‘Colitis’ treatment and control
(The grey scour syndrome)

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Octagon Services Ltd
Overview

• Diseases – organisms
• Sensitivity - MICs – MBCs,
• Resistance / Breakpoints
• Medications
• Pharmacokinetics (PK) – in the gut
• Efficacy
• Immunity
• Approaches to control
Overview – diseases and organisms

- Spirochaetal diarrhoea (colitis)
- Swine dysentery
- Porcine proliferative enteropathy (ileitis)
- Salmonellosis
- Yersinia
- Collibacillosis
- Clostridium

- Brachyspira pilosicoli
- B. hyodysenteriae
- Lawsonia intracellularis
- S. enterica Typhimurium
- Y. enterocolitica
- E. coli
- Clostridium perfringens
Infectious causes of colitis and their incidence (Thomson et al, 1998)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Single</th>
<th>Mixed</th>
<th>Total</th>
<th>Ident (%)</th>
<th>Farms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. pilosicoli</td>
<td>21</td>
<td>23</td>
<td>44</td>
<td>39</td>
<td>52</td>
</tr>
<tr>
<td>Atypical B. hyo</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>B. hyodysenteriae</td>
<td>6</td>
<td>3</td>
<td>9</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>L. intracellularis</td>
<td>3</td>
<td>10</td>
<td>13</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Y. pseudotuberculosis</td>
<td>4</td>
<td>13</td>
<td>17</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>E. coli</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>C. perfringens</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Conclusions

• B. pilosicoli may be more widespread than thought (Scottish phenomenon – doubt it?)
• Lawsonia may be less problematic than we expect (95% farms, 62% pigs - Mortimer et al, 2000) - (Control measures good – Salinomycin, CTC & Tylosin?) – acute deaths (PHE)
• B. hyodysenteriae low – good - severity
• Salmonella – on-going problem (PMWS)
• Yersinia?
• Others?
### Comparative effects of *Brachyspira* on production

(Thomson et al, 2003)

<table>
<thead>
<tr>
<th>Group</th>
<th>Feature</th>
<th>Clinical score (%)</th>
<th>Path score (%)</th>
<th>ADG (g)</th>
<th>ADG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Uninfected</td>
<td>0</td>
<td>1</td>
<td>810</td>
<td>-</td>
</tr>
<tr>
<td>B. hyodysenteriae</td>
<td>Path form</td>
<td>29</td>
<td>45</td>
<td>590</td>
<td>-27</td>
</tr>
<tr>
<td>B. hyodysenteriae</td>
<td>Mild form</td>
<td>8</td>
<td>16</td>
<td>740</td>
<td>-9</td>
</tr>
<tr>
<td>B. pilosicoli</td>
<td>-</td>
<td>10</td>
<td>19</td>
<td>710</td>
<td>-12</td>
</tr>
</tbody>
</table>
Bacterial susceptibility to antimicrobials

• Sensitivity discs – plate test – zone diameter (13mm VLA) – sensitive / intermediate / resistant
• Minimum inhibitory concentrations (MICs)
  – Level of antimicrobial that prevents growth
  – Plate dilution tests - antibiotic in the agar – less sensitive
  – Broth dilution – doubling dilutions – can be very sensitive
• Minimum bactericidal concentrations (MBCs)
  – Usually broth culture and sub-culture to plate or broth
  – Level of drug that prevents growth on sub-culture
• Bacteriostatics – macrolides, lincosamides, pleuromutilins, tetracyclines
  – MBC/MIC can be very large
• Bactericidals – Aminoglycosides, aminocyclitols, fluoroquinolones, penicillins, trimethoprim/sulphas
  – MBC/MIC small or the same
## MICs against B. hyodysenteriae (76 isolates) (Karlsson et al, 2002)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC 50 (µg/ml)</th>
<th>MIC 90 (µg/ml)</th>
<th>Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valnemulin</td>
<td>0.031</td>
<td>0.5</td>
<td>≤0.016 - 2.0</td>
</tr>
<tr>
<td>Tiamulin</td>
<td>0.125</td>
<td>1.0</td>
<td>≤0.016 - 2.0</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>16</td>
<td>64</td>
<td>≤1.0 - 64</td>
</tr>
<tr>
<td>Tylosin</td>
<td>&gt;256</td>
<td>&gt;256</td>
<td>≤2.0 - &gt;256</td>
</tr>
</tbody>
</table>
MICs against B. hyodysenteriae (76 isolates) (Karlsson et al., 2002)
# Sensitivity – breakpoints

(Ronne and Szancer, 1990)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC breakpoints (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitive</td>
</tr>
<tr>
<td>Tiamulin</td>
<td>≤1</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>≤4</td>
</tr>
<tr>
<td>Tylosin</td>
<td>≤1 (8)</td>
</tr>
<tr>
<td>Dimetridazole</td>
<td>≤8</td>
</tr>
</tbody>
</table>
Ronne and Szancer are about right for tiamulin, lincomycin and dimetridazole.

Probably a bit low for tylosin (>16?).

Valnemulin breaks lower than tiamulin?

Precision difficult.

Difference in susceptibility patterns – waves.

Dosage/concentration effect in gut.

Mutations – change to site of activity.

Resistance – Step to Jump (tylosin).
### MICs B. pilosicoli (25 isolates)

*(Kinyon et al, 2002)*

<table>
<thead>
<tr>
<th>Antibiotic (Breakpoint)</th>
<th>MIC 50 (µg/ml)</th>
<th>MIC 90 (µg/ml)</th>
<th>Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valnemulin (&gt;4)</td>
<td>0.06</td>
<td>0.5</td>
<td>0.03 - 2.0</td>
</tr>
<tr>
<td>Tiamulin (&gt;4)</td>
<td>0.125</td>
<td>1.0</td>
<td>0.06 - 8.0</td>
</tr>
<tr>
<td>Lincomycin (&gt;36)</td>
<td>32</td>
<td>64</td>
<td>&gt;512</td>
</tr>
<tr>
<td>Tylosin (&gt;16)</td>
<td>&gt;512</td>
<td>&gt;512</td>
<td>&lt;16 - &gt;512</td>
</tr>
</tbody>
</table>
## MICs L. intracellularis (intracellular)
(McOrist et al, 1995; Mackie, 1996)

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC &gt;99% inhibition (2-3 isolates)</th>
<th>MIC &gt;90% inhibition (1 isolate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlortetracycline</td>
<td>1</td>
<td>≤1</td>
</tr>
<tr>
<td>Tiamulin</td>
<td>4</td>
<td>≤2</td>
</tr>
<tr>
<td>Valnemulin</td>
<td>&lt;1</td>
<td>≤1</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>32</td>
<td>≤0.25</td>
</tr>
<tr>
<td>Tylosin</td>
<td>64</td>
<td>≤2</td>
</tr>
<tr>
<td>Tilmicosin</td>
<td>2</td>
<td>≤0.125</td>
</tr>
<tr>
<td>Spectinomycin</td>
<td>32</td>
<td>&lt;64</td>
</tr>
</tbody>
</table>
MICs L. intracellularis (intracellular)  
(McOrist et al, 1995; Mackie, 1996)

- Intracellular MICs – bathe infected cells in antibiotic for 6 days – difficult work
- It is a bio-model – like gut being bathed in medication – intracellular concentration of AM required
- MIC 99% - could not correlate with AM concentrations in the small intestine
- MIC 90% - demonstrates strong inhibitory bio-effect – correlates quite well
Intracellular/extracellular inhibitory effect of tylosin (MIC 99% 64µg/ml) (Mackie, 1996)
## Other organisms – resistance (%)

<table>
<thead>
<tr>
<th>Antimicrobial (Disc strength)</th>
<th>Salmonella spp (VLA, 2003)</th>
<th>E. coli (VLA, 2004)</th>
<th>Y. enterocolitica (Fossler et al, 1996) MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (10ug)</td>
<td>61</td>
<td>44</td>
<td>97</td>
</tr>
<tr>
<td>Tetracycline (10ug)</td>
<td>84</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td>Neomycin (10ug)</td>
<td>7</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Apramycin (15ug)</td>
<td>5</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Trimethoprim/S (25ug)</td>
<td>63</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>Enrofloxacin (5ug)</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Spectinomycin (Laperle et al, 1996)</td>
<td>44</td>
<td>69</td>
<td>0</td>
</tr>
</tbody>
</table>
### ‘Colitis’ medications and dosage rates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Injection</th>
<th>Water</th>
<th>Feed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treat</td>
<td>Treat</td>
<td>Prevent</td>
</tr>
<tr>
<td>Tylosin</td>
<td>2-10</td>
<td>25</td>
<td>3-6 (5)</td>
</tr>
<tr>
<td>Lincomycin</td>
<td>10</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>LINCO/spectin</td>
<td>-</td>
<td>3.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Linco/SPECTIN</td>
<td>-</td>
<td>6.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Tiamulin</td>
<td>10</td>
<td>8.8</td>
<td>5</td>
</tr>
<tr>
<td>Valnemulin</td>
<td>-</td>
<td>-</td>
<td>3.75</td>
</tr>
</tbody>
</table>
## ‘Colitis’ medications and dosage rates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Injection</th>
<th>Water</th>
<th>Feed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxyccillin</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>Apramycin</td>
<td>-</td>
<td>7.5-12.5</td>
<td>4-8</td>
</tr>
<tr>
<td>Neomycin</td>
<td>-</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Trimethoprim/S</td>
<td>15</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>-</td>
<td>10-20</td>
<td>10-20</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>10-20</td>
<td>10-30</td>
<td>20</td>
</tr>
</tbody>
</table>
‘Colitis’ medications and dosage rates

• Watch dosage rates
  – Inclusion levels
  – Appetite
  – Age (20kg - feed 5% bwt; 80kg - 2.5% bwt)
  – Sensitivity/tolerance

• Dose/effect – don’t expect treatment with prevention level – Cost/benefit

• Duration – long low; short high

• Immunity – Biosecurity – Disease Severity
Gut pharmacokinetics – single feed
(Clemens et al, 1975)
Gut pharmacokinetics – single feed
(Clemens et al, 1975)
Gut pharmacokinetics

• Simple rules of thumb
  - Feed to faeces 1kg to 0.4 kg = X 2.5
    • Non-absorbed products - eg spectinomycin approx 44ppm in feed could give 110ppm in colon
    • Absorbed products – eg valnemulin 75ppm in feed gives 1.68ppm in colon
  - Colon contents to ileal contents (rolling means) = ÷ 4
    • eg spectinomycin 27.5ppm
    • eg valnemulin 0.42ppm
  - Approaching MICs for Lawsonia
Efficacy – dose titration valnemulin for the prevention of SD (Burrows et al, 1996)
Efficacy – dose titration valnemulin for the treatment of SD (Burrows et al 1996)
SD treatment conclusions

• Prevention is a valid claim - dose/effect
• Prevention low dose – can control infection
• Treatment higher dose (10 times prevention)
  – More organisms
  – Deeper infection
  – Drug concentration gradient
  – Higher risk of incomplete elimination?
  – Higher risk of resistance?
• Eradication potential – bactericidal levels
Spirochaetes in a colonic crypt (Thomson 2004)
Efficacy – dose titration lincomycin for the prevention of ileitis (Winkelman et al, 1998)
Ileitis prevention conclusions

- Good dose/effect correlation with intracellular MIC and in feed level
- Lincomycin 22ppm too low
- Lincomycin 44ppm and above good effect, little improvement as dose increases to 110ppm
- Lincomycin 220ppm in feed, 25ppm in ileum and 101ppm in colon (DeGeeter et al, 1980)
Immunity

• Immunity can develop usually 2 weeks after infection
  – Ileitis (L. intracellularis)
  – Colitis (B. pilosicoli)
• Self cure seen
• Performance deterioration though
• Prolonged protection
• Strategic medication – moderate disease
• Antibiotic resistance?
Colitis prevention trial (Glossop et al, 2000)
Ileitis treatment trial (Jones et al, 2004)

Days

Ave diarrhoea score

0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8  0.9  1.0  1.1

0  7  14

Control  Valnemulin 75ppm
Ileitis patterns of infection (McOrist, 2004)

- Chronic form (PIA)
- Acute form (PHE)
Approaches to ‘colitis’ control

• Eliminate infections
  – Eradication – SD done, difficult ileitis, colitis (Bp), salmonella
  – High level treatment short period at break in production on entry to the finishers
  – When move to clean buildings (poultry approach)
  – Water medication may be better approach
    • Higher levels
    • Better kill
    • Better control – timing, duration and levels
Approaches to ‘colitis’ control

• Long term low level approach
  – Salinomycin (GPs) all the time
  – Tylosin all the time?

• Acceptability any more?
  – Processors / supermarkets
  – Banning GPs
  – Reduction in AB usage
Approaches to ‘colitis’ control

• Strategic use plus immunity (unclean units)
  – Allow some disease to build immunity
  – Use ABs strategically to bring infection under control to reduce production losses
  – Not suitable for severe diseases such as SD
  – Possible for Ileitis and Colitis?

• Need history and good diagnostics – source/batch basis
  – Lowest common denominator

• Medication built in with other disease patterns on unit eg respiratory (CTC, TMPS, EP vaccination)
  – High, low level
  – In feed (routine / delays / mills) or water – even injectables
  – Timing – on arrival – when disease expected?
  – Duration – infection dies out LI 14 days, Bp 28 days, Bh 60days
  – Medication selection

• Production performance / cost / value
Thank you for your kind attention

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