UPDATE ON LOCAL TREATMENT OF ORTHOPAEDIC INFECTIONS
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Key Points

- Local delivery of antibiotics is an effective and safe technique to achieve high levels of antibiotics at the infection site.
- Many different options exist to deliver high-level antibiotics locally.
- Implant antibiotic-coating should prevent and diminish the rate of infection following fracture fixation.

Infection can be a devastating complication in equine orthopaedic surgery, potentially fatal. Reported infection rates associated with equine orthopedic procedures range from 8-52%. Prompt and effective treatment must be instituted to maximize the chances of a successful outcome. A synovial cavity, bone or, implant, for example, once colonized by bacteria, constitute problematical environments to deal with. Although other aspects of treatment such as surgical debridement of necrotic debris, control of inflammation, and appropriate rehabilitation are important, the prompt elimination of the invading bacterial population is paramount for a favorable outcome. Since the widespread use of different methods of local antibiotic therapy, it seems that the success in eliminating infections has increased. However rehabilitating the affected horses back to athletic endeavors remains a barrier. Prevention of implant-associated infections continues to be one of the main challenges in orthopaedic surgery. This challenge is further complicated by the concern over the development of antibiotic resistance as a result of using traditional antibiotics for infection prophylaxis.

Implant surfaces

Orthopaedic implant surfaces provide the bacterial growth with ideal substrates. Common pathogens such as the Staphylococcus species, S. aureus and S. epidermidis, and Pseudomonas aeruginosa, can be acquired at the time of surgery or at a later stage (via a haematogenous route) and can attach to the surfaces of the implants to nucleate infections. This can potentiate the formation of complex biofilms resulting in up to 1000-fold decrease in susceptibility to antimicrobial agents, largely due to poor antibiotic penetration into the biofilm and the stationary phase of growth of the bacteria underlying the surface layer. The presence of biofilms and the poor vascularization of the bone implant interface, make infections extremely difficult to treat. For example, the current treatment solutions for the deep infection include two-stage radical debridement with implant removal if indicated, antibiotic therapy, and bone marrow grafting. If the fracture is unstable additional methods of stability have to be pursued. Lack of fracture stability impairs bone healing and guarantees fixation failure.

An ideal strategy to combat implant-associated infections would be prevention of infection at the site of the implant in the first place. Among the techniques explored, local delivery of antibiotics such as gentamicin, tobramycin and vancomycin through implant surfaces has received much attention recently in human medicine particularly due to their potential and low systemic side effects of this approach. There are two challenges facing the local delivery of antibiotics through orthopaedic implants. The first one is avoiding antibiotic resistance; the second one is achieving antimicrobial activity without impairing peri-implant bone growth (i.e. osseointegration). A preferred solution would be to employ non-conventional antimicrobial drugs that do not potentiate the development of resistant phenotypes. One example of such non-classical drugs is the cationic antimicrobial peptides (AMP). This technology has not yet been
refined and in veterinary medicine we rely on local antimicrobial delivery to exceed the MIC of possible or present bacteria.

Local methods of antimicrobial delivery

A high local drug concentration at the site of infection can be achieved with a local drug delivery system, while maintaining low systemic drug levels; therefore, avoiding possible side effects. The modalities of local administration of antimicrobials involve biodegradable and non-biodegradable implants, constant rate infusion or indwelling systems and regional limb perfusion either by intravenous or intraosseous routes.

Non-biodegradable antimicrobial-impregnated implants

*Polyethylene methacrylate (PMMA):* The elution of the antimicrobial from the PMMA bead depends upon the pore size, permeability, size and the shape of the implant, the type of antimicrobial and the amount of antimicrobial present in the bead. The amount and rate of wound exudate alters the elution kinetics of an antimicrobial from the bead. In general, the larger the PMMA bead the less elution of antimicrobial. Making the bead’s surface irregular seems to also increase antibiotic elution.

*Collagen:* Gentamicin impregnated collagen sponges are easy to implant, prevent subinhibitory antimicrobial concentration, which could occur with PMMA beads and obviates the need for implant removal. Complete elution occurs over a period of two weeks with high elution rates during the first week.

*Hydroxyapatite:* Hydroxyapatite cement (HAC) implanted within bone and subcutaneous tissue is reabsorbed and in bone it has osteoconductive properties. Although HAC appears to have optimal qualities for a biodegradable delivery system in vivo studies are necessary to determine its overall safety and efficacy.

*Plaster of Paris:* POP gentamicin-impregnated beads are inexpensive, biocompatible, biodegradable, osteoconductive and easily manufactured using a liquid antimicrobial and a bead mold. In vivo 80 % of the gentamicin is released within the first 48 hours and E. coli growth is inhibited. [44] In addition, POP gentamicin-impregnated beads released bactericidal concentrations of drug after ethylene oxide sterilization and for 5 months of storage at room temperature. The relatively short duration of a high gentamicin concentration may suggest that POP beads may be ideal for antimicrobial prophylaxis in high-risk cases, such as fracture repair.

*Polyanhydrides (Septacin™):* In vitro and in vivo studies, including a horse model of tarsocrural joint septic arthritis, have demonstrated clinical efficacy and high local gentamicin concentrations. The elution of gentamicin from Septacin™ (Abbott Laboratories, Abbott Park, Illinois) occurs over a period of 4 weeks, after an initial burst (40% elution) within the first week.

*Hyaluronan:* Rapid release of amikacin occurred from a ferric hyaluronan implant with sustained concentrations above MIC for a period of approximately 24 hours. Although in this in vivo study infection was eliminated within 24 hours of implantation, its rapid release makes it impractical as a long-term antimicrobial delivery system. Modifications to this system are
required to ensure a high in vivo elution of amikacin for a longer period of time to make it practical in a clinical situation.

*Polylactide-Polyglycolide:* The release of gentamicin is biphasic. There is a slow induction period and then a period of rapid release. The period of rapid release consists of a high burst release of gentamicin in the first 24 hours and then a sustained release for 10 days, after which the gentamicin concentration is <10 μg/mL until 14 days. No clinical reports exist of the use of this delivery system in horses.

Constant rate infusion (CRI) or indwelling systems

Constant delivery of antimicrobials is best suited for synovial cavities such as joints or tendon sheaths. The use of commercially available CRI pumps (MILA International, Florence, KY) has been reported with amikacin or gentamicin. Alternatively, the use of an in-house manufactured delivery system has also been reported by using an intravenous fluid bag and fenestrated catheter placed inside the joint or affected area.

Direct intrarticular injection

Antimicrobials such as gentamicin, amikacin, and ceftiofur can also be administered into a joint by direct daily injection. This technique results in high concentrations of intra-synovial antimicrobials as well as bone.

Regional perfusion

Antimicrobial concentrations several fold the MIC of common equine pathogens, in a region of interest of the distal extremity, can be accomplished by the administration of a drug solution into the vasculature of a selected portion of the extremity, which has been previously isolated from the systemic circulation by the controlled application of a tourniquet. This is termed regional limb perfusion and has greatly contributed to the successful treatment of musculoskeletal infections. Adequate vascular isolation is essential to perform this procedure successfully. RLP has been more effective than systemic antimicrobial administration for the treatment of experimentally induced joint infections and has resulted in the elimination of infection in clinical cases of septic arthritis and osteomyelitis. Factors determining the efficacy of the RLP procedure include characteristics of the infectious process being treated, duration of the septic process prior to treatment, the ability to debride the infected and necrotic tissue, the susceptibility pattern of the organism, the dose and action mechanism of the antimicrobial, the chronicity and extent of the infection, and the technique used for RLP.

*Clinical use:* Antimicrobial synovial concentrations following RLP are not as high as those achieved after direct intraarticular injection but concentrations as high as 100 times above the MIC for time periods of up to 36 hours have been reported. Compared with systemic antimicrobial delivery, RLP produces higher regional antimicrobial concentrations and Cmax/MIC ratios 3 to 30 times higher than the target ratios of systemic therapy. Both IV and IO techniques have been used for perfusion of digital structures of horses.

*Antimicrobial dose:* The optimal antimicrobial dose for RLP is not known. Doses as low as 125 mg of amikacin produced extremely high concentrations (235 ± 82 μg/mL) in synovial fluid and doses of 125–250 mg of amikacin or 100–300 mg of gentamicin have been used successfully in adult horses as well as 1.5mg/kg of enrofloxacin. However, higher doses of aminoglycosides, between 500 mg and 1 gram are commonly used clinically. β-lactams have been used less commonly, but RLP with sodium or potassium penicillin (dose of 10 x 10⁶ IU], ticarcillin/clavulanic acid (1 gram), and sodium ampicillin (9 g) have produced satisfactory clinical outcomes. For young foals, lower doses such as 50 mg of amikacin are recommended,
but doses as high as 500 mg have also been used with a satisfactory outcome. Osteonecrosis and pathological fracture can occur secondary to the use of the systemic dose of gentamicin when used as intraosseous RLP. Enrofloxacin and vancomycin have been associated with vasculitis.

**Volume of perfusate solution:** The optimal volume of perfusate is not known. As a general rule, the higher the volume perfused, the higher the intravascular pressure achieved, thus the higher the drug diffusion rate into the surrounding tissues. Antimicrobial perfusion distal to the antebrachium of adult equine limb has been commonly performed using 60 ml of perfusate solution, whereas 20 mL and 40 ml have also been used clinically and the results were satisfactory with 18 out of 24 horses surviving in one study. Similar volumes have been used for perfusion of other anatomic locations, such as the carpus and the tarsus. In foals smaller volumes 10 to 35 mL are recommended for IORLP or IVRLP. When a perfusate volume of 30- and 60-mL was compared for tarsal perfusion, higher antimicrobial concentrations in synovial fluid were reached after the administration of the higher volume.

**Tourniquet characteristics:** To assess the effects of different tourniquet types Levine and co-workers designed a study where bilateral forelimb RLP with amikacin sulfate (2.5 g) were administered through the cephalic vein in standing sedated horses. Limbs were randomly assigned to the 3 tourniquet types (Narrow ~ 1cm, Wide ~ 12.5 cm and pneumatic ~ 10.5 cm) applied above the carpus. Metacarpophalangeal synovial fluid was obtained 0.5 hour after perfusion. The study concluded that administration with pneumatic and wide tourniquets achieved adequate amikacin concentrations but that the narrow tourniquet was ineffective and should not be used for RLP above the carpus in the standing horse. In addition motion during the perfusion procedure is also associated with loss of tourniquet efficacy and decreased antibiotic concentration. Therefore adequate sedation is paramount to prevent loss of efficacy. An Esmarch-type tourniquet has also been shown to be effective in isolating the distal extremity from the rest of the circulating blood.

**Number of perfusions and selection of procedure:** There is no one general treatment protocol (i.e. number and the frequency of RLP or dose) to achieve the resolution of orthopedic infections. One to 9 procedures have been used for different clinical cases, and they are usually performed once daily or every 2 or 3 days. In human patients with long standing infections, the antimicrobials were regionally infused twice daily for 5 to 7 days, which could be indicated in equine patients when using time-dependent antimicrobials. Other equine patients have responded after a single perfusion. In practice, the number of perfusions is usually made on the basis of clinical evidence of improvement. In foals undergoing IV RLP, systemic administration of antimicrobials prior to the procedure has been recommended to prevent septicemia, although in the majority of cases, foals are already undergoing systemic antimicrobial treatment.

Comparative studies have not been conducted to determine the optimum duration of each perfusion. The time period that the tourniquet should be maintained could be dependent on physicochemical, pharmacological, and pharmacodynamic characteristics of the antimicrobial, microbiologic factors, and individual attributes of the patient and the clinical case. In those cases where the antimicrobial solution is slowly infused, tourniquet maintenance for a longer period than the infusion time is preferred to allow the antimicrobial to completely distribute into the tissues.