Digital Dermatitis in Beef Cattle: Management Strategies and Applicable Research

What is Digital Dermatitis?

- Hairy Heel Warts or Footwarts
- Papillomatous Digital Dermatitis
- Strawberry Foot Disease
- Interdigital Dermatitis
- Raspberry Heel
- Mortellaro’s Disease

DD in Beef Cattle?

- Described in dairy cattle in 1994 in US
- Increasing incidence in feedlots over last several years
- Increasing number of inquiries and calls regarding beef DD
- Lame animals that are nearing harvest

Economic and Welfare Implications

- Minimal data on the beef side
- DD is the leading cause of lameness in dairy cattle in the US – 28% Prevalence
  - 62% of lameness in bred heifers
  - 49% of lameness in cows
- Most costly of all dairy lameness disorders
  - $126-$133 per clinical case
  - $190 million per year in lost revenue in US
- DD has the greatest impact on welfare of all bovine lameness disorders due to the high incidence and long duration

Digital Dermatitis

Typical posture of steer with digital dermatitis (photo at right)

Lesion in the plantar interdigital cleft

Cow stands on toe to avoid weight bearing on the heel

Lesions and lameness often occur within 3-4 weeks prior to slaughter
Treatment/Control of Digital Dermatitis

Managing Digital Dermatitis in Feedyards

- Treatment
  - Topical Sprays
  - Footbaths
  - Individual treatment

Footbath for DD Control

Etiology of the Disease

- Association of *Treponema* spp. with lesions
- Other bacterial species implicated
  - *Dichelobacter nodosus*, *Porphyromonas* spp.,
  *Bacteroides* spp., *Fusobacterium* spp., and
  *Campylobacter* spp.
- Responds to topical antibiotic therapy
- Prior vaccines focused on Spirochetes failed to provide significant protection in field use

So how did we proceed?

- Ideal approach to study a potentially complex polymicrobial disease from a scientific perspective
  - Remove the need to culture the organisms
    - Less than 10% of bacteria can be cultured at present
  - Look at the earliest lesions possible and follow the progression through to active lesions
  - Be able to reliably identify all morphologic stages of disease relevant to bacterial lesion progression
16S Metagenomics

- Culture independent
- Purification and sequencing of total DNA from a sample
- Tells us “who” is there and how abundant they are without having to specify what we are looking for
- Output is relative abundance

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Observing Natural Lesion Development

- 61 Adult Holstein Cows - ISU Dairy Farm
  - Assigned to random pens within herd
  - RFID collars diverted cows away from herd footbath
  - Cows lifted on tilt table every 3-4 weeks
  - Biopsy lesions throughout development
  - Metadata collected on systemic treatment, illness and other medical interventions
  - Monitor and treat lameness

Study Statistics

- 32 months of natural lesion development
- 900+ tilt-table examinations of trial cows
- 10,000+ digital photographs taken
- 1000+ biopsies taken
- 350+ blood samples collected

Development of Novel Staging System

- Initially used “M” staging system
  - Failed to differentiate 2 different morphologic variants of early stage lesions (focal ulcerated vs diffuse crust/acantholytic) needed for analysis
- Stepwise selection process relying on retrospective analysis of pictures followed by confirmation of actual progression
- Two additional iterations to get to present system
Observations

- "Classic" digital dermatitis lesions were always preceded by consistent morphologic changes to the foot skin
- Some of the early lesions look nothing like "classic" digital dermatitis and were being overlooked
- When lesions are treated they regress to earlier stages in a systematic manner (with exception of short term scab)

"Classic" Lesions

- Type 3 Lesion
- Type 4 Lesion

Natural Progression and Regression of DD Lesions

- 25% Pre-Clinical Lesions
- 55% Clinical Lesions
- 20% Regressing Lesions
- Treatment

Uses of Scoring System

- Tx
- Calving

Clinical Use of Scoring System

- With a variety of scoring systems available the question is often asked, what scoring system should we use?
  - What is the goal of scoring?
    - For research we may need a more refined system
    - For clinical decision making we need less refinement

For clinical decision making we prefer a simple 3 point scale Normal, Pre-clinical, Clinical
DEEP SEQUENCING ANALYSIS REVEALS THE TEMPORAL MICROBIOTA CHANGES ASSOCIATED WITH THE DEVELOPMENT OF BOVINE DIGITAL DERMATITIS

Metagenomic Analysis

- Shotgun based metagenomics
  - 24 biopsies from various stages
  - 100bp paired end reads on Illumina Hiseq
  - 156,433,474 total sequences
- 16S based metagenomics
  - 48 biopsies (same 24 as shotgun + 24 additional)
  - Golay barcoded primers of V3-V4 region
  - 300bp paired end reads on Illumina Miseq
  - 20,042,461 total sequences

Krull et al. 2014

Shotgun Metagenomics Bacteria Families per Lesion Stage

16S Metagenomics Bacteria Families per Lesion Stage

Comparison between Platforms

- Procrustes Analysis
  - Bray-Curtis distances
  - 10,000 Monte Carlo Simulations
  - p value < .001
- The results from either pipeline yield similar results

A closer look at Treponema spp.

Mock Simulation

Mock Simulation
16S Principle Component Analysis

**ANOSIM p value <0.001**

**Metagenomic Conclusions**

- Minimal Fungal or Viral DNA
- Significant changes in bacterial microbiota as lesions change morphologic appearance
  - Evidence that disease process in polybacterial
  - Identification of unique biomarkers associated with each lesion stage
- Increased relative abundance of *Treponema* spp. as lesions progress
  - shift in species between lesion stages
- Statistical and bacterial validation of novel scoring system

**So what about etiology?**

- Strong evidence for a polybacterial pathophysiology that goes through systematic changes similar to periodontal disease
  - *Treponema* sp.
    - Species and abundance change during disease progression
    - Over 40 different *Treponema* OTUs identified
    - High abundance in late lesions but much lower in early lesions
    - For the most part there are completely different trep profiles in pre-lesions vs advanced lesions

**What have we learned about lesion development?**

- Lesions develop very slowly
- Only advanced lesions cause lameness, and not all advanced lesions cause lameness
- Using lameness to identify cases of DD has a very low sensitivity
- In dairy cattle study – injectable antibiotics showed no effect
- Topical antibiotics did decrease lesion score, but majority did not heal completely
- Using our staging system we were able to prognosticate risk of recrudescence

**DD Lesion Development**

- DD lesions developed at a rate of 4 lesions per 100 cow feet-months
- Average time for a clinical lesion to develop was 133 days (range: 38 – 315 days)
- The average time from clinical lesion development (stage 3) to lameness was 161 days (range 0-330 days)
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Locomotion Score

- Assume locomotion score of 3/5 or greater is lame and that a lesion score of 3 or 4 is classic DD
- Sensitivity = 0.36
- Specificity = 0.64
- Assume prevalence of 30%
- PPV = 0.32
- NPV = 0.68

The Effect of Various Events of DD Lesion Stage

<table>
<thead>
<tr>
<th>Event</th>
<th># (n)</th>
<th>DD Score Change</th>
<th>n</th>
<th>DD Score Change</th>
<th>Event Score Criteria</th>
<th>Event Recurrence</th>
<th>Event Score Criteria</th>
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<tbody>
<tr>
<td>Systemic Disease</td>
<td>42</td>
<td>-0.01</td>
<td>19</td>
<td>0.13</td>
<td>+/-14 days of event</td>
<td>+/-14 days after event</td>
<td>+/-14 days after event</td>
</tr>
<tr>
<td>Systemic Antibiotics</td>
<td>26</td>
<td>-0.46</td>
<td>7</td>
<td>-0.27</td>
<td>+/-14 days of event</td>
<td>+/-14 days after event</td>
<td>+/-14 days after event</td>
</tr>
<tr>
<td>Topical DD Therapy</td>
<td>27</td>
<td>-1.08</td>
<td>21</td>
<td>-1.13</td>
<td>+/-14 days of event</td>
<td>+/-14 days after event</td>
<td>+/-14 days after event</td>
</tr>
<tr>
<td>Dry Period</td>
<td>26</td>
<td>-0.10</td>
<td>26</td>
<td>-0.13</td>
<td>+/-80 days of calving</td>
<td>+/-14 days after event</td>
<td>+/-14 days after event</td>
</tr>
<tr>
<td>Post-partum Period</td>
<td>46</td>
<td>0.11</td>
<td>39</td>
<td>0.03</td>
<td>Days 0-28 post calving</td>
<td>+/-14 days after event</td>
<td>+/-14 days after event</td>
</tr>
</tbody>
</table>

DD Lesion Treatment and Recrudescence

<table>
<thead>
<tr>
<th>Lowest DD Score</th>
<th># Lesions</th>
<th># Recur</th>
<th>%</th>
<th>days to recur</th>
<th>days monitored</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>100%</td>
<td>0</td>
<td>298 (265-323)</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>13</td>
<td>59%</td>
<td>120 (85-431)</td>
<td>289 (52-603)</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>4</td>
<td>29%</td>
<td>224 (52-306)</td>
<td>265 (56-679)</td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0%</td>
<td>N/A</td>
<td>420 (252-567)</td>
</tr>
</tbody>
</table>

Krull et. al 2016
Digital Dermatitis: Rates of Recurrence

- Rates of reoccurrence following “topical spray treatment”
  - Read et al. 48% Various treatments
  - Van Amstel 52% Tetracycline 8 g/L
  - Shearer 43% Oxetraycline 25 g/L

- Rates of reoccurrence following “treatment under a bandage”
  - Berry SL 41-45% Lincomycin paste

How does DD spread?

- Polymicrobial disease infection dynamics are complex due to involvement of multiple organisms
- Once introduced into pen or herd it can spread rapidly
- Macerated lesion material readily induces lesions when the skin is compromised
- However, direct contact with lesions is not required – can spread between animals that have feet wrapped to cover lesions

How does DD spread?

- Infectious dose is relatively small
  - Sufficient material can make it out of one wrap and down another wrap to transfer disease
  - We can use small volumes of macerate to induce lesions
- Organisms are most abundant in lesions, but can be found in the environment and on equipment

Environmental Contamination

- Non-DD Treponema
- DD Associated Treponema
- Treponema phagedeni
- Early DD lesion Treponema
- Late DD lesion Treponema

Role of Encysted Organism?

- In laboratory cultures Treponema spp. are observed to form a “round” cell morphology later in the growth curve and when exposed to oxygen
- Based on the morphology these have been suggested to be an “encysted” form of the organism that forms in non-favorable conditions and that may allow for persistence in lesions or in the environment
Role of Encysted Organism?
• Preliminary data from our laboratory suggest that these are actually dead cells
• Further work to confirm this using other methods is underway

Live-Dead Stain based on membrane integrity demonstrates that corkscrew shaped bacteria have intact cell membranes while round forms have lost their membrane integrity.

Where do we go next?
• Better understanding of immunity and the role that it plays in disease
• Improved treatment regimes
• Improved prevention regimes
• Continued work towards development of efficacious vaccines
• Better understanding of the specifics of etiology – who is really required and how do they work together

Tools to study DD
• Induction model to study immunity, etiology, treatment and candidate vaccine efficacy
• In total, 21 protocols from five experiments were evaluated on their effectiveness in inducing DD lesions in 126 Holstein calves (504 feet).
• Protocol capable of inducing DD lesions in 95% feet over a 28 day period
• Can induce as many as 120 feet per experiment
• Can utilize frozen inoculum to allow replicates

Normal Skin Preinduction
Normal Skin Natural
Induced DD
Natural DD

Metagenomic comparison of induced and natural DD lesions shows that the induction method results in a bacterial population representative of natural lesions.

Take Home Messages
• DD is a complex polymicrobial disease process
• Lesions develop through a systematic process
• Limited data to suggest that injectable therapy is beneficial
• Topical therapy is beneficial but has a high failure rate following single application
• Other management strategies such as footbaths may be helpful
• There is a lot we still need to learn
Beef Specific Lameness Course

- Two-day workshop with hands on laboratory
- All forms of beef lameness covered including DD
- August 23-24 at Amana Farms in Amana, Iowa
- To preregister, contact Leslie Shearer by phone at 515-294-2836 or ishearer@iastate.edu

This program is sponsored by the makers of Bovi-Bond foot block adhesive, Amana Farms, HoverChute, ISU Veterinary Diagnostic and Production Animal Medicine, Iowa Beef Center and ISU Extension and Outreach.