A review of local antibiotic implants and applications to veterinary orthopaedic surgery

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Summary
In the face of increasing incidence of multi-drug resistant implant infections, local antibiotic modalities are receiving increased attention for both infection prophylaxis and treatment. Local antibiotic therapy that achieves very high antibiotic drug concentrations at the site of the implant may represent an avenue for treatment of biofilm-forming bacterial pathogens. Randomized controlled trials in human patients have demonstrated an infection risk reduction when antibiotic-impregnated cement is used for infection prophylaxis in implanted joint prostheses, and when a gentamicin-impregnated collagen sponge is used for infection prophylaxis in midline sternotomy. The other modalities discussed have for the most part yet to be evaluated in randomized controlled trials in veterinary or human patients. In general, the *in vivo* pharmacokinetics and appropriate dosing profiles for local antibiotic modalities have yet to be elucidated. Toxicity is possible, and attention to the dose applied is warranted.

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Introduction

Postoperative surgical site infections (SSI) remain an inherent risk of any surgical procedure. The Centers for Disease Control and Prevention standard definition of a SSI is shown in ▶Table 1 (1). The incidence rate of SSI in clean orthopaedic procedures performed on human patients is reported to range from 0.3-1.3%, while the equivalent range in veterinary procedures is 2.6-10% (2). The reasons for the differences are not clear. While absolute prevention of SSI is not achievable, there is a continued focus on SSI prevention in veterinary medicine.

The epidemiology of infection following surgical incision can be conceptualized as a patient/pathogen/procedure triangle. Patient factors include those related to the local wound such as the depth of adipose tissue and oxygen tension as well as systemic host defences against infection such as diabetes and poor nutritional status (3, 4). Pathogen factors include bacterial load and behaviour. Procedural factors may be the most modifiable, and include those related to both perioperative management (e.g. exposure to hypothermia, transfusion therapy, antibiotic prophylaxis) and intraoperative management (e.g. aseptic technique, tissue handling, drain placement) (3-5). Successful infection control protocols address all of these factors. While antibiotic prophylaxis and treatment constitutes only one avenue of SSI prevention and control, it is one of the most emphasized. Antibiotic prophylaxis is defined as the use of antibiotic therapy to prevent infection while treatment occurs in the face of established infection.

Although systemic antibiotics are considered standard of care for both SSI prophylaxis and treatment, a number of factors may compromise efficacy. These include antibiotic penetration to provide adequate concentrations for sufficient time at the surgical site, acquisition of antibiotic resistance traits by the infective organism, administration compliance, and dose-limiting antibiotic toxicity profiles (6). In response to these issues, there has been increasing interest in products providing local antibiotic therapy. There are several purported advantages of local antibiotic use, both for treatment and prophylaxis. High local antibiotic concentrations can be achieved at the surgical site, improving penetration of biofilm and necrotic tissue and increasing bacterial kill for antibiotics with concentration-dependent kill characteristics (7). Improved bacterial kill reduces the risk of bacterial mutation and acquisition of horizontally transmissible resistance traits in polymicrobial infections (6). Exposure to high antibiotic concentrations may achieve kill even for organisms classified as resistant according to standard pharmacokinetic profiling (8). As long as systemic uptake from the site is minimised and there is no cytotoxicity, acceptable safety may be maintained despite very high local concentrations – a significant advantage for antibiotics of the aminoglycoside class. Finally, when antibiotic agents are implanted directly at the surgical site, administration

compliance is assured. Local antibiotics may be used alone or in combination with systemic therapy. In common with all therapeutic antibiotic use, good practice mandates culture and susceptibility testing to assist antibiotic selection. Prophylactic use should be evidence-based rather than speculative, ideally following studies demonstrating measurable patient benefit.

The incidence of multi-drug resistant nosocomial infections in veterinary species appears to be rising (8, 9). This is postulated to be a direct consequence of increased and in some cases inappropriate antibiotic use. Therapeutic options for local antibiotic therapy in the form of antibiotic impregnated cements, gels, and sponges as well as antibiotic or antibacterial-coated implants and devices are becoming increasingly available, however high quality evidence supporting their use, particularly in veterinary species, is lacking. The purpose of this review is to summarize available information on the unique challenges of orthopaedic infections, and the advantages, disadvantages, and available evidence for clinical use of local antibiotics.

Biology of implant-associated infections

Many orthopaedic procedures involve the use of implants. For this reason, orthopaedic surgical site infections pose unique challenges. Bacteria adhering to the surface of implants change their behaviour, exhibiting both biofilm formation and facultative intracellular dormancy (10). Starting at the time of implant placement, a 'race for the surface' begins, as adhering bacterial contaminants compete with integrating host tissue for dominance of the implant surface environment (10). One of the most studied SSI pathogens are the *staphylococci*, especially *Staphylococcus aureus* and *Staphylococcus pseudintermedius*, which account for more than 50% of orthopaedic infections in dogs, and *Staphylococcus aureus* and other coagulase-negative *staphylococcus* species which account for more than 50% of prosthetic joint infections in humans (11, 12). Once the devices have been implanted, they acquire a film of extracellular matrix (ECM) proteins consisting of fibrinogen, fibronectin, albumin and collagen. The ECM coating can then serve as a platform for host cell adhesion and fibroblast colonization. However, staphylococci also express receptors for the ECM. Biofilm formation is initiated in the first one to two hours post-implantation as bacteria interact with the ECM. In the following hours, irreversible molecular bridging occurs between the bacteria and the implant surface. The bacteria then begin to secrete an exo-polysaccharide layer, and a multi-layered biofilm develops (13). Within the biofilm, they are protected from phagocytosis and antibiotics. In some cases, it has been found that killing bacteria in a biofilm requires roughly 1000 times the local antibiotic concentration required to kill bacteria in suspension (13). Biofilm density can increase with exposure to sub-minimum inhibitory concentrations (MIC) of some antibiotics, indicating an adaptive response (14).

Within the *Staphylococcus sp.*, small colony variant strains are recognized. These strains exhibit a slow metabolism and can occupy a facultative intra-cellular position within host cells. Both biofilm formation and intracellular dormancy render these bacteria relatively resistant to antibiotic therapy in the context of implant-associated infections (15).

While *Staphylococcus sp.* are a key pathogenic species in the biology of SSI, a number of other bacteria are frequently implicated, including *Escherichia coli*, *enterobacter*, *pasteurella* and *pseudomonas* (11, 16). Plasmid mediated transmission of multi-drug resistant traits are common among these species. Antibiotic treatment selects for resistance in both pathogenic and commensal Enterobacteriaceae, and is considered the most important risk factor for acquiring extraintestinal infection with multi drug resistant strains (16). This emphasises the need for appropriate antibiotic use guided by culture and susceptibility results.

Table 1 The Centers for Disease Control and Prevention definition of a surgical site infection (1).

An infection occurring either:
– Within 30 days of a surgical procedure **OR**
– Within 1 year of a surgical procedure if an implant is used
With at least one of the following:
– Purulent drainage or abscess formation at the surgical site
– Organisms cultured from an aseptically obtained sample
– Characteristic clinical signs
– Clinician diagnosis

Principles of local antibiotic use

Any exposure of infective organisms to an antibiotic applies a selection pressure. This in turn predisposes to the emergence of drug resistance traits and the potential for therapeutic failure (6). For systemic antibiotic therapy, information on the typical tissue concentrations reached with standard antibiotic dosing is integrated with pharmacodynamic information (notably the MIC) to determine the MIC breakpoints (MIC_{BP}) which are reported for each antibiotic drug by the Clinical and Laboratory Standards Institute (17). It should be emphasised that the Clinical and Laboratory Standards Institute has made recommendations for relatively few veterinary pathogens and that each recommendation is specific for a single host species, a particular dosage regimen, and often a single site of infection. The relationship between the measured MIC for the infective organism population and the reported MIC_{BP} for that antibiotic determines whether the infection is reported as susceptible, intermediate, or resistant to that therapy in that patient. This system has been established both to guide individual therapy and ensure that across the patient population, exposure to sub-therapeutic antibiotic concentrations is minimized. However, inherent in the system are a number of assumptions. The antibiotic in question is assumed to be dosed appropriately, with full owner and patient compliance, and fully penetrate to the infection site. The preferential concentration within certain organ systems shown by some antibiotics is not accounted for. The ability of the infective organism to show *in vivo* 'escape' behav-

iour by biofilm formation or facultative intracellular dormancy is not accounted for (18). The cultured isolate is assumed to be representative of the infecting organism despite the possibility of off-target sampling and the time lag inherent in culture results. These pitfalls may account for some of the discrepancies between culture result predictions and therapeutic response.

While the MIC:MIC_{BP} relationship is a good guide to effectiveness, additional recommendations have been made with respect to antibiotic tissue concentrations to minimize the likelihood of emergent resistance. Following the mantra 'dead bugs don't mutate', concentration-dependent antibiotics such as aminoglycosides and fluoroquinolones should have a peak plasma drug concentration (PDC)/ MIC of greater than 10-12 at the infection site (6). In contrast, the efficacy of time dependent antibiotics such as β-lactams is best predicted by the time that PDC >MIC; this should be 50-100% of the dosing interval, depending on the antibacterial agent and target pathogen (6). These targets may not always be achievable with standard antibiotic dosages or dosing intervals, and more research is needed to help guide the clinician attempting to meet these targets. In addition, the appropriate duration of antibiotic therapy is frequently poorly established. Recent studies investigating this issue have shown a trend toward identifying shorter courses to be of equivalent efficacy (19, 20, 21). As antibiotic exposure is well established as a risk factor for generating clonal expansion of antibiotic resistant endogenous microflora which may subsequently occupy a pathogenic niche, the ideal course duration can be defined as the minimum duration required to achieve clinical resolution in the majority of patients (16).

Treatment of orthopaedic surgical infections, specifically osteomyelitis, poses some unique challenges. Following fracture and vascular impairment, the medullary cavity constitutes a relatively closed compartment with a paucity of local phagocytic cells. The inflammatory cascade may potentiate additional vascular obstruction and tissue damage from free radical release. The combination of implants, surgical contamination, and impaired vascular supply with consequent impaired endogenous immunity and impaired penetration of systemically administered antibiotics sets the stage for nosocomial infection (22). In response to these challenges, local antibiotic therapy has found a niche in the management of osteomyelitis.

The biological reasons for treatment failure can be broadly categorised into three groups: 1) the drug fails to reach its target, 2) the drug is not active against the target pathogen, or 3) the target is altered (23). Penetration of drugs into sites of infection almost always depends on passive diffusion and is thus proportional to the driving concentration gradient (24). For systemically administered drugs, this mandates good vascular supply to the target site. The outer membrane of Gram-negative bacteria is a semi-permeable barrier in which are embedded porin protein channels that restrict the entry into the cell of small polar molecules such as antibiotics (24). Porin channel absence or mutation may prevent antibiotic entry reducing drug concentration at the target site. The β-lactam antibiotics depend on this mechanism of bacterial cell entry. For drugs requiring active transport across the cell membrane, a mutation closing down this transport mechanism can confer resistance. For example, gentamicin transport depends on energy generated by respiratory enzymes during oxidative phosphorylation (24). A mutation in the key enzyme or anaerobic conditions slows entry of gentamicin into the cell, resulting in resistance. Drugs may also be transported out of the cell by efflux pumps, and resistance to numerous drugs is mediated by this mechanism, for instance chloramphenicol, fluoroquinolones, and β-lactams (24-27).

Drug inactivation is the second general mechanism of treatment failure. The contents of pus can bind antibiotics, reducing the active free drug fraction. Antibiotic modifying enzymes can be produced by the target bacteria, for example β-lactamases (24).

The third general mechanism of drug resistance is target alteration, for example a mutation in the binding domain of the target DNA gyrase enzyme in the case of fluoroquinolones (27) . It is of note that while the first and second mechanisms may be at least partially overcome by sufficient increases in drug concentration gradients, the third is not likely to be assisted by this approach.

While the therapeutic framework for systemic antibiotics is relatively well established, no such equivalent system applies for antibiotics administered locally into the surgical wound bed, or used to coat implants or other devices. The antibiotic concentrations achieved locally may be much higher than those that typically result from systemic administration, and thus standard susceptibility reporting criteria and MIC_{BP} will not apply. The change in drug concentration with time or pharmacokinetics of local therapy is also very different to systemic therapy, with a profile typically characterized by the rapid onset of a single peak concentration followed by a variable elimination phase, rather than the pulsatile pattern of sequential dosing. Thus the dose delivered by local administration may be more sustained than that delivered by systemic administration. To complicate matters further, evidence-based information on the appropriate duration of antibiotic therapy is frequently lacking. There is also the potential for local antibiotic therapy to compromise the wound environment either by a direct cytotoxic effect or by introduction of a delivery vehicle which persists long after the antibiotics have dissipated; these issues are typically not addressed in *in vitro* studies (28). The delivery vehicle itself, particularly if non-biodegradable, may act as an implant and subsequently become colonised as well as potentiating the emergence of resistance. There are reports of antibiotic-loaded cement beads contributing to the emergence of gentamicin resistant *staphylococci sp* (29). Theoretical advantages and disadvantages of local therapy are shown in ▶Table 2. The following information attempts to summarise available data on the characteristics of various local antibiotic therapies.

Antibiotic-impregnated cement

Various forms of bone cement, including polymerized polymethylmethacrylate (PMMA), calcium sulphate, and hydroxya-

Table 2 Advantages and disadvantages of local antibiotic therapy.

Advantages	Disadvantages
High local antibiotic concentrations achievable in the wound bed may eliminate bacteria not susceptible to systemic therapy and penetrate biofilm	Risk of direct host cytotoxicity from antibiotic or carrier
Focused delivery may maximize therapeutic benefit while minimizing systemic toxicity	Risk that delivery vehicle may have a negative effect on wound healing, act as a nidus for persistent infection, or require surgical removal
Reduced systemic exposure and consequent faecal output of antibiotics may reduce environmental antibiotic exposure and selection for resistant traits (30)	Risk of promotion of resistant traits, if the pharmacokinetic profile provides a period of sub-therapeutic antibiotic exposure
Antibiotic delivery not dependent on the presence of vascularized tissue	Limited available information on dosing, efficacy, and wound or species specific pharmacokinetic and pharmacodynamic profile
	Concurrent systemic therapy may still be appropriate

patite are in use in veterinary orthopaedics, predominantly for prosthesis implantation, and management of SSI with antibiotic-impregnated cement beads. All of these cements may be impregnated with antibiotics for either infection prophylaxis or treatment.

Powdered PMMA mixed with liquid methylmethacrylate undergoes an exothermic reaction to form non-absorbable bone cement five to 10 minutes later. The antibiotic powder or liquid solution is mixed with the PMMA prior to the addition of methylmethacrylate. Therefore, the antibiotic used must be stable in the face of the heat generated during the polymerization reaction. The cement material can then be formed into non-absorbable beads or used for infection prophylaxis of cemented arthroplasties (31). Conversely, calcium sulphate (plaster of Paris) and hydroxyapatite cement undergo no exothermic reaction during setting, are bioabsorbable, use water for admixture rather than a chemical polymer, and have also been studied as beaded antibiotic release vehicles (19, 20).

There are a number of *in vitro* studies evaluating antibiotic elution from these materials. Unfortunately, inter-study comparison and extrapolation of *in vitro* results to a clinical setting are hampered by lack of a standardised or validated model for the drug elution environment. Models typically use differing elution volumes and volume change intervals, and make no attempt to replicate the dynamic flow state of the *in vivo* environment. The cement/antibiotic mix ratios investigated as well as the elution concentrations considered efficacious are also highly variable. All studies investigating cement mixed with more than one antibiotic found the elution times were substantially shorter than when the antibiotics were used as a single agent (32-34). Use of a liquid rather than a powdered antibiotic was not necessarily associated with loss of efficacy (32-34). The rate of elution of gentamicin from PMMA was similar for both the powdered and liquid form, however amikacin eluted faster when powdered rather than liquid form was used (32). Idiosyncrasies were observed, for instance metronidazole delayed cement setting by 12 hours and meropenem lost all biological activity when autoclaved (35, 36). Findings from seven *in vitro* and two *in vivo* studies are summarized in ▶Table 3. There have been no good quality randomized controlled trials in human or veterinary clinical patients investigating the therapeutic benefit of antibiotic impregnated beads to treat osteomyelitis when compared with systemic therapy alone or in combination. Existing studies are either underpowered or experienced difficulties with protocol lapses. An experimental study in dogs evaluated treatment of induced *Staphylococcus aureus* osteomyelitis of the tibia with PMMA bead implants (37). Systemic gentamicin therapy for four weeks was compared with gentamicin-impregnated PMMA, using a 1:1 mix with a single 1 cm x 1.5 cm bead implanted in each dog at the site of infection. An improved rate of resolution was identified in the gentamicin-impregnated PMMA group (89%) compared with the systemic therapy group (63%), $p = 0.049$ (37). A randomised controlled trial evaluated systemic versus local therapy for 52 adult human patients undergoing debridement and reconstruction for infected non-unions. Four weeks of intravenous antibiotics were compared to local gentamicin PMMA beads together with two to five days of peri-operative systemic therapy. Resolution rates were 83% versus 89% ($p = 0.53$) respectively (38). A multi-centre randomized controlled trial compared systemic to local therapy using a similar methodology and also did not find any difference in resolution rates, however 75% of the patients in the local therapy group broke protocol and exceeded the five day limit to concurrent systemic therapy set by the investigators (39).

The effect of using antibiotic-loaded cement for infection prophylaxis in hip and knee arthroplasties in human patients has been investigated. A recent systematic review reported an absolute risk reduction of eight percent and relative risk reduction of 81% when antibiotic-loaded cement is used ($p < 0.001$) (40).

Findings regarding the effect of antibiotic admixture on cement mechanical properties have been variable. The addition of cefazolin powder to PMMA powder at a 1:40 dry weight ratio was reported to have no effect on compressive strength, while gentamicin powder at a 1:400 ratio caused significant reductions in compressive strength (41). The use of gentamicin in liquid form has been reported to have a greater negative impact on mechanical characteristics of cement than use in powder form, with a reduction in elastic modulus, but no difference in ultimate load (7). A recent review on the influence of antibiotic admixture on mechanical char-

acteristics of cement concluded that there is limited consensus on either the effect of the antibiotic or on the method used to blend the antibiotic with the cement, with conflicting results found across multiple studies. However, in general, the addition of antibiotic powder was found to cause a significant reduction in the fatigue life of the cement (42).

Antibiotic beads have also been investigated for infection prophylaxis in the context of open fracture management. A retrospective non-randomised study in 914 human patients identified an absolute risk reduction of 8.3% when comparing treatment with aminoglycoside-impregnated PMMA beads in conjunction with systemic therapy against systemic therapy alone (43).

Potential negatives surrounding the use of antibiotic impregnated cement include the risk of systemic toxicity and the generation of resistant organisms by prolonged exposure to sub-therapeutic concentrations of antibiotic. The available pharmacokinetic data for use of antibiotic impregnated cement in veterinary patients is very limited, and it would appear prudent to take concurrent parenteral dosing into account. However, there have so far been no veterinary reports of adverse patient events for this treatment modality. Serum levels of gentamicin remained undetectable when mongrel dogs were treated with PMMA containing 100 mg of gentamicin per dog (37). The generation of resistant organisms remains a concern. A cross-sectional study identified a 22% prevalence of bacterial colonisation of antibiotic loaded PMMA beads, with documented emergence of resistance (29). There is a case report of gentamicin impregnated beads removed from a human patient five years after placement, at which time low levels of eluting gentamicin were still detectable, and the bead sur-

Table 3 Summary of *in vivo* and *in vitro* studies investigating antibiotic elution from cement beads.

Antibiotic & current CLSI MIC_{BP} for *Staph. sp*	Study author	Drug/cement mix evaluated (dry weight ratio)	Cement type	Elution substrate	Elution concentration considered efficacious (C_{effic})	Time >C_{effic} (days)	Maximum elution concentration documented (µg/ml)	Time >MIC_{BP} (days)
Cefazolin 8 µg/ml	Phillips (34) Adams (88)[a] Udomkusonsri (89) Udomkusonsri (89) Weisman (41)	1:6 1:9 1:10 1:10 1:40	PMMA PMMA PMMA CS PMMA	PBS Seroma PBS PBS PBS	4 x MIC_{90} N/a 0.125 µg/ml 0.125 µg/ml N/a	>30 N/a >14 >14 7–13	~530 88 ~1200 ~1300 N/a	>30 >28 >14 ~13 N/a
Ceftiofur 2 µg/ml	Ethell (32) Ethell (32)	1:10 1:10	PMMA HA	PBS PBS	2 µg/ml 2 µg/ml	7 7	~350 ~2000	77
Ticarcillin 64 µg/ml	Adams (88)[a]	1:3.33	PMMA	Seroma	N/a	N/a	6100	<9
Vancomycin 2 µg/ml	Atilla (33) Adams (88)[a]	1:30 1:10	CS PMMA	Seroma	4 µg/ml N/a	84 N/a	1776 48.1	>84 >28
Meropenem 4 µg/ml	Baez (36)	1:5	PMMA	PBS	4 µg/ml	15–18	~1100	15–18
Gentamicin 4 µg/ml	Ramos (35) Ethell (32) Ethell (32) Anagnostakos (90) Weisman (41)	1:20 1:20 1:20 1:80 1:400	PMMA PMMA HA PMMA PMMA	PBS PBS PBS PBS PBS	N/a ~0.5 µg/ml ~0.5 µg/ml N/a N/a	>21 >30 >30 N/a 6–12	N/a ~50 µg/ml ~2000 µg/ml 116µg/ml N/a	N/a ~7 >30 ~12 N/a
Tobramycin 4 µg/ml	Adams (88)[a]	1:4	PMMA	Seroma	N/a	N/a	155 µg/ml	>28
Amikacin 16 µg/ml	Phillips (34) Ethell (32) Ethell (32)	1:8 1:8 1:8	PMMA PMMA HA	PBS PBS PBS	8 x MIC_{90} MIC MIC	>30 >30 >30	~1000 ~200 ~3000	>30 >30 >30
Metronidazole	Ramos (35)	1:20	PMMA	PBS	N/a	>21	N/a	N/a
Clindamycin 0.5 µg/ml	Adams (88)[a]	1:6.66	PMMA	Seroma	N/a	N/a	1517	>28
Ciprofloxacin 0.5 µg/ml	Adams (88)	1:6.67	PMMA	Seroma	N/a	N/a	74.5	>28

[a]*In vivo* study, 5 x 9 mm diameter beads implanted in medullary cavity in dogs and tissue/bone concentrations measured at 28 days. CLSI = Clinical and Laboratories Standards Institute; MIC = minimum inhibitory concentration; BP = breakpoint; PMMA = polymethylmethacrylate; CS = calcium sulphate; HA = hydroxyapatite; PBS = phosphate buffered saline; N/a = not available.

face had been colonized by a gentamicin-resistant coagulase-negative *Staphylococcus spp* (44). Where possible, the timely removal of PMMA implants may reduce this risk.

In summary, there is some evidence, even though it is cross-species, for the use of antibiotic-impregnated cement in joint arthroplasty, although this may come at the expense of shortened fatigue life. There is also good experimental data demonstrating the efficacy of antibiotic-impregnated cement beads in the treatment of osteomyelitis.

Gentamicin-impregnated collagen sponge

Gentamicin-impregnated collagen sponge[a] (GICS) is a local antibiotic delivery product finding increasing application worldwide for prophylaxis and treatment of surgical infections. The product consists of bovine or equine collagen impregnated with gentamicin and lyophilized to provide uniform drug distribution. This facilitates accurate patient dosing by unit sponge area. Applications in human patients include the treatment of implant-associated infections, soft tissue infections, and infection prophylaxis in oncologic, orthopaedic and cardiac surgery, including the management of open fractures at the time of open reduction and internal fixation (45-52). Reported veterinary usages are similar, with a focus on the management of intra-articular infections (53-55). Randomised controlled trials investigating human patient populations have reported prophylactic GICS to reduce infection rates following median sternotomy, however conversely the sponge was reported to increase infection rates when used prophylactically during colo-rectal surgery (56, 57).

The GICS product information[a] lists advantages which include the delivery of very high local antibiotic concentrations combined with rapid biodegradability. A study investigating antibiotic release following GICS implantation in equine tarsocrural joints at 0.26 mg/kg identified median peak intra-synovial concentrations of 169 µg/ml, although gentamicin concentrations fell to sub-MIC (4 µg/ml) by 48 hours post-implantation (58). A similar study investigating pharmacokinetics following GICS implantation in canine stifles at a dose of 6 mg/kg identified mean peak intra-synovial concentrations of 2397 µg/ml with a decline to sub-MIC concentrations by 23 hours post-implantation. Plasma levels reached approximately 33% of those anticipated after intravenous gentamicin administration (59). While the standard mg/kg dosing used for systemic therapy does not extrapolate well to the local environment in terms of efficacy, reporting dosing in this manner may be of assistance when considering potential systemic toxicity concerns, The pharmacokinetic studies performed to date support the manufacturer's claims for delivery of high local antibiotic concentrations. Studies investigating the biodegradation of GICS following subcutaneous and intramuscular implantation identified a marked inflammatory response persisting to at least five days following implantation (60, 61). A study investigating intra-articular inflammation following GICS implantation identified elevated cytokines and cellular inflammatory response persisting to at least four weeks post implantation (62). Thus delayed biodegradation may be an issue, and persistence of a collagen nidus in the face of sub-therapeutic local antibiotic concentrations may explain the increased infection risk found in some studies.

Toxic serum gentamicin levels and compromised renal function have been reported in association with intra-articular sponge use in human patients at gentamicin doses ranging from 7-9 mg/kg (63). A study investigating renal function in normal dogs following subcutaneous implantation of GICS found normal serum creatinine for at least seven days postoperatively; the gentamicin dose used was not stated and it is therefore not possible to know the clinical significance of this finding (64). A study investigating sensitive renal markers following intra-articular implantation of the GICS at 6 mg/kg in dogs found a reduction in glomerular filtration rate in the treatment group (62).

In summary, cross-species data suggests that while there may be a role for GICS in antibiotic prophylaxis for clean surgeries where the consequences of infection may be devastating, there is also the potential for GICS to worsen infection rates when used in the face of bacterial contamination (56, 57). Canine data evaluating intra-articular GICS suggests a rapid decline in eluted gentamicin to sub-MIC levels, with persistence of collagen-associated inflammation for several weeks (59, 62). The persistence of the collagen sponge may be the cause of the deleterious effects on wound healing seen in some circumstances (57). There is currently no high quality data on the efficacy or safety of GICS for the treatment of established infections.

Antibiotic-impregnated gel

An injectable, antibiotic-impregnated dextran polymer hydrogel has recently become available. The gel consists of two ingredients that form a gel within two minutes of mixing, and is suitable for injection or topical application. The residence time of the gel *in vivo* is four to five weeks, with degradation via hydrolysis. The gel is reported to be fully biodegradable and non-immunogenic. Available antibiotics include amikacin, vancomycin, or amikacin and clindamycin[b]. A recent *in vitro* study suggested release of high local concentrations of antibiotic within the first 24 hours (C_{max}:MIC>300 for amikacin and clindamycin) with concentrations sustained above the MIC for 10 days (65). To date, no results of case series or treatment trials have undergone peer-reviewed publication.

Antibiotic-impregnated demineralised bone matrix

Demineralised bone matrix impregnated with tobramycin and gentamicin has been investigated *in vitro*, with a view to clinical application in the management of infected non-unions. Potential advantages include

a Gentamicin Surgical Implant: Innocoll Technologies, Athlone, Ireland.

b R-gel: Royer Animal Health, Frederick, MD, USA

osteoinduction and osteoconduction together with no requirement for a second procedure to remove the implants. *In vitro*, continued osetoblastic activity was identified, and antibiotic levels were maintained above MIC for 13 days (66, 67). Reduction in positive cultures in an experimental model was demonstrated when compared with standard demineralized bone matrix alone, however the effect on bone healing *in vivo* was not evaluated, and no comparison was made between antibiotic impregnated demineralized bone matrix and standard bone matrix in combination with systemic antibiotic therapy (67).

Antibacterial properties and coatings for surgical implants

Veterinary metal orthopaedic implants are typically composed of 316L stainless steel. This is a 2.8% molybdenum, 15% nickel, 18% chromium and 64.2% iron alloy (68). Alternative materials include titanium alloys, and various absorbable materials such as polycaprolactone and polylactide (69, 70). Stainless steel implants have been associated with significantly greater infection rates than titanium implants, although the topic is controversial (71-73). A postulated reason for this is that soft tissue adheres firmly to titanium implant surfaces, while a fibrous capsule containing a fluid filled void is formed around steel implants. The consequent dead space is more susceptible to bacterial colonization, and less accessible to host defence mechanisms (15). An experimental study investigating *Staphylococcus aureus* biofilm formation found biofilm to form more readily on stainless steel than on titanium implant surfaces (74).

Various metal implant coatings, including hydrophobic materials, antibiotics, nitric oxide releasing compounds and silver, have been assessed in both *in vitro* and *in vivo* studies for potential to decrease implant colonization. The hydrophobic material polycation N,N- dodecyl,methyl-**polyethylenimines** (**PEI**) was shown to prevent implant colonization in a sheep osteomyelitis model (75). Various antibiotic-loaded, biodegradable polymers have shown efficacy as implant coatings however there is a theoretical risk of inducing resistant bacterial strains if the antibiotic release profile shows prolonged periods of sub-MIC antibiotic concentrations (13, 76). Experimental studies in rats have demonstrated efficacy of a gentamicin-coated tibial nail for improving bone healing when used in the face of bacterial contamination, and a follow-up case series reported minimal complications when gentamicin-coated nails were used for management of open fractures in human patients (77, 78). Gentamicin-coated polyurethane sleeves fitted to external skeletal fixator pins have been investigated as a method of prevention of pin-tract infections (79). Nitric oxide releasing coatings have been applied to external skeletal fixator pins and shown to reduce bacterial colony counts in a rat model (80). A method of covalently linking antibiotics to a titanium implant surface has been developed, offering the theoretical advantages of no additional delivery vehicle together with long-term activity and reduced tissue toxicity. No clinical trials have been performed to date (81).

Silver is bactericidal, disrupting the function of bacterial cell membranes and metabolic proteins (82). Silver-resistant bacterial strains are reported (83). *In vitro* studies evaluating silver nanoparticle coatings have shown promise, however the technology has yet to be fully assessed in appropriate *in vivo* models or clinical trials (84, 85). A randomised controlled trial investigating silver-coated external fixator pins compared with standard stainless steel pins in 24 human patients identified a 10% reduction in positive culture rates. This difference did not reach statistical significance due to the small number of patients enrolled in the study and associated lack of power. Silver-coated pin implantation resulted in a significant increase in silver serum level, resulting in termination of this study (86). A subsequent randomised controlled trial evaluated the effect of applying a silver coating to a titanium-vanadium megaprosthesis used for limb salvage in 51 human patients following major oncologic resection. Infection rates were 5.9% in the silver coating group versus 17.6% in the uncoated group ($p = 0.062$), however the groups lacked homogeneity, with operating times on average 30 minutes shorter in the silver coating group ($p = 0.03$). A single patient in the treatment group was reported as suffering from silver toxicity (87).

Conclusion

In the face of increasing incidence of multidrug resistant implant infections, local antibiotic modalities are receiving increased attention for both infection prophylaxis and treatment. Local antibiotic therapy that achieves very high antibiotic concentrations at the site of the implant may represent an avenue for treatment of infections including those by biofilm-forming bacterial pathogens. Randomised controlled trials in human patients have demonstrated an infection risk reduction when antibiotic-impregnated cement is used for infection prophylaxis in implanted joint prostheses, and when a gentamicin-impregnated collagen sponge is used for infection prophylaxis in midline sternotomy (40, 56). The other modalities discussed have for the most part yet to be evaluated in randomized controlled trials in veterinary or human patients. In general, the *in vivo* concentration-time profile and appropriate dosing regimen for local antibiotic modalities have yet to be elucidated. Toxicity is possible locally and systemically, and attention to the dose and characteristics of the dosage form applied are warranted (63). There is currently an emphasis on *in vitro* studies in the veterinary literature on this topic, which do not necessarily assist robust clinical decision making. A central web-based registry of orthopaedic surgical site infections providing a running database documenting clinical isolate, context, treatment and outcome might go some way towards alleviating the veterinary-specific information void on this important topic.

In summary, for therapy of established orthopaedic surgical site infections, the principles governing responsible antibiotic use should be adhered to. Antibiotic selection should be targeted by culture and susceptibility results, and narrow spectrum agents should be used wherever possible and appropriate. The use of local antibiotics fulfilling these criteria in addition to standard systemic therapy may be judicious if there are reasonable clinical con-

cerns regarding vascularity at the surgical site which cannot be addressed by surgical debridement, or if there is an implant burden which cannot be removed until healing has further progressed. In these instances, either antibiotic-impregnated cement or collagen have undergone the greatest clinical research. If PMMA beads are used, removal of the beads together with the implants once the infection has resolved and bone healing progressed is recommended.

Conflict of interest

None declared.

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