Cow’s Immune Response and Stray Voltage; Overview of Bovine Immunity

Lorraine M. Sordillo
College of Veterinary Medicine
Michigan State University

Health Disorders of Dairy Cows

Disease resistance is dependent on effective immunity.

Immune System Overview

- Several layers of defense
  - Physical barriers (teat end)
  - Innate immune system
  - Adaptive immune system
**Immune System Overview**

- **Innate Immunity (minutes to hours)**
  - Predominant during early infection
  - Activated quickly by numerous stimuli
  - Not augmented by repeated exposure
  - Can eliminate microbes without visible changes to milk or tissues
  - Adequacy of inflammatory response

---

**Inflammation**

*(Essential Innate Immune Response)*

- **Purposes of inflammation:**
  - Eliminate or neutralize source of injury
  - Assist in repairing damaged tissues to normal function
  - Complex and tightly regulated response
  - Initiated by release of mediators from damaged tissue

---

**Inflammatory Response**

- **Recognition of Bacteria**
  - Toxin & bacterial factors (i.e. endotoxin)
  - Pathogen associated molecular patterns (PAMPs)
  - Binds receptors on host cells (Toll-like receptors, TLR)
  - Stimulates production of inflammatory mediators (cytokines & oxylipids)
Sources of Inflammatory Mediators

- Macrophages & lymphocytes
- Various local cell populations
  - Endothelial cells
  - Fibroblasts
  - Epithelial Cells

White Blood Cell Recruitment

Inflammatory mediators: Cytokines, Prostaglandins, & Leukotrienes

Neutrophils are Essential for Protection

- First cells to accumulate into tissues during inflammation
- Up to 97% of cells found in mastitic milk
- Key role in eliminating bacteria
Leukocyte Removal of Bacteria

**Neutrophil Antimicrobial Functions**
- Phagocytosis
- Releases toxic oxidizing agents (H$_2$O$_2$, O$_2^-$, & HOCl) called ROS
- Antibacterial peptides (proteases and lysozymes)
- Neutrophil extracellular traps (NET) formation

*Neutrophil functions dictate the outcome of infection.*

Resolution of Inflammation

**Return tissues to normal function**
- Anti-inflammatory oxylipids and cytokines
- Vascular permeability changes
- Leukocyte infiltration stops
- Local macrophages removes damaged cells
- Growth factors help heal tissues

What if innate defenses of the cow fail to eliminate disease-causing pathogens?
### Immune System Overview

- **Adaptive Immunity (> 96 hours)**
  - Important when innate defenses fail
  - Recognizes specific antigens
  - Heightened reaction upon repeated exposure
  - Ability to recognize self and non-self (MHC)
  - Basis of vaccination protocols

---

### Adaptive Immunity

**Pathogen Recognition**

- **Antigen presenting cells**
  - Macrophages and Dendritic Cells
  - Important link with innate immunity

---

### Adaptive Immunity

**Effector Phase**

**Humoral Immune Response**

- T helper cell
- B cell
- Recognition of same antigen
- Plasma Cells
- Memory

---


Pearson Education, Inc., 2011
Adaptive Immunity

(Effector Phase)

- Re-exposure to pathogen
  - Circulating memory cells differentiate
  - Response is faster and more robust
  - Plasma cells produce 10-100 fold more antibodies

Antibody-Mediated Removal of Pathogens

Neutralization
Opsonization
Activation of Complement System

Effective Immune System

highly interactive & coordinated

Innate Immunity
(Early Response) → Adaptive Immunity
(Later Response)

Disease Resistance

Imurity is Important!
Increased Disease Incidence & Severity  
Periparturient Period

- Physiological transition from late gestation to early lactation
- Majority of all disease occurs the first weeks of lactation
- 50% of all cows experience disease
- Major reason for culling

LeBlanc et al., 2006; Nordlund et al., 2006; BeVeger et al., 2012; Pinedo et al., 2010

Inadequate Innate and Adaptive Immunity

- Transition Cow Immune Dysfunction
- Innate Immunity
  - Cytokines
  - Neutrophils
  - Macrophages
- Adaptive Immunity
  - Antibodies
  - Lymphocyte Function

Uncontrolled Inflammation

- Poor Vaccine Response
- Increased Disease

Common linkage between metabolic and infectious diseases

Uncontrolled Inflammation in Periparturient Cows

- Inflammatory responses help disease progression
  - Inability of local defenses to detect and eliminate pathogen (inadequate neutrophil function)
  - Uncontrolled leukocyte recruitment and activation of inflammatory response (altered cytokine expression)
  - Delicate balance of robust initial response and inflammatory resolution is lost
  - Bystander damage to host tissues
  - **MASTITIS & METRITIS**
Evidence of Immune Dysfunction
*Altered Periparturient Cytokine Expression*
Impact on Neutrophils & Inflammation

**Suppression/Dysfunction**
- Tumor necrosis factor
- Interleukin-1
- Interleukin-4
- Interleukin-10

**Enhancement/Optimization**
- Interferon-γ
- Interleukin-2
- Colony Stimulating Factors (granulocyte/macrophage)


**Cytokines in Milk During Mastitis**
*Robust Initial Response*

![Graph showing cytokine levels over time relative to E. coli challenge](image)

Shuster et al., 1995

**Cytokine Response in Periparturient Cows**
*Coliform Mastitis Challenge*

![Graph showing cytokine levels over time](image)

Evidence of Inflammatory Dysfunction

**Reduced Periparturient Neutrophil Function**

Indicator of bacterial killing capacity

Graph courtesy of Marcus Kehrli, USDA, NADC

Optimal neutrophil function is critical for inflammation

Hoeben et al., 2000. J. Dairy Sci. 87:249

Evidence of Immune Dysfunction

**Reduced Periparturient Neutrophil Function**

Indicator of neutrophil migration


Graph courtesy of Marcus Kehrli, USDA, NADC

Neutrophils are Essential for Uterine Health

- **Retained Placenta**
  - Decreased immune function contributes to placental retention (Beagley et al. 2010. J. Vet. Intern. Med. 24:261)
  - Impaired neutrophil functions leads to development of retained placenta (Gammie, 1984. Vet Q. 6:49)

- **Metritis**
  - Innate immunity is needed postpartum to prevent clinical metritis (Dellmann et al., 2011. Theriogenol. 76:1640)
  - Reductions in neutrophil functions are associated with more clinical disease (Hammon et al., 2006. Vet. Immunol. Immunopathol. 113:21-29)
Ramification of Immune Dysfunction

Reduced Neutrophil Function

Indicator of bacterial killing capacity


Retained Placenta

Healthy

Indicator of migration from blood to tissue


Retained Placenta

Healthy

Indicator of bactericidal activity

Neutrophils are Essential for Mastitis Resistance

- First cells to accumulate into mammary tissues during initial stages of infection (Schalm et al., 1964. AJVR 25:90-96)
- Represents 97% of cells found in mastitic milk (Paape et al., 1963. J. Dairy Sci. 36:1211-1216)
- Key role in eliminating bacteria (Jain et al., 1971. AJVR 32:1955-)

Ramifications of Immune Dysfunction

Bacterial Growth During Mastitis

- Epidemiological Evidence of Coliform Mastitis
  - 25% cases occur by first 2 weeks lactation
  - 45% cases occur by first 4 weeks lactation
  - 60% cases occur by first 8 weeks lactation

Smith et al., 1985, J. Dairy Sci. 68:402
Hogan et al., 1989, J. Dairy Sci. 72:1747
Factors that Impact Immune Dysfunction

- Genetic variation based on heritability estimates (Detilleux et al., J Dairy Sci. 77:2640, 1994)
- Nutritional Factors (Sordillo, J Dairy Sci. 99:4967, 2016)

The nexus between nutrient metabolism, oxidative stress, and inflammation in transition cow
L.M. Sordillo, & V. Mavangira

Increased Need:
- Energy
- Proteins
- Glucose
- Minerals
- Vitamins

Altered Nutrient Metabolism
- Transition from late lactation to dry period
- Transition from late gestation to early lactation
- Fetal demands
- Onset of copious milk production
- Linked to changes in nutrient requirements
Altered Nutrient Metabolism in Periparturient Cows
(Negative Energy Balance)

Nutrient Requirements

Dry Matter Intake

Altered Nutrient Metabolism
Negative Energy Balance

Energy Ingested
Energy Required

Babcock Institute

Metabolic Adaptations to NEB

• Lipid and protein mobilization
• Alterations in blood lipids
• Increased nonesterified fatty acids (NEFA)
• Increased beta-hydroxybutyrate (BHB)

Suriyasathaporn et al., 2000
Consequences of Altered Nutrient Metabolism

Compromised immunity increases disease susceptibility

**Periparturient Period**

<table>
<thead>
<tr>
<th><strong>Observed Effect</strong></th>
<th><strong>Reference</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces antibody formation (van Knegsel, 2007) &amp; neutrophil functions</td>
<td></td>
</tr>
<tr>
<td>Compromised lymphocyte functions (Lacetera et al., 2004), impaired cytokine production (Sordillo et al., 2005), reduced neutrophil function (Giribello et al., 2000)</td>
<td></td>
</tr>
<tr>
<td>Compromised functions (Hammon et al., 2006)</td>
<td></td>
</tr>
<tr>
<td>Impaired lymphocyte functions (Lacetera et al., 2004), impaired cytokine production (Scalia et al. 2006), reduced neutrophil function (Ster et al. 2012)</td>
<td></td>
</tr>
<tr>
<td>Impairs neutrophil function (Grinberg et al., 2008)</td>
<td></td>
</tr>
<tr>
<td>Alters cytokine production (O’Boyle et al., 2006) &amp; reduces lymphocyte functions</td>
<td></td>
</tr>
<tr>
<td>Increases disease susceptibility and affects innate and acquired immune parameters</td>
<td></td>
</tr>
<tr>
<td>Increases disease susceptibility and affects innate and acquired immune parameters</td>
<td></td>
</tr>
</tbody>
</table>

Elevated NEFA

Body Condition Score

Ketosis (BHB levels)

Micronutrient Deficiencies (Vitamins & Minerals)

Decline in Antioxidant Micronutrients During the Periparturient Period

Plasma Vitamin E

Plasma Vitamin A

Goff and Stabel. 1998 J. Dairy Sci. 71:3193

Micronutrients and Bovine Immunity

**Micronutrient**

**Observed Effect**

- **Selenium**
  - improves neutrophil function; decreases severity of mastitis
- **Vitamin E**
  - increase neutrophil killing; decrease clinical mastitis
- **β-carotene**
  - increase killing by phagocytes; increase lymphocyte proliferation
- **Chromium**
  - improves lymphocyte functions; increased antibody responses
- **Copper & Zinc**
  - deficiency decreases neutrophil functions & increases susceptibility to disease

Metabolic Adaptations During the Transition Period

**Balance is Essential**

Practical Considerations

- **Reduce intense lipid mobilization during the transition period**
  - Minimize reductions in dry matter intake (DMI)
  - Design diets to increase energy without affecting DMI
  - Prevent over-conditioning in the dry period

- **Optimize inflammatory responses and oxidant balance**
  - Reduces sources of stress (heat stress, exposure to pathogens)
  - Micronutrient supplementation (Se, Vitamin E, etc.)
  - Immunomodulators (vaccines, supplements, etc.)

- **Comprehensive Approach to Reduce Metabolic Stress**
  - Monitoring Programs
  - Inclusive of entire dry period and early lactation
  - Early intervention