Vaccinations to optimize reproductive efficiency
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What is Behind Reproductive Failure?

- Overview Reproductive Diseases
- The anatomy of the bovine cow-fetal connection (multilayered placenta) precludes antibodies and other immune cells from crossing the placenta and providing protection for the developing fetus.
- Thus the developing bovine fetus is susceptible to small amounts of infectious agents.
Placentas can be classified based on which maternal layers are retained in the placenta. The bovine placenta has more layers than most other species.

### Maternal Layers Retained

<table>
<thead>
<tr>
<th>Type of Placenta</th>
<th>Endometrial Epithelium</th>
<th>Connective Tissue</th>
<th>Uterine Endothelium</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epitheliochorial</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cows, horses, pigs, ruminants</td>
</tr>
<tr>
<td>Endotheliochorial</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Dog, cats</td>
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<tr>
<td>Hemochorial</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Humans, rodents</td>
</tr>
</tbody>
</table>
What is Behind Reproductive Failure?

Overview Reproductive Diseases (cont.)

- Reproductive diseases are difficult to protect against
- Little research has been done to assess reproductive efficiency of most currently licensed vaccines including those with known reproductive syndromes
- For many diseases the route of infection is in question (uterine versus blood carried)
Reproductive Disease Overview (cont.)

- For most diseases there is no established reproductive challenge model
- It may be difficult to assess the ability of a vaccine to improve reproductive efficiency
- Control of non-reproductive diseases can have significant reproductive impact
- Review the literature carefully
"Unfortunately, the fact that a vaccine is licensed and available does not mean that it works."

Viral Diseases With Reproductive Ramifications

BVD
IBR
Bovine viral diarrhea syndromes are caused by a group of related viruses.
These related viruses may cause severe disease in unprotected animals

- Immune suppression
- Severe diarrhea
- Bleeding problems due to platelet destruction (type 2s only)
- Severe respiratory
- High death loss
BVD Immune Suppression

Results in more severe disease

- BRD (Bovine Respiratory Disease)
  - BRSV
  - IBR
    - Pasteurella (Mannheimia) haemolytica
- Salmonella
- Neospora
- Calf diarrhea
  - Rotavirus
The majority of BVDV infections are unnoticed (subclinical)

Over 75% of all BVDV infections are subclinical
Often not noticed
In dairy and beef herds will show up as:
  Reproductive failure
  Immune suppression in adult animals
  Calf problems
    pneumonia
    scours
BVDV Background
Cytopathic versus Noncytopathic BVDV
Virology

Each BVD virus can be isolated *in vitro* into 2 biotypes

**Non-cytopathogenic or ncp biotype**

Synthesises protein p120

**Cytopathogenic or cp biotype**

Synthesises protein p120 and protein p80 (from p120)
Cytopathic versus Noncytopathic BVDV

Noncytopathic BVDV is the natural state of the virus
Cytopathic strains arise from mutation of a noncytopathic strain
It is a laboratory differentiation
It is not related to virulence
Primary importance of the difference is in the reproductive form of BVDV
Relationships Among the Pestivirus Family…
Cerebellar ataxia
Motor incoordination
Clinical Reproductive Syndromes Associated with BVDV Infection

**Fetal Infections**

Abortion / Return to Estrus
- 0-40 days

Production of “PI” Calves
- 40-120 days

Fetal anomalies / Weak Calves
- 120-160 days

Impacts on ovarian function is debatable
BVDV PI in Breeding Bulls / infected semen

1. Higher levels of BVDV in semen than in serum
   – Shedding is constant in the semen of PI bulls
   – It is not within the spermatozoa
   – Adverse impact of the infection on sperm quality is debated
   – Primary sites of viral replication are most likely to be prostate gland and seminal vesicles
   – No BVDV antibodies in seminal fluid
Impact of BVDV PI in Breeding Bulls and Infected Semen

1. Relatively low number of PI calves result from the breedings with PI bulls
2. In sero-negative animals dramatic decreases in conception rates and increases early fetal death
3. Uterine infections can occur in both sero-negative and sero-positive animals.
4. Sero-conversion will occur in sero-negative animals after exposure to semen from PI bulls
5. Horizontal and vertical transmission important with PI bulls
Impact of PI in Embryo Transfer

PI donor cows
- have not been shown to cause PI calved to be born
- May cause decrease conception rates
- May be a source of BVDV contamination

PI recipients
- have been shown to cause PI calves to be born
- May cause decrease conception rates
- May be a source of BVDV contamination

Thus both the donor and recipient should be screened for BVDV
Persistent Infection

Only occurs following in utero exposure

Virus crosses the placenta before the immune system has developed

Calf learns to recognize that strain of BVD virus as part of self
Persistent Infection - Routes

- Acute infection - pregnant female exposed to NCP BVDV (93%)
- Persistently infected female giving birth (7%)

 Persistently Infected calf

Persistently infected Calves

May be born weak and runted

May be born clinically normal

Are immunologically frail

Are persistently infected forever

Are the source of BVDV spread in most herds

May remain in the herd as cows and bulls spreading the virus
Outcomes of Persistently Infected Calves

50% of PI cattle will die within first year of life

Outcomes

– Death at/near time of birth
– Death due to mucosal disease
– Death from other cause but BVD immune compromising was factor
– Survive to maturity but less than healthy
– Survive to maturity and reproduce

(Duffell & Harkness Vet Rec 117:240-245, 1985)
Persistently infected (PI) cattle are the primary source of virus in herds

(Baker, JAVMA (1987)190:1449-1458)

Presence of any PI cattle has significant herd impact

STOP·ALTO

BIO-SECURITY
AREA

EMPLOYEES ONLY PAST THIS POINT
VISITORS MUST REPORT TO OFFICE
The Goal of Vaccination and BVDV Control is Stopping Persistent Infection

Clinical protection is assumed
  type 1
  type 2
BVDV Seeder (not CIDR!) Studies

16 month Study

Seeder studies truly recreate field exposure to assess protection from BVDV vaccines
- D. L. Grooms, S. R. Bolin et.al. Fetal protection against continual exposure to bovine viral diarrhea virus following administration of a vaccine containing an inactivated bovine viral diarrhea virus fraction to cattle, AJVR, 2007
Bovine herpesvirus 1

**Virus classification**
- Group: Group I (dsDNA)
- Family: Herpesviridae
- Genus: Varicellovirus
- Species: *Bovine herpesvirus 1* (BHV-1)
BHV-1

Genetically stable
Rapid transmission, primarily aerosol
Immunosuppressive
Trigeminal nerve latency via the latency gene
  – Recrudescence
  – Vaccine latency
Causes intracellular bridges – blocks antibody neutralization, cell mediated immunity very important protective component
Infectious bovine rhinotracheitis / Infectious pustular vulvovaginitis (IBR / IPV)

Aetiology

IBR / IPV, or IBR for short, is caused by bovine herpesvirus 1 (BHV-1) in the genus Varicellovirus of the subfamily Alphaherpesvirinae, which belongs to the Herpesviridae family. The genome of the virus is linear double-stranded DNA.

Only a single serotype of BHV-1 is recognized, but subtypes of it are distinguished. These types are referred to as 1.1 (respiratory subtype) and 1.2 (respiratory and genital subtype). The subtype 1.2 has been further classified with molecular tools into 2a and 2b.

The former encephalitic subtype 1.3 has been reclassified as a distinct herpesvirus, designated as BHV-5.
Infectious bovine rhinotracheitis / Infectious pustular vulvovaginitis (IBR / IPV)

Intrinsic determinants of the agent

**Infectivity**
Intranasally, a dose of $10^{7.7}$ TCID$_{50}$ was sufficient to infect cattle in age groups 2 and 5 weeks, and 6 and 18 months. Others determined that the intranasal infective dose was $10^{3.2}$ TCID$_{50}$ for a virulent strain, while $10^{32}$ TCID$_{50}$/ dose of AI semen were not sufficient to infect any of 44 inseminated dams. However, others estimated that the minimal dose to infect a cow by AI was 32 infectious viral particles.

**Virulence**
Morbidity to the infection approaches 100% and mortality may reach 10%, particularly if complications occur. The subtype 1 is generally considered more virulent than subtype 2.

**Pathogenicity**
While BHV-1 causes infections predominantly in domestic and wild cattle (OIE, 2004), it has occasionally been isolated from cases of vaginitis and balanitis in swine and from aborted equine fetuses.
Infectious bovine rhinotracheitis / Infectious pustular vulvovaginitis (IBR / IPV)

Intrinsic determinants of the agent

Persistence

The virus proceeds from the primary mucosal lesion by neuronal axonal transport in a naked nucleocapsid form to the nearest ganglion, usually trigeminal or sacral (dorsal root), and the viral DNA either causes a cytolytic infection or establishes a persisting latent infection. A wide variety of stimuli, such as stress, transport, parturition and treatment with glucocorticoids may reactivate the infection and lead to secretion of the virus. The mechanisms of latency and reactivation have been extensively studied, but the details are not yet fully understood. It has been shown that only a small region of the viral genome, referred to as “latency-related” (LR), is transcriptionally active in latently infected neurons. The LR gene products may even promote neuronal survival by inhibiting programmed cell death, thereby also sustaining the infection in the cell.
Once an animal infected: latent carrier for ever

Once an animal infected: latent carrier for ever

LATENCY \(\rightarrow\) Persistence of IBR, even in a closed herd

REACTIVATION \(\rightarrow\) REEXCRETION

REEXCRETION \(\rightarrow\) VIRAL EXCRETION CYCLES

SOME WEEKS TO SOME YEARS BETWEEN CYCLES
Rapid transmission
Bovine herpesvirus 1 Disease

Syndromes

Severe respiratory infections
Reproductive losses
Eye and nerve lesions
Venereal form

– infectious pustular vulvovaginitis in cows
  and infectious balanoposthitis in bulls
Bovine herpesvirus 1 Disease Syndromes

Respiratory disease (rednose)
  – Most recognized syndrome
  – Primarily upper respiratory tract and tracheal involvement
    Reddening of nasal passages and nasal discharge
    Anorexia, lethargy, weight loss
    Tracheal damage and pseudomembranes
    Uncomplicated death loss usually less than 5%
    Complicated infections may hit mortality rates of 60%
Bovine herpesvirus 1 Disease Syndromes

Reproductive losses

- Can cause mid to late term abortions
  - Conception failure
  - Early embryonic death loss
  - Follicular and luteal necrosis
    - Does not occur in sero-positive cattle
      - Spire and Cortese
    - Can occur with MLV vaccination
IBR Reproductive Effects

Abortion storms
- Abortions may be delayed
- Feti are often autolyzed

Reduced milk production

Reported up to 50% abortion rate in outbreaks
Bovine herpesvirus 1 Disease
Syndromes

Venereal form

– infectious pustular vulvovaginitis in cows
  and infectious balanoposthitis in bulls
Vaccinations to optimize reproductive efficiency

Bovine herpesvirus type 1

- Primary reproductive protection is measured by the ability to stop BHV-1 abortions
- Secondary level would be to stop ovarian effects
Bacterial infections

Leptospirosis
Maintenance host infections
Incidental host infections
Salmonella
Brucella
Histophilus somnus
Vibrio
LEPTOSPIROSIS

Nomenclature

Pathogenic Bovine leptospirosis were formerly classified under the species *L. interrogans*

- *L. interrogans*-5 way

Serovars are identified based on antigens on the surface of the organism:

- *L. interrogans* serovar hardjo bovis, prajitno, pomona, etc
Bovine leptospirosis nomenclature

Bovine Leptospirosis

Leptospira borgpetersenii
serovar hardjo

(Formerly) *L. hardjo* Bovis

Leptospira interrogans
serovar hardjo

(Formerly) *L. hardjo* Prajitno

• Predominates
Leptospires important to cattle

Leptospira borgpetersenii serovar hardjo (bovis)
Leptospira interrogans serovar hardjo (prajitno)
Leptospira interrogans serovar pomona
Leptospira kirschneri serovar grippotyphosa
The bacteria

*Leptospira*
gram negative
outer envelope
outer membrane protein
cell wall
two flagella
The bacteria

*Leptospira*

likes wet warm conditions
susceptible to dry conditions
susceptible to anaerobic conditions
sensitive to acid conditions $\leq$ pH 6.8
survives in alkaline pH of 7.8-7.9
temperature extremes are detrimental
Bovine leptospirosis

Leptospirosis is an important zoonotic bacterial disease that can cause abortions, embryonic death, stillbirths, infertility, and loss of milk production.
The diseases caused by *Leptospira* can best be delineated into two categories, depending on the serovar and the target host:  
1) maintenance hosts and  
2) incidental hosts.
Epidemiology

Maintenance hosts:
Efficient transmission between hosts
Low pathogenicity
Low antibody response
Prolonged shedding/chronic disease
The most important cattle serovar worldwide is *Leptospira borgpetersenii* serovar hardjo

- Maintenance host infection
- High incidence of infection
- Persistent infections
- Insidious economic loss
- Public health concerns
Epidemiology

Incidental hosts: experience severe disease. Other species are source of infection marked antibody response short duration of shedding
Classification of cattle serovars

hardjo-bovis  Maintenance
hardjo-prajitno  Maintenance
pomona  Incidental
grippotyphosa  Incidental
Renal carrier status - key to maintaining the disease

Leptospires from contaminated urine enter via mucous membranes

- Uterus - infertilty/ abortion/ weakly calves
- Udder - milk drop syndrome “flabby bag”

• Urinary shedding occurs for 11-542 days
• Places other cattle at risk
• Places handlers at risk

Evidence of early infection

‘25-30%’ of US dairy heifers are seropositive before vaccination prior to breeding

Transplacental infection leads to congenitally infected calves (seropositive prior to suckling)
Salmonella sp

Losses due to
placentitis
endotoxin induced luteal lysis
fetal death (following a fetal infection)
Ingestion of contaminated feed
Can lead to
  Early embryonic loss
  Abortions (expulsion of fetus can be delayed)
  Stillbirths
  neonatal septicemia
Most common isolates are Salmonella dublin and Salmonella typhimurium
Vaccinations to optimize reproductive efficiency

• *Brucella abortus*
  – The best example of a very efficacious reproductive vaccine if given at the correct ages
Vaccinations to optimize reproductive efficiency

Bovine genital Campylobacteriosis

- *Originally classified as Vibrio*, Campylobacter fetus subspecies venerialis causes a venereal infection of cattle
- Vaccination has been shown to be effective in protecting heifers even when vaginal cultures are positive for the bacteria.
Vaccinations to optimize reproductive efficiency

Bovine genital Campylobacteriosis (cont.)

– The uterus is very resistant to the bacteria after vaccination.
– Vaccination with double doses has been shown to be effective at clearing infections from carrier bulls.
– Timing of vaccination may be critical
Vaccinations to optimize reproductive efficiency

*Histophilus somnus*

- *Histophilus somnus* has been associated with early embryonic deaths, abortions and conception failure.
- The bacteria can be cultured from both normally bred animals and is a normal inhabitant of the vaginal tract.
- No reproductive challenge model has been established.
Protozoal infections

- Neospora
- Trichomonas
Protozoal infections

Neospora caused by Neospora caninum
canids primary host
pass oocysts after ingestion of an infected
intermediate host
Other wildlife hosts?
Cattle ingest infected feed
May require immunosuppression
BVDV most often incriminated
Vertical transmission but not horizontal
transmission
Neospora impacts

The number one diagnosed cause of abortion in last 5 years
  – Usually off of serology – what does it mean
  – Brain lesions

Basically all the same reproductive signs as BVD
  – Abortions
  – Mummified feti
  – Weak calves
  – Early Embryonic death loss
Neospora control

More information is needed!
Vaccination efficacy is questionable
Control of dogs and other wildlife access to feedstuffs
Test and cull of carrier animals?
   particularly repeat aborters
Check for other problems i.e. BVDV etc
Vaccinations to optimize reproductive efficiency

- Trichomoniasis is a venereal infection of cattle caused by the protozoal agent *Trichromononas fetus*

- Efficacy of Tritrichomans vaccines is questionable

- Management practices must be incorporated along with vaccination
Thank you!

Hwy 30, traveling to London, KY
Adverse Reactions

- Immediate anaphylaxis
  - epinephrine
- Local reactions
- Gram negative bacterial reactions
  - banamine, steroids, calcium
Gram Negative Reactions

- Reactions determined by:
  - Genetics
  - Nutritional deficiencies
  - Herd or individual Sensitivities
  - Amount of endotoxin or gram negative bacterins
Gram Negative Reactions include

- milk depression
- Anorexia
- early embryonic death
- induced parturition
- abortions
- delayed death loss
Gram negative vaccines:

- 5-way leptospirosoa
- Brucellosis
- J -5
- Salmonella
- *E. coli*
- Vibriosis
- *Pasteurella multocida*
- *Hemophilus*
- *Moraxella bovis (pinkeye)*
- *Mannhiemia haemolytica*