ROLE OF BOVINE CORONAVIRUS IN ENTERIC AND RESPIRATORY DISEASE

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Outline of Presentation

- Economic Significance
- Etiology: BCV
- Transmission
- Epidemiology including Molecular Epidemiology
- Clinical Syndromes
- Diagnosis
- Prevention
- Vaccines
- Conclusions
Economic Significance of Enteric and Respiratory Diseases

- Millions of dollars in economic losses
- Gagea et al., 2006
- Diseases and pathogens associated with mortality in Ontario beef feed lots. JVDI 18: 18-28

- Pneumonia was the most frequent cause of mortality of beef calves during the first 2 months of arrival in feed lots, 69 % of total deaths
  - Viral respiratory disease (19 %)
  - Bovine corona virus (2 %)
  - (Busato et al., 1997)
  - 36 % due to diarrhea, 26 % respiratory disease, and 15 % umbilical problems in young calves
RESPIRATORY DISEASE IN DAIRY CALVES

- Francoz et al., 2015.
- BRD is a significant cause of morbidity and mortality in dairy calves
- Preweaned dairy calves=95
- Dairy herds=11
- Viruses detected=BRSV and BCV
- BCV=40% calves from 11 herds
- Main pathogens identified= Mycoplasma, Pasteurella multocida, and BCV.

BCV was most commonly detected.
CORONAVIRUSES
Coronavirus Antigenic Groups

- **Antigenic Group I**
  Transmissible gastroenteritis virus, feline infectious peritonitis, canine enteric coronavirus

- **Antigenic Group II**
  Bovine Coronavirus

- **Antigenic Group III**
  Infectious bronchitis virus

Field’s Virology, 5th edition
Coronaviruses are named after the species from which the virus is isolated.
Classification of the Agent

- Biology of BCV is easy to explain as a typical member of family Coronaviridae:
  - Spike protein
  - Haemagglutinin-Esterase

from Lai and Holmes
EPIDEMIOLOGY
Geographical Distribution

- World-Wide Distribution
- Calf Enteric Disease: 35% calf scours
- Age-based reduction in shedding of BCV in feces
- Based on BCV antigen ELISA
- 0-30 days: 37%
- 4-12 months: 26%
- 2-7 years: 18%
- Stress triggers the shedding of BCV
Hosts of BCV

- Cattle
- Water buffalo
- Other wild ruminants
- Zoo animals: Giraffe
- Deer
- Elk
- Camelid corona virus (Alpaca)
- Sheep & Goats: Serological evidence
- BCV-like viruses can infect other related species, such as EqCV
Pre-disposing Factors

- Stress
- Winter
- Snow Storm
- Shipment (BRD cases)
- Parturition
- Warmer Weather?
Mortality of Cattle on Long Haul

- Moore et al., 2014. JVDI.
- Number of deaths 215 of hauls from Australia to Middle-East, Russia and China
- 93/130 had bacterial
- VIRUS INFECTION: 3%
- Mixed infections 22% of cattle
- BCV detected in 13% of cattle
- Stress of shipment is an established risk factor for BCV
Routes of Transmission

- Adult cattle to calves soon after birth
- Calves to calves due to shedding in large amounts
- Calves to adults
- Feces
- Aerosols
- Direct and indirect contact
- Stable in organic materials for longer time
- BCV Stable on foliage
Stability of BCV in Environment

- Enveloped virus
- Susceptible to heat, lipid solvents, and pH
- Soil
- Binds to clay and soil particles

BVC Associated Clinical Conditions: Pneumo-Enteric

- Calves
- Enteric disease
- Age group: 1-8 weeks
- Blood-stained, mucus containing feces
- Respiratory disease

- Adult cattle
- Winter-dysentery
- Respiratory disease
- Upper respiratory tract
- Lower respiratory tract
Role of dogs in BCV transmission

- Unknown? Unproven?
- Kaneshima et al., 2007
- Experimental infection of 3 infected and 2 contact controls with BCV
- PCR positive
- No symptoms observed
- Passengers of BCV?
- Virus related to BCV detected in CIRDC in UK
Does season affect virus properties?

- Evidence that RDE (receptor destroying activity) lacking in BCV isolates in summer

*Park et al., 2006 J Clin Microbiol 44:3178-3188*

- Seasonal pattern for BCV and BRSV observed

- BCV (23%) and BRSV (12%) were most common in nasal swabs

*O’Neill et al., 2014 Vet Rec*
Biological Classification of BCV Isolates

- 50% Pneumoenteric
- 25% enteric only
- 25% only detected in respiratory tract
- MN 1988 pneumo-enteric BCV isolate

Kapil et al., 1991

- Experimental infection with a virulent pneumoenteric isolate of BCV
- First enteric disease
- Then, respiratory disease after 3-4 days
Molecular Epidemiology

- Spike gene hyper variable region
- Nucleotide Identity: 98 %
- Two major clusters
- Cluster 2: deletion of 6 amino acids domain II of spike protein

*Brandao et al., 2006, Arch Virol 151:1735-1748*
Calf Respiratory Disease

- Tracheo-bronchial lavage
- 12 % respiratory samples BCV positive
- 25 % of calf herds were positive
Enteric Infection

- After oral infection of calves, BCV is excreted for 3 days at high titer
- then, intermittently.

Respiratory Disease

- In the last 3 decades, there has been increasing evidence for BCV-associated BRD.
- In the period of 1995-2000, several publications reported the possible association between BRD and BCV in feed-lot, transported, stressed cattle in USA.

BCV Association with BRD

- Adult cattle
- Few positive cells
- Detected by direct fluorescent antibody test
- Other bacterial agents also involved
- About 25% of lungs, nasal, and trachea samples were positive
- Total specimens examined = 450

Enteric-Respiratory BCV Isolate Pairs

- 107 positions/31028 nucleotides
- Except 5’ UTR

Concurrent Shedding of BCV

- Nasal swabs
- Feces
- Associated with loss of weight

Winter Dysentery

- Evidence for WD-BCV association?
- Adult cattle shed BCV at low levels intermittently
- Few cases detected last 3 years at OADDL
- Pathologist: intestinal rupture
- SK and pathologist agreed that BCV may have predisposed the cow to rupture
- Occurrence of snow storm before the individual cases of BCV associated WD at OADDL
Case Report

- n=1
- Herd: 23 dairy cows
- Calves: 4 calves
- Age: 27 months old, blood in feces, 2-day history of diarrhea. Severe anemia, no history of BCV vaccine
- Small and large intestine involved
- BCV confirmed; no Salmonella
- Lesions of BCV present in colon
Winter Dysentery

- Experimental reproduction
- Exposed by infected calves
- Watery diarrhea with small amounts of blood
- Same strain of BCV WD and calf diarrhea
- Cows were seronegative for BCV

*Traven et al. 2001. Vet. Microbiol. 81;127-151*
Chronic Persistent Infections

- Adult animals
- Cell culture
- Low level of shedding in feces and respiratory tract
- Affected by stress, season
DIAGNOSIS
Specimens for BCV

- Ante-mortem samples: Feces (2-5 grams) in red top tube
- Over ice packs
- Post mortem: Fresh and frozen spiral colon
- Fed-Ex overnight to diagnostic laboratory
Easy Shipment of BRD Respiratory Samples

- Fast technology analysis (FTA) cards real time RT-PCR
- Chemically treated filter paper
- Without the need for cold chain or special liquid media
- FTA cards provided the same results as traditional methods of sample collection
- No statistically significant differences observed up to 14 days at room temperature
BCV Monoclonal Antibodies

- 8F2 monoclonal antibody
- Target: Nucleocapsid protein
- Reacts with antigenic group 2 corona viruses
  - Bovine corona virus
  - Equine corona virus
  - Camel corona virus
  - Elk corona virus
Diagnostic Techniques

- **Post Mortem Diagnosis**
  - Fluorescent antibody test
  - Spiral colon
  - Lungs
  - Upper 1/3 of trachea

- **Ante-Mortem**
  - Fecal samples
  - BCV antigen capture ELISA at KSUDL
  - Nasal swabs
  - RT-PCR on fecal samples at OADDL
Tests at OADDL

- Feces: RT-PCR test
- Immuno histochemistry for intestinal samples
- Sample of choice is spiral colon
- Direct fluorescent antibody test on nasal swabs, trachea, and lung tissues
Antigenic Variation

- Three major antigenic groups
  - Group I: Mebus strain
  - Group III: Majority of the current BCV isolates
  - Group II: Weakly reacts with Mebus hyper immune serum
- Hemagglutination-Inhibition Test, Mouse Erythrocytes

VACCINES
Non-Specific Immunity

- Induction of interferon
  
  Baudoux et al., 1998. 72:8636-8643. IFN-Alpha

- Intestinal IEL cytotoxic to BCV infected cells in non-MHC-restricted
  
Major Antigens

- Surface proteins of BCV
- S1 and HE proteins contain neutralizing epitopes

*Vautherot et al., 1992.73:1725-1737*
BCV Vaccines

- Major goal of these vaccines should be to provide passive immunity to newborn calves during the susceptible age group of 1-8 weeks for BCV
- Immunize the pregnant cows with BCV antigen
- It will be nice if the problem can be solved in herds having a high incidence of BCV-associated respiratory disease in adult cattle
MLV Respiratory BCV

- Respiratory isolate of BCV (438/06-TN)
- Vaccine was safe
- I/muscular injection of vaccine
- Induced high antibody titers
Sources of Passive Antibodies

- Colostrum
- Yolk of immunized hens

Mucosal Immunity

- Regional antibody responses
- Spiral colon, ileum and jejunum

*Kapil et al. 1994. 17:139-149.*
Vaccine for BRCV

Vaccination for BCV before shipping to feed lots may provide protection against BCV infection in the induction of respiratory disease.

*Thomas et al. 2006. AJVR 67:1412-1420*
Colostrum Antibodies

- Pardon et al., 2015. Prev Vet Med
- Colostrum antibodies for BCV and BRSV
- Provide protection in veal calves up to 3 weeks of age
NASAL SHEDDING OF ORGANISMS

- In Australia, 1484 nasal swabs were collected.
- Nasal shedding of BCV=40%
- Differences in different geographic areas of respiratory pathogens
- Implementation of vaccination strategy to raise antibody levels of common viral pathogens prior to export may mitigate BRD during shipment
Viral Causes of Calf Diarrhea

- Bovine rotavirus: small intestine
- Bovine coronavirus: small and large intestine
- BCV is more severe cause of calf diarrhea
- Can be difficult to diagnose
Pathology
BCV IHC
BCV IHC Lung
BCV FAT Nasal Swab
One-minute Cow Side Tests
Mucosal Immunity

- Intestinal Antibody
- IgG1
- IgA
- Spike protein major immunogenic protein
- Passive immunity totally protective for calves
- Maintain mucosal immunity by colostrum
Pathogenesis

- Receptor: N-acetyl neuraminic acid
- Anti receptor protein: spike protein
- HE protein also plays role in binding of virus
- BCV multiples in the cytoplasm of cells
Pathogenesis

- SARS: human coronavirus damage due to cytokine storms
- Not been studied in BCV
- Coronaviruses are susceptible to interferon responses
Disinfection

- Susceptible to soap
- Easy to disinfect
Conclusions

- Bovine coronavirus is responsible for significant economic impact on feedlot cattle
- Responsible for enteric and respiratory disease
- Oral passive immunity is proven to prevent BCV infections in calves
- High quality monoclonal antibodies to detect in formalin and fresh tissues are available
- Vaccines for BCV to provide passive colostral immunity to calves are available
References


