Antibiotic Therapy of Bovine Mastitis

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It’s Nice to be in Sunny Sicily!

Current Conditions in Kalamazoo, Michigan:
-10º C and 0.5 m of snow!

Components of Effective Mastitis Control Programs

- Control the Rate of New Infections
  - Properly functioning milking machines
  - Post-milking teat antisepsis
- Reduce the Duration of Existing Infections
  - Lactational antibiotic therapy (LCT)
  - Dry cow therapy (DCT)
  - Culling of refractory animals
Antimicrobial Susceptibility Testing of Mastitis Pathogens

Antibiotic Susceptibility Testing of Mastitis Pathogens

- Is it relevant?
- When is it necessary?

- Antibiotic Susceptibility Testing (ASTs) *guide* the clinician in selecting the most appropriate agent
  - Not a treatment recommendation
  - Response/Expectations should be adjusted according to disease state
AST Assay Components

- Method (CLSI M31)
  - Agar disk diffusion (qualitative)
  - MIC method (quantitative)
  - Methods are not designed to mimic in vivo conditions
    - Specific conditions of test
    - Quality control information
- Interpretive criteria
  - Are not “portable”
  - Veterinary specific
    - Host/pathogen/drug specific
      - Linked to approvals

Interpretive Categories

- **Susceptible**: implies that there is a high likelihood of a favorable clinical outcome when the drug is administered at label dosage.

- **Resistant**: implies that there will not be a favorable clinical outcome, because the achievable systemic concentrations of the agent will be lower than the MIC of the causative organism with normal dosage schedules and/or fall in the range or where specific microbial resistance mechanisms are likely (e.g., β-lactamases), and clinical efficacy has not been reliable in treatment studies.
Data Requirements for Development of Interpretive Criteria

- **Microbiological** - The breakpoint should fit within the limits of clusters of susceptible bacterial populations
- **Pharmacological** - The upper MIC limit for establishing susceptibility should be lower than physiologically achieved levels; when appropriate
- **Clinical** - The population defined as susceptible should be documented as responding clinically and reasonably correlated to *in vivo* results

Development of Interpretive Criteria for Mastitis Therapeutics

- Current efficacy protocols require pre- and post-treatment cultures with cure based upon elimination of the pathogen
- MIC breakpoints will have to be based upon the achieved drug levels in the milk
- *In vitro/in vivo* correlations can probably be established for organisms confined to milk such as the streptococci
- It may be difficult to establish *in vitro/in vivo* correlations for chronic *S. aureus* or coliform IMI
  - Scar tissue barriers or intracellular organisms

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Therapy of S. aureus Mastitis

- Overall efficacy is 30-40% for chronically infected animals
  - Efficacy is >80% if infection is <2 wk duration
- Treatment may be indicated as long as these criteria are met:
  - Animal has a single quarter infected
  - Animal is ≤3 lactations
  - Infection is less than 30-60 days in duration
  - Animal is valuable genetically
- Otherwise, general recommendation is to cull the animal from the herd

Penicillin-Novobiocin Interpretive Criteria
In vitro/in vivo Correlation Study

- Provisional Breakpoints of ≤1/2 µg/ml for susceptible established based upon MIC data of mastitis pathogens and achieved milk levels
- Pre-treatment cultures to determine pathogen and susceptibility
  - All isolates categorized as susceptible
- Treated as per label recommendation
- Cure based upon eradication of pathogen 28 days post-treatment

IMI Treated by Pathogen

- Pathogens treated (No.)
  - *S. aureus*
    - Short-duration (20)
      - <2 weeks in duration
    - Chronic (20)
  - *S. agalactiae* (20)
  - *S. dysgalactiae* (20)
  - *S. uberis* (22)

Results of P/N Correlation Study

- % Eradication

- S. agalactiae: 35%
- S. dysgalactiae: 70%
- S. uberis: 91%
- S. aureus (SD): 0%
- S. aureus (Chronic): 90%

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Interpretive Criteria for Penicillin/Novobiocin
CLSI M31, Table 2

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Disk Content</th>
<th>Zone Diameter (mm)</th>
<th>MIC Breakpoint (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
<td>R</td>
</tr>
<tr>
<td>Penicillin-novobiocin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovine mastitis</td>
<td>≥18</td>
<td>≤15</td>
<td>≤14</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus dysgalactiae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus uberis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AST Summary

- Mastitis specific interpretive criteria can be developed
  - Excellent agreement for streptococci (>90%)
  - Scar tissue formation and other factors confound *S. aureus* data
    - Treatment cascade must be followed for susceptible isolates
- Severity of disease impacts response
- Agents with mastitis specific interpretive criteria
  - Penicillin/novobiocin, pirlimycin, ceftiofur (LC/DC)
When should you conduct ASTs?

- Resistance tends to be herd specific
- If resistance is low or known, empiric therapy may be used for initial treatment
  - For treatment failures after initial therapy
    - Consider DCT or culling *S. aureus* infected cows
    - Species level identification and ASTs should be useful in guiding therapy for environmental streptococci
      - Different susceptibility patterns
        - *S. dygalactiae*, *S. uberis*, enterococci

Efficacy of Antibiotic Therapy for Bovine Mastitis
How do we measure efficacy for LCT products?

- Basic protocol used in both US and EU
  - Naturally occurring infections
  - Infections are established pre-treatment
  - Cows are sampled at 0, 7, 14, 21, 28 days post-treatment
    - Must be negative for original pathogen at all sampling intervals
    - US – negative control, test agent must be statistically different
    - EU – positive control, non-inferiority design
  - Indications are organism specific (label indicated pathogens)

How do we measure efficacy for DCT products?

- Basic protocol used in both US and EU
  - Naturally occurring infections (field trials)
  - Infections are established pre-treatment at DO
  - Cows are sampled at within 7 days after calving
    - Post-calving samples must be negative for original pathogen
    - US – negative control, test agent must be statistically different
    - EU – positive control, non-inferiority design
  - Indications are organism specific (label indicated pathogens)

FDA-CVM Guidance No. 49

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Future Consideration for Efficacy Studies

- Susceptibility testing performed prior to treatment and only cows with susceptible isolates enrolled in study
- Genotyping to eliminate new infections and confirm re-occurrence of original infection
- Lack of sufficient infections in well managed herds makes approvals for contagious pathogens difficult
- No approvals of prevention claims for DCT
  - Treatment claims only


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Antibiotic Efficacy against Contagious Mastitis Pathogens
**Staphylococcus aureus**

- Efficacy confounded by factors that limit bug-drug interaction
  - Scar tissue barriers
  - Sequestration inside phagocytic cells
- Other factors that may impact efficacy
  - Strain differences (virulence)
  - Antimicrobial resistance


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### Efficacy Table

<table>
<thead>
<tr>
<th>Mastitis Type</th>
<th>Agent</th>
<th>Penicillin - susceptible</th>
<th>Penicillin-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% Efficacy</td>
<td>Agent</td>
</tr>
<tr>
<td>Subclinical</td>
<td>Various</td>
<td>34</td>
<td>Various</td>
</tr>
<tr>
<td>Subclinical</td>
<td>Penicillin G Penethamate</td>
<td>48.9 - 56.5, 62.7 – 66.8</td>
<td>Penicillin G Penethamate, Methicillin Tamethicillin</td>
</tr>
<tr>
<td>Clinical</td>
<td>Penicillin</td>
<td>43</td>
<td>Spiramycin or Enrofloxacin</td>
</tr>
<tr>
<td>Clinical</td>
<td>Various</td>
<td>59</td>
<td>Various</td>
</tr>
<tr>
<td>Clinical</td>
<td>Penicillin G + Neomycin or Penicillin G</td>
<td>75.6</td>
<td>Amoxicillin + Clavulanate or Spiramycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56.1</td>
<td></td>
</tr>
</tbody>
</table>


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### Extended Therapy of *S. aureus*

<table>
<thead>
<tr>
<th>Mastitis Type</th>
<th>Agent</th>
<th>Standard Therapy</th>
<th>Extended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical</td>
<td>Pirlimycin</td>
<td>2 days</td>
<td>8 days</td>
</tr>
<tr>
<td></td>
<td>Penicillin G</td>
<td>2 days</td>
<td>4 days</td>
</tr>
<tr>
<td></td>
<td>Penethamate</td>
<td>62.7%</td>
<td>68.8%</td>
</tr>
<tr>
<td></td>
<td>Methicillin</td>
<td>24.4%</td>
<td>32.4%</td>
</tr>
<tr>
<td></td>
<td>Tamethicillin</td>
<td>20.0%</td>
<td>48.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mastitis Type</th>
<th>Standard Therapy</th>
<th>Extended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Various</td>
<td>3 – 4 days</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>2 days</td>
</tr>
</tbody>
</table>


### *Streptococcus agalactiae*

- Penicillin highly effective (>90-95%)
  - No need for susceptibility testing
- Other antimicrobial classes
  - Approximately 10-15% of strains will be resistant to macrolides-lincosamides
    - Erythromycin
    - Pirlimycin

Antibiotic Efficacy against Environmental Mastitis Pathogens

Environmental Streptococci

- Three organisms comprise majority of isolates in this category
  - *S. dysgalactiae*
  - *S. uberis*
  - *Enterococcus* spp.
    - Distribution may vary substantially from herd to herd
    - Antimicrobial resistance is primary factor influencing efficacy
- Teat Seal products may provide a non-antibiotic solution to controlling environmental streptococci
  - May also be used in combination with DCT to treat existing infections
Coliforms

- *E. coli, Klebsiella* spp.
  - Acute clinical mastitis
    - Infections are short lived
    - Supportive therapy important
  - Antibiotic therapy
    - Ceftiofur (Hallberg et al.)
      - IMM: 86%
    - Cefquinome (Shpigel et al., JDS2003)
      - IMM: 82.6%
      - IM/IMM: 95.2%

Summary

- Antimicrobial therapy is an essential component of mastitis control programs
- ASTs may provide useful information provided that IC are mastitis specific
  - Too costly for routine use
- Efficacy of mastitis therapies varies by pathogen
  - An understanding of the response rates by pathogen is critical in proper use of antimicrobial agents as well as proper management of the disease within a herd
Il Finito!