Local Antimicrobial Therapy for the Treatment of Equine Orthopedic Infections

IVMA 127th Annual Meeting

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Local Antimicrobial Therapy

- Delivery of antimicrobial drugs directly to the site of infection
- Adjunct to systemic antimicrobial drug administration
- Achieves very high levels of antimicrobials at the local site of infection
- Low total doses reduce systemic toxicity

Purpose

- Describe methods of LAT (no details)
- Describe indications and complications for LAT
- Review outcomes of horses treated with LAT for musculoskeletal contamination or orthopedic infection
- EVIDENCE BASED MEDICINE
  What is the evidence for use of LAT in clinical practice?
**Minimum Inhibitory Concentration (MIC)**

- Potency of an antimicrobial drug as defined by the concentration of the drug that inhibits or kills bacteria in the laboratory.
- Resistance and susceptibility of microorganisms on lab reports is based upon levels of antimicrobials drugs that can be obtained with systemic administration.
- MIC of most susceptible staphylococcus spp. to gentamicin is 2-4 µg/ml.
- Gentamicin at 6.6 mg/kg can be expected to achieve peak tissue concentrations of ≈ 25 µg/ml.

**Normal horses with healthy tissues**

- Tissue levels and synovial fluid levels of antimicrobial drugs are 20-30% of the levels measured in the serum.

**Factors which reduce levels of antimicrobial drugs at the site of the infection**

- Ischemia, vascular thrombosis, necrosis.
- Microabscesses and macroabscesses.
- Biologic membranes (synovium) are poorly permeable to aminoglycoside drugs.
- Increased joint pressure decreases blood flow to the joint.
Factors which reduce antimicrobial effectiveness at the site of infection

- Low pH
- High numbers of bacteria (Inoculum effect)
- Fibrin
- Biofilms (extracellular polysaccharide that covers microbes)
  **Increases MIC by 500-5000 times**

Rationale for Local antimicrobial therapy
Antimicrobial levels at site of infection are 10-1000 times higher than levels obtained by systemic administration

Local antimicrobial delivery systems

- Intra-articular infusions
  - Direct injection
  - Frequent intermittent infusion via catheter
  - Constant intra-articular infusion
- Biocompatible implants impregnated with antimicrobials
- Regional limb perfusion
  - Intravenous regional perfusion
  - Intraosseous regional perfusion
Intra-articular Injections

- Very high concentrations of AM obtained initially and levels above MIC maintained for about 24 hours
- Easy and quick
- Subchondral bone levels equal to those obtained by IVRP in experimental horses
- 150 mg Gentamicin results in peak level in joint of 4750 µg/ml and > 2 µg/ml for 24 hours
- 500 mg Amikacin in inflamed joints results in 24 h mean level of 20 µg/ml and levels > 4 µg/ml for 48 h

Joint Catheterization with Frequent Intermittent Infusion of Antimicrobial Drugs

- Catheters inserted arthroscopically
  - Large Bore Extension Set with male adaptor cut off
  - Fenestrated drains – Jackson Pratt, Mila multipurpose
- Percutaneous insertion catheters
  - Guidewire introduction catheters
  - Peel-away introduction catheters
  - Mila International (DMS)

Treatment of contaminated or septic synovial structures

- Hogan PM: Proc AAEP 2004
  - Amikacin 500 mg every 2-4 hours
  - Timentin 400-800 mg every 2-4 hours

- Stewart AA et al: Aust Vet J 2010
  - Amikacin 750 mg every 6-8 hours
  - Timentin 250 mg every 6-8 hours
Contant Intraarticular Antimicrobial Infusion (CIAI)

- Antimicrobial drugs are pumped into the synovial cavity through an indwelling catheter using a disposable administration pump.
- Can be used effectively with concentration dependent and time dependent antimicrobial drugs.

Constant Intraarticular Antimicrobial Infusion (CIAI) - Materials

- Joint Infusion System - Mila International
  - infusion pump, air filter, flow control tubing, catheter, peel-away introducer
- Gentamicin, Amikacin
  - Ceftiofur
  - Ticarcillin

Constant Intra-articular Infusion
Dose Calculation
General Guidelines

- **JOINT DOSE** - Give 1/3 of total calculated dose based upon the body weight per 24 hours
- **SYSTEMIC DOSE** – Give 2/3 dose IV
- **TOTAL DOSE SHOULD NOT EXCEED RECOMMENDED DAILY DOSE**
- **TOXICITY** can occur in foals****

Complications of IA antimicrobial administration

- **Synovitis**
- **Catheter failure** – most common in CIAI systems
  - Occluded
  - Dislodged
- **Systemic toxicity** from overdose

Septic joint studies – intermittent or constant joint infusions

<table>
<thead>
<tr>
<th>Number of Horses</th>
<th>LAT Technique</th>
<th>Survived (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Repeated injection every 2-4 h via joint catheter</td>
<td>100</td>
<td>Hogan PM 2004</td>
</tr>
<tr>
<td>38</td>
<td>Repeated injections 4 times daily via joint catheter</td>
<td>86</td>
<td>Stewart AA et al 2010</td>
</tr>
<tr>
<td>7</td>
<td>Constant intra-articular infusion *</td>
<td>57</td>
<td>Adams SB 2000</td>
</tr>
<tr>
<td>31</td>
<td>Constant intra-articular infusion *</td>
<td>90</td>
<td>Lescun TB et al 2006</td>
</tr>
<tr>
<td>23</td>
<td>Constant intra-articular infusion</td>
<td>100</td>
<td>Meagher DT et al 2006</td>
</tr>
</tbody>
</table>

**Overall Survival Rate = 92%**
*Adams, Lescun (Purdue Studies)*

- Septic joints in which treatment has been delayed 5 days or more
- Septic joints which have not responded to conventional therapy
- Septic joints with adjacent osteomyelitis

Intraosseous and Intravenous Regional Limb Perfusion

- Orthopedic infection of limbs from carpus and tarsus distally - osteomyelitis, septic joints, septic physeitis, septic tenosynovitis
- Tourniquet above infected area for 30 minutes or longer to keep drug in limb
- All AM should be diluted in 30-70 ml of sterile saline
  - Minimize tissue reaction to AM
  - Volume needed to distribute the AM in all tissues

Antimicrobial Drugs for IVRP & IORP

(Concentration Dependent Drugs Are Preferable)

- Gentamicin  250-1000 mg
- Amikacin  250-1000 mg
- K Penicillin  $10 \times 10^6$ units
- Timentin  500-1000mg
- Ceftiofur  500-1000mg
Concentrations of antimicrobial in synovial fluid following RLP

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Concentration (µg/ml)</th>
<th>Plasma or Serum</th>
<th>Synovial Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>IORP</td>
<td>1 g</td>
<td>23.7</td>
<td>589 mean, &gt;4 at 24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IORP</td>
<td>1 g</td>
<td>-</td>
<td>221 peak</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>IVRP</td>
<td>125 mg</td>
<td>&lt;1</td>
<td>235 peak at 1 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVRP</td>
<td>500 mg</td>
<td>3</td>
<td>896 mean</td>
<td></td>
</tr>
</tbody>
</table>

Intravenous Regional Perfusion
- Easy technique if good vein exists
- Local tissue levels of antimicrobial as good or better than IORP
- Can be done standing
  - Use same catheter multiple times
  - 20 gauge pediatric jugular catheter

Intraosseous Regional Perfusion
- Useful in foals with small fragile veins
- Can be repeated under sedation once bone hole has been drilled
Tourniquets

- Esmarch tourniquet reduces antimicrobial loss to systemic circulation compared to pneumatic tourniquet in standing horses

Effect of joint lavage done simultaneously with IVRLP on gentamicin concentrations in the lower limb

- Negligible loss of gentamicin in lavage fluids, and acceptable levels in joints

Complications of IVRLP and IORLP

- **IVRLP**
  - Perivascular injection
  - Hematoma
  - Vasculitis
  - Loss of vein (thrombosis)
  - Loss of limb

- **IORLP**
  - Difficult to inject drugs
  - Screw breakage
### IVRLP Studies – Orthopedic Infections

<table>
<thead>
<tr>
<th>Number of Horses</th>
<th>Septic conditions treated</th>
<th>Survived (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>Joints, tendon sheaths, navicular bursa, bone, foot wounds</td>
<td>86</td>
<td>Santchi et al. AAEP 1998</td>
</tr>
<tr>
<td>24</td>
<td>Limb extremities, specific structures not defined</td>
<td>75</td>
<td>Palmer &amp; Hogan AAEP 1999</td>
</tr>
<tr>
<td>18</td>
<td>Joints, bone, foot wounds</td>
<td>89</td>
<td>Cimetti et al AAEP 2004</td>
</tr>
<tr>
<td>9</td>
<td>Tendon sheath, joints, navicular bursa, physis</td>
<td>78</td>
<td>Kelmer G AAEP 2008</td>
</tr>
<tr>
<td>22</td>
<td>Distal phalanx</td>
<td>86</td>
<td>Neil KM JAVMA 2007</td>
</tr>
<tr>
<td>30 (17 received IVRLP)</td>
<td>Navicular bursa, distal phalanx, coffin joint</td>
<td>88*</td>
<td>Caporali F Italian Vet Assoc 2009</td>
</tr>
</tbody>
</table>

**Overall Survival Rate = 84%**

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### Biocompatible implants which can be impregnated with antimicrobial drugs

- Nonbiodegradable implants
  - Polymethylmethacrylate (PMMA)***
- Biodegradable implants
  - Collagen sponges
  - Calcium sulfate (plaster of paris)
  - Ferric-Hyaluronate
  - Polylactide-polyglycolic polymers
  - Microencapsulated doxycycline
  - Dextran gel

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### Antimicrobial impregnated PMMA Beads (AI-PMMA)

- PMMA beads used in humans since early 1970s
- Most commonly used implant for delivery of antimicrobial drugs in humans and animals
PMMA BEADS

- Antimicrobial release bimodal - rapid release for 24 h and sustained release for weeks to years
- Initial local concentrations of antimicrobial are often 200 times higher than can be achieved with systemic administration
- Sustained release >MIC is UNKNOWN
  - Less than 10 days in some trials
  - Many elution trials done in vitro
  - Fibrous tissue impedes diffusion into surrounding tissues

Antimicrobials that may be added to PMMA

- Amikacin
- *Gentamicin
- Tobramycin
- Amoxicillin
- Ciprofloxacin
- Imipenem
- *Ticarcillin
- Cephalosporin
- Clindamycin
- Vancomycin
- Erythromycin
- Metronidazole
- Floroquinolones
- Vancomycin/amikacin
- Cephalosporin/amikacin
- Cephalosporin/metronidazole
- Gentamicin/metronidazole

Antimicrobial powder or liquid to PMMA powder ratio should be < 1:10 or use 10% or less AM

AI-PMMA Case Reports in greater than 5 horses

<table>
<thead>
<tr>
<th>Number of Horses</th>
<th>Contaminated or septic conditions</th>
<th>Survived (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 *</td>
<td>Synovial cavities</td>
<td>92</td>
<td>Butson et al Vet Rec 1996</td>
</tr>
<tr>
<td>22</td>
<td>Wounds, synovial cavities</td>
<td>93</td>
<td>Blackford et al AAEP 1997</td>
</tr>
<tr>
<td>19</td>
<td>Joints, fractures</td>
<td>63</td>
<td>Holcombe et al JVMAA 1997</td>
</tr>
<tr>
<td>8</td>
<td>Pastern joints (infected)</td>
<td>50</td>
<td>Groom et al Can Vet J 2000</td>
</tr>
<tr>
<td>11</td>
<td>Small tarsal joints (infected)</td>
<td>82</td>
<td>Booth et al Vet Rec 2001</td>
</tr>
</tbody>
</table>

Overall Survival Rate = 80%

* 10 cattle also reported
**Gentamicin-impregnated PMMA in Joints**

- Gentamicin-PMMA beads placed in normal tarsocrural joints *
  - 300 mg gentamicin gave 28 µg/ml peak and above 2 µg/ml for 9 days
  - Caused superficial cartilage erosion
- Effective but at what cost to joint?

*Farnsworth et al. Vet Surg 2001

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**Biodegradable Antimicrobial Impregnated Implants**

- Collagen sponges
- Calcium sulfate (plaster of paris)
- Calcium sulfate wrapped in porcine SIS
- Ferric-Hyaluronate
- Polylactide-polyglycolic polymers
- Microencapsulated doxycycline
- Dextran gel/gentamicin

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**Treatment of traumatically induced synovial sepsis with gentamicin impregnated collagen sponges**

<table>
<thead>
<tr>
<th>Number of horses</th>
<th>Contaminated or infected structure</th>
<th>Survival (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Joint, tendon sheath</td>
<td>100</td>
<td>Summerhays GES Vet Rec 2000</td>
</tr>
</tbody>
</table>

- All had arthroscopy/tenoscopy and lavage
- 6/8 had wounds 12 hours or less duration
Biodegradable Antimicrobial Impregnated Implants

- In vitro elution profiles for all implants looks promising.
- In vivo elution profiles in tissues have been promising.
- In vivo elution profiles in joints for all implants that have been tested have been poor.

Joint levels of Gentamicin following insertion of Impregnated Collagen Sponges *

- Synovial fluid levels when 1 sponge (130 mg gentamicin is implanted into tarsocrural joint
  - Peak concentration at 150 µg/ml at 3 h
  - Concentration < 4 µg/ml at 48 hours
- A single intra-articular injection has similar or better pharmacokinetics (and is much less expensive)

* Ivester, Adams. AJVR 2006

Dextran gel/gentamicin

- R-Gel® - Royer Animal Health
- Polymer that can be injected into joints through standard hypodermic needle
- In vitro elution profile: levels >MIC for 5 d
- In vivo elution in tarsocrural joints: levels <MIC in 24 h (Adams, Elrashidy unpublished data)
Summary: Mean Peak Synovial Fluid Concentrations of Gentamicin after LAD

<table>
<thead>
<tr>
<th>Method of delivery</th>
<th>Gentamicin Dose</th>
<th>Mean Peak Synovial Fluid Concentrations (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>8 mg/kg (4gm/500kg)</td>
<td>10.5</td>
</tr>
<tr>
<td>Intraarticular</td>
<td>150 mg</td>
<td>4750</td>
</tr>
<tr>
<td>IVRLP</td>
<td>1,000 mg</td>
<td>580</td>
</tr>
<tr>
<td>IORLP</td>
<td>1,000 mg</td>
<td>385</td>
</tr>
<tr>
<td>PMMA</td>
<td>300 mg</td>
<td>28</td>
</tr>
<tr>
<td>CIAI</td>
<td>50 mg/h</td>
<td>459</td>
</tr>
</tbody>
</table>

What is the evidence that LAT improves survival or soundness when used to treat orthopedic infections?

Levels of evidence for efficacy of LAT

- Level 1: Randomized control trials and all or none case series
- Level 2: Cohort studies with one group receiving exposure and one not
- Level 3: Retrospective case-control studies of patients with and without outcome of interest to determine exposures
- Level 4: Case series and poor quality cohort studies
- Level 5: Expert opinion based upon clinical experience

Most veterinary papers fall into last 2 categories.
What is the evidence – research?
Vancomycin impregnated hydroxyapatite implants for treatment of osteomyelitis in rabbits

- Tibial osteomyelitis with methicillin resistant staphylococcus treated 2 weeks after infection
- 8 Treatment groups
  - Debrided and Not debrided
    - Systemic antibiotics
    - PMMA beads + VMC
    - Hydroxyapatite
    - Hydroxyapatite + VMC
- Clearance of bacteria
  - Debrided + Hydroxyapatite + VMC 82%
  - Debrided + PMMA beads + VMC 70%
  - All others had less than 50%

Shirtliff, Clin Orthop 2002

What is the evidence – research?
"Due to the difficulties in comparing results of animal and human studies, the predictive value of animal studies about osteomyelitis is still unclear."

Experimental ostemyelitis: what have we learned from animal studies about the systemic treatment of osteomyelitis?
Lazzarini et al. J Chemother 2006

What is the evidence – humans?
- PubMed search for papers (May 2010)
  - Osteomyelitis and PMMA 66
  - Osteomyelitis and LAT 57
- Two level 2 case studies (cohort studies) comparing patients treated with or without LAT. All patients received systemic antimicrobials.
  - Outcomes for both studies were similar
What is the evidence – humans?

“Despite three decades of research, the available literature on the treatment of osteomyelitis is inadequate to determine the best agent(s), route, or duration of antibiotic therapy.”

Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials?
Lazzarini et al. Int J Infect Disease 2005

What is the evidence - humans

“Local antibiotics effectively have controlled infection in animal models and, despite limitations of the existing literature, seem to be useful in the clinical setting.”

Local antibiotic therapy in the treatment of open fractures and osteomyelitis.

What is the evidence – horses?

♦ EQUALLY SPARSE
- No randomized controlled studies or cohort studies
- Hundreds of case reports, many just mentioning LAT as being used
Survival of horses treated for septic distal phalanx - Comparison of horses with IVRVP and No IVRLP

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>IVRP</th>
<th># Horses</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cauvin &amp; Munroe, EVJ</td>
<td>1998</td>
<td>No</td>
<td>18</td>
<td>89</td>
</tr>
<tr>
<td>Gaughan, JAVMA</td>
<td>1998</td>
<td>No</td>
<td>9</td>
<td>78</td>
</tr>
<tr>
<td>Neil et al, JAVMA</td>
<td>2007</td>
<td>Yes</td>
<td>22</td>
<td>86</td>
</tr>
</tbody>
</table>

Survival of horses treated for septic joints - Comparison of horses treated with CIAI with horses with no LAT

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>LAT</th>
<th># Horses</th>
<th>Adult Survival (%)</th>
<th>Foal Survival (%)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider et al, EVJ</td>
<td>1992</td>
<td>No*</td>
<td>192</td>
<td>83</td>
<td>62</td>
<td>77</td>
</tr>
<tr>
<td>Meijer et al, J Vet Med</td>
<td>2000</td>
<td>No</td>
<td>39</td>
<td>74</td>
<td>42</td>
<td>84</td>
</tr>
<tr>
<td>Lescun et al, JAVMA</td>
<td>2006</td>
<td>Yes</td>
<td>31</td>
<td>91</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Meagher et al, JAVMA</td>
<td>2006</td>
<td>Yes</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

* 30/157 horses received IA AM

Evidence for use of LAT in horses

- Comparison difficult due to many variables
  - Contaminated versus infected tissues
  - Year of study (1990 vs 2005)
    - New surgical techniques such as arthroscopy
    - Minimally invasive surgical procedures
    - Wider availability of antimicrobial drugs
    - Better diagnostic capabilities
  - Different criteria for success
- No randomized controlled trials (RCT) or systematic reviews of cohort studies
Endoscopic treatment of contaminated or infected synovial cavities – 121 horses
- 90% survival
- All received intra-articular antibiotics
- 20 with established infection had IVRLP
  "OR 3.1 for reduced performance or death"
Wright et al. EVJ 2003

Conclusions – LAT in horses
- “Despite limitations of existing literature, LAT seems to be useful in preventing and treating orthopedic infections in the clinical setting.” Adams SB
- Expert opinion? – Level of evidence?
- Few complications associated with LAT
- Most methods of LAT require readily available equipment and can be easily performed in practices

Techniques for LAT in horses
- HOW TO ARTICLES in PROCEEDINGS OF THE AAEP (American Assoc Equine Practitioners)
- International veterinary information service
  - Ivis.org
- Ivester, Adams Comp Eq Edition 2007