Regional Perfusion of Antimicrobials as a Complementary Treatment for Soft Tissue, Bone, or Joint Infections in Sheep, Goats, and Camelids

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Abstract

Commonality exists between infections of soft tissue, bone, and joints because they involve bacterial infection of important structures, and considerable effort on the part of the veterinary practitioner may be necessary for successful treatment. Our discussion will focus on treatment methodologies, with emphasis on regional perfusion, which may be of value effecting a cure. The methods are applicable to small ruminants and camelids, although success may not require using all methods of treatment.

Résumé

Il y a une similitude entre les infections touchant les tissus mous, les os et les articulations car elles impliquent toutes une infection bactérienne de structures importantes qui nécessitent bien des efforts de la part des vétérinaires praticiens pour les traiter efficacement. Notre discussion vise les méthodes de traitement et met l'accent sur la perfusion régionale qui peut assister la guérison. Les méthodes sont applicables aux petits ruminants et aux camélidés bien que le succès n'implique pas l'utilisation de toutes les méthodes de traitement.

Introduction

Prompt diagnosis and aggressive treatment are essential to obtain a successful outcome. Once initial samples have been obtained, treatment should not be delayed waiting for culture results. Therapeutic goals include: good drainage of joints or debridement of infected bone, effective levels of systemic and local antibiotics for adequate duration, effective anti-inflammatory treatment, and rest. Efforts are directed toward rapid resolution of the septic process with minimization of long-term damage to the affected area. Early treatment has the best chance of rendering the affected area sterile, without the necessity for more involved treatment modalities. Lack of response to initial treatments often results in employment of additional treatment modalities. Extent and duration of effort will be predicated upon value of the patient, client emotional and financial constraints, and expectation for future use. Two general strategies of treatment include physical reduction of bacterial numbers and delivery of antimicrobials to the site of infection.

Strategies to Physically Reduce Bacterial Numbers : Drainage / Lavage / Debridement

Synovial irrigation and lavage relieves intra-articular pressure and removes protein, cellular enzymes, fibrin, inflammatory cells, and degradation products. Decisions on what type of drainage to employ depends on duration of the infection, economic factors, resource availability, and numbers of involved joints. Typically, through and through drainage using large bore needles is most commonly employed. We usually perform the procedure under sedation or general anesthesia daily or every second day for two to three treatments unless drainage remains purulent and clinical signs are not improving. Arthroscopy allows direct visualization of articular surfaces, thorough lavage with large amounts of fluid, and the ability to debride infected focal cartilage and subchondral bone. An arthrotomy used as an egress portal has been shown to result in rapid sterility of the joint, but complications have been associated with healing of the incision. Closed suction drains have been used successfully to maintain continuous evacuation of septic fluid from a joint, but they require high maintenance effort. They can be applied to almost any joint and should be considered in cases of chronic joint sepsis, non-responsive to through and through lavage.

Lavage solutions should be balanced isotonic electrolyte solutions with a neutral pH (Normosol). Lactated Ringers (pH=6.7) would be the next appropriate solution. Medical grade DMSO (90%) can be added to fluids to make a 20% solution for lavage, but this step is not commonly done. DMSO may be beneficial as an anti-inflammatory agent, and does not irritate the synovium. Antibiotics can be added to lavage solutions to improve local levels of the antimicrobial. Opinion varies regarding benefit of this addition, but most clinicians will add 125 - 250 mg of gentamicin or amikacin to the joint space after lavage is completed.[a,b] High antibiotic levels, even over a short term of exposure, may have significant detrimental effects on bacteria in the log phase of growth.

Concerning osteomyelitis, surgical debridement while sedated or during general anesthesia is usually necessary if long bone sequestration is apparent or for physeal infection accompanied by draining tracts and sequestra. Bone infections not responsive to antibiotics, which are readily accessible without risk to bone integrity or damage to soft tissue structures, should also be debrided. Infected bone should be debrided thoroughly, and if there is a large void of bone, cancellous graft material could be placed in the defect.

Strategies to Deliver Antimicrobials to the Site of Infection

Resolution of infection requires delivery of an appropriate antibiotic to infected tissue in concentrations above the minimum inhibitory concentration (MIC). We usually rely on systemic antimicrobials to achieve adequate MIC. However, vascular injury in bone or synovium may prevent adequate delivery of antimicrobials. Efficacy of some antimicrobials may be enhanced by maintaining local tissue concentrations well-above normal serum levels. The following techniques result in elevation of local antibiotic levels and have proven useful on cases in our clinic. They are techniques which are adaptable to application within a private practice. They do not involve extensive financial outlay, and are simple enough to be used on a regular basis (always in combination with systemic therapy) for the treatment of either septic arthritis or osteomyelitis.

1) Systemic Antimicrobials

Having obtained synovial fluid samples or infected bone, systemic antibiotics should be initiated immediately based on the types of organisms commonly encountered. These would include coliforms, staphylococcus, and streptococcus species. If positive cultures are obtained, antibiotic therapy should be re-evaluated and changed to specific therapy indicated by sensitivity results. Initially, our best choices appear to be parenteral antibiotics in the form of aqueous penicillin G (10,000 IU/lb or 22,000 IU/kg IV) every six hours with either amikacin (9.1 mg/lb or 20 mg/kg IV) or gentamicin (3.0 mg/lb or 6.6 mg/kg IV) every 24 hours. Aminoglycosides are usually used for three to five days, with longer use requiring assessment of renal function. Antibiotic treatment should continue for three weeks after resolution of the lameness, but we often will use ceftiofur (1.0 mg/lb or 2.2 mg/kg IM, IV, or SC) every 12 hours or trimethoprim sulpha (13.6 mg/lb or 30 mg/kg combined dose) every 12 hours in crias less than three months.

Gentamicin and amikacin are not approved for food producing animals, and practitioners should be familiar with position statements issued by the American Association of Bovine Practitioners and the Academy of Veterinary Consultants.[a,b]

2) Regional (intravenous or intraosseous) Perfusion of Antibiotics

Regional perfusion involves delivering an antibiotic under pressure to a selected region of a limb through the venous system. The antibiotic reaches necrotic, infected tissue by diffusion from the surrounding vascular tissues. Regional perfusion appears to be an effective method of delivering high concentrations of antibiotic to infected tissues. The technique has been tested on normal horses and a model of septic arthritis, and was found to provide local synovial concentrations of gentamicin 30 to 100 times serum levels obtained after intravenous dosage. The technique involves placing a catheter into a superficial vein, or drilling and tapping a 4.5 mm hole into the medullary cavity of the involved or adjacent long bone. An Esmarch bandage (elastic tourniquet) is applied above and below the site of sepsis to occlude the superficial venous system and open a collateral osseous venous system. The appropriate antibiotic is added to sterile, balanced polyionic solution for a final volume of 60 ml in adult horses; small ruminants would require a smaller cortical screw and less infusion volume. Perfusions are performed through the intravenous catheter or a special cannulated 4.5 screw threaded into the drill hole. Tremendous pressure is necessary for successful injection. Electronic delivery devices are available, but a three-way stopcock fitted to a large reservoir syringe and a small pressure syringe with twist fittings have been successful. By delivering the antibiotic solution under pressure, the perfused fluid is forced along a path of least resistance and into the venous system of the loosely wrapped infected region. High concentrations of antibiotic are obtained in poorly perfused or avascular tissue by diffusion from surrounding vascular tissue containing a high antibiotic concentration. Thirty minutes is allowed to elapse from the time of injection.

After perfusion, the Esmarch wrap is removed, catheters or cannulated screws are removed, and soft tissues are closed. The procedure can be repeated daily if needed, but in our experience we have performed the procedure on consecutive or every second day intervals for one to three treatments. Despite benefits noted with this technique, it is necessary to maintain systemic antibiotics during the treatment process. If the perfused antibiotic is the same as that used systemically, we will reduce the systemic dose by the amount perfused for the day of the perfusion only. The procedure is usually performed under general anesthesia or sedation.

3) Antibiotic Impregnated Polymethylmethacrylate (AIPMMA)

In human patients, implantation of AIPMMA beads into a site of infection results in higher concentrations of local antibiotic than can be achieved by systemic administration, and this methodology has been used

Table 1. Concentration-dependent antimicrobials used for local delivery (intrasynovial, regional perfusion, impregnated beads) in horses with synovial infections.

Antimicrobial	Dosage	Methods of delivery
1. Cefazolin	1 g	All modes of local delivery
2. Ceftazidime/Ceftriaxone	2 g (100 mg/hour)	Intrasynovial continuous infusion
3. Na penicillin/ampicillin	¼ - ½ systemic dose	Intrasynovial or regional perfusion
4. Gentamicin[a,b]	0.5 – 1 g 1.8 mg/kg/day	All modes of local delivery Intrasynovial continuous infusion
5. Amikacin[a,b]	0.5 – 1 g 5.5 mg/kg/day 2 - 3 g (100 mg/hour)	All modes of local delivery (Used most often by author) Intrasynovial continuous infusion
6. Ceftiofur	150 mg – 1g	Intrasynovial or regional perfusion
7. Ticarcillin + clavulanate	300 – 400 mg	All modes of local delivery
8. Tobramycin	0.5 – 2 g	PMMA or other impregnated beads
9. Vancomycin	300 mg	Regional perfusion PMMA or other impregnated beads
10. Enrofloxacin[c]	500 mg	All modes of local delivery

Table 1 is adapted from the notes of Dr. Ted Stashak presented at the Annual Northwest Equine Practitioners Association Conference in Bend, Oregon on January 31, 2009. Aminoglycosides are not approved for use in cattle, sheep, or goats in the US.
[a]AABP Position Statement on Aminoglycoside Use: The American Association of Bovine Practitioners, being cognizant of food safety issues and concerns, encourages its members to refrain from the intramammary, intramuscular, subcutaneous or intravenous extralabel use of the aminoglycoside class of antibiotics in bovines. (www.avma.org/onlnews/javma/dec05/051201j.asp)
[b]AVC Aminoglycoside Antibiotic Position Statement: The systemic use of aminoglycoside antibiotics presents a potential conflict to the stated objectives of the AVC Standards of Practice because scientific justification for such use is limited, and because it is known that identifiable residues in kidney tissue can result for an undetermined extended period of time. Therefore, the AVC hereby resolves that until further scientific information becomes available alleviating safety and efficacy concerns, aminoglycoside antibiotics should not be used in cattle, except as specifically approved by the FDA. (www.avc-beef.org/Policy/positionstatements.asp)
[c]Extra-label use of this drug is prohibited by the FDA in food producing animals.

to treat and prevent orthopedic infections. Polymethylmethacrylate is a high density plastic formed by mixing a powdered polymer with a liquid monomer. Antibiotics are added during the hardening process, and are effectively suspended within the plastic. The AIPMMA can be molded into beads or cylinders appropriate for tissue implantation. Antibiotics are released from the plastic by diffusion across a concentration gradient highest at the implant and decreasing in distant tissues. Highest concentrations in adjacent tissues are reached within a few days and decrease slowly thereafter. High local concentrations (10 to 50 times toxic serum levels) are not reflected in the circulating plasma, and thus risk for toxicosis is less than after parenteral administration. Once the AIPMMA is incorporated into fibrous tissue, antibiotic concentrations are limited to the peripheral 2 to 3 mm of tissue. Rate of elution of the antimicrobial from the plastic is related to type of PMMA, surface area of the implant, as well as antimicrobial type and concentration. Antibiotic choices are extensive and include gentamicin, tobramycin, cefazolin, and amikacin.

Preparation of implants is done sterilely if they are to be used immediately, or they can be made in advance and ethylene oxide sterilized. Usually 1 to 2 gm of antibiotic powder are added and thoroughly mixed with the 40 gms of polymer powder before addition of the liquid. Once mixed, the material is formed into round beads placed on a wire, or narrow cylindrical shapes. Cylindrical implants are easiest to remove from tissue. Implants can be placed within soft tissues, adjacent to bone, within the medullary cavity, and reportedly have been used in joints. Usually implants are removed weeks to months after implantation, but they can be allowed to remain in place if no reaction is apparent.

Implantation of AIPMMA should be considered in the management of various infections in animals. Best adaptability would be adjacent or within defects secondary to osteomyelitis. We have placed them in soft tissue adjacent to open fracture wounds, within a defect associated with septic physitis, and within open wounds subjected to delayed closure.

Table 2. Antibiotic options and effectiveness for treatment.*,a,b

Gram-positive bacteria	
Enterococcus faecalis	ampicillin (100%), amoxicillin/clavulanic acid (100%), chloramphenicol (90%), tetracycline (90%), erythromycin (40%)
Enterococcus faecium	ampicillin (90%), amoxicillin/clavulanic acid (90%), chloramphenicol (80%), tetracycline (70%), erythromycin (10%)
Rhodococcus equi	ceftiofur (100%), ceftizoxime (100%), gentamicin (100%), trimethoprim-sulfonamide (100%), rifampin (88%), amikacin (87%), chloramphenicol (63%), erythromycin (63%), cephalothin (39%), tetracycline (25%)
Staphylococcus aureus	chloramphenicol (97%), amikacin (94%), enrofloxacin (94%), rifampin (94%), cephalothin (91%), amoxicillin/clavulanic acid (88%), erythromycin (76%), ceftiofur (69%), oxacillin (67%), trimethoprim-sulfonamide (55%), gentamicin (45%), ceftizoxime (36%), tetracycline (36%), penicillin G (30%)
coagulase-negative *Staphylococcus* spp	amikacin (100%), amoxicillin/clavulanic acid (100%), cephalothin (97%), rifampin (97%), enrofloxacin (96), chloramphenicol (94%), tetracycline (81%), ceftiofur (77%), oxacillin (77%), ceftizoxime (74%), gentamicin (74%), trimethoprim-sulfonamide (74%), erythromycin (61%), penicillin G (13%)
Streptococcus zooepidemicus	amoxicillin/clavulanic acid (100%), ampicillin (100%), ceftiofur (100%), ceftizoxime (100%), cephalothin (100%), chloramphenicol (100%), erythromycin (100%), penicillin G (100%), trimethoprim-sulfonamide (100%), rifampin (71%), gentamicin (7%), amikacin (0%)
Gram-negative bacteria	
Actinobacillus spp (*A. suis*-like, *A. equuli, A. lignieresi*)	amikacin (100%), amoxicillin/clavulanicacid (100%), ceftiofur (100%), ceftizoxime (100%), cephalothin (100%), chloramphenicol (100%), gentamicin (100%), penicillin G (100%), ampicillin (89–100%), tetracycline (86–100%), trimethoprim-sulfonamide (86–100%), erythromycin (0–30%)
Escherichia coli	amikacin (100%), enrofloxacin (100%), ceftizoxime (97%), ceftiofur (94%), ticarcillin (94%), amoxicillin/clavulanic acid (93%), chloramphenicol (91%), gentamicin (86%), cephalothin (73%), tetracycline (71%), ampicillin (68%), trimethoprim-sulfonamide (60%)
Klebsiella pneumoniae	amikacin (100%), ceftiofur (100%), ceftizoxime (100%), enrofloxacin (100%), ticarcillin (87%), chloramphenicol (80%), amoxicillin/clavulanic acid (79%), gentamicin (67%), trimethoprim-sulfonamide (67%), cephalothin (66%), tetracycline (54%), ampicillin (14%)
Pasteurella spp	amikacin (100%), amoxicillin/clavulanic acid (100%), ampicillin (100%), cephalothin (100%), chloramphenicol (100%), gentamicin (100%), penicillin G (100%), tetracycline (100%), trimethoprim-sulfonamide (100%), ceftiofur (83%), ceftizoxime (83%), enrofloxacin (83%), erythromycin (33%)
Salmonella spp (*S. agona, S. typhimurium, S.* sp)	amikacin (100%), amoxicillin/clavulanic acid (100%), ceftiofur (100%), ceftizoxime (100%), cephalothin (100%), enrofloxacin (100%), tetracycline (73–92%), ticarcillin (54–91%), gentamicin (49–82%), trimethoprim-sulfonamide (15–82%), ampicillin (0–82%), chloramphenicol (0–82%)
Serratia marcescens	ceftizoxime (100%), enrofloxacin (100%), ceftiofur (75%), tetracycline (50%), amikacin (0%), amoxicillin/clavulanic acid (0%), cephalothin (0%), chloramphenicol (0%), gentamicin (0%), ticarcillin (0%), trimethoprim-sulfonamide (0%)

Table 2 is adapted from the notes of Dr. Ted Stashak presented at the Annual Northwest Equine Practitioners Association Conference in Bend, Oregon on January 31, 2009. Several antimicrobials cited in this table are not approved for use in food producing animals, or are prohibited from use in food producing animals, or extra-label use is prohibited by the FDA. Veterinarians should contact the Food Animal Residue Avoidance Databank (www.farad.org/index.asp) for further information and guidance on antimicrobial selection and use.

*Organisms isolated from horses at the University of California, Davis during 1998.

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Cancellous Bone Graft

Autogenous cancellous bone grafts are commonly used to augment fracture healing and may also be used to treat osteomyelitis. Sites for obtaining cancellous bone in camelids (also applicable to small ruminants) include the sternum, proximal tibia, and proximal humerus. The shaft of the ilium is too narrow to obtain substantial quantities of cancellous material. Because of high fat content, risk of weakening the bone, and minimal volume of osteogenic precursor cells in the medullary cavity of long bones, we feel the sternum represents the optimal site for obtaining autogenous cancellous bone from camelids.

Under general anesthesia, and using instruments separate from the recipient site, a sterile approach is made over the fourth sternebra. A 2.4 inch-long (6 cm) skin incision is centered 7 inches (17 cm) cranial to the xiphoid and is continued through the subcutaneous tissues to an average depth of about 1.2 in or 3.0 cm. Use of an appropriate tissue retractor will allow visualization of the underlying body of the sternebra. Use of an osteotome and mallet will allow creation of a 1 inch (2 cm) square window into the medullary cavity. A large curette allows removal of the soft, deep red cancellous bone. When deeper cortical bone is observed, curettage should be discontinued. If additional graft is necessary, the incision could be extended cranial or caudal and the adjacent sternebral body could be approached through an incision centered 2.4 in (6 cm) cranial or caudal to the initial entry. Closure includes a deep layer of subcutaneous tissue apposed with 0 absorbable suture as a continuous or interrupted pattern, a similar superficial layer, and skin. The majority of incisions did involve all or part of the keratinized sternal pad.

Conclusions

Prognosis for successful treatment of septic conditions varies with regard to location, surgical accessibility, and timeliness of therapy. Given appropriate therapy, a single septic joint has a favorable prognosis. Evidence of intraarticular radiographic changes implies significant joint damage, and a poorer associated prognosis. Septic epiphysitis always carries a guarded prognosis because of the possibility of unresolved infection and potential for secondary angular limb deformities. Osteomyelitis cases associated with puncture wounds or fractures usually enjoy favorable outcomes if they are debrided and stabilized.

Footnotes

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