Immunity and the transition cow – role of metabolic imbalances

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Periparturient immunosuppression

1. High incidence of mastitis. 25% of coliform mastitis cases occur in first 2 wks of lactation.
2. Clinical manifestation of chronic disease; Johne’s, Salmonellosis after calving.
3. RETAINED PLACENTA, METRITIS, ENDOMETRITIS DUE TO POOR IMMUNE FUNCTION!!

137 Holstein Cows

- Lymphocyte IgM Production

- Neutrophil Iodination

Detilleux et al., 1995
WHY ARE DAIRY COWS SO IMMUNE SUPPRESSED AROUND THE TIME OF CALVING???

Hormones?

Metabolic stress?
Plasma Progesterone (ng/ml)

Plasma Estrogen (ng/ml)

Time Relative to Parturition (d)

Plasma Cortisol (ng/ml)

Horst and Jorgensen, 1982

Horst and Jorgensen, 1982
Major Metabolic Challenges facing the Transition Cow

1. Negative Energy Balance
2. Mineral Imbalances (Ca, P, Mg, Trace)
3. Vitamin Depletion

Effect of Ketosis on Immune Cell Function

1. Fatty Infiltration of Liver could reduce Acute Phase Protein Response
2. Failure to produce glucose needed to fuel immune response.
3. Ketone bodies, free fatty acids in blood
Production of Interferon by immune cells isolated from cows in differing states of energy balance.

Stimulated cells with New Castle’s Disease Virus

<table>
<thead>
<tr>
<th>Condition</th>
<th>NDV</th>
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<tbody>
<tr>
<td>Normal cows</td>
<td>980+ 400</td>
</tr>
<tr>
<td>Subclinical ketosis</td>
<td>210+ 55</td>
</tr>
<tr>
<td>Ketosis</td>
<td>84 + 32</td>
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Kandefer-Szersen, et al., 1992

Negative Protein Balance??

- lasts 2-4 wks in early lactation
- Glutamine is a major source of energy for many tissues of the body
  - especially immune cells.
Meijer et al., 1995
Fixing Energy and Protein Balance

**Energy**

High Straw diets to keep cows hungry?  
Get rid of fat cows??  
Propylene glycol or glycerin drenches?  
Additives (Yeast, Choline, niacin, B-vitamins??)

**Protein**

Make sure you are getting enough MP into cows  
Use of rumen bypass methionine, lysine

Milk Fever = The Gateway Disease

**Reduces muscle function**

= more mastitis  
= more displaced abomasum

**Reduces feed intake**

= more ketosis/fatty liver  
= more displaced abomasum

**Reduces immune function**

= more mastitis  
= more retained placenta
Incidence of hypocalcemia in USA confinement herds

- Normal: 0% (0.5% of cases)
- Subclinical: 25% (0.7% of cases)
- Milk Fever: 54% (2% of cases)

Incidence of hypocalcemia in USA confinement herds

- 1st Lactation: 0.50%
- 2nd Lactation: 0.55%
- ≥3rd Lactation: 0.60%

Incidence of high NEFA levels

- Ca < 8.0 mg/dl: 0.70 mM
- Ca ≥ 8.0 mg/dl: 0.90 mM
Clinical exam findings in 19 milk fever cows vs 19 normal matched cows in same herds (Whiteford and Sheldon, 2005)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Milk fever</th>
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</thead>
<tbody>
<tr>
<td># clinical endometritis</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Diameter of gravid horn</td>
<td>31</td>
<td>49</td>
</tr>
<tr>
<td>Diameter of non-gravid</td>
<td>25</td>
<td>39</td>
</tr>
<tr>
<td># animals with a CL</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

EFFECTS OF HYPOCALCEMIA AND MILK FEVER ON DISEASE RESISTANCE

1. Lack of muscle contraction
   - impairs teat sphincter closure
   - failure to expel contents of uterus after calving

2. Reduction in Immune Cell Response to Stimuli
   - Calcium is the “second messenger” of immune cells
Signal transduction in immune cells

A rise in intracellular Ca acts as the second messenger during immune cell activation.

Normal Lymphocyte activation

Cytokine, antigen, or bacterial cell wall
Normal Lymphocyte activation

Cytokine, antigen, or bacterial cell wall

Endoplasmic reticulum

\[ \text{IP}_3 \]
Normal Lymphocyte activation

Cytokine, antigen, or bacterial cell wall

Endoplasmic reticulum

IP₃

Ca²⁺
Normal Lymphocyte activation

Cytokine, antigen, or bacterial cell wall

Antibody, Antibacterial peptide production, etc.

Endoplasmic reticulum

[Ca^{2+}]_i response to activation before and after treatment of Milk Fever

Fold increase in Fluo-4/Fura red
Lymphocyte activation during Hypocalcemia

Cytokine, antigen, or bacterial cell wall

Endoplasmic reticulum

Ca^{++}

Ca^{++}

Ca^{++}

Ca^{++}
Lymphocyte activation during Hypocalcemia

Cytokine, antigen, or bacterial cell wall

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IP$_3$

Ca$^{++}$

Ca$^{++}$

Ca$^{++}$

Ca$^{++}$
Lymphocyte activation during Hypocalcemia

Cytokine, antigen, or bacterial cell wall

Endoplasmic reticulum

Ca++

IP_3-R

Antibody, Antibacterial peptide production, etc.
A. pH=7.35 Normal Mg
B. pH=7.45 Normal Mg
C. pH=7.35 Hypomagnesemia

Is this cow immune suppressed?

Gunnink, 1983, Vet Q J
Immunological Theory of Retained placenta

1. Association between RP and use of glucocorticoids to induce calving:
   - immune suppression induced by glucocorticoids?

2. Vitamin E and Se deficiency increase RP and mastitis.
   - Well known that neutrophil function is reduced by Se and Vit E deficiency.

Could Retained Placenta be due to reduced neutrophil function?
Immunological Theory of Retained placenta

1. **Association between RP and use of glucocorticoids to induce calving:**
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Could Retained Placenta be due to reduced neutrophil function?
Plasma IL-8 level is lower in RP cows.

Interleukin-8 is a cytokine responsible for recruiting neutrophils to the site of an infection.
Immune Suppression and Uterine Health

Kim et al., 2005. Leukocytes from cows diagnosed with endometritis (cloudy discharge and enlarged uterus at 4 weeks post-calving) exhibited poor phagocytic activity at -1, 1, 2, 3, and 4 wks around calving.

Urton et al., 2005. Cows developing metritis (first 3 wks of lactation) had spent 22 minutes / day less time eating than cows that would have a healthy uterus.

- every 10 minute decrease in feeding time doubled chance for metritis!! (75 min or less = threshold)

Hammon et al., 2006

- Studied 83 cows going thru calving period
- Blood samples weekly to assess neutrophil function
- Cows examined for metritis first ten days of lactation - foul smelling, watery, brown discharge with or without a fever
- Endometritis diagnosed at 28 days post calving based on uterine wash cytology
B-hydroxybutyrate and Metritis

Metritis = fetid discharge or purulent discharge at 3 to 7 DIM with or without fever

Nonesterified Fatty Acids and Metritis

Metritis = fetid discharge or purulent discharge at 3 to 7 DIM with or without fever
Neutrophil Function and Metritis

Metritis = fetid discharge or purulent discharge at 3 to 7 DIM with or without fever

Disease effect, P < 0.01

Neutrophil Function and Uterine Health

Endometritis

(n=13)

Affected

Not Affected
Dry Matter Intake and Metritis

Metritis = fetid discharge or purulent discharge at 3 to 7 DIM with or without fever

Disease Effect, P < 0.01

Nutritional Immunology

Order of Importance of nutrients to Immune system

Energy
Protein
vitamin A
vitamin E
Copper, Zinc, Selenium
IRON
Granulocyte Colony Stimulating Factor (G-CSF)

Cytokine (hormone) released by endothelium, macrophages and other immune cells in response to inflammation or infection.

G-CSF acts on stem cells within the bone marrow causing them to proliferate and differentiate into new granulocytes, primarily neutrophils, for release into the bloodstream.
Kimura et al., 2014  Effect of G-CSF bound to polyethylene glycol (PEG rbG-CSF) on total polymorphonuclear neutrophil number. One dose administered 6 days before calving and one 24 hrs after calving.

Kimura et al., 2014  Effect of G-CSF bound to polyethylene glycol (PEG rbG-CSF) on the percentage of myeloperoxidase released from stimulated neutrophils
Vaccinating dry and fresh cows

• Cow is immune suppressed for up to 2 wks on either side of calving.

• Reduces response to any vaccine administered at this time.

Vaccinating dry and fresh cows

• Since highest risk of disease (mastitis, Salmonellosis) is at calving vaccines must be given before the cow is at risk.

• My opinion for mastitis vaccines
  – 2 weeks before dry off
  – Boost at dry off
  – Boost again >2 wks before calving
Management factors- close-up and fresh cows
Nordlund et al.- Wisconsin group
Weary & von Keyserlingk- British Columbia
Grant – Miner Institute

• Moving cows into close-up pens ten or fewer days before calving= problems
• Less than 30 inches bunk space / cow
• More than 85% stocking rate in free stalls of close-up and perhaps fresh cows
• Offering fresh feed twice / day – not just push-ups

Figure 1. Milk production of cows categorized by days in the close up pen (Dicup).

Corbett R 2013 Penn State Dairy Symposium
Coetzee, 2015 personal communication