Current concepts in hypocalcemia

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Cornell Dairy Center of Excellence

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Disclosure

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Overview

- Calcium demands of early lactation
- When is hypocalcemia a problem?
- Postpartum calcium supplementation

The transition period

- Time of physical and physiologic change
- 3 weeks before to 3 weeks after calving

Calcium demands of milk production

Daily maintenance = 21 g Ca

Colostrum = 23 g Ca

100 lb milk = 56 g Ca

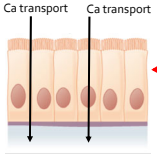
- Human recommended dietary allowance = 1,000 mg Ca
- 1 cup milk = 300 mg Ca

Increasing blood calcium

↑PTH secretion

↓ Ca excretion
25-OH vit D→ 1,25(OH)$_2$D
(minutes)

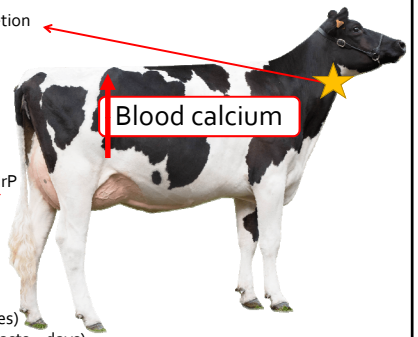
Paracellular Ca transport
Transcellular Ca transport



↑Ca absorption
(days)

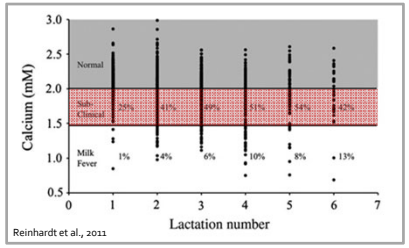
↑Ca release
(osteocytes = minutes)
(osteoblasts/osteoclasts = days)

PTHrP



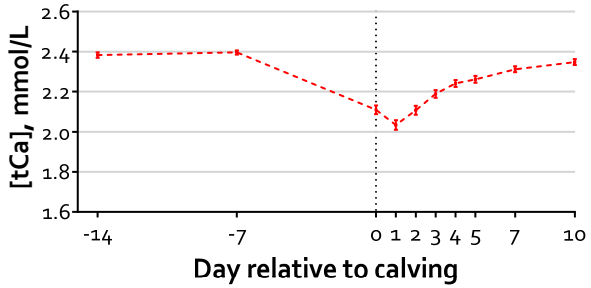
Hypocalcemia

- Clinical disease has been well addressed, focus now on subclinical disease



- Milk fever incidence <5% on dairies
- Subclinical hypocalcemia (SCH) incidence up to 50%

Peripartal change in blood calcium



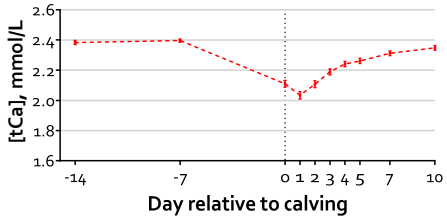
Mean calcium concentration of 407 cows in 2 NY dairy herds.
Bars represent 95% confidence intervals.

Subclinical hypocalcemia (SCH)

- Multiple studies have explored categorization of blood calcium concentrations in early lactation
  Oetzel et al., 1988; Oetzel et al., 1996; Martinez et al., 2012
- Recent studies use epidemiologic outcomes to improve characterization
  Chapinal et al., 2011; Rodriguez et al., 2017; Wilhelm et al., 2017; Neves et al., 2018; Venjakob et al., 2018
- No consensus on optimal test day or what cut point to use for classification of SCH

Is subclinical hypocalcemia bad?

- When to test:
  - At calving?
  - At 24 hrs?
  - At 48 hrs?
  - Later?



- What cut-point to use:
  - Definition of "normal"
  - Based on health and production outcomes

Does calcium concentration at calving matter?

- Prospective cohort study in 5 dairy herds in NY
- 1,416 cows, blood collected by farm employees
- Mean time from calving to blood collection = 3 h

	Farm				
	A	B	C	D	E
Milking cows, n	1,474	567	1,282	1,677	1,222
Milk production, lb	85.5	85.6	81.4	82.1	81.0
Prepartum DCAD, mEq/100 g DM	-6.9	-2.8	-5.5	7.3/14.1	-2.8

Conclusions *tCa: 2.0 mmol/L = 8.0 mg/dL*

- Primiparous cows: tCa immediately after parturition was non-informative
- Multiparous cows:
  - Greater tCa increased the risk of culling
    - Every 0.1 mmol/L increase, RR = 3.4 (95% CI = 1.0 to 12.0)
  - Cows with tCa ≤1.95 mmol/L made more milk
    - 94.4 vs. 92.0 lb per test-day ($P < 0.001$)
  - Cows with tCa ≤1.85 mmol/L were more likely to get a DA
    - RR = 2.8 (95%CI = 1.4 to 5.9)

Take-home message (and more questions…)

- Caution in classifying subclinical hypocalcemia based on a single time-point collected within 12 h of calving
- Are our cut-points for subclinical hypocalcemia too high?
- Is it the duration of subclinical hypocalcemia, not the value that is important?

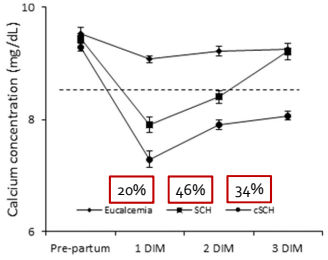
Chronic subclinical hypocalcemia (cSCH)

Theriogenology. 2017 May;94:1-7. doi: 10.1016/j.theriogenology.2017.01.039. Epub 2017 Jan 25.

Association between subclinical hypocalcemia in the first 3 days of lactation and reproductive performance of dairy cows.

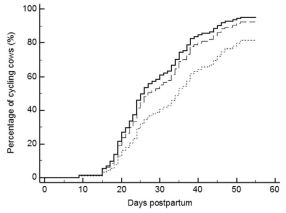
Caixeta LS[1], Ospina PA[1], Capel MB[2], Nydam DV[3].

- 2 dairy farms, 97 cows
- Definitions:
  - SCH = serum tCa ≤2.15 mmol/L (8.6 mg/dL)
  - cSCH = SCH at 1, 2, and 3 DIM
- Incidence cSCH:
  - Parity 1 = 20%
  - Parity 2 = 32%
  - Parity ≥3 = 46%



Caixeta et al.: chronic SCH on reproduction

- Return to cyclicity:
  - Eucalcemic cows were more likely to return to cyclicity by end of VWP than cSCH cows
  - HR = 1.8 ($P = 0.06$)

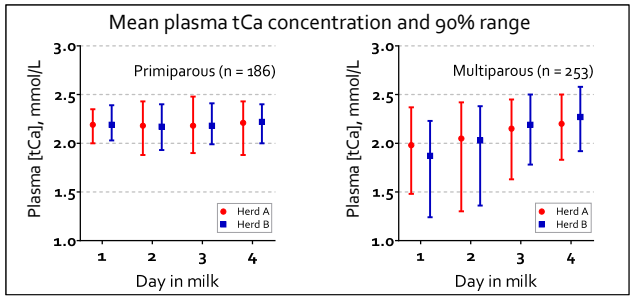


- Pregnancy at first service:
  - cSCH cows had lower odds of pregnancy compared to eucalcemic cows
  - OR = 0.27 ($P = 0.04$)

When does calcium concentration matter?

- Prospective cohort study on 2 dairy herds in NY
  - 396 cows, blood sample collected daily for first 4 DIM
  - Health disorders and daily milk production collected from farm computer records
- Describe temporal association of tCa with:
  - Risk of metritis and/or displaced abomasum
  - Average daily milk yield for first 15 weeks

Descriptive results



Disease	Primiparous, n	Multiparous, n
Metritis	19 (13.9%)	22 (8.5%)
Displaced abomasum	0 (0.0%)	12 (4.6%)

Disease results – primiparous cows

- Reduced tCa at 2, 3, or 4 DIM associated with an increased risk of metritis

DIM	n	*P*-value	AUC	Cut point, mmol/L	% below cut point	RR	95% CI
1	137	0.22	—	—	—	—	—
2	137	0.001	0.78	≤2.15	36.5	4.0	2.0 to 8.0
3	137	<0.001	0.80	≤2.10	26.3	5.2	2.6 to 10.3
4	134	<0.001	0.80	≤2.15	25.4	6.1	3.0 to 12.2

Adapted from Neves et al., 2018. J. Dairy Sci 101: 9321-9331.

Milk results – primiparous cows

- Reduced tCa at 1 DIM associated with increased milk

DIM	n	*P*-value	AUC	Cut point, mmol/L	% below cut point	Milk yield, lb/d
1	137	0.01	0.57	≤2.15	40.0	6.4 (±1.8)

Adapted from Neves et al., 2018. J. Dairy Sci 101: 9321-9331.

- No association of tCa at 2, 3, or 4 DIM with milk yield

Disease results – multiparous cows

- Association with metritis and/or DA differed by parity

Parity	DIM	n	*P*-value	AUC	Cut point, mmol/L	% below cut point	RR	95% CI
2	1	105	0.17	—	—	—	—	—
	2	105	<0.001	0.67	≤1.97	20.0	4.1	1.8 to 9.5
	3	104	0.24	—	—	—	—	—
	4	103	0.25	—	—	—	—	—
3+	1	151	0.17	—	—	—	—	—
	2	151	0.50	—	—	—	—	—
	3	151	0.60	—	—	—	—	—
	4	148	0.04	0.70	≤2.20	43.2	3.1	1.4 to 6.8

Milk results – multiparous cows

- Association of tCa with milk yield differed by DIM
  - Reduced tCa at 1 DIM associated with increased milk yield
  - Reduced tCa at 4 DIM associated with decreased milk yield

DIM	n	*P*-value	AUC	Cut point, mmol/L	% below cut point	Milk yield, lb/d
1	256	0.002	0.61	≤1.77	23.5	5.7 (±1.8)
4	251	0.04	0.52	≤2.20	39.0	-4.0 (±1.8)

Adapted from Neves et al., 2018. J. Dairy Sci 101: 9321-9331.

Conclusions

- Day in milk at time of testing and parity are important factors when characterizing SCH!
  - Parity 1 cows at 2 DIM
  - Parity 2 cows at 2 or 4 DIM ⟶ ???
  - Parity 3+ cows at 4 DIM
- Need more large field studies to validate these thresholds

Implications for the real world …

- We need to stop diagnosing SCH at 1 DIM.
- Should we evaluate herd-level calcium status based on parity group?
- What is a practical testing strategy in commercial herds?

Measure total calcium at 2-4 DIM

- Does postpartum calcium supplementation affect longer-term calcium homeostasis?

Determining Calcium Status

Cold ears?

J. Dairy Sci. 99:6542–6549
http://dx.doi.org/10.3168/jds.2015-10734

Evaluation of ear skin temperature as a cow-side test to predict postpartum calcium status in dairy cows

P. L. Venjakob,*† S. Borchardt,* G. Thiele,† and W. Heuwieser*[1]
*Clinic for Animal Reproduction, Faculty of Veterinary Medicine, Freie Universität Berlin, Koenigsweg 65, 14163 Berlin, Germany
†Veterinary practice G. Thiele, Baruth, Germany

- 7 herds
- 251 cows, 0-48 hr postpartum

- Manual scoring
- Rectal temperature
- Infrared thermometer
- Blood calcium

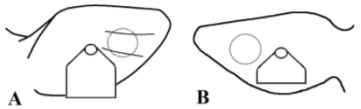


Figure 1. Schematic presentation of the measuring points for the infrared thermometer on the front (A) and rear side (B) of the ear.

- Hypocalcemia defined as blood calcium < 2.0 mmol/L

Calcium threshold, mmol/L	Prevalence, %	Temperature variable[1]	Threshold, °C	Sensitivity	Specificity	AUC[2]	*P*-value
2.0	29.6	STEar	27.0	49.3	73.8	0.641	0.001
		STCox	30.0	52.2	78.7	0.668	0.001
		RT	39.0	75.4	42.7	0.606	0.009

- Decrease in ear temp of 0.39°C associated with decrease of 0.1 mmol/L in calcium
- Ambient temp was a major confounder
- Conclusions: ear temperature cannot be recommended for diagnosis of subclinical hypocalcemia

Direct measurement of calcium

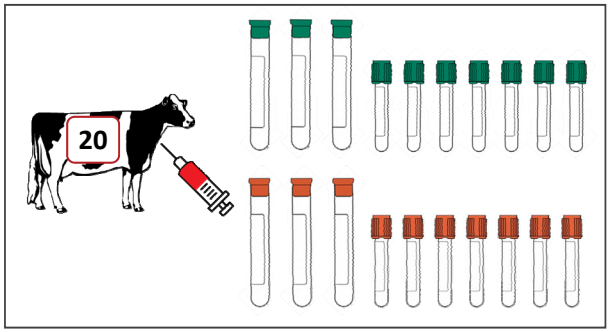
- Calcium is differentiated into 3 forms in blood:
  - Free or ionized (50-60%)
  - Bound to proteins (30%)
  - Complexed (10%)
- 2 options:
  - Total calcium (tCa)
  - Ionized calcium (iCa)

Total calcium

- Collect in green or red top tubes
- Fairly stable

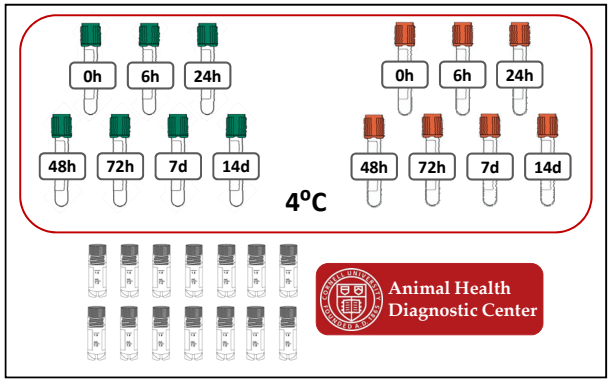
- Methods of analysis:
  - Benchtop analyzer in laboratory @ $5-15/sample
  - Analyzer in vet clinic @ $5-7.50/sample

Study design



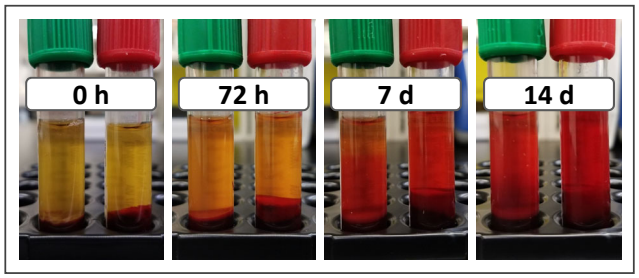
Courtesy: Kathryn Bach

Study design



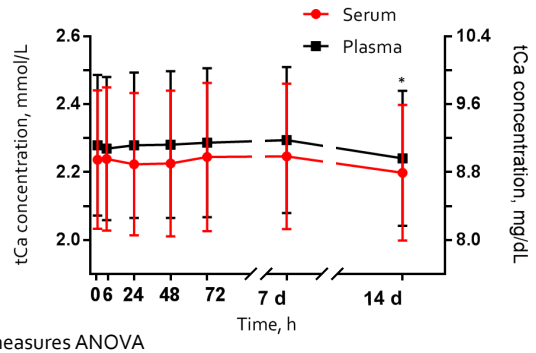
Courtesy: Kathryn Bach

Results



Courtesy: Kathryn Bach

Results



- n = 13
- Repeated measures ANOVA
  - Time, $P < 0.001$
  - * = different from Time 0, $P < 0.05$
  - Sample type, $P = 0.64$

Ionized calcium

- iCa thought to have greater biological relevance than tCa
- Ion-selective electrode technology is largely employed for clinical use (blood-gas analyzers)
- Measurement of iCa is expensive, special handling procedures
  - Heparin salts bind calcium
  - Use of electrolyte-balanced syringes
  - Exposure to air changes blood pH

Ionized calcium – methods of analysis

- Cowside = not practical
- Machines targeted for on-farm use:
  - iSTAT, VetScan, Nova Stat
  - $5,000-$15,000 + sample costs
- Fast, accurate, and inexpensive tools that measure iCa do not currently exist
- Why not just measure tCa?
  - Relationship between tCa and iCa varies following parturition (Leno et al., 2017, J. Dairy Sci)

Postpartum calcium supplementation

Treatment/prevention options:

- Calcium borogluconate 23% (~10 g Ca)
  - Intravenous
  - Subcutaneous
- Oral drench with calcium propionate
  - 1 lb
  - Not practical
- Oral boluses
  - 40 – 50 g calcium
  - Different release speeds
- Oral gels

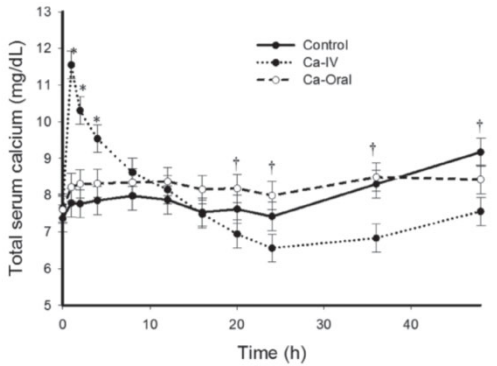
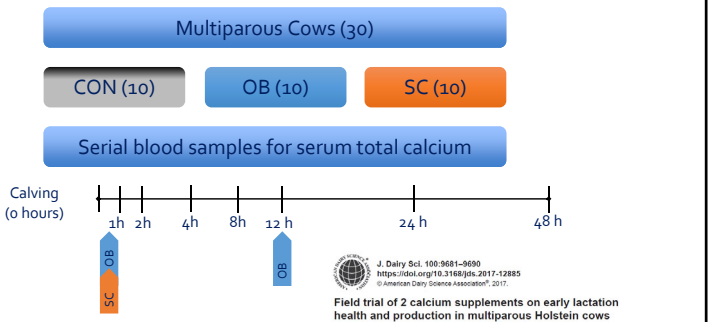


Figure 1. Total serum Ca levels (LSM ± SEM) after postpartum prophylactic treatment of subclinical hypocalcemia in control (no Ca supplementation; n = 11), intravenous Ca [Ca-IV, 500 mL of 23% calcium gluconate (Durvet, Blue Springs, MO) at postpartum; n = 11], and oral Ca [Ca-Oral, 2 Bovikalc (Boehringer Ingelheim, St. Joseph, MO) boluses 12 h apart at postpartum; n = 11]. We detected a significant ($P < 0.001$) effect of time and treatment × time interaction. Significant treatment × time differences at each time point are indicated by † ($P < 0.05$) and * ($P < 0.001$).

Journal of Dairy Science Vol. 97 No. 11, 2014

Blanc et al., *JDS*, 2014

Aim: To observe serum Ca concentrations during the first 48 h postpartum in cows supplemented with oral Ca or subcutaneous Ca and non-supplemented cows



J. Dairy Sci. 100:9681–9690
https://doi.org/10.3168/jds.2017-12885
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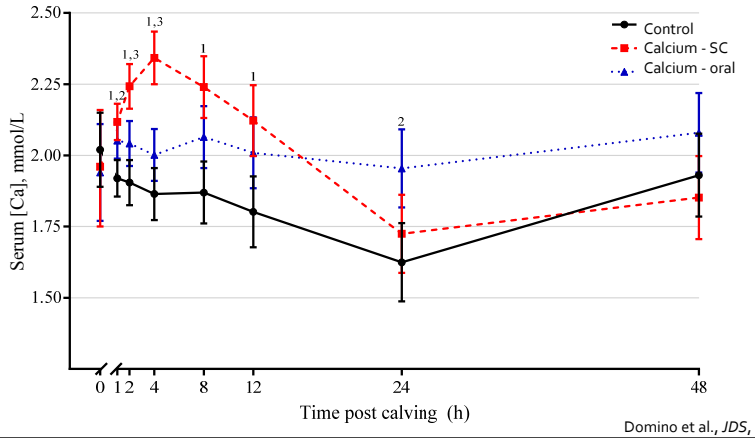
Field trial of 2 calcium supplements on early lactation health and production in multiparous Holstein cows

Antonia R. Domino, Helen C. Korzec, and Jessica A. A. McArt[1]
Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853

Courtesy of A. R. Domino



Domino et al., *JDS*, 2017

So, what is best?

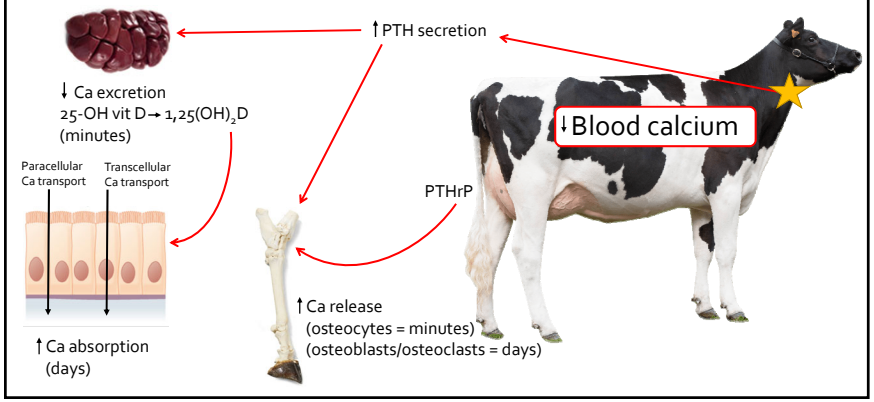
- Subcutaneous calcium? Oral calcium? Nothing?
  - Increase blood calcium for a short period of time
  - Does supplementation prevent disease or improve milk yield?
- Answer: it depends.
  - Blanket therapy not always beneficial
  - Target groups: high producing cows, older cows, lame cows, cows with difficulty calving
  - Avoid other groups: primiparous cows

Prevention

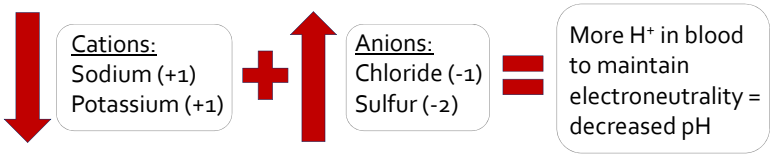
Nutritional strategies to reduce hypocalcemia

- Prepartum nutrition:
  - Feeding a dietary cation anion difference diet
  - Feeding a low Ca diet
    - Ca < 20g/d absorbed (practically difficult)
    - Calcium binder
- Postpartum nutrition:
  - Ensure adequate minerals

Increasing blood calcium



Altering blood pH via DCAD



- Improved sensitivity of PTH receptor to PTH stimulation
- Increased urinary Ca excretion = increased Ca flux
- May result in greater bone resorption and/or increased intestinal Ca absorption

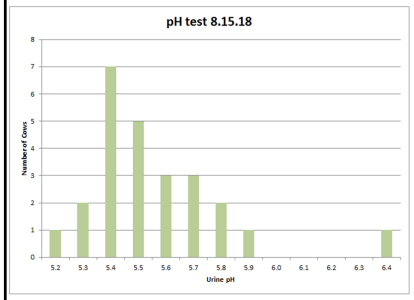
Courtesy of Brittany Leno

Goff et al., 2014; Goff and Horst, 2003; Martin-Tereso and Verstegen, 2011

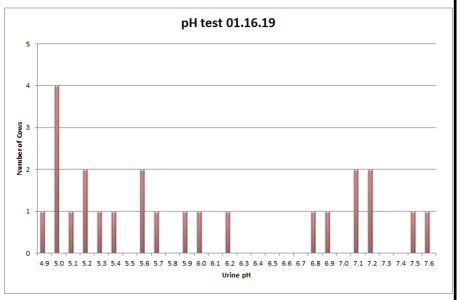
Is the DCAD working?

- Urine pH:
  - Midstream urine samples
  - Measure ~12 to 15 cows weekly
  - Consistent measurement relative to feeding time

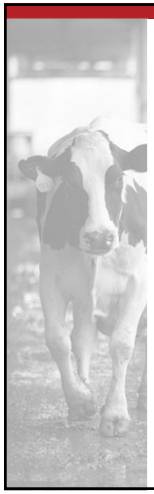
- Goals:
  - 80% cows between 5.5 – 6.5
  - CV < 8%



- Median urine pH = 5.5 (5.2-6.4)
- 60% of cows between 5.5 – 6.5
- CV = 4.4%



- Median urine pH = 5.7 (4.9-7.6)
- 25% of cows between 5.5 – 6.5
- CV = 15.8%

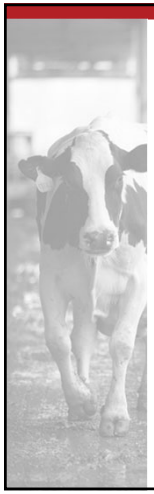


Feeding DCAD

- Feeding DCAD but normal urine pH values?
  - Cows not consuming expected DM or TMR not mixed properly
  - Improper evaluation and adjustment for other free-choice minerals or forage content
- Large variation between cows may indicate unequal consumption of ration.
  - Overcrowding or social factors
  - Sorting due to poor mixing

Feeding DCAD

- Variation between weeks can indicate inconsistency in ration mixing or changes in feed ingredient composition.
- Use this information to improve feeding and management strategies!



Calcium binders

- Sodium aluminum silicate (Zeolite A)
  - Can bind dietary Ca, P, Mg
  - Show to increase active form of vitamin D prepartum
  - Studies done in USA and New Zealand
    - Targeted 500 g/d as fed
- Decreased prevalence of hypocalcemia
- No change in postpartum milk yield

Summary …

- Hypocalcemia is a normal occurrence in immediate postpartum dairy cows.
- Diagnostic testing is expensive – use your money wisely.
- Calcium supplementation is beneficial to an important group cows – the key is determining which group needs it and when!
- Prevention is always better than treatment.

Goal: *identify optimal strategies to monitor and prevent hypocalcemia*

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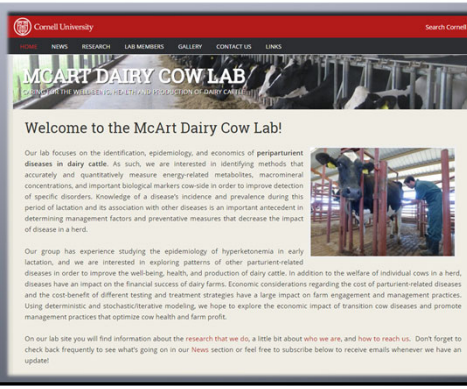
Questions?



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