

## QUESTION 5: Can fresh-frozen allograft (FFA) be used as a carrier to deliver local antibiotics during revision arthroplasty?

RECOMMENDATION: Emerging evidence suggests that specialized preparations of antibiotic-impregnated allograft are more effective than FFA mixed with antibiotics.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 63%, Disagree: 14%, Abstain: 23% (Super Majority, Weak Consensus)

### RATIONALE

Bone allograft is one of the reconstructive options that can be used during revision arthroplasty. However, there are risks of bacterial colonization due to the fact that allografts are non-vascularized, and so they are not suitable for use alone during the management of periprosthetic joint infections (PJIs). The addition of antibiotics to bone cement is one method to potentially reduce the risk of PJIs and surgical site infections (SSIs). However, another factor that must be taken into account in such situations is the role of the biofilms. Formation of biofilms on implant surfaces enables bacteriae to evade the host immune system, as well as to attenuate the effectiveness of antibiotics. Biofilm-embedded bacteria, therefore, require higher concentrations of antibiotics for elimination, in comparison to their planktonic counterparts [1,2].

The antibiotic-carrying capability of allograft far exceeds that of bone cement [3–5]. A number of studies have reported on the use of FFAs mixed with antibiotics during revision surgery for PJIs [5–7]. These studies support the use of FFAs as an antibiotic carrier in aseptic revision arthroplasty and in the second stage of two-stage revisions. However, in such situations, only antibiotics in powder form can be added to FFAs which limits the choice of antibiotics. Another drawback of FFAs applies to the local tissue effect of the high local antibiotic concentrations. While some antibiotics (e.g., vancomycin or tobramycin) are tolerated very well, others show a deleterious effects on osteoblasts (e.g., ciprofloxacin) [8–10]. Nevertheless, FFAs with antibiotic powder mixed have been used clinically in sites without evident florid infection as a more prophylactic tool [5]. The generated concentrations show a burst release for some days that appear sufficient for avoiding bacterial colonizations. However, the concentrations are not maintained for a prolonged period of time, which is necessary for eliminating chronic infections mediated by biofilms [11,12].

This has led to the development of specially-prepared allografts that are more suitable for one-stage revisions, due to their ability to provide the necessary high antibiotic concentrations for prolonged durations [13,14]. The use of these antibiotic-loaded allografts may be considered safe and incorporation of allografts into the host bone seems to not be impaired [5,7,15]. The removal of bone marrow (i.e., fat and cellular components) in such allograft preparations improves the safety of allograft due to immunological reactions, increases the antibiotic storage capacity of the graft and aids better incorporation of allograft into the host bone. Other investigators have demonstrated that antibiotics bonded to bone grafts avoid bacterial colonization and biofilm formation, thereby enhancing osteogenesis and integration of the graft and implant [16,17]. However, published literature on the clinical use of such allograft preparations is limited and further studies are necessary to determine their long-term effectiveness [18].

### REFERENCES

- [1] Costerton JW. Biofilm theory can guide the treatment of device related orthopaedic infections. *Clin Orthop Rel Res.* 2005;7–11.
- [2] Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science.* 1999;284:1318–1322.
- [3] Witsø E, Persen L, Løseth K, Bergh K. Adsorption and release of antibiotics from morselized cancellous bone. In vitro studies of 8 antibiotics. *Acta Orthop Scand.* 1999;70:298–304.
- [4] Witsø E, Persen L, Løseth K, Benum P, Bergh K. Cancellous bone as an antibiotic carrier. *Acta Orthop Scand.* 2000;71:80–84. doi:10.1080/00016470052943955.
- [5] Witsø E, Persen L, Benum P, Aamodt A, Husby OS, Bergh K. High local concentrations without systemic adverse effects after impaction of netilmicin-impregnated bone. *Acta Orthop Scand.* 2004;75:339–346. doi:10.1080/00016470410001295.
- [6] Buttaro MA, Pusso R, Piccaluga F. Vancomycin-supplemented impacted bone allografts in infected hip arthroplasty. Two-stage revision results. *J Bone Joint Surg Br.* 2005;87:314–319.
- [7] Buttaro MA, Gimenez MI, Greco G, Barcan L, Piccaluga F. High active local levels of vancomycin without nephrotoxicity released from impacted bone allografts in 20 revision hip arthroplasties. *Acta Orthopaedica* 2005;76:336–40. doi:10.1080/00016470510030797.
- [8] Edin ML, Miclau T, Lester GE, Lindsey RW, Dahners LE. Effect of cefazolin and vancomycin on osteoblasts in vitro. *Clin Orthop Relat Res.* 1996;333:245–251. doi:10.1097/00003086-199612000-00027.
- [9] Miclau T, Edin ML, Lester GE, Lindsey RW, Dahners LE. Effect of ciprofloxacin on the proliferation of osteoblast-like MG-63 human osteosarcoma cells in vitro. *J Orthop Res.* 1998;16:509–512. doi:10.1002/jor.1100160417.
- [10] Lindsey RW, Probe R, Miclau T, Alexander JW, Perren SM. The effects of antibiotic-impregnated autogeneic cancellous bone graft on bone healing. *Clin Orthop Relat Res.* 1993;303–312.
- [11] Coraça-Huber DC, Ammann CG, Nogler M, Fille M, Frommelt L, Kühn KD, et al. Lyophilized allogeneic bone tissue as an antibiotic carrier. *Cell Tissue Bank.* 2016;17:629–642. doi:10.1007/s10561-016-9582-5.
- [12] Miclau T, Dahners LE, Lindsey RW. In vitro pharmacokinetics of antibiotic release from locally implantable materials. *J Orthop Res.* 1993;11:627–632. doi:10.1002/jor.1100110503.
- [13] Winkler H, Janata O, Berger C, Wein W, Georgopoulos A. In vitro release of vancomycin and tobramycin from impregnated human and bovine bone grafts. *J Antimicrob Chemother.* 2000;46:423–428.
- [14] Winkler H, Stoiber A, Kaudela K, Winter F, Menschik F. One stage uncemented revision of infected total hip replacement using cancellous allograft bone impregnated with antibiotics. *J Bone Joint Surg Br.* 2008;90-B:1580–1584. doi:10.1302/0301-620X.90B12.20742.
- [15] Buttaro MA, Morandi A, Rivello HG, Piccaluga F. Histology of vancomycin-supplemented impacted bone allografts in revision total hip arthroplasty. *J Bone Joint Surg Br.* 2005;87-B:1684–1687. doi:10.1302/0301-620X.87B12.16781.
- [16] Ketonis C, Barr S, Adams CS, Shapiro IM, Parvizi J, Hickok NJ. Vancomycin bonded to bone grafts prevents bacterial colonization. *Antimicrob Agents Chemother.* 2011;55:487–494. doi:10.1128/AAC.00741-10.
- [17] Ketonis C, Barr S, Shapiro IM, Parvizi J, Adams CS, Hickok NJ. Antibacterial activity of bone allografts: comparison of a new vancomycin-tethered allograft with allograft loaded with adsorbed vancomycin. *Bone.* 2011;48:631–638. doi:10.1016/j.bone.2010.10.171.
- [18] Anagnostakos K, Schröder K. Antibiotic-impregnated bone grafts in orthopaedic and trauma surgery: a systematic review of the literature. *Int J Biomater.* 2012;2012:538061. doi:10.1155/2012/538061.