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QUESTION 5: What is the ideal composition of antibiotic-impregnated intramedullary (IM) nails?

RECOMMENDATION: The ideal composition of antibiotic-impregnated IM nails is unknown. The core should consist of a rigid structure such as an Ender's IM nail, Ilizarov threaded rods, IM locked nails, carbon fiber nails or sectioned pins or guidewires. We recommend at least 2 grams of vancomycin and 2.4 grams of an aminoglycoside be added to each pack (40 grams) of polymethyl methacrylate cement. If a specific micro-organism is isolated, targeted antibiotic therapy should be included.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Infection following IM nailing of long bone fractures is a recognized complication that can be difficult to treat successfully [1]. The incidence is variable depending on the degree of soft tissue and bone compromise, ranging from 1.8% in closed fractures and Gustilo type I open fractures up to 12.5% in type IIIb open fractures [2]. Almost half of these are caused by multiple organisms. Zych et al. [2] reported that 56% of these infections were caused by a single organism, predominantly caused by *Staphylococcus aureus* (50%) followed by *Bacteroides fragilis* (3%) and *Streptococcus pyogenes* (3%). The remaining cases were caused by a combination of these and *Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Escherichia coli,* and *Pseudomona aeruginosa*. In all infections, *Staphylococcus aureus* was present in 64% of cases.

Antibiotic cement-impregnated IM nails (ACIMNs) have been described as a treatment option for this complication. These are designed to provide stability while delivering local antibiotics. Initially described by Paley and Herzenberg in nine cases, they used a chest tube as a mold and a guidewire as a core, covered with antibiotic-loaded bone cement [3]. The treatment strategy with the use of ACIMNs is generally performed in a two-stage fashion. An initial debridement and implantation is followed by subsequent removal with or without definitive hardware exchange [4–6].

The greatest disparity among ACIMNs is the element used as the core. Investigators have reported different components including Ender's IM nails, Ilizarov threaded rods, IM locked nails, interlocked carbon fiber nails, sectioned pins or guidewires [7]. ACIMNs act as antibiotic-loaded cement spacers, similar to those used in two-stage exchange arthroplasty for periprosthetic joint infection treatment, [8] with additional temporary fracture or bone stabilization [9].

Regarding construct rigidity, the core diameter is the most important factor. It is important to note that these are significantly weaker than conventional IM nails given the antibiotic coating. Thus, a balance between the core diameter and planned diameter of ACIMN should be carefully calculated. In a mechanical study by Marmor et al. [10] different core diameters were evaluated. A 5.8-mm-core diameter cement rod bending stiffness was reportedly higher, 4.96 ± 0.67 N/m2, than a 3-mm-core, 3.07 ± 0.28 N/m2, ($p = 0.0039$). The second important factor is the thickness of the cement mantle, which is currently unknown given different variables of the cement composition. Vaishya et al. [11] suggest a cement mantle thickness of 2 to 3 mm without clear evidence supporting this statement. The reduction in the volume of cement coating raises concerns regarding the effectiveness of antibiotic delivery. However, the elution properties of the impregnated antibiotics have been shown to depend on the surface area and porosity of the mixture, not the thickness. In a study by Karek et al. [12], they demonstrated that a thin mantle would potentially allow for higher elution of antibiotics caused possibly by the result of a cooler exothermic reaction.

Different techniques of ACIMN fabrication have been described [3,7,13]. The use of a mold and manual fabrication has been commonplace for the past two decades. These have different advantages and disadvantages such as fabrication speed and the morphology of the implant. Molds such as chest tubes seem to be the best option as they generate a smooth implant that facilitates their later removal. Kim et al. [5] evaluated the time required to peel the chest tube off the ACIIN using different cement-cooling techniques. They found that the fastest and most effective way is cooling the cement in cold water and pre-lubricating the chest tube with mineral oil. They also recommend the use of 3-mm beaded IM guidewire that is cut to a length 3 cm longer than the length of the tube allowing creation of a hook or loop for subsequent removal.

Broad-spectrum antibiotics are routinely used as infections are generally poly-microbial. The most commonly used antibiotics are vancomycin, tobramycin, gentamycin or a mixture of these [14]. Antibiotics must have certain properties in order not to compromise their efficacy. Anagnostakos et al. [15] identified these properties as availability in powder form, wide spectrum coverage, bactericidal activity, high elution properties, thermo-stable and hypoallergenic [16]. Targeted therapy if a micro-organism has been isolated is desired if certain criteria are met.

Reported success rates range with the use of ACIMNs range from 69% to 100% with the use of different constructs and similar antibiotic compositions [4,6,17–21]. We, therefore, consider the ideal composition currently unknown. We do consider, with the available literature descriptions, that there are several considerations that need to be employed in the construction of these devices. The core should consist of a rigid structure with the largest diameter possible to increase rigidity while not compromising cement mantle stability. The system should have an extraction element for subsequent removal. Based on recommended antibiotic concentrations for spacers, most authors use a mixture of at least 2 gm of vancomycin and 2.4 gm of an aminoglycoside in 40 gm of bone cement. Prior research has shown that this is the minimum concentration needed for attaining long-lasting antibiotic elution in the surrounding space [22]. There is little evidence of systemic toxicity with high antibiotic concentrations in the cement mixture used to coat nails, but a dosage safety range has not been established. If a specific micro-organism is isolated, targeted antibiotic therapy should also be considered.

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QUESTION 6: What is the ideal composition of antibiotic impregnated (ABI) spacers/beads in post-traumatic infections? Is preoperative microbial identification necessary?

RECOMMENDATION: There is currently limited evidence with regards to the ideal composition of ABI polymethyl methacrylate (PMMA) spacers or beads in post-traumatic infections and the need for preoperative identification of the causative organism. Available data suggests that PMMA spacers, empirically impregnated with at least 2 gm of vancomycin per 40 mg of PMMA (with or without gentamycin), may result in quiescence of infection in a high percentage of cases with an acceptable associated rate of bony union. Preoperative microbial identification is of unclear utility.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

The challenge of achieving adequate local tissue antibiotic concentrations with systemic antibiotics has prompted the addition of local antibiotic therapy in the majority of bone infection protocols. The use of ABI PMMA beads is well established in the treatment of chronic osteomyelitis. Klemm reported a cure rate of over 90% in 405 cases of chronic sequestrating osteomyelitis with the use of gentamycin-impregnated PMMA bead chains [1]. Notably, the beads were pre-manufactured with gentamycin and Klemm found no change in the gentamycin resistance profile over a seven-year period. The use of local antibiotic therapy has also been advocated in the post-traumatic setting. Numerous review articles advocate for the use of ABI PMMA or other forms of local adjuvant antibiotic therapy in the setting of septic non-union or post-traumatic infections [2–5]. Interestingly a recent comparison of the outcomes of treatment with ABI beads versus spacers revealed no difference in the rate of infection control, time to union or complication rate with either configuration [6].

The induced membrane ("Masquelet") technique has gained popularity in the management of post-infective bone defects [7]. The procedure involves the placement of a PMMA spacer in the defect, followed by a subsequent second-stage bone grafting into the resulting induced membrane [8]. Originally the procedure was described using bone cement without antibiotics. Masquelet reasoned that the inclusion of antibiotics may increase the risk of resistance to the offending organisms and that it changed the biological characteristics of the induced membrane [9]. This concern was validated, in an animal model by Nau et al., who demonstrated variations in the nature of the induced membrane with different types of bone cement and supplemental antibiotics [10]. Notably, Palacos[a] with gentamycin still resulted in a positive rate in cell growth. However, in clinical studies involving post-traumatic (not post-infective) bone defects the concerns regarding inhibition of bone healing were not realized, with reported union rates of 82% (in cylindrical defects) to 100% (in conical defects) with the use of ABI spacers [11,12].

While the original technique involved PMMA without antibiotics, several other authors have utilized the potential advantage of local antibiotic elution during the construction of the spacer [13–18]. If the data from the meta-analysis by Morelli et al. is scrutinized it appears that there may well be a therapeutic advantage with the addition of antibiotics in terms of infection control. When evalu-