The Neonatal Calf Immune Response - When Should We Vaccinate?

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Neonatal Immunology
- All food animals are immunocompetent at birth.
- Colostrum supplies immediate specific and non-specific immunity.
- The normal neonate is agammaglobinemic.
- Fetal Calf: Respond to viruses at 90-120 days. >180 days responds to bacteria.
- Usually consider 150 days of gestation breakpoint for immunocompetence

Immunity in the Neonate
- Essentially all components of the immune system develop in utero in domestic animals
- Less efficient than in the adult
- Gradually improve over the first weeks of life

Maternal Immune Suppression
- Offspring immature immune system
- Placenta
- Maternal immune system
- Environment
- Infection
- Vaccination
- Prevent immunological rejection of fetus

Colostral Anti-inflammatory Cytokines
- Th2 cytokines - TGF-beta, IL-4, IL-10
- Maternal Interference

Credits
- Kuby Immunology
- Immunobiology, 6th edition
- David Topham, University of Rochester

All food animals are immunocompetent at birth. Colostrum supplies immediate specific and non-specific immunity. The normal neonate is agammaglobinemic. Fetal Calf: Respond to viruses at 90-120 days. >180 days responds to bacteria. Usually consider 150 days of gestation breakpoint for immunocompetence Immunity in the Neonate
- Essentially all components of the immune system develop in utero in domestic animals
- Less efficient than in the adult
- Gradually improve over the first weeks of life
Anti-inflammatory factors from Colostrum keep the Gut from Overreacting

Immunodeficiency in the Neonate - Innate Response
- Humoral elements ↓-complement and IFN
- Neutrophils
  - ↓ Phagocytic Activity & Oxidative Burst
  - ↑ Recovered with Colostrum in vivo and in vitro
- Monocytes
  - Slightly lower
  - Phagocytic activity is normal but Oxidative Burst ↓
- Natural Killer Cells
  - Lower?

Immunodeficiency in the Neonate-Acquired
- Decreased acquired immune mechanisms
  - Decreased lymphocyte responsiveness
  - ↓ MHC II- ↓ Antigen presented to T cells
  - Born with no memory T or B cells
  - Antibody production ↓ CD40 ↓ CD40L B-cell differentiation
  - Must obtain antibody from the mother
    - From the colostrum

How Early Can the Calf Respond?

Lymphocyte Development in Calves

Kampen et al Vet Immunol Immunopath 2006 113:53-63

Lymphoid levels for T cells are similar- no gamma delta cells
Intranasal vs Parenteral

- Intranasal- immediate
- Parenteral- delayed
- In all routes between day 4-14 in response

Intranasal studies

- Nasalgen
  - Day old calves
- Onset
  - Conducted in young calves (3-8 days of age)
  - Challenged with virulent strains of IBRV, BVD 1, BVD 2, BRSV, Pasteurella multoidea – 21 to 28 days post-vaccination
- BRSV Nasal studies 14 day old calves-Inforce 3
- BVDV- 3-4 week old calves- Roth, Ridpath study

Intranasal Vaccines

- Beware of sensitive diagnostics-PCR
- Not sure how long animals will be PCR positive
- Animals IBR or BRSV positive from vaccine
- Booster with parenteral vaccine

Neonates-Acquired Immunity

Calves vaccinated at 7 days of age- CMI response but no Ab


Overcoming Neonatal Immunosuppression

- Adjuvants- increase immune response and Th1 response
- Antigen- Danger signal Omp but no LOS or LPS- too much inflammation
**Immunomodulators**

- Inactivated organisms
  - *Propionibacterium acnes (PA)* gram-positive
  - Parapoxvirus ovis- (PPVO) orf virus
- Innate Immunity-
  - Neutrophil, Macrophage phagocytosis ↑
  - Microbial killing ↑
- Adaptive Immunity-
  - Not as clear-
    - no increase in T or B cell cytokines PA,
    - ↑ T cell cytokines PPVO

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**The "common mucosal immune system"**

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**Mucosal Immunology**

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**Epithelial Cells and Mucosal Immunity**

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**Mucosal Immunity**

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**Organization of Mucosal Inductive Centers**
Organization of MALT

Mucosa Associated Lymphoid Tissue (MALT)

Secretory IgA is the most important Immunoglobulin for Mucosal Immunity

Intraepithelial lymphocytes

Maternal Antibody Interference

• Antibody produced by the dam
• Transferred via the colostrum to the calf

Maternal Interference

THE WINDOW OF SUSCEPTIBILITY TO HERD INFECTIONS

MATERNAL DERIVED IMMUNITY

FULL IMMUNE COMPETENCE

Colostral IgG half-life is 17 to 32 days
Half Life of Maternal Antibody

<table>
<thead>
<tr>
<th>Virus</th>
<th>Half Life (days)</th>
<th>Time to 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBR</td>
<td>12.7 ± 5.5</td>
<td>65.1 ± 37.8</td>
</tr>
<tr>
<td>BVDV1</td>
<td>20.5 ± 6.2</td>
<td>117.7 ± 37.7</td>
</tr>
<tr>
<td>BVDV2</td>
<td>20.5 ± 12.4</td>
<td>93.9 ± 61.9</td>
</tr>
<tr>
<td>PI3</td>
<td>21.7 ± 9.6</td>
<td>183.8 ± 100.0</td>
</tr>
<tr>
<td>BRSV</td>
<td>28.1 ± 19.4</td>
<td>200.2 ± 116.7</td>
</tr>
</tbody>
</table>

Kirkpatrick et al Bov Prac 35:47-55, 2001

Number of Seropositive Calves Responding to MLV

<table>
<thead>
<tr>
<th>Virus</th>
<th>Seropositive calves responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>BVDV1</td>
<td>3/8 (Titers 4-16)</td>
</tr>
<tr>
<td>BVDV2</td>
<td>3/4 (Titers 4-8)</td>
</tr>
<tr>
<td>BRSV</td>
<td>0/23 (Titers 4-128)</td>
</tr>
</tbody>
</table>

IBR were all seronegative PI3- no animals responded to vaccine
Kirkpatrick et al Bov Prac 35:47-55, 2001

Maternal Interference-Mechanism

- Booster Vaccine
- Secondary Response Mat Ab+
- Primary Response Mat Ab-

Primary Response Mat Ab- Booster Vaccine Secondary Response Mat Ab+

Vaccine Vulnerability to Antibody

- Size of Antigenic Mass
- Antigenic Agent
- Type of Adjuvant used in the Vaccine

Humoral Effector Mechanisms against Viruses

NEUTRALIZATION

- Adhesion to host cells blocked
- Prevents infection
- Virus uncapping blocked
- Prevents viral gene expression

Size of Antigenic Mass

- Conventional MLV Vaccine in naive animals
- Small antigenic mass
- Vaccine virus migrates via circulation to target cells of an animal
- Vaccine virus replicates in animal cells
- Stimulates a strong immune response
MODIFIED-LIVE VACCINES

INACTIVATED (KILLED) VACCINES

Size of Antigenic Mass
- Conventional injectable MLV vaccine in the presence of humoral antibody
- Small antigenic mass
- Vaccine virus is neutralized by antibody
- Vaccine virus fails to reach and infect animal cells
- Vaccine virus fails to replicate
- Vaccine virus fails to stimulate immune response

Maternal Interference
- Mucosal - Minimal to no interference
- Parenteral - INTERFERENCE

Parenteral Vaccine
- Adjuvants help protect

Maternal Ab and Parenteral Vaccine

Summary

- BVDV response was present as early as 1-2 weeks
- BHV-1, BRSV were inhibited

Maternal Interference

<table>
<thead>
<tr>
<th>BVDV</th>
<th>BHV-1</th>
<th>BRSV</th>
<th>Maternal Interference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>None</td>
</tr>
</tbody>
</table>

What About Bacterins in Cattle?

- Site specific- Only if you have problem- many of these management related (nutrition, sanitation, environment)- efficacy is variable
- Clostridials
- Respiratory Pathogens
- Leptospira
- Salmonella

What About Bacterins in Cattle?

- Clostridials- Exception to the bacterin age: Calves less than 3 weeks will respond to clostridial toxoids
  - C. tetani- site specific
  - C. perfringens C & D- site specific-young calves will respond
  - C. perfringens A- Some people swear by it, other swear at it
- Clostridial 5-8 way vaccines- give to animals 3-4 months of age and booster
- annual if problem- can be used in cows if C perfrigens type C scours is a problem

What About Bacterins in Cattle?

- Respiratory Pathogens
  - Mannheimia hemolytica (M.hemolytica)-typically over 3 months of age- normal microflora
    - Parenteral vaccines
      - Subunit vaccines that contain leukotoxin and OMP- avoid endotoxin
      - Live whole cell?
      - Killed whole cell???
    - Intranasal- Like concept mucosal immunity and competitive exclusion?? too early to tell
    - Efficacy- better with leukotoxin- fair at best
- Pasturella multicipa (P.multicida)-typically over 1-6 months of age- normal microflora-dairy calves big problem
  - Parenteral vaccines
    - Cross protection from M.hemolytica H.somni subunit vaccines that contain leukotoxin and OMP- ??
    - Live whole cell?
    - Killed whole cell???
    - Killed whole cell- Salmonalla typhimurium mutant R-17 Bacterin- toxicid- Endovac
  - Intranasal- Like concept mucosal immunity and competitive exclusion?? too early to tell
  - Efficacy- marginal at best
What About Bacterins in Cattle?

- Respiratory Pathogens
  - *Histophilus somni* (H.somni)-typically over 3 months of age- not normal microflora- California calf study isolation of H.somni was the highest risk factor for BRD
  - Parenteral vaccines
    - Subunit vaccines that contain leukotoxin and OMP- outer membrane proteins- avoid LOS endotoxin- only available in Canada
    - Killed whole cell - disaster- LOS endotoxin
  - Efficacy- good subunit, otherwise don’t recommend it unless there is a known problem- give it as the only bacterin if use whole cell

- Mycoplasma bovis (M.bovis)-typically over 1 month of age- normal microflora
  - Parenteral vaccines
    - Autogenous Killed whole cell???
  - Efficacy- marginal at best usually poor

- Leptospira
  - Environmentals- L.interrogans serovars pomona, hardjo, canicola, icterohaemorrhagiae. L. kirshneri serovar grippotyphosa- standard 5-way lept-
    - Two doses prebreeding vaccine
    - Revacinate annually- most alum based adjuvant- memory is poor
  - Cattle reservoir-Leptospira borgpetersenii serovar hardjo (Type:hardjo-bovis)(HB) Once infected difficult to clear all the animals- reservoir for herd
    - Vaccinate young stock??? 1-2 months of age Protect against reservoir
    - Can calves become colonized right after birth?

- Salmonella
  - MLV- *Salmonella dublin*-EnterVene-d-
  - Killed whole cell- *Salmonella typhimurium* mutant R-17 Bacterin-toxoid- Endovac
  - Subunit Siderophore Receptor and Porin (SRP) *Salmonella newport*
  - Salmonella is a management problem- nutrition and environment
  - Efficacy- variable

- Endotoxin Stacking and Vaccines (ranked most reactive to least reactive)
  - E.coli Mastitis vaccines
  - Pinkeye (Moraxella bovis)- Whole cell LOS very reactive
  - Histophilus somnus Whole cell LOS very reactive
  - Salmonella-Whole cell LPS
  - Scour vaccines E.coli-Whole cell LPS
  - Mannihemia hemolytica- Whole cell LPS
  - Pasturella multocida
  - Subunit vaccines- no issues, leukotoxin, fimbraie. OMP
  - If need to use more than one- administer on other side of the neck
What is your recommended vaccine protocol from birth to mature cow?

**Heifers**
- 4-5 months old: MLV IBR-BVD-PI3-BRSV-Heifers-LEPTO 5
- 7-9 months old: MLV IBR-BVD-PI3-BRSV-Heifers-LEPTO 5, must be 60 days prior to first breeding

**Calf Viral Respiratory-Reproductive Development Programs**

**Number Of Immunizations**
- MLV 2 to 3 doses by time 8 to 10 mos
- Inactivated 2 to 3 doses by time 8 to 10 mos
- Combination MLV 1 to 2 followed by Inactivated 1 dose

**BVDV Vaccination-Fetal Protection**
- Prior to breeding
- MLV- need in heifer development
- Inactivated-
  - Cattlemaster has PI claim
  - Virashield has been shown to give fetal protection

**The Components of Immunity in the Calf**

<table>
<thead>
<tr>
<th>Time of Susceptibility</th>
<th>Innate Immunity</th>
<th>Passive Immunity</th>
<th>Active Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception</td>
<td>Passive (maternal)</td>
<td>Innate immunity</td>
<td>Active immunity</td>
</tr>
<tr>
<td>Birth</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Weaning</td>
<td></td>
<td></td>
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<tr>
<td>Puberty</td>
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**Summary**
- Neonate immune system influenced by maternal hormones
- Neonatal immune system influenced by colostrum
- Immune response delayed both innate and acquired
- Adjuvants will help overcome neonatal immunosuppression

**Summary**
- Neonate responds to viral antigens very early 3-7 days intracellular T cell response
- Neonate responds to bacterial antigens later (after 21 days)-extracellular antibody response
Harvey Dunn (1886–1952) Prairie is My Garden, South Dakota Art Museum