needed concentration of calcium gluconate is 23%. In countries other than the US, IV calcium solutions are typically labeled (and correctly so) as calcium borogluconate and provide between about 8 and 12 grams of elemental calcium per standard dose of 400 to 500 mL. It is interesting to note that boric acid from a standard US dose of 23% calcium gluconate (which includes 17.5 grams of boric acid) constitutes sufficient acid to lower urinary pH substantially (from about 6.6 to 5.8 at 1 hour post-treatment).<sup>3</sup> The acid load from giving 2 bottles of 23% calcium gluconate has not been evaluated but could be clinically relevant. Urinary pH below 5.5 suggests excessive acid load, uncompensated metabolic acidosis, and decreased dry matter intake.<sup>15</sup>

Hypocalcemic cows do not need large doses of IV calcium in order to restore depleted stores of intracellular calcium. Intracellular calcium concentrations are extremely low in dairy cows (about 0.004 mg/dL) and the total intracellular calcium pool is miniscule (about 0.01 grams).<sup>13</sup> The major challenge for hypocalcemic cows is the ongoing drain of calcium via colostrum or milk production. This is best resolved by the cow's own mobilization of body stores of calcium along with oral calcium supplementation, which does not interfere with calcium mobilization.

**Providing multiple electrolytes in addition to calcium for IV treatment.** Many products marketed for treatment of hypocalcemia include calcium plus phosphorus, magnesium, glucose, or potassium. None of these additional electrolytes is clearly needed, and some could be harmful.

Cows suffering from clinical milk fever typically have low blood phosphorus, high blood magnesium, high blood glucose, and normal to slightly low blood potassium.<sup>25</sup> This information should inform what electrolytes can be used appropriately.

Hypophosphatemia typically follows hypocalcemia; however, it does not require treatment, as detailed later in this paper. Additionally, the phosphorus source (hypophosphites) used in these multiple electrolyte solutions is not biologically available to the cow. This is discussed in detail later in this paper.

Hypermagnesemia often accompanies hypocalcemia because of the effect of PTH on the kidneys. Administering additional magnesium to hypocalcemic cows is not necessary but probably is not harmful.

In an empirical field trial, treating cases of clinical milk fever with either IV calcium alone (10.5 grams from calcium borogluconate) or an IV solution containing calcium (12.4 grams from calcium borogluconate), phosphorus (1.5 grams from glycerophosphate), and magnesium (2.6 grams from magnesium chloride) resulted in no difference in treatment response. These results support the theory that the addition of these 2 electrolytes to IV calcium infusions is unnecessary.

Hyperglycemia accompanies hypocalcemia because calcium is necessary for glucose to stimulate insulin secretion from the pancreas. Administering additional glucose IV is not necessary, and could prolong the cow's period of hyperglycemia if her hypocalcemia is not corrected. The effect of a large dose of IV glucose in a cow that is already hyperglycemic has not been formally evaluated. Prolonged hyperglycemia lowers GI motility and may increase the risk for displaced abomasum.<sup>21</sup>

The inclusion of potassium in multiple electrolyte solutions could have minor benefits from a potassium standpoint. Cows with clinical milk fever may have a mild hypokalemia; however, it usually self-corrects following the administration of IV calcium and the restoration of gastro-intestinal motility. The amount of potassium contained in multiple electrolyte products is quite small (1 to 2 grams) relative to the extracellular pool of potassium (19 to 20 grams). However, providing enough potassium in an IV solution to correct clinically significant hypokalemia is nearly impossible because of the risk for cardiac side effects and sudden death if more than about 2 grams of potassium is given IV.<sup>13</sup>

The addition of a small amount of potassium to an IV solution for the treatment of clinical milk fever may reduce the risk for cardiac problems secondary to IV calcium administration. Potassium is known to counteract the toxic effects of calcium on the electrical potential of cardiac muscle. This is an interesting theory; however, there is no empirical evidence that the addition of potassium to IV solutions to treat clinical milk fever is actually safer or improves the clinical response to treatment.<sup>13</sup> It is reasonable to assume that the very small dose of IV potassium found in multiple electrolyte solutions at least does no harm.

In conclusion, the use of multiple electrolyte solutions containing additional phosphorus, magnesium, and glucose for the treatment of clinical milk fever is irrational. Dairy practitioners should actively discourage their use and should work against the notion that adding more ingredients to an IV solution makes it better for the cow. Cases of clinical milk

fever should be treated with a single bottle of a solution that provides 7 to 10 grams of calcium from calcium borogluconate. Nothing else is needed.

**Preventing hypocalcemic relapses following successful IV treatment.** About 25%<sup>36</sup> to 38%<sup>9</sup> of cows successfully treated with IV calcium will become recumbent again within about 12 to 24 hours. An even higher percentage will return to biochemical hypocalcemia but remain standing.

To reduce the risk for hypocalcemic relapse, oral calcium is indicated following successful IV calcium treatment. The mean efficacy of oral calcium drenches in preventing relapses in cows successfully treated for clinical milk fever is about 50 to 60%.<sup>52</sup> Bolus formulations of oral calcium were developed later and have not been directly evaluated for the prevention of hypocalcemic relapses. They are safer for the cow than oral drenches and should be as effective in reducing the risk for a hypocalcemic relapse. A reasonable recommendation is to administer 1 oral bolus after the cow is standing, alert, and able to swallow, followed by a second bolus about 12 hours later.

Subcutaneous calcium administration is an alternative approach to preventing hypocalcemic relapses following successful IV treatment of cases of clinical milk fever. It has been shown to reduce the risk for a clinical relapse by about half compared to cows not given any source of slower release calcium after IV calcium administration.<sup>9</sup> An important practical limitation of subcutaneous calcium administration is tissue irritation and the risk for abscessation. High amounts of extracellular calcium can overwhelm the ability of cells to maintain low intracellular calcium concentrations and cause cell death.<sup>13</sup> The amount of solution per injection site should be limited to 1.0 to 1.5 grams of calcium, or about 50 to 70 mL per site for a typical IV calcium preparation.<sup>13</sup> Solutions that contain glucose should never be given subcutaneously. Glucose is poorly absorbed because it requires active uptake by cells, and there is not much cellular activity in the subcutaneous space. Additionally, glucose supports bacterial growth and increases the osmolarity of the solution,<sup>13</sup> which increases swelling and tissue irritation.

**Managing subclinical hypocalcemia in early lactation.** Since cows with SCH (by definition) do not exhibit clinical signs, it is not possible to treat them individually. Blanket treatment of cows after calving with 2 doses of oral calcium from a bolus formulation is beneficial. In a large field study, blanket oral calcium supplementation for second and greater lactation cows reduced the risk for health events in lame cows and increased milk yield in cows with higher previous lactation milk production.<sup>40</sup> The herds that participated in this study were fed supplemental anions and had an extremely low incidence of clinical milk fever. It is interesting to note that the age of the cow at calving or her blood calcium concentration at calving had no effect on response to oral calcium supplementation.<sup>40</sup>

Blanket use of IV calcium for the management of SCH is clearly not recommended due to concerns about cardiac complications and rebound hypocalcemia mentioned above. Cows that were given a blanket, single dose treatment of IV calcium at calving had lower blood calcium concentrations by 48 hours after calving than cows given no supplemental calcium at all.<sup>3</sup>

**Treating secondary hypocalcemia in early lactation cows.** Transient hypocalcemia can occur in cows whenever they go off feed or have periods of decreased intestinal motility. Experimental induction of hypocalcemia causes severe ruminal stasis.<sup>24</sup> It is also possible that gastrointestinal stasis could cause hypocalcemia, or at least make it worse. In either case, oral calcium supplementation is indicated for any off-feed cows in early lactation. Many oral fresh cow drench products contain an effective dose of oral calcium. Sick cows that are still standing should not be exposed to the risks that come with IV calcium administration.

## Diagnosis and Treatment for Hypophosphatemia

**Overview of hypophosphatemia.** Primary hypophosphatemia (due to a diet deficient in phosphorus) in dairy cattle is extremely unusual. In reality, almost all dairy cows are fed diets that provide excessive amounts of dietary phosphorus. Because phosphorus is an important environmental pollutant, dairy nutritionists have appropriately focused on reducing dietary phosphorus intakes. Nonetheless, milk production results in a significant phosphorus outflow and colostrum is higher in phosphorus than milk.<sup>20</sup> This makes early lactation a challenging time for phosphorus homeostasis in dairy cows.

When hypophosphatemia does occur in early lactation dairy cows, it is typically secondary to hypocalcemia. Blood concentrations of phosphorus and calcium are highly correlated, and 90 to 100% of cows with clinical milk fever will be hypophosphatemic.<sup>4</sup> Two physiological principles explain this relationship. First, during periods of hypocalcemia PTH causes renal excretion of phosphorus in order to retain calcium. Second, salivary phosphorus (in the form of phosphate buffers) pool in the rumen, which is hypomotile during hypocalcemia. The amount of phosphorus transiently unavailable in the rumen can be substantial; salivary production of phosphorus is between 25 and 100 grams per day and saliva contains about twice the concentration of phosphorus as blood.<sup>20</sup> Phosphorus cannot be absorbed across the rumen wall; it must pass on to the small intestine before it can be absorbed back into circulation.

Fortunately, the vast majority of hypophosphatemia in hypocalcemic cows self-corrects once the hypocalcemia is corrected. Lowered blood PTH quickly decreases renal phosphorus excretion. Restored blood calcium improves ruminal motility, allowing pooled salivary phosphorus to exit the rumen and be absorbed back into the bloodstream at the small intestine.

Empirical field data support the theoretical assertion that hypophosphatemia self-corrects following restoration of blood calcium. Adding IV sodium phosphate to IV calcium for the treatment of cows with clinical milk fever did not improve response to treatment, despite the finding of hypophosphatemia in almost all of the affected cows.<sup>4</sup>

A small proportion of cows with hypophosphatemia secondary to hypocalcemia remain hypophosphatemic following correction of the hypocalcemia. Blood phosphorus concentrations in these cows are typically 0.15 to 0.30 mmol/L (0.5 to 0.9 mg/dL),<sup>13</sup> which is well below the normal range of 1.3 to 2.6 mmol/L (4.0 to 8.0 mg/dL). Some of these cows remain recumbent and are termed “creeper” cows. The exact reasons for persistent hypophosphatemia are unknown, and the role that hypophosphatemia might play in the continued recumbency of these cows is unclear and controversial. Because phosphorus plays a role in muscle strength, it has been hypothesized that hypophosphatemia directly contributes to continued recumbency. However, there is no empirical evidence that hypophosphatemia actually causes prolonged recumbency.<sup>20</sup> Rather, the recumbency may be secondary to hypocalcemia-related musculoskeletal damage, gastrointestinal stasis, and inappetance.

Another potential cause of hypophosphatemia is the IV administration of glucose. Parenteral administration of a bolus of IV glucose lowers blood phosphorus concentrations quickly and dramatically.<sup>18,53</sup> This effect is mediated by insulin, which increases dramatically following IV glucose administration. Insulin release triggers an intracellular shift of phosphorus, moving it from the extracellular space into the cells.<sup>20</sup>

The diagnosis of hypophosphatemia is complicated by several unique features of phosphorus metabolism. Because the salivary glands harvest so much phosphorus to buffer the rumen, blood collected from the jugular vein contains less phosphorus than blood collected from the coccygeal vein.<sup>35,53</sup> Therefore, a false positive diagnosis of hypophosphatemia is possible if the blood was collected from the jugular vein or if it was collected after the cow was given IV glucose.

Whether hypophosphatemia directly contributes to prolonged recumbency or not, it is reasonable to attempt to correct the hypophosphatemia when it is diagnosed.<sup>13,20</sup> Although many practitioners report clinical improvements in cows following phosphorus treatment, there are no empirical data that support the value of phosphorus therapy for recumbent cows with hypophosphatemia.<sup>20</sup> As long as phosphorus treatment is not seen as a replacement for excellent management of downer cows (humane handling, prompt flotation, and excellent nursing care) it likely does no harm.

**Intravenous treatment for hypophosphatemia.** The need for and value of intravenous treatment for hypophosphatemia is controversial. One author has suggested that it should be reserved for unusual cases, such as when severe

intravascular hemolysis may be resulting from the hypophosphatemia.<sup>20</sup> Another author is open to using it more widely.<sup>13</sup>

A precise dose of phosphorus needed for IV treatment cannot be determined.<sup>20</sup> However, a reasonable dose can be estimated from the known phosphorus deficit in the cow. The entire extracellular pool of inorganic phosphorus for a dairy cow is about 6 grams.<sup>13</sup> Assuming that blood phosphorus is a valid surrogate for extracellular phosphorus<sup>20</sup> and that the phosphorus concentration in extracellular fluid decreases from about 1.6 to 0.3 mmol/L (5 mg/dL to 1 mg/dL) during hypophosphatemia, the extracellular phosphorus deficit in a hypophosphatemic cow is about 4.8 grams. Providing a modest amount of additional phosphorus to help cover for continued phosphorus loss in the milk is reasonable. Therefore, typical recommended doses for IV phosphorus are about 5 to 7 grams.<sup>13</sup> Intracellular phosphorus is likely not depleted during short periods of hypophosphatemia and is not considered in the dosage calculations.<sup>13</sup>

There are no commercial products available in the US that can be recommended for the IV correction of hypophosphatemia. The only recommended IV treatment is 30 grams of sodium phosphate (monobasic, monohydrate, reagent grade) mixed in 300 mL sterile water. This solution provides 6.7 grams of phosphorus. It should be infused slowly (10 minutes or longer). Intravenous phosphorus supports blood phosphorus concentrations for only 3 to 4 hours.<sup>13</sup>

Intravenous phosphorus administration should not be regarded as innocuous. Blood phosphorus concentrations rise well above the normal range soon after IV infusion; this apparently does not cause overt clinical signs but is associated with transient reductions in blood calcium. The presumed cause of this secondary hypocalcemia is the formation of insoluble calcium phosphate crystals in the bloodstream.<sup>20</sup> The value of IV phosphorus infusions must be weighed against risks associated with the subsequent hypocalcemia.

Do not mix IV sodium phosphate with calcium salts prior to administration, as the phosphates will immediately form insoluble calcium phosphate crystals in the bottle. Do not administer IV phosphorus within 2 hours after giving IV calcium, as the abundance of calcium will simply favor the formation of insoluble calcium phosphate crystals in the bloodstream.<sup>13</sup>

Some saline enemas designed for use in humans contain a reasonable dose of phosphorus (6 to 7 grams) from reasonable sources (monobasic and dibasic sodium phosphate). Thus, saline enemas have been used for IV treatment of hypophosphatemia in dairy cattle. The enema solution should first be diluted with water to 1000 mL in order to reduce the tonicity of the IV infusion.<sup>13</sup> The amounts and effects of other ingredients in these human enema solutions (benzalkonium chloride and disodium EDTA, for example) are unknown. Administering more than 1 saline enema IV (or any infusion of more than about 8 grams of phosphorus) will cause severe and unnecessary hyperphosphatemia. High blood phosphorus by itself is apparently not a clinical problem, but it could lead to more severe secondary hypocalcemia.<sup>20</sup>

### Ineffective sources of parenteral phosphorus.

Hypophosphites ( $\text{PO}_2$ ) such as calcium hypophosphite are often added to commercially available multiple electrolyte solutions labeled for the correction of hypocalcemia or hypophosphatemia. This is done because hypophosphites do not precipitate, as phosphates would. Unfortunately, phosphites are biologically unavailable to the cow.<sup>6</sup> Phosphates ( $\text{PO}_4$ ) are biologically available and are the dominant form of phosphorus in the body.<sup>13</sup> Phosphites are not metabolized and are simply excreted in the urine. They do no apparent harm, but have no value in treating hypophosphatemia. The addition of hypophosphites to multiple electrolyte IV solutions is unfortunate, and the label indication for these products falsely includes treatment of phosphorus deficiency.

Numerous products contain organic phosphorus sources that are labeled for parenteral use to correct phosphorus deficiencies. Examples of these include sodium glycerophosphate, butafosfan, toldimfos, and aminoethyl dihydrogen phosphate. None of these products is recommended. All either use a metabolically useless form of phosphorus or severely under dose phosphorus even if the source might be metabolically useful.<sup>20</sup>

**Oral treatment for hypophosphatemia.** Oral supplementation of phosphorus is the preferred method of correcting and sustaining blood phosphorus in mild to moderate cases of hypophosphatemia.<sup>20</sup> An example of oral phosphorus supplementation is 200 to 300 grams of feed-grade monosodium phosphate ( $\text{NaH}_2\text{PO}_4$ ) mixed with about 1.5 L warm water and administered via oro-gastric tube or as a drench.<sup>13,18</sup> Pumping the solution is preferred, as oral drenching results in about a 13% loss of product due to spillage.<sup>23</sup> As mentioned previously, extreme care must be used administering oral supplements to recumbent cows.

Oral administration of 200 to 300 grams of monosodium phosphate provides 45 to 67 grams of phosphorus. This dose seems adequate to support blood phosphorus concentrations for about 12 to 24 hours without causing hyperphosphatemia.<sup>13,23</sup> Monopotassium phosphate ( $\text{KH}_2\text{PO}_4$ ) at a similar dose (263 grams, which provides 60 grams of phosphorus) is similarly effective in supporting blood phosphorus.<sup>23</sup> Monopotassium phosphate has the advantage of providing an effective dose of available potassium as well, which could be needed during periods of anorexia in early lactation cows. Monocalcium phosphate ( $\text{Ca}(\text{H}_2\text{PO}_4)_2$ ) raises blood phosphorus concentrations somewhat, but not as much as the monosodium or monopotassium phosphates.<sup>23</sup> Dicalcium phosphate ( $\text{CaHPO}_4$ ) has little to no effect on blood phosphorus concentrations and is not considered an effective oral phosphorus supplement.<sup>23,49</sup>

It is possible to administer oral monosodium phosphate or monopotassium phosphate in gelatin capsules.<sup>13</sup> A number 7 gelatin capsule (1.5 ounces) has a 24 mL capacity and should hold about 49 grams of monosodium phosphate (2.03 grams per cubic centimeter) or 56 grams of monopotas-

sium phosphate (2.34 grams per cubic centimeter). Thus, a reasonable dose would be about 4 to 6 capsules of this size per cow for either compound.

This author is not aware of any commercially available paste, gel, or bolus formulations that provide a comparable amount of phosphorus from monosodium phosphate. Oral products in the US that contain phosphorus typically are combined with other nutrients and provide relatively small amounts of phosphorus from less available sources. These products create a false impression that they are useful for correcting hypophosphatemia.

#### **Subcutaneous treatment for hypophosphatemia.**

As for IV treatments, there are no commercially available products for subcutaneous administration of phosphorus. The subcutaneous administration of monosodium phosphate solutions is strongly discouraged.

Unbuffered preparations of monosodium phosphate have a very low pH (< 3.5) and will likely cause severe tissue irritation if given subcutaneously.<sup>33</sup> Unfortunately, buffering a monosodium phosphate solution to a pH above about 5.8 will impair its solubility.<sup>13</sup>

#### **Diagnosis and Treatment for Hypomagnesemia**

**Clinical hypomagnesemia.** Clinical hypomagnesemia (grass tetany) is uncommon in dairy cattle housed in confinement facilities and fed stored feeds. However, it can be a problem in grazing herds during the spring months, when pasture is relatively high in potassium and low in magnesium. Potassium is very soluble in water and is readily taken up by plants during the wet, early spring months. Unfortunately, soil potassium competes with magnesium for plant uptake and ruminal potassium competes with magnesium for ruminal absorption. Grass tetany may be seen year-round in the southern USA on cool season pasture grasses during periods of high moisture. Cows have no readily available body stores of magnesium and must consume adequate amounts of available magnesium from the diet each day.

The clinical signs of grass tetany in grazing cows are readily recognized. Affected cows initially have mild anorexia that progresses to hyperexcitability. Affected cows may separate from the rest of the herd. Upon closer examination, they may display ear twitching, muscle fasciculations and hyperesthesia around the head. Some cows can be maniacal and aggressive. These signs quickly progress to more severe whole body tremors, ataxia and recumbency with seizure activity. Low magnesium concentrations in the CSF are thought to be the main cause for the clinical signs of grass tetany.<sup>1,42</sup> The diagnosis of clinical hypomagnesemia can be confirmed by pre-treatment blood magnesium below 0.5 mmol/L (1.1 mg/dL) or preferably cerebrospinal fluid (CSF) magnesium below 0.4 mmol/L (<1.0 mg/dl).<sup>13</sup> Blood magnesium concentrations may occasionally be unreliable (falsely normal) because severe tetany may cause damage to muscle cells and

leakage of magnesium from the cells (which have relatively high magnesium concentrations) into circulation. Magnesium concentration in the CSF is not affected by muscle damage and is a reliable indicator of magnesium status during episodes of tetany and for up to 12 hours after death.<sup>13</sup>

Hypomagnesemic cows that exhibit signs of tetany are almost certainly hypocalcemic, as well. Tetany may not even be possible unless the cow is also hypocalcemic.<sup>15</sup>

**Treatment of clinical hypomagnesemia.** Cows with clinical hypomagnesemia need treatment with parenteral magnesium and calcium. Calcium is included in the treatment because affected cows are also hypocalcemic, and because intravenous calcium reduces the severity of the potential side effects of IV magnesium such as respiratory paralysis and cardiac arrest. An appropriate magnesium dose has been reasonably estimated to be between 1.5 and 2.25 grams. This allows for 50 to 75% replacement of all of the cow's extracellular magnesium.<sup>13</sup> Multiple electrolyte preparations available in the US typically contain about 1.6 grams of magnesium from magnesium borogluconate, which is an adequate dose.

Other components of some multiple electrolyte solutions may be unnecessary (phosphorus and potassium) or potentially harmful (glucose – since cows with clinical hypomagnesemia are likely to already be hyperglycemic). Nonetheless, a multiple electrolyte solution that contains both magnesium and calcium may be the most practical choice for the initial correction of severe hypomagnesemia.

Intracellular magnesium concentrations are very high relative to extracellular magnesium and represent about 29% of total body magnesium.<sup>47</sup> However, intracellular magnesium does not appear to be depleted during hypomagnesemia.<sup>13</sup> Correction of the extracellular magnesium deficit should be sufficient.

Cows with clinical grass tetany should be treated IV whenever practical.<sup>13</sup> The infusion should be given as slowly as possible, with careful monitoring of heart and respiratory rates.

Some cows affected with clinical grass tetany are too aggressive for IV treatment. In these cases, the solution may be administered by safer routes. Magnesium sulfate (about 200 to 400 mL of a 25% solution of  $MgSO_4 \cdot 7 H_2O$ ) can be given subcutaneously (50 to 100 mL per injection site).<sup>13</sup> This provides 4.9 to 9.9 grams of magnesium, which should be adequate. Absorption will be slower than if the cow was given IV magnesium. If the cow has cold extremities, she may have poor peripheral perfusion and not be a good candidate for subcutaneous magnesium. There are no commercially available magnesium solutions for injection in the US, so this preparation must be made up and sterilized by the veterinarian.

Expect the response to IV treatment to be slower for cows with clinical grass tetany than for cows with clinical milk fever. It takes time to restore magnesium in the CSF,

which is necessary for clinical recovery. The animal should not be stimulated during treatment, as this could trigger fatal convulsions. After IV treatment, cows should be left in a quiet location and allowed time (at least 30 minutes) to respond on their own without any stimulation to rise.<sup>13</sup>

Rectal administration of magnesium is indicated for hypomagnesemic cows with severe convulsions and/or poor peripheral perfusion. This route is safer for the cow and for the person administering the treatment. Example enema formulations are 60 grams of magnesium chloride or 60 grams of magnesium sulfate. Either compound may be dissolved in 200 mL warm water and administered by tube into the descending colon.<sup>13</sup> Absorption of magnesium is surprisingly good when administered rectally; blood magnesium concentrations increase within 10 minutes and CSF magnesium concentrations increase in about 30 minutes.<sup>44</sup> Cows should be observed to make sure that they do not prematurely evacuate the magnesium solution. Be careful not to administer more concentrated magnesium solutions rectally, as this could cause severe rectal mucosal sloughing.<sup>13</sup>

Hypomagnesemic relapses are highly likely to occur following initial treatment of clinical grass tetany unless preventive measures are taken. Options include subcutaneous administration of magnesium sulfate (200 mL of a 50% solution, which provides 9.9 grams magnesium). Alternatively, 400 mL of a 50% magnesium sulfate solution<sup>13</sup> (200 grams of magnesium sulfate in 400 mL of water) can be drenched orally; this provides 19.7 grams of magnesium. Extreme caution should be exercised if any oral supplement is given to a recumbent cow; the best approach is to defer oral magnesium administration until the cow is standing, alert, able to swallow, and not aggressive. This could be 30 to 90 minutes after the initial treatment.

Commercial gel preparations (typically packaged in 300 mL tubes) are also available in the US for oral magnesium supplementation. Most of these preparations are based on magnesium chloride, which is a very available source of magnesium. Some products provide about 6 grams of magnesium per tube; 2 or 3 tubes would provide a reasonable dose for prevention of hypomagnesemic relapses. Some multiple nutrient oral tubes provide only about 3 grams of magnesium per tube, which is probably not an adequate dose. The other nutrients in the tube may be helpful, depending on the clinical situation.

Fresh cow drench formulations typically provide about 200 grams of magnesium sulfate (19.7 grams of magnesium), along with other nutrients such as calcium, a glucose precursor, phosphorus, or potassium. This category of drench product is appropriate for preventing hypomagnesemic relapses.

**Subclinical hypomagnesemia.** Most hypomagnesemia in dairy cattle managed in confinement is subclinical. Subclinical hypomagnesemia can be diagnosed at the herd level by evaluating blood magnesium concentrations in apparently healthy cows. The cutpoint that defines subclinical

hypomagnesemia has not been formally characterized but is probably about 0.74 mmol/L (1.8 mg/dL). Unfortunately, there has been no evaluation of the optimal days-in-milk range for testing cows and no evaluation of appropriate alarm levels for herd-level hypomagnesemia. The author's limited clinical experience suggests that the highest-risk period for subclinical hypomagnesemia may be about 4 to 14 days-in-milk, and a reasonable alarm level may be over about 15% of the herd affected with subclinical hypomagnesemia.

There is no cowside test for diagnosing subclinical hypomagnesemia, so blanket treatment strategies are the only option for treatment. Unfortunately, there are no studies to evaluate the effectiveness of blanket oral magnesium supplementation strategies.

The most logical treatment for subclinical hypomagnesemia is oral supplementation. An oral drench containing about 200 grams of magnesium sulfate (19.7 grams of elemental magnesium) has been suggested.<sup>13</sup> Magnesium sulfate at this dose (which is well below the dose at which magnesium sulfate would cause catharsis) is very appropriately included in many fresh cow drench products.

### Diagnosis and Treatment for Hyperketonemia (Ketosis)

**Overview of hyperketonemia.** Ketosis occurs in early lactation dairy cows when 2 conditions are met: 1) energy demands (dominantly from milk production) exceed dietary energy intake, resulting in negative energy balance and 2) negative energy balance is sufficient to cause excessive mobilization of body adipose tissue relative to carbohydrate supply, leading to incomplete oxidation of fatty acids and production of ketone bodies. Because the clinical signs of ketosis are vague and because the key blood ketone (beta-hydroxybutyric acid or BHBA) can be measured rapidly and inexpensively with a cowside test, ketosis is best described as hyperketonemia based on blood BHBA  $\geq 1.2$  mmol/L. Approximately 40% of postpartum cows experience at least 1 hyperketonemic event in early lactation.<sup>31</sup> Early detection followed by early treatment of hyperketonemia is very beneficial in terms of both clinical outcomes and economic returns.<sup>29,30,32</sup>

**Intravenous treatment of hyperketonemia.** The traditional approach to treating hyperketonemia has been with IV glucose, usually dosed as 500 mL of a 50% solution and infused rapidly. The value of IV glucose for treating hyperketonemia (especially mild to moderate cases) is uncertain, and information regarding the effectiveness of IV glucose from controlled clinical studies is surprisingly lacking.<sup>16</sup>

A 50% glucose solution is 10 times the isotonic concentration of glucose. Hypertonic glucose given IV acts as an osmotic diuretic with the potential to increase urinary excretion of electrolytes. In addition, IV infusion of 50% glucose rapidly increases blood glucose to very high concentrations



(about 170 mg/dL for a 500 mL infusion and 310 mg/dL for a single 1000 mL infusion).<sup>53</sup> These concentrations exceed the renal threshold for glucose (about 100 to 140 mg/dL), leading to glucosuria and potential electrolyte loss. Blood glucose concentrations return to baseline values in about 1.5 hours after IV administration.<sup>19</sup> Hyperglycemia also has the potential to interfere with the normal process of hepatic gluconeogenesis and cause a rebound hypoglycemia.

Significant hypophosphatemia follows IV administration of 500 mL of 50% glucose.<sup>18,53</sup> The authors advised caution when administering glucose intravenously to cows already at risk for hypophosphatemia. Unfortunately, there are no clear criteria for identifying such cows.

Intravenous glucose is often reserved for use in cows with more severe hyperketonemia and is administered in conjunction with oral propylene glycol. A recent report indicated that IV glucose (500 mL of a 50% solution once daily for 3 days) in combination with oral propylene glycol (300 mL once daily for 3 days) was more effective in lowering blood BHBA than either treatment alone.<sup>27</sup>

Using a lower dose of IV glucose (e.g., 250 mL of 50% glucose, which provides 125 grams of glucose) has been advocated based on empirical evidence that 250 grams of intravenous glucose is a very large dose with the potential to impair gluconeogenesis in the liver. This has not been evaluated experimentally, but appears to be a reasonable physiological concern.

Long-term hyperglycemia reduces GI motility and could be a risk factor for displaced abomasum (DA).<sup>21</sup> However, no studies have evaluated the effects of a single dose of IV glucose on GI motility.

The duration of the suppression of blood BHBA following IV glucose administration is very short (<12 hours).<sup>53</sup> This suggests that when IV glucose is given, oral propylene glycol should be administered at the same time.

Future experiments are very much needed to clarify the benefits and potential risks from giving IV glucose to treat hyperketonemia. In the meantime, it seems prudent to limit the use of IV glucose to severe cases, to consider using a lower dose of IV glucose, and to follow IV glucose administration with oral propylene glycol.

**Oral treatment of hyperketonemia.** Oral glucose precursors are the preferred treatment for mild to moderate cases of hyperketonemia (blood BHBA between 1.2 and 2.9 mmol/L). The effectiveness of 300 mL propylene glycol for this purpose has been clearly demonstrated.<sup>29,30</sup> In a large, randomized, and controlled study, cows with blood BHBA between 1.2 and 2.9 mmol/L that were treated with propylene glycol were 1.50 times more likely to resolve their hyperketonemia by 16 days-in-milk, were 1.85 times less likely to develop severe hyperketonemia (blood BHBA  $\geq$ 3.0 mmol/L), gave about 3.3 lb (1.5 kg) more daily milk (for 2 of the 4 farms enrolled in the study), were 1.6 times less likely to develop a displaced abomasum (DA), were 2.1 times less

likely to be removed from the herd by 30 days-in-milk, and were 1.3 times more likely to conceive at first service (in 3 of the 4 study herds) compared with cows that had mild to moderate hyperketonemia and were not treated.<sup>29,30</sup> The economic benefits of aggressive early diagnosis and early treatment of hyperketonemia are impressive.<sup>32</sup> The best return for dairy herds with a typical prevalence of hyperketonemia comes from blanket testing cows twice between 2 and 9 days-in-milk.

Cows with low blood glucose (<2.2 mmol/L or 39.6 mg/dL) along with hyperketonemia respond better to oral propylene glycol treatment than cows with higher blood glucose.<sup>17</sup> Low blood glucose was found in 37% of the hyperketonemic cows. This is an interesting finding; however, it is difficult to apply under field conditions.

## Diagnosis and Treatment for Hypokalemia

**Hypokalemia overview.** Hypokalemia may occur in early lactation dairy cows due to prolonged anorexia (often associated with chronic ketosis or another primary condition). Additional risk factors include repeated administration of isofluprednone acetate, IV glucose, or insulin.<sup>14</sup> Depletion of total body potassium leads to severe muscle weakness and flaccid paralysis.<sup>46</sup> The flaccid paralysis can be so severe that cows have a complete inability to keep their head in a straight position and cannot eat unless their head is placed into a feed bucket.<sup>46</sup>

Hypokalemia is confirmed by low serum or plasma potassium. Samples must be separated from the red blood cells within about an hour after calving; otherwise, potassium from the red blood cells (which is approximately 30 times greater than in serum or plasma<sup>14</sup>) could falsely elevate the measured potassium concentration and cause the diagnosis to be missed. Blood potassium below the normal range (<3.9 mEq/L) is considered hypokalemia, although most cows with clinical signs of hypokalemia have blood potassium concentrations below about 2.5 mEq/L.<sup>7,46</sup> There is no consensus on the exact cut point for blood potassium that defines hypokalemia.<sup>46</sup>

About 25 to 40% of cases of hypokalemia are also hypophosphatemic.<sup>46</sup> Both conditions may be related to prolonged anorexia.

**Intravenous treatment of hypokalemia.** Treatment of hypokalemia via IV infusions requires slow infusion and daily monitoring of blood potassium.<sup>46</sup> This is rarely practical under field conditions. The rate of IV infusion should not exceed 0.5 mEq of potassium per kg bodyweight per hour.

**Oral treatment of hypokalemia.** Oral administration of potassium chloride is the method of choice for treating clinical cases of hypokalemia. Potassium chloride provides the needed potassium to help correct whole-body potassium depletion, and chloride is needed for cows that may

be alkalemic and have a pH-induced compartmental shift of potassium into the intracellular space.<sup>7</sup>

Current recommendations are to dose oral potassium chloride at 0.88 g/lb (0.4 g/kg) body weight (300 grams of potassium chloride for a 1650 lb [750 kg] cow), divided into 2 or more treatments during the 24 hour period.<sup>8</sup> This practically translates to an initial treatment of about 150 grams of potassium chloride (79 grams of potassium and 71 grams of chloride) that is repeated 12 hours later. There was no advantage of dividing this dose into 8 smaller doses administered every 3 hours.<sup>8</sup> Higher doses of oral potassium chloride are dangerous (due to risk for diarrhea, convulsions, or death) and should be reserved for cows with severe hypokalemia.<sup>8,43</sup> Oral supplementation is often necessary for 3 to 5 days.

**Prevention of hypokalemia.** Essentially all cases of hypokalemia can be prevented by avoiding repeated administration of isofluprednone acetate, IV glucose, or insulin and by supplementing early lactation cows that are anorectic more than 3 days with oral potassium chloride. An empiric dose of 100 grams of potassium chloride once daily appears to be safe and effective.<sup>46</sup> Oral potassium chloride may be supplemented as part of a fresh cow drench package (most commercial drench mixes in the US provide this much potassium chloride) or in gelatin capsules. A number 7 gelatin capsule (1.5 ounce) has a 24 mL capacity and can hold about 48 grams of potassium chloride (1.98 grams per cubic centimeter). Thus, a reasonable dose is 2 capsules of this size per day.

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### References

- Allsop TF, Pauli JV. Magnesium concentrations in the ventricular and lumbar cerebrospinal fluid of hypomagnesaemic cows. *Res Vet Sci* 1985; 38:61-64.
- Austin J. Process for stabilization of calcium gluconate solutions. US Patent Office No. 2,007,786, 1935.
- Blanc CD, Van der List M, Aly SS, Rossow HA, Silva-del-Rio N. Blood calcium dynamics after prophylactic treatment of subclinical hypocalcemia with oral or intravenous calcium. *J Dairy Sci* 2014; 97:6901-6906.
- Braun U, Zullinger P, Liesegang A, Bieul U, Hassig M. Effect of intravenous calcium borogluconate and sodium phosphate in cows with parturient paresis. *Vet Rec* 2009; 164:296-299.
- Caixeta LS, Ospina PA, Capel MB, Nydam DV. Association between subclinical hypocalcemia in the first 3 days of lactation and reproductive performance of dairy cows. *Theriogenology* 2017; 94:1-7.
- Cheng Y, Goff JP, Horst RL. Restoring normal blood phosphorus concentrations in hypophosphatemic cattle with sodium phosphate. *Vet Med* 1998; 93:383-388.
- Constable P, Grünberg W, Staufenbiel R, Stampfli HR. Clinicopathologic variables associated with hypokalemia in lactating dairy cows with abomasal displacement or volvulus. *J Am Vet Med Assoc* 2013; 242:826-835.
- Constable PD, Hiew MW, Tinkler S, Townsend J. Efficacy of oral potassium chloride administration in treating lactating dairy cows with experimentally induced hypokalemia, hypochloremia, and alkalemia. *J Dairy Sci* 2014; 97:1413-1426.
- Curtis RA, Cote JF, McLennan MC, Smart JF, Rowe RC. Relationship of methods of treatment to relapse rate and serum levels of calcium and phosphorus in parturient hypocalcaemia. *Can Vet J* 1978; 19:155-158.
- Doze JG, Donders R, van der Kolk JH. Effects of intravenous administration of two volumes of calcium solution on plasma ionized calcium concentration and recovery from naturally occurring hypocalcemia in lactating dairy cows. *Am J Vet Res* 2008; 69:1346-1350.
- Ellenberger HB, Newlander JA, Jones CH. Calcium and phosphorus requirements of dairy cows. II. Weekly balances through lactation and gestation periods. *Vermont Agric Expt Sta Bull* 342, 1932.
- Goff JP, Horst RL. Oral administration of calcium salts for treatment of hypocalcemia in cattle. *J Dairy Sci* 1993; 76:101-108.
- Goff JP. Treatment of calcium, phosphorus, and magnesium balance disorders. *Vet Clin North Am Food Anim Pract* 1999; 15:619-639.
- Goff JP. Macromineral disorders of the transition cow. *Vet Clin North Am Food Anim Pract* 2004; 20:471-494.
- Goff JP. Calcium and magnesium disorders. *Vet Clin North Am Food Anim Pract* 2014; 30:359-381, vi.
- Gordon JL, Leblanc SJ, Duffield TF. Ketosis treatment in lactating dairy cattle. *Vet Clin North Am Food Anim Pract* 2013; 29:433-445.
- Gordon JL, LeBlanc SJ, Kelton DE, Herdt TH, Neuder L, Duffield TF. Randomized clinical field trial on the effects of butaphosphan-cyanocobalamin and propylene glycol on ketosis resolution and milk production. *J Dairy Sci* 2017; 100:3912-3921.
- Grünberg W, Morin DE, Drackley JK, Barger AM, Constable PD. Effect of continuous intravenous administration of a 50% dextrose solution on phosphorus homeostasis in dairy cows. *J Am Vet Med Assoc* 2006; 229:413-420.
- Grünberg W, Morin DE, Drackley JK, Constable PD. Effect of rapid intravenous administration of 50% dextrose solution on phosphorus homeostasis in postparturient dairy cows. *J Vet Intern Med* 2006; 20:1471-1478.
- Grünberg W. Treatment of phosphorus balance disorders. *Vet Clin North Am Food Anim Pract* 2014; 30:383-408.
- Holtenius K, Sternbauer K, Holtenius P. The effect of the plasma glucose level on the abomasal function in dairy cows. *J Anim Sci* 2000; 78:1930-1935.
- House WA, Bell AW. Mineral accretion in the fetus and adnexa during late gestation in Holstein cows. *J Dairy Sci* 1993; 76:2999-3010.
- Idink MJ, Grünberg W. Enteral administration of monosodium phosphate, monopotassium phosphate and monocalcium phosphate for the treatment of hypophosphataemia in lactating dairy cattle. *Vet Rec* 2015; 176:494.
- Jorgensen RJ, Nyengaard NR, Hara S, Enemark JM, Andersen PH. Rumen motility during induced hyper- and hypocalcaemia. *Acta Vet Scand* 1998; 39:331-338.
- Larsen T, Moller G, Bellio R. Evaluation of clinical and clinical chemical parameters in periparturient cows. *J Dairy Sci* 2001; 84:1749-1758.
- Little dike ET, Glazier D, Cook HM. Electrocardiographic changes after induced hypercalcemia and hypocalcemia in cattle: reversal of the induced arrhythmia with atropine. *Am J Vet Res* 1976; 37:383-388.
- Mann S, Yepes FAL, Behling-Kelly E, McArt JAA. The effect of different treatments for early-lactation hyperketonemia on blood beta-hydroxybutyrate, plasma nonesterified fatty acids, glucose, insulin, and glucagon in dairy cattle. *J Dairy Sci* 2017; 100:6470-6482.
- Martinez N, Risco CA, Lima FS, Bisinotto RS, Greco LF, Ribeiro ES, Maunsell F, Galvao K, Santos JE. Evaluation of periparturient calcium status, energetic profile, and neutrophil function in dairy cows at low or high risk of developing uterine disease. *J Dairy Sci* 2012; 95:7158-7172.
- McArt JA, Nydam DV, Ospina PA, Oetzel GR. A field trial on the effect of propylene glycol on milk yield and resolution of ketosis in fresh cows diagnosed with subclinical ketosis. *J Dairy Sci* 2011; 94:6011-6020.
- McArt JA, Nydam DV, Oetzel GR. A field trial on the effect of propylene glycol on displaced abomasum, removal from herd, and reproduction in fresh cows diagnosed with subclinical ketosis. *J Dairy Sci* 2012; 95:2505-2512.
- McArt JA, Nydam DV, Oetzel GR. Epidemiology of subclinical ketosis in early lactation dairy cattle. *J Dairy Sci* 2012; 95:5056-5066.

32. McArt JAA, Nydam DV, Oetzel GR, Guard CL. An economic analysis of hyperketonemia testing and propylene glycol treatment strategies in early lactation dairy cattle. *Prev Vet Med* 2014; 117:170-179.
33. McCaughan CJ. Treatment of mineral disorders in cattle. *Vet Clin North Am Food Anim Pract* 1992; 8:107-145.
34. Ménard L, Thompson A. Milk fever and alert downer cows: Does hypophosphatemia affect the treatment response? *Can Vet J* 2007; 48:487-491.
35. Montiel L, Tremblay A, Girard V, Chorfi Y. Preanalytical factors affecting blood inorganic phosphate concentration in dairy cows. *Vet Clin Path* 2007; 36:278-280.
36. Mullen PA. Clinical and biochemical responses to the treatment of milk fever. *Vet Rec* 1975; 97:87-92.
37. Mullen PA. Milk fever: A case against polypharmacy solutions. *Vet Rec* 1977; 101:405-407.
38. National Research Council. *Nutrient Requirements of Dairy Cattle*. 7th rev ed: Natl Acad Sci, Washington, DC, 2001.
39. Oetzel GR. Parturient paresis and hypocalcemia in ruminant livestock. *Vet Clin North Am Food Anim Pract* 1988; 4:351-364.
40. Oetzel GR, Miller BE. Effect of oral calcium bolus supplementation on early-lactation health and milk yield in commercial dairy herds. *J Dairy Sci* 2012; 95:7051-7065.
41. Oetzel GR. Undertaking nutritional diagnostic investigations. *Vet Clin North Am Food Anim Pract* 2014; 30:765-788.
42. Pauli JV, Allsop TF. Plasma and cerebrospinal fluid magnesium, calcium and potassium concentrations in dairy cows with hypomagnesaemic tetany. *NZ Vet J* 1974; 22:227-331.
43. Peek SF, Divers TJ, Rebhun WC. Hypokalemia in dairy cattle. *Compend Contin Educ Pract Vet* 2002; 24:S18-S24.
44. Reynolds CK, Bell MC, Sims MH. Changes in plasma, red blood cell and cerebrospinal fluid mineral concentrations in calves during magnesium depletion followed by repletion with rectally infused magnesium chloride. *J Nutr* 1984; 114:1334-1341.
45. Rodriguez EM, Aris A, Bach A. Associations between subclinical hypocalcemia and postparturient diseases in dairy cows. *J Dairy Sci* 2017; 100:7427-7434.
46. Sattler N, Fecteau G. Hypokalemia syndrome in cattle. *Vet Clin North Am Food Anim Pract* 2014; 30:351-357.
47. Schonewille JT. Magnesium in dairy cow nutrition: An overview. *Plant and Soil* 2013; 368:167-178.
48. Shappell NW, Herbein JH, Deftos LJ, Aiello RJ. Effects of dietary calcium and age on parathyroid hormone, calcitonin and serum and milk minerals in the periparturient dairy cow. *J Nutr* 1987; 117:201-207.
49. Shu S, Bai Y, Wang G, Xiao X, Fan Z, Zhang J, Zhao C, Zhao Y, Xia C, Zhang H. Differentially expressed serum proteins associated with calcium regulation and hypocalcemia in dairy cows. *Asian-Australasian J Anim Sci* 2017; 30:893-901.
50. Smith BP, George LW, Angelos S, House JK. Down cows: Causes and treatments. *Proceedings. 30<sup>th</sup> Annu Conf Am Assoc Bov Pract* 1997; 43-45.
51. Taylor MS, Knowlton KF, McGilliard ML, Swecker WS, Ferguson JD, Wu Z, Hanigan MD. Dietary calcium has little effect on mineral balance and bone mineral metabolism through twenty weeks of lactation in Holstein cows. *J Dairy Sci* 2009; 92:223-237.
52. Thilsing-Hansen T, Jørgensen RJ, Østergaard S. Milk fever control principles: A review. *Acta Vet Scand* 2002; 43:1-19.
53. Wagner SA, Schimek DE. Evaluation of the effect of bolus administration of 50% dextrose solution on measures of electrolyte and energy balance in postpartum dairy cows. *Am J Vet Res* 2010; 71:1074-1080.