Decreasing Osteomyelitis Occurrence in Remaining Bone After Partially Resected Infected Bone

Jeffrey C. Karr, DPM*

Background: After partial bone resection for osteomyelitis there is a high rate of osteomyelitis occurrence in the remaining bone due to adherent bacterial biofilm, dysvascular infected spongiosum bone, and absence of a surgical technique that can prevent osteomyelitis developing in the remaining bone.

Methods: Presented is a surgical procedure using a dicalcium phosphate bone void filler putty with antibiotics placed into the remaining bone to prevent the development of osteomyelitis, therefore preventing amputation.

Results: This procedure has an osteomyelitis eradication rate of 94.8% and also decreases the rate of lower-extremity amputations.

Conclusions: This procedure provides a single stage surgical technique for infected open bone defects decreasing the previously reported high osteomyelitis reoccurrence rate of 57.1% to 5.2%. (J Am Podiatr Med Assoc 112(6), 2022)

Osteomyelitis development in the remaining bone after partial bone resection for osteomyelitis is a significant cause of recalcitrant osteomyelitis and amputation. The occurrence of osteomyelitis in the remaining metatarsal after partial metatarsal resection has been reported to be 35% to 57.1%.[1-4] Barshes et al[5] reported that of 184 episodes of foot osteomyelitis, treatment failure occurred in 53 patients (28.8%) and leg amputation in 21 (11.4%). Lee et al[6] described cumulative rates of reamputation after infection per person stratified by original rate of amputation of 26.7% at 1 year, 48.3% at 3 years, and 60.7% at 5 years. A patient is at greater risk for further same-limb amputation in the 6 months after the initial procedure.[6] Foot osteomyelitis treatment failure is common, resulting in additional surgery or leg amputation.[1,7] This chronic osteomyelitis after partial bone resection also contributes to chronic foot ulcers, prolonged treatment and hospitalization, and mortality.[8]

One has to ask why there is a high osteomyelitis occurrence rate in the remaining bone after partial bone resection. This reoccurrence is due to the presence of bacterial biofilm harbored in the dysvascular and avascular remaining bone. Unlike sessile bacteria, bacterial biofilm is very resistant to antibiotics. The disadvantage of using a liquid bone void filler (BVF) with antibiotics is that when the antibiotics are placed in the remaining bone after partial bone resection for osteomyelitis, the BVF will leak out. This leaking will not allow sufficient antibiotic minimal inhibitory concentration to be achieved to eradicate the biofilm. A more effective BVF would be a synthetic bone graft substitute putty that when added to antibiotics would not leak from the remaining bone.

Such a BVF is a synthetic bone graft substitute putty consisting of semispherical phosphate granules and a powder. Each granule is composed of dicalcium phosphate ($CaHPO_4$, aka monetite) and newberyite ($MgHPO_4{\cdot}3H_2O$) tightly bonded with silica (SiO_2), NovoGro (OsteoNovus Inc, Toledo, Ohio). The granules have a diameter of 1 to 2 mm. The powder consists of sodium carboxy methylcellulose (NaCMC). When these components are mixed together, a moldable and nonsettable putty is generated, with excellent handling properties. This BVF putty (BVFP) mixes nicely, retains antibiotics, and is resistant to washout. NovoGro BVFP was shown in vitro to be a suitable carrier for vancomycin, with a 14-day duration of antibiotic release.[9]

Methods

Thirty-seven patients with 58 infected distal lower-extremity bones requiring partial bone resection were reviewed. Lakeland Regional Medical Center Institutional review board approval was obtained

*The Osteomyelitis Center of Central Florida, 5421 S Florida Ave, Lakeland, FL 33813
(E-mail: drkarr@gmail.com)

for retrospective data collection. The location and extent of osteomyelitis involving a single bone was determined preoperatively with magnetic resonance imaging (MRI), or with a technetium three-phase bone scan if the MRI was contraindicated. The location and extent of Charcot deformity osteomyelitis requires a combination of information obtained from the preoperative examination, intraoperative findings, and MRI findings. The Charcot deformity bone destruction due to osteomyelitis was determined to be present if there is an ulcer to bone or exposed bone present with obvious cortical bone osteonecrosis, a cortical defect, or a gray pale cortical bone color. Additional consideration may be given when the bone in question is in contact with an abscess or necrotic tissue. If there is advanced Charcot's collapse and bone reabsorption in an area of known osteomyelitis, then assume that the area of the Charcot collapse and bone reabsorption is also infected. Diabetic and nondiabetic patients were included. Seventeen patients presented with chronic foot ulceration with underlining osteomyelitis. Four patients presented without ulceration but with gangrene and infection, and eight presented without ulceration but with infection/abscess (see Supplemental Table 1, available online). There were no age restrictions. Patients with lower-extremity peripheral artery disease (PAD) demonstrated by resting ankle brachial index values of 0.9 or less, abnormal segmental pressure study findings, or transcutaneous oxygen levels less than 30 mm Hg underwent abdominal angiography with lower-extremity runoff with arterial intervention when deemed necessary by the interventional radiologist or vascular surgeon before foot surgery for osteomyelitis. Intravenous or oral antibiotics per infectious disease recommendations were continued for 4 weeks after the bone procedure.

After partial bone resection for osteomyelitis, the remaining spongiosum bone that has bacterial bioburden is easily identified by placing blunt pressure on the bone. Healthy spongiosum bone will resist collapse from the blunt pressure. Unhealthy, infected spongiosum bone will collapse very easily under blunt pressure and has a partially liquified appearance once blunt pressure is applied. Any blunt surgical instrument will do; I prefer the blunt end of a Steinmann pin. After manual reaming of the spongiosum bone with a Steinmann pin, irrigation and bone cultures are completed. Sterile water (2 cc) is then placed in the 2.5-g NovoGro syringe and mixed for 15 sec. The top of the syringe can easily be unscrewed for adding the antibiotics. Add 0.5 g of vancomycin and 0.6 g of tobramycin, both in dry form, to the syringe and mix for 30 sec. Mixing consisted of an up and down motion of the plunger while turning the plunger clockwise and counterclockwise. After final mixing, the syringe top can again be removed for access to the BVFP with antibiotics. A freer elevator is used to remove the BVFP and place it at the spongiosum defect. The blunt end of a Steinmann pin is then used to pack the BVFP into the spongiosum defect under intraoperative fluoroscopy.

Successful treatment, treatment failure, and amputation rates were identified in the 58 procedures. Patients were followed, on average, weekly to week 12, then monthly to 1 year, then every 6 months. Patients were seen weekly past week 12 if they had an ulcer that required weekly debridement. Success was measured as no osteomyelitis recurrence as deemed by no further clinical infection or abscess formation, wound resolution, or no bone reabsorption or collapse on postoperative radiographs. Failure was measured as bone resection or amputation due to continued osteomyelitis. Cases that involved amputation or bone resection secondary to other factors, such as gangrene secondary to advanced PAD and not the osteomyelitis, were not counted as failures. When this occurred, the data were collected until the surgery date. In the case of patient death unrelated to the procedure, the data were collected until the date of death, and it was not counted as a failure.

Results

I reviewed 58 infected distal lower-extremity bones from 37 patients that required partial bone resection followed by placement of BVFP with antibiotics. The infected bones involved 48 metatarsals, two medial cuneiforms, two intermediate cuneiforms, two lateral cuneiforms, one navicular, and three cuboids. Patient follow-up ranged from 6 to 33 months. Group 1 was followed for 6 to 12 months. Group 2 was followed for 13 to 24 months. Group 3 was followed for 25 to 36 months. There were 33 patients in group 1, 11 in group 2, and 14 in group 3.

Four of the 33 patients in group 1 required bone resection due to PAD. These four cases involved tissue loss with new onset of exposed bone due to PAD. One patient required a below-the-knee amputation secondary to progressive tissue necrosis due to PAD. Four patients required midfoot amputation secondary to tissue necrosis due to PAD. There was one patient death unrelated to the BVFP with antibiotics. None of these outcomes were related to the BVFP with antibiotics.

Supplemental Table 1 Patient Demographics

Patient Patient	Case	Bone	Bone resection secondary to the bone infection	Negative outcome unrelated to the product	Negative outcome background	Level of surgery	Follow up period	Age	Sex	Antibiotic(s) used	Diabetic A1c	Smoker	PAD	PAD intervention
1	1	MT					25-36 months	65	F	Mixture 1	N/A	1	1	1
2	2	MC		1	Advanced PAD with Gangrene	Local bone resection	0-12 months	59	F	Mixture 1	9.2	1	1	1
2	3	MT		1	Advanced PAD with Gangrene	Local bone resection	0-12 months	59	F	Mixture 1	9.2	1	1	1
3	4	MT					0-12 months	55	M	Antibiotic 2	8.2	0	0	0
3	5	MT					0-12 months	55	M	Antibiotic 2	8.2	0	0	0
3	6	MT					0-12 months	55	M	Antibiotic 2	8.2	0	0	0
3	7	MT					0-12 months	55	M	Antibiotic 2	8.2	0	0	0
4	8	MT		1	Uncontrolled Diabetes	Local bone resection	0-12 months	49	F	Mixture 1	6.8	0	0	0
5	9	MT					25-36 months	53	F	Mixture 1	9.8	0	0	0
6	10	MT					25-36 months	56	M	Mixture 1	8.3	0	1	1
6	11	MT					25-36 months	56	M	Mixture 1	8.3	0	1	1
6	12	MT					25-36 months	56	M	Mixture 1	8.3	0	1	1
6	13	MT					25-36 months	56	M	Mixture 1	8.3	0	1	1
7	14	MT					25-36 months	58	M	Mixture 1	9.8	0	1	1
8	15	MT		1	Advanced PAD	BKA	0-12 months	58	M	Mixture 1	N/A	0	1	0
9	16	MT					25-36 months	63	M	Mixture 1	N/A	0	0	0
10	17	MT		1	Advanced PAD	CA	0-12 months	56	M	Mixture 1	8.3	0	1	1
10	18	MT		1	Advanced PAD	CA	0-12 months	56	M	Mixture 1	8.3	0	1	1
10	19	MT		1	Advanced PAD	CA	0-12 months	56	M	Mixture 1	8.3	0	1	1
10	20	MT		1	Advanced PAD	CA	0-12 months	56	M	Mixture 1	8.3	0	1	1
11	21	MT					25-36 months	75	M	Mixture 1	N/A	0	1	1
12	22	MT					25-36 months	58	M	Mixture 1	7.2	0	1	1
13	23	MT					25-36 months	64	M	Mixture 1	8.2	0	1	1
14	24	MT					25-36 months	49	M	Mixture 1	7.3	0	0	0
15	25	C					25-36 months	68	M	Mixture 1	7.9	0	1	1
16	26	MT					25-36 months	54	F	Mixture 1	9.8	0	1	1
17	27	MT					0-12 months	83	M	Mixture 1	9.1	0	1	1
18	28	MT		1	Death, respiratory arrest		13-24 months	48	M	Mixture 1	6.5	0	1	1

Supplemental Table 1 continued

Patient Patient	Case	Bone	Bone resection secondary to the bone infection	Negative outcome unrelated to the product	Negative outcome background	Level of surgery	Follow up period	Age	Sex	Antibiotic(s) used	Diabetic A1c	Smoker	PAD	PAD intervention
18	29	MT					13-24 months	48	M	Mixture 1	6.5	0	1	1
19	30	MT		1	Uncontrolled Diabetes, exposed bone	Local bone resection	0-12 months	47	M	Mixture 1	6.5	0	1	1
20	31	MT					13-24 months	50	M	Mixture 1	N/A	0	0	0
21	32	MT					13-24 months	61	M	Mixture 1	N/A	0	0	0
22	33	MT					13-24 months	51	M	Mixture 1	N/A	0	0	0
23	34	MT	1		Advanced PAD, non-compliance	Local bone resection	0-12 months	63	M	Mixture 1	12.3	0	1	1
24	35	MT					13-24 months	63	M	Mixture 1	10.3	0	1	1
25	36	MT					13-24 months	41	F	Mixture 1	8.8	0	0	0
26	37	MT					13-24 months	52	M	Mixture 1	9.8	0	0	0
27	38	MT					13-24 months	39	M	Mixture 1	6.8	0	0	0
28	39	MT					0-12 months	82	F	Mixture 1	10.2	0	0	0
29	40	MT					13-24 months	36	M	Mixture 1	11.2	0	0	0
30	41	MT					13-24 months	68	M	Mixture 1	8.6	0	1	1
31	42	MT	1		Bone collapse uncontrolled Diabetes	Local bone resection	0-12 months	53	F	Mixture 1	8.8	0	0	0
32	43	MT					0-12 months	76	F	Mixture 1	7.8	0	0	0
33	44	MT					0-12 months	60	M	Mixture 1	11.2	0	1	1
34	45	MT					0-12 months	62	M	Mixture 1	N/A	0	1	1
35	46	MT					0-12 months	73	M	Mixture 1	8.5	1	1	1
35	47	MT					0-12 months	73	M	Mixture 1	8.5	1	1	1
35	48	MT	1		Bone collapse, uncontrolled Diabetes	Local bone resection	0-12 months	73	M	Mixture 1	8.5	1	1	1
36	49	N					0-12 months	42	M	Mixture 1	7.8	0	0	0
36	50	MT					0-12 months	42	M	Mixture 1	7.8	0	0	0

Supplemental Table 1 continued

Patient Patient	Case	Bone	Bone resection secondary to the bone infection	Negative outcome unrelated to the product	Negative outcome background	Level of surgery	Follow up period	Age	Sex	Antibiotic(s) used	Diabetic A1c	Smoker	PAD	PAD intervention
36	51	MC					0-12 months	42	M	Mixture 1	7.8	0	0	0
36	52	IC					0-12 months	42	M	Mixture 1	7.8	0	0	0
36	53	LC					0-12 months	42	M	Mixture 1	7.8	0	0	0
36	54	C					0-12 months	42	M	Mixture 1	7.8	0	0	0
37	55	MT					0-12 months	48	M	Mixture 1	9.4	0	0	0
37	56	C					0-12 months	48	M	Mixture 1	9.4	0	0	0
37	57	LC					0-12 months	48	M	Mixture 1	9.4	0	0	0
37	58	IC					0-12 months	48	M	Mixture 1	9.4	0	0	0
Totals			3	10								5	24	22
Average								55.7			7.7			

Legend:
MT: Metatarsal
MC: Medial cuneiform
IC: Intermediate cuneiform
LC: Lateral Cuneiform
N: Navicular
C: Cuboid
PAD: Peripheral artery disease
BKA: Below the knee amputation
CA: Chopart amputation
F: Female
M: Male
Mixture 1: Vancomycin .5 grams, tobramycin .6 grams
Antibiotic 2: Tobramycin .6 grams
N/A: Not applicable, not diabetic

There were three failures where the bone infection continued to destroy bone, and additional bone was resected. All three cases involved metatarsals. The success rate for bone eradication up to 12 months in group 1 was 90.9%. Among the 11 patients in group 2, there were four deaths unrelated to the BVFP with antibiotics. Otherwise, there was no bone resection or amputation related or unrelated to the BVFP with antibiotics. In group 2, the success rate for bone eradication from 13 months up to 24 months was 100%. There were no deaths among the 14 patients in group 3. There was no bone resection or amputation related or unrelated to the BVFP with antibiotics. In group 3, the success rate for bone eradication from 25 months to 36 months was 100%. The longest follow-up was at 33 months. No systemic antibiotic toxicity was observed in any patients. The overall success rate for all of the patients (groups 1, 2, and 3) was 94.8%.

Discussion

This surgical technique allows for single-stage delivery of a BVFP with antibiotics after partial bone resection for osteomyelitis addressing any residual bacteria, preventing recalcitrant osteomyelitis, and preventing subsequent amputation or complete bone resection. All of the partially resected bones demonstrated osteomyelitis on the pathology report. After the partial resection of infected bone, the remaining bone demonstrated spongiosum collapse under blunt pressure and had a partially liquified appearance consistent with residual bacteria in the bone. The occurrence rate of osteomyelitis after this surgical procedure is 5.2%. This 5.2% occurrence rate is significantly lower than the previously published 57.1%[1] occurrence rate. This BVFP added to antibiotics maintained its properties of being highly cohesive and adhesive to bone and resisting surgical lavage without any BVFP leakage. Adding antibiotics to the BVFP did not change the device, the BVFP handling characteristics, or the availability for handling. The distinct spherical nature of the BVFP allows clear visualization on radiographs to confirm placement in the bone.

Osteomyelitis resolution after partial bone resection in the remaining bone was significant in all three groups. The three failures in group 1 had two failures at month 1 and one failure at month 5. There were no amputations due to BVFP with antibiotics among all three groups. The five amputations in group 1 were due to PAD and not the BVFP with antibiotics. There were four cases of amputation at month 1 and one case at month 3. In group 1 there was a slightly higher incidence of amputation due to PAD than the incidence of continued osteomyelitis (15.2% versus 9.0%, respectively). The amputation rate from peripheral vascular disease is still below the reported reamputation incidence for diabetic patients in the first 3 years of 26.7% at 1 year. There were no amputations in groups 2 and 3. The data show that all of the additional surgical procedures to address the operative limb after partial bone resection occurred within the first 6 months. This demonstrates that after this procedure, complications from PAD are more likely to occur than is failure after using this surgical technique. Patients with a resting ankle brachial index value less than 0.90 had an abdominal angiogram with lower-extremity runoff before the osteomyelitis surgery. When the patient had tissue necrosis or gangrene after the osteomyelitis procedure, a repeated abdominal angiogram with lower-extremity runoff was completed. All of the vascular bypass and endovascular options were exhausted before bone resection or amputation. Peripheral artery disease was determined to be the cause of failure when repeated angiography demonstrated decreased arterial perfusion to the limb or repeated transcutaneous oxygen values decreased from the preoperative measurement. Preoperative evaluation of the angiogram runoff imaging will allow the user to determine avoidance of use in the patient with PAD. Patients to avoid using this procedure with are those with angiogram runoff imaging that terminates at the ankle or rearfoot with no decent distal perfusion into the foot.

Conclusions

This technique of placing NovoGro BVFP with antibiotics into remaining bone after partial infected bone resection has decreased the previously reported high osteomyelitis reoccurrence rate of 57.1% to a rate of 5.2% (94.8% success rate). There was no occurrence of amputation directly linked to the BVFP with antibiotics.

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References

1. Kowalski TJ, Matsuda M, Sorenson MD, et al: The effect of residual osteomyelitis at the resection margin in patients

with surgically treated diabetic foot infection. J Foot Ankle Surg **50:** 171, 2011.
2. Atway S, Nerone VS, Springer KD, et al: Rate of residual osteomyelitis after partial foot amputation in diabetic patients: a standardized method for evaluating bone margins with intraoperative culture. J Foot Ankle Surg **51:** 749, 2012.
3. Jenny G: Local antibiotic therapy using gentamicin-PMMA chains in post-traumatic bone infections: short and long-term results. Reconstr Surg Traumatol **20:** 36, 1988.
4. Jogia RM, Modha DE, Nisal K, et al: Use of highly purified synthetic calcium sulfate impregnated with antibiotics for the management of diabetic foot ulcers complicated by osteomyelitis. Diabetes Care **38:** e79, 2015.
5. Barshes NR, Mindru C, Ashong C, et al: Treatment failure and leg amputation among patients with foot osteomyelitis. Int J Low Extrem Wounds **15:** 303, 2016.
6. Lee S, Harkless LB: Risk of reamputation in diabetic patients stratified by limb and level of amputation: a 10-year observation. Diabetes Care **29:** 566, 2006.
7. Izumi Y, Satterfield K, Lee S, et al: Risk of reamputation in diabetic patients stratified by limb and level of amputation: a 10-year observation. Diabetes Care **29:** 566, 2006.
8. Cierny G III. Surgical treatment of osteomyelitis. Plast Reconstr Surg **127:** 190S, 2011.
9. Lin BR, Caldwell C, Bhaduri S, et al: Optimizing vancomycin release from calcium phosphate-based cement by carboxymethyl cellulose for prevention of osteomyelitis. Surg Infect **18:** 221, 2017.