Immune Development in the Bovine Neonate

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Outline

- Brief overview of the immune system
- Immune development in the calf
  - Prenatal
  - Neonatal
- Role of colostrum in neonatal immunity
- Role of nutrition in neonatal immunity
- Vaccination in the face of colostral (maternal) antibody

Immune System: Overview

- Innate immune response
  - Immediately and always active
  - Doesn’t improve with repeated exposure

- Acquired immune response
  - Takes several days-weeks to be fully active
  - Improves with repeated exposure: “memory”
  - Target of vaccination

Innate Immune Response

- Cells
  - Granulocytes: immediate responders
    - Neutrophils: especially important for bacterial infection
    - Eosinophils: especially important for nematodes (worms)
    - Basophils: help other granulocytes
  - Macrophages (“big eaters”)
    - Kill agents targeted for destruction
      - Phagocytosis
      - Secretes antimicrobial products

Innate Immune Response

- Cells, continued
  - Natural killer (NK) cells
    - Kill virus-infected cells, tumor cells
  - Gamma delta T lymphocytes
    - Similar to NK cells
    - Particularly important in cattle

Innate Immune Response

- Soluble factors
  - Complement
    - Destroys bacteria and other pathogens
    - Targets pathogens for destruction
  - Lysozyme
    - Destroys wall of Gram positive bacteria
  - Lectins
    - Bind to bacterial carbohydrates
    - Target bacteria for destruction

Acquired Immune Response

- Soluble factor: ANTIBODY
  - Antibody: protein molecule that binds specifically to foreign substances
  - Produced by B lymphocytes
  - Immunoglobulin classes
    - IgM: multivalent, produced first
    - IgA: mucosal surfaces (respiratory, gut, mammary gland)
    - IgG: serum, colostrum
    - IgE: anti-parasitic, mediates allergy
Acquired Immune Response

- Cells
  - B cells: produce antibody
  - T cells
    - Cytotoxic T cells
      - Kill infected cells, tumor cells
    - Viral immunity
    - Intracellular infections
    - Helper T cells
      - Modify responses of other cells

- TH1 and TH2 responses are (somewhat) mutually exclusive
  - Strong TH1 → weaker TH2
  - Strong TH2 → weaker TH1

- Infections early in life may impact response to other types of infection later?

All cells influence other cells by release of chemical messages called "cytokines"

- Cytokines...
  - Activate the immune response
  - Direct specific types of responses
    - Anti-viral, anti-bacterial, anti-parasitic
  - Contribute to inflammation and sometimes death
    - "Septic shock"

Different types of helper T cells stimulate different types of immunity

- T helper type 1 (TH1): intracellular infections
  - Viruses
    - TB, Johnes', Salmonella
  - T helper type 2 (TH2): extracellular infections
    - Bacterial pneumonia
    - E. coli diarrhea
    - Extracellular parasites (worms)
• TH1 cytokines
  – Interleukin 2 (IL-2): T cell proliferation
  – Interferon gamma: activates macrophages

• TH2 cytokines
  – IL-4, IL-5: increase IgA, IgE production
  – IL-10: suppresses TH1 activation

Immune Development, Neonatal Calf

• At birth, calf has no antibody in serum
  – Unless infected before birth

• Other issues
  – Serum complement levels lower than adults
  – Cell functions lower than adults
    • Neutrophils
    • Macrophages
    • T and B cells

Immune Development: Prenatal Calf

• Immune system begins developing before calf is born
  – Thymus (T cell development) evident at 40 days gestation
  – Response to some viruses possible at 70 days gestation
  – By third trimester, can respond to many different infections
  • At birth, see serum antibody titers elevated before colostrum intake

Immune Development, Neonatal Calf

• Immune response of neonatal calf is functional, but naïve and immature

• Colostrum is a solution to this problem

Colostrum

• Colostrum
  – Present in the mammary gland at parturition
  – Once removed from gland, is replaced by milk
  – Contains very high levels of antibody
  – Also contains soluble factors
    • Lactoferrin
    • Also contains maternal cells

• Few days before and after birth, immune responses of calf are suppressed
  – Maternal and fetal steroid production
    • Necessary to initiate parturition
    • Immunosuppressive
Colostrum

- Antibody molecules in colostrum absorbed by calf’s intestine intact
- Absorption only continues for first 24-36 hours
  - Time shortens once calf nurses (“gut closure”)  
  - Feeding something before colostrum could impair absorption of colostral antibodies
- Colostral antibodies persist in serum for 2-6 months

Maternal Cells in Colostrum

- Maternal cells in colostrum migrate across calf intestine
  - Found in calf tissues in first few days after birth
  - Associated with changes in immune development in neonatal calf

Colostrum

- Colostral antibodies also provide protection against intestinal infection
  - Before absorption
  - When secreted back from blood into intestine
- Important for controlling infectious causes of calf diarrhea

Importance of Cells in Colostrum

- Calves receiving colostrum containing maternal cells...
  - Developed ability to activate an immune response sooner
    - Reber et al, 2005
  - Had measurable responses to bovine pathogens at 1 day of life
    - Donovan et al, 2007
- ...as compared to calves receiving colostrum without cells

Adequate colostrum intake is CRITICAL to calf health

- Calves without colostrum are
  - more likely to develop disease
  - more likely to die
  - more likely to fail to reach their potential for growth and production

![Graph](image)
Development of Acquired Immune Response

- Frozen colostrum does not contain whole cells
  - Need fresh colostrum to give cells

- What if you have high antibody titer frozen colostrum, or low antibody titer fresh?
  - Need more research!
  - At this time, must recommend high antibody titer frozen
  - Stay tuned for more information

- Calf can respond to infection in first few days of life
  - Weaker and less effective than adult response
  - Very high levels of colostral antibody will diminish response
    - Newborn calves with failure of passive transfer respond better to infection
      - Still better to get colostrum!

Development of Acquired Immune Response

- “Passive” immunity from colostrum only lasts weeks to months

- Calf develops its own responses during this time

- Newborn immune response has TH2 bias
  - Better antibody production
    - Better protection against extracellular pathogens
      - Most bacteria
      - Some parasites (nematodes)
    - Less effective cell-mediated immunity
      - Less effective against intracellular pathogens
        - Viruses
        - Some bacteria (Johnne’s)
        - Some parasites (coccidia)

Current research focused on ways to improve TH1 responses in neonates

![Graph](image)

**Figure 18.2** Immunoglobulin levels in newborn serum during the first 15 weeks of life indicating the relative contributions of maternal antibody and antibody synthesized by the newborn animal.

From Tizard, 2009
**Nutrition and immunity**

- Well known that nutrient deficiency impairs immunity
  - Protein and energy
  - Fat soluble vitamins
    - Vitamin A, D, E
  - Minerals
    - Copper, selenium, zinc, chromium
- Correct deficiency: improve immune response
- Supplement in excess: not always helpful

**Nutrition and Calf Immunity**

- Newborn Holsteins fed 50% of maintenance energy and protein
  - Decreased lymphocyte response to stimulation
  - Decreased ability to produce antibody following vaccination
- Correction of deficit: responses returned to normal
  
  Griebel et al, 1987

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**Nutrition and immunity**

- Note that newborn calf is born with energy stores that only last a few days
  - Colostrum and milk needed for adequate energy and protein
- Fat soluble vitamins do not cross the placenta
  - Colostrum is rich in fat soluble vitamins
  - Failure of adequate colostrum ingestion leads to deficiency of fat soluble vitamins

**Nutrition and Calf Immunity**

- Effects of energy, protein, and amount fed
  - Calves fed 30% CP, 20% fat at 2.5% BW on DM basis
  - Controls: fed 20% CP, 20% fat at 1.4% BW on DM basis
- Calves on “intensified” diet
  - Lymphocytes produced more nitric oxide
  - Lymphocytes produced less interferon gamma
  - Decreased percent response to stimuli (but same response overall)

  Nonnecke et al 2003, Foote et al 2005

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**Immunity and amount fed**

Nonnecke et al, 2003
Immunity and supplements
(in nursing dairy calves)

- Significance of changes in calves on intensified milk replacer diet?
  - Both interferon gamma and nitric oxide are important in immune response
  - Both can be harmful in excess
- Fewer percent lymphocytes responding to stimuli, but same overall response
  - Cells more efficient?
- Not clear if intensified calves have immune advantage or disadvantage
  - More research needed

- Effect of fish oil supplementation of milk replacer (MR) on immune function
  - 51 Jersey bull calves
  - Fed 23% CP, 18% fat MR with 2% extra fat as either
    - 3:1 corn:canola oil
    - Half corn: canola oil, half fish oil
    - Fish oil only
  - 150 mg vitamin E added
- Calves fed to gain 200, 400, then 600 g/d in weeks 1-2, 3-4, and 5-6

Ballou and DePeters JDS 91:3488, 2008

In a similar study, white blood cells from Jersey calves fed a high plane of nutrition showed better killing of pathogenic bacteria than calves fed a low plane of nutrition.

Ballou et al
Effect of fish oil supplementation on response to vaccination (d.0) and booster (d. 14)

- Although some measureable effect of diet on some immune functions, feeding fish oil did not correlate with changes in health

- No effect of fish oil supplementation on growth or occurrence of diarrhea or respiratory disease

- Effect of yeast culture on calf health and immunity
  - 512 Holstein calves divided into 2 groups
  - 2% yeast culture (Saccharomyces cerevisiae) in grain
  - No yeast culture
  - Grain fed free choice through d. 70
  - Pasteurized milk fed through d. 60

- Diets with fish oil had small effect on ability of white blood cells to engulf bacteria
- No difference between milk replacer with or without fish oil on antibody response to vaccination
  - Decreased response to booster on blend diet

- Trend toward increased bacterial phagocytosis and killing by WBC of calves fed yeast culture
- No effect on antibody production to vaccination
• Effect of pomegranate extract on calf health and immunity
  – 67 Holstein calves divided into 3 groups
  • No pomegranate extract (POM) in starter
  • POM added at 5 g/d
  • POM added at 10 g/d
  – Pasteurized milk fed through d. 60
  – Started offered for entire study (through d. 70)
  Oliveira et al, JDS 93:4280, 2010

• Calves fed yeast culture had
  – Significantly fewer days of diarrhea
  – Significantly fewer days of treatment for any disease

• Did NOT have significantly different rate of respiratory disease

• In calves fed POM:
  – Improved production of cytokines by white blood cells
  – Improved production of antibodies following vaccination

• No difference among groups in rate of diarrhea or respiratory disease

• Feeding yeast culture in starter had significant effect on health outcomes

• Not much effect on immune functions measured in the study

• Perhaps other immune functions not measured were more important?

• BUT:
  – Feed intake decreased with increasing POM
    • Calves fed POM at 5 g/d weighed 4 pounds less than controls at d. 70
    • Calves fed 10 g/d weighed 10 pounds less at d. 70

  – Perhaps different POM formulation could improve intake?
• Summary, feed additives and health and immunity:
  – Feed additives sometimes improve immune function, but not always correlated with obvious health improvements
  – Sometimes improve health without improving measured immune functions
  – Best studies look at both immunity and health
    • Identify practical benefit
    • Improve our understanding of how immune function is related to health

Vaccination and Maternal Antibody

• Vaccination in the face of maternal antibody (IFOMA) traditionally considered ineffective

Vaccination and Maternal Antibody

• Failure of seroconversion considered to indicate failure of response to vaccination
  • In some cases, disease in vaccinated juveniles also indicated vaccine failure
    – Distemper in puppies
  • Maternal antibody thought to “bind up” vaccine and prevent immune response

Calf vaccination IFOMA

• Several studies indicate calves CAN respond to vaccination IFOMA
  – Measurements other than seroconversion indicate response
  • Some limitations, but clearly beneficial in some situations
Vaccination IFOMA can prime for memory response when maternal antibodies are present.

Vaccination IFOMA can decrease disease when calves are later exposed to infection.

Vaccination IFOMA can prolong titers.

Vaccination IFOMA, limitations:

- Vaccination IFOMA most effective when modified live vaccines used
  - May require 2 doses

- Vaccination IFOMA not reliable in very young calves with high maternal titers
  - Less than 1 month old with good passive transfer

Vaccination IFOMA can induce T cell responses even when antibodies don’t increase.

Need more information on vaccination IFOMA from field trials:

- Studies that measure disease and productivity of vaccinated calves
  - Best measure of efficacy of any preventative or therapeutic practice
• More guidelines needed, but several studies indicate calves CAN respond to vaccination IFOMA
  – Anamnestic response when maternal antibodies gone
  – Measures of T cell responsiveness in absence of seroconversion
  – Protection against disease when later infected