# G94: Is there a role for immunotherapy in patients with orthopedic implant associated infections?

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**Recommendation:** Preclinical models are promising in multiple areas of immunotherapy, so while the potential is high, human clinical studies are still needed to elucidate the role of immunotherapy in management of orthopedic infections.

**Level of Evidence:** Moderate

**Delegate Vote:** Agree: Disagree: Abstain:

**Rationale:**
With the recent boom in biomedical implants due to an aging population, implant associated infection (IAI) has become a widespread threat [1,2]. Humans possess powerful armament in their own immune system. The immune system can respond rapidly and specifically to pathogens; however, function is affected by the implanted biomaterials [1,3]. Most current biomaterials are identified as foreign by the immune system and targeted for destruction, leading to reduction of immune cells available to combat bacteria [1]. This targeting leads to chronic inflammation, reducing wound healing as well [1]. Neutrophils (PMNs) are the predominant immune cell present immediately after invasion and utilize various strategies to clear pathogens [1,4,5]. Macrophages follow neutrophils in the immune response and come in 2 main categories; pro-inflammatory and anti-inflammatory [1,6]. Pro-inflammatory macrophages aid by phagocytosing remaining pathogens and secreting inflammatory cytokines such as IL-12 and TNF-a, while anti-inflammatory macrophages promote wound healing and reduce antibacterial activity by producing markers such as IL-10 and arginine [1,7]. Another population of cells, myeloid-derived suppressor cells (MDSCs), possess a unique ability to suppress T-cells, and several studies have illustrated increased MDSCs surrounding an IAI, playing a role in biofilm formation by bacteria [7-9]. Emerging evidence indicates T-cells and B-cells may play a role in IAI, however, their exact role has not been elucidated [1,7].

Historically, traditional biomaterials lacking antibacterial activity have been used, necessitating antibiotic administration [1,10]. Further, many bacteria form biofilms, which increase resistance to antibiotics, promoting bacterial proliferation and reducing efficacy of the immune system [11]. The traditional biomaterials such as titanium have been shown to break down in response to IAI and promote inflammation, reducing osseous integration and wound healing [12]. Nonmetallic biomedical implants have been developed, however these face similar challenges regarding implant failure, predilection for infection via biofilms, and the ability to create sustained inflammation that impedes the ability of the immune system to fight off pathogens [1,13,14]. Given the susceptibility to infection and growing antibiotic resistance of bacteria, newer strategies to prevent IAI have begun focusing on manipulating the immune system instead of solely focusing on direct anti-bacterial activity. Two main strategies evolved: passive and active immunomodulation [1,7,15].

Passive immunomodulation relies on changing surface morphology to deter biofilm formation and stimulate auto-immunity [7,15,16]. To further complement passive strategies, bioactive molecules such as host defense peptides, metal nanoparticles, and gasotransmitters are loaded onto the biomaterial [1,7,17]. Promising results have arrived from many animal and *in vitro* studies. Regarding metal ions [17-21], Whu et al. demonstrated enhanced phagocytosis of bacteria by loading Cu-Sr onto titanium alloy [17]. Guo et al. demonstrated the ability of $CuFe_5O_8$ nanocubes to pro-inflammatory polarization and enhanced phagocytosis [18]. However, this was only achieved with disrupted biofilms. Xiao et al. created a $Cu^{2+}$ dressing that promoted pro-inflammatory polarization while simultaneously exerting direct anti-bacterial effects in rat models [19]. Raza et al. found small spherical shaped Ag nanoparticles demonstrated strong antibacterial effects *in vitro* [20]. All very promising but remain largely in preclinical stage.

Host defense peptides are proposed to contain antibacterial and immunomodulatory effects [1,22-24]. IDR-1, an innate defensin, modulated genetic transcription leading to a controlled inflammatory environment that resulted in enhanced bacterial clearance in vitro and in mice [22]. Qu et al. loaded LL-37 plasmid onto a scaffold and illustrated extracellular and intracellular antimicrobial effects, along with continued production of LL-37 by incorporating the gene into neighboring cells to facilitate continual effects including inflammation control [23]. Wang et al. utilized DJK-5 to promote direct antimicrobial killing, along with promoting enhanced macrophage phagocytosis along with inhibiting potentially harmful inflammatory cytokines such as IL-6 and TNF-$\alpha$ [24].

Other strategies include manipulating topography along with embedding metal ions/nanoparticles [25-26]. Fisher et al. created a diamond nanocone surface mimicking cicada wings which demonstrated bactericidal activity *in vitro* despite adhesion to the surfaces, with less uniform surfaces having higher activity [25]. Liu et al. fabricated a porous surface which effectively trapped bacteria, allowing the embedded copper to exert antibacterial effects *in vitro* and animal models along with pro-inflammatory macrophage promotion [26]. Recently, attention has turned to innate molecules such as beta-defensin-2 (BD2) and other similar molecules secreted by the immune system. Borysowski et al. recently used *E. coli* phages to induce expression of BD2 along with other cytokines, suggesting the ability to modulate the immune system via phages [27-28]. Su et al. utilized an acidity-activated metal organic framework to release $H_2S$ that stimulated cytokine production by anti-inflammatory macrophages to promote wound healing along with direct antibacterial effects [29].

The one true immunotherapy for IAI clinical study identified to date involved the postoperative injection once daily for 7 days of human β-defensin 3 (HBD-3) into the joint after TKA [30]. This study demonstrated that, compared to placebo saline injection, HBD-3 injection resulted in modulation of the local immune system toward a more pro-inflammatory profile (increased IL-2, TNF-$\alpha$, TLR-4, ALP, and TH1 cells) at 1-month postop. While severely underpowered, the study found a non-statistically significant decrease in 1-year PJI rate for HBD-3 patients (3.1%) compared to saline patients (9.4%) ($p=0.306$) [30]. So, promising but limited.

Given the many different strategies employed for immunomodulation in IAI, trends are beginning to emerge on possible strategies. Most studies utilized methods to promote pro-inflammatory and anti-inflammatory macrophages at specific time points during IAI. The metal ion-based and HDP studies typically utilized the direct and indirect antibacterial effects inherent to the metal ion and HDP. The appearance of the theme of dual action, both direct antibacterial and indirect via stimulation of the immune system may be the most promising course of action pre-clinically. However, there have been few studies performed in humans, with many of these experiments being in vitro or in animal models only. Future human clinical studies are necessary to identify the true role of immunotherapy in IAI prevention/management.

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