

Intramedullary Canal Injection of Vancomycin- and Tobramycin-loaded Calcium Sulfate: A Novel Technique for the Treatment of Chronic Intramedullary Osteomyelitis

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ABSTRACT

Aim: In this study, we present a detailed surgical technique for treating chronic osteomyelitis (COM) of the intramedullary canal with injectable tobramycin and vancomycin-loaded calcium sulfate (CS).

Background: Chronic osteomyelitis of the long bones has been treated using antibiotic-impregnated polymethyl methacrylate (PMMA), which typically requires a second procedure for removal.

Technique: Removal of the infected intramedullary nail (if any), copious irrigation, canal reaming, and intramedullary canal injection of vancomycin- and tobramycin-loaded calcium sulfate as a single-stage procedure for the treatment of COM of long bones.

Conclusion: Intramedullary injection of vancomycin- and tobramycin-loaded CS can be used as a single-stage procedure for the treatment of long bone intramedullary COM. Further studies are necessary to compare the long-term outcomes of antibiotic-coated CS vs other antibiotic carriers for infection eradication.

Clinical significance: The authors have endeavored to explain the best surgical technique to eradicate long bones COM with injectable tobramycin and vancomycin-loaded CS.

Keywords: Antibiotic-loaded calcium sulfate, Bone infection, Chronic osteomyelitis, Local antibiotic delivery, Long bone infection, Retrospective review.

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BACKGROUND

Osteomyelitis management can be challenging for any orthopaedic surgeon.¹ Chronic osteomyelitis is most accurately classified by histopathological findings, including lymphoplasmacytic infiltrate, marrow fibrosis, and reactive new bone formation.²⁻⁴ The most commonly used classification for COM is the Cierny-Mader (CM) classification system, which classifies the infection based on the anatomic location and the host condition.⁵

Treatment usually involves debridement, removal of the infected implant, antibiotic therapy, and management of dead space. Bacterial biofilm limits immunological and antibiotic penetration and results in an altered metabolic state of the bacterial colony to promote survival.³ Tobramycin, gentamicin, and vancomycin are often used, usually in combination, to have effective antimicrobial coverage.⁶ Combining local and systemic antibiotics has shown improvement in the eradication of infection in animal models when compared to systemic antibiotics only.⁷ Local antibiotic delivery and dead space management can be achieved by using antibiotic-impregnated spacers.¹ Antibiotic-impregnated PMMA cement can be used as a spacer or for coating implants in the treatment of COM.⁶ Limitations of PMMA include a decrease in antibiotic elution following implantation and lack of resorption, which usually mandates spacer removal.^{8,9}

Recently, there has been a growing interest in the use of ceramic biocomposites for dead space management and local antibiotic delivery.^{10,11} Calcium sulfate is a relatively inexpensive

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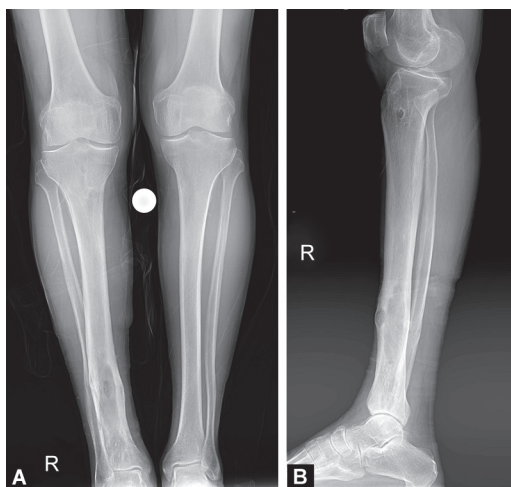
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Figs 1A and B: (A) Preoperative AP and lateral (B) Images show a case of Cierny-Mader type I intramedullary osteomyelitis (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)

ceramic biocomposite with unique features. Osteoconductivity, biodegradability, and drug-elution predictability make CS an attractive alternative for single-stage treatment of osteomyelitis.^{12,13} Typically, intramedullary osteomyelitis has been treated with antibiotic-impregnated PMMA-coated nails.^{14–17} Cement debonding during insertion or removal of PMMA-coated intramedullary nailing can be technically challenging. Another limitation is the subsequent drop of antibiotics to a subtherapeutic level due to rapid elution over 48–72 hours,⁸ which can promote biofilm formation and the development of multidrug-resistant organisms. Accordingly, a removal procedure of PMMA may be required.^{8,16}

We aim to report our technique of intramedullary canal injection of vancomycin- and tobramycin-loaded CS as a single-stage procedure for the treatment of COM in long bones. This study represents a single surgeon's experience at a single institute.

After obtaining Institutional Review Board approval, medical records were retrospectively reviewed to identify consecutive patients with COM who underwent CS injection at our institution between January 2016 and February 2020. Chronic osteomyelitis diagnosis was based on any of the following: (1) Histopathological intraoperative specimens confirming infection and (2) Clinical signs of infection, presence of a sinus tract or a fistula connected directly to the affected bone. All patients had elevated inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).¹⁸ Magnetic resonance imaging was done to confirm the preoperative diagnosis and extent of COM in two patients who did not have implants. Figure 1 show preoperative X-ray images of a case of CM type I intramedullary osteomyelitis.

A total of 66 patients were identified, but only patients meeting the following criteria were included in our study: (1) Diagnosed with a long bone (humerus, femur, or tibia) CM type I COM, (2) Intact long bone (excluded cases of infected non-union), (3) Patients with host type A and type B classes only, and (4) Patients who have completed a minimal follow-up of 18 months.

All patients received a postoperative course of intravenous antibiotics for 6 weeks according to their culture results, or according to the hospital protocol in case of negative cultures. Regularly Ancef (cefazolin) is used in all cases unless the previous

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culture results in the patients' medical records showing organism sensitivity to a different antibiotic. During the follow-up period, all patients were assessed clinically for any symptoms or signs of infection recurrence. Failure of remission was identified as persistent infection or infection recurrence with the need for another major procedure to eradicate infection during the follow-up period. Inflammatory markers (ESR and CRP) were checked during the initial follow-up serially until they were settled to the normal values. Plain radiographs were obtained at 6 weeks postoperatively to assess for absorption of the injected calcium sulfate. Infection remission was identified as the absence of clinical, laboratory, and radiological signs of osteomyelitis with completely healed wounds.

Fourteen patients (11 tibiae, three femora) met the inclusion criteria (Table 1). There were 10 males (71.4%) with a mean age (\pm standard deviation) of 43.4 years (\pm 16.1; range, 17–73 years). The average CCI was 1.9 m (\pm 1.9 m) and the mean duration of follow-up was 30.1 months (range, 20–49 months). Six patients had previous surgeries for osteomyelitis treatment, which included incision and drainage, nail removal, debridement, and exchange nailing with an antibiotic-coated PMMA nail. All patients were on full weight-bearing ambulation before and after the procedure, except for one patient who was non-ambulatory due to lower extremity paresis from an anoxic brain injury and maintained his status after the procedure (case 8). Culture results were positive for MRSA in eight cases, methicillin-sensitive *S. aureus* in two cases, *Pseudomonas aeruginosa* in one case, and negative for three cases. In this case series, no incidence of iatrogenic fracture occurred; however, prophylactic nailing after canal injection with antibiotic-loaded CS was performed in a patient with a healed tibia pseudoarthrosis (case 2). Incisional wound vac was used in three cases for a few days and no wound seroma was observed in any case.

This study is primarily limited by its retrospective nature and small sample size, as well as the lack of a group with COM managed by ACCIN to compare the outcomes.

TECHNIQUE

The standard procedure involved the removal of the infected implants (if any), copious irrigation, canal reaming, and injection of antibiotic-loaded CS (Stimulan; Biocomposites Ltd, Wilmington, North Carolina). All patients were prepared and draped in a standard sterile fashion. Surgical incisions were tailored to minimize soft-tissue disruption (Fig. 2).

Intramedullary canal reaming under fluoroscopy guidance with a serial increase in diameter is essential until the infected area is debrided. If further debridement is needed, a bone trough with minimal periosteal stripping over the targeted area in the metaphysis is made using a high-speed burr. Attention must be made not to remove more than one-third of the bone diameter.^{19–21} An angled curette together with the high-speed burr were used to access and debride all pockets of sequestrum under fluoroscopic guidance and to harvest samples for cultures (Fig. 3). Debridement, until punctuate cortical bleeding was achieved, was done under

Table 1: Demographics, Cierny-Mader classification, wound culture results, additional procedures, complications, and follow-up duration

Case	Age/sex	Bone affected	CCI	CM classification	Culture results	Number of previous procedures to eradicate infection	Previous procedures to eradicate infection	Additional procedures	Follow-up (months)	Outcome
1	59 M	Tibia	1	IB	Negative	2	Incision and drainage (twice)	—	25	FWB mobilization
2	17 F	Tibia	0	IA	MSSA	0	—	Prophylactic nailing	29	FWB mobilization
3	24 M	Femur	0	IA	MSSA	1	Incision and drainage	—	33	FWB mobilization
4	64 M	Tibia	3	IB	MRSA	1	Debridement + nail exchange with ACCIN	—	43	FWB mobilization
5	25 M	Tibia	0	IA	MRSA	1	Debridement + nail exchange with ACCIN	—	45	FWB mobilization
6	37 F	Tibia	3	IB	MRSA	0	—	—	25	FWB mobilization
7	39 M	Tibia	0	IA	Negative	0	—	—	25	FWB mobilization
8	57 M	Femur	2	IB	MRSA	0	—	—	25	Non-ambulatory (bed ridden)
9	55 M	Tibia	0	IA	MRSA	1	Removal of implant + debridement	—	24	FWB mobilization
10	73 F	Tibia	4	IB	MRSA	1	Debridement + antibiotic-coated nailing	—	49	FWB mobilization
11	52 M	Tibia	5	IB	MRSA	0	—	—	22	FWB mobilization
12	34 F	Tibia	5	IB	<i>Pseudomonas aeruginosa</i>	0	—	—	33	FWB mobilization
13	36 M	Femur	4	IB	MRSA	0	—	—	20	FWB mobilization
14	36 M	Tibia	0	IA	Negative	0	—	—	24	FWB mobilization

ACCIN, antibiotic-coated cement intramedullary nail; CCI, Charlson comorbidity index; CM, Cierny-Mader; F, female; FWB, full weight bearing; M, male; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*

direct visualization and using an image intensifier to reach all sclerotic areas (Fig. 4).

After thorough debridement, canal reaming and irrigation with a minimum of 6 L of normal saline were performed. In cases of an extensive debridement that might affect the stability or the occurrence of an iatrogenic fracture, prophylactic nailing (not reported in our series) can be performed after antibiotic-loaded CS canal injection. Re-preparation and re-draping of the patient were done in the same sterile fashion.

The antibiotic-loaded CS formula was prepared on a sterile table. For each 20.0 mL of CS, 1.0 gm of vancomycin and 0.6 gm of tobramycin were mixed. We used 80.0 mL of CS for the femur and



Fig. 2: Surgical incisions were modified to avoid areas with soft-tissue compromise (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)



Figs 3A to C: Under fluoroscopic guidance, an angled curette was used to reach all areas of the sequestrum through a cortical trough (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)

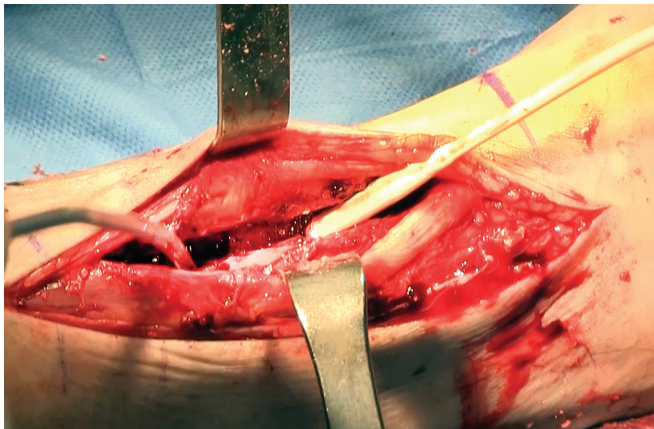


Fig. 4: A bony trough was made and a focused-light source was used to inspect for hidden pockets of necrotic tissue and to visualise the bleeding after curettage (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)

60 mL for the tibia. Therefore for tibia cases, 3.0 gm of vancomycin and 1.8 gm of tobramycin were used per case. The mix was loaded in the cement gun (Revolution Cement Mixing System; Stryker, Kalamazoo, Michigan). Using the humeral nozzle (preferred by the senior author for its small diameter) to inject the CS (Fig. 5), complete filling of the canal was achieved under fluoroscopic guidance by starting inferiorly and gradually backing out



Fig. 5: Cement injection gun loaded with an intramedullary nozzle inserted into the tibial intramedullary canal (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)

(Figs 6 and 7). Final radiographs were obtained with hardened CS. Regular wound closure was performed followed by the application of the regular sterile dressing.

The distal egress hole (the distal screw hole from the previous nail) was used in all 14 cases to allow inflow and outflow. Another option would be to use the reamer-irrigator-aspirator, but this was not used in the current series.

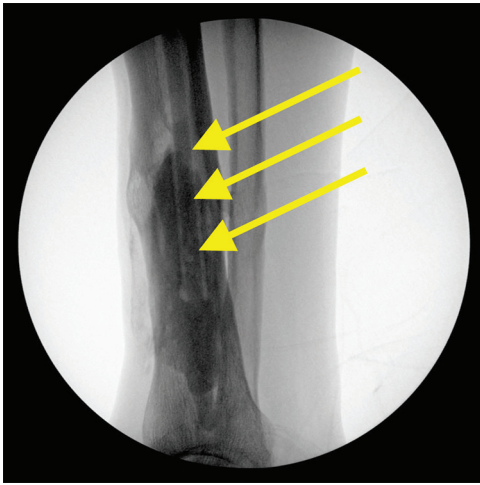


Fig. 6: Canal injection performed under fluoroscopic guidance, calcium sulfate is evident along the canal and filling the debrided intramedullary space (arrows) (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)



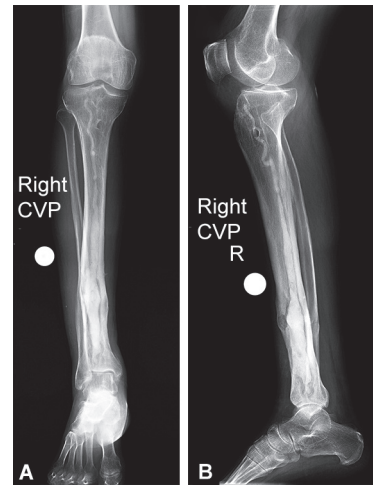
Fig. 7: Tibial canal filled with antibiotic-loaded calcium sulfate (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)

Video is available as supplemental content of a 57-year-old male patient with a distal tibia fracture treated with an intramedullary rod who presented to the authors' clinic with a draining medial sinus. The radiographs, surgical technique, and formula preparation are displayed in the video with narration from the senior author (Video 1).

Immediate weight-bearing as tolerated can be allowed depending on mechanical stability. Figure 8 show X-ray images taken 2 weeks after surgery with the tibial canal still filled with CS. Administration of intravenous antibiotics according to culture and sensitivity results followed for 6 weeks.

DISCUSSION

This case series highlighted antibiotic-coated CS as a single-stage procedure for the treatment of intramedullary COM in long bones. With its unique features, low mixing temperature, gradual elution



Figs 8A and B: (A) AP and lateral (B) View radiographs obtained 2 weeks postoperative demonstrating mild resorption of calcium sulfate (© 2021, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, used with permission)

profile, and predictable resorption time that eliminates the need for removal, this technique can counter the drawbacks of the antibiotic-impregnated PMMA usual techniques.^{12,15,22-24} In the current study, the presented series of antibiotic-coated CS showed a 100% remission rate with no recurrence during a minimum follow-up of 18 months (12 patients completed a minimal follow-up of 2 years, 1 patient had 20 months and 1 patient had 22 months). Additionally, there was no need for extra procedures for infection control or hardware removal, which is usually encountered with antibiotic-impregnated PMMA.^{8,16,25}

Persistent serous wound discharge as a side effect after the use of CS has been reported in several studies.^{6,7,22,26} Serous wound discharge is not necessarily associated with surgical site infection.^{6,11,26,27} In this case series, seroma was not observed in any case, which may be related to the proper technique, avoidance of canal overfilling, prophylactic usage of incisional wound vac in selected cases, less tobramycin and more vancomycin, or the usage of the synthetic CS rather than the conventional CS.²⁸⁻³¹ Pathological fractures following the use of CS may be a concern, given that CS does not provide any structural support due to its resorption. However, in this series using our described technique, we did not encounter any pathological fractures. Intramedullary nailing remains an option in case of iatrogenic fractures, mechanical compromise, or prophylactic fixation according to the surgeon's preference.

Single-stage treatment of COM with a variety of antibiotic-loaded calcium biocomposites has been reported in the literature (Table 2).^{10,11,26-33} Ferguson et al.¹¹ reported the outcomes of using tobramycin-loaded CS in 195 cases with COM (12 cases with CM type I, one with CM type II, 144 with CM type III, and 38 with CM type IV osteomyelitis). Only 18 cases (9.2%) experienced recurrent infection, and nine cases sustained postoperative fracture through the debrided segment of bone.¹¹ McNally et al.¹⁰ reported the outcomes of using gentamicin-loaded CS/hydroxyapatite biocomposite as a single-stage treatment for COM in a series of 100 patients with 105 infected bones, of which 78 had CM type III and 22 had CM type IV. Only four patients (4.0%) experienced recurrent infection, and three patients (3.0%) experienced postoperative

Table 2: Summary of studies using single-stage treatment of osteomyelitis with a variety of antibiotic-loaded calcium biocomposites

Year	Authors	Number of patients	Sex	Age (range) (years)	Affected bones	Type of antibiotic depot used	Complications	Infection recurrence	Follow-up
2002	McKee et al. ²⁶	25 (prospective)	M = 15, F = 10	43 (27–69)	Chronic osteomyelitis (16 patients with associated non-union); Humerus = 1, ulna = 3, femur = 6, tibia = 15	Calcium sulfate alpha-hemihydrate bone void filler incorporated with 4% tobramycin sulfate (OsteoSet-T, Wright Medical, Memphis, Tennessee, USA)	Refracture = 3/25, persistent non-union = 2/25, superficial wound necrosis = 1/25, persistent sterile draining sinus = 8/25	2/25	28 months (2–38 months)
2014	Ferguson et al. ¹¹	193 patients, 195 bones (prospective)	M = 150, F = 43	46.1 (16.1–82)	Chronic osteomyelitis; Tibia = 88, femur = 73, humerus = 10, ankle = 6, radius = 5, knee fusion = 4, pelvis = 4, calcaneum = 3, ulna = 1, forefoot = 1	OsteoSet-T	Fracture = 4.6%, early oozing = 18.5%	9.2%	3.7 years (1.3–7.1 years)*
2016	McNally et al. ¹⁰	100 patients (prospective)	M = 65, F = 35	51.6 (23–88)	Chronic osteomyelitis with 10 cases of infected non-union; Tibia = 38, femur = 24, humerus = 16, radius/ulna = 10, calcaneus = 3, clavicle = 2, fibula = 1, sacrum = 1, scapula + humerus = 1, femur + tibia = 1, tibia + talus = 3	175 mg gentamicin in 10 mL calcium sulfate/hydroxyapatite (Cerament, Bonesupport, Lund, Sweden)	Fracture = 3/100, sterile wound leakage = 6/100, persistent non-union = 2/100, bulky fasciocutaneous flap = 1/100, tibial ulceration = 1/100	4%	19.5 months (12–34 months)
2019	Andreacchio et al. ²⁷	12 (retrospective)	M = 8, F = 4	10.3 (2–15)	Chronic osteomyelitis; Clavicle = 1, humerus = 2, radius = 1, femur = 4, tibia = 3, IV metatarsal = 1	OsteoSet-T	None	None	Minimum 2 years (range 2–6 years); mean not reported

2020	Zhou et al. ³²	42 patients, 43 limbs (retrospective)	M = 24, F = 18	42 (12.8–77.5)	Type III osteomyelitis; Tibia = 43	0.5 gm vancomycin + 2 mL gentamicin + 5 cm ³ calcium sulfate (Stimulan, Biocomposites Ltd., Wilmington, North Carolina, USA)	Prolonged aseptic drainage = 13/43, joint stiffness = 1/38, fibrous scar formation = 2/38, slight pain after long distance walk = 4/38, limb weakness = 4/38, slight claudication = 1/38	11.6%	42.8 months (12.8–77.5 months)
2020	Zhang et al. ³³	19 (retrospective)	M = 15, F = 4	39 (2356)	Bone infection after intramedullary nailing; Femur = 7, tibia = 12	0.5 gm vancomycin + 2 mL gentamicin + 5 cm ³ calcium sulfate (Stimulan); total volume of calcium sulfate per patient <50 mL	Prolonged aseptic drainage = 7/19, refracture = 1/19, joint stiffness = 1/19	5.3%	38.1 months (24–55 months)
2020	Current study	10 (retrospective)	M = 7, F = 3	29 (18–45)	Chronic osteomyelitis; Femur = 2, tibia = 8	Total volume = 60.0 mL of calcium sulfate was injected (3.0 gm vancomycin and 1.8 gm tobramycin)	None	None	45 years (17–73 years)

F, female; M, male; *Seven patients died during follow-up

fractures.¹⁰ Andreacchio et al.²⁷ reported the outcomes of using tobramycin-impregnated CS pellets for the treatment of COM in 12 paediatric patients with a 100% remission rate without recurrence or postoperative fracture.²⁷

In their series of 25 patients, McKee et al.²⁶ demonstrated that tobramycin-loaded CS is as effective as PMMA in the treatment of COM.²⁶ In our series, all patients were treated with a standard dose of 1.0 gm of vancomycin and 0.6 gm of tobramycin for each 20.0 mL of CS injection. The synergistic effect of these two antibiotics in addition to their broad microbial coverage makes them a good combination.^{6,34} Vancomycin is the antibiotic of choice for methicillin-resistant *Staphylococcus aureus* (MRSA), and 60% of the culture results of patients in our series were positive for MRSA. Previous studies using CS as the vehicle for local antibiotic delivery have used a single antibiotic.^{6,11,22,27} Recently, Zhou et al.³² retrospectively studied 43 tibiae with CM type III COM managed by debridement and vancomycin/gentamicin-loaded CS implantation with a remission rate of 88.4% without recurrence for a mean follow-up of 42.8 months.³² Zhang et al.³³ also presented a case series of 19 patients managed with intramedullary reaming, irrigation, and vancomycin/gentamicin-loaded CS implantation for treatment of infection after intramedullary nailing, with successful infection remission in 18 patients.³³

CONCLUSION

This retrospective study suggests that intramedullary injection of vancomycin- and tobramycin-loaded CS can be used as a single-stage procedure for the treatment of long bone intramedullary COM. Further studies are necessary to compare the long-term outcomes of antibiotic-coated CS vs other antibiotic carriers for infection eradication.

Clinical Significance

The authors have endeavoured to explain the best surgical technique to eradicate chronic osteomyelitis according to the senior author who has broad experience in the treatment of osteomyelitis.

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SUPPLEMENTARY MATERIAL

A supplemental video to this article is available online on the website of www.stlrjournal.com.

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