“Digital dermatitis: Where are we going?”

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Bovine Digital Dermatitis: the problem

A disease of dairy cattle which causes severe lameness.

Lesions mainly in housing months and on rear feet
BDD Lesions

- Lesions may be acute or chronic, mild or severe
- Can be large (up to 10 cm in diameter)
- Very sensitive to touch
- Easily bleed
- Cause pain and lead to lameness
Importance of Digital Dermatitis

- Major cause of lameness: welfare issue
- Milk drop
- Treatment – efficacy, costs, environment, milk discard
- Higher culling rate
- More labour costs
- Costs = £100+ per case
- England & Wales costs = £40 - £100 million per year (DEFRA 2002).
Digital dermatitis: history and spread

• First reported in Italy in 1974 (Cheli and Mortellaro)

• Took 14 years to spread to UK (Roger Blowey, 1987)

• 2009 – Present in majority of UK dairy herds

• Worldwide problem – seen in all countries with dairy cattle
Intensive agricultural practises have:

- Failed to prevent spread of digital dermatitis
- Probably encouraged its spread
- Spread is between tissues, between cows, between farms, between species!
Treatment

- No single effective treatment

Common usage:
- Footbaths
  - Lincospectin/tetracycline
  - Formalin/copper sulphate
- Topical treatments
  - Tetracycline
  - Milk withdrawal for ca 2 weeks
- Improve farm hygiene
- Recurrence of DD is common/normal
- Immunity is generated by cows – not effective
- Vaccination – no efficacy to date
Background: What causes DD?

- Precise cause not proven
- Antibiotics lead to transient improvement
- Bacteria are present in lesions – very many
  - Fusobacteria, Dichelobacter, Campylobacter, Mycoplasma
  - Spirochaetes
- Of all these organisms, spirochaetes are the most frequently reported organism in DD tissues – found in all BDD lesions
Spirochaetes – what are they?

- Group of very motile bacteria
- Spiral shape – twisting motion (like a screw)
- Include:
  - Leptospira
  - Borrelia (eg Lyme disease)
  - Treponema (eg syphilis)
- Little known about them in cattle
BDD skin stained to identify these characteristic spiral organisms

Spirochaetes **always** seen in BDD lesions; not seen in normal skin
As if digital dermatitis in cows wasn’t bad enough...

Contagious Ovine Digital dermatitis

First (world) report in UK in 1997
Emerging disease (ie spreading) in UK flocks (serious in many areas)

Sheep lameness problem

More severe condition in sheep than BDD in cattle

Pathology is very similar to BDD, though lesion site is different

Treated with antibiotics – not very successful

Spirochaetes (treponemes) identified in all lesions

Questions:

Are the same organisms responsible for ovine and bovine digital dermatitis?

Has the ovine disease come from cattle?

Could there be any further spread?
Identifying treponemes in BDD/CODD lesions

• Treponemes are very difficult to purify from lesions and grow in the laboratory

• Hence, only a few previously isolated worldwide from cattle

• However, we have been very successful by use of anti-treponeme antibodies and magnetic beads & by use of selective medium
Treponeme isolations from DD lesions

Previous studies had limited success

- Walker et al, 1995, USA (7 isolates)
- Schrank et al, 1999, Germany (*T. brennaborensis*)
- Demirkan et al, 1999, UK (1 isolate)
- Edwards et al, 2003, UK (1 isolate)
- Trott et al, 2003, Australia (4 isolates)
- **Total = 14 isolates**

In our hands, every BDD biopsy has yielded one or more Treponeme isolates = Very high success rate.

*We now have a total of 85 treponeme isolates (from 45 BDD/CODD samples)*
Success in obtaining treponeme isolates allows:

- Identify treponeme strains relevant to BDD
- Compare with other treponemes present in cattle/man etc
- Analyse pathogenic mechanisms
- Consider for serodiagnostics
- Monitor disease (epidemiology)
- Test for effective antibiotic treatments
- Consider vaccine development
- Identify route(s) of transmission –
  - Design prevention measures
  - Change farm management
Identifying and classifying BDD treponemes

Important to help understand how they cause disease.

Classified by:

- Morphology
  - Electron microscopy
- Gene sequencing
  - 16S rDNA gene
  - Flagellin gene
- Cell wall proteins
- Enzyme secretion patterns
Digital dermatitis treponemes:
Isolates from digital dermatitis in cattle and sheep

Bovine DD treponeme

Ovine DD treponeme
T. denticola-like

T. phagedenis-like

T. vincentii / T. medium-like

16S rDNA Phylogenetic Analysis
Of BDD treponemes.
Flagellin gene sequences in BDD:

1: T. medium-like

2: T. phagedenis-like

3: T. denticola-like

Within groups: Close homology. Between groups: significant heterogeneity.
Identifying BDD treponemes by Enzyme secretion.

<table>
<thead>
<tr>
<th>Species/Group</th>
<th>DSM 12168</th>
<th>ATCC 700293</th>
<th>ATCC 35580</th>
<th>Reiter</th>
<th>ATCC 700334</th>
<th>ATCC 35405</th>
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<td>Group 3</td>
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</tr>
</tbody>
</table>

- indicates negative activity; + indicates positive activity.
Digital dermatitis treponemes: 3 groups

Characterised by:

- Gene sequences for:
  - Flagellin gene
  - 16S RNA gene
  - Enzyme secretion

- Confirmed by:
  - SDS-Page protein profiles
  - Serology by ELISA
  - Western blotting with DD sera

- Three clear BDD treponeme groups – apparently unique to BDD/CODD

- Proposed 3 new subspecies of treponemes.

New treponeme species


*Treponema pedis* sp. nov., a novel spirochete isolated from Bovine Digital Dermatitis lesions.

How do treponemes cause digital dermatitis?

- What is the infection reservoir?
- How are they transmitted between animals/farms/host species?
- Why such a fast disease spread?
- How do they damage tissues?
Transmission of BDD

- What is the treponeme reservoir(s)?
- What are the transmission routes?
Outbreaks of BDD within herds are season dependent, with the highest incidence in winter (housing) months.

Antibiotics have a temporary effect

Treated cattle develop disease soon again

Cattle can carry disease onto new farms

Cleaner farms have fewer outbreaks
What is route of disease transmission?
Tracking treponemes in DD lesions

- Normal foot skin
- DD skin
- Treponemes between and within skin cells
- DD skin, showing treponemes in hair follicles
Immunohistochemistry of a BDD lesion.

Treponemes found in hair follicles and sebaceous glands. Potential route of invasion of organisms into foot tissues.

Q - Why?
A - Weakest point in skin physical barrier
Are spirochaetes common infective agents between affected cattle and sheep?

Do they transmit DD across the two species?


Origin of DD treponeme infections?

- Skin flora?
- GI tract?
- Feet?
- Farm environment?
- Other beasties?
What is the main reservoir of infection?
Detecting the 3 BDD treponeme groups

Designed PCR detection systems for all 3 BDD treponeme groups and for treponemes in general

Used to probe various tissues from cows & the farm environment
**Results: Association of BDD treponemes with DD lesions**

<table>
<thead>
<tr>
<th>Biopsy Source</th>
<th>Farm &amp; Date Collected</th>
<th>DNA Ext. date</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Trep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow 13</td>
<td>Claypits Manor, 08/12/03</td>
<td>23/01/2007</td>
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<tr>
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<td>Cow 167 Right Hind</td>
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<td>Cow 200</td>
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<tr>
<td>Cow 819</td>
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<tr>
<td>Cow 187</td>
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<td>nd</td>
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<tr>
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<tr>
<td>Cow 159</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Cow 323</td>
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<tr>
<td>Cow 100</td>
<td>Woodpark 13/08/05</td>
<td>21/11/2006</td>
<td>\</td>
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<tr>
<td>Cow 5</td>
<td>Woodpark 16/12/05</td>
<td>09/01/2006</td>
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<td>nd</td>
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<tr>
<td>Cow 67 Left Hind</td>
<td>Woodpark 23/06/06</td>
<td>20/11/2006</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Cow 67 Right Hind</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<td>nd</td>
</tr>
<tr>
<td>Cow 577</td>
<td>Manor Park 15/11/06</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>nd</td>
</tr>
<tr>
<td>Cow 87</td>
<td>Badgers Reke 29/11/06</td>
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<td>Cow 256</td>
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<tr>
<td>Cow 574</td>
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<td></td>
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<td>X</td>
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<td>Cow X</td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

**Most BDD lesions have all 3 BDD treponemes present**

**Why?**

Symbiotic need?

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Association of BDD treponemes with normal tissues

BDD treponemes are NOT found in normal feet or other host tissues.

Must be elsewhere?

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Date/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rumen 2</td>
<td>Abbatoir 15/12/05</td>
</tr>
<tr>
<td>Colon</td>
<td>Abbatoir 15/12/05</td>
</tr>
<tr>
<td>Rectum</td>
<td>Abbatoir 15/12/05</td>
</tr>
</tbody>
</table>
Association of BDD Treponemes with tissues

- Treponemes could be found in all hoof tissues
- BDD treponemes found in ALL BDD lesions
- However, those found on normal skin were not those readily identified in BDD lesions.
- No other tissues were PCR+ve for the BDD treponemes
- Where are the BDD treponemes coming from?
- Why do we find all 3 treponemes in most BDD lesions?
Are BDD treponemes in the farm environment?

<table>
<thead>
<tr>
<th>Source</th>
<th>Farm and Date Collected</th>
<th>DNA Date</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Trep</th>
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</thead>
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<tr>
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<tr>
<td>Cow 138 Faecal</td>
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<tr>
<td>Slurry sample (straw)</td>
<td>&quot;</td>
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<tr>
<td>Slurry sample (Floor of yard)</td>
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<tr>
<td>Slurry sample (Floor of yard)</td>
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<td>Slurry sample (Field gate)</td>
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<td>Slurry + Straw (shed floor)</td>
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<td>Slurry near shed</td>
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<td>Slurry/soil near waterbutt</td>
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<td>Acute DD Cow's urine sample</td>
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<td>Cow 547 (DD negative) urine sample</td>
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<td>Acute DD Cow 67 start faecal sample</td>
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<tr>
<td>Acute DD Cow 67 middle faecal sample</td>
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<tr>
<td>Cow pat in barn</td>
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<td>&quot;</td>
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<tr>
<td>Slurry in barn sample 1</td>
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<td>Puddle in barn</td>
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<td>Acute DD cow's faeces + 100µl T19</td>
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</tbody>
</table>

All farm environment samples NEGATIVE for BDD treponemes
Detection of BDD Treps in farm environment?

- The "general" treponeme PCR detected treponemes in the majority of samples from dairy farms.

- However, environmental or faecal samples were negative for the BDD-specific treponemes.
Do Digital dermatitis treponemes come from cow GI tract?

- Have obtained 4 bovine GI treponeme isolates
  - 2 from colon
  - 2 from abomasum
- 16S rDNA gene sequenced
  - Low homology with DD treponemes (80-87%)
  - Thus, are different organisms to those seen in BDD lesions
- GI tract **NOT** shown to be source of DD treponemes
Origin of BDD treponemes?

- Skin flora?
  - Not likely
- GI tract?
  - Not likely
- Feet?
  - Probable
- Free living organisms?
  - No +ve data
- Other possible reservoirs
  - Small mammals/wildlife?
  - Arthropods (eg eye gnats, flies)?
  - Not found
Cow-cow transmission of BDD treponemes?

- Evidence currently suggests that the main/only infection reservoir is the BBD lesion itself.

- Thus, transmission is assumed to be from foot to foot with brief survival in slurry enabling this transmission.
Prevention or treatment of BDD/CODD?

- Need to break transmission route.
- Farm management or vaccine
- Once infection established, need another approach.
- Antiseptics/antibiotics?
Which antibiotics work against the BDD treponemes?
## Antibiotic treatment?

### Minimum Bactericidal Concentrations of antibiotics v DD treponemes

<table>
<thead>
<tr>
<th>Trep isolate</th>
<th>Bactericidal concentration of antimicrobial agents (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pen</td>
</tr>
<tr>
<td>G187</td>
<td>0.01</td>
</tr>
<tr>
<td>T323C</td>
<td>0.03</td>
</tr>
<tr>
<td>T184</td>
<td>0.06</td>
</tr>
<tr>
<td>T19</td>
<td>0.06</td>
</tr>
<tr>
<td>T35</td>
<td>0.06</td>
</tr>
<tr>
<td>T54</td>
<td>0.03</td>
</tr>
<tr>
<td>T56</td>
<td>0.06</td>
</tr>
<tr>
<td>T257</td>
<td>0.03</td>
</tr>
<tr>
<td>T272-1A</td>
<td>0.03</td>
</tr>
<tr>
<td>T3552B</td>
<td>0.03</td>
</tr>
<tr>
<td>G169A</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Penicillin is the most effective antibiotic against all BDD/CODD treponemes.

Lincomycin and spectinomycin (common BDD treatments) are relatively ineffective.

Lincomycin and spectinomycin are probably very effective versus other bacteria present in lesions.

3rd generation cephalosporins eg ceftiofur are potentially useful (do not get into milk)

According to Tesco, key areas that will be focussed on through the collaboration will include:

- Improved milk quality
- Higher returns for farmers
- Best practices in terms of environmental production impacts.
- Better consumer service and product innovation.

First project:
Trial of an antibiotic to treat digital dermatitis
Treponemes and hoof tissues: interactions

Processes:
- Attachment/adhesion
- Penetration
- Cell viability
- Cell activation
- Antimicrobial activities
- Inflammatory response
- Tissue damage/remodelling

Cells to be analysed:
- Keratinocytes
- Dermal cells
- Fibroblasts
- Hair follicle cells
- Sebaceous gland
- Sweat gland
Virulence factors of BDD Treponemes.

Why are these Treponemes associated with BDD?

Is it because they are particularly motile, aerotolerant or pathogenic within the foot environment?

Studies of human Treponemes suggest a strong genetic component to virulence (pathogenicity) of organisms.
Virulence factors are mechanisms/products of pathogens that promote their ability to cause infection and disease.

Two types:

- Factors promoting colonisation/invasion of host.
- Factors causing damage to host.

Could be caused by a bacteriophage (Subviral particle which infects bacteria and changes their function).
Digital dermatitis treponemes: an associated bacteriophage

- A bacteriophage seen in BDD treponeme cultures by EM.
- Role: transferring pathogenicity elements between bacteria?
Unravelling the treponeme genetic code

- The treponeme genome is comprised of almost 1 million base pairs (bp)
- Circa 1,000 genes
- Today’s technology puts sequencing such organisms as this within our grasp
- We have this technology in University of Liverpool
Two whole treponeme genomes sequenced so far
- T medium spp bovis
- T medium (human)

Already have evidence of inserted sequences in BDD treponemes which are from bacteriophages or are seen in other pathogenic bacteria (Fusobacterium, Dichelobacter and Clostridium)

Another 3 treponemes are being sequenced.........
BDD Treponeme Genome Sequencing: Benefits

- Understand where organisms originate
- Identify pathogenicity factors
- Identify microbial interactions
- Identify chemotherapeutic targets
- Identify transmission pathways
- Provide rationale for vaccine development
Preliminary studies show aerotolerance by some BDD treponemes (normally anaerobic).

If a recently acquired characteristic, may explain why disease has spread so quickly

Answer in the genome?

Watch this space...
Could the BDD treponemes be involved in any other new diseases?

Many other existing foot lesions in cattle, generally considered non infectious:

- White line disease
- Sole ulcers
- Toe necrosis.

Recently, there have been many reports of severe infected forms of these diseases which have not responded to treatment. Could this be due to BDD treponeme infection?

Tested for presence of BDD treponemes (PCR)
Is there BDD Treponeme involvement in other cattle foot diseases?

<table>
<thead>
<tr>
<th>Disease</th>
<th>N</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Gen trep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toe necrosis</td>
<td>19</td>
<td>18</td>
<td>17</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Non healing Sole ulcer</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Non healing White line disease</td>
<td>16</td>
<td>14</td>
<td>15</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Heel horn erosion</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Ulcerative Mammary Dermatitis</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>
Some cows are more susceptible to BDD than others: is this due to genetic differences between cows?
Summary

- Identified bacteria associated with BDD & CODD
- Identified just one reservoir of infection - the foot
- Good ideas about how infection enters cow feet
- Know which antibiotics to test in vivo
- Understand genetic basis for BDD susceptibility/resistance
- Genome sequencing BDD treponemes should inform:
  - Why they cause BDD
  - Any vaccine potential
  - Therapeutic targets
  - Transmission studies
  - Provide high and low tech answers to disease prevention or treatment
The real workers

Å Nick Evans
Å Jenni Brown
Å Tony Hart
Å Rachel Scholey
Å Dorina Timofte
Å Richard Birtles
Å Prem Singh

And those who paid for it: DEFRA, BBSRC

Å Richard Murray
Å Rob Smith
Å Roger Blowey
Thank youéééé.

This stuff never goes off, does it?