A Single Center Retrospective Evaluation of a Surgical Strategy to Combat Persistent Soft Tissue Wounds Utilizing Absorbable Antibiotic Beads

Joseph W. Gorvetzian,[1] Ryan P. Kunkel,[2] and Christopher P. Demas, MD[2,*]

[1]Health Sciences Center, University of New Mexico School of Medicine, Albuquerque, New Mexico.
[2]Division of Plastic Surgery, University of New Mexico Hospital, Albuquerque, New Mexico.

Christopher P. Demas, MD

Submitted for publication April 8, 2018. Accepted August 30, 2018.

*Correspondence: Division of Plastic Surgery, University of New Mexico Hospital, MSC10 5610, 1 University of New Mexico, Albuquerque, NM 87131-0001 (e-mail: cdemas@salud.unm.edu).

Objective: To determine whether use of absorbable antibiotic-imbued beads in chronic soft tissue wounds presents a viable therapeutic modality.
Approach: Retrospective analysis of all cases utilizing calcium sulfate antibiotic beads was conducted. Cases comprised complex wound and breast reconstruction performed by the senior author (C.P.D.) over 4 years at the University of New Mexico Hospital. All-cause need for reoperation and reoperation for infection in the 90 days following bead-assisted surgery were compared to traditional surgical intervention in the 90-day period preceding bead-assisted surgery. Paired-samples t-test and corrected Cohen's d were calculated for outcome significance and effect size.
Results: A total of 60 patients underwent 84 bead-assisted surgeries. There was a significant decrease in rate of reoperation following bead surgery ($M = 0.32$) compared with prebead surgery ($M = 2.2$), $p < 0.001$. Rate of reoperation for infection significantly decreased from 1.7 before bead surgery to 0.05 following bead surgery, $p < 0.001$. Results remained significant when stratified by complex wound or breast reconstruction, $p < 0.01$. Cohen's d ranged from 1.25 to 2.13, with probability of superiority between 80% and 93%.
Innovation: Use of antibiotic-laden materials is well established in the orthopedic literature, but poorly characterized in soft tissue applications. Biofilms are increasingly implicated as a unifying pathologic foe underlying chronic wound infection and nonhealing. Antibiotic beads have demonstrated activity against biofilm *in vitro*. This study demonstrates diminished reoperative burden for these wounds following antibiotic bead surgery, possibly as a result of *in vivo* biofilm antagonism.
Conclusion: Antibiotic bead-assisted surgery was associated with significantly decreased infectious and all-cause reoperations for chronic and infected wounds.

Keywords: antibiotic beads, biofilm, wound infection, chronic wounds

INTRODUCTION

Chronic wounds are variably defined as those wounds that do not heal within 4–6 weeks, that are not reduced in area by 20–40% after 2–4 weeks, or that have not healed in 3 months.[1–3] These wounds contribute tens of billions of dollars to global healthcare expenditures and are commonly associated with underlying infection.[4] For decades, the standard treatment of wound infection has been debridement and systemic antibiotics. However, the success of this paradigm can be ren-

DOI: 10.1089/wound.2018.0795

dered variable by a number of factors, including the complexity of aggressive debridement within proximity of vital structures and the need to administer high-dose systemic antibiotics to achieve adequate local concentrations.[5–7] The presence of occult bacterial biofilm in wound sites further complicates this scenario. Biofilms are increasingly recognized as major barriers to wound healing and may affect between 60% and 90% of chronically infected wounds in humans.[8–10] Indeed, it has been suggested that this phenotypic state represents a unifying pathologic feature of all chronic wounds.[8,11] Biofilms present a potent adversary with regard to current wound infection management as debridement can drive biofilm constituents deeper into surrounding tissues,[12] biofilms can regenerate to predebridement levels within 24–48 hours, and bacteria in the biofilm matrix have enhanced resistance to immunologic and antimicrobial eradication.[8,13,14] It would be prudent to identify new methods that may help bolster the efficacy of current wound infection management, particularly with regard to biofilms.

One such technique may be the use of antibiotic-impregnated materials for localized infection control and biofilm prevention. For years, studies in the orthopedics literature have demonstrated significant reductions in infection rates associated with joint arthroplasty following the prophylactic use of antibiotic-loaded polymethylmethacrylate (PMMA) beads and cement.[15–17] Recently, the plastic surgery literature has also found success in using PMMA beads for salvage of infected left ventricular assist devices.[18] Potentially more attractive than PMMA beads are antibiotic-loaded calcium sulfate beads, which are completely biodegradable and have superior antibiotic-eluting properties.[7,19–23] *In vitro* studies have demonstrated the bactericidal capacity of these beads as well as their potent ability to prevent biofilm formation.[24] Given these properties and the reported successes of antibiotic-impregnated beads in conjunction with orthopedic prostheses, the off-label use of this technology presents an intriguing possible therapeutic modality in the setting of complex wound management and infection-prone breast reconstruction. Recent publications by White *et al.*[25] and Sherif *et al.*[22] have helped substantiate the potential utility of antibiotic beads in these contexts. However, the use of antibiotic-impregnated beads in infected soft tissue wound management is still a topic of nascent investigation.[8]

We report a single-center retrospective evaluation outlining our surgical strategy in 60 high-risk patients who underwent 84 operations using calcium sulfate-based absorbable antibiotic-impregnated beads (AAIBs). These patients, all of whom had failed previous traditional wound management interventions, endured either breast reconstructive surgery or flap-based complex wound reconstruction. The goal of this analysis was to determine whether AAIB therapy might diminish reoperative burden and associated complications (*e.g.*, surgical site infection [SSI], readmission) compared to standard surgical management in difficult soft tissue wounds.

CLINICAL PROBLEM ADDRESSED

With this study, we aim to address the clinical problem of persistent, problematic, and infected chronic wounds. These wounds are often afflicted by biofilms, which challenge traditional management strategies. We hope to provide evidence as to whether AAIB therapy confers advantages with regard to reoperative burdens in the treatment of difficult wounds.

MATERIALS AND METHODS

Institutional Review Board (IRB) approval was obtained before the initiation of this study, which was HIPAA compliant. Retrospective analysis was performed on all cases of complex wound reconstruction and breast reconstruction involving calcium sulfate AAIBs performed by the senior author (C.P.D.) at the University of New Mexico Hospital between August 2013 and May 2017. AAIB use was ultimately at the discretion of the surgeon, based on a combination of current inflammatory signs, extent and duration of exposed structures/hardware, and/or persistence of nonhealing wound despite optimal previous management. When utilized, AAIBs were prepared using absorbable Stimulan calcium sulfate (Biocomposites, Wilmington, NC) mixed with the chosen antibiotics. The resulting paste was then shaped into beads using preformed molds, and once dry, they were placed directly into the wound bed on the deep surface of the flap or within the implant/tissue expander pocket following wound debridement and before wound closure. In the majority of cases, the AAIBs carried 1,000 mg of vancomycin combined with 1,000 mg of an aminoglycoside. Tailored therapy was used in select cases. Eight particularly difficult thoracic wounds were supplemented with 600 mg of rifampin. Three patients had a concomitant fungal infection requiring addition of 500 mg of voriconazole. Daptomycin was substituted for vancomycin in two cases due to allergy. Patients received a standard intravenous dose of preoperative antibiotics (clindamycin or cephalosporin), which was repeated after four hours if required for all operations. The number, type, and indication for surgical interventions in the 90 days before AAIB surgery were evaluated and

Table 1. *Patient and wound characteristics among 60 patients undergoing reconstruction with absorbable antibiotic-impregnated bead therapy*

	Group 1—Complex Wound	*Group 2—Breast*	*Total*
No. of patients (%)	46 (77)	14 (23)	60 (100)
Age (SD)	52 (11)	52 (19)	52 (17)
Sex (%)	M: 31 (67), F: 15 (33)	M: 0 (0), F: 14 (100)	M: 31 (52), F: 29 (48)
No. of reoperations, pre-AAIB surgery (%)	117 (91)	12 (9)	129 (100)
No. of AAIB-assisted operations (%)	63 (75)	21 (25)	84 (100)
Medical comorbidity			
Heart disease (%)	14 (30)	—	14 (23)
Chronic obstructive pulmonary disease (%)	2 (4)	—	2 (3)
Diabetes mellitus (%)	11 (24)	2 (14)	13 (22)
Chronic kidney disease (%)	4 (9)	1 (7)	5 (8)
Breast cancer (%)	—	14 (100)	14 (23)
Radiation (%)	3 (7)	9 (64)	12 (20)
Surgical comorbidity			
Mediastinitis (%)	11 (24)	—	11 (18)
Exposed hardware/ prosthesis (%)	11 (24)	6 (43)	17 (28)
Exposed organ/ structure (%)	26 (57)	—	26 (43)
Open wound (%)	32 (70)	7 (50)	39 (65)
Infected open wound, hardware, or prosthesis (%)	18 (39)	9 (64)	27 (45)

AAIB, absorbable antibiotic-impregnated bead; SD, standard deviation.

compared to the incidence of reoperation and SSI in the 90 days following AAIB-assisted surgery. Exposed organs, prostheses, and type of flap surgery were also recorded. Infection was defined per CDC's National Healthcare Surveillance Network criteria or when explicitly stated in the patient record based on clinical signs (warmth, erythema, tenderness, edema, and so on) and/or positive wound cultures. Fourteen patients were maintained on oral/intravenous antibiotic regimens following bead-assisted surgery.

Statistical analysis was performed using STATA v15 (StataCorp, LLC, College Station, TX). Two-tailed paired sample t-test was used to compare per-patient reoperation rates in the 90-day period preceding versus 90-day period following the index AAIB surgery. Effect size of antibiotic bead intervention was assessed using a within-group variant of Cohen's d ($d = [M_1 - M_2]/\sqrt{(s_1^2 + s_2^2/2)}$ with Hedge's correction formula ($d_c = d(1 - [3/(4[N-1] - 1)])$) to minimize bias. Cohen's U_3 ($U_3 = \Phi(d_c)$, where Φ is the cumulative distribution function of the standard normal distribution, and probability of superiority [PS; $CL = \Phi(d_c/\sqrt{2})$] were subsequently generated. The primary endpoint was the need for reoperation within 90 days of AAIB surgery. Secondary endpoints included etiologically defined rates of reoperation (*e.g.*, for hematoma, acute infection, and so on) within the 90 days preceding and following AAIB surgery. A difference was considered statistically significant at $p < 0.01$.

RESULTS

Patient Presentation

A total of 60 patients underwent 84 surgeries involving AAIBs. Patients had required 129 reoperations in the 90 days preceding index AAIB-assisted surgery (M = 2.2, standard deviation [SD] = 1.7), which included reoperation for wound infection ($n = 100$, 78%), dehiscence ($n = 15$, 12%), exposed prosthesis ($n = 7$, 5.4%), and wound necrosis ($n = 7$, 5.4%). There were 31 males and 29 females; mean age at AAIB surgery was 52 years. Patient characteristics and surgical comorbidities are summarized in Table 1. Analyzed cases consisted of two broad categories: group 1 ($n = 46$, 77%) underwent nonbreast-related flap surgery for complex wound reconstruction (Fig. 1), while group 2 ($n = 14$, 23%) underwent breast-related flap or implant-based reconstructive surgery.

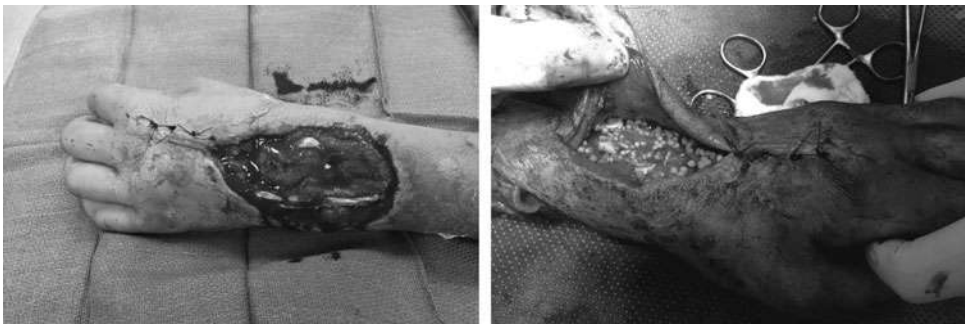

Figure 1. Absorbable antibiotic bead-assisted reconstruction of chronic open hand wound. (*Left*) Patient was referred to our facility with chronic open wound of the dorsal hand with exposed tendons. (*Right*) Following debridement and flap elevation, antibiotic beads are placed directly into the wound bed to facilitate wound sterilization and impede biofilm reestablishment.

Table 2. *Flap utilization among 63 flap-based cases involving absorbable antibiotic-impregnated beads*

Flap type	*No. of Flap Performed*	*No. of Nonviable Flap (%)*
Fasciocutaneous		
Radial forearm (free)	1	—
Saphenous artery	1	—
Posterior tibial perforator	2	—
Sural	2	—
Reverse sural	5	1 (20)
VY plantar perforator	1	—
Cross chest	1	—
Keystone	2	—
ALT (free)	1	—
Bipedicled advancement	1	—
Perforator propeller	7	5 (71)
Other local fasciocutaneous	9	1 (11)
Total fasciocutaneous	33	7 (21)
Myocutaneous		
Pectoralis	11	—
Gastrocnemius	1	—
Rectus femoris	5	—
Gluteal thigh	1	—
Rectus abdominis	1	—
Trapezius	1	—
Gracilis	1	—
Latissimus dorsi	12	—
Triple muscle[a]	1	—
Total myocutaneous	34	—
Total	67	7 (10)

[a]Included latissimus dorsi, serratus anterior, and pectoralis major.
ALT, anterolateral thigh.

Surgical Treatment

Sixty-seven flaps were performed across 63 cases, of which 34 were myocutaneous and 33 were fasciocutaneous (Table 2). Cases included orthopedic wounds ($n=32$), mediastinal wounds ($n=16$), vascular-related wounds ($n=5$), breast-related wounds ($n=21$), and other wounds (*e.g.*, neck, perineum, and so on; $n=10$). Of the 21 breast-related surgeries, 18 involved tissue expanders or implants. All AAIBs contained a combination of two or more antimicrobial agents, including tobramycin (95%), vancomycin (87%), gentamycin (12%), rifampin (10%), voriconazole (3.6%), and daptomycin (2.4%).

Surgical Outcomes

Nineteen reoperations were required for complications within 90 days of AAIB-assisted surgery, including flap nonviability ($n=7$, 8.3%), dehiscence ($n=5$, 6.0%), hematoma ($n=4$, 4.8%), and infection ($n=3$, 3.6%) (Fig. 2). There were four total instances of infection (4.8%), three of which required reoperation. Readmission rate was 6.0%. On average, reoperation was performed on postoperative day 29 (SD = 23). Flap nonviability was managed with new flap over residual AAIBs ($n=5$) or new flap over new AAIBs ($n=2$). Of the 14 patients receiving oral/intravenous antibiotics following AAIB-assisted surgery, almost half required reoperation ($n=6$, 43%).

Outcomes by Group

Group 1 involved 64 flaps across 63 total operations. Reoperation was required for infection ($n=3$, 4.8%), hematoma ($n=4$, 6.3%), flap loss ($n=7$, 11%) and dehiscence ($n=5$, 7.9%). All readmissions ($n=5$, 7.9%) and reoperations ($n=19$, 30%) occurred in this group. The most prevalent wound type in this study was orthopedic-related; these wounds also comprised the group with highest overall reoperation requirement ($n=10$, 53%) (Fig. 2).

Group 2 ($n=14$, 23%) included patients who underwent a total of 21 breast-related flap or non-flap surgeries. Three flaps were performed in this group. Wound infection developed in one case (4.8%), which was treated uneventfully with outpatient antibiotics. Rates of hematoma formation, dehiscence, readmission, and reoperation within 90 days were all 0% for this group (Fig. 2).

Statistical Analysis

There was a significantly higher incidence of flap loss for fasciocutaneous ($M=0.21$, $SD=0.41$) compared with myocutaneous flaps ($M=0$, $SD=0$); $t(65)=2.98$, $p=0.004$ (Table 1). Overall reoperation rate following AAIB surgery ($M_1=0.32$, $SD_1=0.5$) was significantly decreased compared with preceding traditional surgeries ($M_2=2.2$, $SD_2=1.7$), $t(59)=9.0$, $p<0.001$. There was also a decreased reoperation rate for infection following AAIB surgeries ($M_1=0.05$, $SD_1=0.22$) compared with traditional surgeries ($M_2=1.7$, $SD_2=1.7$), $t(59)=7.4$, $p<0.001$ (Fig. 3). These differences remained significant when stratified by group for both all cause reoperation rate [group 1: $M_{1,2}=0.41$, 2.5; $SD_{1,2}=0.54$, 1.7; $t(45)=8.6$, $p<0.001$; group 2: $M_{1,2}=0$, 0.86; $SD_{1,2}=0$, 0.53; $t(13)=6.0$, $p<0.001$] and reoperation rate due to infection [group 1: $M_{1,2}=0.07$, 2.0; $SD_{1,2}=0.25$, 1.8; $t(45)=7.4$, $p<0.001$; group 2: $M_{1,2}=0$, 0.57; $SD_{1,2}=0$, 0.65; $t(13)=3.3$, $p=0.006$]. Effect size using a corrected Cohen's d ranged from 1.3 to 2.1 (Table 3). Results did not differ significantly when the 14 patients receiving oral/intravenous antibiotic therapy following AAIB-assisted surgery were excluded.

DISCUSSION

The tightly regulated process of wound healing can be impeded by many factors. Among them, wound infection represents the most common preventable obstacle.[26] Failure of the host response to overcome this burden predisposes to chronic

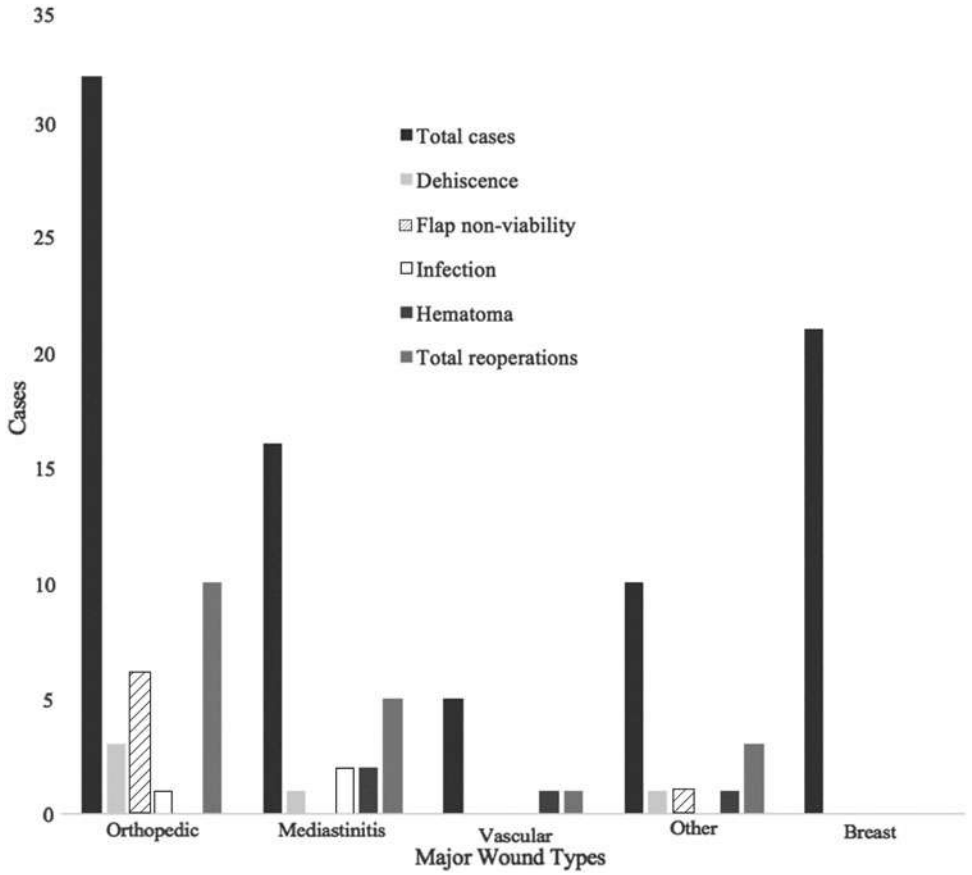

Figure 2. Number of bead-assisted operations and indications for reoperation by wound type. Group 1 consisted of complex wound reconstructive cases involving orthopedic, mediastinal, vascular, and other wounds; group 2 consisted of breast reconstruction cases. Orthopedic wounds had the highest number of cases as well as highest overall incidence of reoperation. Reoperation rates were ~30% for orthopedic, mediastinal, and other wound categories, while 20% of vascular cases required reoperation. No reoperations were required following any of the 21 breast cases.

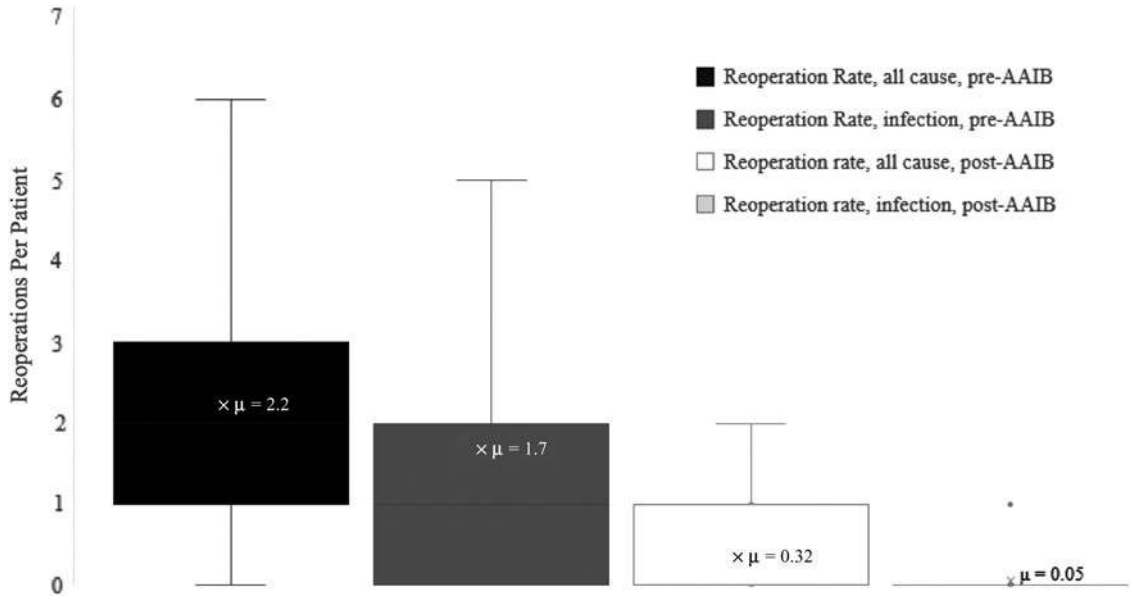

Figure 3. Mean per patient reoperation rates in the 90 days preceding versus 90 days following bead-assisted surgery. There was a significant decrease in the overall rate of reoperation following bead surgery (M = 0.32) compared with traditional surgery (M = 2.2), $p < 0.0001$. Rate of reoperation for infectious complication was also significantly diminished following bead surgery (M = 0.05) compared with traditional surgical intervention (M = 1.7), $p < 0.0001$. Error bars represent the standard error of the mean.

Table 3. *Effect size of absorbable antibiotic-impregnated bead therapy on reoperation rate compared with traditional surgical intervention*

	Reoperations—AAIB, M (SD)	*Reoperations—traditional, M (SD)*	*Cohen's D*	*Hedge's correction*	*Cohen's U_3, %*	*Probability of superiority, %*	p
Overall, all cause	0.32 (0.50)	2.2 (1.7)	1.47	1.45	93	85	<0.001
Overall, infection	0.05 (0.22)	1.7 (1.7)	1.35	1.33	91	83	<0.001
Group 1, all cause	0.41 (0.54)	2.5 (1.7)	1.67	1.64	95	88	<0.001
Group 1, infection	0.07 (0.25)	2.0 (1.8)	1.54	1.51	93	86	<0.001
Group 2, all cause	0 (0)	0.86 (0.53)	2.27	2.13	98	93	<0.001
Group 2, infection	0 (0)	0.57 (0.64)	1.25	1.18	88	80	0.006

wound development, the management of which is estimated to cost over $25 billion annually in the United States alone.[27] Surgical debridement is a critical tool in the treatment of chronic wounds, whereby an attempt is made to convert the chronic wound into an acute wound and to stimulate the healing cascade.[28,29] However, in the face of an increasingly morbid patient population and with the elucidation of the role of biofilms in chronic wound infection, new adjunctive therapies that help combat the impediments to proper healing are being widely pursued.

The ability of antibiotic-laden beads to deliver supratherapeutic concentrations of drug while minimizing the adverse effects of systemic therapy make them potentially attractive.[30–32] Buchholz and Engelbrecht first described the use of these materials in the 1970s; their work was advanced by Klemm who used gentamycin-imbued cement beads for defect filling after infected bone debridement and achieved a cure rate of over 90% with several hundred patients.[17,33–35] PMMA continues to be widely used in orthopedic operations, but there are a number of disadvantages associated with PMMA beads, including suboptimal drug elution profiles (thus risking promotion of antibiotic resistance), nonresorption necessitating reoperation (lest the material serve as a nidus for future infection), and the highly exothermic polymerization reaction generated by PMMA setting (thereby precluding the use of thermosensitive antibiotics).[8,19–21,24,33,35–37] In contrast, calcium sulfate beads provide sustained release of drug over the course of weeks (Howlin *et al.* demonstrated zones of inhibition up to 39 days with calcium sulfate beads compared to 12 days with PMMA), are completely biodegradable, and exhibit much less thermogenicity.[18,19,23,24] A possible detriment of these beads is that their prolonged elution profile may portend an elevated risk of systemic toxicity.[38] However, pharmacokinetic studies evaluating vancomycin-imbued calcium sulfate beads have demonstrated safe overall systemic levels even in patients with postoperative renal failure, while maintaining sufficient local levels of vancomycin to theoretically exert activity versus *Staphylococcus* biofilm for 2–3 weeks following their placement.[23] None of the patients in our study demonstrated any evidence of toxicity following antibiotic bead therapy. Heterotopic ossification (HO) is another rare risk associated with calcium sulfate beads when large volumes are used (*e.g.*, 30 cc or more)[39]; significantly smaller volumes were utilized here, and no HO was appreciated in any of our patients.

The properties of calcium sulfate AAIBs make them potentially well suited for a variety of soft tissue applications. The patients in this study all had contaminated and potentially biofilm-afflicted wounds by virtue of their exposed structures, exposed hardware, and chronic state of nonhealing (Table 1). In addition, their wounds had proved recalcitrant to more conservative surgical strategies of debridement and parenteral antibiotics despite a combined 129 attempts in the 90 days preceding AAIB therapy. Thus, these patients represented a group that might benefit from the high dose, long term, targeted drug delivery that antibiotic beads afford. We propose that using the beads in this manner may have helped prevent new biofilm formation following wound debridement,[9,23] thereby facilitating the healing capacity of the wound. However, this retrospective data set lacks the molecular and microscopic elements to fully substantiate whether reduced operative burden was truly a byproduct of this mechanism.

A small number of recent studies have explored the use of antibiotic-loaded beads in similar patient groups. White *et al.* demonstrated an overall success rate of >85% following use of AAIBs in complex wounds involving critical structures and prosthetic devices in 104 cases.[25] Similarly, Sherif *et al.* found one step immediate salvage of infected implants using AAIBs had a 75% higher success rate than conventional salvage therapies.[22] Our results largely echo the potential of AAIBs suggested in these studies. We found that reoperative requirements were significantly diminished in the 90-day period

following AAIB-assisted surgery compared to the 90-day period preceding AAIB surgery (Fig. 3). This significance persisted when stratified by all-cause reoperative requirement (*e.g.*, dehiscence, hematoma, and flap loss), reoperation for SSI, and when the two groups were considered together or in isolation ($p < 0.01$). The per-patient all-cause reoperation rate fell from 2.2 with traditional surgical interventions to 0.32 following AAIB intervention. Similarly, rates of reoperation due to clinically evident infection fell from 1.7 per patient to 0.05 (Fig. 3). There were notable differences in outcomes between the 2 groups: all 19 cases requiring reoperation following AAIB surgery occurred in group 1 (comprising complex wound reconstruction), whereas group 2 (breast reconstruction cases) had no postoperative complications requiring reoperation (Fig. 2).

Orthopedic-related wounds were both the most prevalent (38%) and most frequently requiring reoperation (52% of overall reoperations, Fig. 2). In six of these cases, reoperation was required due to flap nonviability. Interestingly, all seven cases of flap nonviability affected fasciocutaneous flaps; no musculocutaneous flaps were lost (Table 2). Musculocutaneous flaps are known to exhibit superior microbial suppression compared with fasciocutaneous flaps, likely due to greater hydroxyproline and collagen deposition in wound spaces facilitating incorporation into adjacent tissues.[40] The presence of foreign material, such as AAIBs, on the deep surface of fasciocutaneous flaps may exacerbate this relative deficiency. Thus, flap type may be an important consideration to make when pursuing AAIB-assisted surgery. Wound dehiscence, which is also associated with underlying infection, occurred in five patients, four of whom had poorly controlled diabetes and two of whom had received radiation therapy. Although none of these cases of flap loss or dehiscence demonstrated any evidence of infection, it is possible that their occurrences were mediated by occult infection, which could increase our reported reoperation rate due to infection, but would not change the overall reduction in reoperations following AAIB-assisted surgery.

All the 60 patients in this study had difficult wounds with almost every individual afflicted by years of operative burden attempting to address them. The surgical complexity of these patients precluded their randomization to a control group. As such, a within-group formulation of Cohen's *d* was used to evaluate the effect size of AAIB intervention. The corrected Cohen's *d* ranged from 1.3 to 2.1 when comparing the outcomes of traditional surgical intervention to outcomes following AAIB therapy, corresponding to a PS of ≥80% for all analyzed stratifications (Table 3). This suggests a ≥80% chance that a patient picked at random from the post-AAIB intervention would have a lower reoperation requirement compared to the pre-AAIB intervention. The highest PS was associated with group 2 all-cause reoperation rates (93%) and group 1 all-cause reoperation rates (88%). Using group event rates, the PS can be converted to a number needed to treat (NNT) value. As infection rates following plastic surgery procedures in typical patients are quite low, the unreasonably large NNT would make routine use of AAIBs ill-advised. However, our study demonstrated a high PS among patients with high event rates, dramatically altering this calculus. As such, our effect size analysis indicates the possibility of distinct advantages for AAIB utilization in a particular, well-selected patient group. Overall, our results suggest that AAIB therapy may be a viable strategy in decreasing reoperation and infection following difficult complex wound and breast reconstruction cases.

This study is not without limitations. The small sample size, the retrospective nature, the relatively short time frames involved, and the lack of randomized control group limit the substantiality of the results. The absence of molecular or microscopic data also makes it impossible to accurately ascertain whether and to what extent biofilm played a role in these wounds, and whether AAIB-therapy actually diminished biofilm burden. Thus, although significant reductions in operative burden were realized, the specific reasons for this remain speculative. Future studies should incorporate such data. Finally, use of AAIB therapy does contribute extra monetary cost to the operations in which they are used and a cost-benefit analysis of their use may be warranted.

INNOVATION

The use of antibiotic-imbued materials for targeted drug delivery is an area of significant research and development. Certain modalities, such as antibiotic-laden PMMA cement, are commonplace. Others, such as the use of AAIBs, have been well characterized *in vitro*, but their clinical applications are relatively unknown. These beads have demonstrated potent antibiofilm activity as well as long-acting supratherapeutic antibiotic delivery capability. Here, we demonstrate clinically significantly decreases in reoperative burden (from 2.2 to 0.32 reoperations per patient) and in-

fection rates (from 1.7 to 0.05 per patient) following their use in complex wound and infection-prone breast reconstruction.

KEY FINDINGS

- A sevenfold decrease in reoperative burden was realized following AAIB-assisted surgery compared with preceding traditional surgical management ($p < 0.001$).
- There was a 34-fold reduction in acute SSI development following AAIB-assisted surgery compared with preceding traditional surgical management ($p < 0.001$).
- Calculated effect size was $d = 1.3–2.1$, corresponding to a PS of 80–93% for bead-assisted surgeries versus traditional surgical intervention.

ACKNOWLEDGMENT AND FUNDING SOURCE

No funding sources to report.

AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article.

ABOUT THE AUTHORS

Joseph W. Gorvetzian, BS, is a third year medical student interested in plastic surgery and the molecular biology of wound healing. **Ryan P. Kunkel, MD,** is a fourth year plastic surgery resident interested in general plastic and reconstructive surgery. **Christopher P. Demas, MD,** is the Division Chief and Program Director emeritus of the University of New Mexico Plastic Surgery Department.

REFERENCES

1. Fowler E. Chronic wounds: an overview. In: Krasner D, ed. Chronic Wound Care: A Clinical Source Book for Healthcare Professionals. King of Prussia, PA: Health Management Publications, Inc., 1990:12–18.
2. Singh A, Halder S, Menon GR, *et al.* Meta-analysis of randomized controlled trials on hydrocolloid occlusive dressing versus conventional gauze dressing in the healing of chronic wounds. Asian J Surg 2004;27:326–332.
3. Brunicardi F. Charles Schwartz's Principles of Surgery, 8th ed. New York: McGraw-Hill, 2004.
4. Siddiqui AR, Bernstein JM. Chronic wound infection: facts and controversies. Clin Dermatol 2010;28:519–526.
5. Henry SL, Galloway KP. Local antibacterial therapy for the management of orthopaedic infections. Clin Phamacokinet 1995;29:36–45.
6. O'Toole RV, Joshi M, Carlini AR, *et al.* Local antibiotic therapy to reduce infection after operative treatment of fractures at high risk of infection: a multicenter, randomized, controlled trial (VANCO study). J Orthop Trauma 2017;31:S18–S24.
7. Aiken SS, Cooper JJ, Florance H, Robinson MT, Michell S. Local release of antibiotics for surgical site infection management using high-purity calcium sulfate: an in vitro elution study. Surg Infect (Larchmt) 2015;16:54–61.
8. Barker JC, Khansa I, Gordillo GM. A formidable foe is sabotaging your results: what you should know about biofilms and wound healing. Plast Reconstr Surg 2017;139:1184e–1194e.
9. James GA, Swogger E, Wolcott R, *et al.* Biofilms in chronic wounds. Wound Repair Regen 2008;16:37–44.
10. Attinger C, Wolcott R. Clinically addressing biofilm in chronic wounds. Adv Wound Care (New Rochelle) 2012;1:127–132.
11. Sen CK, Roy S, Gordillo G. Wound healing. In: Neligan P, Warren RJ, Van Beek A, eds. Plastic Surgery, 4th ed. London: Elsevier, 2018:165–195.
12. Roy S, Elgharably H, Sinha M, *et al.* Mixed-species biofilm compromises wound healing by disrupting epidermal barrier function. J Pathol 2014;233:331–343.
13. Zarick CS, Benkert EA, Oliver NG, *et al.* Preliminary results of a topically applied bacteria-specific antibiotic gel to improve wound healing. Wounds 2017;29:380–386.
14. Wolcott RD, Rumbaugh KP, James G, *et al.* Biofilm maturity studies indicate sharp debridement opens a time-dependent therapeutic window. J Wound Care 2010;19:320–328.
15. Garvin KL, Hanssen AD. Infection after total hip arthroplasty: past, present, and future. J Bone Joint Surg 1995;77A:1576–1588.
16. Parvizi J, Saleh KJ, Ragland PS, Pour AE, Mont MA. Efficacy of antibiotic-impregnated cement in total hip replacement. Acta Orthop 2008;79:335–341.
17. Jamsen E, Huhtala H, Puolakka T, Moilanen T. Risk factors for infection after knee arthroplasty: a register based analysis of 43,149 cases. J Bone Joint Surg Am 2009;91:38–47.
18. Kretlow JD, Brown RH, Wolfswinkel EM, *et al.* Salvage of infected left ventricular assist device with antibiotic beads. Plast Reconstr Surg 2014;133:28e–38e.
19. Mader JT, Calhoun J, Cobos J. In vitro evaluation of antibiotic diffusion from antibiotic-impregnated biodegradable beads and polymethylmethacrylate beads. Antimicrob Agents Chemother 1997;41:415–418.
20. Chotanaphuti T, Surijamorn P, Luenam S, Ongnamthip P. In vitro antimicrobial activity of phramongkutklao hydroxyapatite antibiotic pellet. J Med Assoc Thai 2008;91:1868–1872.
21. Drosos GI, Babourda EC, Ververidis A, Kakagia D, Verettas DA. Calcium sulfate cement in contained traumatic metaphyseal bone defects. Surg Technol Int 2012;22:313–319.
22. Sherif RD, Ingargiola M, Sanati-Mehrizy P, Torina PJ, Harmaty MA. Use of antibiotic beads to salvage infected breast implants. J Plast Reconstr Aesthet Surg 2017;70:1386–1390.
23. Wahl P, Guidi M, Benninger E, *et al.* The levels of vancomycin in the blood and the wound after the local treatment of bone and soft-tissue infection with antibiotic-loaded calcium sulphate as carrier material. Bone Joint J 2017;99-B:1537–1544.
24. Howlin RP, Brayford MJ, Webb JS, Cooper JJ, Aiken SS, Stoodley P. Antibiotic-loaded synthetic calcium sulfate beads for prevention of bacterial colonization and biofilm formation in periprosthetic infections. Antimicrob Agents Chemother 2015;59:111–120.

25. White TL, Culliford AT, Zomaya M, Freed G, Demas CP. Use of antibiotic-impregnated absorbable beads and tissue coverage of complex wounds. Am Surg 2016;82:1068–1072.

26. Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. Adv Ther 2017;34:599–610.

27. Brem H, Stojadinovic O, Diegelmann RF, *et al*. Molecular markers in patients with chronic wounds to guide surgical debridement. Mol Med 2007;13:30–39.

28. Kirshen C, Woo K, Ayello EA, Sibbald RG. Debridement: a vital component of wound bed preparation. Adv Skin Wound Care 2006;19:506–517.

29. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. J Am Coll Surg 1996;183:61–64.

30. Kanellakopoulou K, Galanopoulos I, Soranoglu V, *et al*. Treatment of experimental osteomyelitis caused by methicillin-resistant *Staphylococcus aureus* with a synthetic carrier of calcium sulphate (Stimulan) releasing moxifloxacin. Int J Antimicrob Agents 2009;33:354–359.

31. Wahl P, Livio F, Jacobi M, *et al*. Wound fluid and serum concentrations of vancomycin after local therapy with calcium sulphate as carrier material. J Bone Joint Surg 2012;94B:79.

32. Tan HL, Lin WT, Tang TT. The use of antimicrobial-impregnated PMMA to manage periprosthetic infections: controversial issues and the latest developments. Int J Artif Organs 2012;35:832–839.

33. Wininger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. Antimicrob Agents Chemother 1996;40:2675–2679.

34. Buchholz HW, Engelbrecht E. Depot effects of various antibiotics mixed with Palacos resins [in German]. Chirurg 1970;41:511–515.

35. Gogia JS, Meehan JP, di Cesare PE, Jamali AA. Local antibiotic therapy in osteomyelitis. Semin Plast Surg 2009;23:100–107.

36. Anagnostakos K, Hitzler P, Pape D, *et al*. Persistence of bacterial growth on antibiotic-loaded beads: is it actually a problem? Acta Orthop 2008;79:302–307.

37. Neut D, van de Belt H, Stokroos J, van Horn JR, van der Mei HC, Busscher HJ. Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopedic revision surgery. J Antimicrob Chemother 2001;47:885–891.

38. Wahl P, Livio F, Jacobi M, *et al*. Systemic exposure to tobramycin after local antibiotic treatment with calcium sulphate as carrier material. Arch Orthop Trauma Surg 2011;131:657–662.

39. McPherson EJ, Dipane MV, Sherif SM. Dissolvable antibiotic beads in treatment of periprosthetic joint infection and revision arthroplasty: the use of synthetic pure calcium sulfate (Stimulan) impregnated with vancomycin & tobramycin. Recon Review 2013;3:32–43.

40. Gosain A, Chang N, Mathes S, *et al*. A study of the relationship between blood flow and bacterial inoculation in musculocutaneous and fasciocutaneous flaps. Plast Reconstr Surg 1990;86:1152–1162.

Abbreviations and Acronyms

AAIB = absorbable antibiotic-impregnated beads
HO = heterotopic ossification
NNT = number needed to treat
PMMA = polymethylmethacrylate
PS = probability of superiority
SD = standard deviation
SSI = surgical site infection