Managing Ketosis in the Transition Cow for Health and Reproduction
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TAKE HOME MESSAGES

- Ketosis is common: several large studies indicate that, on average, more than 40% of cows experience ketosis at least once during the first 2 weeks after calving. Even in very well-managed herds, 10% incidence is common.
- Depending on the severity and timing of onset, ketosis may reduce milk production in early lactation.
- Ketosis is associated with increased risk of endometritis, anovulation, decreased pregnancy at first AI, and more days to pregnancy.
- Accurate, practical, and economical cow-side tests are available to detect ketosis in blood, milk, or urine. Most herds would benefit from a routine ketosis screening and treatment program administered once or twice weekly.
- Cows with ketosis should be treated with 300 mL propylene glycol by drench once daily for 3 to 5 days and then retested the day after the last treatment.
- Management practices generally recommended for peripartum dairy cows are likely to contribute to prevention of ketosis and to good reproductive performance.

INTRODUCTION
Ketosis occurs when blood concentrations of the ketone bodies (β-hydroxybutyric acid [BHBA], acetone and acetoacetate) are elevated to the point that undesirable effects are directly or indirectly caused or are made more likely. Ketosis also is referred to as hyperketonemia. Clinical ketosis refers to a condition with visible signs (decreased milk production, decreased feed intake, dry manure, rapid loss of body condition, and in exceptionally severe cases, neurological signs such as leaning or walking against the stall front, licking, or chewing). Clinical ketosis may be either primary (occurring as the main disease condition) or secondary (concurrent with another disease; e.g., cows with displaced abomasum [DA] commonly also have ketosis at the time of diagnosis). Time of diagnosis of the condition does not necessarily equate to its onset. For example, subclinical ketosis commonly precedes the DA diagnosis. Cows with clinical ketosis typically have blood BHBA >2.5 mmol/L, but this is variable, and no clear threshold exists at which clinical signs occur. It is important to realize that clinical ketosis at best represents the “tip of the iceberg” of the prevalence of ketosis in a herd. A very poor correlation exists between the herd rate of actual or recorded cases of clinical ketosis and the incidence of subclinical ketosis.

Subclinical ketosis (SCK) refers to a condition without outward physical signs, but where circulating ketone concentrations are above a threshold that is associated with increased likelihood of undesirable outcomes. Depending on the outcome in question and the stage of lactation, the threshold for SCK is blood BHBA >1.1 to 1.4 mmol/L.

Physiology
Circulating concentrations of non-esterified fatty acids (NEFA) and BHBA measure the success of adaptation to negative energy balance. Concentrations of NEFA reflect the magnitude of mobilization of fat from storage. In contrast, BHBA reflects the completeness of oxidation (“burning”) of fat in the liver. Ketone bodies are the result of incomplete oxidation of fatty acids. As the supply of NEFA to the liver exceeds the ability of liver to completely oxidize the fatty acids to supply energy (Acetyl CoA for
the TCA cycle), the amount of ketone production increases. Ketone bodies can be used by muscle as an alternative fuel source to glucose, sparing glucose for milk production. Ketone production, however, does not result in as much net energy release as complete oxidation of fatty acids. In addition, increasing concentrations of ketones are thought to suppress feed intake.

Glucose is the primary metabolic fuel, and is absolutely required for vital organ function, fetal growth, and milk production. In dairy cows, the massive energy demand to support milk production is partly met through gluconeogenesis. Glucose concentrations are under tight homeostatic control. Therefore, although glucose has a central role in metabolism, it is a poor analyte for monitoring or investigating herd problems.

Each of the three main ketones (i.e., BHBA, acetone and acetoacetate) is present in blood, milk, and urine and can be measured, but acetoacetate is volatile and unstable, and relatively difficult to measure, and is therefore not commonly used in the field to measure ketosis. In contrast, BHBA is the predominant ketone body in blood, where it is stable. Ketones are excreted in urine, resulting in greater concentrations in urine than in blood. Therefore, all things being equal, urine tests for ketones tend to lack specificity relative to serum. Concentrations of BHBA in milk reflect concentration in serum, but are only 10 to 15% as large.

**Prevalence and Incidence**

Several field studies have concurred that, measured once or three times weekly, 41 to 43% of cows have blood BHBA >1.2 mmol/L at least once during the first 2 to 3 weeks postpartum (McArt et al., 2012; Gordon, 2013). The mean cumulative incidence varied among 20 herds from 15 to 78% (Gordon, 2013). In another study, 40% of herds had >15% of cows with ketosis. This herd-level threshold was associated with increased DA risk, decreased pregnancy rate, and decreased early lactation milk yield (Ospina et al., 2010c). With once-weekly testing between 3 and 24 days in milk (DIM), 50% of ketosis cases were diagnosed between 3 and 5 DIM (Gordon, 2013), and with testing 3 times per week 75% of ketosis was diagnosed between 3 and 7 DIM (McArt et al., 2012). This is consistent with older data in which the peak incidence (first diagnosis of new cases) of SCK was 30% and occurred during the first week after calving, with few new cases beyond the third week of lactation. Because the average duration of an untreated case of ketosis is about 1 week (McArt et al., 2012), peak prevalence (proportion of cows testing positive at a given time point) of SCK was approximately 33% and occurred in week 2 after calving (Duffield et al., 1998). Therefore, the first 2 weeks postpartum are the optimal time to test for SCK. The median overall prevalence of SCK during the first 2 weeks across several field studies in different regions was 15 to 20%.

### IMPACT OF KETOSIS

**Disease**

Subclinical ketosis (BHBA >1.2 to 1.4 mmol/L) during the first or second week after calving is associated with:

- 3 to 8 times increased odds of displaced abomasum (LeBlanc et al., 2005; Duffield et al., 2009; Ospina et al., 2010a)
- 3 times greater risk of metritis when serum BHBA during week 1 was >1.2 mmol/L (Duffield et al., 2009)
- 4 to 6 times increased risk of clinical ketosis (Duffield et al., 2009)
- Increased probability of subclinical endometritis during week 4 of lactation (Hammon et al., 2006)
- Increased duration and severity of mastitis (Suriyasathaporn et al., 2000), but not with the incidence of mastitis (Duffield et al., 2009)
- Inconsistent effects on neutrophil function (Ster et al., 2012; see details below)
- 1.8 times increased odds of culling <60 DIM (Roberts et al., 2012)
**Production**

Milk yield during early lactation was reduced when BHBA was >1.2 mmol/L in week 1 or >1.4 mmol/L in week 2. Daily yield at first milk test was reduced by 1.9 kg (4.2 lb) when BHBA was >1.4 mmol/L in week 1 and by 3.3 kg (7.3 lb) when BHBA was >2.0 mmol/L in week 2. Cows with serum BHBA >1.8 mmol/L in week 1 had >300 kg (661 lb) lower projected production for the whole lactation. Conversely, cows with BHBA >1.0 to 1.6 mmol/L in week 2 (despite having lower production at first test) were projected to produce approximately 200 kg (441 lb) more milk in the whole lactation (Duffield et al, 2009).

**Reproduction**

Ketosis is associated with reduced reproductive performance, which extends its impact much longer than many producers realize. It is worth emphasizing that health in the weeks before and after calving influences reproductive traits at least 2 months later. Cows that experienced ketosis during the first 2 weeks of lactation had reduced probability of pregnancy at the first insemination.

Subclinical ketosis (serum BHBA >1.0 to 1.4 mmol/L) during early lactation is associated with:

- 3 times greater odds of metritis (Hammon et al., 2006; Duffield et al., 2009; not in all studies—see discussion below)
- 1.4 times greater odds of endometritis (uterine inflammation based on cytology) at 35 DIM (Dubuc et al., 2010)
- 1.5-fold increased odds of being anovular (not cyclic) at 63 DIM (19 vs. 13% of cows; Walsh et al., 2007; Dubuc et al., 2012)
- Decreased pregnancy at first AI (Walsh et al., 2007)

Furthermore, cows that had ketosis in one or both of the first 2 weeks after calving had poorer pregnancy risk until 165 DIM. The median interval to pregnancy was approximately 108 days in cows without ketosis, was significantly longer (124 days) in cows with ketosis during the first or second week postpartum, and tended to be longer still (130 days) in cows that had SCK in both of the first 2 weeks of lactation (Walsh et al., 2007).

In a large field study in New York (778 cows in 38 herds), producer-recorded clinical ketosis (incidence = 5%) was a risk factor for endometritis (OR = 3.8), particularly in multiparous cows (Cheong et al., 2011). In contrast, in an even larger study, no association of producer-reported clinical ketosis or serum BHBA measured systematically in week 1 postpartum with metritis was detected (Chapinal et al., 2011). In another study (n = 1,295), cows having BHBA >1.1 mmol/L in week 1 of lactation were at risk for endometritis (increased odds by 40%), but not for purulent vaginal discharge or for metritis (Dubuc et al., 2010). Plasma BHBA was greater at calving in cows that developed metritis, and similar to previous results (Dubuc et al., 2010), greater at week 1 postpartum in cows that later had endometritis (Galvão et al., 2010). Likewise, cows with metritis or endometritis had greater BHBA from 1 until 4 weeks after calving, although no association was detected of BHBA with neutrophil-killing ability (Hammon et al., 2006). In vitro titration of BHBA did not affect proliferation of blood mononuclear cells or their production of IFNγ, or oxidative burst activity of neutrophils (Ster et al., 2012). Therefore, the effect of ketones per se on immune function is at best inconsistent. It is not clear if the mechanism accounting for the association of fatty liver-ketosis with diminished neutrophil function is direct (and if so, whether it is on mature polymorphonuclear cells [PMN] in circulation, or whether NEFA, ketones, or other signals or metabolites affect PMN in the bone marrow), or through effects on mononuclear cells responsible for antigen presentation and initial chemokine signaling/stimulation of neutrophils (Zerbe et al., 2000).
TESTING STRATEGIES AND INTERPRETATION

Test Selection and Sampling

Serum or plasma NEFA concentrations measured during the week before calving (samples collected 4 to 10 days before expected calving) provide a uniquely useful component of assessment of peripartum health. Unfortunately, no on-farm diagnostic tests are presently available to measure NEFA, which implies the cost and delay of submission of samples to a diagnostic laboratory. In cows fed a TMR, a greater prevalence of elevated serum NEFA occurs 1 hour before first feeding than at 4 or 10 hours after feeding, but serum BHBA concentrations are quite stable across these time points. For monitoring, samples should be collected at approximately the same time of day to avoid confounding of the results by diurnal or postprandial variations.

Ketosis is associated with management in the pre-fresh, maternity, and early post-fresh periods. Recognition of when ketosis is occurring should give direction to practical preventive efforts. When ketosis is detected primarily during the first two weeks of lactation, emphasis should be placed on: (1) bringing cows into the dry period in moderate body condition (BCS = 3 to 3.5); (2) avoiding energy intakes greater than the maintenance requirement between dry off and 3 weeks prepartum (Dann et al., 2006); and (3) allowing unrestricted access to feed intake by all cows during the last few weeks before, and through the calving period. Further investigation of an elevated prevalence of ketosis in early lactation may be aided by NEFA testing of cows during the 10 days before expected calving. If little evidence of ketosis exists during the first 2 weeks postpartum, but an increased incidence is evident from 3 to 6 weeks postpartum, preventive measures should emphasize enhancing feed intake in post-fresh period. Ketosis that occurs later than the first 2 to 3 weeks of lactation also may be associated with failure to meet the nutritional needs of cows with high production, or with poorly fermented wet grass or legume silage with high levels (>0.5 to 1% of dry matter) of butyric acid. Further research to describe the occurrence of subclinical ketosis under different management conditions is warranted. Until such data are available, present evidence indicates that most subclinical ketosis occurs during the first 2 weeks after calving. Therefore, testing programs with the objective of monitoring the prevalence of subclinical ketosis should focus on the first 2 weeks after calving.

Used with knowledge of their test characteristics to inform interpretation, serum BHBA, whole blood BHBA measured with Precision XTRA® (now sold as Freestyle Neo®), milk BHBA measured with Keto-Test®, or Ketostix® in urine (Table 1) are valid diagnostic tests for subclinical ketosis. These 3 cow-side tests are economical, practical, and sufficiently accurate relative to laboratory analysis of serum for use in the field. Selection of the 100 or 200 µmol/L cut-point for classification of the Keto-Test® will depend on the objective of the testing. If the objective is group-level monitoring for early detection of increased prevalence of ketosis (as a reflection of the general success of transition management), then greater sensitivity is desirable and the 100 µmol/L should be used. If the objective is to select individual cows for treatment with the goal of preventing clinical disease, then fewer false positives may be desirable and the 200 µmol/L cut-point would be appropriate.

The costs and benefits of various ketosis screening and treatment programs were modelled (McArt et al., 2014). They considered treating every cow without the labor and cost of diagnosis versus testing 1, 2, or 3 times per week with all ketotic cows treated with propylene glycol for 5 days. Given the model assumptions and their variations, for herds with 15 to 50% incidence of ketosis (i.e., the vast majority of herds), the most cost-effective option was to test 2 times per week between 3 and 9 DIM, which detected 80% of cases. The herd DA and early culling risk were the most influential variables (each of which is associated with ketosis; there was greater benefit at higher risks of these problems).
**Number of Samples and Interpretation**

The number of samples required for group or herd-level interpretation depends on the prevalence of affected animals that is judged important to detect, the certainty of detection that is desired, and the size of the group of interest. Fortunately, the latter criterion has the least influence. Examples are given in Table 2. Practically, the minimum number of samples is 5, and 10 to 12 samples will allow for interpretation in most situations. Typically, 18 to 35% of cows have NEFA >0.4 mmol/L during the last week before calving (Oetzel, 2004; Le-Blanc, 2005). Published reports indicate a typical prevalence of subclinical ketosis of approximately 15% (Oetzel, 2004). Studies in Canada have found average prevalence of 20% (Duffield et al, 1998; Duffield et al, 2003). Adjusting for cow-side test performance, a threshold of 10% true prevalence of subclinical ketosis corresponds to an apparent prevalence (proportion of tests that are positive) of 25% when using the Keto-Test® with a 100 µmol/L cut-point, or 11% at the 200 µmol/L cut-point (Oetzel, 2004).

### Table 1. Performance of cow-side tests for detection of subclinical ketosis

<table>
<thead>
<tr>
<th>Test substrate</th>
<th>Blood</th>
<th>Milk</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred test</td>
<td>Precision XTRA (= Freestyle Optium or Freestyle Neo, Abbott)</td>
<td>Keto-Test (KetoLac BHB) Sanwa Kagaku Kenkyusho Co.</td>
<td>Ketostix (Bayer)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>87 to 93%</td>
<td>At 100 µmol/L on the strip: 83% At 200 µmol/L: 82%</td>
<td>At “small” level, when read after 5 seconds 79%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93 to 100%</td>
<td>At 100 µmol/L on the strip: 54% At 200 µmol/L: 94%</td>
<td>96%</td>
</tr>
<tr>
<td>Approximate cost</td>
<td>$2 per test; $ 40 for the meter</td>
<td>$ 2/test</td>
<td>$0.25 per test</td>
</tr>
<tr>
<td>Comments</td>
<td>Glucose tests available for this meter are valid for use in cattle</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

1Relative to serum BHBA ≥ 1.4 mmol/L measured in a diagnostic laboratory.

It is important to interpret both NEFA and ketosis tests as the proportion of animals above a meaningful threshold because this best describes the biology of the condition. It is misleading to calculate the average BHBA or NEFA from a group of samples and similarly most information is lost if samples from multiple animals are pooled together.

**PREVENTION OF KETOSIS**

Few management practices or interventions exist presently that can be supported specifically to prevent ketosis. In a large study, only 11% of the variation in the incidence of ketosis was explained by readily-measured cow-level risk factors (i.e., parity, BCS; Duffield et al., 1998). Therefore, a large part of the controllable variation lies at herd or management level, including bunk space and feed availability, movement and grouping, heat abatement, feed quality, TMR consistency, water access, and where approved, use of monensin controlled-release capsules.

Based on current understanding of ketosis and its effects on disease, the general objective is...
to support metabolic health, prevent severe or maladaptive responses to negative energy balance, and thus reduce the risks of reproductive disease and impaired reproductive function.

**Table 2.** Sample size for monitoring ketosis in groups of 50 to 1,000 cows in the risk period for ketosis (e.g., 1 to 3 weeks postpartum) ¹

<table>
<thead>
<tr>
<th>Minimum prevalence to detect (P)</th>
<th>Desired level of confidence of detection (C)</th>
<th>Number of samples needed (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>75%</td>
<td>12 to 14</td>
</tr>
<tr>
<td>10%</td>
<td>95%</td>
<td>22 to 29</td>
</tr>
<tr>
<td>20%</td>
<td>75%</td>
<td>6 to 7</td>
</tr>
<tr>
<td>20%</td>
<td>95%</td>
<td>12 to 14</td>
</tr>
<tr>
<td>25%</td>
<td>95%</td>
<td>10 to 11</td>
</tr>
</tbody>
</table>

¹Use the table as follows: If I test [n] samples and all are negative (BHBA <1.2 mmol/L), then I can be [C]% confident that the prevalence of ketosis is <[P]%.

The critical principles are to investigate and ensure that all cows have unrestricted access to feed at the time of fresh feed delivery, clean water, and a comfortable resting place. Although a great deal remains to be learned about the determinants of health in dairy cattle during the transition period, Table 3 proposes management practices generally recommended for peripartum dairy cows that are likely to contribute to reducing the incidence of ketosis during early lactation and its associated consequences.

**TREATMENT OF KETOSIS**

Based on currently available data (Nielsen and Ingvartsen, 2004; McArt et al., 2011; 2012), drenching cows with 300 mL of propylene glycol once daily for 5 days is a reasonable treatment for cows with blood BHBA ≥1.2 mmol/L. In a large randomized controlled trial in four herds in New York and Wisconsin, all fresh cows were tested 3 times per week and those with BHBA >1.2 mmol/L were treated with propylene glycol or left untreated. Treated cows had a shorter time to ketosis cure (5 vs. 7 days), 1.5 times greater probability of cure, and on average, 0.69 kg (1.5 lb)/cow per day greater milk production (varied among herds), 37% lower risk of DA, and 68% lower risk of culling during early lactation (McArt et

![Table 3. Checklist of management practices to support metabolic and reproductive health in transition dairy cows](image)

**Management**

- Feed daily for 3 to 5% left over
- ≥75 cm (30") bunk space per cow or no more than 4 cows per 5 headlocks
- ≤85% stall stocking density
- >11m² (120 ft²) of bedded pack/cow
- Build for 130 to 140% of the average number of monthly calvings
- Comfort in stalls; adaptation
- <24 h in calving pen
- House heifers in pens separate from mature cows if possible
- Minimize group changes
- Heat abatement (sprinklers and fans) when THI > 68
- BCS = 3.0 to 3.5 at calving

**Transition diet**

- 3 to 4 weeks on close-up diet or 6 weeks as 1 dry group
- Meet but do not exceed energy requirement 8 to 3 weeks prepartum
- Water ad lib; 10 cm (4") linear trough space per cow; 2 sources per pen
- 1000 IU vitamin E/d; up to 2000 IU/d for RP; 0.3 ppm selenium (ideally approx. 6 mg/d)

**Monitoring**

- Serum total calcium >2.15 mmol/L from 1 day in milk
- NEFA <0.4 in last week prepartum; <0.7 in week 1
- BHBA <1.1 mM in week 1 postpartum
- BHBA <1.2 mM weeks 2 to 3 postpartum
In two randomized clinical trials with weekly testing for ketosis, cows with blood BHBA >1.2 mmol/L were treated with 300 g/day of propylene glycol for 3 or 5 days, with or without treatment for 3 days with injections of vitamin B12 and phosphorus (Catosal, Bayer Inc; Gordon, 2013). Based on cure of ketosis and production responses, the conclusions were:

- If blood BHBA ≥1.2, but <2.4 mmol/L, treat with propylene glycol for 3 days.
- If blood BHBA >2.4 mmol/L, treat with propylene glycol for 5 days.
- If blood BHBA >1.2 mmol/L and glucose <2.2 mmol/L, also include treatment with Catosal for 3 days to either of the previous propylene glycol recommendations.

CONCLUSIONS

Ketosis is common and is associated with increased risk of metabolic and uterine disease, decreased milk production, and decreased reproductive performance. Routine monitoring of the prevalence, and treatment of subclinical ketosis during the first 2 weeks of lactation is useful to mitigate the effects of the condition and motivate preventive management. Timing, magnitude, and duration of peripartum increases in circulating concentrations of BHBA are associated with the risk of abomasal displacement, uterine disease, and reproductive performance from 1 through 20 weeks later. Cows that experience ketosis during the first 2 weeks postpartum have a reduced pregnancy rate until 165 DIM because affected cows are more likely to have uterine disease, less likely to have resumed ovulation by the start of breeding, and less likely to become pregnant per AI. Peripartum energy metabolism and immune function will plausibly be favored when cows have unrestricted access to diets formulated to meet nutrient requirements and to water in the transition period. Proactive management and investigation of problems should focus on minimizing nutritional, housing, social, and environmental factors that may impair feed and resting access for all or some members of the groups of peripartum cows.

REFERENCES


