WAGENINGEN UNIVERSITY & RESEARCH

International Dairy Nutrition Symposium 2017

The transition period and metabolic diseases in relation to fertility

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DAIRY at GUELPH
CANADA'S DAIRY UNIVERSITY

Transition Health and CR at 1st AI 5719 cows in 7 US herds

Table 2. Impact of health problems in the first 60 d postpartum on pregnancy at first postpartum AI of dairy cows[1]

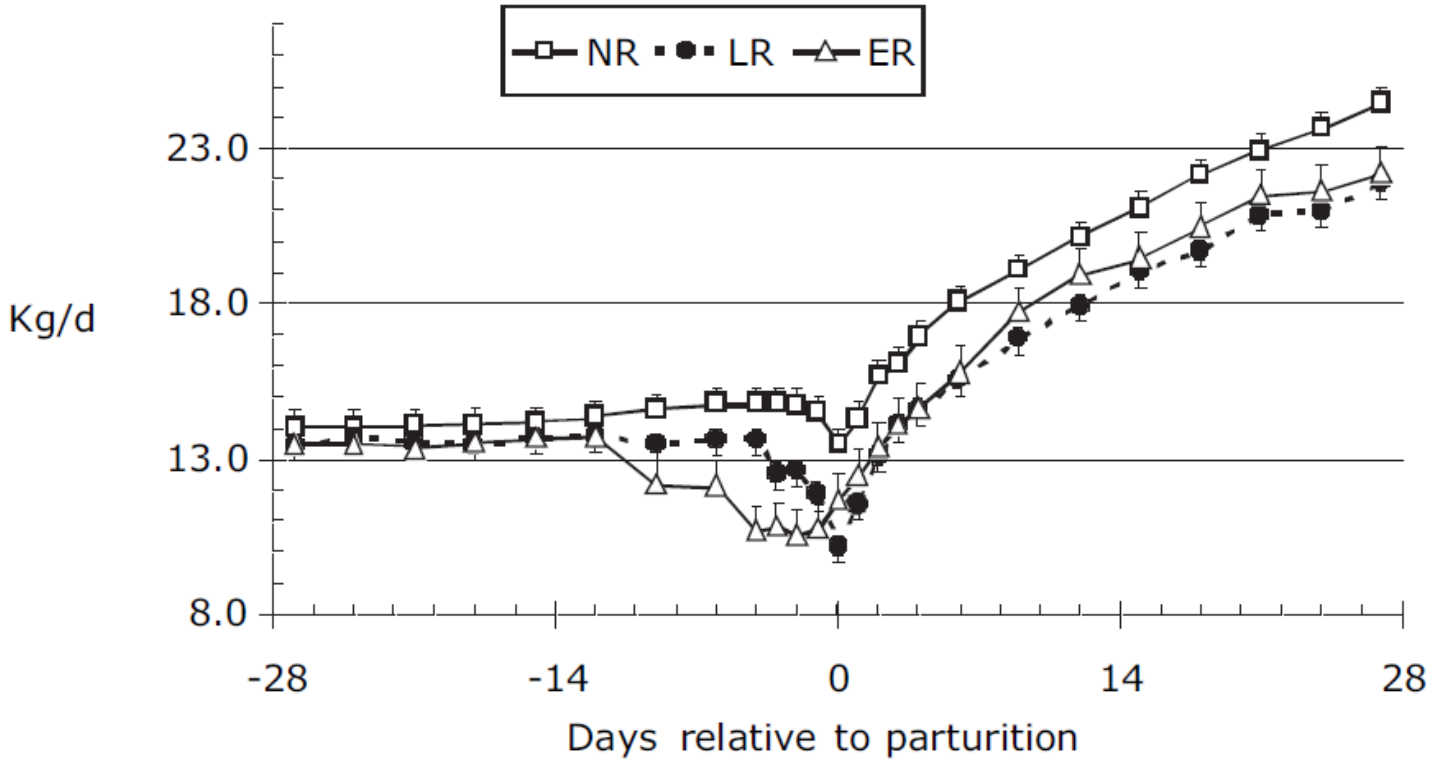
Health status	**Prevalence**	Pregnant, %	Adjusted OR (95% CI)[2]	*P*
Health problem				
Healthy	**56**	51.4	1.00	
1 case of disease	**27**	43.3	0.79 (0.69 – 0.91)	0.001
> 1 case of disease	**17**	34.7	0.57 (0.48 – 0.69)	< 0.001
Type of health problem[3]				
Calving problem	**15**	40.3	0.75 (0.63 – 0.88)	< 0.001
Metritis	**16**	37.8	0.66 (0.56 – 0.78)	< 0.001
Clinical endometritis	**20**	38.7	0.62 (0.52 – 0.74)	< 0.001
Fever postpartum	**21**	39.8	0.60 (0.48 – 0.65)	< 0.001
Mastitis	**12**	39.4	0.84 (0.64 – 1.10)	0.20
Clinical ketosis	**10**	28.8	0.50 (0.36 – 0.68)	< 0.001
Lameness	**7**	33.3	0.57 (0.41 – 0.78)	< 0.001
Pneumonia	**3**	32.4	0.63 (0.32 – 1.27)	0.20
Digestive problem	**2**	36.7	0.78 (0.46 – 1.34)	0.38

Santos et al RepDomRum 2010

Dry period nutrition and reproduction

- Pooled analysis of 7 studies of controlled (≤ 100% NRC) vs. high (> 100% NRC) energy factorial experiments in far-off and close-up dry period (Cardoso et al 2013)
- CE in close-up associated with
  - Shorter time to pregnancy (157 vs 167 d)
  - Higher NE_L intake postpartum

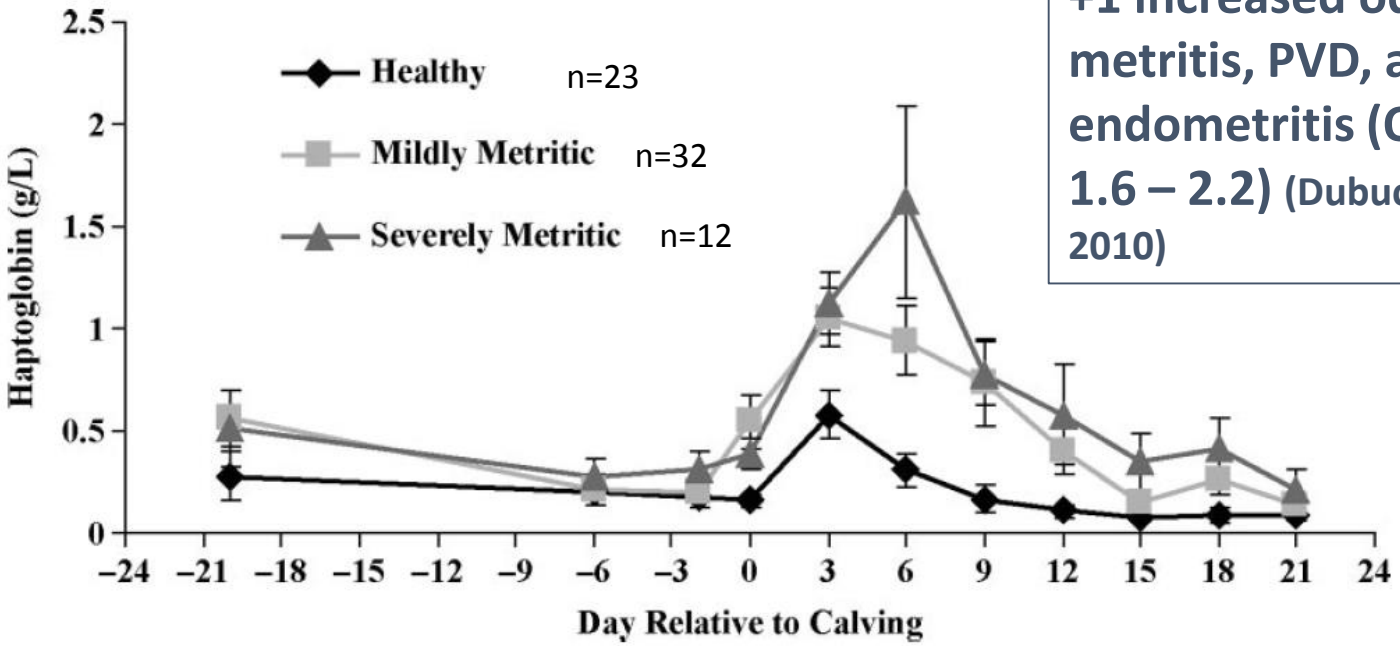
Patterns of DMI in the transition period



Bertoni et al Ital.J.Anim.Sci. vol. 8, 491-518, 2009

Increased Haptoglobin Precedes Reproductive Disease

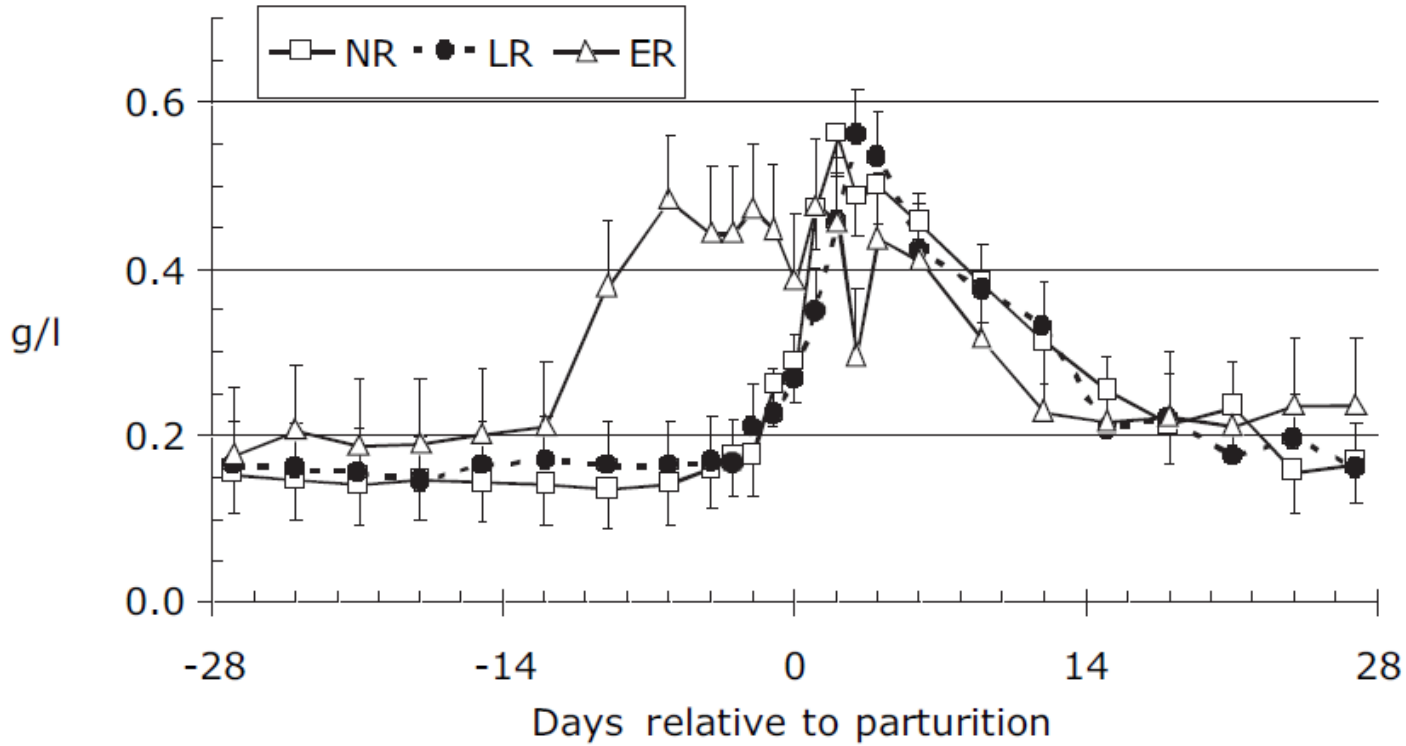
Hp > 0.8 g/L in week +1 increased odds of metritis, PVD, and endometritis (OR = 1.6 – 2.2) (Dubuc et al 2010)



Hp ≥ 1 g/L at 3 DIM OR = 6.7 for metritis Se = 50% Sp = 87%

Huzzey et al 2009

Association of haptoglobin with DMI



Bertoni et al Ital.J.Anim.Sci. vol. 8, 491-518, 2009

Inflammation

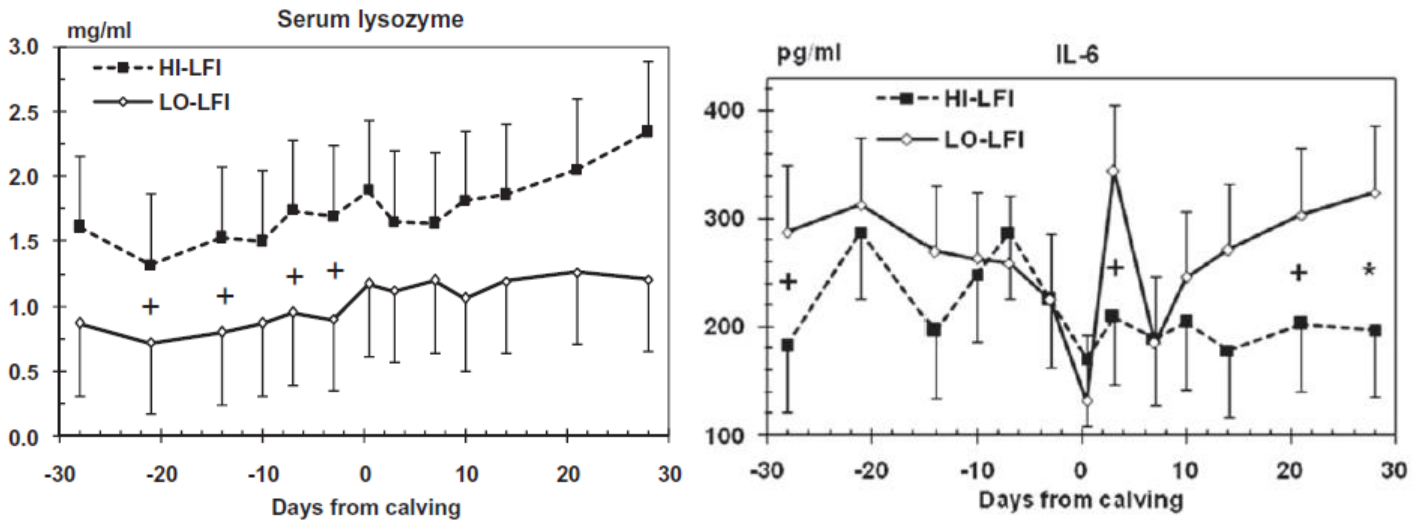
- Acute/classical inflammation
  - Injury → heat, pain, swelling, redness
  - Infection → fever, decreased feed intake
  - Disease causes inflammation

- Metabolic/chronic inflammation
  - No clinical signs
  - Oxidative stress, obesity, fat mobilization (?) → Slight elevations in pro-inflammatory mediators and acute phase proteins; changes in signalling
    - Contributes to insulin resistance
  - Inflammation contributes to disease

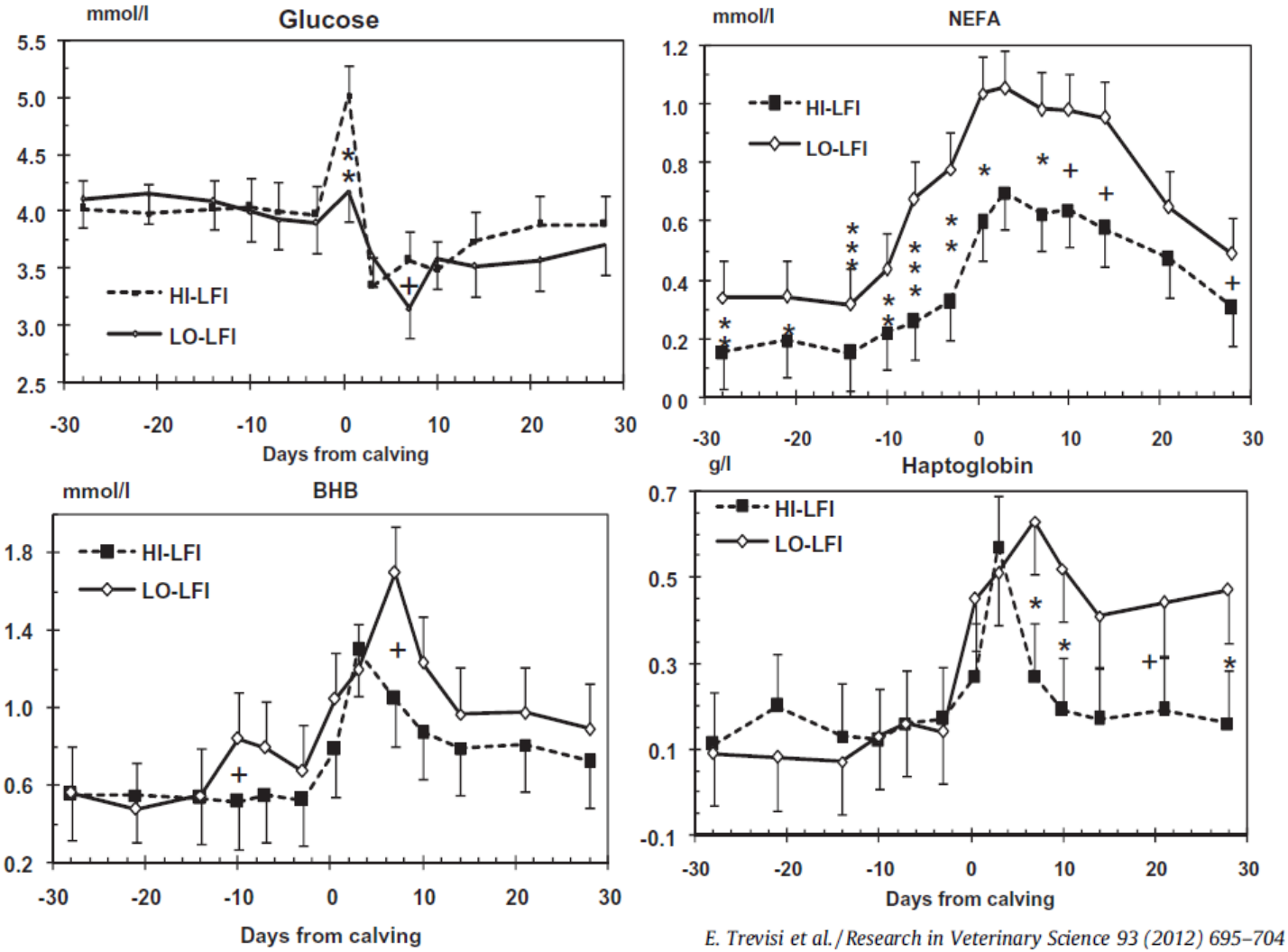
Adapted from Barry Bradford

Associations of inflammation and metabolism

54 cows tested – lowest and highest 20% "Liver Functionality Index" (score based on albumin, cholesterol and bilirubin at 3 DIM and Δ 3 to 28 DIM (n=6 per group) presented



E. Trevisi et al. / Research in Veterinary Science 93 (2012) 695–704



E. Trevisi et al. / Research in Veterinary Science 93 (2012) 695–704

Hypocalcemia – moving the goal posts?

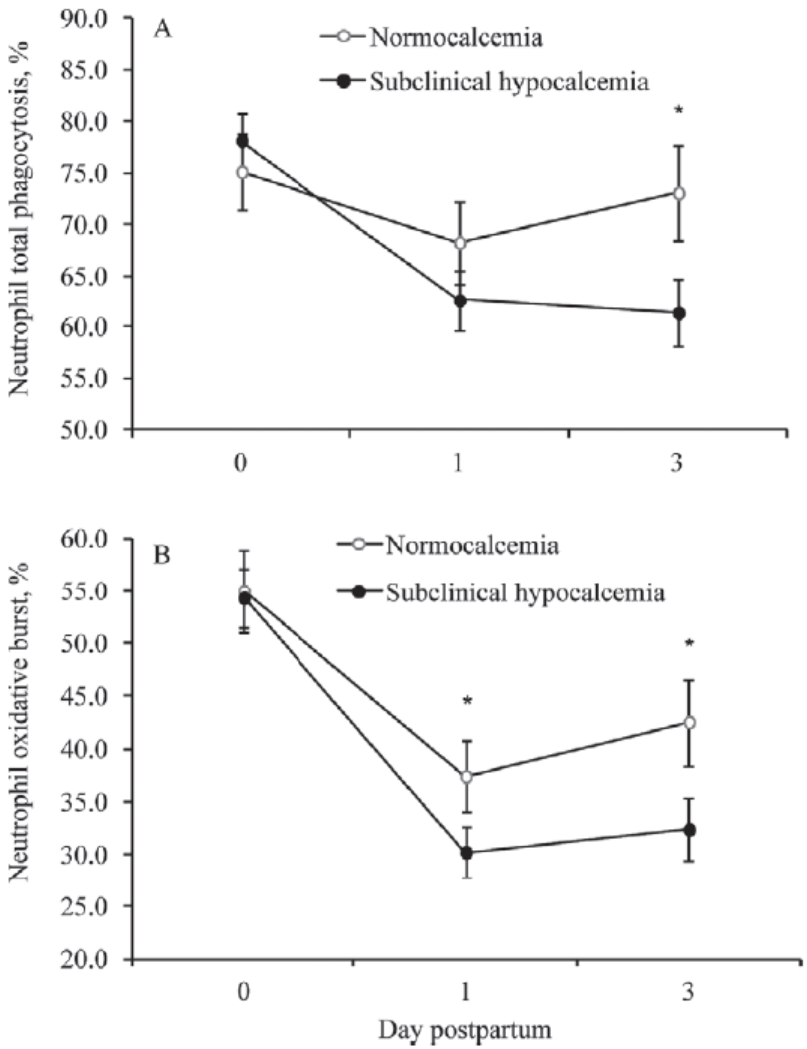
- Subclinical hypocalcemia traditionally defined as < 2.0 mmol/L 1 – 3 DIM

In week 1 postpartum (2365 cows in 55 herds Canada & US; Chapinal et al JDS 2011, 2012)

- Ca ≤ 2.2 mmol/L (38% of cows) OR = 2.7 for DA (accounting for NEFA week -1 and +1)
- Ca ≤ 2.1 mmol/L (23% of cows)
  - -2.6 kg at 1st DHI test
  - ~ 29 % vs. 35% CR at 1st AI

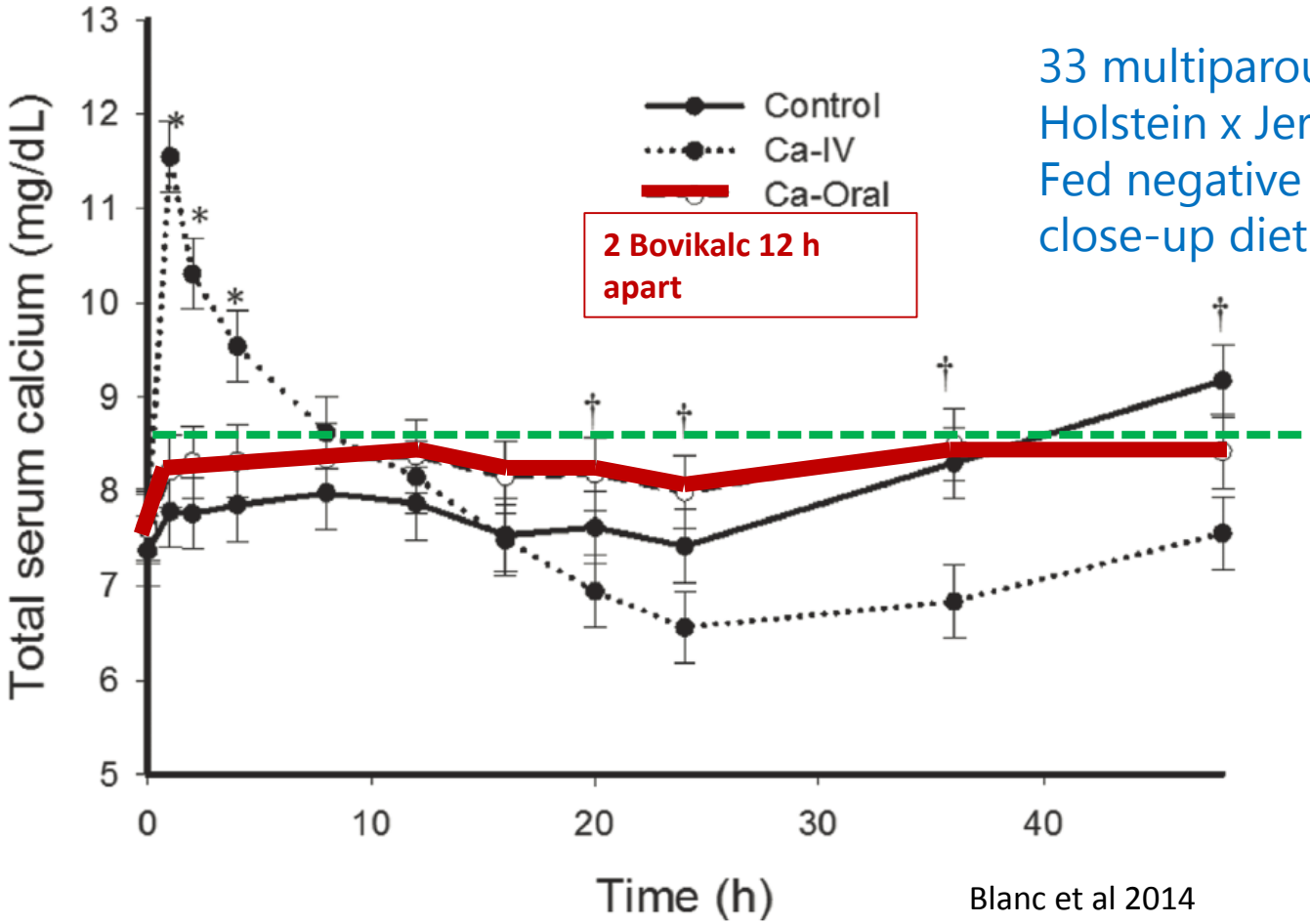
Association of blood calcium with neutrophil function

- 110 cows in 1 herd in Florida
- Pair-matched "high risk" (twins, stillbirth, dystocia, RP) with low risk cows
- Subclinical hypo-Ca = ≤ 2.15 mmol/L at least once 1 – 3 DIM



Martinez et al JDS 2012

Effect of Ca supplements

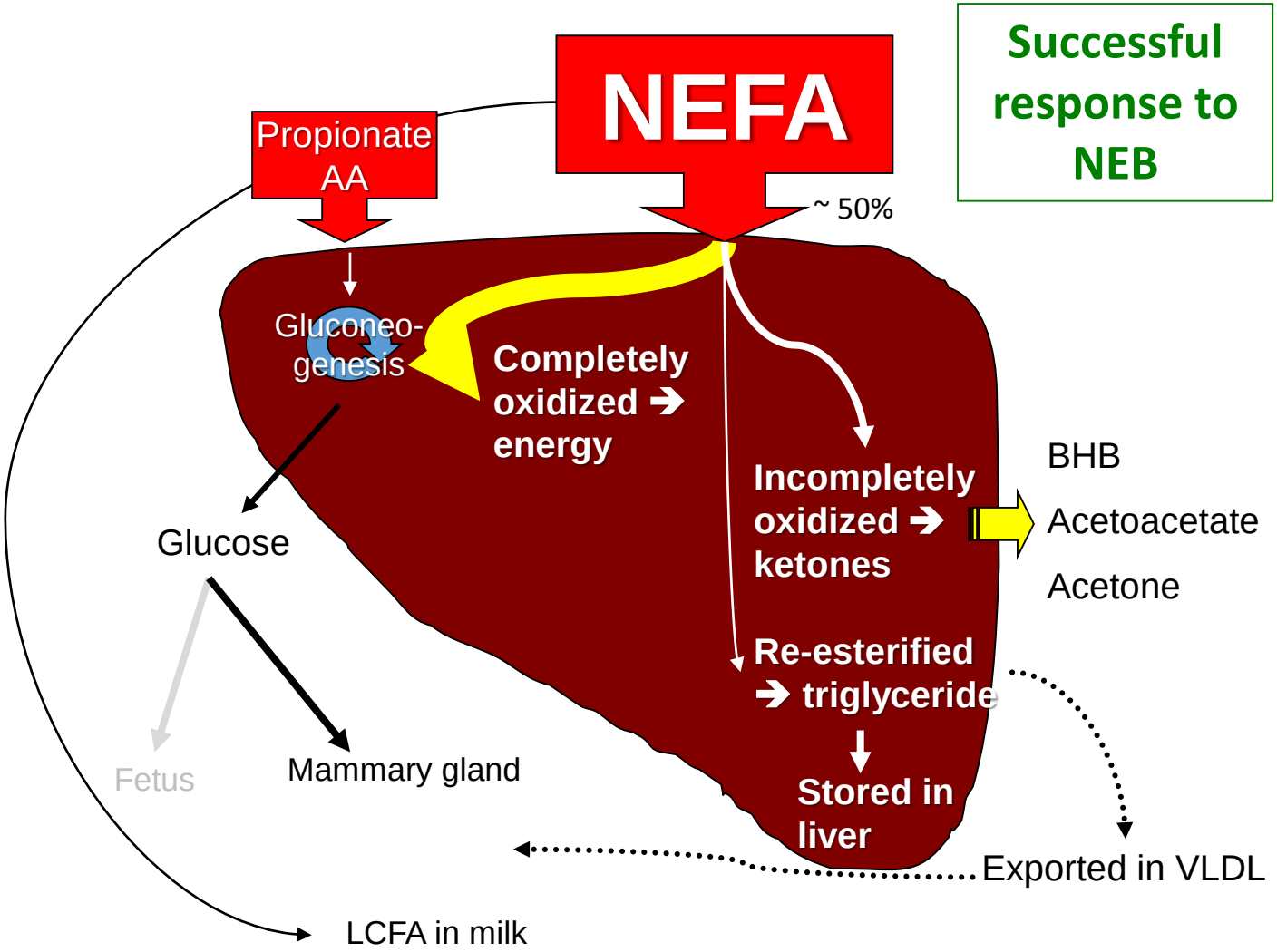


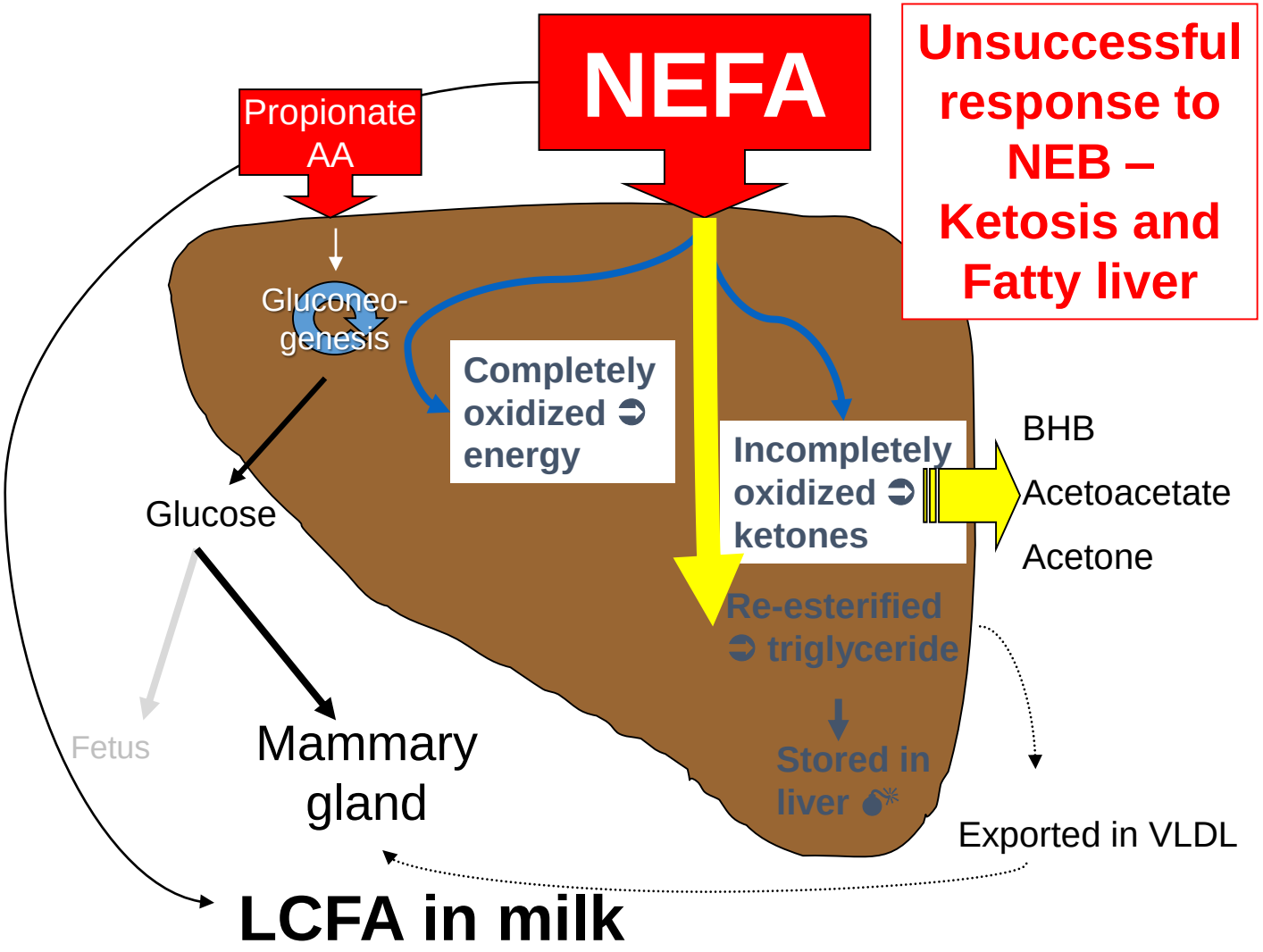
33 multiparous
Holstein x Jersey cows
Fed negative DCAD
close-up diet

Blanc et al 2014

Prevention or treatment of hypocalcemia

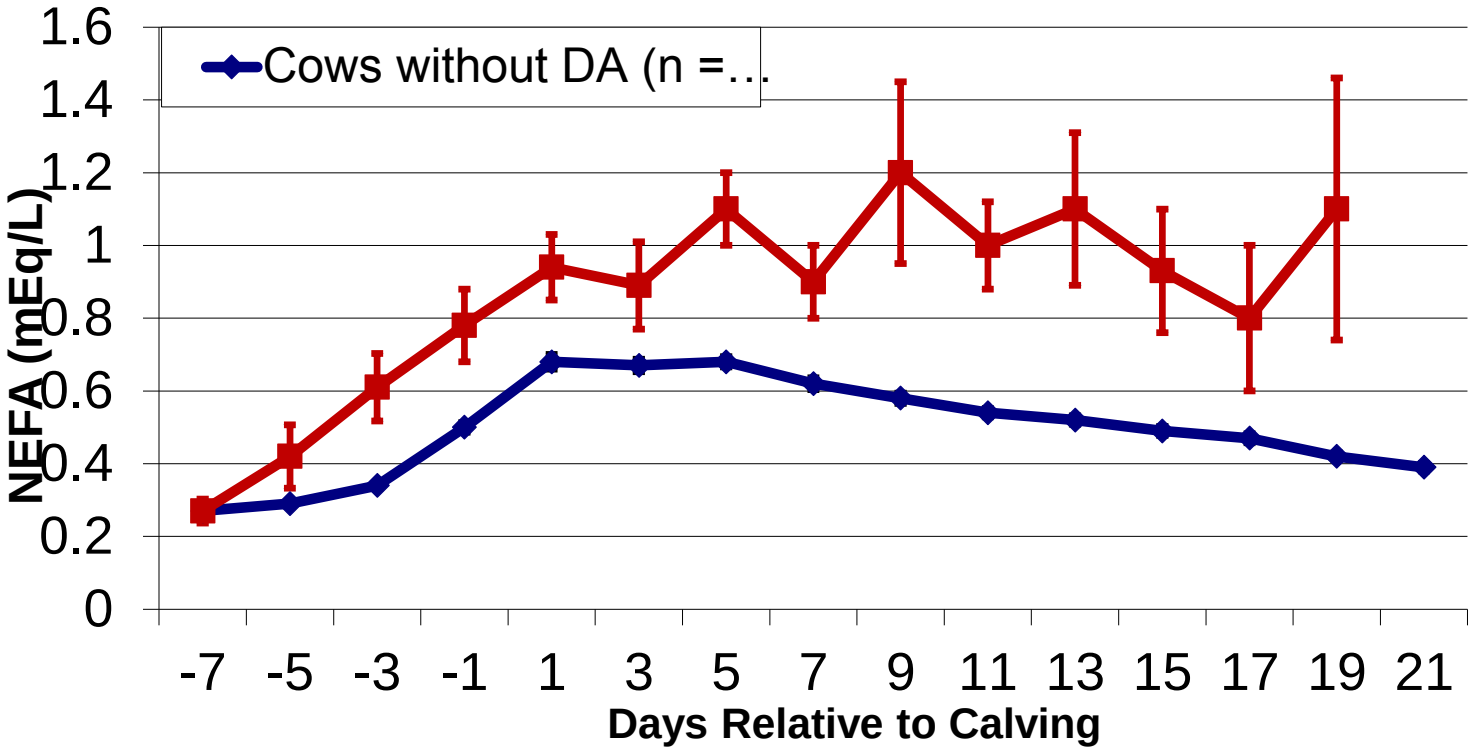
- One study (Miller and Oetzel, 2012) supplemented cows with oral calcium after calving found:
  - an increase in milk production in higher producing cows
  - decrease in health problems among lame cows
- Calcium supplements can reduce clinical milk fever
- Calcium supplements can modestly increase blood [Ca] in cows with low blood [Ca] (Miltenburg et al, 2016; Blanc et al 2016; Martinez et al 2016; Amanlou et al 2016)
- Effects of calcium supplements on risk of disease
  - None Miltenburg et al, 2016
  - None to worse Martinez et al 2016 a, b
  - Better Amanlou et al 2016


Successful response to NEB
NEFA
Propionate
AA
~ 50%
Gluconeo-genesis
Completely oxidized ➔ energy
Incompletely oxidized ➔ ketones
BHB
Acetoacetate
Acetone
Glucose
Re-esterified ➔ triglyceride
Stored in liver
Fetus
Mammary gland
Exported in VLDL
LCFA in milk


Unsuccessful response to NEB – Ketosis and Fatty liver
NEFA
Propionate
AA
Gluconeo-genesis
Completely oxidized ➲ energy
Incompletely oxidized ➲ ketones
BHB
Acetoacetate
Acetone
Glucose
Re-esterified ➲ triglyceride
Stored in liver
Fetus
Mammary gland
Exported in VLDL
LCFA in milk

Association of serum NEFA and DA

NEFA in week -1 and +1 are more predictive of disease than BHBA alone (Ospina et al 2010; Chapinal et al 2011) but can't be measured cow-side or on-farm



Data from Chapinal et al 2011

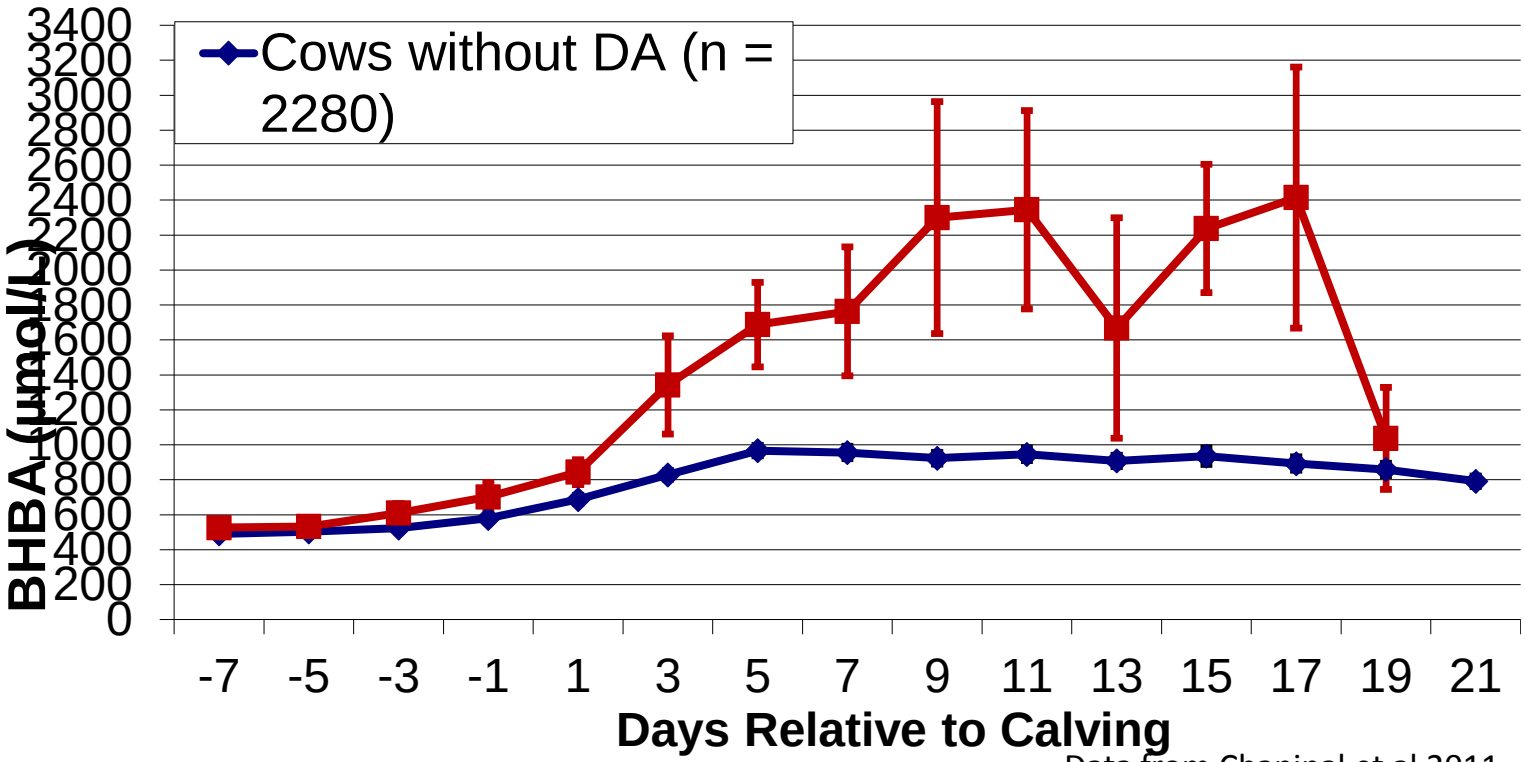
Associations of NEFA with health and performance

Week relative to Calving	Source	Cut-point mmol/L	Outcome	Impact
-1	Chapinal 2011	0.3	Retained Placenta	OR = 1.8
-1	Quiroz-Rocha 2007	0.4	Retained Placenta	OR = 1.2
-1	Chapinal 2011	0.3	Metritis	OR = 1.8
-1	Chapinal 2011	0.5	Displaced Abomasum	OR = 2.4
-2 or -1	Ospina 2010	0.3	RP, Metritis or DA	RR = 1.8
			305 ME milk	-683 kg
			Pregnancy by VWP + 71 d	HR = 0.81
-1	LeBlanc, 2005	0.5	Displaced Abomasum	OR = 3.6
-1	Chapinal 2012	0.5	Milk Yield	↓ 1.6 kg/d
-1	Carson, 2008	0.3	1st Test LS	↑ 0.24
+1	Chapinal 2011	1.0	DA	OR = 3.1
+1 or 2	Ospina 2010	0.6	RP, Metritis or DA	RR = 4.4
		0.7	Pregnancy by VWP + 71 d	HR = 0.84
		0.7	305 ME milk	-647 kg

Association of serum BHBA and DA

Ketosis typically precedes DA

BHBA increase starts before calving but is most predictive in week +1



Data from Chapinal et al 2011

Impacts of ketosis
Health and production

Subclinical ketosis (serum BHB > 1.0 – 1.4 mmol/L) in early lactation is associated with:

- 4-8X increased risk of LDA

  Geishauser, 2000; LeBlanc et al, 2005; Ospina et al 2010a

- Decreased milk production (-1.2 to 3.3 kg/d) at test 1 > 1.2 in week 1 and 1.4 in week 2; yet increased full lactation yield when 1.0 to 1.6 mmol at week +2

  Duffield, 2009

- 1.8 X increased odds of culling < 60 DIM

  Roberts et al 2012

- Increased severity of mastitis

  Suriyasathaporn et al, 2000

- Inconsistent effects on neutrophil function

Impacts of ketosis - Reproduction

Subclinical ketosis (serum BHB > 1.0 – 1.4 mmol/L) in early lactation is associated with:

- 3 X Increased risk of metritis (not in all studies)

  Hammon et al 2006; Duffield et al 2009

- 1.4 X greater odds of endometritis (uterine inflammation based on cytology) at 35 DIM

  Dubuc et al 2011

- 1.5 X increased odds of being anovular (not cyclic) at 63 DIM (19% vs. 13% of cows)

  Walsh et al 2007; Dubuc et al 2012

- Decrease in pregnancy at first AI

  Walsh et al, 2007

- Point prevalence (20 cows, 1 test, BHB ≥ 1.4 mmol/L) ≥ 20% associated with herd annual pregnancy at 1st AI < 40%

  Dubuc & Denis-Robichaud, 2017

- BHB > 1.2 mmol/L in any of 1st 5 weeks postpartum associated with lower 6-week in-calf in pasture system (78 vs. 85%)

  Compton et al 2015

Impacts of ketosis Reproduction

- Ketosis in week 1 or 2 decreased pregnancy rate (Walsh et al 2007)
  - Median time to pregnancy (days) — CR at 1st AI
    - 108 (no ketosis) — 42%
    - 124 (ketosis in 1 week) — 36%
    - 130 (ketosis for 2 weeks) — 28%

P=.003

Cow-side tests for ketosis

(relative to serum BHB ≥ 1.4 mmol/L)

Systematic review and meta-analysis of diagnostic tests for ketosis: Tatone et al PVM 2016

Milk

Keto-Test

100 µmol/L
- Sensitivity = 83%
- Specificity = 82%

200 µmol/L
- Sensitivity = 54%
- Specificity = 94%
- Oetzel, 2004

Cost = $2/test

Powder lacks sensitivity

Urine

Ketostix

(read at 5 seconds)

"small" (15µmol/L)
- Sensitivity = 79%
- Specificity = 96%

Carrier et al, 2004

Cost = $0.25/test

Blood

Precision XTRA (Freestyle Neo)

Sensitivity = 87-100%

Specificity = 74-100%

Iwersen, 2009; Bach 2016

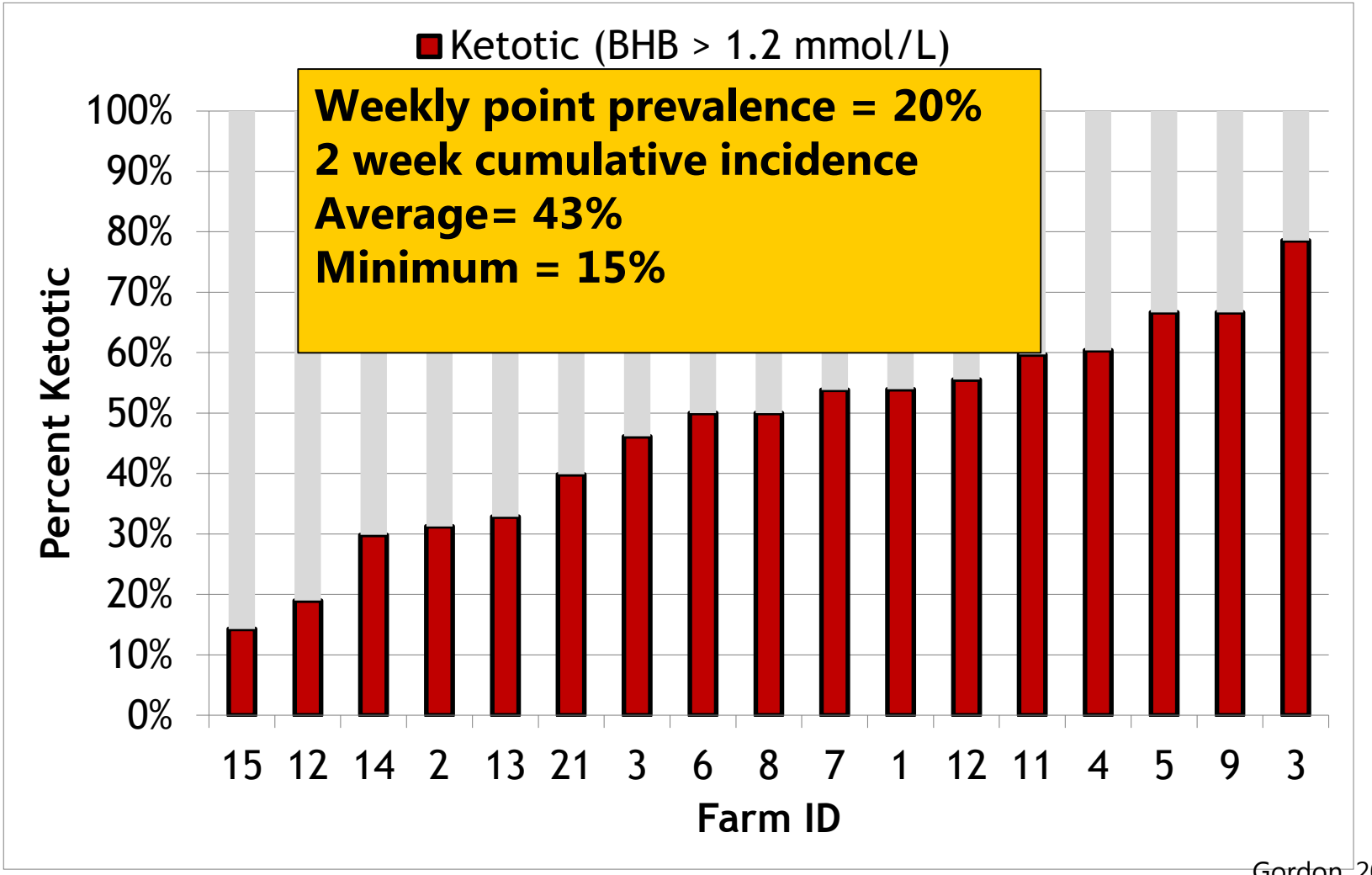
Cost = $2/test

Alternatives: NovaVet; TaiDoc (Bach 2016) ± NovaMax (LeBlanc)

Ketosis is a global problem

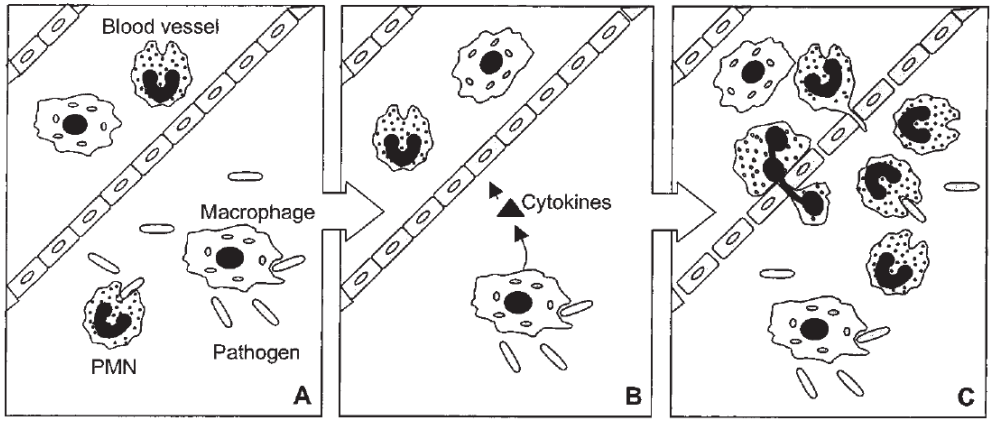
Country/ Region	Diagnostic criteria	Prevalence	Reference
USA, Canada	2365 cows, 55 herds BHB ≥ 1.2 mmol/L	Week 1: 18% of cows Week 2: 19% of cows	Chapinal et al 2010
EU (UK, Netherlands, Italy, Germany, France)	4709 cows, 7-21 DIM, > 12 cows/herd, 1 test/cow, 131 herds Milk BHB ≥ 100 µmol/L	39% of cows 85% of herds had > 25% prevalence	Berge & Vertenten 2014
Canada	20 cows/herd, 1-14 DIM 126 herds point prevalence BHB ≥ 1.4 mmol/L	Median herd prevalence= 19%	Dubuc & Denis-Robichaud 2017
New Zealand	40 cows/herd1620 cows, 57 herds BHB ≥ 1.4 mmol/L	7-12 DIM: 17% of cows 14% mean herd prevalence	Compton et al 2014
New Zealand	Weekly testing 585 cows, 15 herds BHB ≥ 1.2 mmol/L	1st week prevalence: 18% Cumulative 5 week incidence: 67%	Compton et al 2015

Cumulative Incidence of Ketosis
Weekly testing of 1653 cows on 17 farms

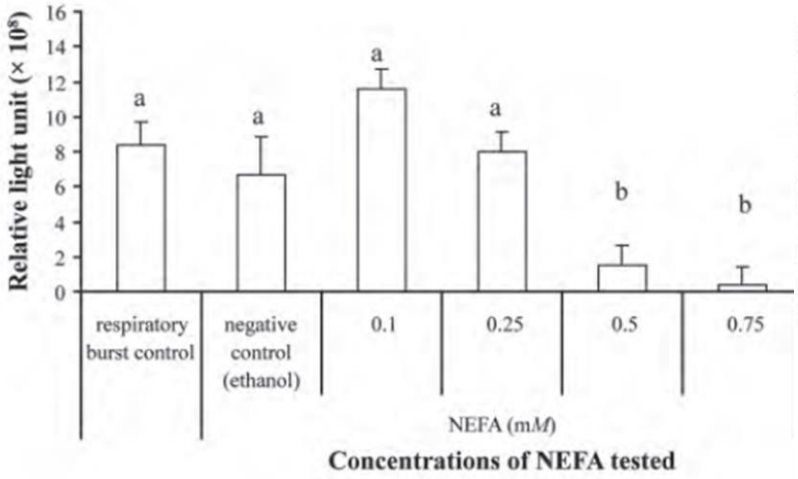


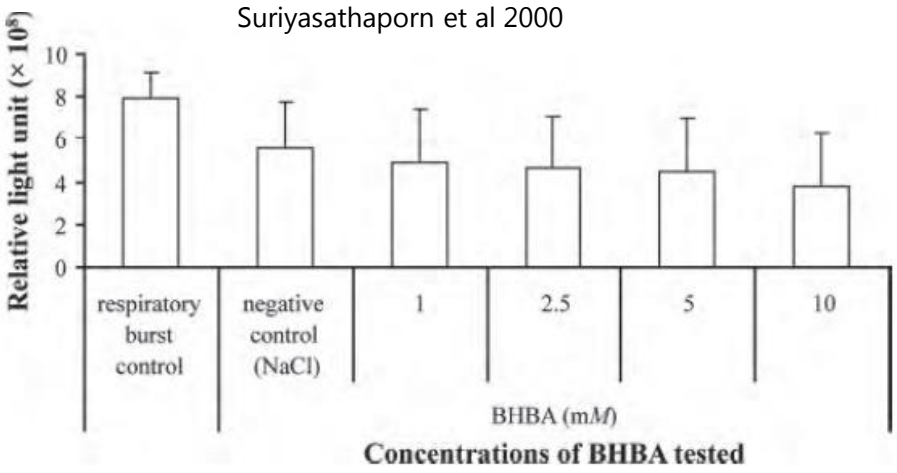
Gordon, 2013

Impact of ketosis Immune function



Suriyasathaporn et al 2000

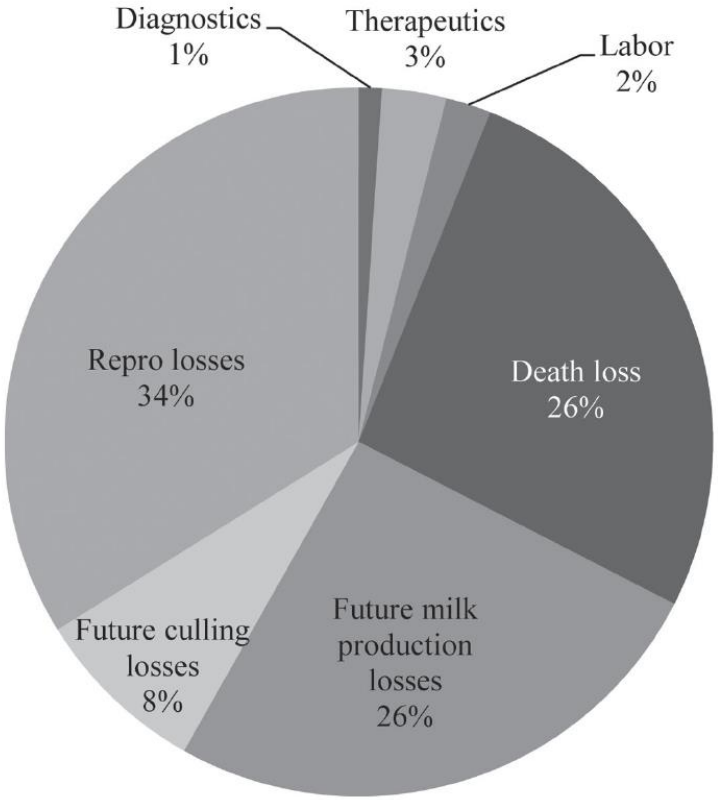




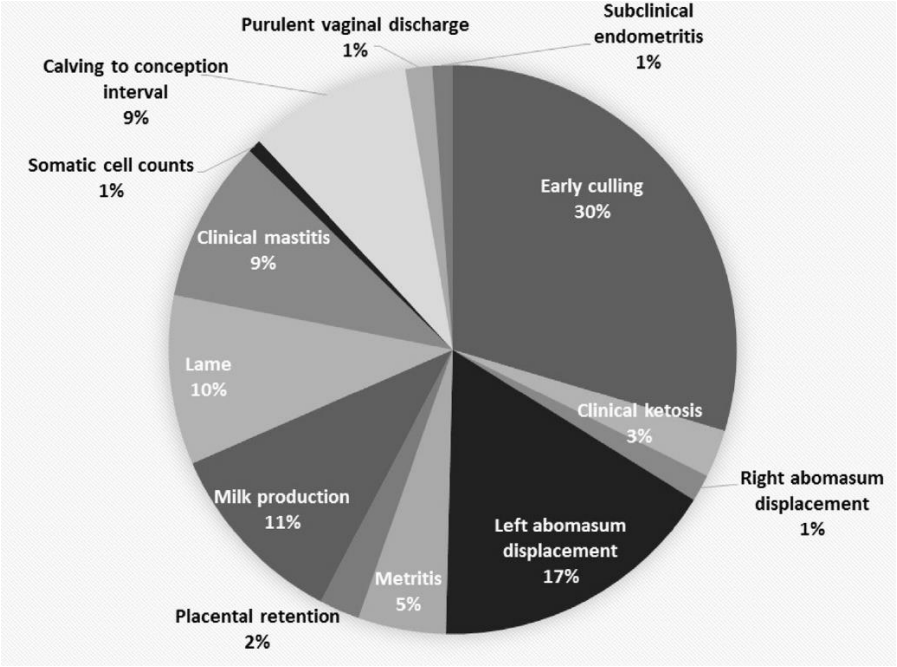
Ster et al 2012 J. Dairy Sci. 95 :708–717

Economic cost of ketosis

- $ 289 US/case (McArt et al 2015)



- €257/case (95% prediction interval €72 – 442 (Raboisson et al 2015)



Routine ketosis screening and treatment

- Large study in New York & Wisconsin, 2010
  - All fresh cows tested 3X per week
  - ½ treated with propylene glycol, ½ untreated
- Treated cows had:
  - Shorter time to ketosis cure (~ 5 vs 7 d)
    - ↑ ketosis cure – 1.5x
    - ↑ milk production – 0.69 kg/d to 30 DIM (varied by herd)
    - ↓ DA risk – 0.63x
    - ↓ culling risk – 0.32x

McArt et al, 2011 and 2012

Glucose measurement to guide ketosis treatment

- **2 clinical trials**
  - **2011** n = 687 cows (17 herds) with BHB ≥ 1.2 mmol/L
    - 3 d glycol ± 25 ml Catosal® SC/d x 3 d ± 200 IU insulin glargine (Lantis) SC once (Gordon et al JDS 2017a)
  - **2012** n = 594 cows (9 herds) with BHB ≥ 1.2 mmol/L
    - 3 or 5 d of glycol ± 25 ml Catosal® SC/d x 3 d (Gordon JDS 2017b)
  - Interactions of treatment with blood glucose at diagnosis in both

Ketosis treatment summary
Gordon et al JDS 2017a,b

- Based on ketosis cure +1 and +2 weeks and milk yield to 30 DIM
- Blood BHB ≥ 1.2 but < 2.4 mmol/L (or KetoTest = 100)
    - **Treat with 3 d glycol 300g 1X/day**
- Blood BHB > 2.4 mmol/L (KetoTest ≥ 200)
    - **Treat with 5 d glycol**
- If BHB > 1.2 mmol/L and glucose < 2.2 mmol/L (38% of cases)
    - **Add treatment with Catosal or B12 (1.25 mg) for 3 d**
  - Re-test at end of treatment
- Addition of dexamethasone not recommended (Tatone et al 2016)

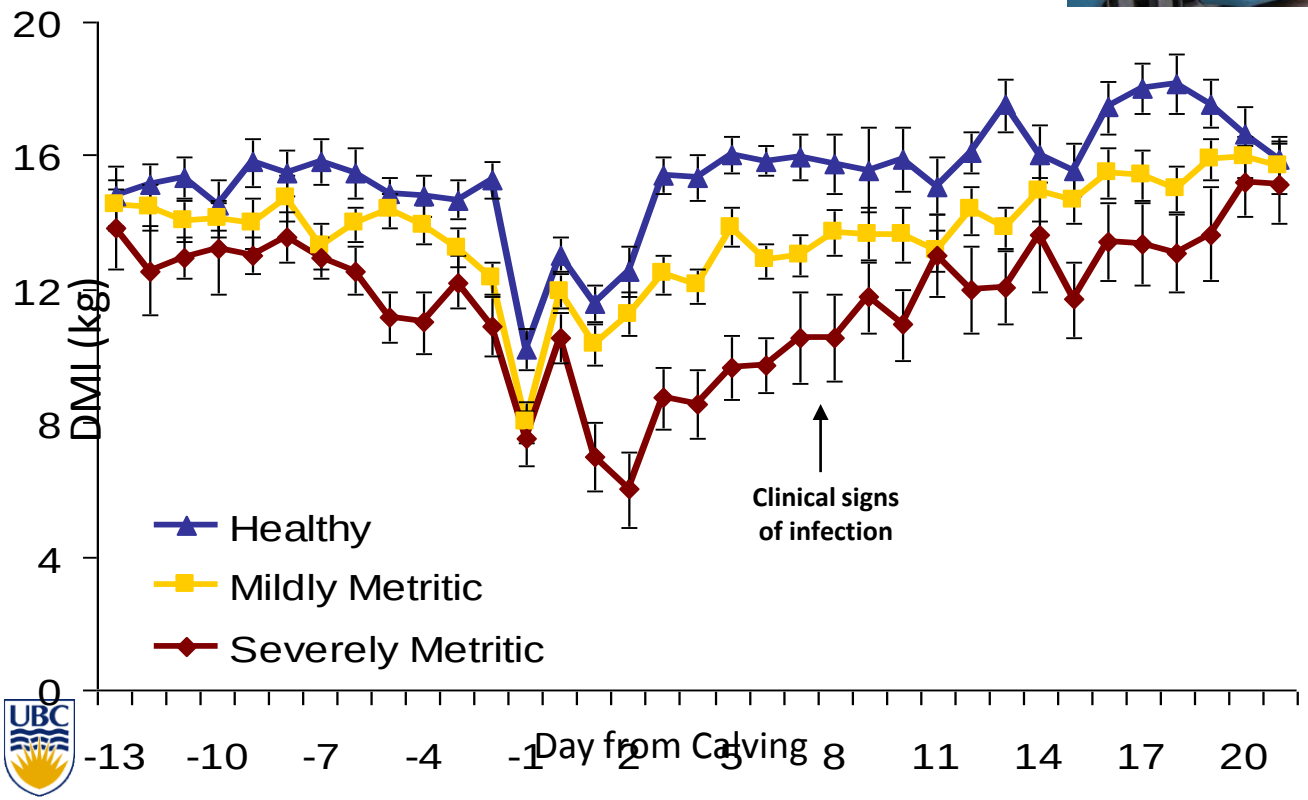
Testing and treatment programs (McArt et al 2014)

- Models of cost-benefit of treating every cow vs. testing 1 – 3 X/week; all ketotic cows treated with propylene glycol for 5 d
- Given the model assumptions and their variations, **for herds with 15 to 50% incidence of ketosis, most cost-effective was to test 2X per week between 3 and 9 DIM (identified 80% of cases)**
- Herd DA and early culling risk were the most influential variables (greater benefit at higher risks)

Ketosis prevention

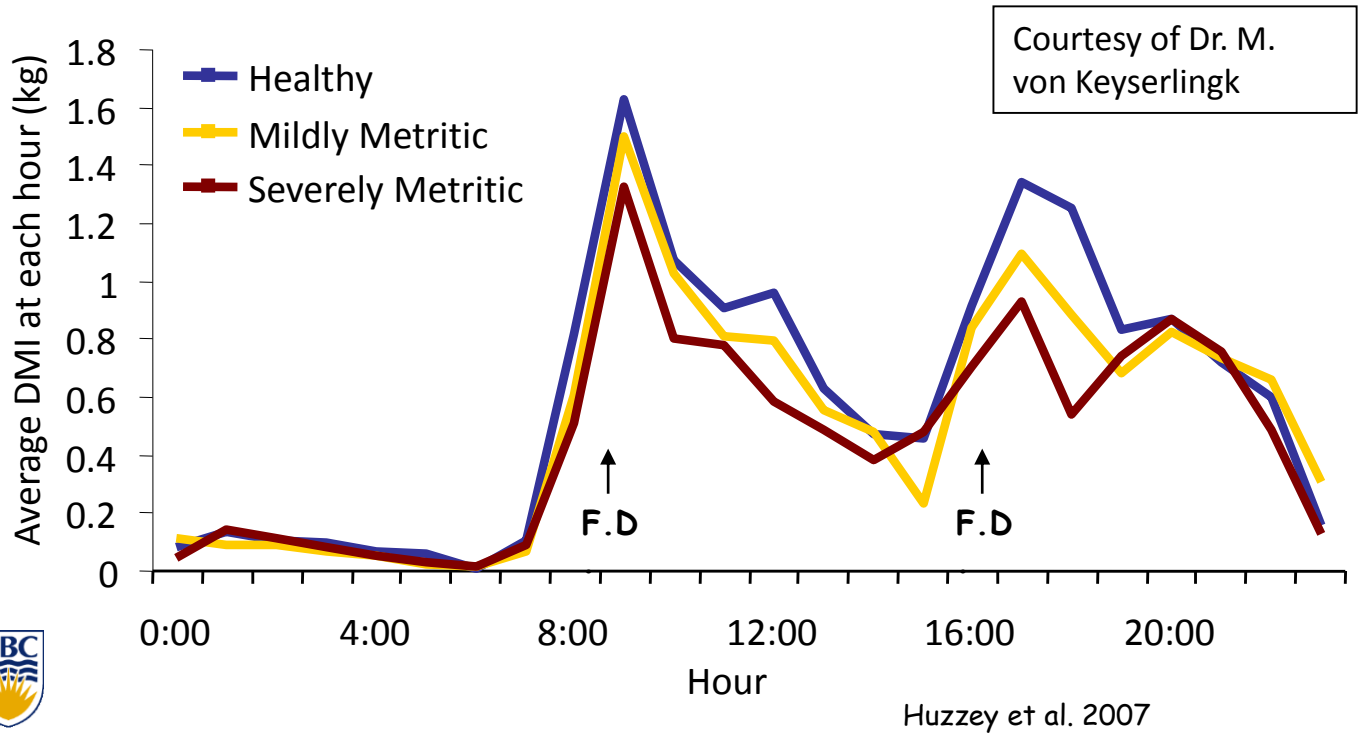
- Only 11% of the variation in the incidence of ketosis was explained by cow-level risk factors (parity, BCS) (data from Duffield et al 1998)
- A large part of the controllable variation lies at herd or management level:
  - Bunk space and feed availability
  - Movement and grouping
  - Heat abatement
  - Feed quality
  - TMR consistency
  - Water access
  - Monensin capsule

Cows with post-partum metritis had lower DMI during the post- and pre-partum periods

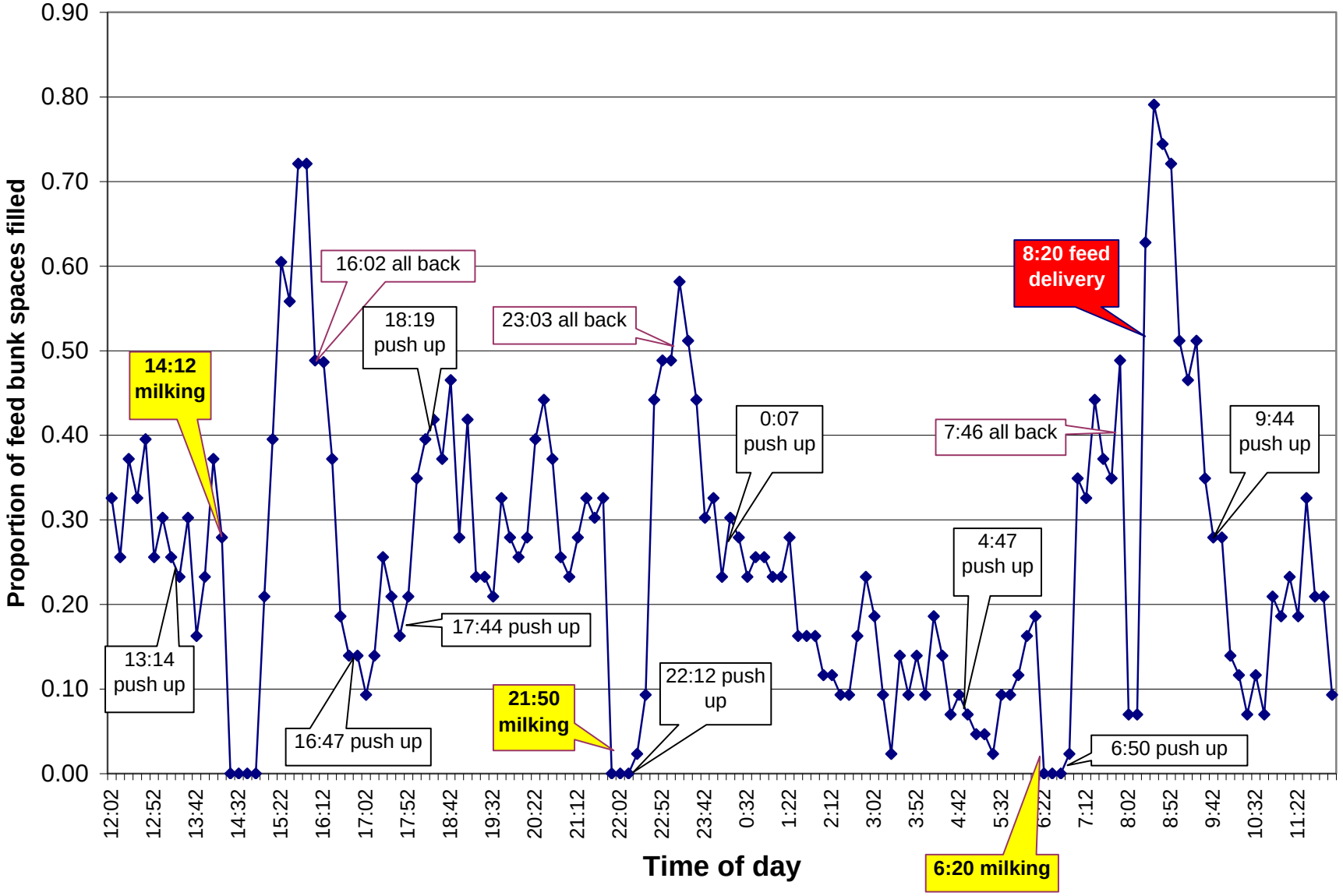


Huzzey et al. 2007

During the week before calving cows that develop post-partum severe metritis (n=12) consume less feed during the period immediately following fresh feed delivery (F.D.)



Huzzey et al. 2007



Cook, AABP 2006

Space – not the final frontier

- Despite recommendations to provide <80% stocking, controlled studies have not found this to benefit health
- 80% vs. 100% cows: headlocks in Jerseys (Silva et al 2014; Lobeck-Lutherhand et al 2015)
    - Changes in behaviour but no effects on health
- 80% stocking + 45 cm feeding space vs. 120% cows:stalls + 90 cm feeding space for 3 wk prepartum (Miltenburg, 2015)
    - Increased feeding competitive behaviour but no overall effects on metabolic health or immune function
- Stable vs. dynamic social groups (Silva et al 2013)
    - No effects on metabolic health or immune function

Risk factors for uterine disease

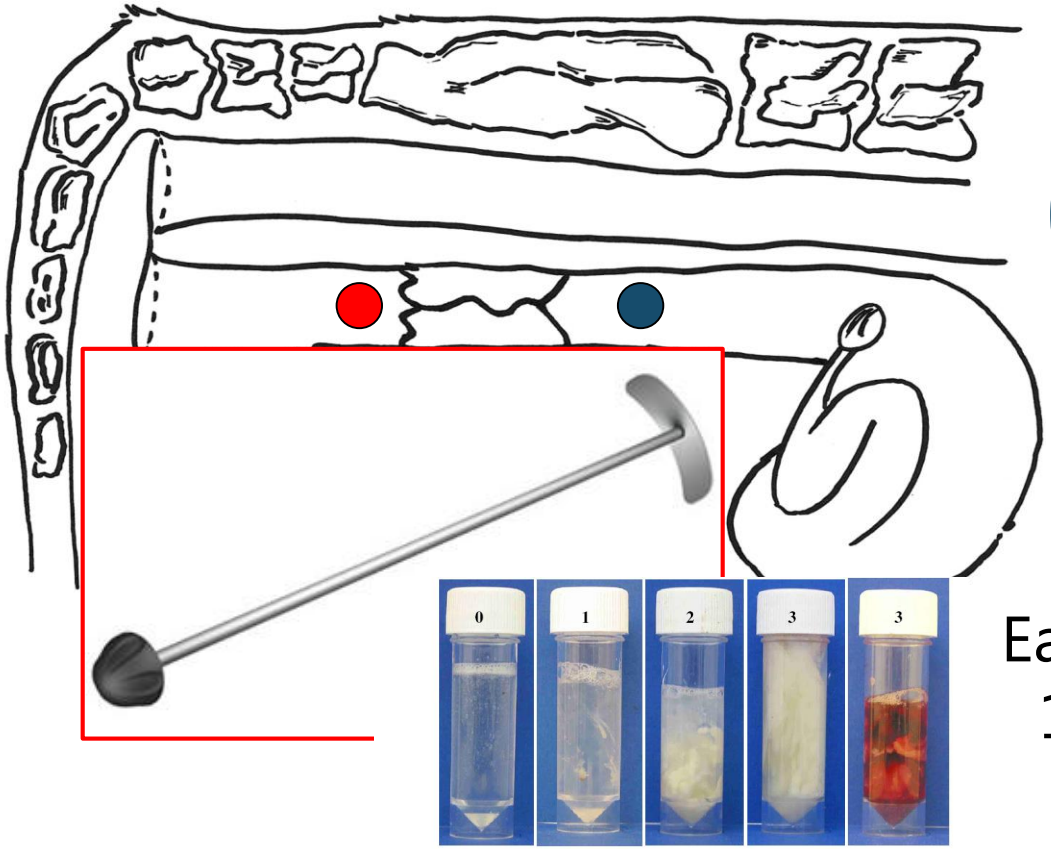
- Species of bacteria
  - Virulence factors
  - Strain
- Level of contamination

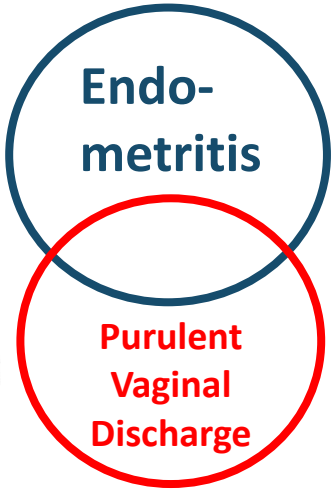
- Dry matter intake
- Energy and lipid metabolic health
- Stressors & hormonal changes
- Hypocalcemia

Bacteria

Immune response
Regulation of inflammation

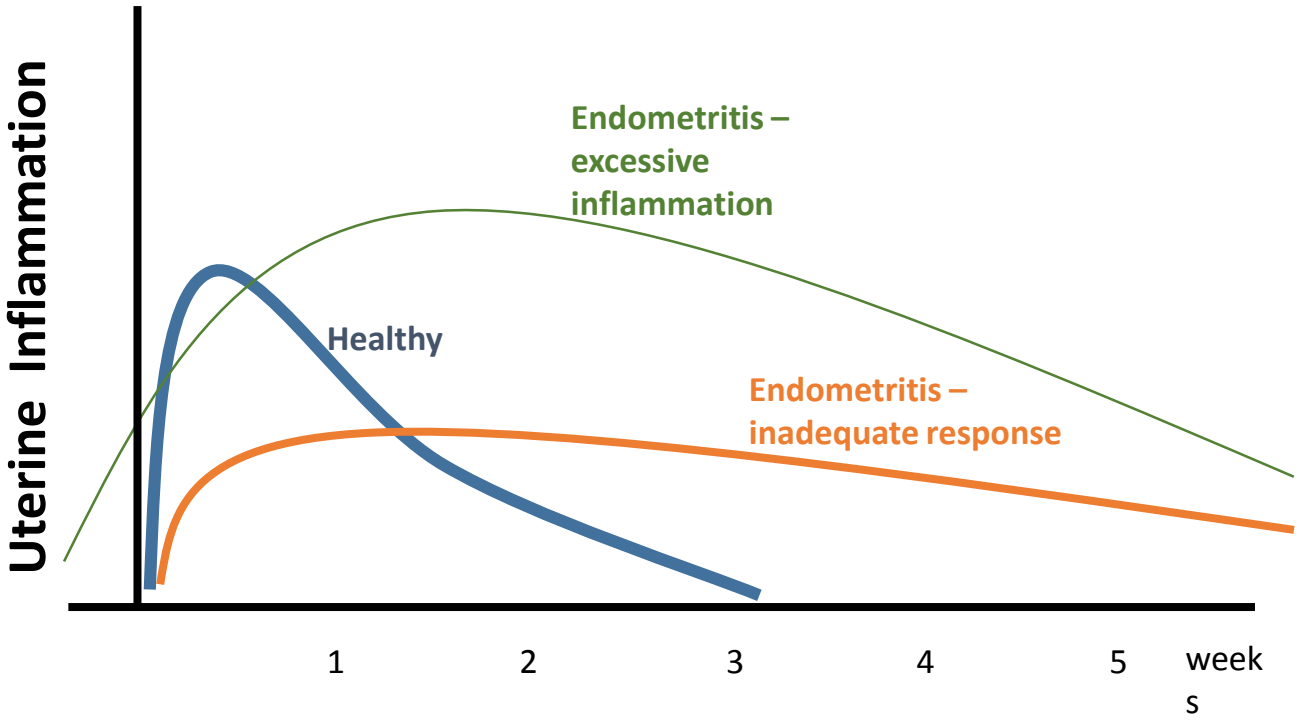
Reproductive tract infection and inflammation





Each affects
15 – 20%
of cows

Concepts of inflammatory response



Transition sets the stage for fertility

126 herds in Quebec, Canada

Dubuc & Denis-Robichaud JDS 2017

Herd prevalence threshold (estimated from 20 cows)	Herd pregnancy at 1st AI < 40%	Herd pregnancy loss > 5%
RP	-	≥ 5%
Ketosis (tested only once 1-14 DIM)	≥ 12%	-
PVD	≥ 5%	≥ 5%
Endometritis (cytobrush)	≥ 19%	-
Anovular (blood P4 30-44 and 44-57 DIM)	≥ 21%	-
DA	≥ 4 %	-

Transition checklist

Goal: Optimize metabolic health & immune function
Means: Manage cows to maintain feed intake

Management

- Feed daily for 3-5% left over; ideally ≥ 2X/d
- ≥ 75 cm feed bunk space per cow
- ≤ 85% cows: freestalls
- > 11 m^2 of bedded pack/cow
- > 5 m^2 of shade/cow; >55 m^2 of drylot
- Build for 130-140% of average monthly calvings
- Large enough stalls; adaptation
- < 24 h in calving pen
- Minimize group changes
- Separate heifers if it does not violate the above
- Heat abatement (fans, soakers) when THI > 68
- BCS = 3.0 - 3.5 at calving

Transition diet

- 3-4 weeks on close-up diet or 6 weeks as 1 dry group
- Meet but do not exceed E requirement 8 to 3 weeks prepartum
- Water ad lib; 10 cm linear per cow; 2 sources per pen
- ≥ 1000 IU vitamin E/d; up to 2000 IU/d for RP; 0.3 ppm selenium (Ideally ~ 6mg/d)
- DCAD < -100 mEq/kg; Urine pH < 6.5

Monitoring

- NEFA <0.3-0.4 in last week prepartum; <0.7-1.0 in week 1
- BHB < 0.8 mM in week -1
- BHB < 1.1 mM in week 1
- BHB < 1.2 mM weeks 2 – 3
- Ca > 2.15 mmol/l in week 1