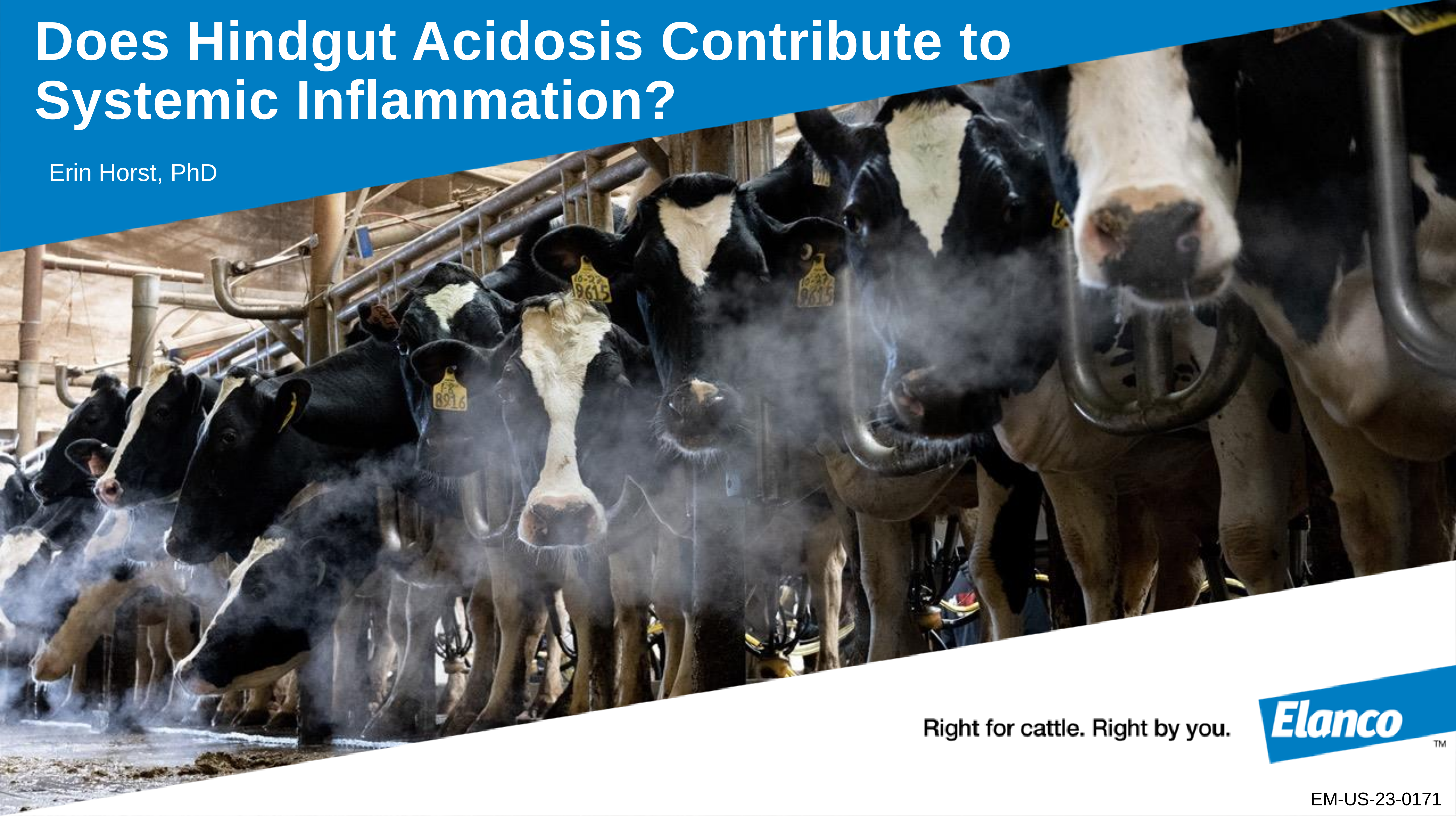
Does Hindgut Acidosis Contribute to Systemic Inflammation?

Erin Horst, PhD



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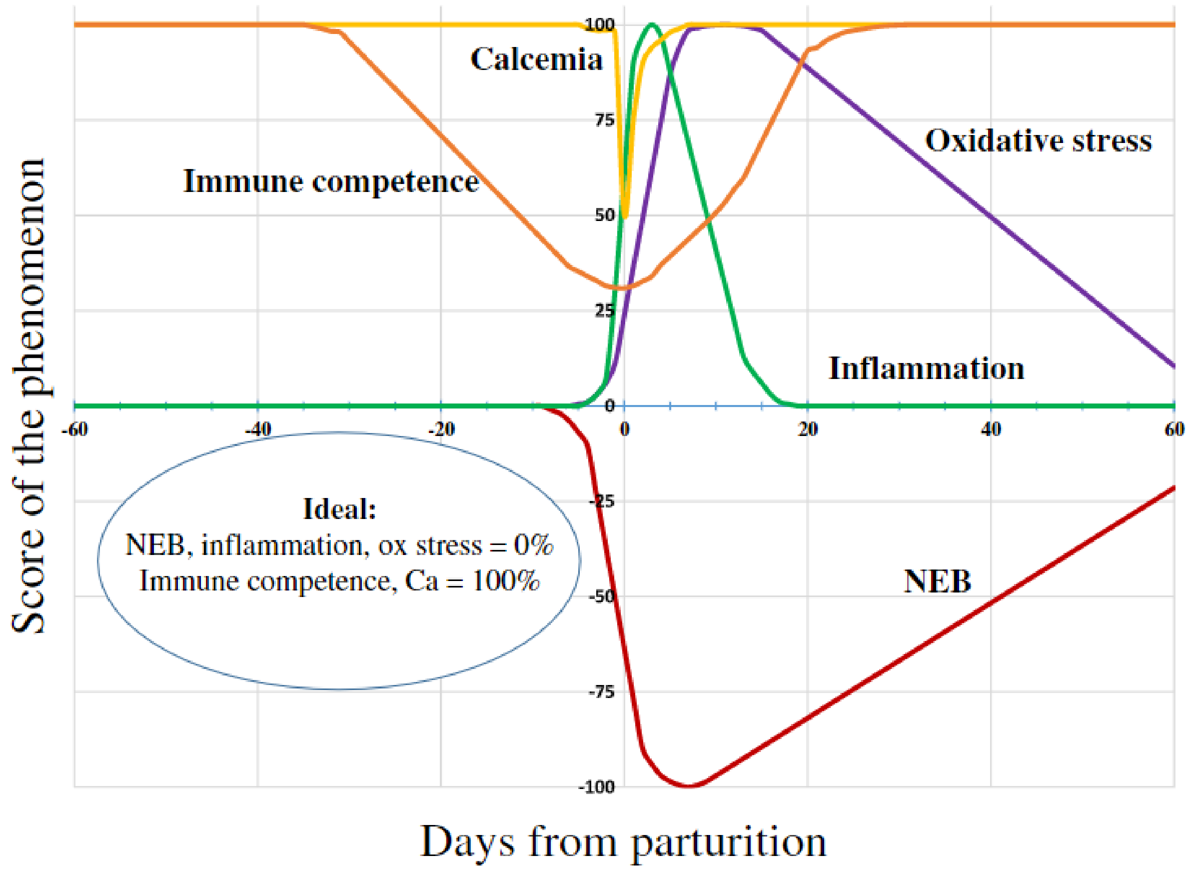
The Transition Period- “The Final Frontier”

- Classically defined as the 3 weeks prior to and 3 weeks following calving

- Critical period characterized by drastic changes in:
  - Nutrient partitioning
  - Calcium homeostasis
  - Immune competence
  - Inflammatory state

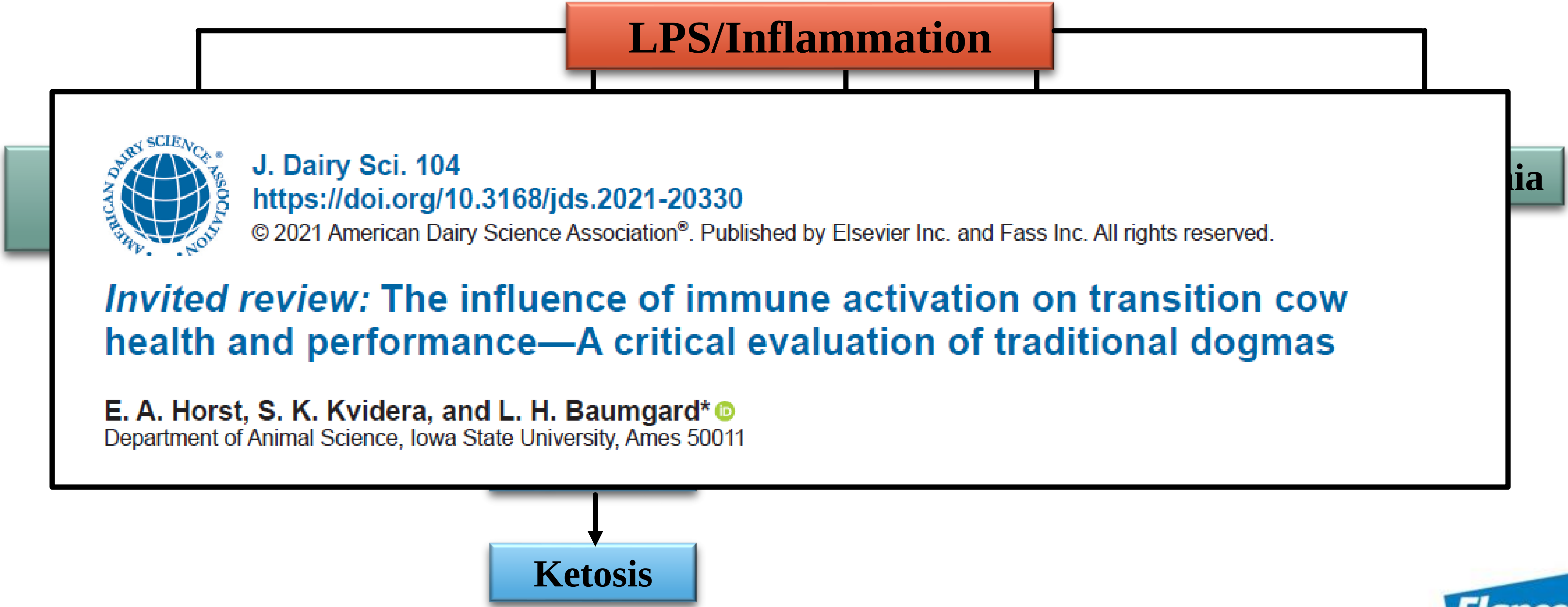
- Disproportionate incidence of health problems and herd culling
  - 30-50% of cows experience metabolic or infectious disease (LeBlanc, 2010)



LEBLANC, S. 2010. “MONITORING METABOLIC HEALTH OF DAIRY CATTLE IN THE TRANSITION PERIOD” J. REPROD. DEV. 56:SUPPL:S29-S35.

Figure from Trevisi, E., and Minuti, A. 2018. “assessment of the innate immune response in the periparturient cow”. Res. Vet. Sci. 116:47-54.

Inflammation and Transition Cow Health



J. Dairy Sci. 104
https://doi.org/10.3168/jds.2021-20330

Invited review: **The influence of immune activation on transition cow health and performance—A critical evaluation of traditional dogmas**

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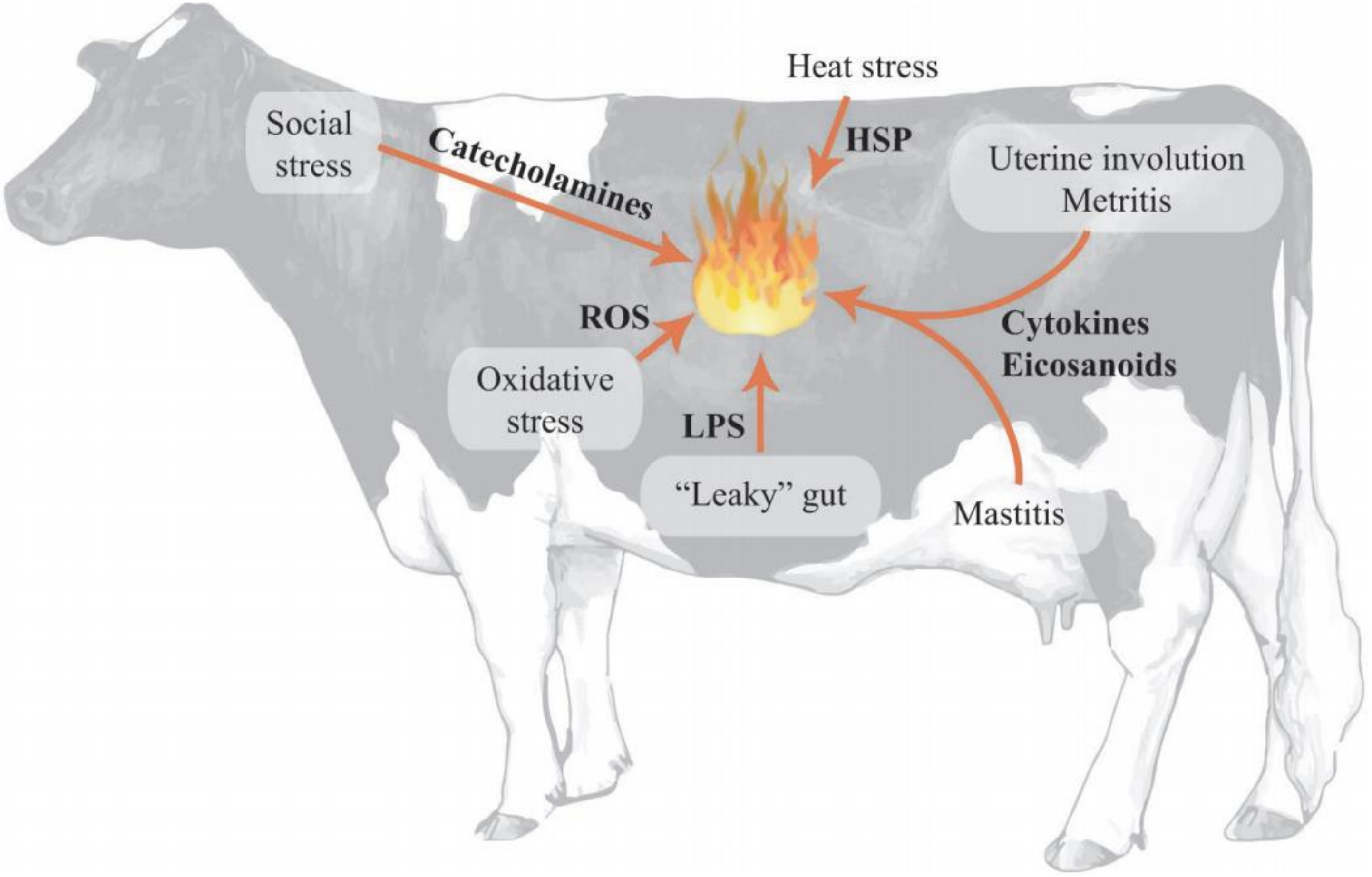
Inflammation in Transition Cows

- Observed in nearly all cows regardless of health status (Bertoni et al., 2008; Bradford et al., 2015)
- Caused by multiple pathologies:
  - Sterile inflammation?
  - Mastitis
  - Metritis
  - Pneumonia
  - **Leaky Gut**



Bertoni, G. et al. 2008. "Effects of inflammatory conditions on liver activity in puerperium period and consequences for performance in dairy cows." J. Dairy Sci. 91:3300-3310.

Figure from Bradford, B.J. et al. 2015. "Invited review: Inflammation during the transition to lactation: New adventures with an old flame." J. Dairy Sci. 98: 6631-6650.

The Gastrointestinal Tract (GIT)

- A tube running from the mouth to the anus
  - Everything inside of the tube is technically "outside" of the body

- Dual function:
  - Digest and absorb nutrients
  - Prevent parasites, pathogens, antigens, enzymes, toxins, etc. from infiltrating "self"
    - Barrier function

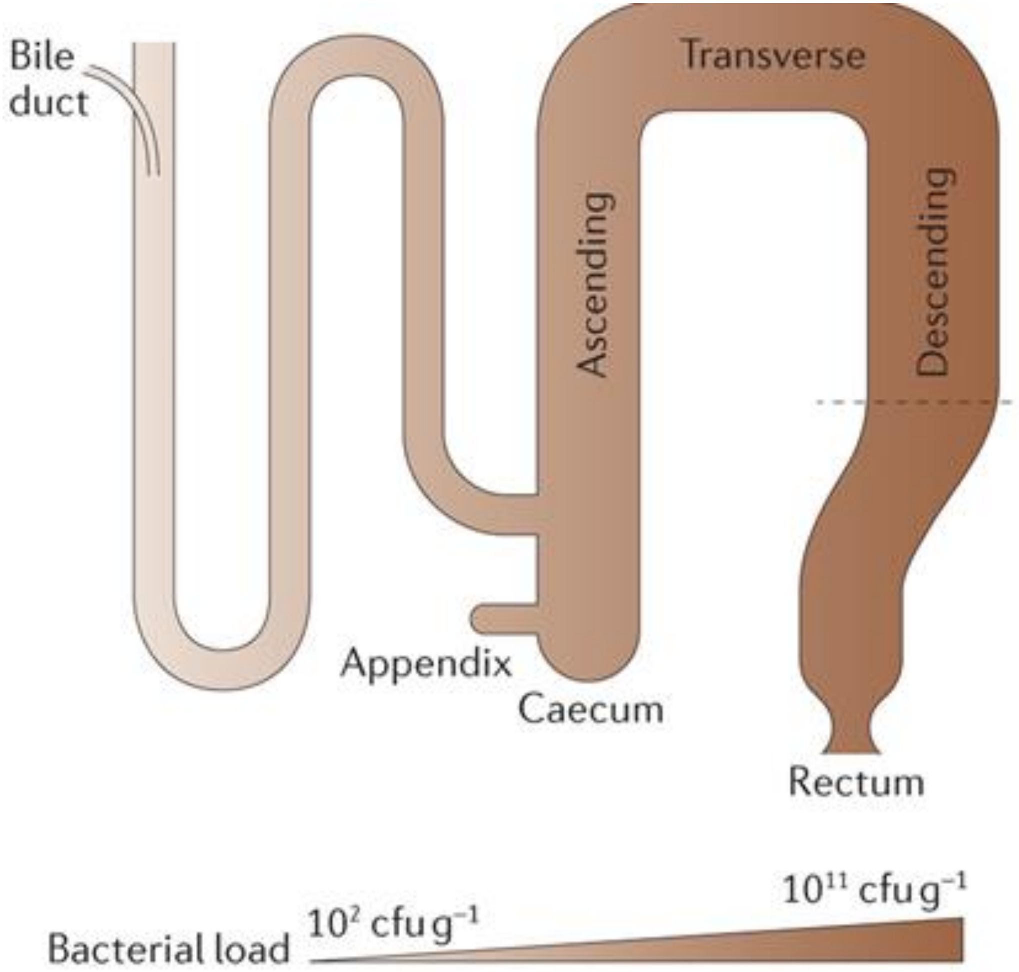
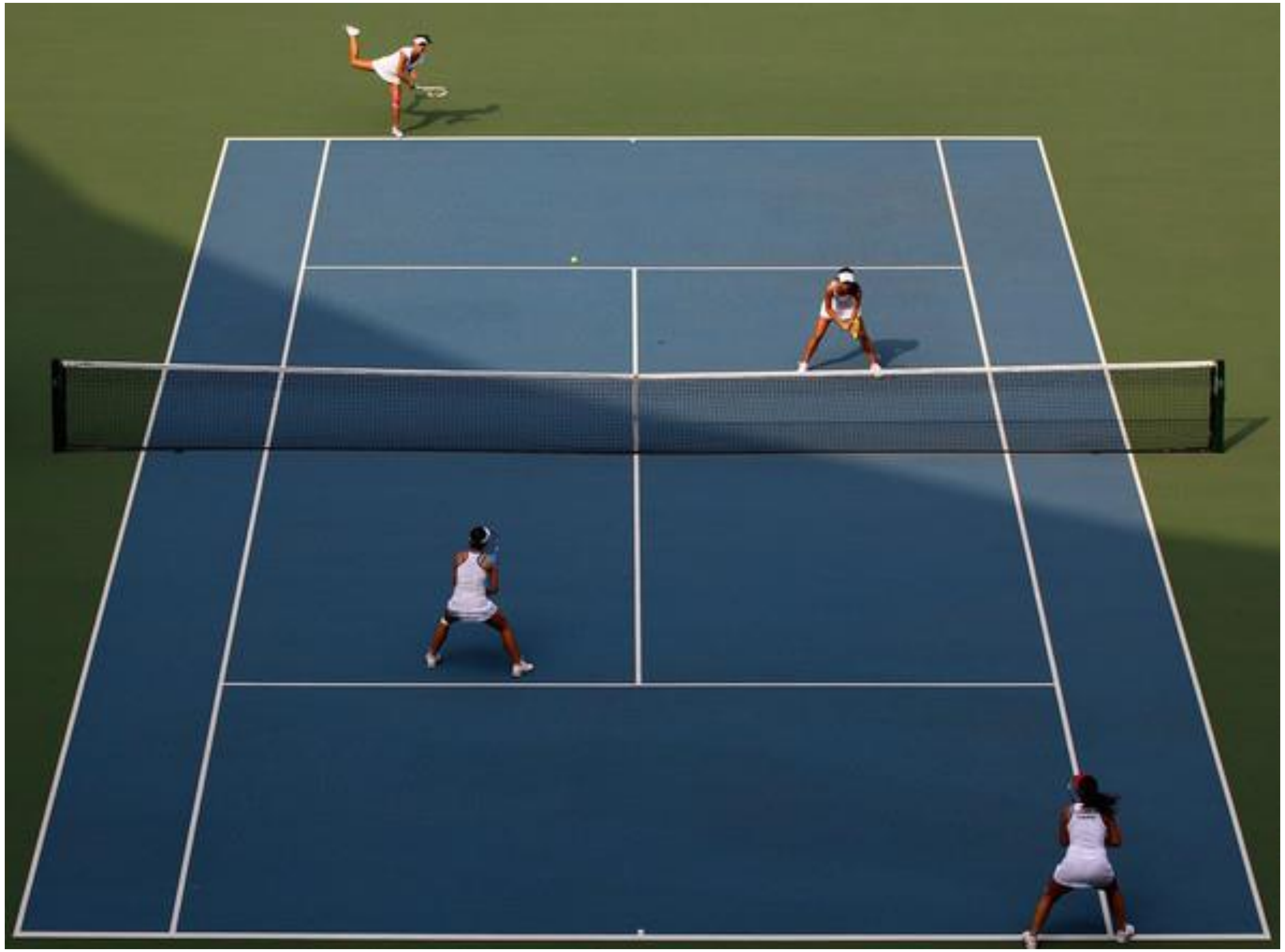


Figure from Donaldson, G.P. et al. 2015. "Gut biogeography of the bacterial microbiota." Nat. Rev. Microbiol. 14.1: 20–32.

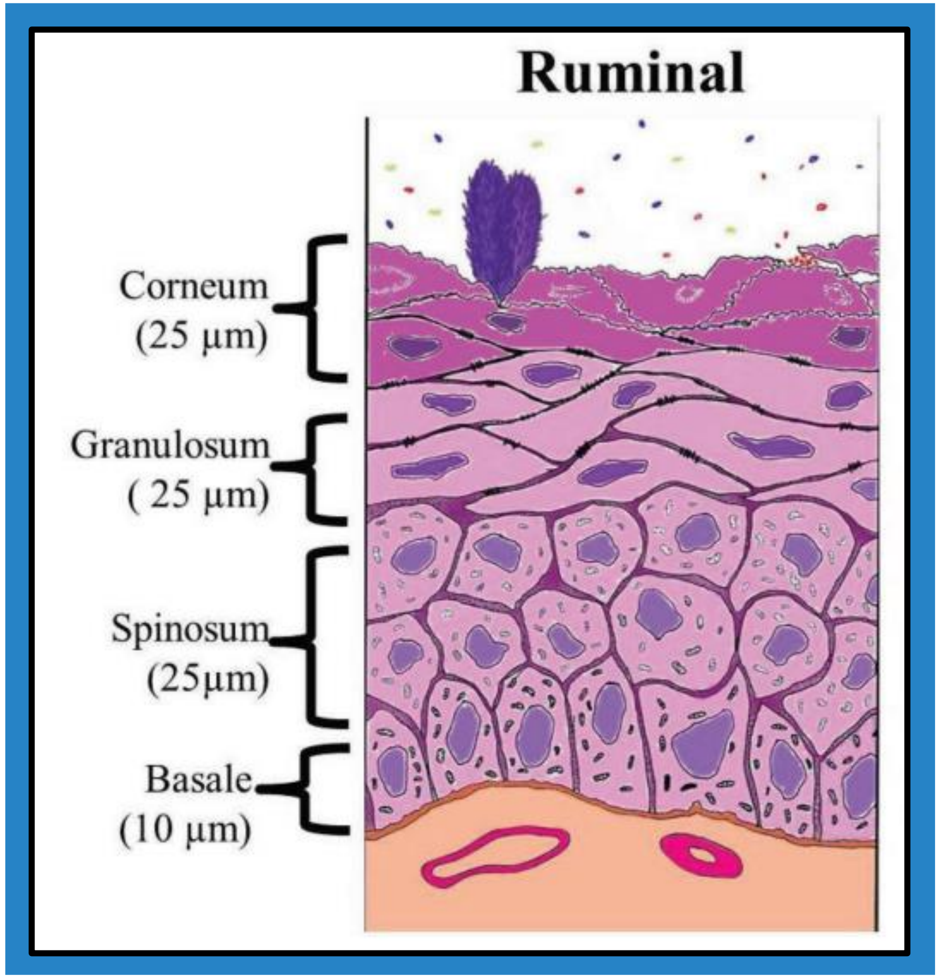
Human Gastrointestinal Tract Surface Area



Anatomical Differences

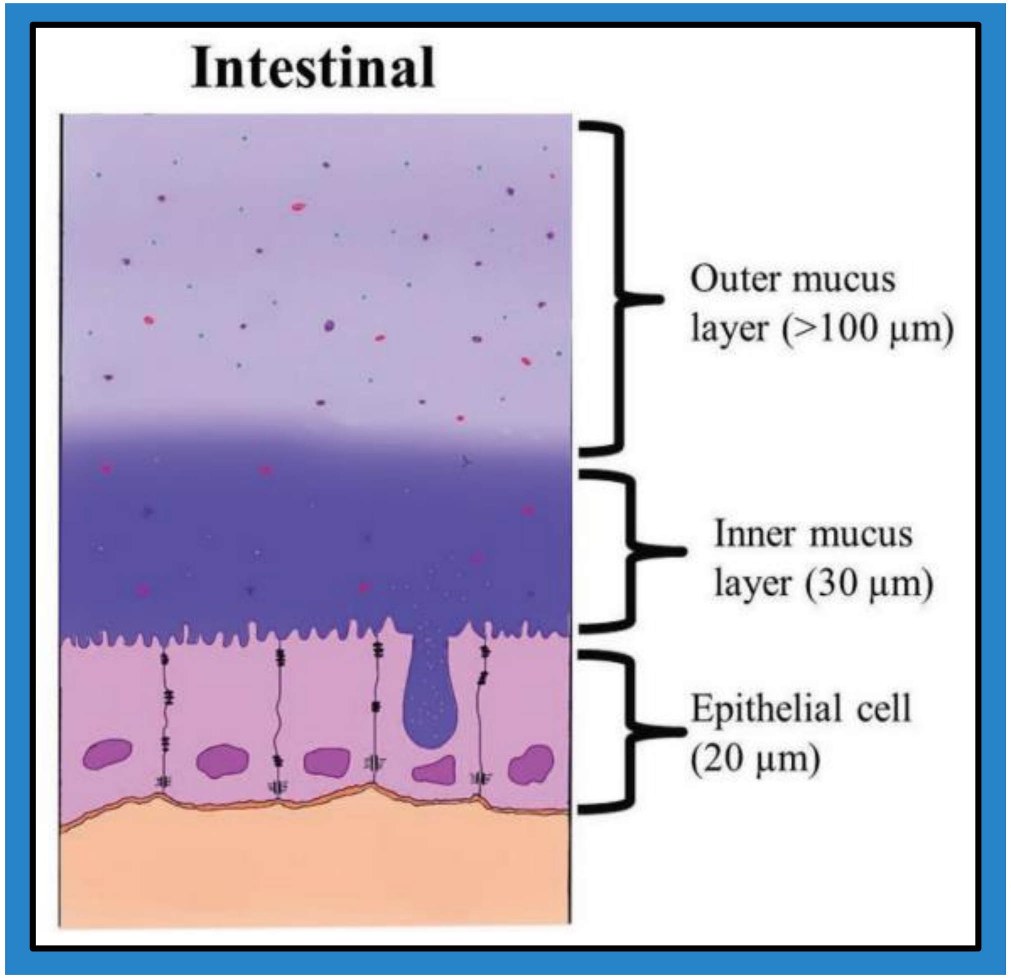
Reticulo-Rumen and Omasum

- Stratified squamous epithelium



Lower Gut

- Columnar epithelium



Steele, M.A. 2016. "Development and physiology of the rumen and the lower gut: Targets for improving gut health." J. Dairy Sci. 99: 4955–4966.

Intestinal Immune System

75% of the immune system resides in the gastrointestinal tract!

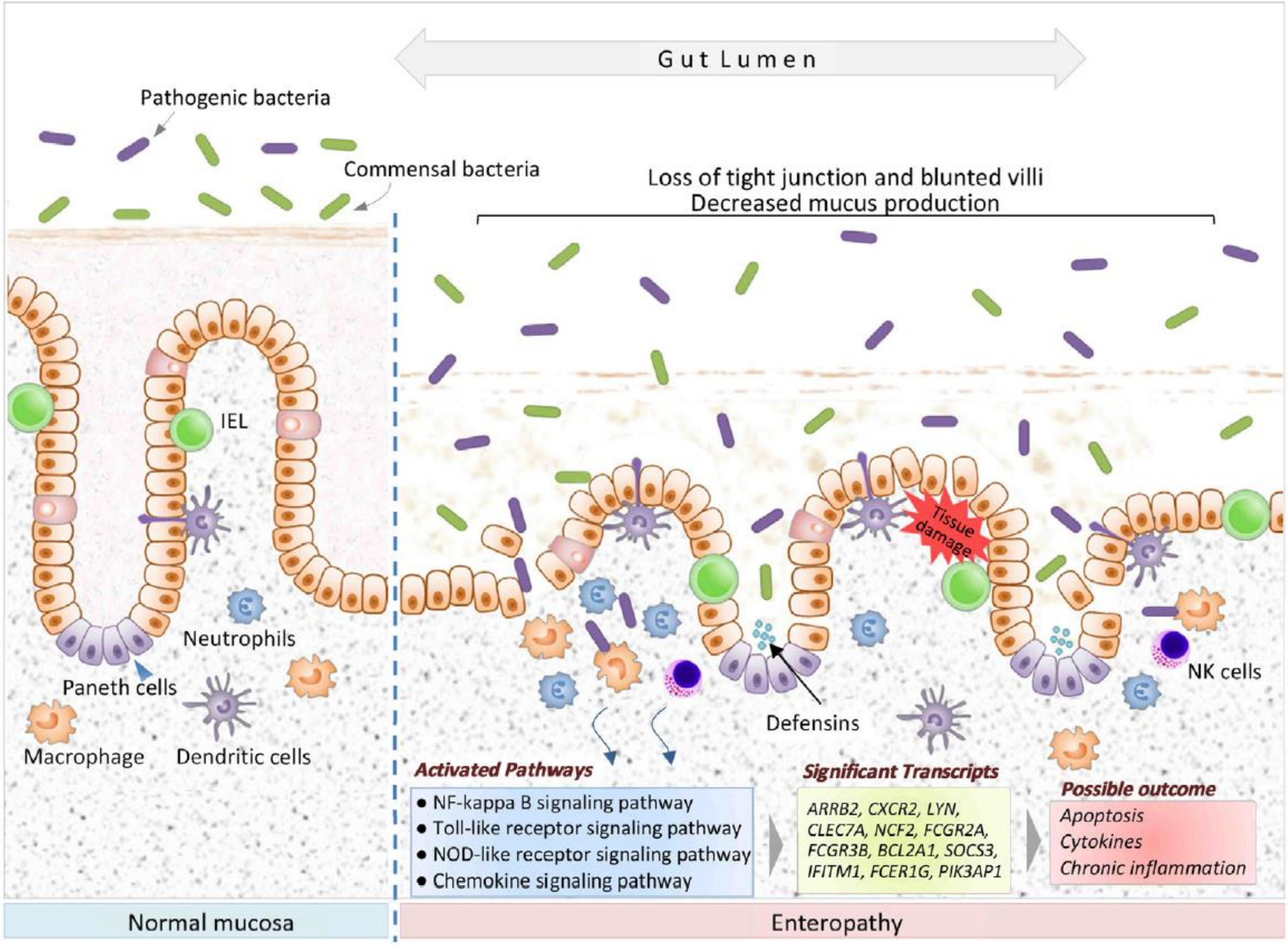
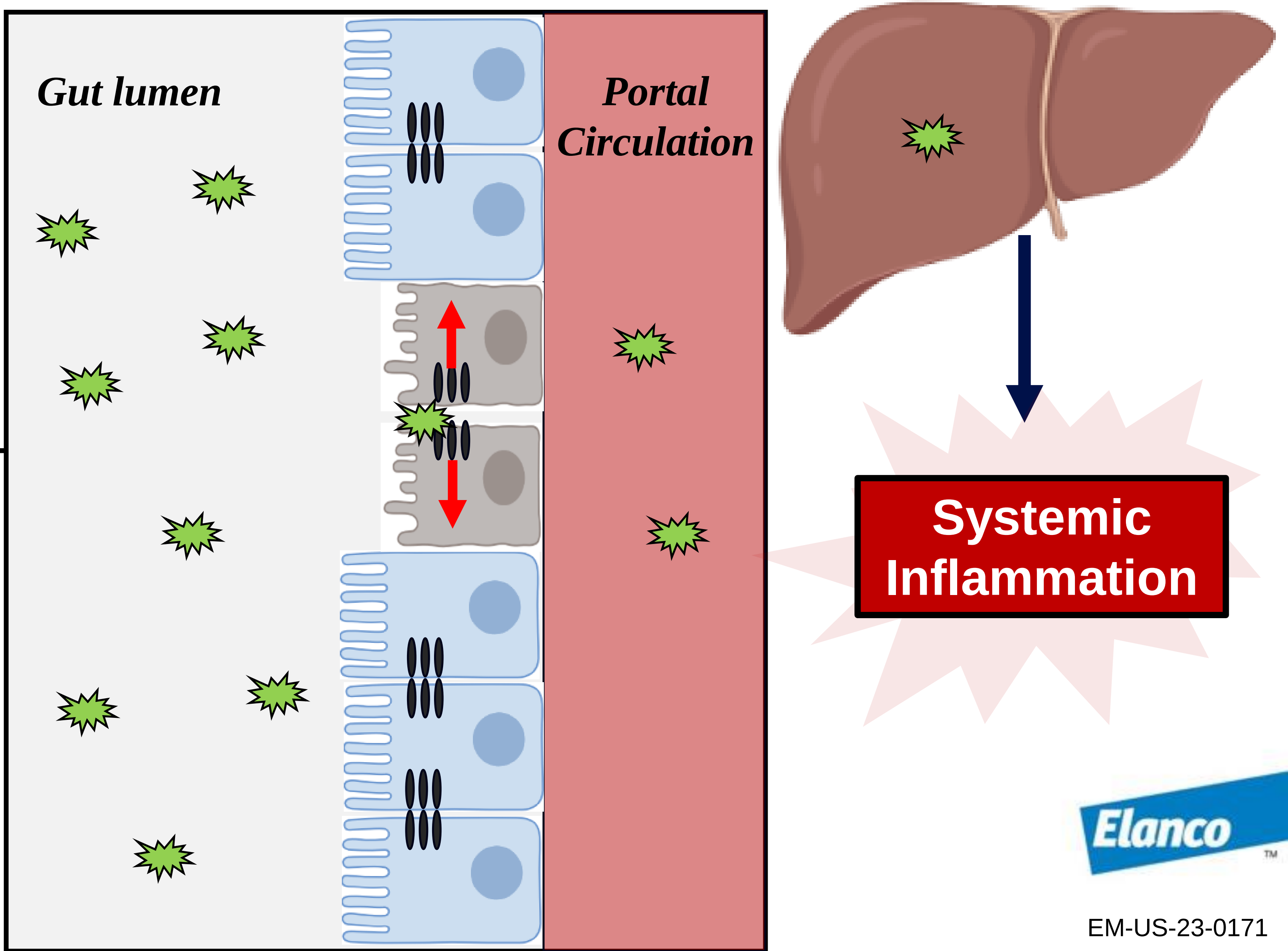


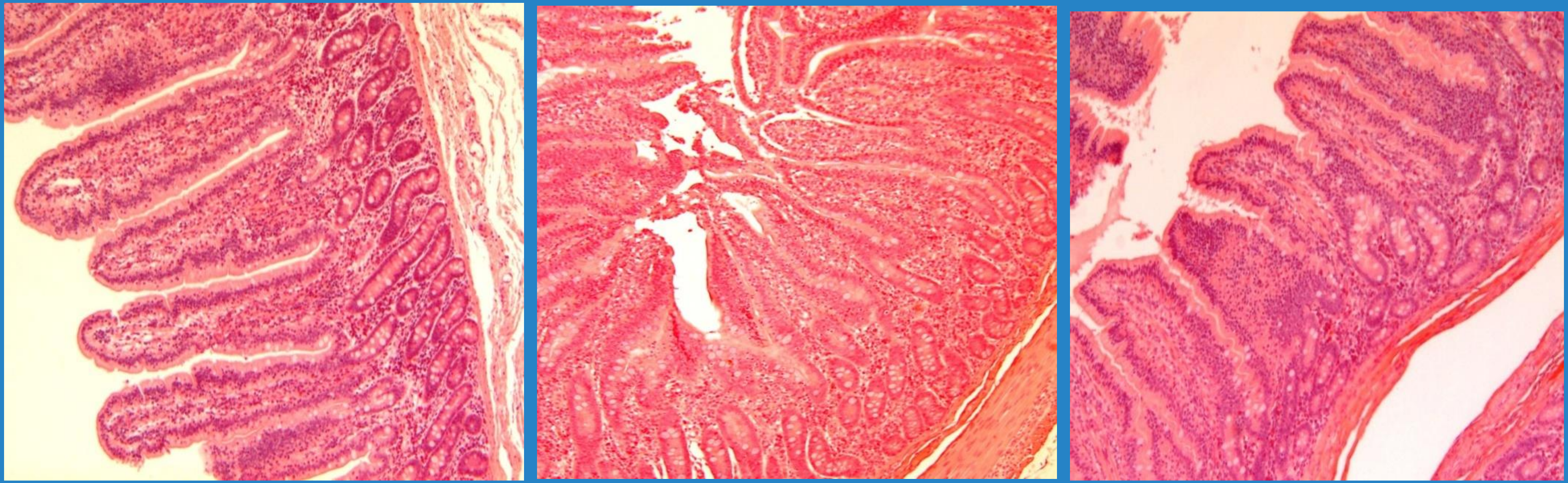
Figure from Yu, J. et al. 2016. “Environmental enteric dysfunction includes a broad spectrum of inflammatory responses and epithelial repair processes.” CMGH. 2: 158-174.e1.

Situations and Outcome of Intestinal Barrier Dysfunction

- Heat stress
- Feed restriction
- Abrupt dietary changes
- Transportation
- Social and psychological stress
- Etc.



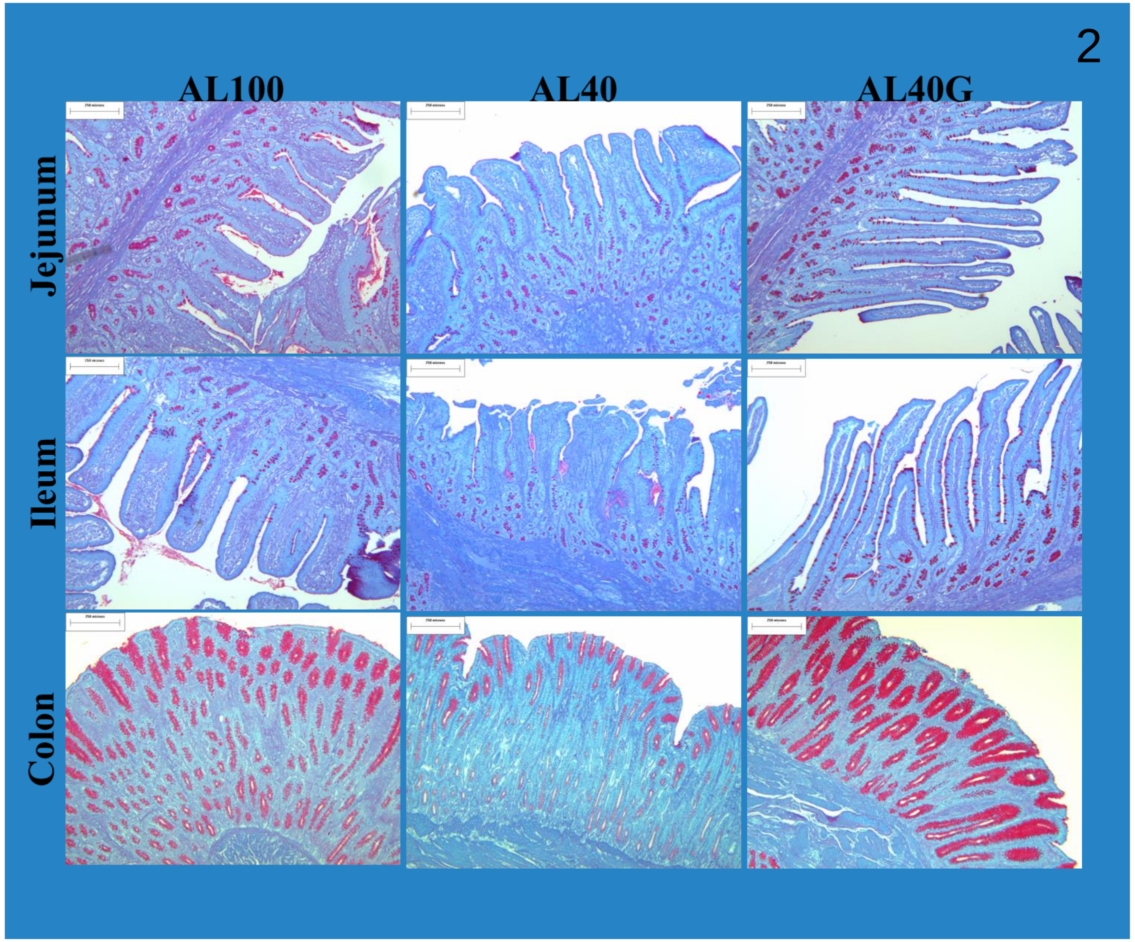
Heat Stress and Leaky Gut

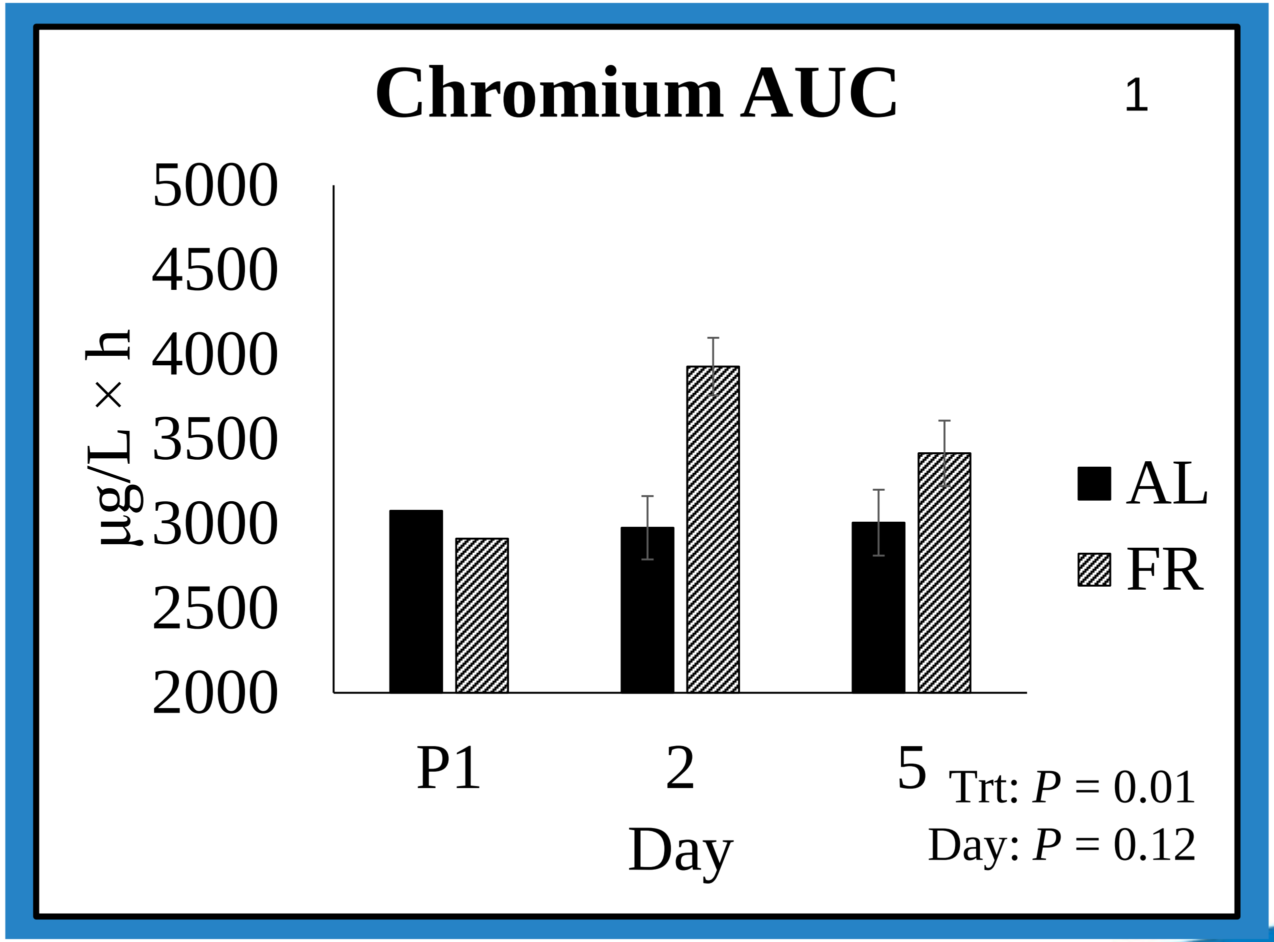


Thermal Neutral | Heat Stress | Pair-fed

Pearce, S.C. et al. 2013. “Heat stress and reduced plane of nutrition decreases intestinal integrity and function in pigs.” J. Anim. Sci 91: 5183–5193.

Feed Restriction and Leaky Gut

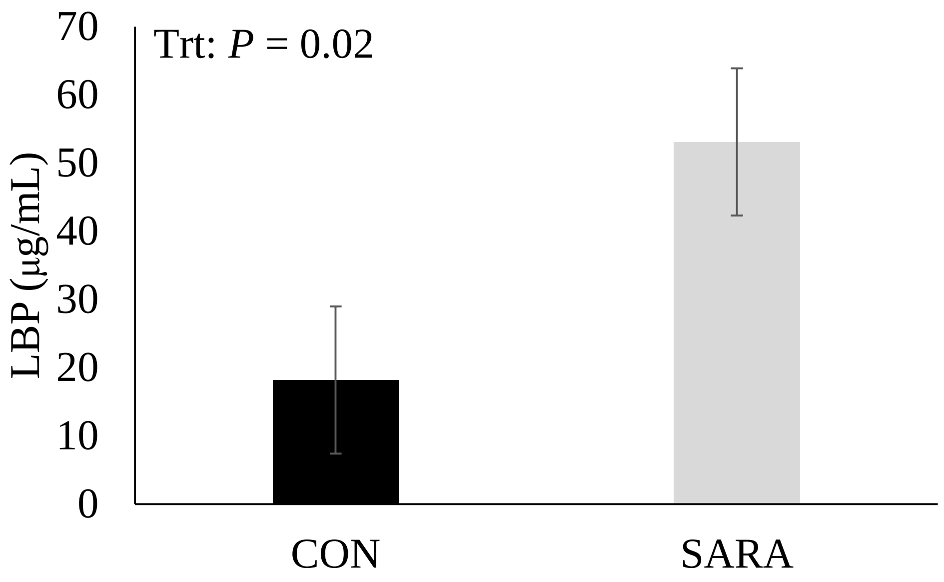




[1]Horst, E. A. et al. 2020. "Evaluating effects of zinc hydoxychloride on biomarkers of inflammation and intestinal integrity during feed restriction" J. Dairy Sci. 103:11911-11929

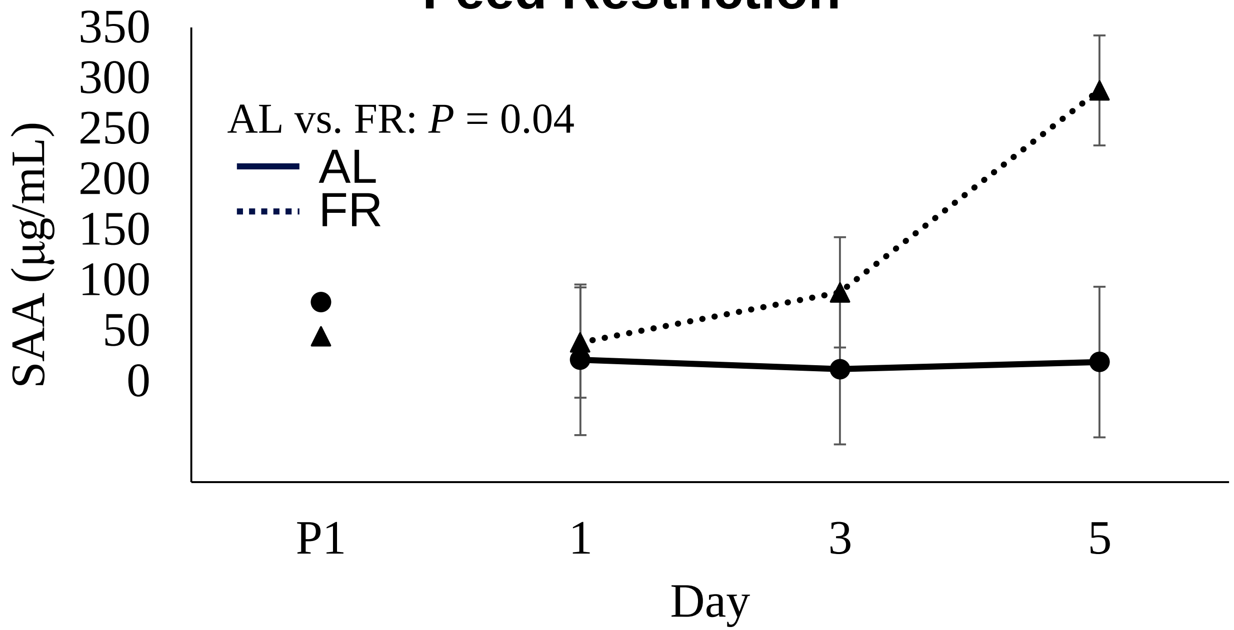
[2]Kvidera, S.K. et al. 2017. "Characterizing effects of feed restriction and glucagon-like peptide 2 administration on biomarkers of inflammation and intestinal morphology." J. Dairy Sci. 100: 9402–9417.

Subacute Rumen Acidosis



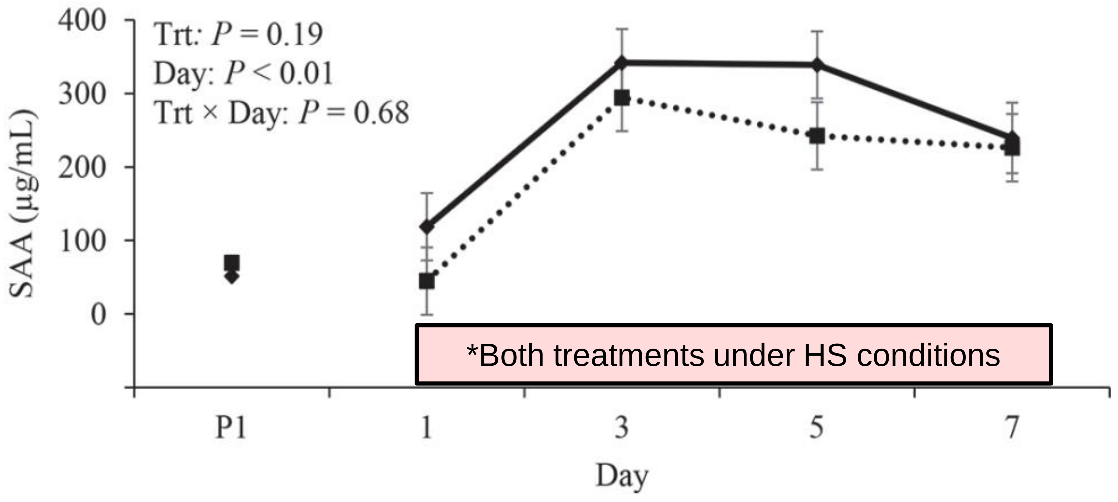
Khafipour, E.et al. 2009. "A grain-based subacute ruminal acidosis challenge causes translocation of lipopolysaccharide and triggers inflammation" J. Dairy Sci. 92:1060-1070.

Feed Restriction



Horst, E. A. et al. 2020. "Evaluating effects of zinc hydoxychloride on biomarkers of inflammation and intestinal integrity during feed restriction" J. Dairy Sci. 103:11911-11929

Heat Stress



Al-Qaisi, M. et al. 2020. "Effects of a Saccharomyces cerevisiae fermentation product on heat-stressed dairy cows." J. Dairy Sci. 103:9634-9645

What are the consequences of leaky gut-induced inflammation?

Right for cattle. Right by you.

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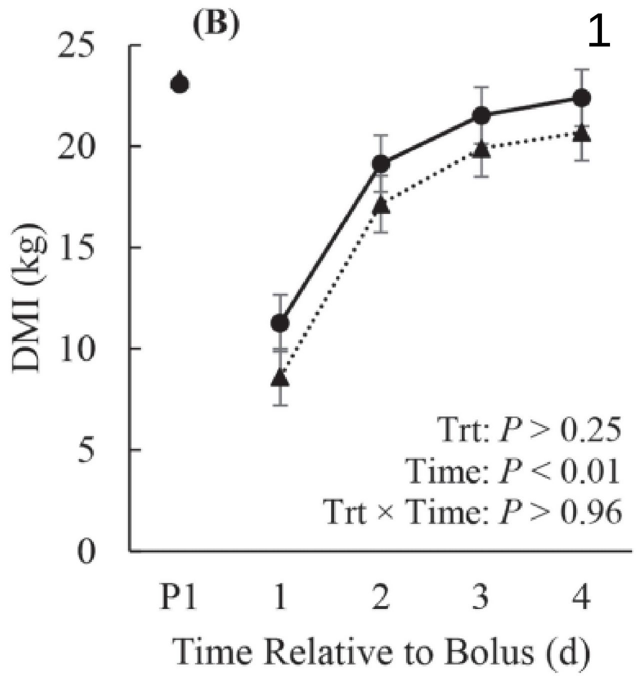
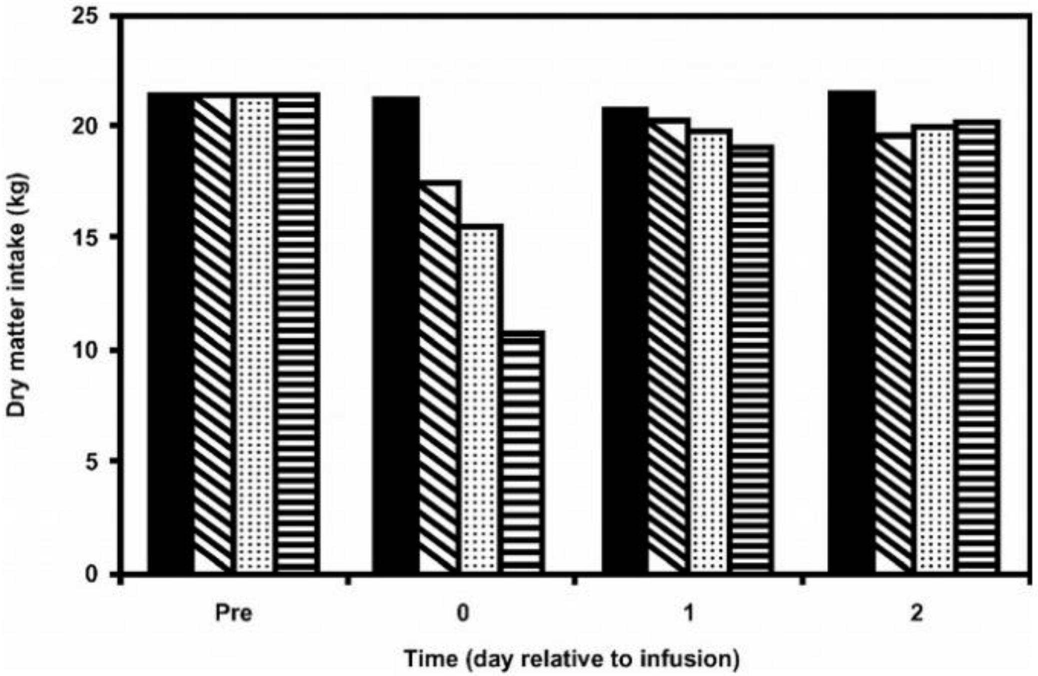
Inflammation—Feed intake

- Inflammatory mediators are potent anorexic compounds (Kushibiki et al., 2003)
- Reduced feed intake is a highly conserved species response to infection (Aubert et al., 1997; Wang et al., 2016)
- Infection decreases feed consumption, even in insects (Adamo, 2005)





1 Horst, e. a. et al. 2020. "effects of maintaining eucalcemia following immunoactivation in lactating Holstein dairy cows." J. dairy sci. 103:7472-7486.
2. Waldron, M. R. et al. 2003. "Effect of lipopolysaccharide on indices of peripheral and hepatic metabolism in lactating cows." J. Dairy Sci. 86:3447-3459
Kushibiki, S. K. et al. 2003. "Metabolic and lactational responses during recombinant bovine tumor necrosis facror-alpha treatment in lactating cows" J. Dairy Sci. 86:819-827.
Aubert, A. et al. 1997. "Differential effects of lipopolysaccharide on pup retrieving and nest building in lactating mice." Brain Behav. Immun. 11:107-118.
Adamo, S. A. 2005. "Parasitic suppression of feeding in the tobacco hornworm, *Manduca sexta:* Parallels with feeding depression after an immune challenge" Arch. Insect Biochem. Physiol. 60:185-197.
Wang, A. et al., 2016. "Opposing effects of fasting metabolism on tissue tolerance in bacterial and viral inflammation" Cell 166:1512-1525.

Immunometabolism – The Warburg Effect

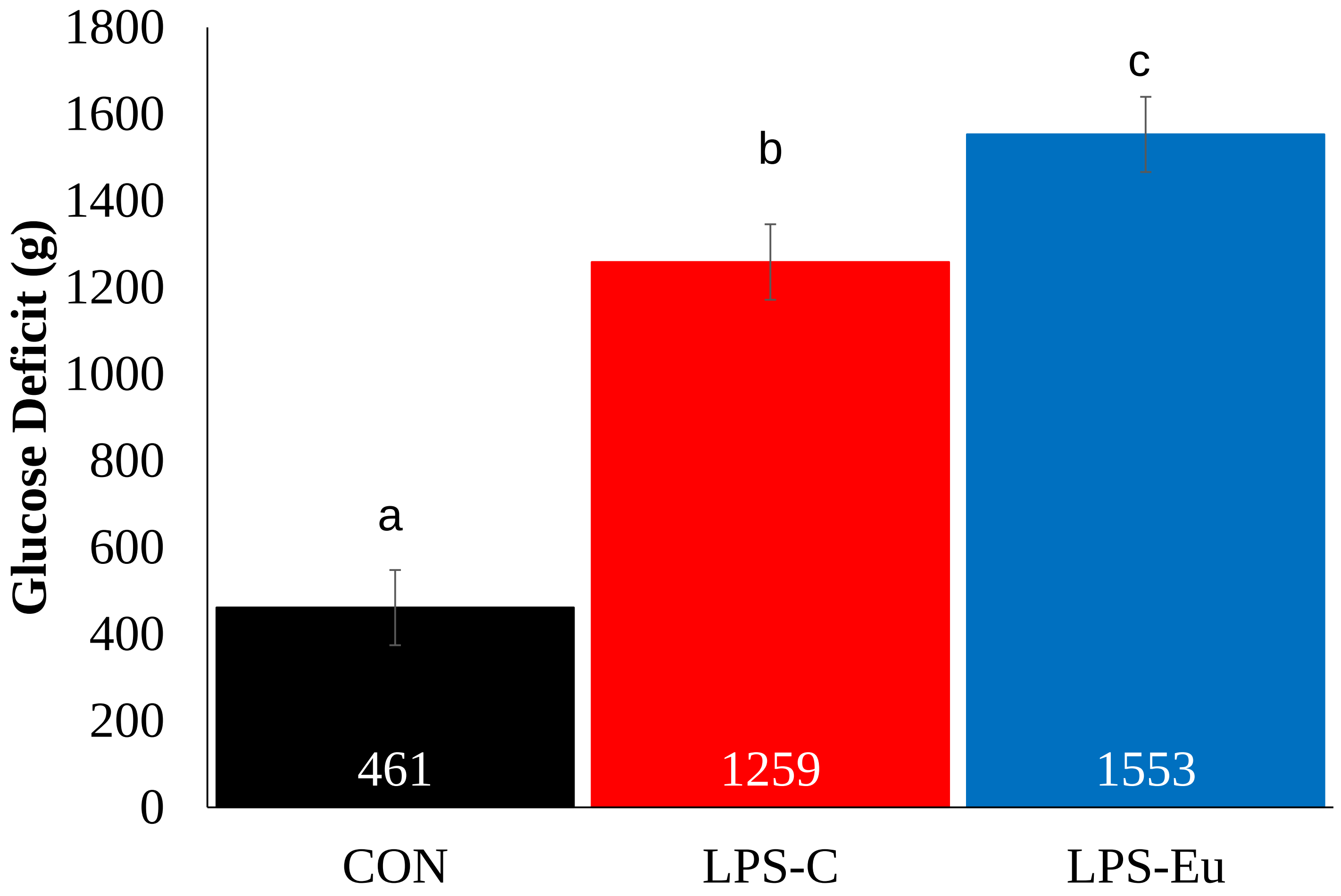
- Immune cells become obligate glucose utilizers when activated
  - Called “The Warburg Effect”

- Advantages of Warburg effect:
  - Rapid production of ATP
  - Synthesis of biomolecules (nucleotides, reducing equivalents, etc.)
  - Adaptation to hypoxic environment
  - Inflammatory signaling

- Seen in both innate and adaptive immune cells

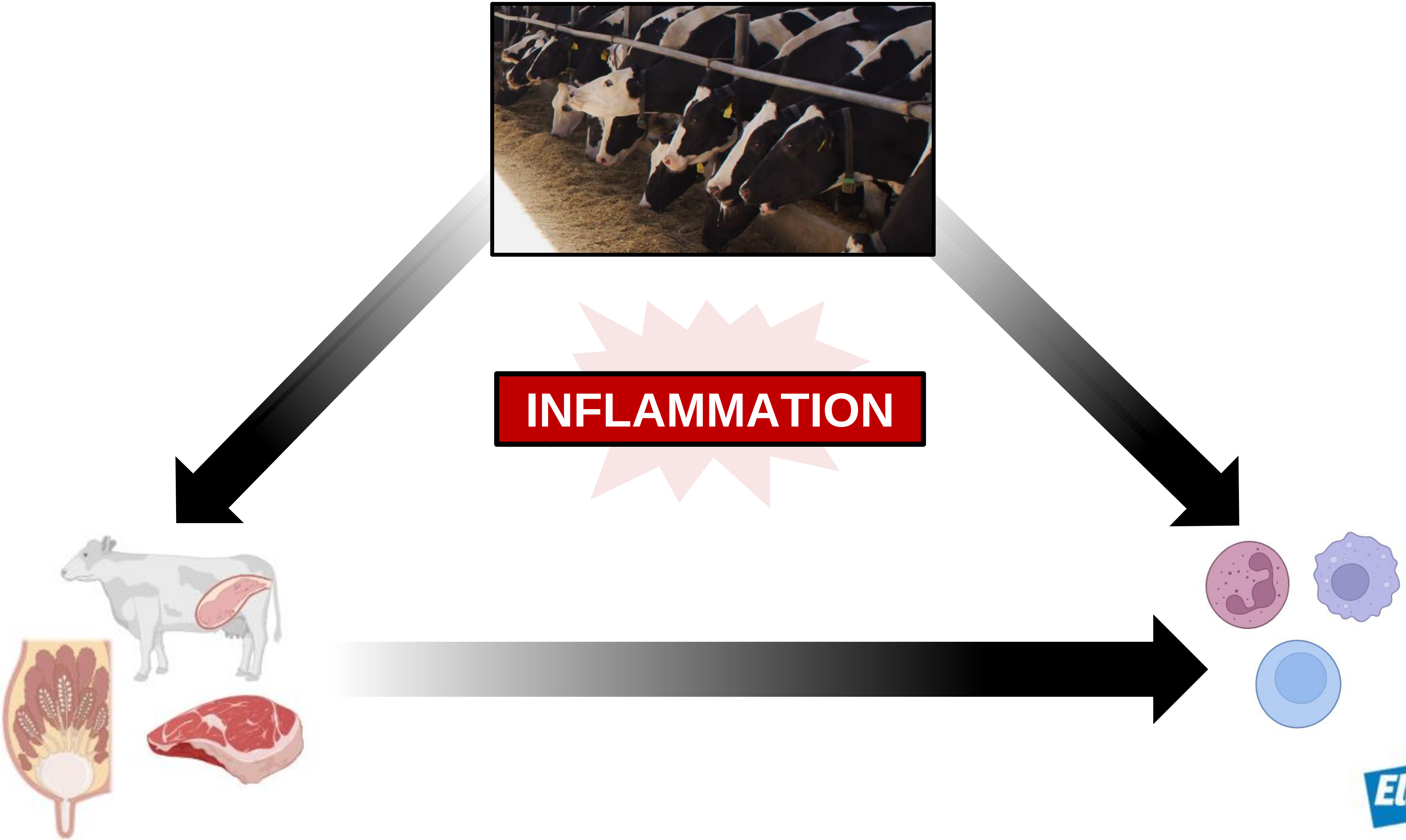
[1]Palsson-McDermott, E.M. and L.A. O'Neill. 2013. “The Warburg effect then and now: from cancer to inflammatory diseases.” Bioessays. 35: 965-973.

Trt: *P*<0.01



1553 g – 461 g = 1092 g in a 12 h period

Kvidera, S.K. et al. 2017. “Glucose requirements of an activated immune system in lactating Holstein cows.” J. Dairy Sci. 100: 2360–2374.



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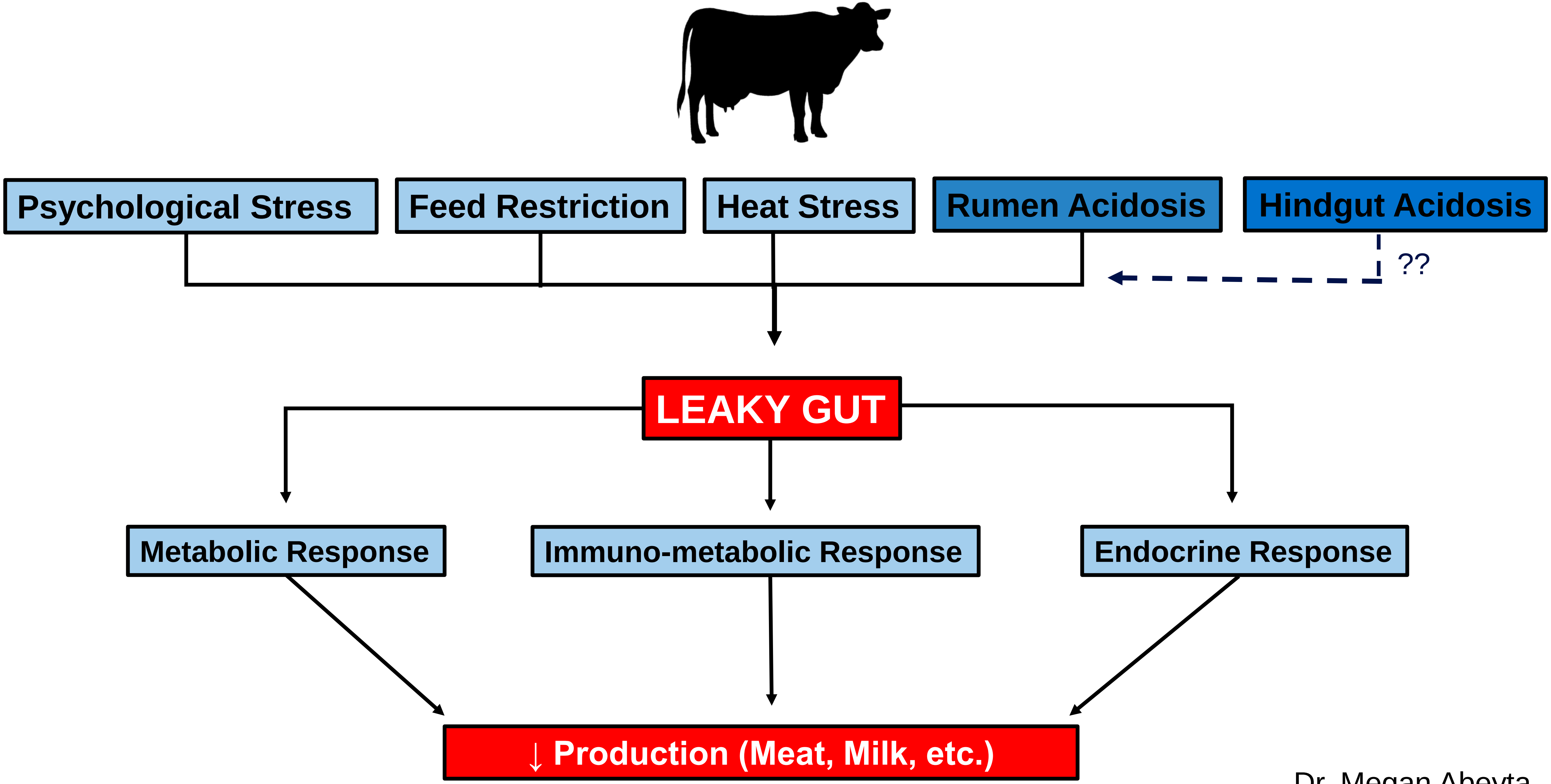
What Causes Leaky Gut?



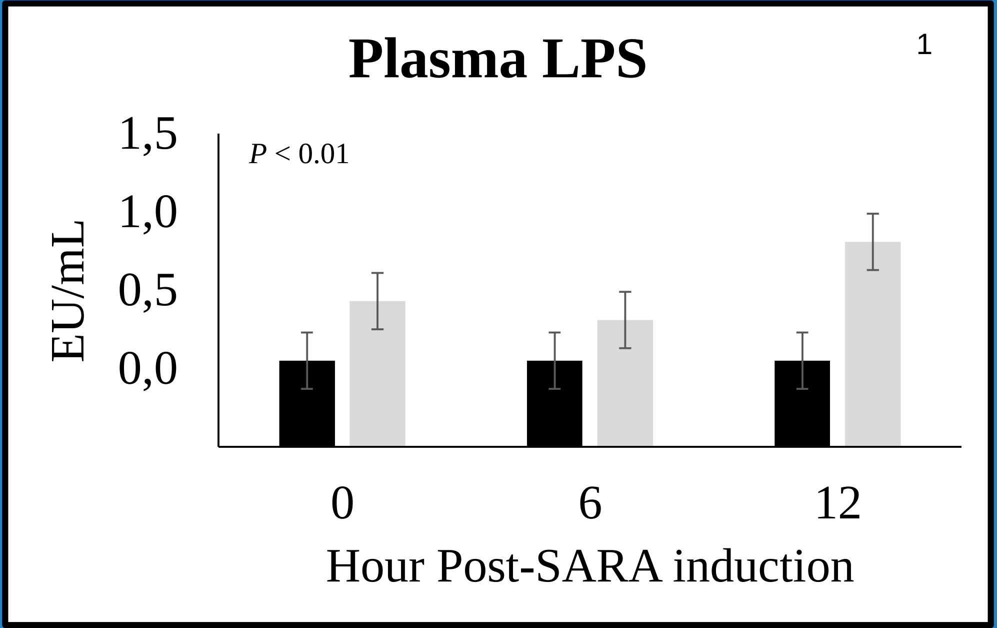
Dr. Megan Abeyta

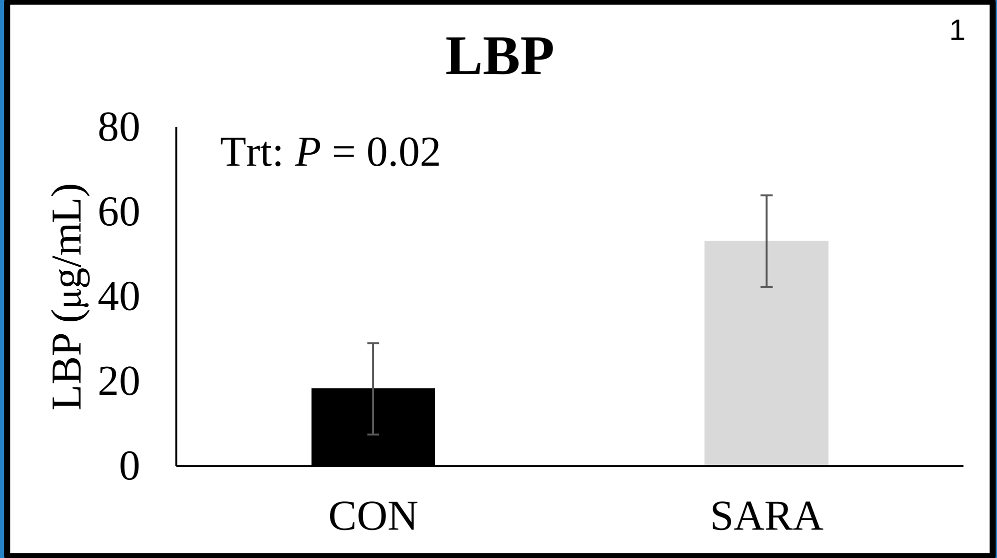
Subacute Rumen Acidosis (SARA)

- Result of high concentrate feeding with insufficient physically effective fiber
  - Particularly common with an abrupt dietary change (i.e., transition from a pre- to postpartum diet)[2]
  - Accumulation of short chain fatty acids resulting in reduced pH below an arbitrary threshold of 5.6-5.8[3]

- Characterized by reduced feed intake, fiber digestion, and performance and different degrees of diarrhea with frothy feces and mucin casts

- Causes GIT hyperpermeability and systemic inflammation[1,3,4]
  - **However, the site of barrier dysfunction along the GIT remains unclear**





[1]Khafipour, E.et al. 2009. "A grain-based subacute ruminal acidosis challenge causes translocation of lipopolysaccharide and triggers inflammation" J. Dairy Sci. 92:1060-1070.

[2]Plaizier, J. C. et al. 2022. "Invited Reivew: Effect of subacute ruminal acidosis on gut health of dairy cows." J. Dairy Sci. 105:7141-7160.

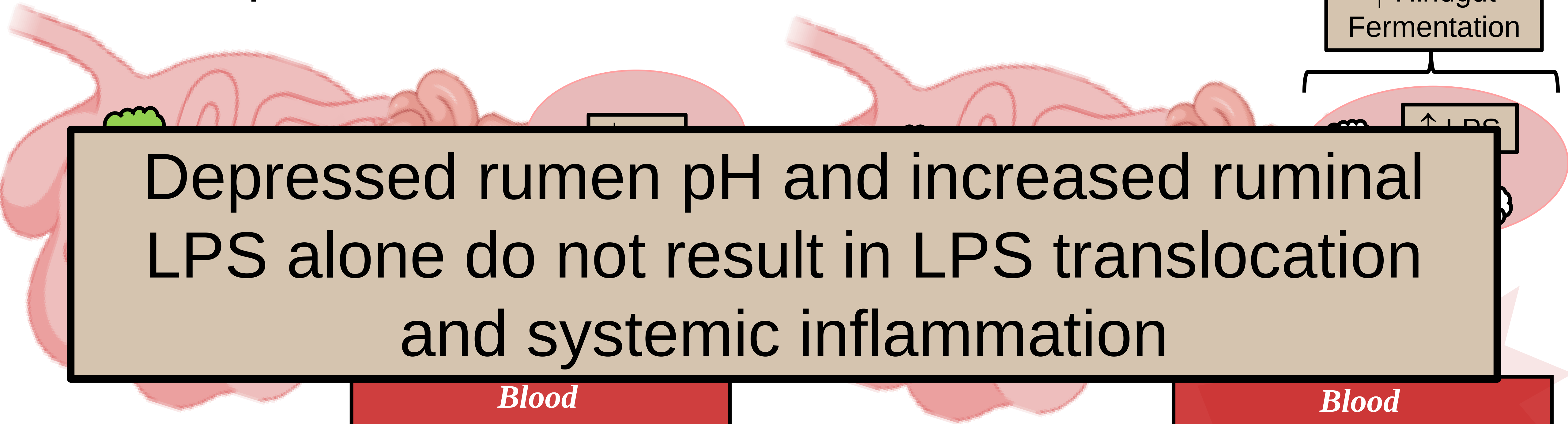
[3]Gozho, G. N. et al. 2005. "Subacute ruminal acidosis induces ruminal lipopolysaccharide endotoxin release and triggers an inflammatory response" J. Dairy Sci. 88:1399-1403..

[4]Danscher, A. M. et al. 2011. "Acute phase protein response during acute ruminal acidosis in cattle" Livest. Sci. 135:62-69.

Not all SARA Challenges are Created Equal

Alfalfa pellet-induced SARA | **Grain-based SARA**

↑ Hindgut Fermentation



Depressed rumen pH and increased ruminal LPS alone do not result in LPS translocation and systemic inflammation

Blood
LPS undetectable
No change in APP[1]

Blood
Increased LPS
Systemic Inflammation

[1]Acute phase proteins (i.e., Serum amyloid A, Haptoglobin, LPS-binding protein)

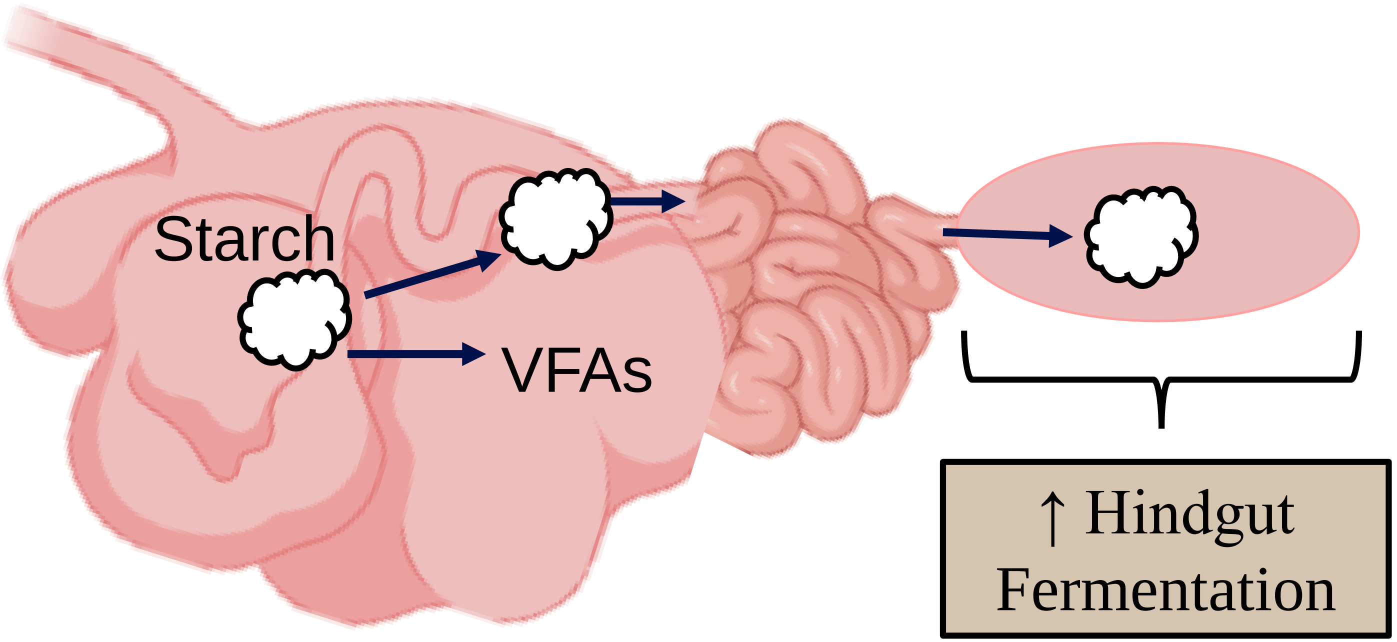
Khafipour, E.et al. 2009. "A grain-based subacute ruminal acidosis challenge causes translocation of lipopolysaccharide and triggers inflammation" J. Dairy Sci. 92:1060-1070.

Khafipour, E.et al. 2009. "Alfalfa pellet-induced subacute ruminal acidosis in dairy cows increases bacterial endotoxin in the rumen without causing inflammation" J. Dairy Sci. 92:1712-1724

Li, S. et al. 2012. "Effects of subacute ruminal acidosis challenges on fermentation and endotoxins in the rumen and hindgut of dairy cows" J. Dairy Sci. 95:294-303.

Hindgut Acidosis

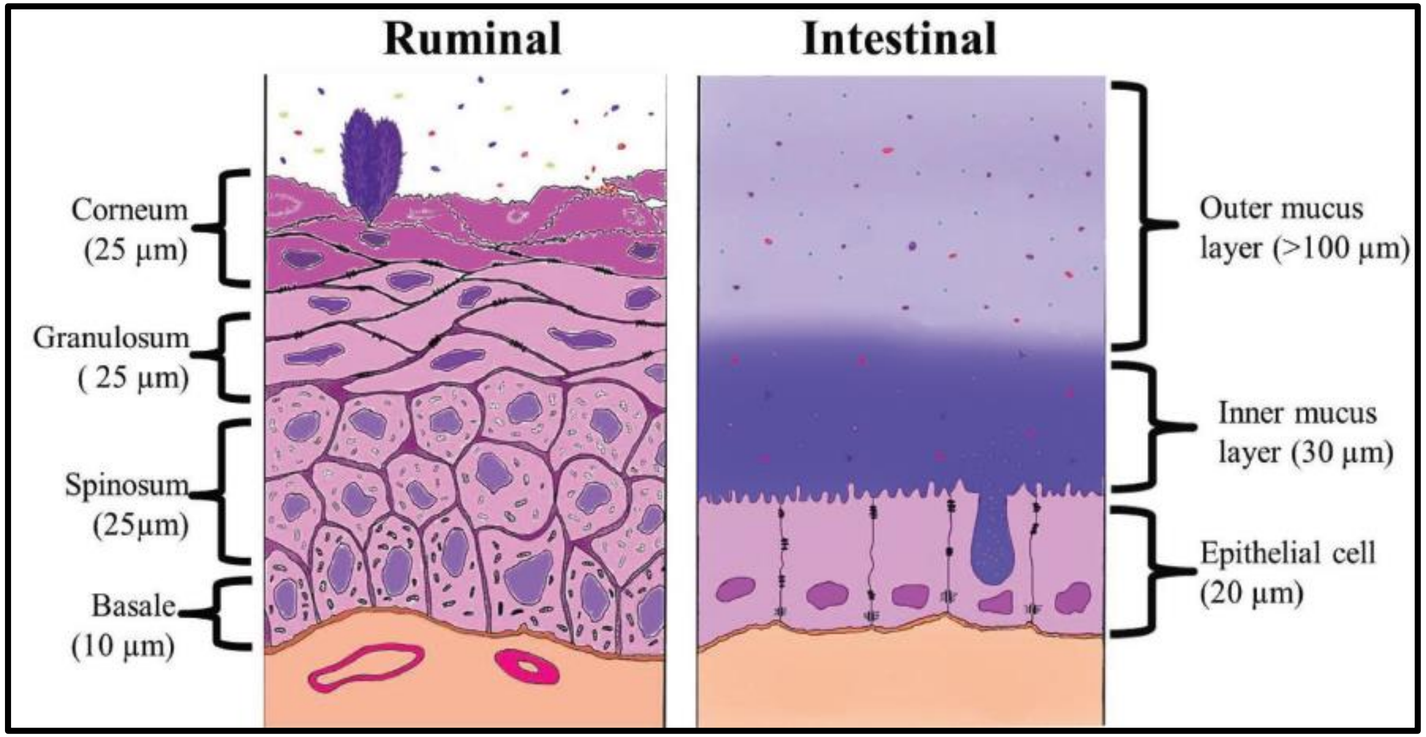
- Hindgut: cecum and colon
- Increased post ruminal starch load
  - High grain feeding
  - Slug feeding
  - Rumen acidosis
- Increased fermentation
  - ↑ VFAs, ↑ free endotoxin, etc.
- Diarrhea, bubbly feces, mucin casts



Hindgut Acidosis

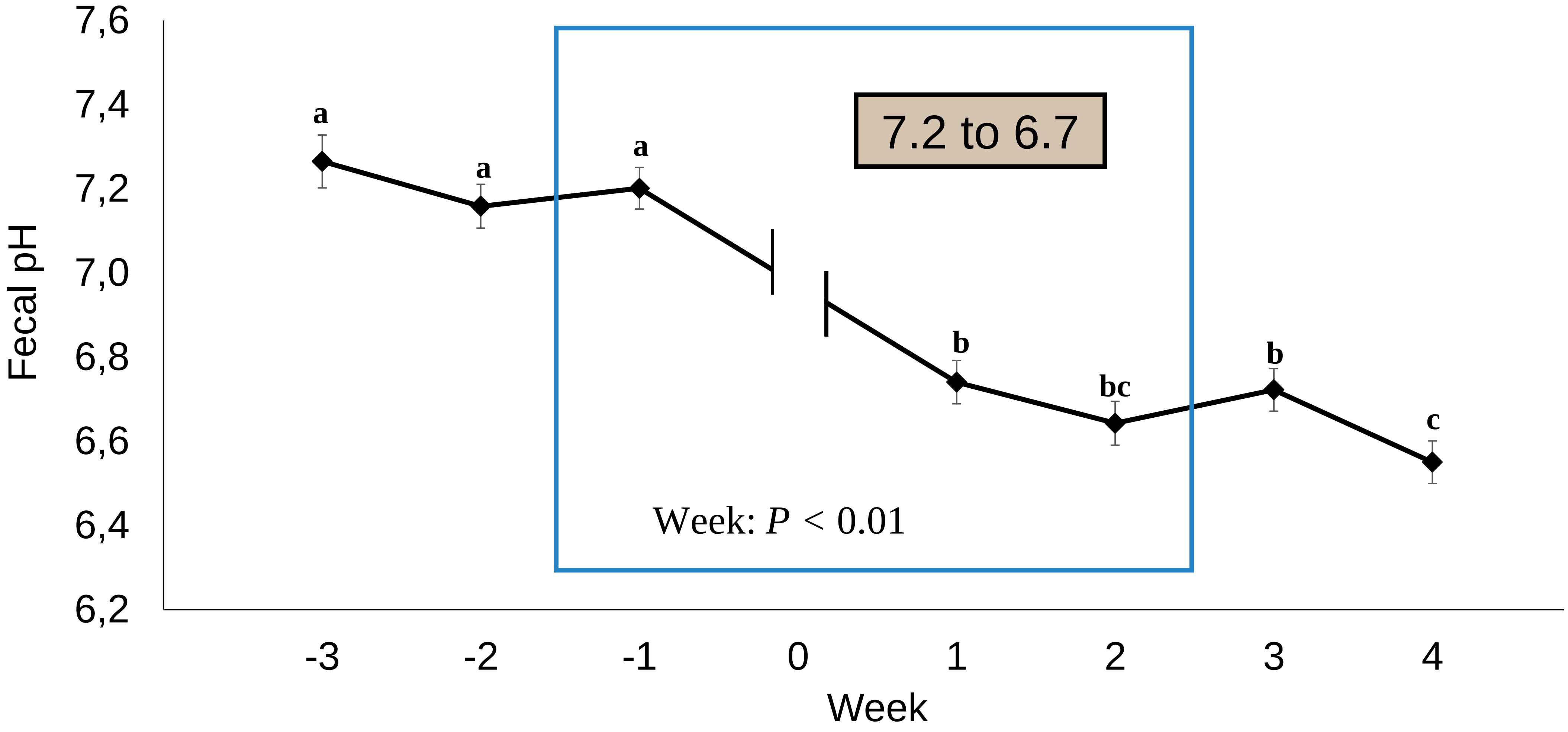
- Post-ruminal GIT is less fortified against insults than rumen
  - Apparent anatomical disadvantage
  - Absence of protozoa
  - No salivary buffering

- Does the hindgut contribute?



Sanz-Fernandez, M. V. et al. 2020. “Targeting the hindgut to improve health and performance in cattle.” Animals 10:1817.
Steele, M.A. 2016. “Development and physiology of the rumen and the lower gut: Targets for improving gut health.” J. Dairy Sci. 99: 4955–4966.

Fecal pH during the Transition Period



McCarthy, C. S. et al. 2020. “Energetic metabolism, milk production, and inflammatory response of transition dairy cows fed rumen-protected glucose” J. Dairy Sci. 103:7451-7461.

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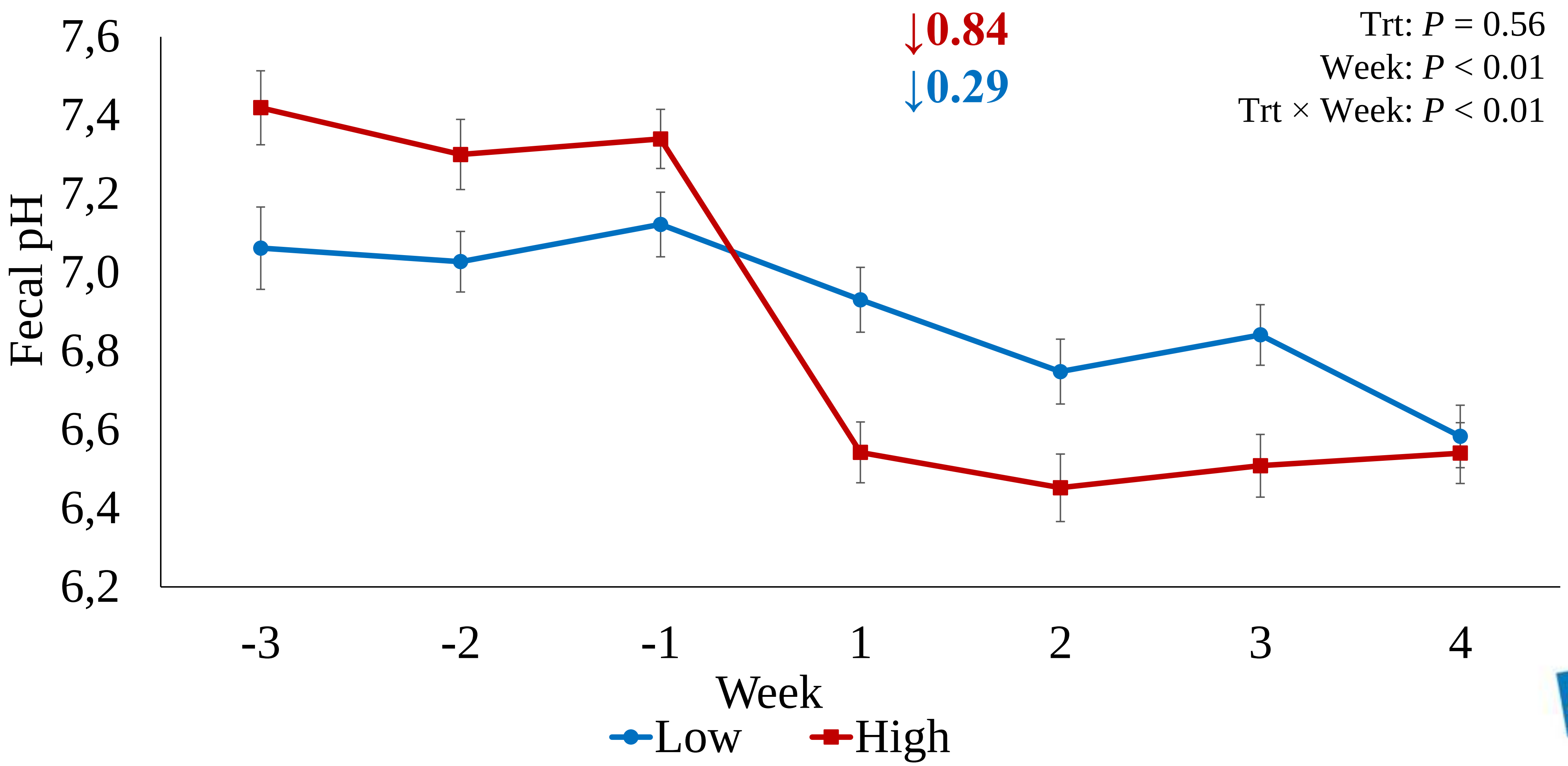
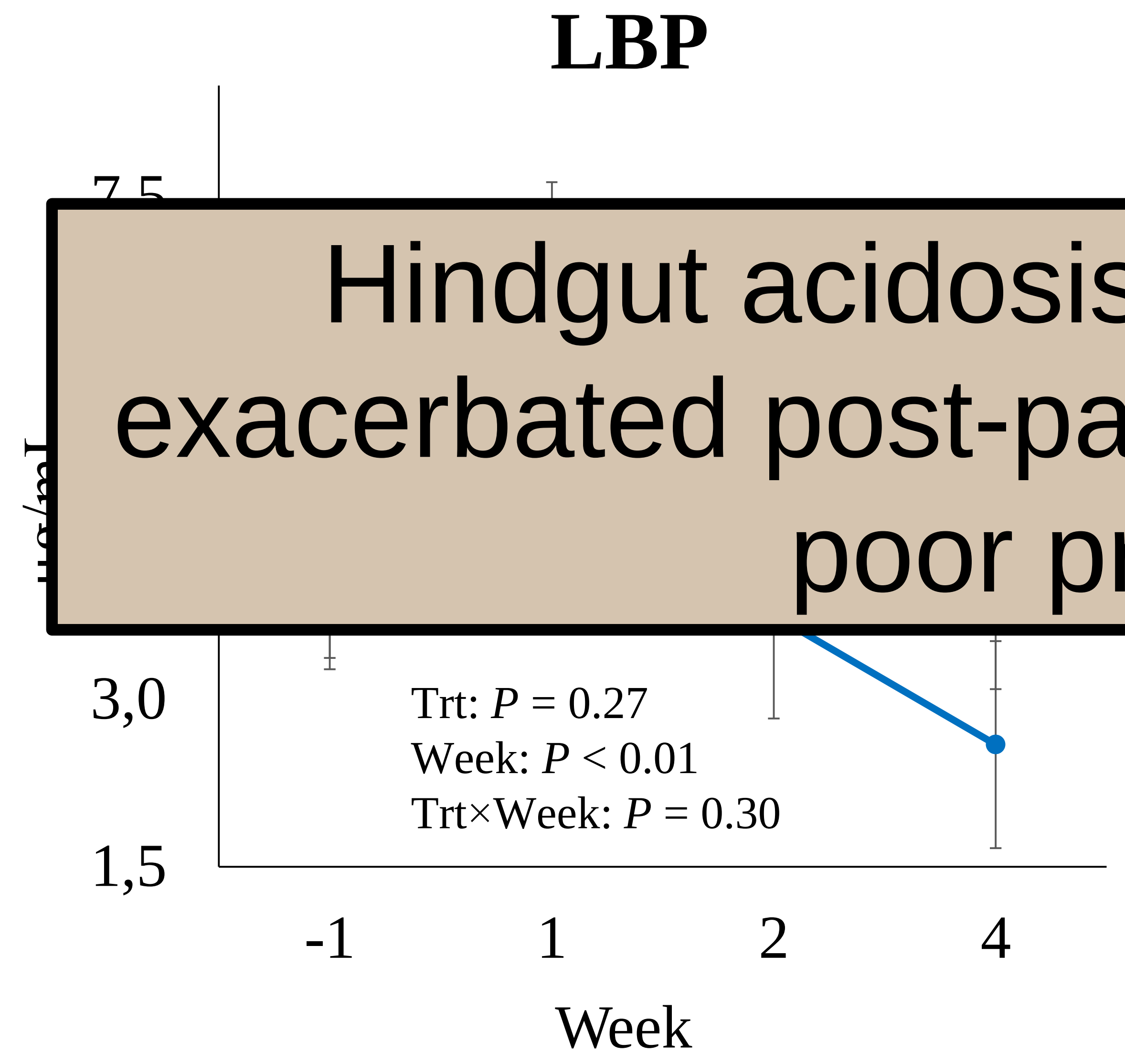
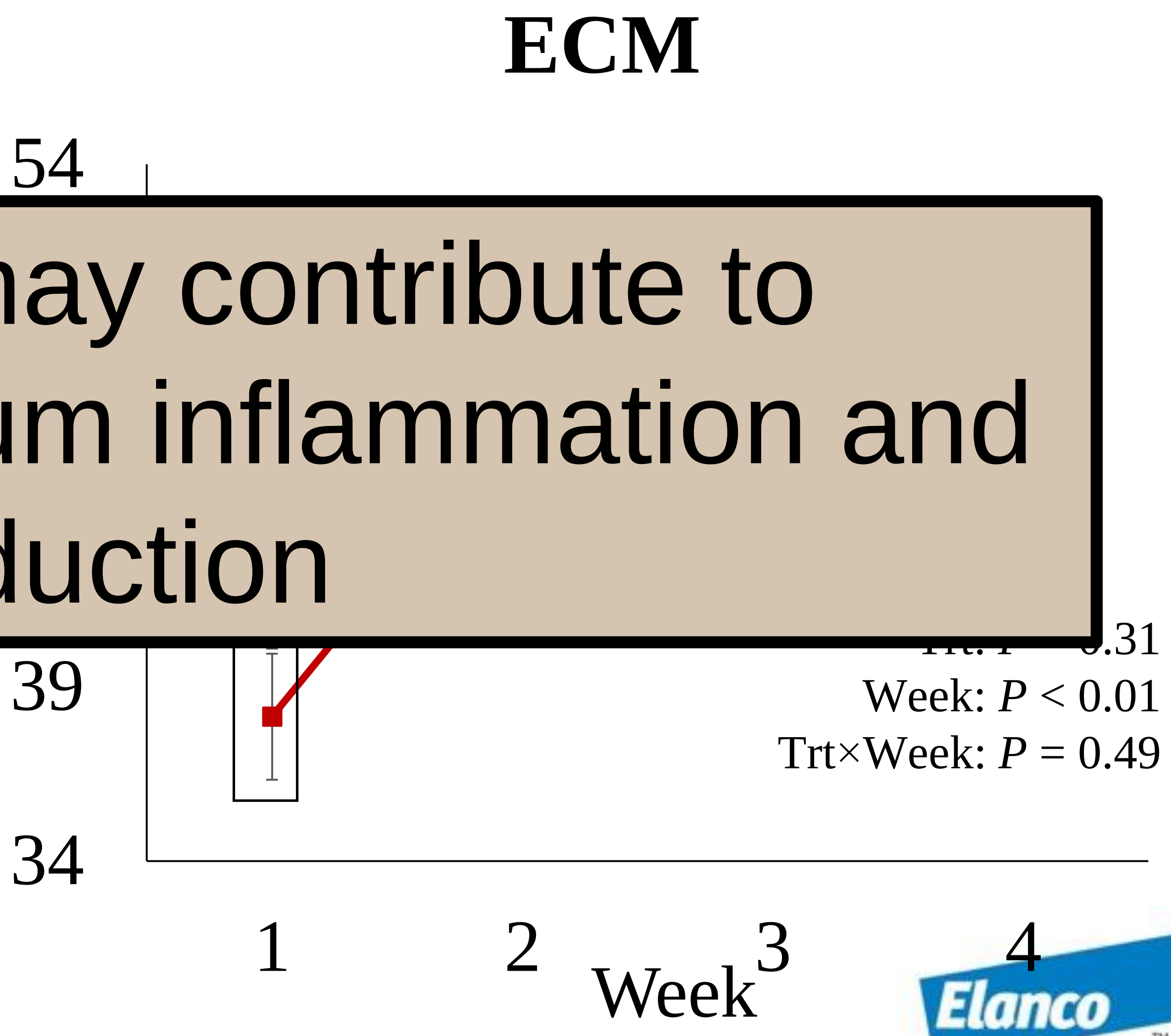
pH Classification from Pre- to Post-partum



Rodriguez-Jimenez, S.et al. 2019. “Relationships between fecal pH and milk production, metabolism, and acute phase protein response in periparturient dairy cows” J. Dairy Sci. 102 (Suppl. 1):402.

Fecal pH Δ

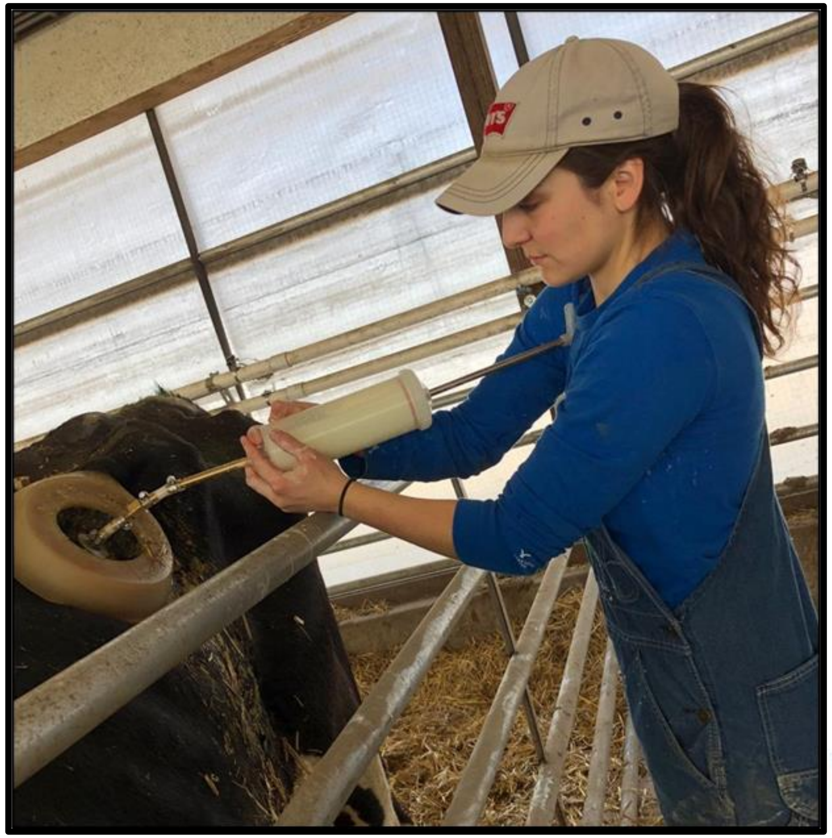




Hindgut acidosis may contribute to exacerbated post-partum inflammation and poor production

Isolating the Hindgut

- Can we isolate the hindgut acidosis challenge to elucidate its role in systemic inflammation?
  - Abomasal starch infusions have been extensively utilized to investigate the independent effect (Zust et al., 2000; Bissell and Hall, 2010; Piantoni et al., 2018; Abeyta et al., 2023)



Piatoni, P. et al. 2022. “Evaluation of feed restriction and abomasal infusion of resistant starch as models to induce intestinal barrier dysfunction in health lactating cows.” J. Dairy Sci. 106:1453-1463.

Bissell, H. A., and Hall, M. B. 2010. “Cattle differ in ability to adapt to small intestinal digestion of starch” J. Dairy Sci. 93(E Suppl. 1):845.

Zust, J. et al. 2000. “Impact of lactic acid fermentation in the large intestine on acute lactic acidosis in cattle” Dtsch. Tierarztl. Wochenschr. 107:359-363

Abeyta, M. A. et al. 2023. “Effects of hindgut acidosis on inflammation, metabolism, and productivity in lactating dairy cows fed a high-fiber diet.” J. Dairy Sci. 106:2879-2889.

The Experimental Journey

- All studies infused 4 kg of pure corn starch daily
  - 1 kg corn starch + 1.25 L H_20/infusion

J. Dairy Sci. 106
https://doi.org/10.3168/jds.2022-22689

Effects of hindgut acidosis on production, metabolism, and inflammatory biomarkers in feed-restricted lactating dairy cows

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J. Dairy Sci. 106
https://doi.org/10.3168/jds.2022-22303

Effects of hindgut acidosis on metabolism, inflammation, and production in dairy cows consuming a standard lactation diet

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J. Dairy Sci. 106:4324–4335
https://doi.org/10.3168/jds.2022-22696

Effects of hindgut acidosis on production, metabolism, and inflammatory biomarkers in previously immune-activated lactating dairy cows

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J. Dairy Sci. 106
https://doi.org/10.3168/jds.2022-22680

Effects of hindgut acidosis on inflammation, metabolism, and productivity in lactating dairy cows fed a high-fiber diet

M. A. Abeyta, E. A. Horst, B. M. Goetz, S. Rodriguez-Jimenez, E. J. Mayorga, M. Al-Qaisi, and L. H. Baumgard*
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J. Dairy Sci. 106:4336–4352
https://doi.org/10.3168/jds.2022-22809

Effects of abomasally infused rumen fluid from corn-challenged donor cows on production, metabolism, and inflammatory biomarkers in healthy recipient cows

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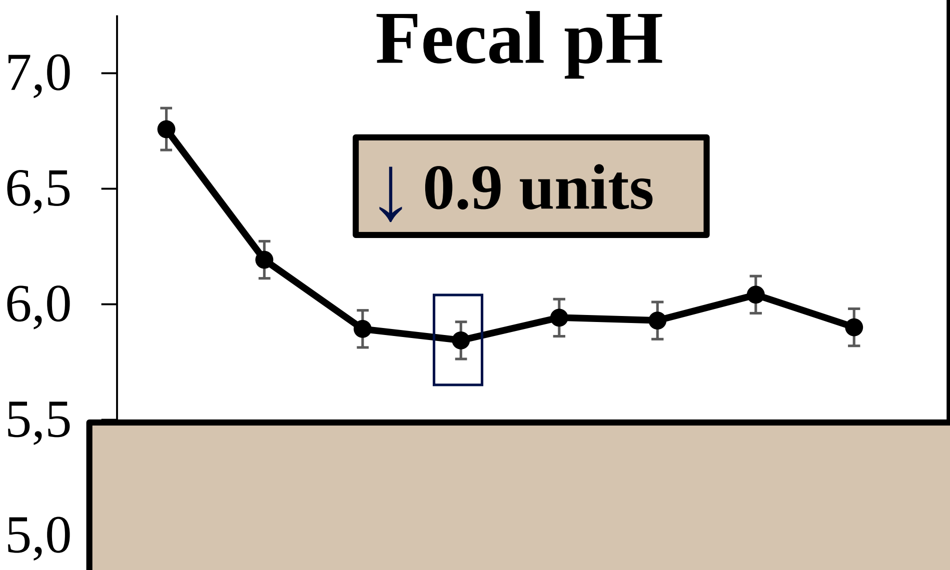
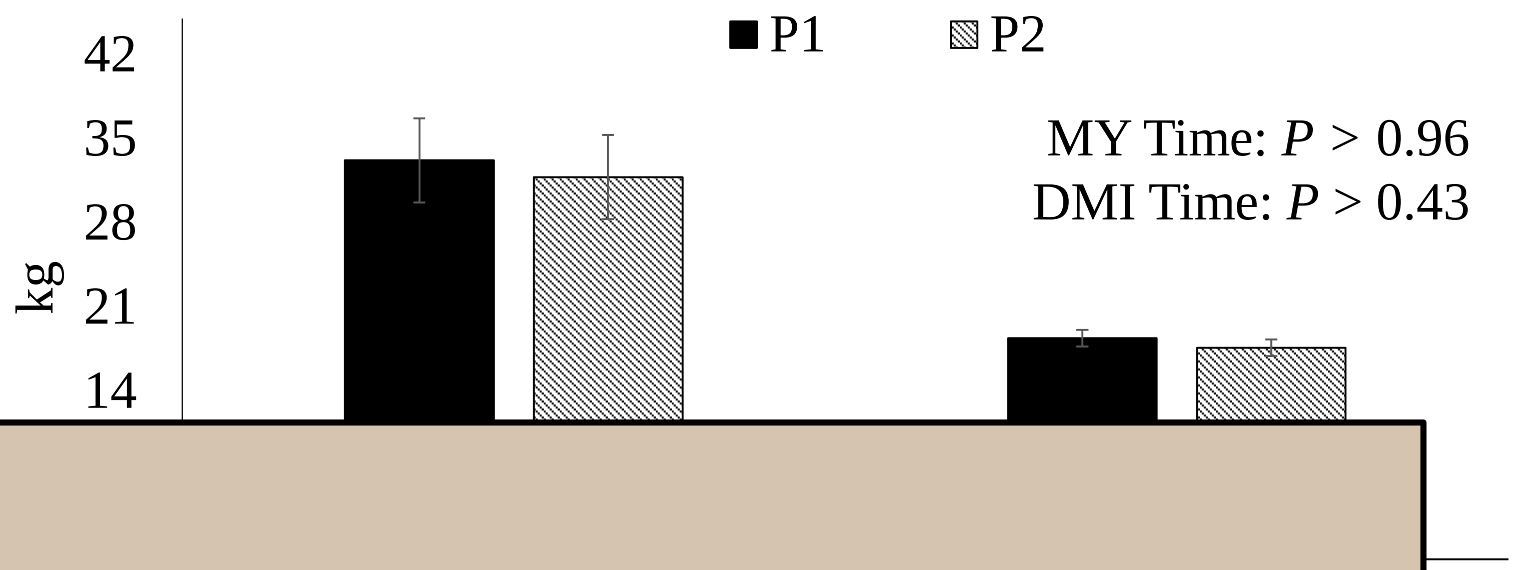
[1]Department of Animal Science, Iowa State University, Ames 50011
[2]Department of Animal and Dairy Science, University of Georgia, Athens 30602





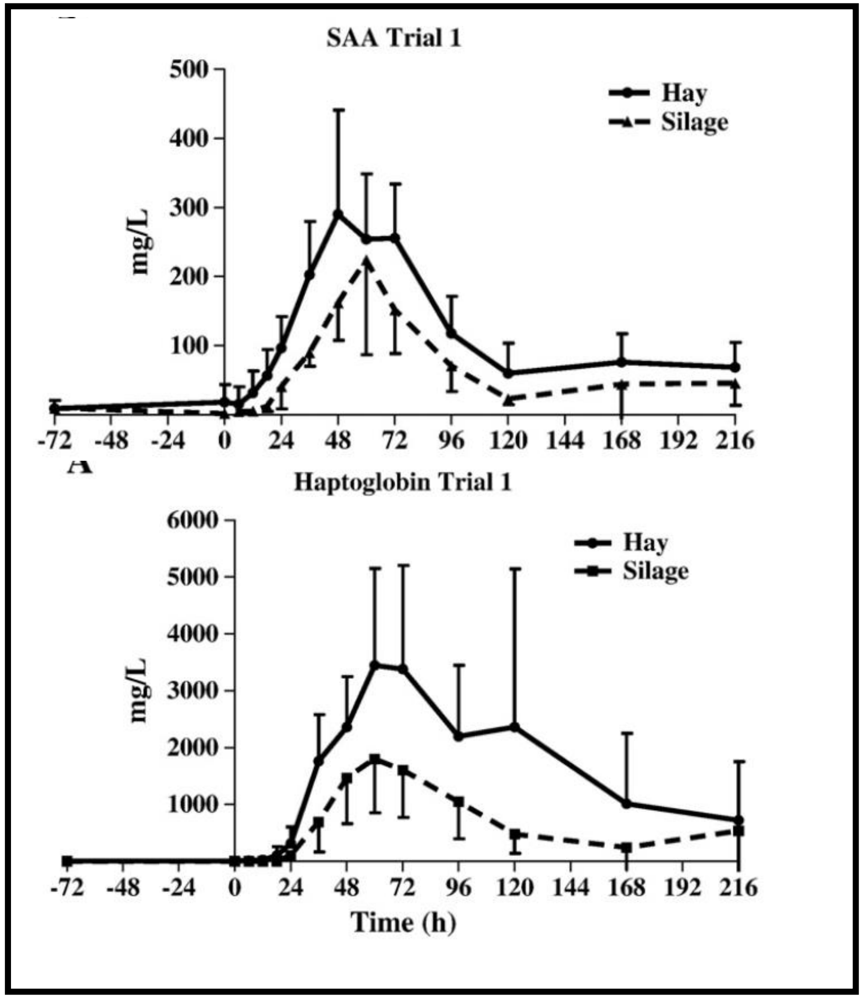
Did acclimation to a high starch diet blunt the inflammatory response to hindgut acidosis?

Pa				
Re				
Inflammatory Biomarkers				
SAA, µg/mL	289.2	311.4	119.2	0.77
LBP, µg/mL	14.1	14.9	2.1	0.54

[1]P1 = baseline (pre-infusion data); P2 = average for daily (rectal temp) or temporal (2, 14, 26, 48, 96, and 168 h relative to the first infusion; SAA and LBP) data

Abeyta, M. A. et al. 2023. "Effects of hindgut acidosis on metabolism, inflammation, and production in dairy cows consuming a standard lactation diet." J. Dairy Sci. 106:2879-2889.

Basal Diet and Acidosis



- Prior adaptation to a barley silage diet (~15% starch dry matter) seemed to ameliorate the inflammatory response to a rumen acidosis challenge (Danscher et al., 2011)

- Abrupt dietary changes increase susceptibility to SARA, and more representative of transition period (switch from high fiber to higher starch diet)

Danscher, A. M. et al.. 2011. "Acute phase protein response during acute ruminal acidosis in cattle." Livest. Sci. 135:62-69.

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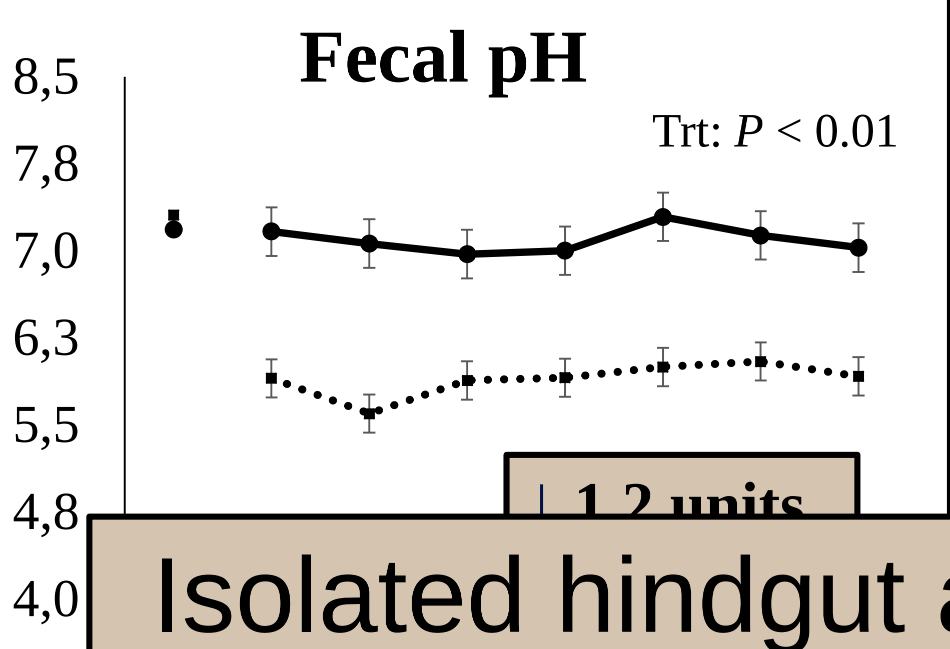

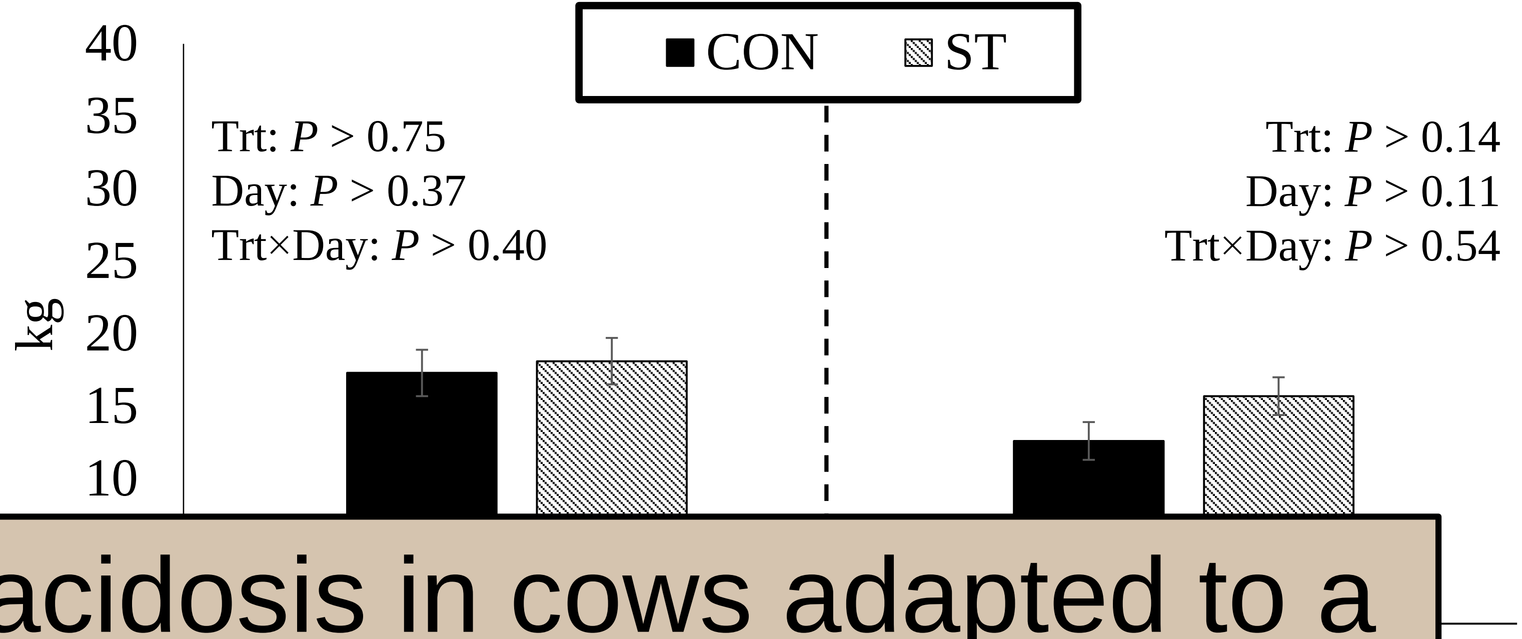

Isolated hindgut acidosis in cows adapted to a high fiber diet did not trigger systemic inflammation or compromise productivity

Parameters	CON	ST	SEM	Trt	Day	Trt×Day
Rectal Temperature, °C	38.0	38.0	0.1	0.99	0.34	0.02
Inflammatory Biomarkers						
SAA, µg/mL	166.3	168.7	43.8	0.97	0.27	0.36
LBP, µg/mL	4.8	5.4	1.1	0.72	0.78	0.96

[1]CON= 6 L H_2O abomasal infusion/head/day; ST= 4 kg of corn starch + 6 L H_2O abomasal infusion/head/day

Abeyta, M. A. et al. 2023. "Effects of hindgut acidosis on inflammation, metabolism, and productivity in lactating dairy cows fed a high-fiber diet." J. Dairy Sci. 106:2879-2889.

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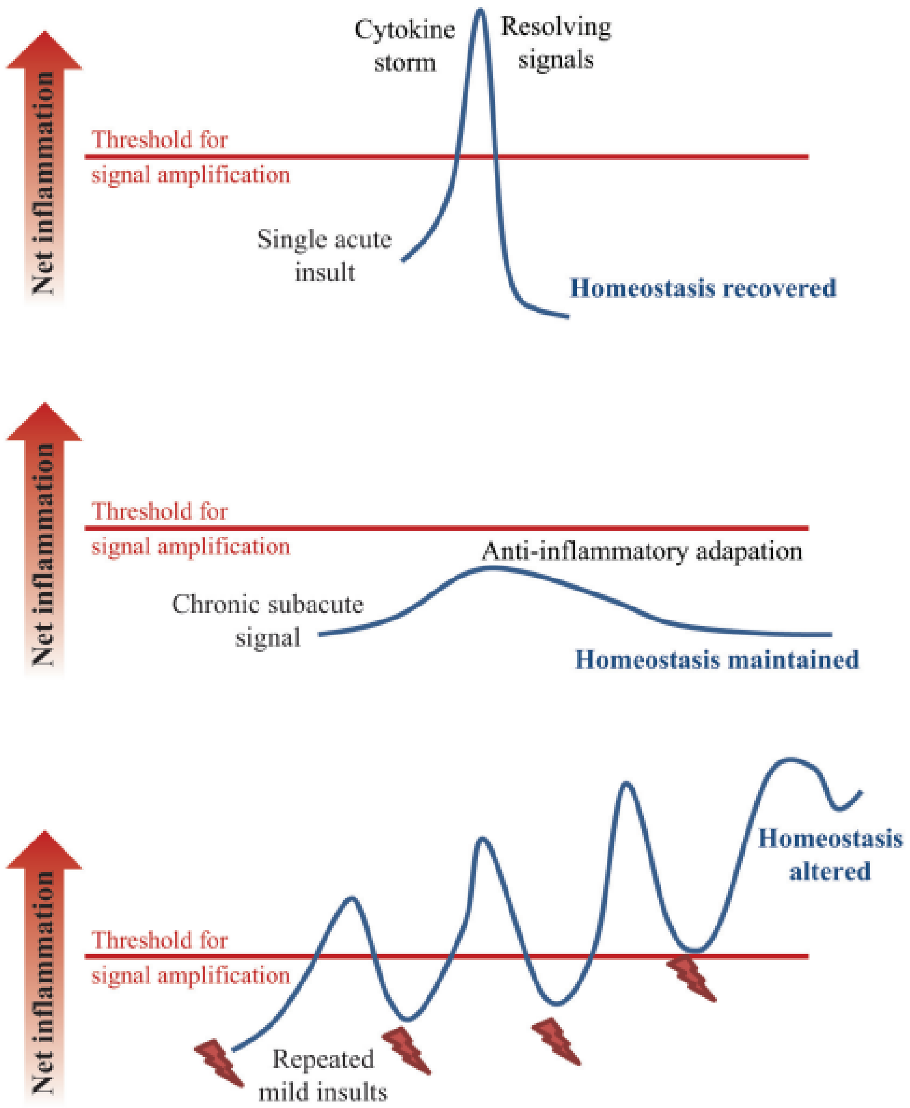
Stacking Stressors?

- Exaggerated production and inflammatory consequences with SARA observed when additional inflammatory events occur concurrently

- Could it be the absence of stacked stressors explaining the lack of response:
  - No change with previous exposure to feed restriction (Abeyta et al., 2023)
  - No change with previous exposure to repeated LPS administration (Abeyta et al., 2023)



Isolated HGA

J. Dairy Sci. 106:1453–1463
https://doi.org/10.3168/jds.2022-22376

Evaluation of feed restriction and abomasal infusion of resistant starch as models to induce intestinal barrier dysfunction in healthy lactating cows

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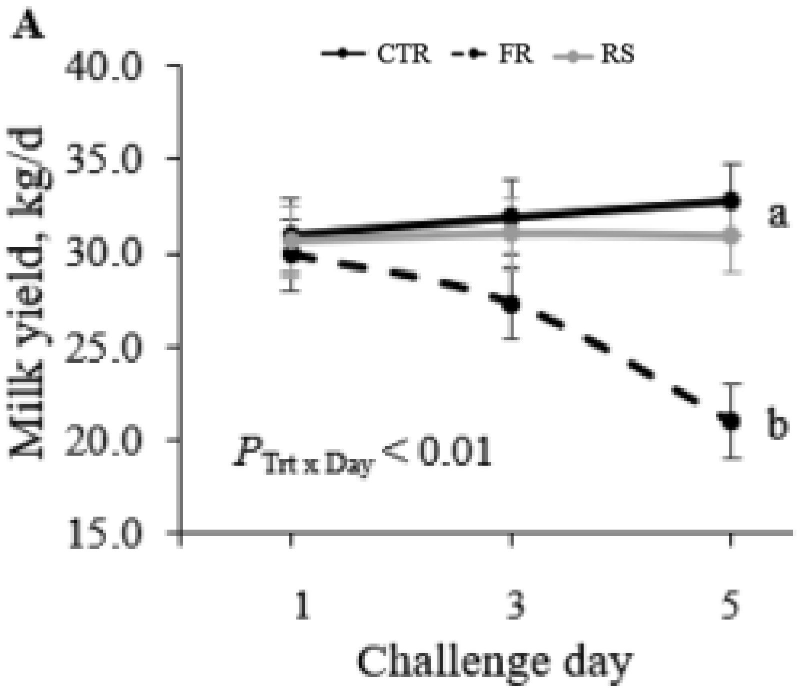

- No change in circulating inflammatory biomarkers (LBP, SAA, Hp)

J. Dairy Sci. 104:12520–12539
https://doi.org/10.3168/jds.2021-20323

Abomasal infusion of corn starch and β-hydroxybutyrate in early-lactation Holstein-Friesian dairy cows to induce hindgut and metabolic acidosis

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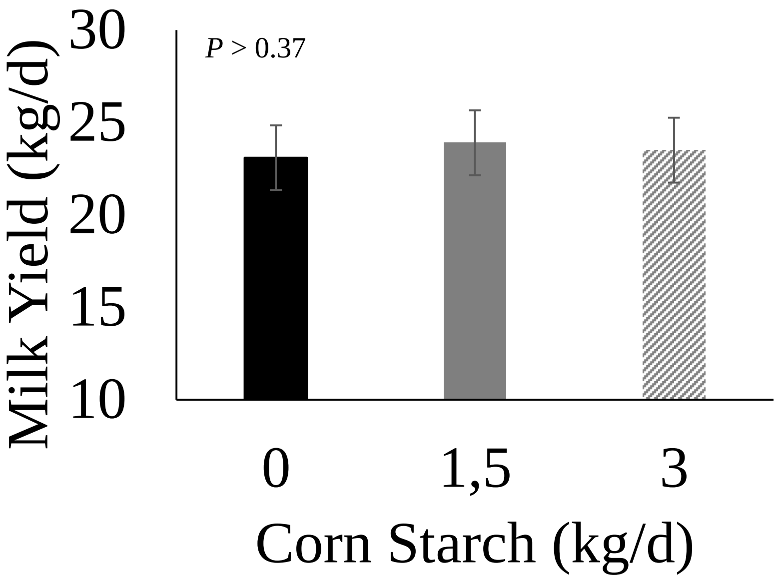

- No change in circulating inflammatory biomarkers (SAA and Hp)

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What about the rumen fluid?

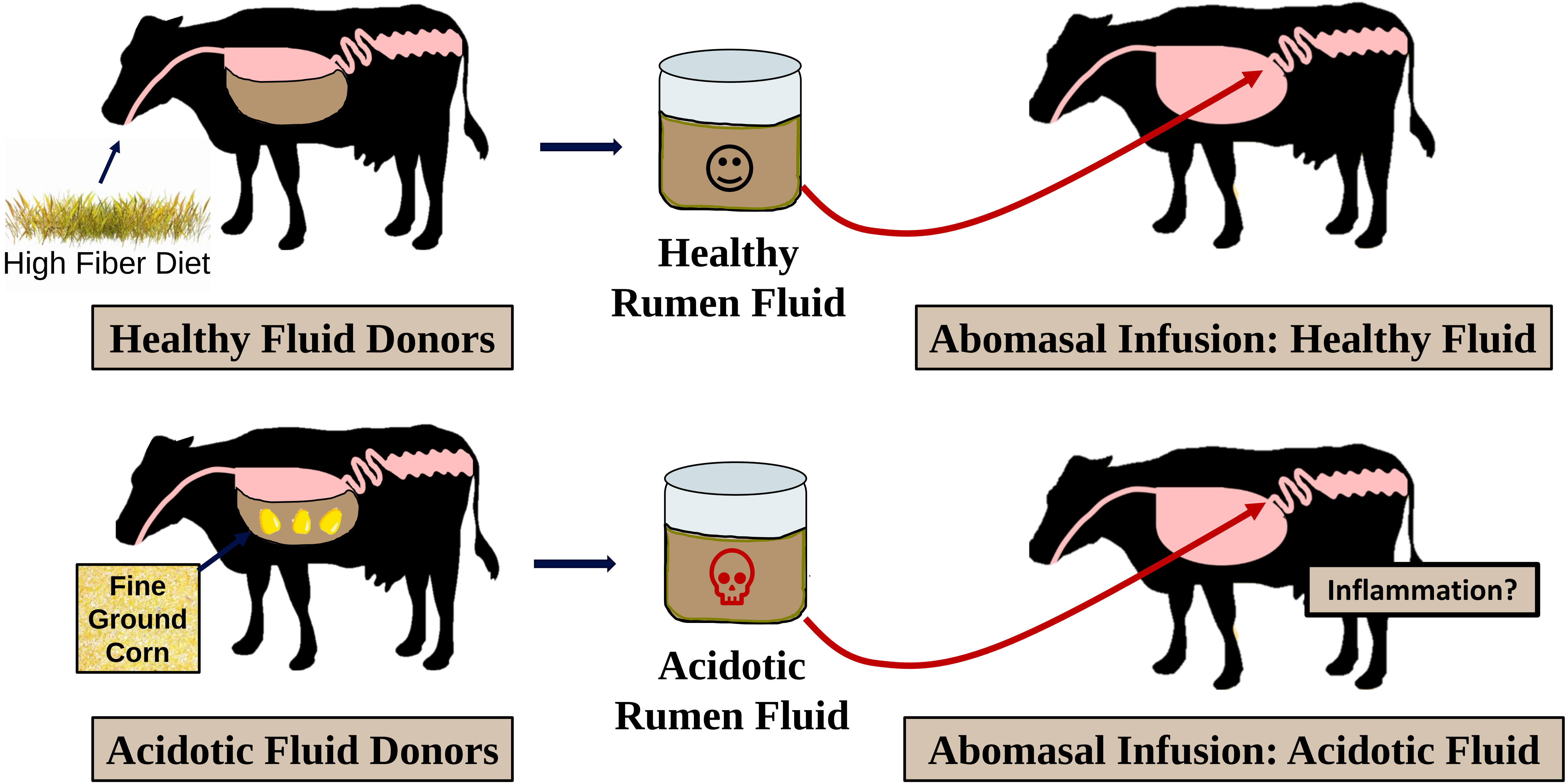
- SARA challenges and high-concentrate feeding induce post-ruminal damage in cows and small ruminants:
    - Decreased tight junction proteins, goblet cell loss, increased cytokine gene expression, etc.
    - Lai et al., 2022; Tao et al., 2014; Samo et al., 2020
- Acidotic rumen fluid contains a plethora of potentially noxious compounds such as ethanol, endotoxin, and bioactive amines (e.g., histamine) which may contribute to compromised post-ruminal barrier function
    - Saleem et al., 2012

Lai, Z. et al.. 2022. "Effects of high-grain diet feeding on mucosa-associated bacterial community and gene expression of tight junction proteins and inflammatory cytokines in the small intestine of dairy cattle." J. Dairy Sci. 105:6601-6615.

Tao, S. et al. 2014. "A high-concentrate diet induced colonic epithelial barrier disruption is associated with the activating of cell apoptosis in lactating goats." BMC Vet. Res. 10:235.

Samo, S. P. et al. 2020. "Supranutritional selenium level minimizes high concentrate diet-induced epithelial injury by alleviating oxidative stress and apoptosis in colon of goat." BMC Vet. Res. 16:462.

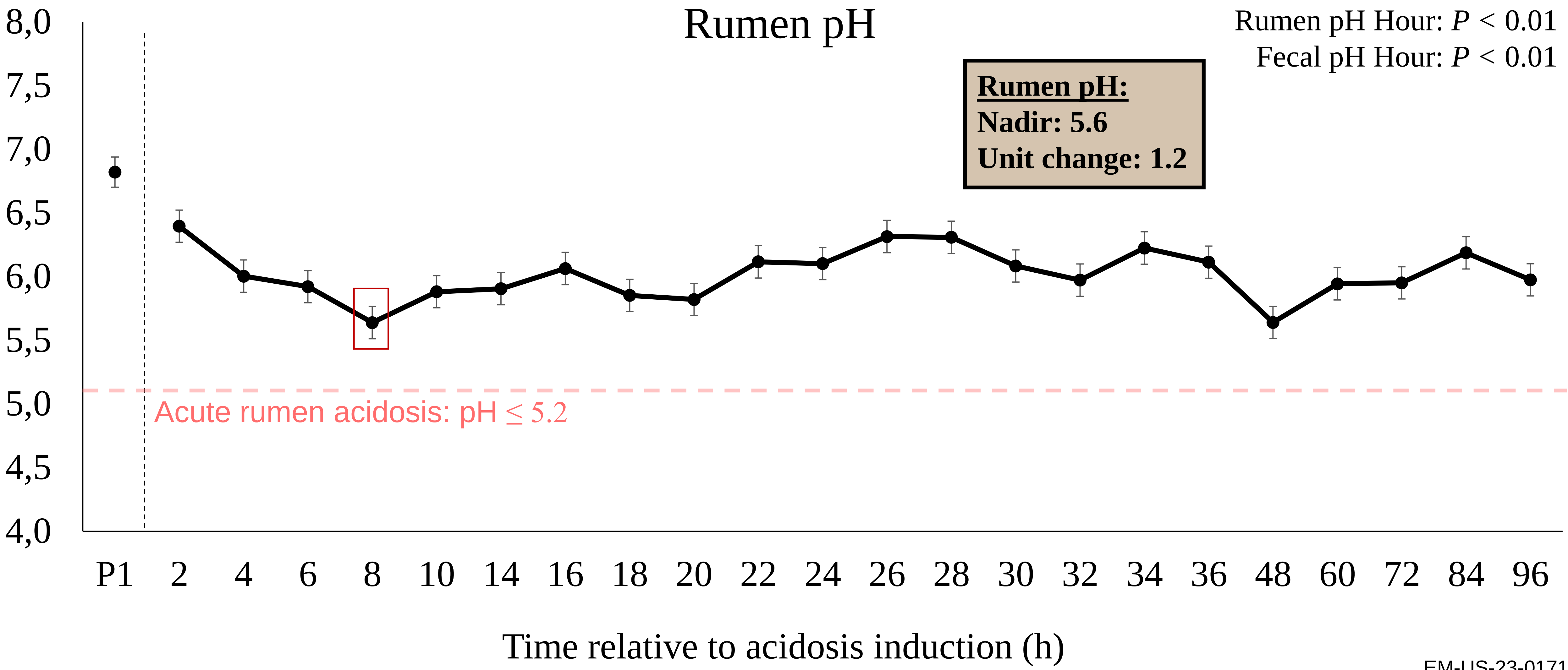
Saleem, F. et al. 2012. "A metabolomics approach to uncover the effects of grain diets on rumen health in dairy cows." J. Dairy Sci. 95:6606-6623.



Dr. Megan Abeyta

Abeyta, M. A. et al. 2023. "Effects of abomasally infused rumen fluid from corn-challenged donor cows on production, metabolism, and inflammatory biomarkers in healthy recipient cows." J. Dairy Sci. 106:4336-4352.

DONORS: Rumen and Fecal pH



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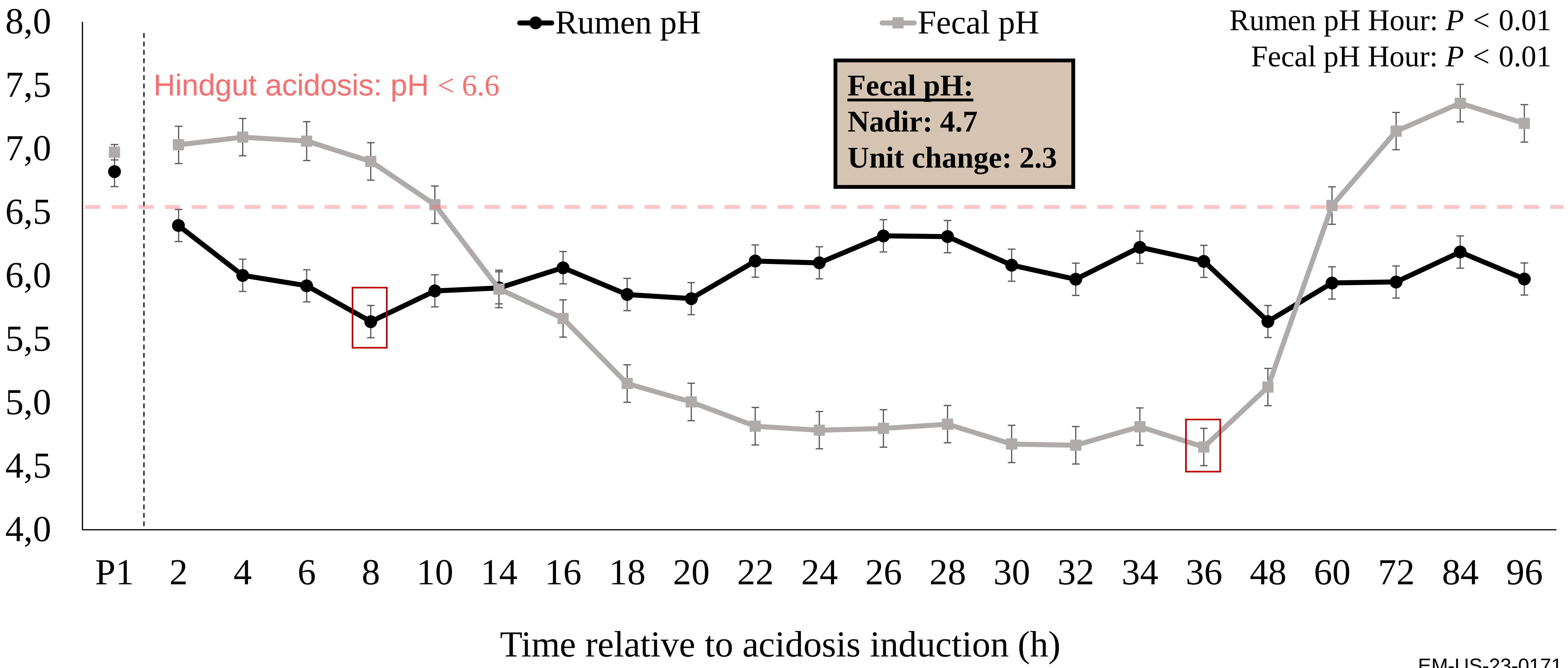

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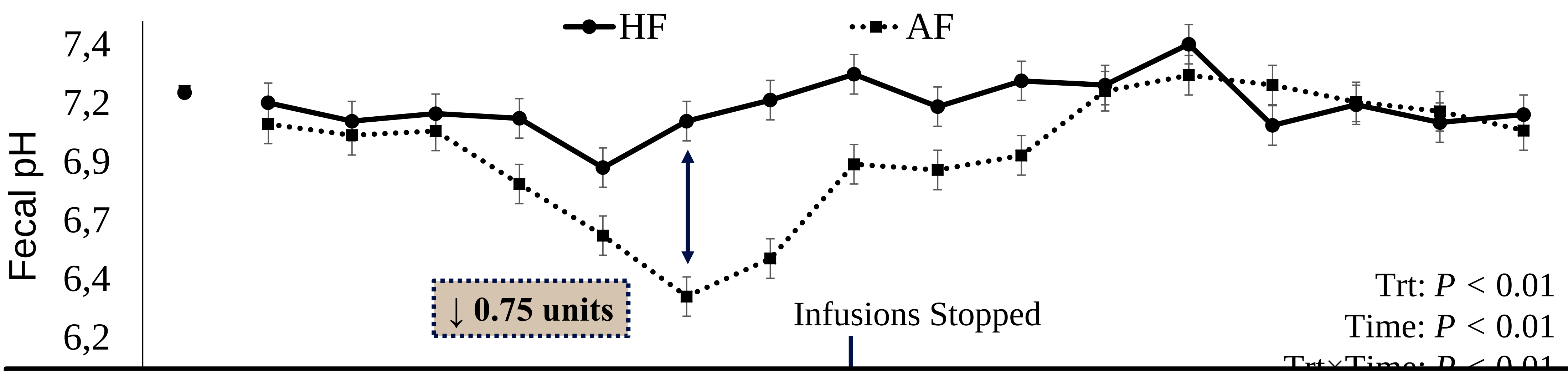

Abomasal infusion of acidotic rumen fluid did not trigger systemic inflammation or compromise productivity

DMI, kg/d	17.5	17.2	0.6	0.77	<0.01	0.47
Rectal Temperature, °C	38.3	38.5	0.1	0.20	0.45	0.52
Inflammatory Biomarkers						
SAA, µg/mL	32.5	32.2	5.2	0.97	0.12	0.35
LBP, µg/mL	3.3	3.3	0.2	0.89	0.61	0.74

[1]HF= healthy rumen fluid infused (5 L/h abomasal infusions of healthy rumen fluid collected from cows eating a high fiber diet; n=5). AF= acidotic fluid infused (5 L/h abomasal infusions of acidotic rumen fluid collected from corn-challenged donor cows; n=5).

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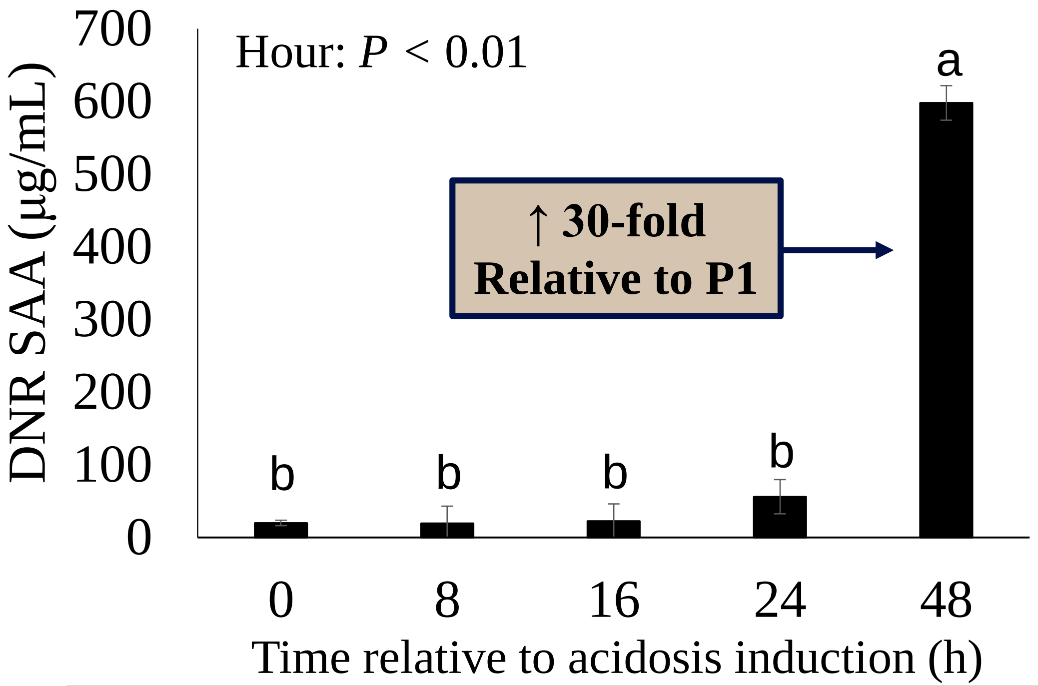
Abeyta, M. A. et al. 2023. "Effects of abomasally infused rumen fluid from corn-challenged donor cows on production, metabolism, and inflammatory biomarkers in healthy recipient cows." J. Dairy Sci. 106:4336-4352.

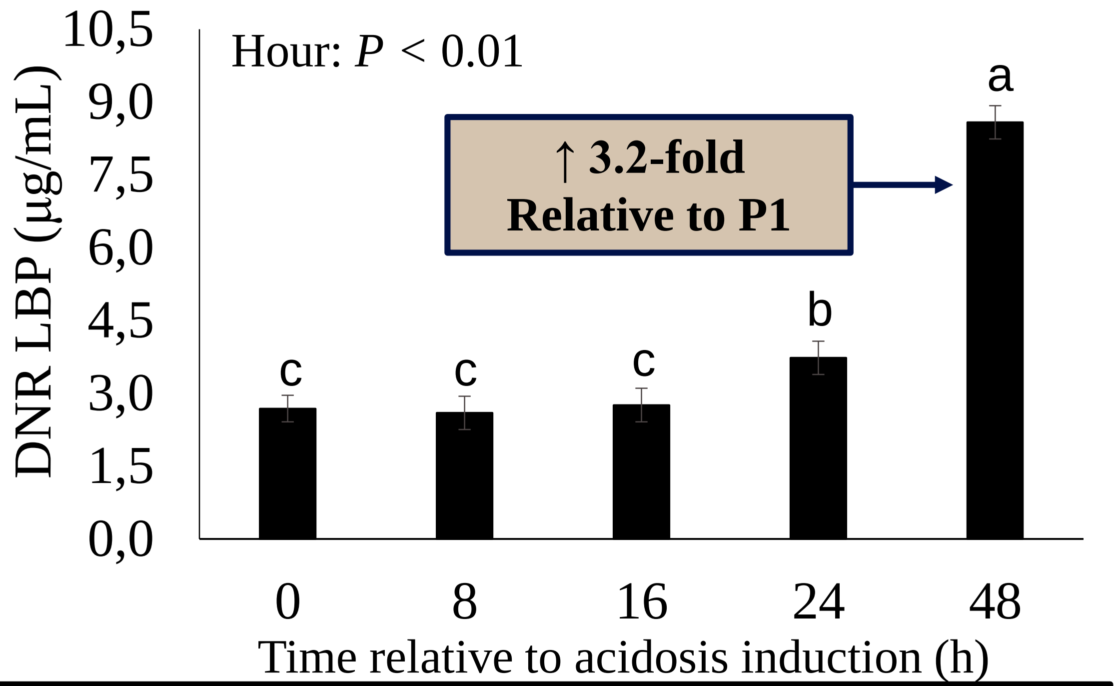
What explains the absence of systemic inflammation in recipient cows?

- Induction of acute rumen acidosis was unsuccessful
  - Target threshold for rumen pH was not achieved
    - Would start collections after 4/8 cows reached a rumen pH of <5.2 (a previously defined threshold for acute rumen acidosis; Owens et al.,1998)
  - Insufficient quantity of rumen fluid obtained from donor cows
    - 7 L of fluid collected from each cow every other hour
    - Collections ended after 28 h due to insufficient fluid
- Further investigation is needed to understand the consequences of acidotic rumen fluid on post-ruminal gut integrity

Owens, F. D. et al. 1998. “Acidosis in cattle: A review.” J. Anim. Sci. 76:275.

Inflammatory response in Donor cows





Temporal pattern of inflammation aligns with nadir in fecal pH suggesting hindgut pathology
HOWEVER, the severity of HGA observed is highly unlikely to occur in on-farm settings

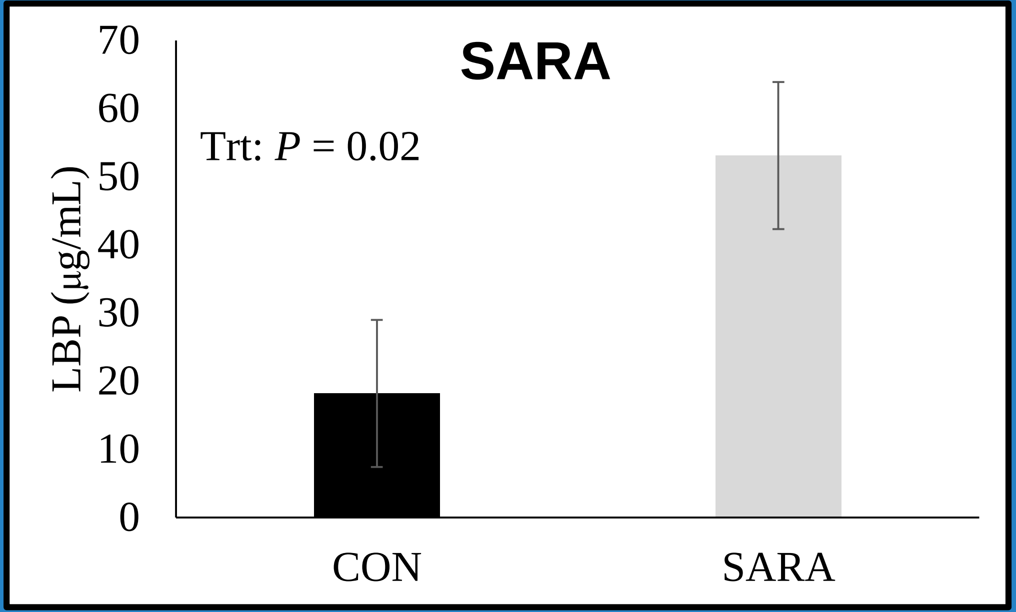
Abeyta, M. A. et al. 2023. "Effects of abomasally infused rumen fluid from corn-challenged donor cows on production, metabolism, and inflammatory biomarkers in healthy recipient cows." J. Dairy Sci. 106:4336-4352.

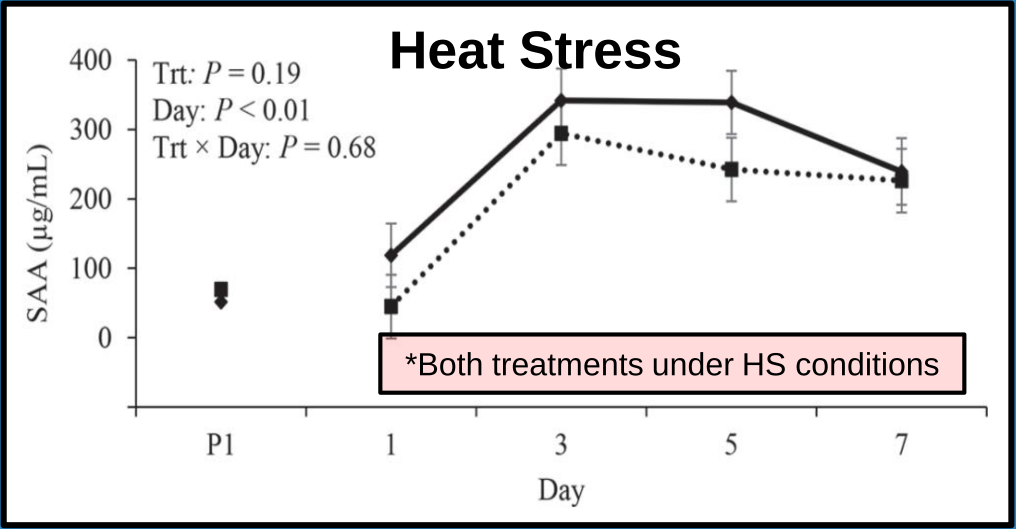
Summary

- Isolated hindgut acidosis does not appear to induce systemic inflammation or compromise productivity
- Rumen acidosis causes leaky gut/inflammation
  - Site of inflammation still unknown
  - Appears to be situation dependent (i.e., stacked stressors, diet, etc.)
  - Noxious substances within acidotic rumen fluid may negatively impact post-ruminal barrier function
    - Study limitations prevented full evaluation of this hypothesis

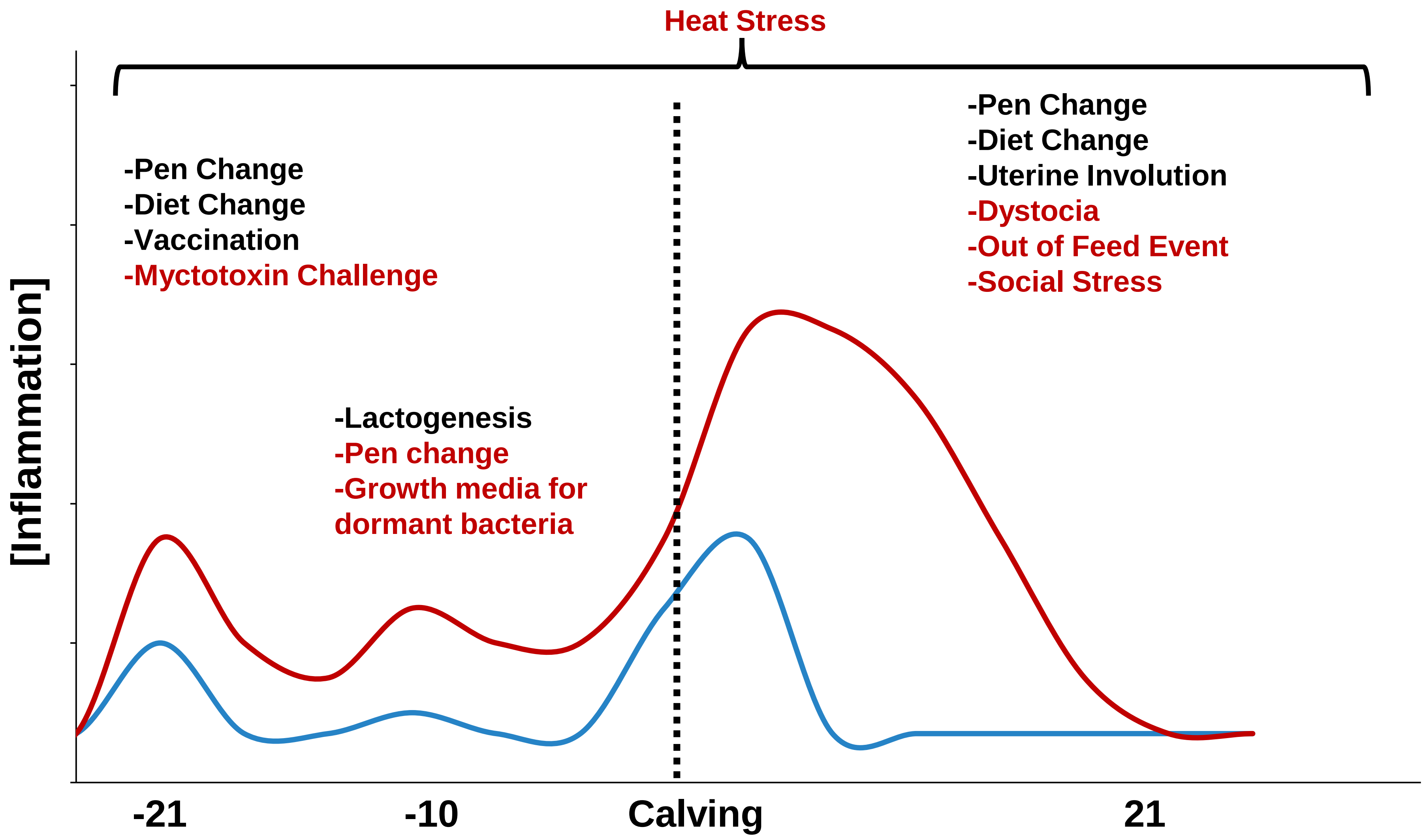
- Regardless of where along the GIT hyperpermeability occurs, there is merit in implementing strategies that support gut health

- **Reminder**: Leaky gut is only one of the many pathologies contributing to systemic inflammation





Inflammatory Triggers Around Calving



Questions??

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