

KETOSIS: Understanding the Biology to Improve the Diagnosis, Treatment, and Outcomes

Heather White, Ph.D. ▪ Assistant Professor ▪ hwhite4@wisc.edu

Tawny Chandler, BS ▪ Graduate Research Assistant ▪ tchandler@wisc.edu

Department of Dairy Science, University of Wisconsin-Madison

Gary Oetzel, DVM, MS ▪ Professor ▪ groetzel@wisc.edu

Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison

The transition to lactation period is known to be the most challenging period in the dairy cow life cycle, specifically in terms of metabolic disorders. Hyperketonemia, or ketosis, is defined as elevated ketone bodies in the blood and is a critical challenge to transition dairy cows that has negative impacts to milk production, animal health, and profitability. Cows with ketosis produce less milk, are more likely to develop a displaced abomasum (DA), and are more likely to be culled from the herd. As with many disorders, ketosis has been historically separated into either clinical ketosis (hyperketonemia with clinical signs) or subclinical ketosis (hyperketonemia without clinical signs; SCK). Incidence of SCK ranges from 40 to 60% of cows while clinical ketosis occurs in 2 to 15% of cows. It has been demonstrated that subclinical ketosis is just as costly and detrimental to animal health as clinical ketosis, largely because it can go undetected without active testing and management protocols. Each case of hyperketonemia costs approximately \$361 and \$247 for cows and first-calf heifers, respectively.

Better understanding the tissue-level metabolism that leads to ketosis onset has allowed for better understanding of disease etiology. Ketosis is an early, fresh cow disorder (onset most commonly detected within 4 to 9 days in milk) and is tightly related to energy balance at, and shortly after, calving. Decreased feed intake prior to and around the time of calving, coupled with increases in energy requirements to meet the needs of lactation, result in cows entering a state of negative energy balance (NEB) after calving. During periods of NEB, stored body fat is mobilized and transported to the liver to aid in meeting energy and glucose demands. Triglycerides (TG) mobilized from the adipose tissue are transported through the blood stream as nonesterified fatty acids (NEFA) and glycerol, and absorbed by the liver, where fatty acids are broken down for four possible fates: complete oxidation through the tricarboxylic acid (TCA) cycle, incomplete oxidation through ketogenesis, TG synthesis and packaging as very-low density lipoprotein for export from the liver, or TG synthesis for storage as liver lipids. When available acetyl-CoA exceeds the capacity of the TCA cycle, there

are increases in production of ketones and deposition of TG, leading to the onset of ketosis and fatty liver syndrome.

While circulating ketones can be used to a certain extent as a fuel source by heart, brain, liver, and mammary tissue, excessive blood ketones can have negative effects. Widely accepted cutoffs for SCK are blood beta-Hydroxybutyrate (BHBA) ≥ 1.2 mmol/L and for clinical ketosis blood BHBA ≥ 3.0 mmol/L. These cutoffs have been established based on increased negative effects and increased relative risk for other diseases and complications (ex. DA, culling, decreased reproductive efficiency, lost milk production) as blood BHBA concentration increase beyond 1.2 mmol/L. Negative impacts and relative risk for other disorders are further increased, based on day of onset and blood concentration of BHBA. Cows with ketosis onset within the first week of lactation are at further increased risk for developing a DA and being culled. Additionally, increases in blood BHBA concentrations above 1.2 mmol/L increase risk for DA and culling as well as result in exponential milk losses. This highlights the importance of early detection and treatment protocols.

Treatment and Detection Methods:

Historically, ketosis has been most commonly treated with intravenous dextrose. However, this treatment may not be ideal. The dose of glucose typically administered (500 mL of 50% dextrose) increases blood glucose concentrations eight times the normal concentration immediately after administration; blood glucose then returns to pretreatment concentrations within 2 hours. This elevation in blood glucose initiates a regulatory cascade that begins with a 12-fold increase in insulin concentration and ends with downregulation of liver glucose production, decreased mobilization of fat stores, and decreased oxidation of mobilized NEFA within the liver. Glucose not transported into the cell during this insulin peak is excreted through the kidneys adding a risk of electrolyte imbalance. High glucose concentrations have also been linked to abomasal dysfunction, decreased mobility, and DA. The benefit of dextrose treatment lasts less than 24 hours and

therefore must be repeated for sustained benefit. Decreased liver production of glucose, coupled with quick disappearance of intravenous glucose sources, results in a secondary blood glucose “crash”. Thus, it is recommended that IV dextrose treatments be reserved for clinical ketosis cases, be limited to 250 mL or 50% dextrose, and always be followed by oral treatment with propylene glycol. Cows with clinical ketosis need the glucose boost provided by the IV dextrose and a 250 mL dose of 50% dextrose does not downregulate liver metabolism as severely.

In contrast to treating ketosis with intravenous glucose, propylene glycol appears to have many advantages. Propylene glycol is delivered as an oral drench and serves as a glucose precursor to the animal. In the rumen, propylene glycol is either converted to propionate or absorbed directly. Propylene glycol generated propionate and directly absorbed propylene glycol can enter the TCA cycle and gluconeogenesis to produce glucose. By providing a precursor that is still dependent on liver gluconeogenesis and TCA cycle oxidation, we are providing a fuel source without leading to a secondary “crash”. Collectively, metabolism of propylene glycol provides a glucose precursor that most closely mimics glucose metabolism in a healthy cow and requires liver metabolism to be maintained, providing an optimal treatment. Glycerol and calcium propionate may also be effective oral treatments for ketosis, but have not been evaluated as fully as propylene glycol.

Application of current research regarding the negative impacts of ketosis and optimal treatment protocols to commercial dairy farm settings is absolutely dependent on accurate and practical detection methods. Ketones are transferred from blood into both urine and milk and concentrations that reflect hyperketonemia in all three fluids have been defined. On-farm ketosis testing is semi-quantitative and utilizes urine and milk test strips. These tests have good specificity but poor to moderate sensitivity (27 to 78%) depending on the test. Urine test strips are typically the cheapest but require obtaining a urine sample, which can be challenging. Recent availability and validation of a cowside blood ketone test (Precision Xtra®) has provided a new cowside test with a much better sensitivity of 95% and specificity of 94%. While this test costs more than the Ketostix urine test strips or KetoCheck powder for milk and about the same as the KetoTest milk test, it provides a highly sensitive on-farm diagnostic tool.

Thoughts on testing and treating:

In order to tailor a detection protocol to a farm, an approximate ketosis prevalence (percent of cows that have the disease on any one day) is needed. The average herd prevalence is between 15 and 25%; however, it is important to remember that prevalence varies by farm and within farm over time. To determine prevalence, start by testing fresh cows between 4 and 20 DIM (or a 30 to 40 cow subset of this group in larger herds) on a few separate dates to establish the prevalence. Then, multiply the herd prevalence by 2.5 to get the herd incidence (the percent of cows in the herd that get ketosis each year).

Weekly testing protocols can be adapted to each farm but should strive to monitor prevalence and to catch early cases of SCK to allow for treating cows and reducing the negative impact of the disease. For any testing strategy, sick or off-feed early lactation cows should always be promptly tested and treated as necessary. Testing cows two days a week will allow checking every cow twice between 3 and 9 days in milk, and will identify 80% of cows with SCK. An alternative testing strategy is to test one day a week, checking all cows between 3 and 16 DIM and aiming to test each cow twice which will successfully identify 70% of cases. Both testing strategies are justified in herds with incidence greater than 15%. If incidence is greater than 50%, blanket treatment protocols should be considered until the underlying causes can be corrected and incidence decreased. Work with the veterinarian and herdsman to update treatment protocols to ensure that cows are being treated appropriately, depending on disease severity. General treatment guidelines are shown in the table below.

<i>Blood BHBA, mM</i>	<i>Treatment Recommendation</i>
<i>0.8 – 1.1 mM</i>	<i>No treatment, recheck cow during next testing day</i>
<i>1.2 to 2.0 mM (SCK)</i>	<i>300 mL propylene glycol via oral drench for 3 to 4 days; B vitamins optional</i>
<i>≥3.0 mM (clinical ketosis)</i>	<i>300 mL propylene glycol via oral drench for 3 to 4 days; 250 mL IV dextrose (limit to 1 time); B vitamins and oral drench of preference optional; physical exam and monitor for DA</i>
<i>Prolonged ≥3.0 mM Or >4 mM</i>	<i>300 mL propylene glycol via oral drench for 3 to 4 days; 250 mL IV dextrose (limit to 2 days); dexamethasone/Predef or other steroid if >14 DIM (limit to 2 times); B vitamins and oral drench of preference optional; physical exam and monitor for DA</i>



DEPARTMENT OF
DAIRY SCIENCE
University of Wisconsin-Madison



**School of
Veterinary Medicine**
UNIVERSITY OF WISCONSIN-MADISON