How do we best diagnose and treat cows with ketosis?

Jessica A. A. McArt, DVM, PhD, DABVP (Dairy Practice)

Population Medicine & Diagnostic Sciences
College of Veterinary Medicine
Cornell University
Ithaca NY 14853

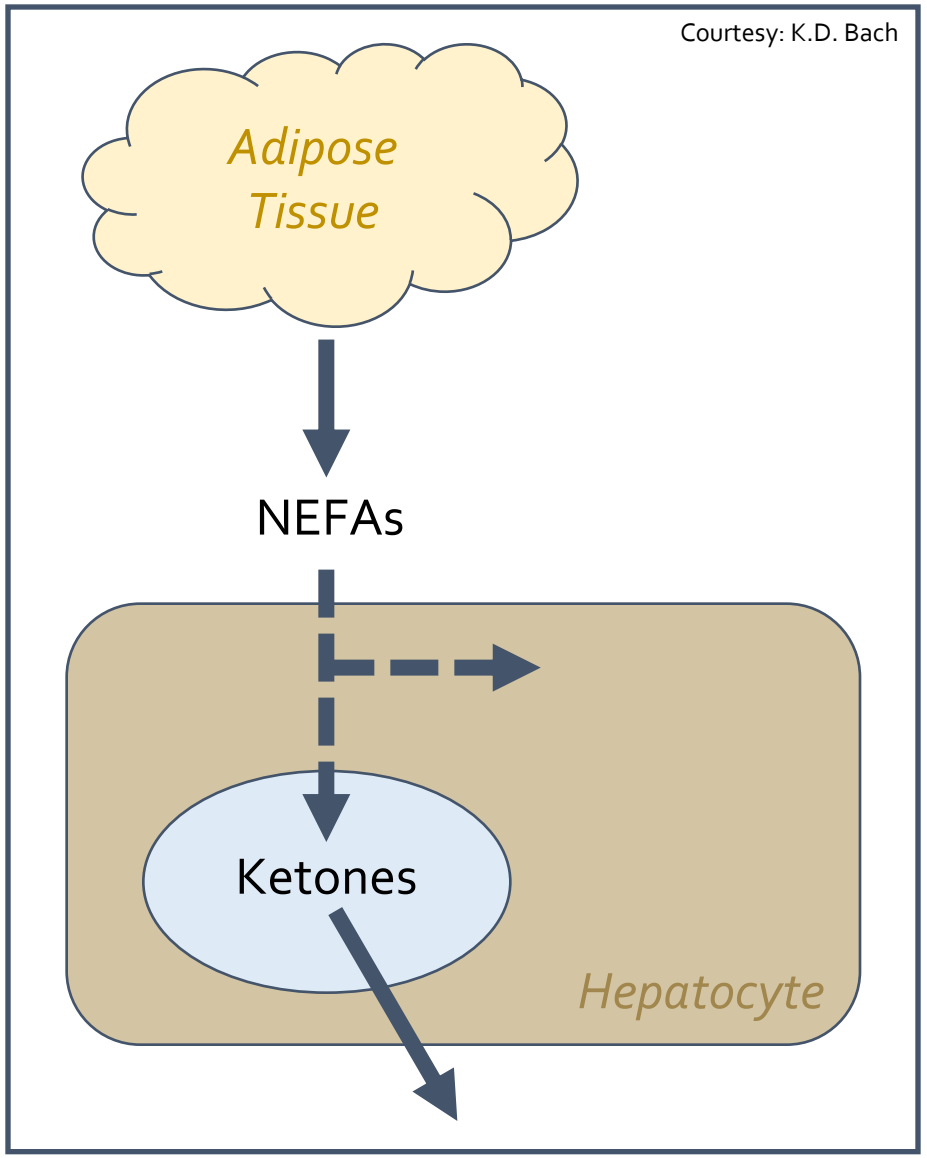
Cornell Dairy Center of Excellence

Overview

- Methods of ketosis diagnosis
- Daily variation of β-hydroxybutyrate
- Association with health and production
- When to focus testing
- Hyperketonemia treatment

Ketosis diagnosis

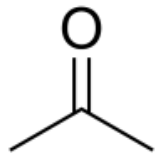
Normal adaptation to energy demands

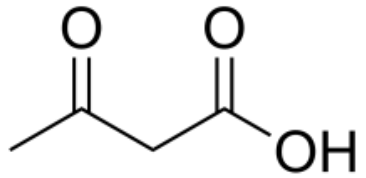


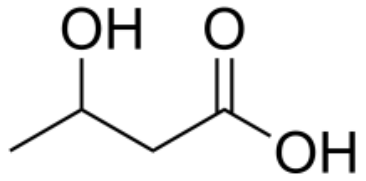
Energy-related metabolites:

- Non-esterified fatty acids (NEFA)
- Ketones
  - Acetone
  - Acetoacetate
  - β-hydroxybutyrate (BHB)

Ketosis monitoring







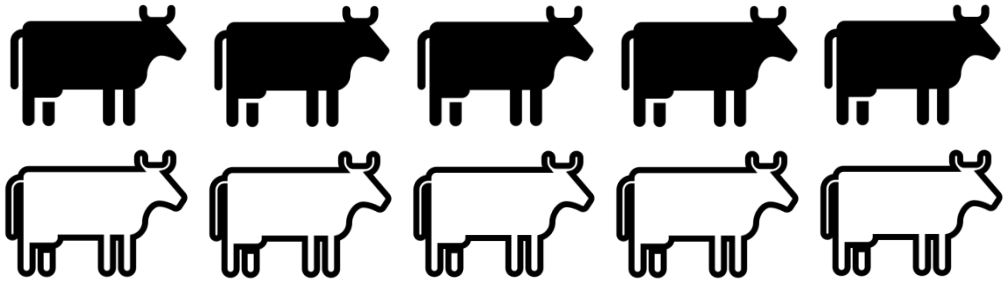
- Ketosis is the elevation of ketone bodies
- Clinical manifestation:
  - Decrease in appetite
  - Weight loss
  - Decrease in milk production
- Excessive elevation of ketones without clinical signs:
  - >80% of cases → *routine testing is important!*

Historical ketosis diagnosis

Sweet smell of breath

- Acetone
- Other volatile compounds
- Not everyone can smell it!

This test for ketosis is only ~ 50% sensitive.



How should we test for ketones?

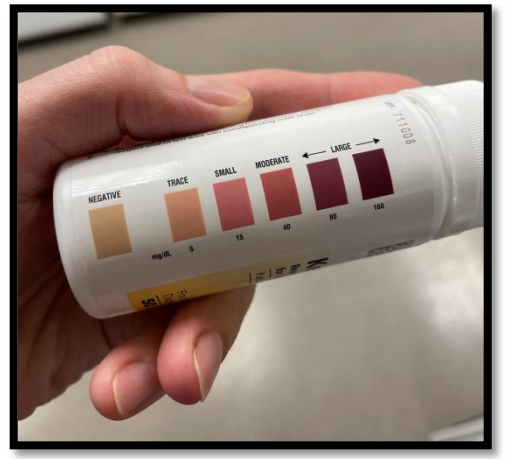
Three fluids can be sampled:

Urine

Milk

Blood

Urine ketone testing



- Dip strip
  - Test for acetoacetic acid
  - Decent accuracy
    - Compared to blood BHB ≥1.4 mmol/L (Oetzel, 2004, *VCNA)*
    - ≥ trace = 90% sensitivity, 80% specificity
    - ≥ small = 80% sensitivity, 95% specificity
    - ≥ moderate = 60% sensitivity, 99% specificity
- About 50% of cows can be induced to urinate
- Difficult with color blindness
- ~US$0.25 per strip

Milk ketone testing – cow side

- Dip strip or powder
  - Test for milk BHB
  - Moderate to poor sensitivity, decent specificity
    - Some ketotic cows will test non-ketotic
    - Most non-ketotic cows will test non-ketotic
- Easy to get sample
- Often used not according to directions
  - Temperature of milk
  - Quantity of sample
- Range ~US$0.60 to $2.00 per test

Milk ketone testing – milk sampling

- Proportional milk samples
- Fourier-transform infrared spectroscopy
- Estimated milk constituents: milk BHB & acetone

Image: K. D. Bach

Blood ketone testing

- Gold standard = laboratory blood BHB
  - Serum, EDTA plasma, heparinized plasma
  - Expensive, lag in time to result

- Handheld BHB meters
  - 1.5 µl of whole blood (or serum/plasma)
  - Excellent sensitivity and specificity

- Quantitative result
- ~US$1.00 to $3.00 per test

Blood ketone meters – how accurate are they?

	1.2 mmol/L		3.0 mmol/L	
Meter	Se (%)	Sp (%)	Se (%)	Sp (%)
Precision Xtra[1,2]	96.0%	97.0%	100.0%	91.6.0%
BHB Check[3]	91.0%	93.0%	92.0%	100.0%
CentriVet[4]	94.7	93.8	100.0	100.0
Nova Vet[2]	94.9	91.8	100.0	100.0

- Good repeatability on all meters
- Some variation from gold standard (1 SD = +/- 0.3 mmol/L)

[1] Iwersen et al., JDS, 2009; [2] Bach et al., JDS, 2016; [3] Sailer et al., JDS, 2018; [4] Bach and McArt, personal communication, 2017

Hints for on-farm electronic meter use

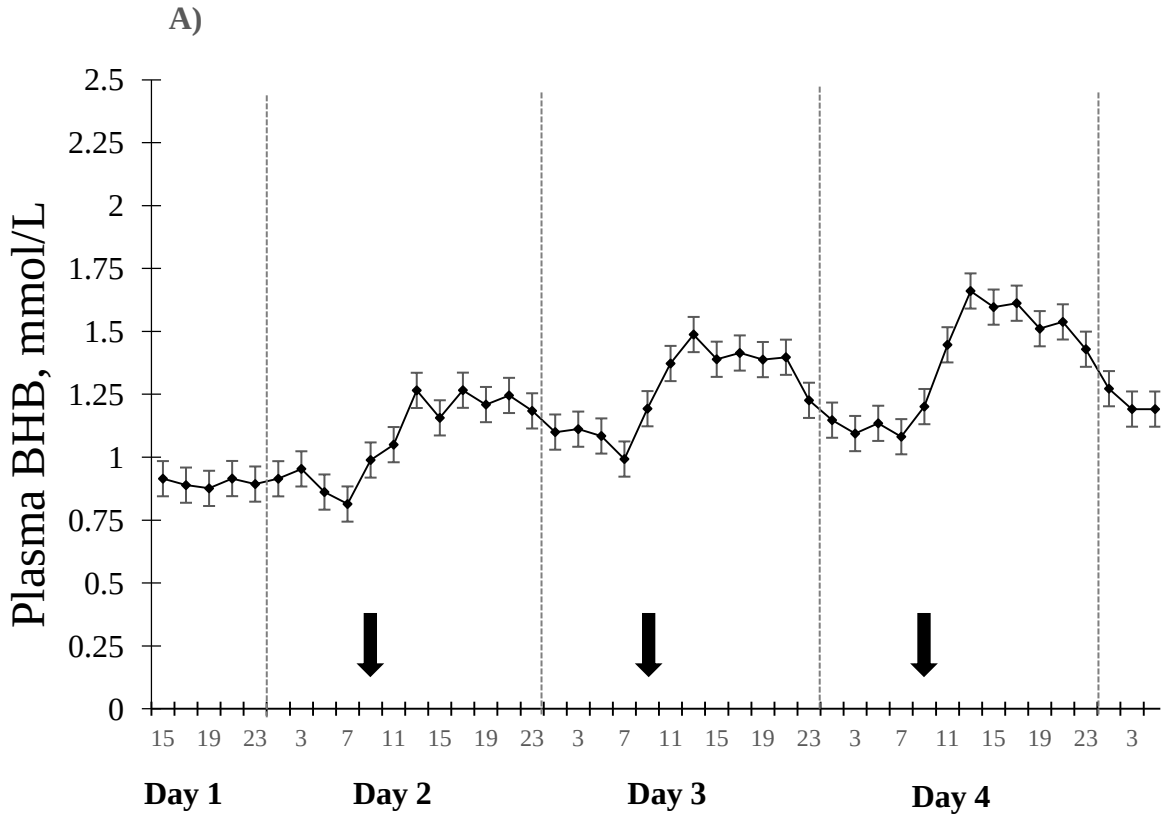
- *Treat your meter AND strips with respect!*

- Read the manual
- Keep meters and strips warm
- Routinely calibrate and/or quality check

Additional info on blood testing:

- Commonly used thresholds:
  - Hyperketonemia ≥1.2 mmol/L
  - Severe hyperketonemia ≥3.0 mmol/L
- Location of sampling
  - Tail vessels = jugular vein
  - Milk vein ~ 0.3 mmol/L lower
  - Ear/vulva prick
- Time of sampling is important!!

Circadian pattern to blood BHB:



Plasma BHB for multiparous Holstein cows (n=28) between 3 and 14 DIM fitted with jugular catheters and sampled bihourly for 5 days. Dashed grey lines depict 24 h and arrows indicate time of feed delivery. Panel A) plasma BHB for all cows; Time $P < 0.001$. Panel B) plasma BHB by HYK group; Group $P < 0.001$, Time × Group $P = 0.39$.

Courtesy of C. R. Seely

When to focus testing

Applications of hyperketonemia testing

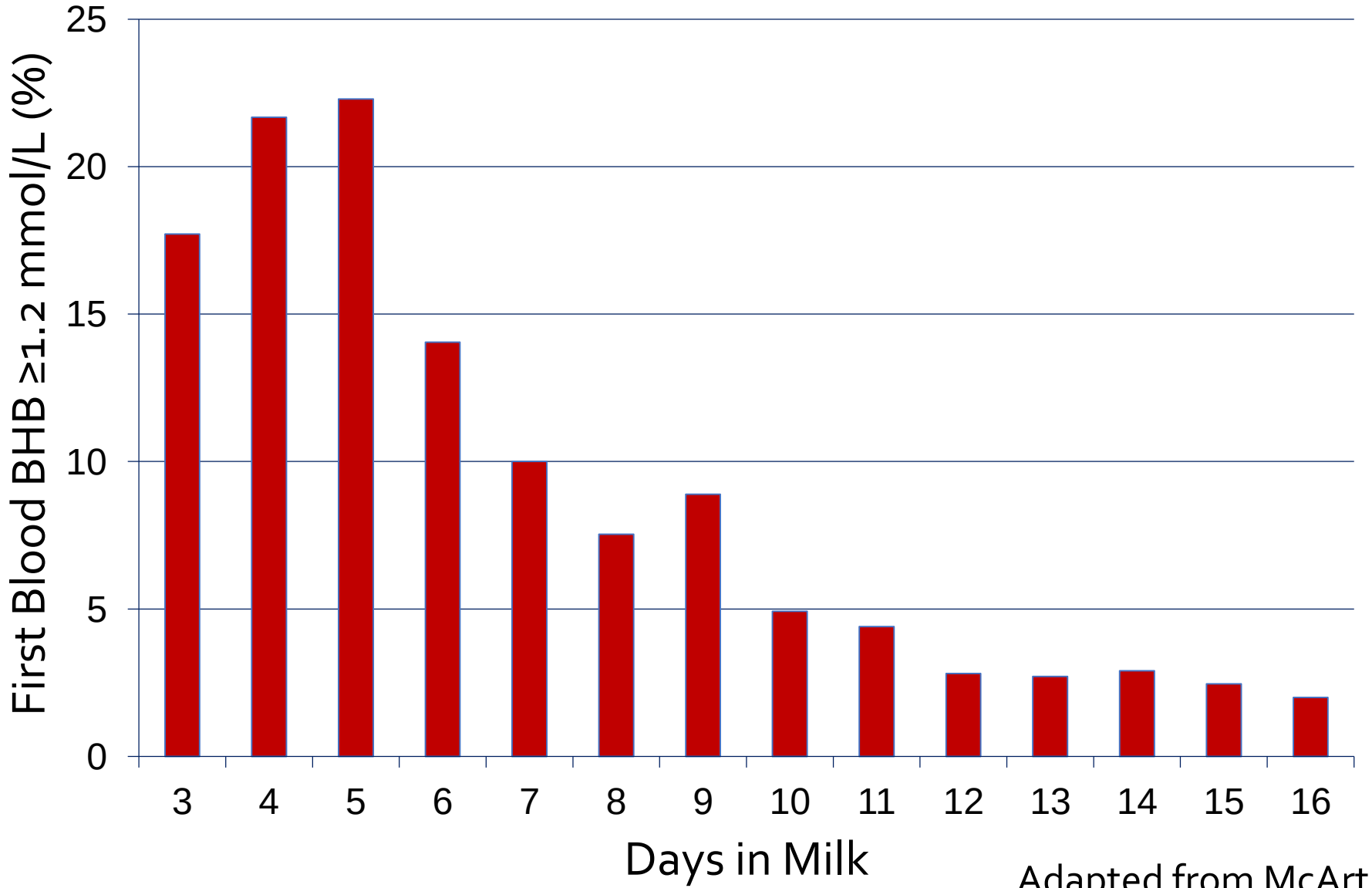
- Identifying individual hyperketonemic cows
  - Cow-side test for treatment decisions
- Identifying herds with hyperketonemia problems
  - Herd-level testing for management decisions

Individual animal consequences of hyperketonemia

- Higher risk for adverse health events
  - Metritis (~3 times)
  - Displaced abomasum (~ 8 times)
  - Culling (~3.5 times)
- Decrease milk yield in early lactation
  - ~ 2 kg per cow per day
- Poorer reproduction
  - ~30% lower preg risk to 1st insemination

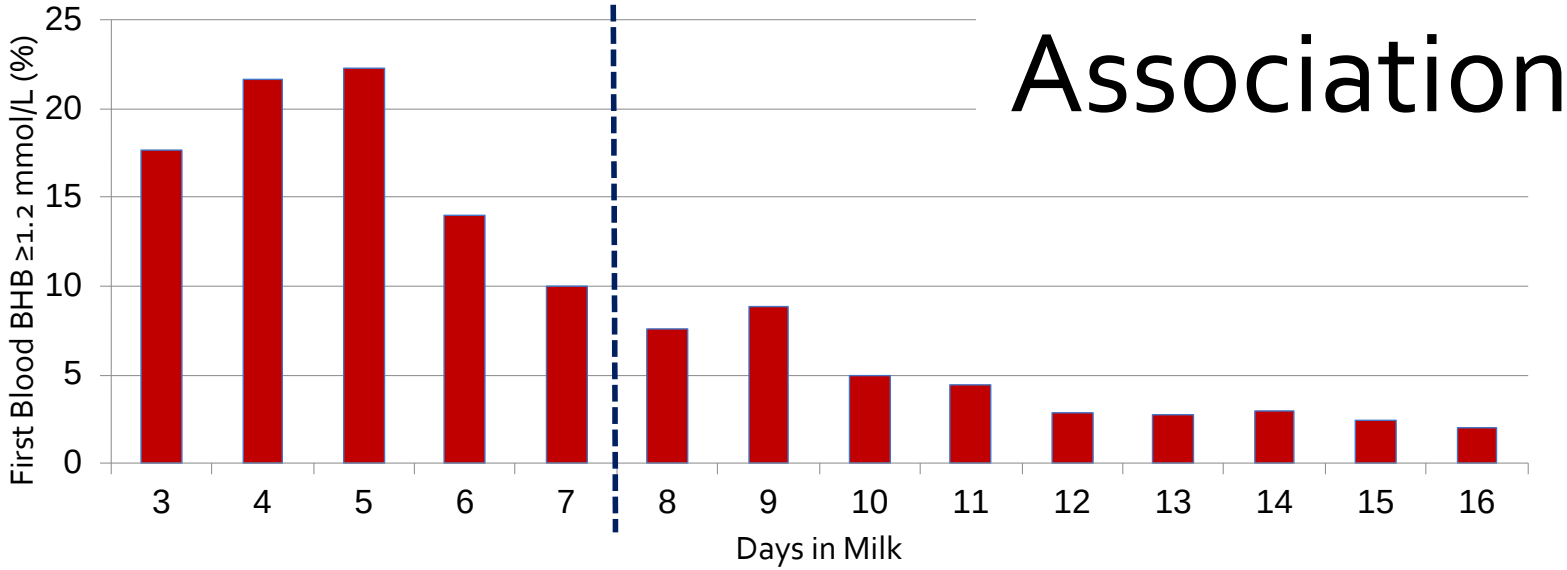
Duffield et al., 2009; Ospina et al., 2010; Chapinal et al., 2012; McArt et al., 2012

Incidence of hyperketonemia by DIM



Adapted from McArt et al., 2012, *JDS*

Association of DIM at Onset



- Risk of adverse health events different
  - Cows first hyperketonemic from 3 to 7 DIM >> 8 to 16 DIM
  - Cows first hyperketonemic from 8 to 16 DIM = non-ketotic cows

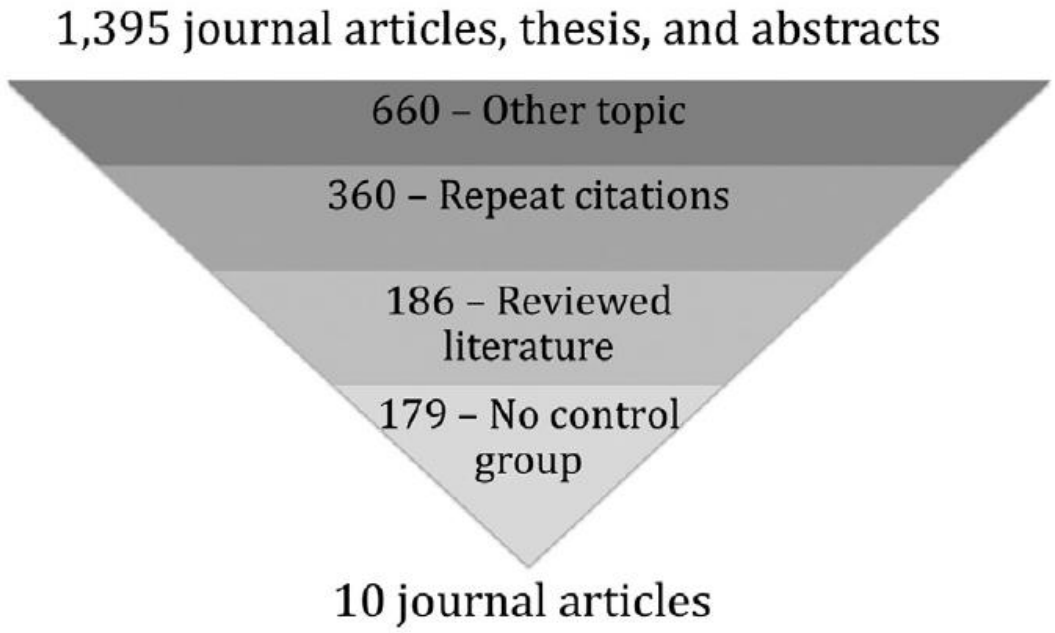
- Milk yield different
  - Cows first hyperketonemic from 3 to 7 DIM << 8 to 16 DIM
  - Cows first hyperketonemic from 8 to 16 DIM >> non-ketotic cows

McArt et al., *JDS*, 2012; Vanholder et al., *JDS*, 2015; Rodriguez et al. *JDS*, 2022

Treatment of hyperketonemia

Hyperketonemia treatment

Gordon et al., 2013, *VCNA*



- Historical use of glucose – no field trials assessing use alone
- Target underlying metabolic derangement

Hyperketonemia treatment

- ↑ Propylene glycol (PG)
  - 300 mL, orally once a day for 3 to 5 days
- ↔ Vitamin B12
- ↔ Glucose
  - 250 to 500 g with high BHB
- ↓ Glucocorticoids
  - Lack of efficacy
  - May be detrimental to cows with high BHB

Propylene glycol

- 100% food grade liquid
  - No method to pellet into concentrate
- Current research into other gluconeogenic substances
  - Glucoboost®
  - No benefit with additional glycerol
- Two modes of action:
  - Increased supply of propionate = glucogenic
  - Reduced insulin sensitivity = decreased glucose demand by peripheral tissues

(Piantoni and Allen, *JDS*, 2015; Oliveria et al., *JDS*, 2019)

Propylene glycol

- Multi-herd study on 1,717 cows
  - Randomized to treatment
  - 300 mL oral PG to cows with BHB ≥1.2 mmol/L

- Speeds resolution of ketosis
- Increases early lactation milk yield (~1.5 kg/cow/d)
- Improves preg to 1st insemination (~30%)
- Fewer displaced abomasa (~40%)
- Fewer culled cows (~50%)

McArt et al., *JDS*, 2011 & 2012

Propylene glycol

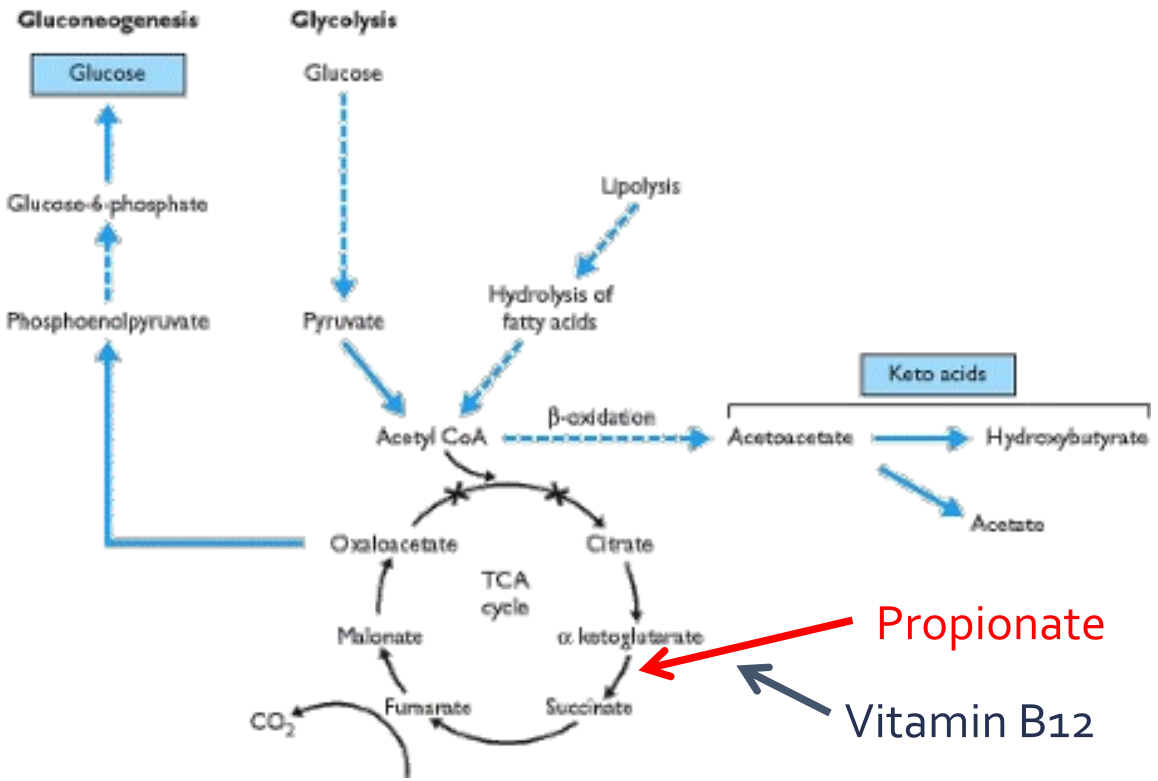
- Oral drenching preferred over mixing in feed
  - Drench larger effect on insulin than feeding in total mixed ration or top dressing
  - Absorbed more quickly when drenched than mixed in ration

- Low palatability
  - Top dressing ~500 g per d reduces feed intake after 1-2 d
  - Similar reduction when fed mixed in ration
  - Drench or mix with concentrates that change flavor (molasses)

(Nielsen and Ingvartsen, Animal Feed Science and Technology, 2004)

Vitamin B12

- Synthesized in rumen
- Methylmalonyl-CoA mutase
  - Converts propionate to succinyl-CoA
  - Vitamin B12 dependent
- Some supporting evidence
  - 1 dose 25 mL Catosal
  - 0.05 mg B12/mL
  - 100 mg butaphosphan/mL



Glucose

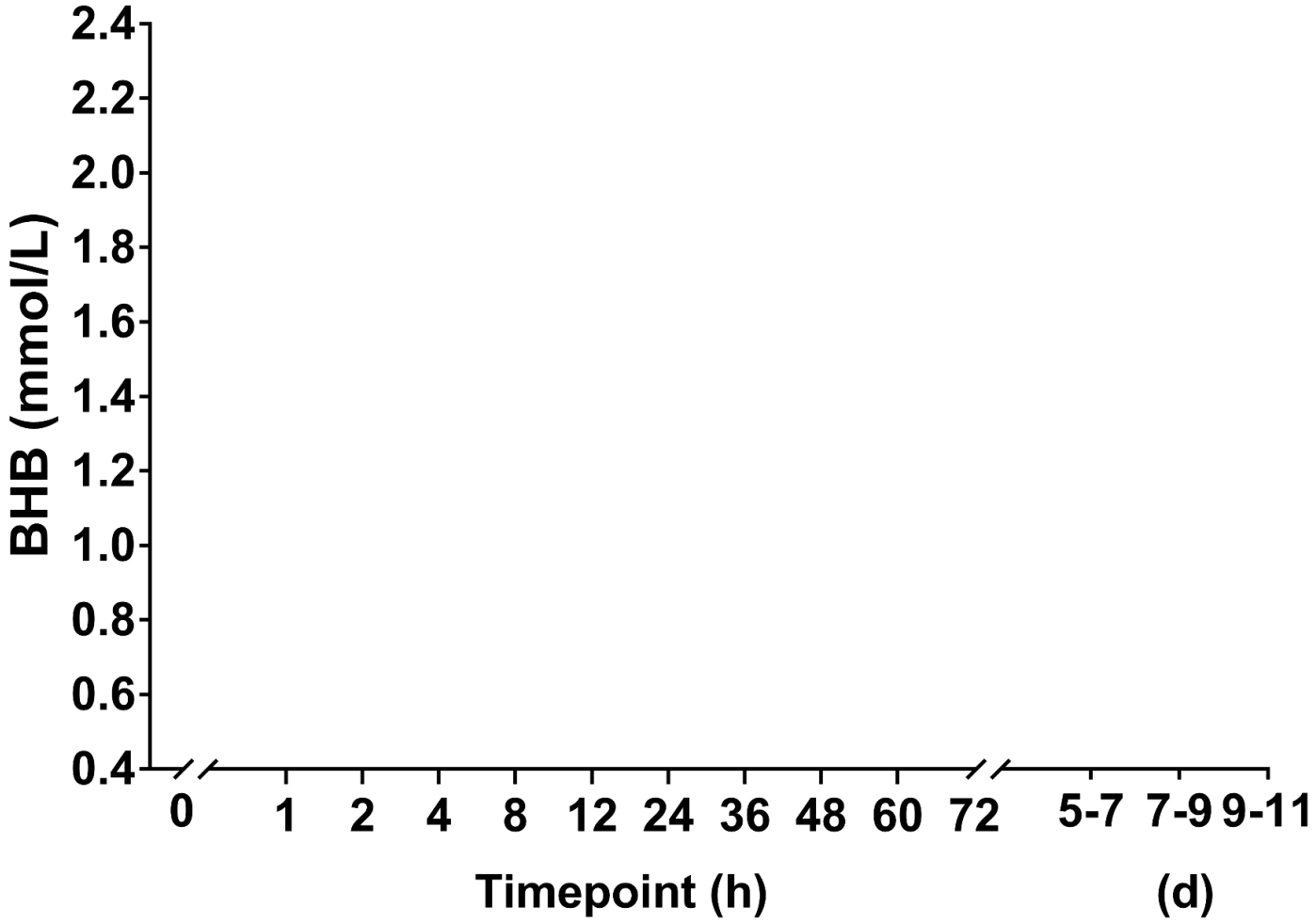
- Small, intensive trial on research herd
- Effects of propylene glycol (PG) and glucose on BHB

Cows 3-9 DIM with BHB ≥ 1.2 mmol/L (n=34)

n = 9	n = 9	n = 8	n = 8
			
500 mL 50% D-glucose i.v. once daily for 3 d	300 mL PG orally once daily for 3 d	500 mL 50% D-glucose i.v. + 300 mL PG orally once daily for 3 d	untreated control

Mann et al., *JDS*, 2017

Glucose – results on BHB



- Combination treatment greatest effect on magnitude and duration of BHB reduction
- Significance beyond treatment period?

Mann et al., *JDS*, 2017

Glucose – field trial

- Large, multi-herd field trial
  - Screened 1,249 cows between 3 to 16 DIM
  - Hyperketonemia defined as blood BHB ≥1.2 mmol/L
  - n = 373 cows were hyperketonemic

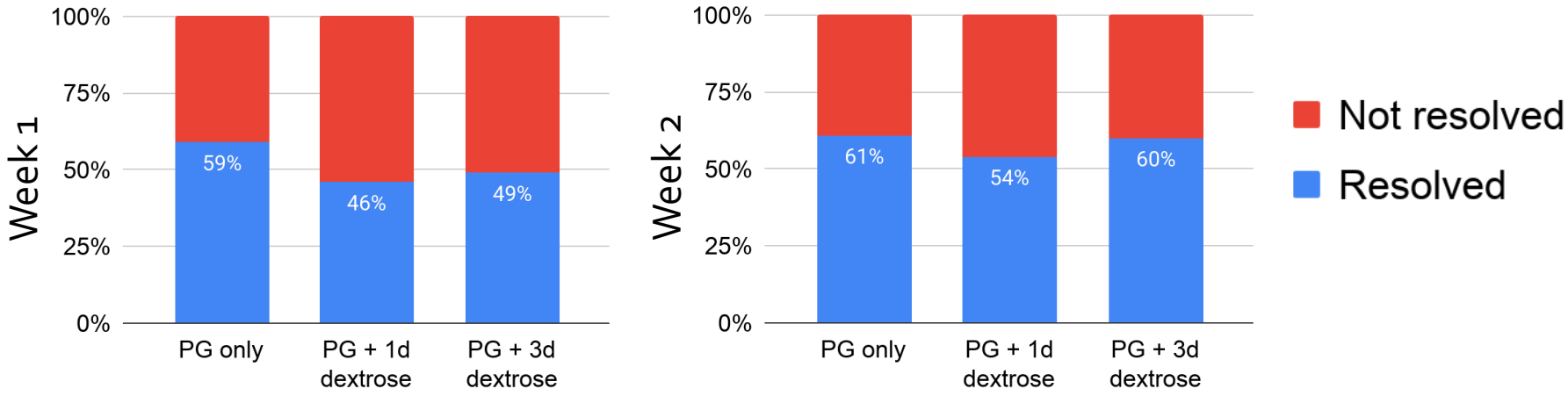
- Randomized to treatment:
  - 300 mL oral PG once daily for 3 days **(PG3)**
  - 300 mL oral PG once daily for 3 days + 500 mL i.v. 50% glucose on day 1 **(PG3D1)**
  - 300 mL oral PG once daily for 3 days + 500 mL i.v. 50% glucose on day 1-3 **(PG3D3)**

Capel et al., *JDS*, 2021

Glucose – field trial results

- Resolution of hyperketonemia (BHB <1.2 mmol/L)
  - No difference between groups (*P* = 0.3)
  - ~50% resolution at 1 wk, ~60% resolution at 2 wk

Resolution (%) by week post-treatment:

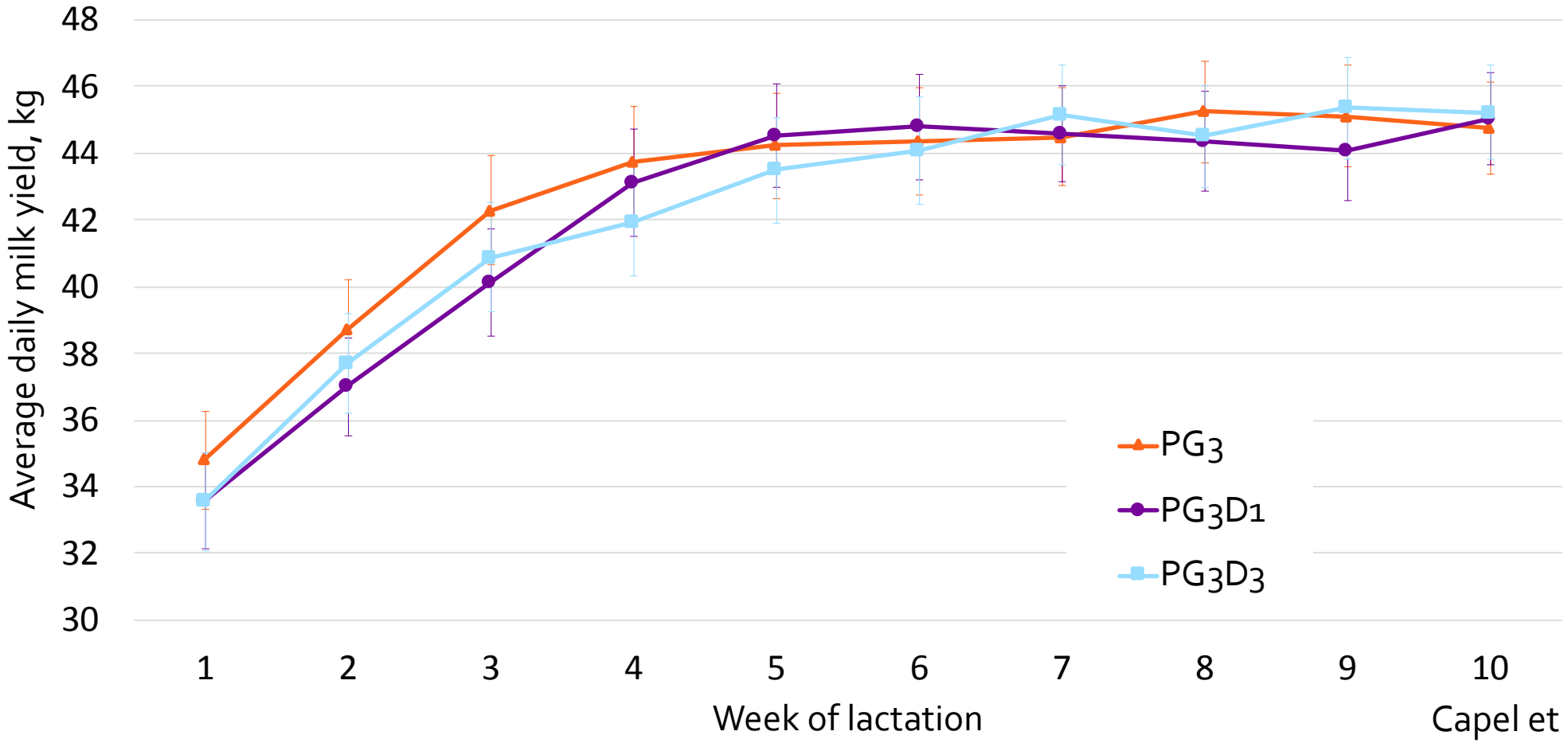


- Risk of adverse events during first 60 DIM
  - No difference between groups (*P* = 0.6)
  - PG3 = 7.6%, PG3D1 = 8.0%, PG3D3 = 12.1%

Capel et al., *JDS*, 2021

Average daily milk, first 10 weeks of lactation

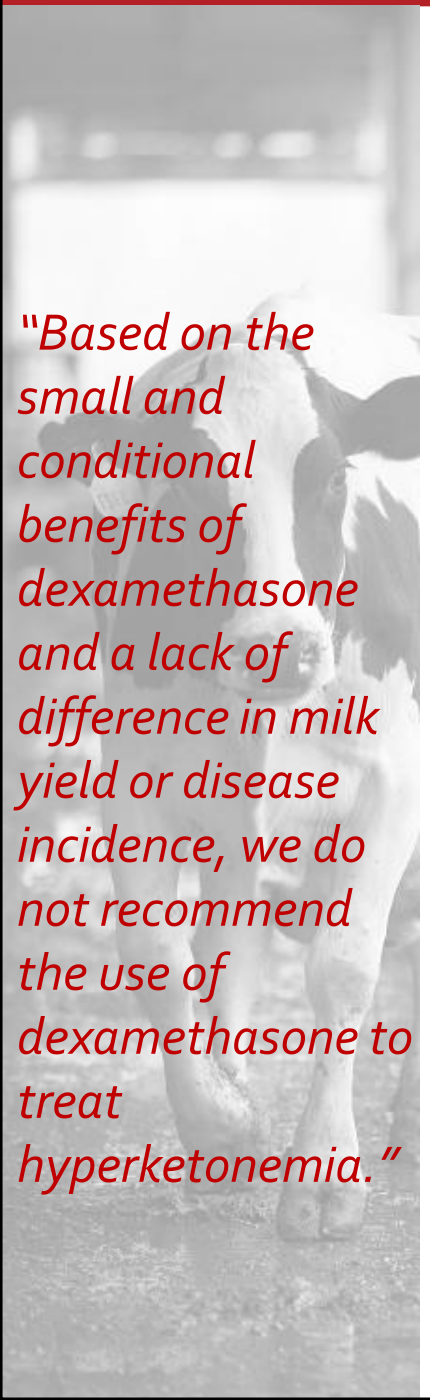
- No difference between groups (*P* = 0.9)
- PG3 = 42.7 kg/d, PG3D1 = 42.4 kg/d, PG3D3 = 42.6 kg/d



Capel et al., *JDS*, 2021

Glucose – treatment summary

- Provide dairies with valid, labor efficient, and cost-effective treatment strategies
- Glucose provides no additional benefit over treatment with oral PG alone
- Eliminating glucose allows for less invasive treatment with no negative impact on success
- Qualifier: only 10% of cows had BHB ≥3.0 mmol/L



"Based on the small and conditional benefits of dexamethasone and a lack of difference in milk yield or disease incidence, we do not recommend the use of dexamethasone to treat hyperketonemia."

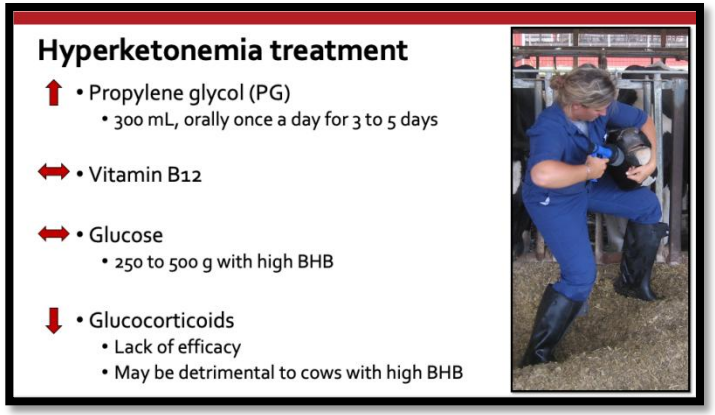
Glucocorticoids

- Multi-farm field trial
- Hyperketonemic cows (BHB ≥1.2 mmol/L; n = 509):
  - 20 mg dexamethasone IM + 300 mL PG orally for 4 d
  - Equal volume saline IM + 300 mL PG orally for 4 d
- No difference in milk yield (P = 0.23)
- No difference in disease incidence (P = 0.98)
- Odds of resolution:
  - Increased for cows with BHB = 1.2 to 1.5 mmol/L
  - Decreased for cows with BHB >3.2 mmol/L

Tatone et al., *JDS*, 2016

Hyperketonemia treatment protocol

- Owner, veterinarian, farm management team
- Understand what type of cow you are treating
  - Clinically ketotic
  - Hyperketonemic with no clinical signs
- Develop a treatment plan that is evidence based and will be followed
- Prevention is more important and cost effective than treatment!



Summary

- Use on-farm blood BHB measuring methods for individual cow diagnosis.
- Implement an evidence-based treatment plan.
- Perform routine prevalence testing and record over time.
- Adjust nutrition and management to keep hyperketonemia prevalence ≤15%.

Acknowledgements

jmcart@cornell.edu
blogs.cornell.edu/jessmcartlab
jmcartdvm