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ORIGINAL RESEARCH

Staged Management of Bone Defects in Chronic Osteomyelitis and Nonunions Using Antibiotic-Loaded Calcium Sulphate-Hydroxyapatite: A Multicenter Retrospective Analysis of 101 Cases

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Purpose: To evaluate the clinical outcomes of an antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite (ALB) used specifically in staged surgical protocols for chronic osteomyelitis and nonunions, including large bone defects resulting from the necessary debridement of necrotic bone.

Patients and Methods: This retrospective multicenter study analyzed 101 patients treated between 2013 and 2020. Inclusion criteria comprised adult patients with bone defects resulting from osteomyelitis, septic nonunion, or aseptic nonunion, treated with ALB (gentamicin or vancomycin) in a staged procedure. The primary outcome was treatment success, defined as infection eradication and stable bone consolidation without unplanned surgical revision. Secondary outcomes included revision rates, reinfection rates, and biomaterial-related side effects such as white drainage.

Results: Treatment success was achieved in 30.7% of patients. The overall revision rate was 58.4%, and the reinfection rate was 45.5%. The mean defect size was 4.1 cm. Statistical analysis identified larger defect sizes and higher volumes of implanted ALB as significant risk factors for failure. "White drainage" was observed in 13.9% of patients and was significantly associated with the use of larger material volumes.

Conclusion: The use of ALB in staged protocols for large bone defects is associated with high revision and reinfection rates. These findings identify the limits of the technique and sharpen its indication spectrum, standing alongside the favorable outcomes reported for single-stage procedures in smaller defects. In large defects, the resorption of the carrier may outpace bone ingrowth, leading to recurrence of infection. Consequently, the use of ALB in large defects cannot be recommended based on these data.

Plain Language Summary: Bone infections (osteomyelitis) and non-healing fractures are challenging conditions that often require complex surgery. Surgeons typically treat these by removing infected tissue and stabilizing the bone. Recently, doctors have utilized a special biodegradable material that fills gaps in the bone and releases antibiotics directly to the affected area. This study aimed to evaluate how well this material works when used in a "staged" procedure, where surgeons clean the bone first and implant the material in a second surgery weeks later. The team analyzed the recovery of 101 patients treated at two specialized trauma centers in Germany. These patients had significant bone loss due to infection and received the antibiotic-loaded filler to help their bones heal. The study found that the success of this treatment depends heavily on the size of the bone gap. For smaller injuries, the material can be effective. For large bone gaps (larger than 5 cm), the results were challenging. Over half of the patients needed additional surgeries, and infection returned in nearly 45% of cases.

The results suggest that in large gaps, the material dissolves faster than the patient's new bone can grow. This creates a fluid-filled space where bacteria can survive. Consequently, the study recommends to use alternative methods for patients with large bone defects, reserving this specific antibiotic-loaded material for smaller injuries. This insight helps ensure patients receive the most effective treatment strategy for their specific condition.

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Introduction

The management of patients with chronic osteomyelitis (COM) and septic (SNU) or aseptic nonunions (ANU) remains a significant clinical challenge.[1,2] For patients, the diagnosis often necessitates revision surgeries and causes severe pain, carrying a risk of permanent disability.[3,4] Moreover, the condition imposes a substantial socioeconomic burden.[2,5]

In Germany, the overall prevalence of osteomyelitis was approximately 16.7 cases per 100,000 inhabitants in 2018, representing an increase of around 10% over the last decade.[2] Factors such as the extent of soft tissue damage and the size of bone defects elevate the risk of postoperative infection, which can exceed 30% when multiple risk factors are present.[6,7]

COM and nonunions (NU) can be managed using either single- or multiple-stage protocols.[8,9] A staged procedure typically begins with radical debridement of all infected tissue, followed by the insertion of an antibiotic-loaded polymethylmethacrylate spacer to manage the resulting dead space. Once the infection is eradicated, a second, definitive surgery is performed to remove the spacer and reconstruct the bone defect, frequently utilizing allogenic or autologous bone graft.[10] In recent years, biomaterials possessing both antibiotic delivery properties and osteoconductive effects have gained prominence.[11] These materials merge the concept of local antibiotic therapy with the stimulation of bone healing.

In this context, several materials have been described in the literature, including resorbable calcium sulphate-hydroxyapatite composites. Two specific antibiotic-loaded calcium sulphate-hydroxyapatite biocomposites (ALB), namely those loaded with gentamicin (ALB+G; Cerament® G, Bonesupport, Lund, Sweden) or vancomycin (ALB+V; Cerament® V, Bonesupport, Lund, Sweden), have garnered particular attention. The underlying biomaterial is commercially available either as a plain carrier or loaded with various antibiotics.[12,13] Antibiotic-loaded biocomposites are reported to provide high local antibiotic concentrations while maintaining safe systemic serum levels during the days following application.[14–16] Several animal studies have already demonstrated the osteoconductive and antibacterial properties of these materials.[17–19] However, contradictory findings exist, such as in an infected mouse model where the material failed to improve bone healing.[20]

Two case series involving 100 patients[21,22] and 163 patients with chronic osteomyelitis and infected nonunions[23] reported infection eradication rates of 95.7% and 96%, respectively, following single-stage treatment using ALB+G or ALB+V in small defects. In contrast to these favorable findings, a smaller, retrospective case series reported a revision rate of 50% following the single-stage use of ALB+G or ALB+V in 20 patients with chronic osteomyelitis. These failures were attributed to persistent infection or local wound complications, including wound dehiscence and prolonged wound drainage.[24]

To date, data regarding the use of ALB in staged procedures for bone infections with associated, often larger, defects remain scarce. Therefore, this German multicenter study evaluated the treatment outcomes of ALB+G and ALB+V in staged procedures, specifically focusing on: (1) surgical revision rates, (2) reinfection rates, and (3) biomaterial-related side effects, such as “white drainage”.

Materials and Methods

Inclusion Criteria

This retrospective case series reviewed clinical records from two tertiary care trauma centers, both featuring specialized units for the treatment of septic musculoskeletal conditions. Patients treated between 2013 and 2020 were included if they received ALB+G or ALB+V as a bone void filler for defects of the extremities resulting from surgical debridement of COM, SNU, or ANU in a staged procedure. NU was defined as a fracture failing to heal at least six months after initial stabilization. Infection in SNU cases was diagnosed using the consensus criteria for Fracture-Related Infection.[25] Chronic osteomyelitis (COM) was defined as a bone infection characterized by a duration of at least six weeks and/or the presence of necrotic bone. In both infectious entities, diagnosis was based on the same infection criteria, with COM being additionally categorized according to the Cierny-Mader classification. NU were categorized as ANU based on the absence of clinical signs of infection and negative microbiological cultures. Furthermore, cases with a history of a single positive culture (one out of five samples) from prior external surgeries were also classified as ANU, provided that all current clinical and microbiological evaluations were completely negative. Across all three diagnoses, ALB was

uniformly utilized to address the shared surgical requirement of managing an osseous dead space following debridement. Exclusion criteria included age <18 years, a follow-up period of less than six months following the implantation of ALB +G or ALB+V, and incomplete medical records regarding the systemic antibiotic regimen.

Surgical Management

All patients underwent a staged surgical protocol. The initial procedure involved the excision of sinus tracts (if present) and the removal of infected implants, followed by radical debridement. Debridement was continued until healthy, bleeding soft tissue and bone were exposed and all necrotic tissue was removed. At least five tissue samples were collected for microbiological and histological analysis. Dead space management was achieved using a non-resorbable antibiotic-loaded spacer. If bone instability was present, stabilization was provided via external or internal fixation. If necessary, debridement was repeated until all clinical signs of active infection had resolved. Primary wound closure was attempted whenever possible; otherwise, negative pressure wound therapy (NPWT) was applied.

The definitive surgery (index surgery) was performed approximately six weeks after the initial procedure in patients with successful primary wound closure. For patients managed with NPWT, the interval between stages was shortened to allow for plastic soft-tissue reconstruction, which was performed concomitantly with the index surgery. At the end of index surgery, all patients had definitive skin closure. During the index surgery, the spacer was removed, followed by renewed debridement and the collection of at least five further samples for microbiological and histological testing. The resulting bone defect was filled with ALB. Preparation and application adhered strictly to the manufacturer's instructions; specifically, the material was allowed to set and cure in situ prior to wound closure. The choice of bone substitute material (ALB+G or ALB+V) was guided by the antibiogram of the causative pathogen identified during previous surgeries. In cases of culture-negative infection, ALB+G was preferred due to its broader antibiotic spectrum, covering Gram-negative bacteria. At the surgeon's discretion, bone defects were additionally filled with autografts or allografts. If temporary stabilization had been used, implants were exchanged or converted to definitive fixation during this stage.

Antibiotic Management

Patients were given perioperative intravenous antibiotics as recommended in the currently available guidelines.[26] All of the patients received intravenous, empirical antibiotic treatment with broad-spectrum antibiotics (eg. glycopeptide and broad-spectrum β-lactam-antibiotic) for the first days after surgery, as this has been shown to cover about 95% of causal microorganisms.[27] If preoperative susceptibility testing was available from prior surgeries, Antibiotics were administered accordingly. Once intraoperative susceptibility testing results became available, therapy was transitioned to specific, targeted antibiotics. Whenever possible, biofilm-active antibiotics were included in the regimen. The total duration of antibiotic treatment usually ranged from 2 to 12 weeks (#This duration was determined on a highly individualized basis through multidisciplinary consultation, accounting for factors such as infection severity, microbiological findings, adequacy of surgical debridement, implant involvement, and patient-specific risk factors. For instance, in ANU patients, empirical antibiotic treatment was discontinued after two weeks if all intraoperative cultures from the index surgery remained negative and no clinical signs of infection emerged.

Data Collection and Outcome Parameters

Patient demographics, infection etiology (COM, SNU, ANU), and the extent of bony involvement (Cierny and Mader classification[28] in case of COM) were extracted from the electronic medical records. Further recorded data included anatomical localization (AO Classification region), number of prior surgical procedures for bone infection, microbiological results (from index and prior surgeries), and details of the index surgery. Intraoperative parameters included the type of orthopedic implants, type and volume of bone substitute (ALB + Gentamicin or ALB + Vancomycin), concomitant use of allografts or autografts, soft-tissue reconstruction techniques, and the systemic antibiotic regimen.

Defect size was measured on radiographic images or CT scans. The maximum extent of the preoperative bone defect was recorded as either the length of segmental bone loss or the maximum diameter of a cavitary defect.

The primary outcome was treatment success, defined as the absence of infection recurrence and stable bone consolidation without the need for unplanned surgical re-intervention following ALB implantation (index surgery). Bone consolidation was

assessed using plain radiographs (minimum two orthogonal views) or CT scans, depending on the anatomical region. Secondary outcomes included infection recurrence (according to fracture related infection criteria[25]) and the presence of prolonged wound leakage ("white drainage"). In patients presenting with prolonged wound drainage, a definitive diagnosis of reinfection was established intraoperatively during subsequent revision surgeries via positive microbiological cultures or histopathological criteria.

Statistical Analysis

Data were collated using comma-separated values files (Microsoft Excel; Redmond, Washington, USA) and analyzed using R (RStudio, version 4.5.1; Foundation for Statistical Computing, Wien, Austria). Variables were categorized into clinically relevant groups. Continuous variables were assessed for normality using the Shapiro–Wilk test and are reported as mean with standard deviation (SD). Categorical variables are presented as absolute counts and percentages. Group differences in categorical outcomes were tested using Pearson's chi-squared test. Fisher's exact test was used when the chi-squared test assumptions were not met due to small expected cell counts. For pairwise post-hoc comparisons, p-values were Bonferroni-adjusted. Univariable logistic regression models were utilized to evaluate the association between the defect size and the number of prior surgical interventions to the probability of reinfection and revision surgery. Time-to-event outcomes were analyzed using cumulative incidence functions with administrative censoring at 24 months. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics and Surgical Treatment

We initially identified 159 patients treated with ALB within the study period as part of a staged procedure. A total of 58 patients were excluded from the final analysis. Reasons for exclusion were insufficient follow-up <6 months (n = 37), age <18 years (n=4) and insufficient documentation of the systemic antibiotic therapy (n = 17). Consequently, 101 patients were available for evaluation. Table 1 summarizes the clinical parameters of the overall cohort, whereas Supplementary Table S1 details patient demographics and comorbidities stratified by underlying diagnosis.

Microbiology

38 patients (45.2% of the 84 patients in the SNU and COM group) had microorganisms detected at the index surgery. Gram-positive bacteria were found in 35/38 patients (92.1%), whereas gram-negative bacteria were only detected in 8/38 patients (21.1%). The most frequently detected organisms were Staphylococcus species (in 22 patients; 57.9%). Table 2 summarizes the pathogens at ALB implantation surgery of the overall cohort. Supplementary Tables S2 and S3 detail the pathogens stratified by underlying diagnosis.

Treatment Outcome

31 patients (30.7%) achieved eradication of infection with uneventful wound healing and stable bone consolidation without surgical revision after index surgery. The remaining 70 patients (69.3%) suffered from complications during the follow up period. 59 patients (58.4%) of all patients had to be surgically revised. Figure 1 details the Treatment outcome.

Surgical revisions were restricted to patients meeting strict criteria, such as mechanical implant failure or established fistulas indicating deep infection. To illustrate the broad spectrum of clinical outcomes observed in this cohort, two representative cases are presented. Figure 2 demonstrates a case of uneventful healing and successful consolidation. Notably, this patient presented with a culture-negative infection; despite the definitive clinical presence of a draining fistula, no bacterial growth could be detected in intraoperative tissue samples. In contrast, Figure 3 depicts a complex clinical course resulting in treatment failure. While intraoperative cultures taken during the index surgery were similarly negative, this patient had a documented history of Methicillin-sensitive *Staphylococcus aureus* identified during the initial surgical debridement.

Table 1 Patient Characteristics and Surgical Treatment

Category		Frequency	Percent [%]	Mean (SD)
Age [years]				54.1 (13.1)
Sex	Male	73	72.3	
	Female	28	27.7	
Diagnosis	COM	80	79.2	
	SNU	4	4.0	
	ANU	17	16.8	
Defect Size [cm]				4.1 (2.6)
	<3	27	26.7	
	3-5	54	53.5	
	>5	20	19.8	
ALB Volume [mL]				10.5 (7.3)
	1-5	35	34.7	
	5-10	49	48.5	
	>10	17	16.8	
Localization	Humerus	4	4.0	
	Radius	1	1.0	
	Ulna	1	1.0	
	Femur	23	22.8	
	Tibia	58	57.4	
	Fibula	3	3.0	
	Calcaneus	11	10.9	
Cierny-Mader anatomic type[a]	I	10	12.5	
	II	0	0	
	III	29	36.3	
	IV	41	51.3	
Antibiotic loading[b]	Gentamicin	70	69.3	
	Vancomycin	32	31.7	
Additional grafting	None	50	49.5	
	Allogenous	12	11.9	
	Autologous	26	25.7	
	Both	13	12.9	
Implant at index surgery	None	38	37.6	
	Plate	48	47.5	
	Intramedullary Nailing	7	6.9	
	External Fixation	5	5.0	
	Others	3	3.0	
Flap coverage as part of index surgery	No	91	90.1	
	Yes	10	9.9	
Previous surgeries				5.1 (3.8)
Follow up [month]				22.8 (19.3)

Notes: [a]Percentages calculated based on the COM subgroup (n=80). [b]One patient received both Gentamicin- and Vancomycin-loaded substitutes; therefore, the total percentage exceeds 100%.

Abbreviations: ALB, Antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite; ANU, Aseptic Nonunion; COM, Chronic Osteomyelitis; SNU, Septic Nonunion.

Table 2 Pathogens at ALB Implantation Surgery

Pathogen Group	Pathogen	Frequency	Percent [%]
Gram-positive[a]	*Staph. aureus (MSSA)*	8	21.1
	Staph. aureus (MRSA)	1	2.6
	Staph. epidermidis	6	15.8
	Staph. epidermidis (MRSE)	8	21.1
	Other Staphylococci	5	13.2
	Enterococcus spp.	4	10.5
	Peptoniphilus spp.	2	5.3
	Finegoldia spp.	2	5.3
	Corynebacterium spp.	1	2.6
	Streptococcus spp.	1	2.6
	Cultibacterium spp.	1	2.6
	Aerococcus spp.	1	2.6
	Bacillus spp.	1	2.6
	Clostridium spp.	1	2.6
	Peptostreptococcus spp.	1	2.6
Gram-negative[a]	*E. coli*	2	5.3
	Pseudomonas spp.	1	2.6
	Proteus spp.	2	5.3
	Enterobacteriaceae	3	7.9
Multidrug-resistant organisms (MDRO)[a,c]		21	55.3
Difficult-to-treat organisms[a,d]		13	34.2
Polymicrobial infection[a,e]		11	28.9
No bacterial growth[b]		46	54.8

Note: [a]Percentage indicates fraction of patients cohort with culture-positive infection (n=38). [b]Percentage indicates fraction of total patient with infection related disease (n= 84). [c]Common multidrug-resistant organisms (MDRO) include vancomycin-resistant Enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Gram-negative bacteria (MDRGN). [d]Difficult-to-treat organisms: Enterococcus spp., MDRGN, MRSA, Candida spp. [e]Polymicrobial infection was defined by more than one detected germ.

Abbreviations: ALB, Antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite; MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus.

Analysis of Revision

Risk factors for revision included larger defect size, increased ALB volume, and localization in the lower extremity (Figure 4a–c). The requirement for external fixation as the definitive osteosynthesis at index surgery was strongly predictive of failure, with 100% of patients in this subgroup needing revision (Figure 4d). In contrast, antibiotic loading type and additional grafting did not significantly affect revision rates. Regarding host physiology, Cierny-Mader Grade 4B patients showed the highest revision rate (29/41; 70.7%), though the difference across classes was not statistically significant. Regarding defect characteristics, no significant difference in revision rates was observed between cavitary and segmental defects (24/43 vs. 35/58; 55.8% vs. 60.3%; $p = 0.65$; Figure 4e). Only 32.2% (19/59) of revisions were necessary earlier than 2 months after the index surgery. Median time to revision was 110.5 days. Figure 4f presents the cumulative incidence of revision, stratified by the cause of revision. To improve comparability with other studies, a subgroup analysis restricted to the 80 patients with COM was performed (Supplementary Figure S1). Within this subset, higher volumes of implanted ALB remained significantly associated with increased revision rates ($p = 0.02$), whereas defect size did not reach statistical significance.

Analysis of Reinfection

During the follow-up period, 46 patients (45.5%) experienced reinfection of the treated bone, verified according to the criteria published by Metsemakers et al[25] The majority of these patients (32/46; 69.6%) presented with an established fistula. The

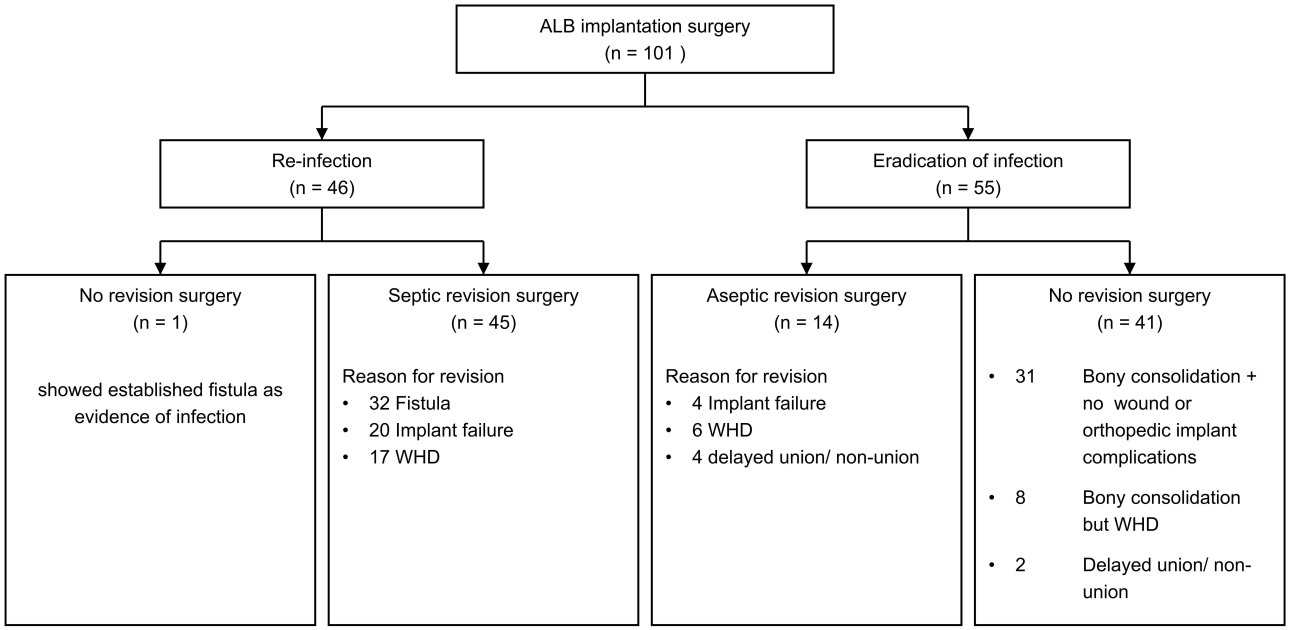

Figure 1 Flowchart illustrating clinical outcomes and treatment pathways.
Abbreviation: WHD, Wound healing disorder.

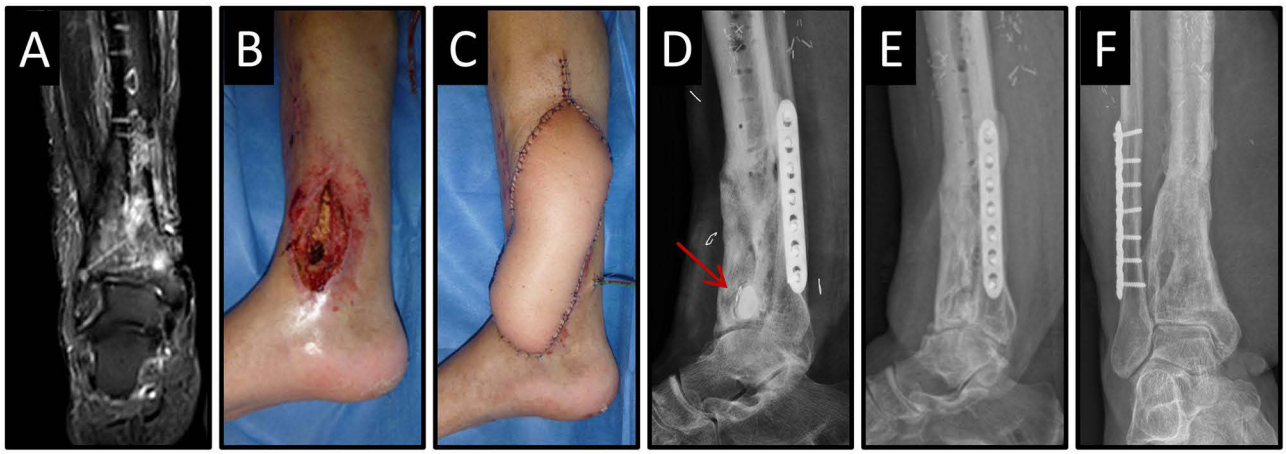

Figure 2 Case example of the treatment of chronic osteomyelitis of the distal tibia in a 55-year-old male associated with an osteocutaneous fistula and an 8×4 cm soft tissue defect following bilateral open fractures. (**A**) MRI displaying the extent of the infection. (**B**) Clinical presentation after initial debridement. The surgical procedure involved radical debridement, filling of the bone defect with 10 mL ALB+G, and simultaneous soft tissue reconstruction using a free parascapular flap (**C**). Postoperative lateral radiograph (**D**) shows the implanted ALB+G (red arrow). Radiographs at 3 years postoperative ((**E**): lateral view; (**F**) AP view) demonstrate the remodeling of the biocomposite and subsequent bone consolidation.

reinfection rate increased significantly with larger defect sizes and higher volumes of ALB used (Figure 5a and b). However, the rate was not associated with the Cierny-Mader classification (Figure 5c), nor was it affected by the use of additional internal stabilization with metallic fixation devices at the time of ALB implantation (without fixation: 16/38, 42.1%; with fixation: 30/63, 47.6%; $p = 0.68$). Regarding additional grafting, the rate of recurrent infection was highest in the ALB + allograft group (8/12; 66.7%), though this difference was not statistically significant (Figure 5d). Moreover, the requirement for flap coverage during the index surgery did not significantly affect the reinfection rate (Figure 5e). Reinfection rates were comparable between the COM and SNU groups. In contrast, the infection rate (reinfection or first occurrence) was significantly lower in the ANU group (Figure 5f). To improve comparability with other studies, a subgroup analysis restricted to the 80 patients with COM was performed (Supplementary Figure S1). Within this subset, larger defect sizes remained

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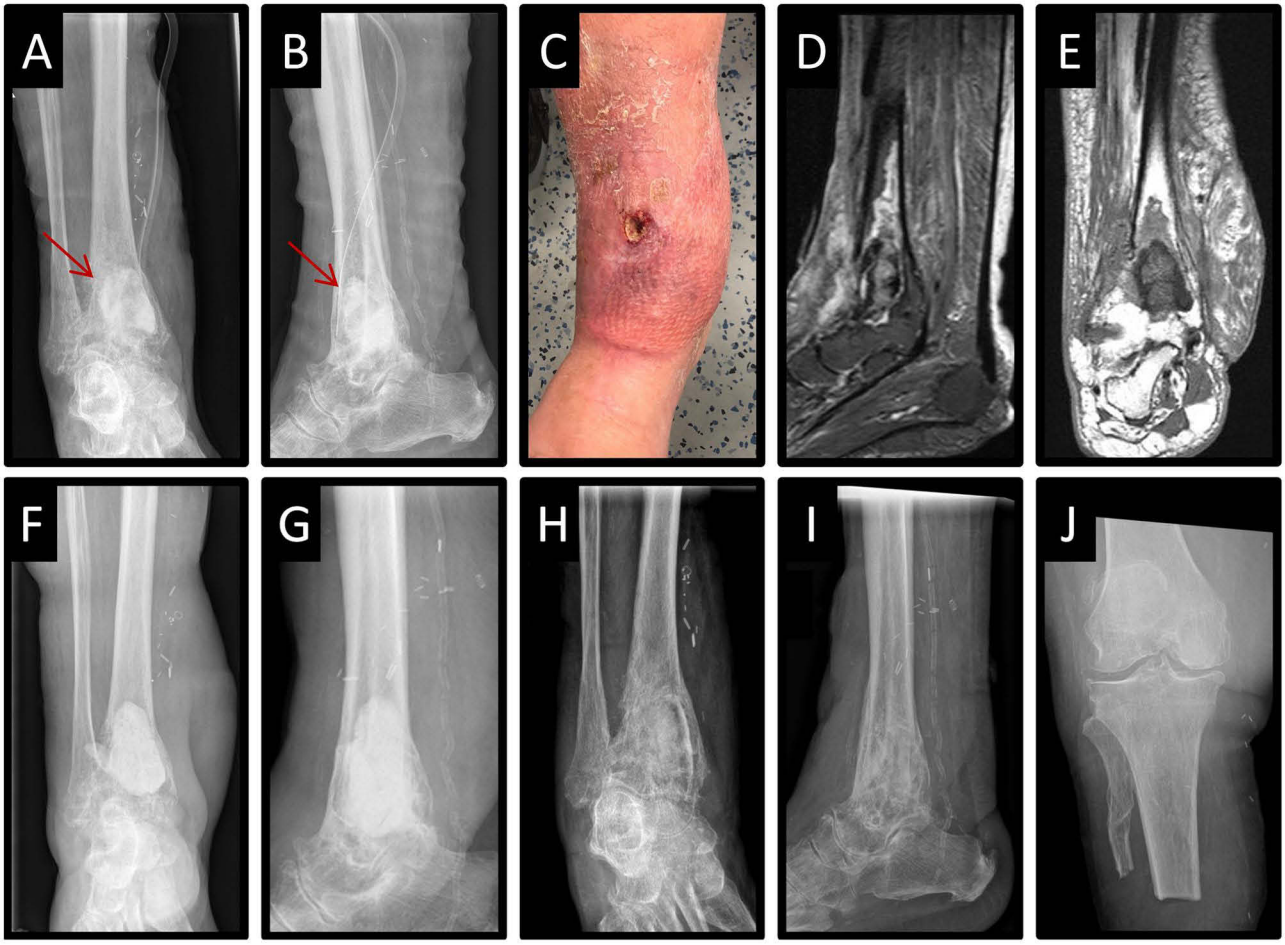

Figure 3 Case example of the treatment of osteomyelitis of the distal tibia in a 74-year-old female following ankle arthrodesis after an initial ankle fracture-dislocation. Staged Treatment with implantation of a cement spacer in the initial stage (AP view: (**A**), lateral view: (**B**)) and implantation of ALB+V in the definitive stage (red arrows; ap view: (**C**), lateral view: (**D**)). Recurrent infection with fistula formation 7 months postoperative (clinical image: (**E**); sagittal T2-weighted MRI: (**F**); coronal T1-weighted MRI: (**G**)). Two-stage revision surgery with autologous cancellous bone grafting in the second stage (ap view: (**H**), lateral view: (**I**)). Second recurrence leading to amputation due to persistent infection (**J**).

significantly associated with higher reinfection rates ($p = 0.047$), whereas ALB volume did not show a statistical significant correlation. No significant correlation was identified between the number of prior surgical interventions and the probability of reinfection or revision (Supplemental Figure S2).

White Drainage

14 patients (13.9%) showed white wound drainage after implantation of the ALB substitute. White drainage rate was significantly associated with the use of larger volumes of ALB (Figure 6a). The rate of reinfection was significantly elevated in patients presenting postoperative white wound drainage (10/14, 71.4%) compared to patients without white drainage (32/87, 36.8%; $p = 0.03$; Figure 6b).

Discussion

Principal Findings

To our knowledge, this study represents the largest multicenter analysis to date investigating the use of this antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite within a staged surgical protocol for chronic osteomyelitis and nonunions.

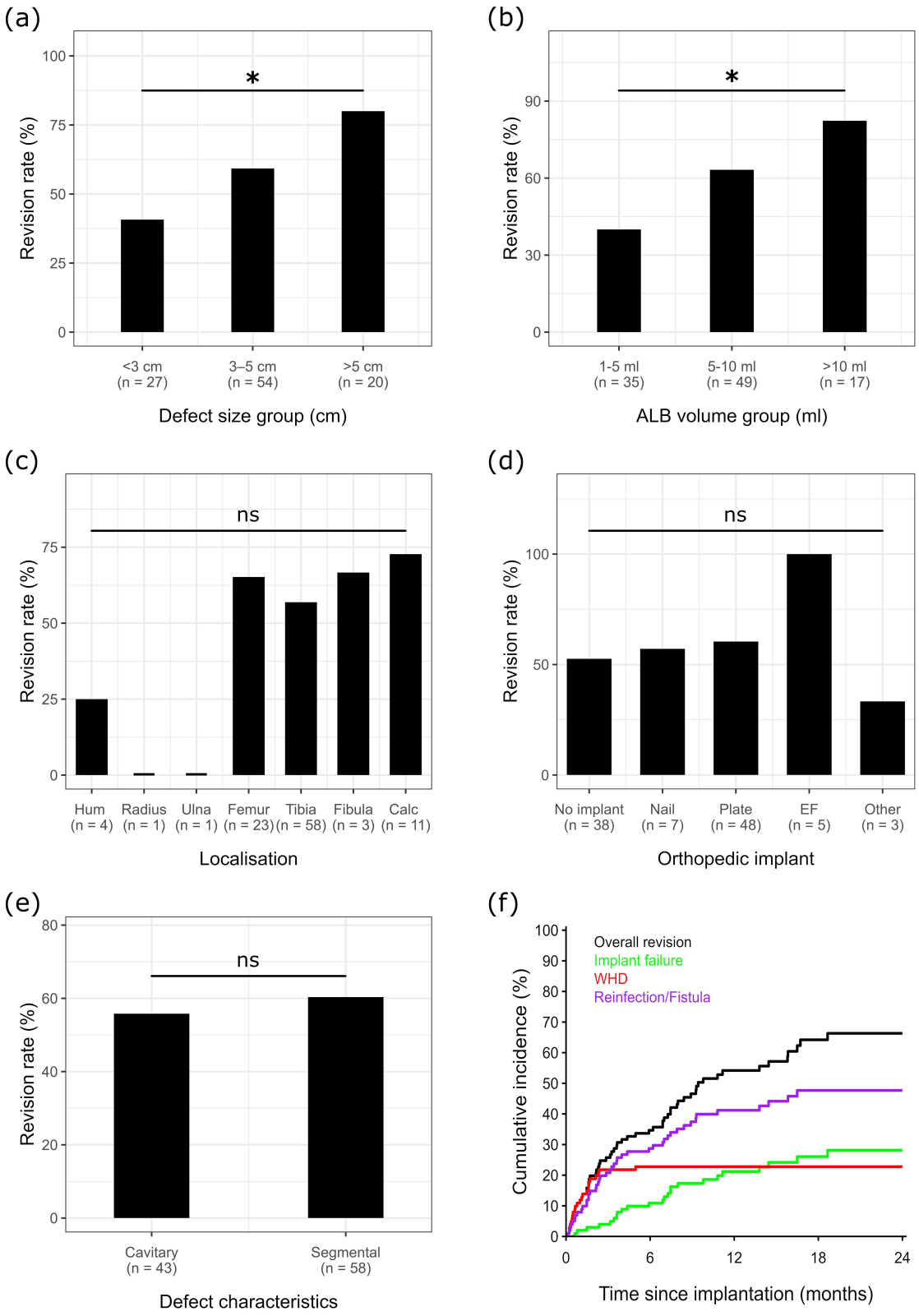

Figure 4 Analysis of revision rates and revision-free survival. Revision rates are stratified by (**a**) defect size group, (**b**) volume of implanted antibiotic-loaded biocomposite, (**c**) localization of the defect, (**d**) type of orthopedic implant, and (**e**) defect characteristics. (**f**) Cumulative incidence of revision surgery. The black line displays the overall cumulative incidence of revision for any cause. The other lines represent the cause-specific cumulative incidence for wound healing disorders, implant failure, and reinfection respectively, calculated using a competing risk analysis. Note that the sum of the cause-specific curves exceeds the overall curve due to patients presenting with simultaneous reasons for revision surgery, who were counted as events in both cause-specific analyses but only once in the overall analysis. The x-axis is truncated at 24 months as no revision events occurred after 19 months. *$p < 0.05$.
Abbreviations: ALB, Antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite; Calc, Calcaneus; EF, External fixation; Hum, Humerus; ns, not significant.

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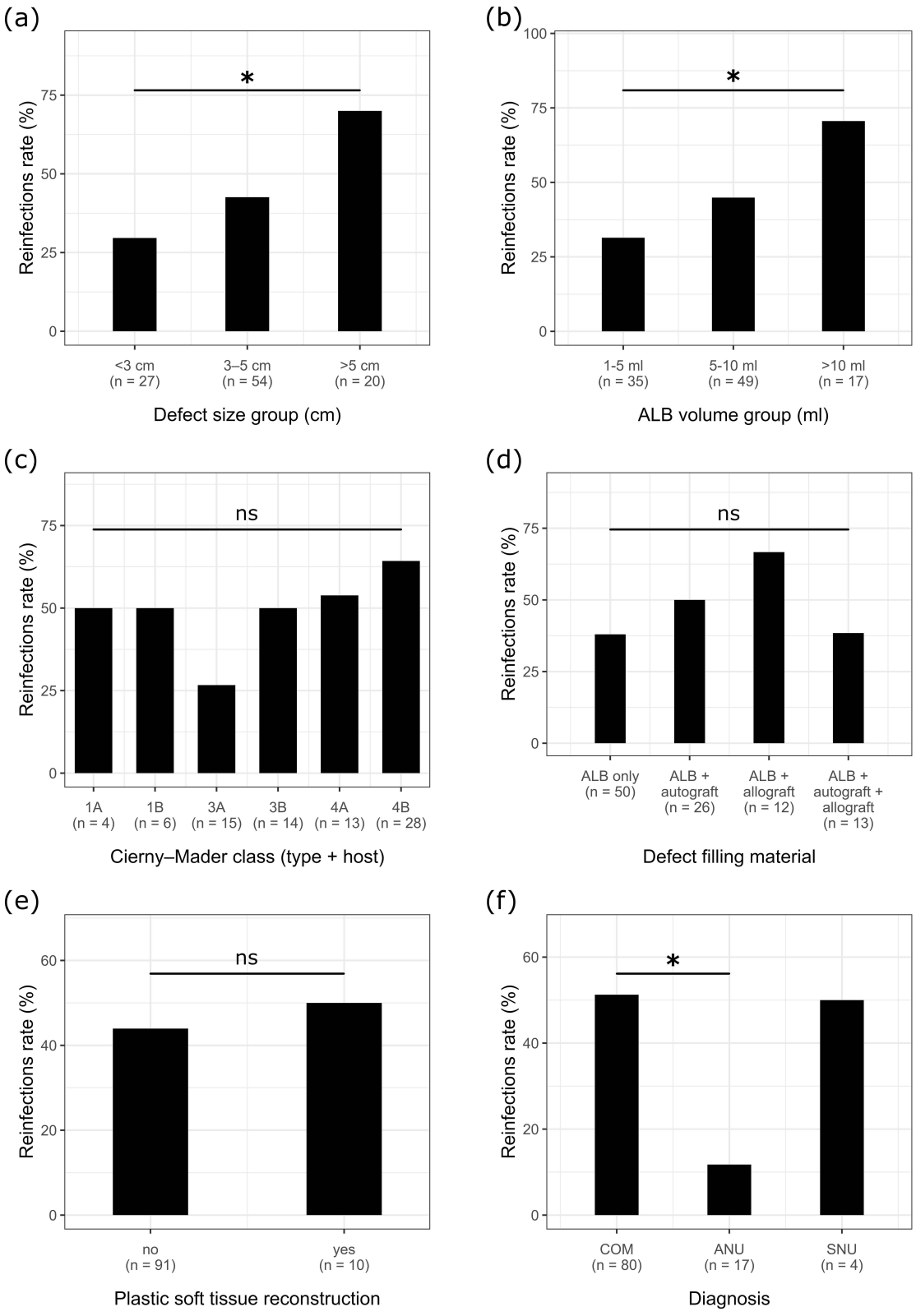

Figure 5 Stratification of reinfection rates by (**a**) defect size, (**b**) volume of antibiotic-loaded biocomposite implanted, (**c**) Cierny-Mader classification, (**d**) defect filling material, (**e**) flap coverage and (**f**) Diagnosis. * = $p < 0.05$.

Abbreviations: ALB, Antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite; ANU, aseptic nonunion; COM, chronic osteomyelitis; SNU, Septic nonunion; ns, not significant.

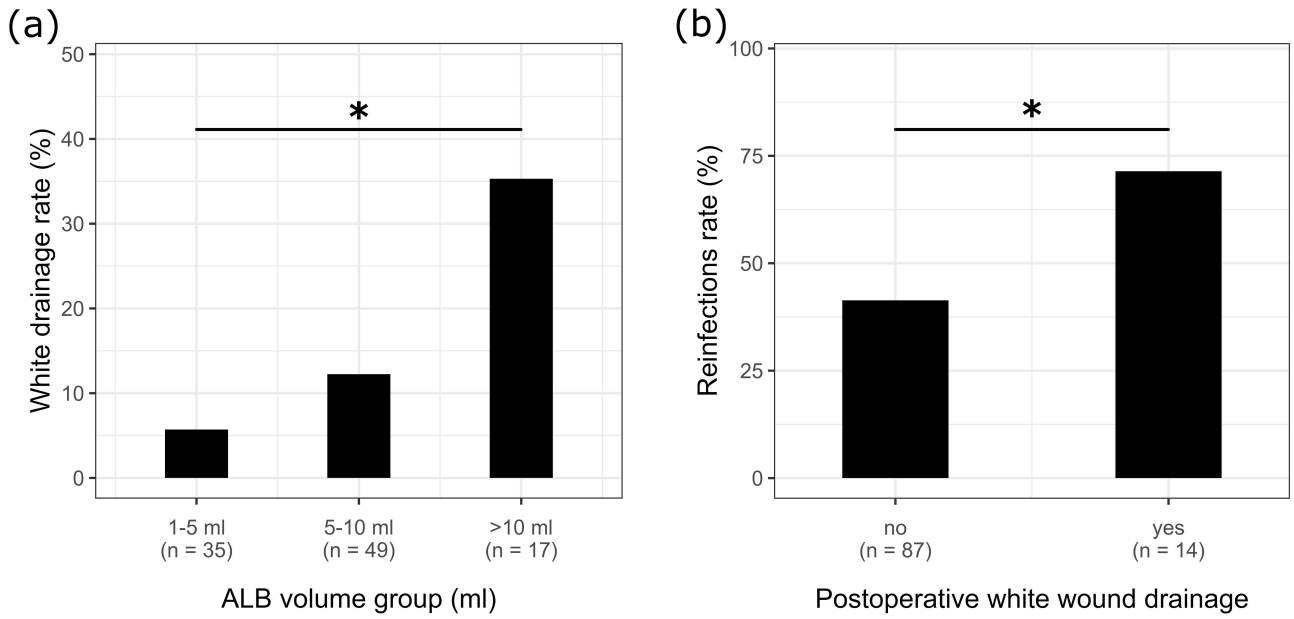

Figure 6 Stratification of (**a**) white drainage rates by volume of antibiotic-loaded biocomposite implanted, and (**b**) reinfection rates by presence of white drainage. *p < 0.05.
Abbreviation: ALB, Antibiotic-loaded calcium sulphate-hydroxyapatite biocomposites.

The patient cohort reflects a typical scenario of complex bone infections in tertiary trauma hospitals, which serve as specialized centers for the most challenging cases. Consequently, the patients presented with significant disease severity, as evidenced by the high prevalence of Cierny-Mader anatomic type III and IV lesions and a substantial history of prior surgeries.

The most striking finding of this investigation is the high rate of complications, with an overall revision rate of 58.4% and a reinfection rate of 45.5%. Treatment success, defined as the eradication of infection, bony consolidation, and no unplanned re-intervention, was achieved in only 30.7% of patients (Figure 1). While this cure rate is lower than those reported in several previously published cohorts, it must be contextualized within the specific demographics of our study. As a maximum-care tertiary referral center, our cohort represents a negative patient selection characterized by severe, recalcitrant cases often excluded from other trials. A deeper analysis reveals a significant correlation between treatment failure and the extent of the bone defect. The revision and reinfection rates were significantly higher in defects larger than 5 cm compared to smaller defects (Figures 4a and 5a). Consistent with this observation, the higher volumes of the implanted biomaterial for those larger defects were also significantly associated with higher revision and reinfection rates (Figures 4b and 5b). Notably, the requirement for external fixation at the index surgery, which serves as a proxy for segmental instability and severe soft tissue compromise, was predictive of 100% failure in the present cohort (Figure 4d). These findings suggest that while the antibiotic-loaded biocomposite is a potent tool, its clinical efficacy appears to be closely linked to the complexity of the defect environment. However, further matched-cohort studies are required to fully substantiate this hypothesis.

Comparison with Current Literature

The results of the present study stand in stark contrast to the excellent outcomes reported in major prospective series on this antibiotic-loaded biocomposite. McNally et al and Ferguson et al reported eradication rates of 96% and 957%, respectively, using the same material.[22,23] This discrepancy can likely be attributed to fundamental differences in patient selection rather than the material itself. The aforementioned studies strictly included patients with chronic osteomyelitis and primarily utilized a single-stage protocol, whereas the current study additionally included patients with bone defects due to aseptic nonunions and the cohort was treated exclusively with a staged approach (see next section for details). Furthermore, and perhaps most importantly, the defect sizes in the present study appear substantially larger. McNally et al explicitly excluded cases with segmental defects larger

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than 1 cm Similarly, Ferguson et al, whose cohort included the patients previously reported by McNally et al, reported the exclusion of Cierny-Mader Type IV cases with segmental defects greater than 1 cm[22,23] Ferguson et al stated a mean defect size of 109 cm^3 following excision While a direct comparison is difficult due to the discrepancy between volumetric and linear measurements, the defects in the current study are considerably larger, evidenced by a mean linear defect size of 4.1 cm and nearly 20% of patients presenting with linear defects larger than 5 cm (Table 1). Importantly, to account for the demographic differences, the isolated analysis of the COM subgroup (Supplementary Figure S1) confirmed that larger defect sizes remain significantly associated with higher reinfection rates. This supports the hypothesis that the biomechanical and structural challenges of managing large dead spaces, rather than the underlying diagnosis alone, are the primary drivers of the increased failure rates.

The present findings align closely with those of Niemann et al, who analyzed the use of the same material in a cohort of 20 patients with corticomedullary defects due to COM and reported a revision rate of 50%[24] While Niemann et al reported higher mean defect volumes in patients requiring revision (73 ± 70 cm^3) compared to those who did not (5.1 ± 4.0 cm^3), this difference did not reach statistical significance. However, given the smaller cohort size in their analysis, the statistical power to detect volume-dependent effects may have been limited compared to the current study.

Indeed, McNally et al already highlighted the need for further clinical evidence before expanding the use of ALB to large segmental defects[22] The present data address this gap in the literature and sharpens the indication spectrum: while the material performs well in small voids, the findings indicate that large defects represent a contraindication for this technique. Interestingly, in the subgroup of patients with defects smaller than 1 cm ($n = 2$), no reinfections were observed. However, given the extremely small sample size, these findings cannot be generalized based on the data of the present study.

The Impact of Staged Protocols and "Dead Space"

The adherence to a staged protocol presents a distinct set of therapeutic trade-offs. While this approach offers proven advantages in complex cases of osteitis, specifically by inducing a well-vascularized membrane rich in growth factors[29,30] and ensuring high local antibiotic delivery,[10,31,32] it also introduces specific vulnerabilities. In the interval between the first debridement and the implantation of the ALB, spacers can become colonized by bacteria, potentially shielding them in a biofilm that persists despite systemic antibiotics.[33,34] When the spacer is removed and replaced with the biocomposite, these residual pathogens may recolonize the new, avascular void filler.

Furthermore, the resorption of the calcium sulphate creates a mismatch between bone ingrowth and the formation of a fluid-filled seroma. In large defects, the biology of the compromised host bone may not be fast enough to populate the scaffold. This results in a dead space filled with seroma fluid, an ideal culture medium for bacteria, before the hydroxylapatite scaffold can integrate. This theory is supported by the finding that high volumes greater than 10 mL were associated with white drainage and subsequent infection (Figure 6). To address this, current research investigates the combination of ALB with biological adjuvants like Bone Morphogenetic Protein-2 or zoledronic acid to either stimulate osteoinduction or modulate the resorption rate.[35]

White Drainage and Wound Complications

White drainage, a leakage of dissolved calcium sulphate material, was observed in 13.9% of the patients. This rate is higher than those reported in the literature, which range from 6% to 10% for ceramic bone grafts,[22,36,37] likely due to the high volumes of ALB required for the large defects in this cohort. Accordingly, white drainage was significantly associated with the use of larger volumes (Figure 6a). While often described as a benign, self-limiting phenomenon, white drainage correlated with higher reinfection rates (71.4% vs. 36.8; $p = 0.03$). Clinically, prolonged wound leakage could prevent the formation of a dry barrier, potentially serving as a pathway for superinfection.

Additionally, a high rate of culture-negative infections was observed despite definitive clinical signs of infection, such as fistulae. This represents a known challenge in patients who have previously received prolonged suppressive antibiotic therapy,[38] a scenario typical of tertiary referral centers. While this reflects real-life conditions, the inability to identify a specific pathogen in half of the cases precludes the application of targeted local antibiotic therapy and may have contributed to the observed reinfection rate.

Limitations

This study has several limitations inherent to its retrospective, multicenter design. First, the treatment protocols, while generally aligned, may have varied slightly between centers regarding the extent of debridement and soft tissue management. Second, the lack of a control group limits the ability to definitively state the cause of failure despite having the above-mentioned correlations. Third, the high rate of culture-negative samples during the index surgery likely stems from prior debridement and suppressive antibiotic therapy, which are known to lower detection rates.[39–41] This creates a potential classification bias, wherein SNU with incomplete external, medical histories or incomplete external-prior microbiological testing may have been mislabeled as aseptic. As a result, the true prevalence of ANU is likely lower than reported. Fourth, the patient cohort exhibits considerable heterogeneity regarding the underlying pathology (COM, SNU, ANU) and soft tissue status, which inherently reflects the complex, real-world population treated at a specialized tertiary referral center. We acknowledge that the limited sample sizes within specific diagnostic subgroups restrict our statistical power to perform robust multivariable regression analyses. Consequently, we cannot fully isolate the potential confounding effects of the local biological environment on the clinical outcome. Nevertheless, the unifying indication across all cases was the surgical management of a clinically relevant osseous dead space. Since our subgroup analyses revealed no significant differences in outcomes based on soft tissue management (flap vs. no flap), defect morphology (cavitary vs. segmental), or comorbidities (see Supplemental Table S1) the data suggests that the observed high failure rates in larger defects are primarily driven by the structural and mechanical limitations of the biomaterial itself, rather than solely by the underlying infectious or biological pathology. Fifth, the minimum follow-up criterion of six months risks underestimating reinfections or revisions. However, the mean follow-up was substantially longer (22.8 months). Furthermore, because the observed failure rate is already considerable, any undetected failures would only reinforce our clinical conclusions. Finally, the assessment of bone consolidation was based on standard radiographs and CT scans without the use of a validated scoring system. Nevertheless, the requirement for revision surgery serves as a robust and clinically indisputable endpoint for treatment failure.

Conclusion

This multicenter, retrospectiveanalysis demonstrates that the use of antibiotic-loaded calcium sulphate-hydroxyapatite in a staged treatment protocol for complex cases is associated with high revision and reinfection rates, particularly in cases with significant bone loss. The data highlights the limits of this material: while reported to be effective for smaller voids, clinical outcomes in this heterogenous cohort deteriorated significantly as defect size increased. Based on these findings, caution is advised for defects larger than 3 cm. Defects exceeding 5 cm showed significantly elevated failure rates, suggesting that such large voids exceed the current biological and structural capacities of this technique. Ultimately, these findings reinforce that clinical outcome in these severe infections is highly multifactorial; while the defect size and local biological environment represent critical limitations for the biocomposite, overall treatment success remains equally dependent on radical debridement, comprehensive soft tissue management, and targeted systemic therapy. Current research is increasingly focusing on enhancing synthetic bone grafts with biological adjuvants. Future studies will determine whether the therapeutic threshold for larger defects can be successfully extended using these next-generation materials.

Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process

During the preparation of this work the authors used ChatGPT v. 5.0 (OpenAI, San Francisco, CA, USA) in order to enhance readability and refine language by improving the vocabulary and structure of pre-generated text by the authors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations

ALB, Antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite; ALB+G, Antibiotic-loaded calcium sulphate-hydroxyapatite biocomposite combined with gentamicin; ALB+V, Antibiotic-loaded calcium sulphate-hydroxyapatite

biocomposite combined with vancomycin; ANU, Aseptic nonunion; Calc, Calcaneus; COM, Chronic osteomyelitis; EF, External Fixation; Hum, Humerus; MDRGN, Multidrug-resistant Gram-negative bacteria; MDRO, Multidrug-resistant organisms; MRSA, Methicillin-resistant Staphylococcus aureus; MRSE, Methicillin-resistant Staphylococcus epidermidis; MSSA, Methicillin-sensitive Staphylococcus aureus; NPWT, Negative pressure wound therapy; NU, Nonunions; SD, Standard deviation; SNU, Septic nonunion; VRE, Vancomycin-resistant Enterococci; WHD, Wound healing disorder.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Medical Association of Rhineland-Palatinate (2019-14425) and by the ethics committee of the University of Duisburg-Essen (22-10615-BO). Patient consent was waived, as the study used anonymized patient data, wich was approved by the ethics committee.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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