Rational treatments for ketosis in fresh cows

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Abstract

Hyperketonemia affects over 40% of dairy cows in early lactation. The prevalence of hyperketonemia (determined by spot checks within herds) is about 20%. Negative impacts of hyperketonemia most notably include decreased milk yield, increased risk for displaced abomasum, and increased risk for early lactation herd removal. Cowside blood beta-hydroxybutyrate tests are now available for rapid and accurate diagnosis of hyperketonemia. Urine and milk tests can also be used, but have substantial disadvantages. Accurate and early diagnosis of hyperketonemia after calving allows early and effective treatment. This mitigates about half of the negative impacts of hyperketonemia such as decreased milk yield, increased risk for displaced abomasum, and increased risk for herd removal. Mild to moderate cases of hyperketonemia in individual cows are best treated with an oral glucose precursor such as propylene glycol. Intravenous glucose should be reserved for severe cases and followed with oral glucose precursors.

Key words: fresh cow metabolic disease, ketosis, hyperketonemia

Résumé

L'acétonémie affecte plus de 40% des vaches laitières en début de lactation. La prévalence d'acétonémie (déterminée par des vérifications ponctuelles dans les troupeaux) est d'environ 20%. Les impacts négatifs les plus fréquents de l'acétonémie incluent une baisse de production laitière, un risque plus élevé de déplacement de caillette et un risque plus élevé de retrait du troupeau tôt en lactation. Des tests du bêta-hydroxybutyrate sanguin sont maintenant disponibles à la ferme pour le diagnostic rapide et précis de l'acétonémie. Des tests d'urine et de lait peuvent aussi être utilisés mais ont de sérieux désavantages. Le diagnostic précis et précoce de l'acétonémie après le vêlage permet un traitement efficace et hâtif. Cela permet d'éviter près de la moitié des impacts négatifs de l'acétonémie comme la baisse de production laitière, le risque plus élevé de déplacement de caillette et le risque plus élevé de retrait du troupeau. Les cas légers à modérés d'acétonémie chez des vaches particulières se traitent le mieux avec l'ajout d'un précurseur du glucose par voie orale comme le propylène glycol. L'administration intraveineuse de glucose devrait être réservée pour les cas sévères et suivie de l'ajout de précurseurs du glucose par voie orale.

Introduction

Hyperketonemia (HYK) is one of the most crucial problems faced by early lactation dairy cattle. Older and higher producing cattle are at the highest risk to develop HYK. The overall risk for HYK is unlikely to abate as genetic progress pushes individual cow milk production higher.

Our ability to understand and to mitigate hyperketonemia has been greatly aided by the availability of cowside blood testing. As a result, we have learned much about this metabolic disorder that can be practically applied on dairies. This paper will review the current science and clinical reasoning for appropriate diagnostic and treatment protocols for HYK in fresh dairy cows.

Overview of Hyperketonemia (Ketosis)

Hyperketonemia 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. The end result is incomplete oxidation of fatty acids, production of ketone bodies, and HYK.

Ketosis is best described as HYK, which in turn is defined as defined as blood beta-hydroxybutyric acid (BHBA) concentrations ≥1.2 mmol/L. Ketosis technically describes a clinical condition; however, the clinical signs of ketosis are vague and largely determined by the subjective skill of the fresh cow observer. We now have a blood BHBA test that allows for rapid and inexpensive blood BHBA determination cowside. This makes it practical to discuss the precisely-defined condition of HYK instead of the vaguely-defined condition of ketosis.

Incidence vs Prevalence of Hyperketonemia

The incidence and prevalence of HYK are often confused. Incidence is the number of new cases of HYK that occurred during the risk period (early lactation) divided by the number of cows who completed the risk period. Most new cases of HYK occur within the first week after calving in intensively managed herds.[17] Cows that are housed in individual stalls and component-fed may develop HYK later (3 to 6 weeks after calving). A specific time period over which the incidence of HYK is measured must be specified (e.g., a week, a month, or a year).

Repeated testing of cows throughout the entire risk period is required to determine the incidence of HYK.

Sampling for HYK must occur twice or more weekly to assess the incidence of SCK, because the median time for the resolution of HYK is about 5 days.[17] A cow might potentially develop and resolve her HYK between test intervals if she was tested only once weekly.[17] Research trials are usually required for the determination of the incidence of HYK. Testing for HYK twice or more weekly throughout early lactation is very costly for a commercial dairy herd.

One large field study (1,756 cows from 4 dairy herds in 2 states) reported a 44% incidence of HYK.[19] Cows were tested 3 times weekly between 3 and 16 days-in-milk (DIM). Hyperketonemia cases were divided into 2 categories: 1) subclinical ketosis (SCK), defined as blood BHBA 1.2 to 2.9 mmol/L at first diagnosis of HYK; and 2) clinical ketosis, defined as blood BHBA ≥3.0 mmol/L at first diagnosis of HYK. The incidence of clinical ketosis was 2% and the incidence of SCK was 42%. Some cows (3%) were initially categorized as SCK and developed clinical ketosis on later tests; including these cows as clinical ketosis increased the overall risk for clinical ketosis to 5%.[19] Another large-scale study reported a similar incidence of HYK.[7]

Prevalence is a 'snapshot' measure of the current HYK status of a group of cows. It is defined as the proportion of cows with blood BHBA concentrations ≥1.2 mmol/L at a given point in time. Prevalence testing is much more practical than incidence testing because it does not require repeated testing of individual cows. The prevalence of HYK is typically determined for a subset of the early lactation cows within a herd. Herds can be repeatedly tested for HYK and the results pooled into a cumulative prevalence; this increases the reliability of the estimate of the herd's true prevalence of HYK. For practical reasons, almost all herd-level evaluations for HYK are conducted as prevalence testing.

Knowing the incidence of HYK in a herd is far more useful than knowing the herd's prevalence. For example, any economic estimate of the cost of HYK must be based on its incidence (not prevalence). Fortunately, the incidence of HYK can be estimated by multiplying the prevalence by about 2.25. This factor was derived from a large field study in which the measured incidence of HYK was 2.25 X the prevalence (45% incidence and 20% prevalence).[7]

Effects of Hyperketonemia on Production and Health

Hyperketonemia and milk production. Many studies report reduced milk yield (about 3 to 7% less) in cows experiencing HYK.[4,19,21] These studies compared milk yield in cows with spontaneous HYK to cows with normal blood BHBA concentrations. Because higher producing cows have inherently higher risk for HYK, this approach probably underestimates the reduction in milk yield associated with it.

One large field study reported that the negative impact of HYK on first test milk yield was linear; each additional 0.1 mmol/L increase in BHBA (beyond the 1.2 mmol/L threshold) was associated with 1.1 lb (0.5 kg) reduced milk yield.[19] For example, the difference between modest (1.2 mmol/L) and moderate HYK (2.4 mmol/L) was 13.2 lb (6.0 kg) less milk yield at first test.

Days-in-milk at the first onset of HYK has also been reported to affect the severity of milk yield loss associated with HYK. Cows first diagnosed with SCK between 3 and 7 DIM produced 4.6 lb (2.1 kg or about 6.0%) less milk at first test compared to cows first diagnosed with SCK between 8 and 16 DIM.[19]

Some studies report higher milk yield in cows affected with HYK.[14,23] These may represent milder cases of HYK, or HYK that was promptly detected and treated.

Hyperketonemia and displaced abomasum. Numerous studies have reported that HYK substantially increases the risk for displaced abomasum (DA).[6,16,22] Cows with more severe HYK at the onset of their SCK had even greater risk for DA; each 0.1 mmol/L increase in BHBA at the first SCK-positive test increased the risk for subsequent DA by a factor of 1.1.[16] Thus, a cow with an initial blood BHBA of 2.4 mmol/L at the onset of her HYK had a 3.1-fold increased risk for a subsequent DA compared to a cow with an initial BHBA concentration of 1.2 mmol/L. Earlier onset of SCK also increased the risk for DA; cows who first developed SCK between 3 and 5 DIM were 6.1 X more likely to develop a DA compared to cows first testing positive for SCK between 6 and 16 DIM.[17]

Hyperketonemia and metritis. Hyperketonemia and metritis occur in nearly the exact same window of DIM. This makes it difficult to determine which condition is primary and which is secondary. One study reported that HYK in the first week after calving increased the odds for metritis by 3.4 X.[6]

Hyperketonemia and herd removal. Early lactation HYK appears to increase the risk for early lactation herd removal (sold or died). In one report, cows with SCK were 3.0 X more likely to be removed from the herd in the first 30 DIM compared to cows with normal blood BHBA.[17] Each 0.1 mmol/L increase in BHBA increased the risk for herd removal 1.4 times. For example, cows with a blood BHBA of 2.4 mmol/L at the onset of SCK would (remarkably) be at 57 times higher risk for herd removal by 30 DIM than a cow with a blood BHBA of 1.2 mmol/L at her onset of SCK.[17]

Hyperketonemia and reproduction. Associations between SCK and fertility have been inconsistent. Several studies have reported negative associations of SCK with reproductive outcomes.[21,24,29] Other studies have reported no effect of SCK on subsequent fertility.[2,16] It is possible that ovulation synchronization programs limit the negative impacts of HYK on reproductive performance.

On-Farm Detection of Hyperketonemia

Early detection of HYK followed by early treatment of HYK is very beneficial in terms of both clinical outcomes and economic returns.[16,19] This becomes particularly important

in light of the fact that about 40% or more cows develop HYK sometime in early lactation. Cowside testing is necessary to diagnose these cows as soon as possible so that treatment can be initiated.

Cowside blood BHBA tests. A blood BHBA test is the preferred cowside test for HYK because of its excellent test accuracy. The Precision Xtra® blood ketone monitoring system[a] has been extensively evaluated for use as a cowside blood BHBA test in early lactation dairy cows. A meta-analysis reported that it has very high summary sensitivity (94.8%) and very high summary specificity (97.5%) at the 1.2 mmol/L cutpoint. The price of the Precision Xtra® test increased dramatically in the US about 5 years ago, which greatly limited its use as a cowside BHBA test. A similar cowside BHBA test (BHBCheck™ blood ketone test system[b]) based on the same test principle is now available in the US market. It had nearly identical test performance to Precision Xtra® when tested under field conditions[25] and is reasonably priced (about $2.00 USD per strip and $25 USD for the meter).

Cowside urine ketone tests. The traditional cowside test for HYK in the US is a semi-quantitative urine strip that measures urine acetoacetate. A meta-analysis of published studies using KetoStix® reagent strips for urinalysis[c] reported 87.6% summary sensitivity and 89.2% summary specificity for predicting HYK using the trace (0.5 mmol/L) threshold on the urine test stip.[26] However, the threshold most commonly used is the field is the "small" reading (1.5 mmol/L). The sensitivity of the KetoStix® dropped to 70.5% using this threshold.[26] The main practical limitation of using urine as the test medium for HYK is the difficulty in collecting a urine sample.

Cowside milk ketone tests. Milk-based tests can be used to diagnose HYK in dairy cows; however, they have reduced sensitivity and specificity compared to blood tests. Milk-based tests for HYK are fundamentally limited because the udder has different options for handling the ketones bodies it takes up from the bloodstream. It may either utilize the ketones or excrete them in the milk. The proportion of ketones either utilized or excreted by the udder varies by week after calving and by HYK status.[20]

Keto-Test® milk ketone body test strips[d] are a cowside HYK test that measures milk BHBA. A meta-analysis of published studies using this test compared to the gold standard of laboratory blood BHBA reported a summary sensitivity of 81.5% and a summary specificity of 81.9% using weak positive (0.1 mmol/L) as the milk test threshold.[26] A similar milk BHBA test (PortaBHB® milk ketosis test[e]) has also been evaluated and produced similar results.[3]

Milk acetoacetate tests (usually test powders) are also available for cowside HYK testing. However, they have very low sensitivity and are not recommended.[26]

Automated milk ketone tests from herd monthly milk samples. Milk samples collected as part of routine herd production monitoring are often tested for milk ketones. These approaches have minimal utility at the cow level because cows are typically tested only once per month. Their best use is for herd-level inference and not for cow-level treatment decisions.[27]

Milk BHBA can be determined in samples from routine herd testing by using automated milk testing equipment; however, milk BHBA alone is only moderately associated with blood BHBA.[27] A more robust approach, available commercially as the KetoMonitor® test day option[f], predicts blood BHBA using automated milk ketone measures plus other test day variables.[1] The accuracy of the prediction of blood BHBA using KetoMonitor® was also enhanced by developing different models by breed (Holsteins vs. Jerseys), by parity groups, and by DIM groups.[1]

Milk fat to protein ratios. Hyperketonemia is associated with increased milk fat percentage with simultaneously decreased milk protein percentage. Thus, the ratio of milk fat to protein (usually evaluated only at the first monthly DHIA test) often increases to above 1.4 during HYK. Milk fat to protein ratios are readily available and involve minimal extra expense beyond normal monthly herd tests. They have some (although limited) value in characterizing herd-level ketosis. In-line milk testing equipment can estimate milk fat to protein ratios at each milking, in real time. However, increased milk fat to protein ratios are not considered accurate enough to diagnose HYK in individual cows.[5,13]

Benefits of Early Detection and Early Treatment of Hyperketonemia

Early detection of HYK followed by early treatment is exceptionally beneficial in terms of both clinical outcomes and economic returns.[16,18,19] Early detection of SCK using a cowside blood BHBA test and early treatment of SCK with propylene glycol (300 ml orally once daily until the HYK resolved) improved milk production by about 3.3 lb (1.5 kg) of daily milk compared to cows whose SCK was left untreated.[19] Early detection and treatment of SCK also reduced the risk for early lactation removal by 2.1X, reduced the risk for DA by 1.6X, and increased first service conception.[16]

The prevention of HYK is obviously of paramount importance to dairy producers. Nonetheless, dairy producers neglect an exceptionally rewarding opportunity if they fail to use current technologies for early detection and early treatment of HYK.

Intravenous Treatment of Hyperketonemia

The traditional approach for individual cows with HYK has been to administer IV glucose. A typical dose has been 500 mL of a 50% solution, infused rapidly. However, the effectiveness of IV glucose for treating HYK (especially mild to moderate cases) is uncertain, and information regarding the effectiveness of IV glucose from controlled clinical studies is surprisingly lacking.[8]

It is very possible that our current dosing of IV glucose

is excessive. A 50% glucose solution is 10 times its isotonic concentration and provides 250 grams of glucose – enough to support about 7% of a cow's daily glucose needed to produce about 110 lb (50 kg) of milk. Unfortunately, there could be complications from giving this much glucose as an IV bolus. Hypertonic glucose given IV acts as an osmotic diuretic with the potential to increase urinary excretion of electrolytes. In addition, IV infusion of glucose rapidly increases blood glucose to very high concentrations. One study reported peak blood glucose concentrations of about 170 mg/dL following a 500 mL infusion of 50% glucose and 310 mg/dL for a single 1000 mL infusion of 50% glucose.[28] These concentrations exceed the renal threshold for glucose, which is about 100 to 140 mg/dL, and may cause glucosuria with electrolyte loss.

Not surprisingly, hyperglycemia is short-lived following IV glucose administration. Blood glucose concentrations return to baseline about 1.5 hours after IV administration.[11]

Hyperglycemia also has the potential to interfere with the normal process of hepatic gluconeogenesis and cause a rebound hypoglycemia. However, this does not appear in short-term studies, and has not been definitively demonstrated in longer-term studies.

Hypophosphatemia can be expected to follow IV administration of 500 mL of 50% glucose.[10,28] Caution should be used when administering glucose intravenously to cows already at risk for hypophosphatemia. Unfortunately, there are no clear criteria for defining cows at high risk for hypophosphatemia. Cows in early lactation with anorexia, high milk yield , and persistent subclinical hypocalcemia are probably at high risk for hypophosphatemia; however, these are not very specific considerations and are quite commonplace.

It seems prudent to reserve the administration of IV glucose for cows with more severe HYK (for example >3.0 mmol/L BHBA) and to always follow IV glucose with at least several days of an oral glucose precursor. One study reported 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.[15]

Using a lower dose of IV glucose (e.g., 250 mL of 50% glucose, which provides 125 grams of glucose) has been suggested. This is based on adverse clinical experiences in herds giving high and repeated doses of IV glucose, plus the theoretical evidence that 250 grams of intravenous glucose is a very large dose relative to metabolic needs.

Long-term hyperglycemia reduces GI motility and increases the risk for displaced abomasum (DA).[12] However, no studies have evaluated the effects of a single dose of IV glucose on GI motility or risk for DA.

Intravenous glucose does reduce blood BHBA concentrations; however, the duration of suppression of HYK is short (<12 hours).[28] This bolsters the recommendation that an oral glucose precursor should always follow IV glucose infusion.

Oral Treatment of Hyperketonemia

Oral glucose precursors are the preferred treatment for mild to moderate cases of HYK (i.e., blood BHBA between 1.2 and 2.9 mmol/L). The effectiveness of 300 mL propylene glycol for this purpose has been clearly demonstrated in a large, randomized, and controlled study.[16,19] Cows with blood BHBA between 1.2 and 2.9 mmol/L that were given propylene glycol were 1.50 times more likely to resolve their HYK by 16 DIM, 1.85 times less likely to develop severe HYK (blood BHBA ≥3.0 mmol/L), and gave about 3.3 lb (1.5 kg) more daily milk (for 2 of the 4 farms enrolled in the study). Cows with SCK who were treated with oral propylene glycol were also 1.6 times less likely to develop a displaced abomasum (DA), 2.1 times less likely to be removed from the herd by 30 DIM, and 1.3 times more likely to conceive at first service (in 3 of the 4 study herds) compared to untreated cows.[16,19] The economic benefits of aggressive early diagnosis and early treatment of HYK have been modeled and are impressive.[18] The best economic return for dairy herds with a typical prevalence of HYK comes from testing each cow twice, between 2 and 9 DIM, followed by appropriate oral treatment.

Cows with low blood glucose (<about 40 mg/dL or 2.2 mmol/L) along with HYK responded better to oral propylene glycol treatment than cows with higher blood glucose.[9] Low blood glucose was noted in 37% of the cows with HYK. This is an interesting finding and suggests that there may be lingering insulin resistance in some cows that carries a poorer prognosis. However, it is difficult to apply this treatment concept under field conditions. Cowside blood glucose testing is possible, but is not as accurate as cowside BHBA testing. There is no alternative treatment at this time for cows with normal to high blood glucose along with their HYK.

Conclusions

Hyperketonemia is one of the most crucial problems faced by higher-producing dairy cows in early lactation. New advances in cowside diagnosis of HYK have substantially increased our ability to diagnose it quickly and treat it effectively. Dairy practitioners can assist dairy clients in implementing programs to promptly detect and properly treat HYK. We can now mitigate about half of the negative impacts of HYK in the herd.

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Footnotes

[a] Precision Xtra® Blood Glucose and Ketone Monitoring System, Abbott Diabetes Care, Alameda, CA
[b] BHBCheck™ Blood Ketone and Glucose Test System, PortaCheck Inc., Moorestown, NJ
[c] KetoStix® Reagent Strips for Urinalysis, Bayer AG, Leverkusen, Germany
[d] Keto-Test® Milk Ketone Body Test Strips, Elanco Animal Health, Greenfield, IN
[e] PortaBHB® Milk Ketone Test, PortaCheck, Moorestown, NJ
[f] KetoMonitor®, AgSource, Verona, WI

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