Can Local Antibiotics Affect Bone Union in Infected Bone Defects Treated with Degradable Bone Substitutes

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FUNDING

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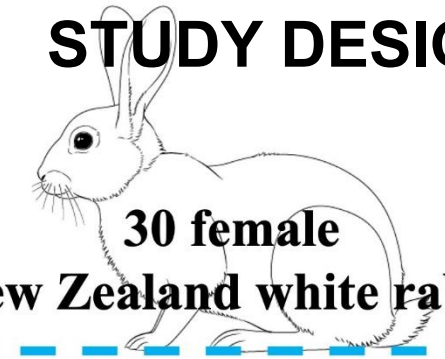
STUDY DESIGN



30 female
New Zealand white rabbit

Bone defect creation

Group assignment

AG

GB

Ab-GB

S. Epidermidis inoculation

S U R G E R Y

X-rays at 0, 4, 8, 12, and 16 weeks

Sacrifice
Femoral diaphysis explant
Tissue samples

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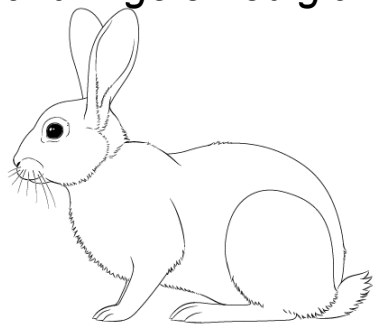
MATERIALS

Thirty female New Zealand white rabbits

Charles River Laboratories Italia S.R.L.
Sant'Angelo Lodigiano, Italy



Gentamicin (40 mg/mL) and Vancomycin (83.3 mg/mL solution obtained by diluting 500 mg of powder in 6 mL of saline)

Cylindric resorbable biomimetic scaffolds
D 10 mm X L 10 mm

GreenBone Ortho, Faenza, Italy

0.5×10^7 CFU/0.5 mL of S. epidermidis (ATCC® 12228TM)

LGC Standards,
Sesto San Giovanni, Italy

Stainless Steel 2.4 mm Locking-Compression Plate

Depuy Synthes Vet, Johnson & Johnson,
New Brunswick, NJ, USA

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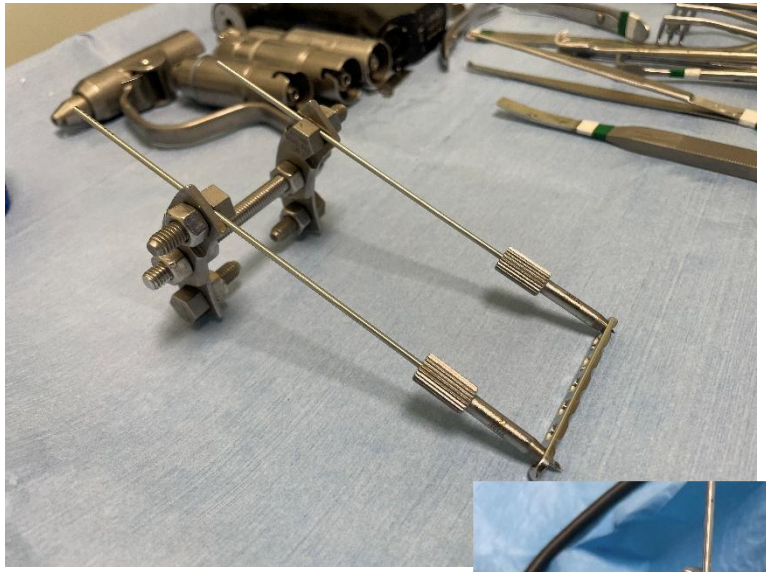
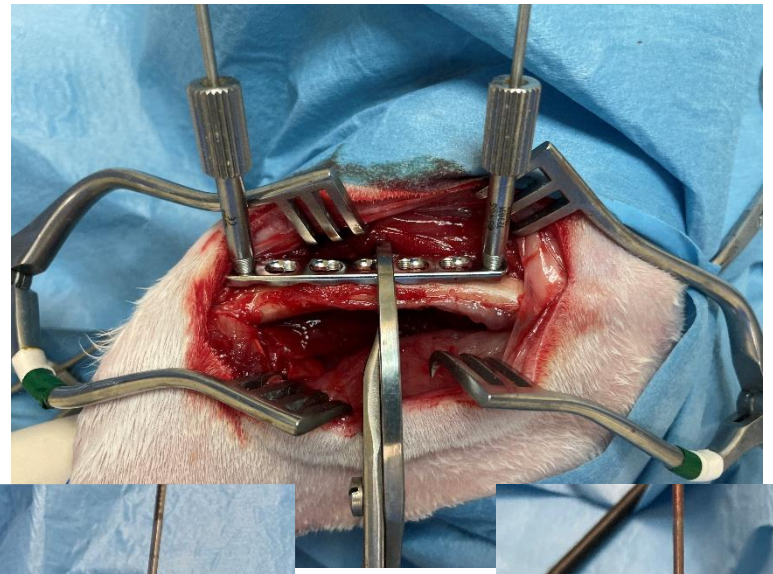
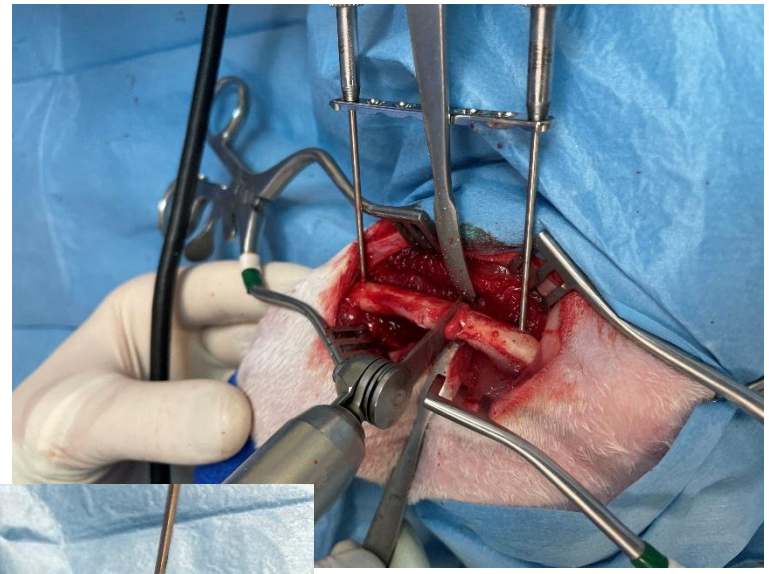
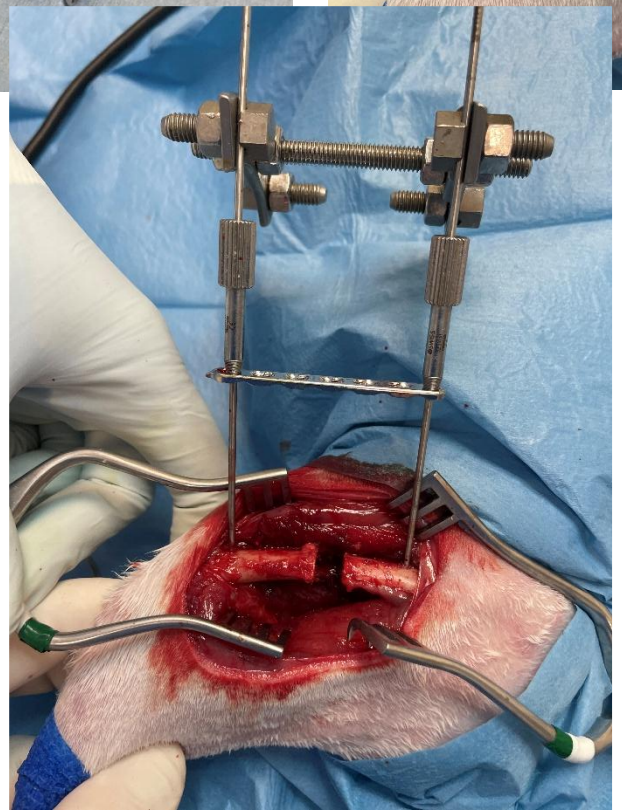
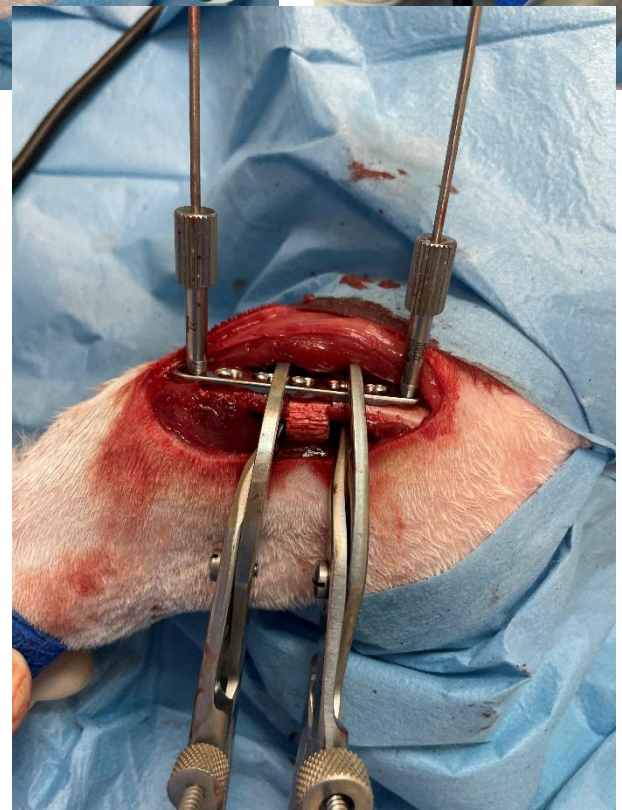
METHODS: surgical procedure











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METHODS

Histological examination

Tiemann, A. 2014 GMS Interdiscip. Plast. Reconstr. Surg. DGPW

Table 1. Histopathological Osteomyelitis Evaluation Score (HOES) template.

	Non-existent = 0	Mild = 1	Moderate = 2	Severe = 3
evaluation in a three-part step		$^1/_3$ of the section area	$^2/_3$ of the section area	the entire section area
A1: Osteonecrosis				
A2: Soft tissue necrosis				
A3: Granulocytic infiltration				
Sum of A1 to A3	$\geq 4 \rightarrow$ signs of acute osteomyelitis;			
C1: Bone neoformation/fibrosis				
C2: Lymphocytic–macrophagic infiltration				
Sum of C1 to C2	$\leq 1 \rightarrow$ no signs of osteomyelitis; $\leq 4 \rightarrow$ signs of subsided (calmed) osteomyelitis; $\geq 4 \rightarrow$ signs of chronic osteomyelitis;			
Sum of A1 to A3 and C1 to C2	≥ 6 signs of active chronic osteomyelitis.			

The table is not intended to present experimental results, but rather to illustrate the data collection framework applied during histological analysis. Therefore, numerical values and specific entries are not included, as the table has been filled out on a case-by-case basis during the evaluation process.

Table 2. Bone maturation grading system template.

Cortical	Intramedullary
0. Absence of newly formed bone.*	
1. Presence of discontinuous spicules of woven bone.	
2. Presence of both woven bone and lamellar bone:	
2a. Woven bone predominant over lamellar bone;	
2b. Woven bone and lamellar bone present in equal proportions;	
2c. Lamellar bone predominant over woven bone.	
3. Presence of lamellar bone only:	
3a. Partially compact Haversian systems with significant intracortical space between osteons;	3a. Trabecular bone; *
3b. Fully compact mature osteons with lamellar bone between osteons and little to no intracortical space.	3b. Trabecular bone with islands of bone marrow. *

* authors' modifications of the grading system.

Shapiro, F. 2021 Bone repair

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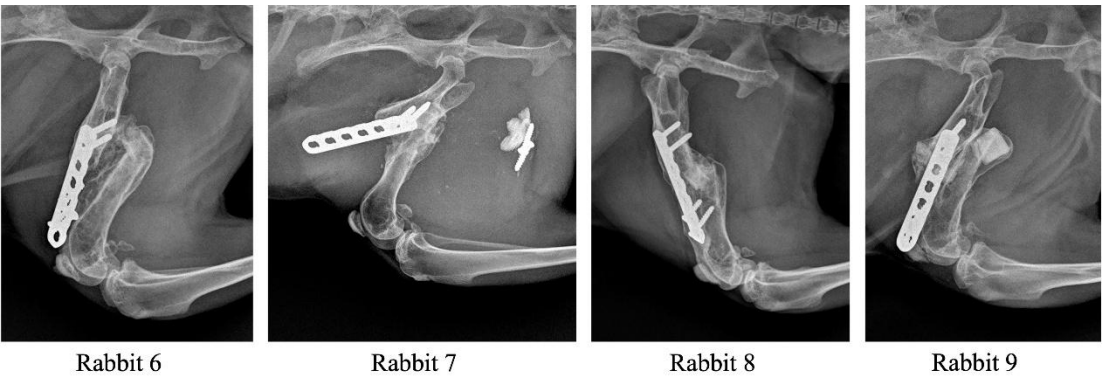
RESULTS

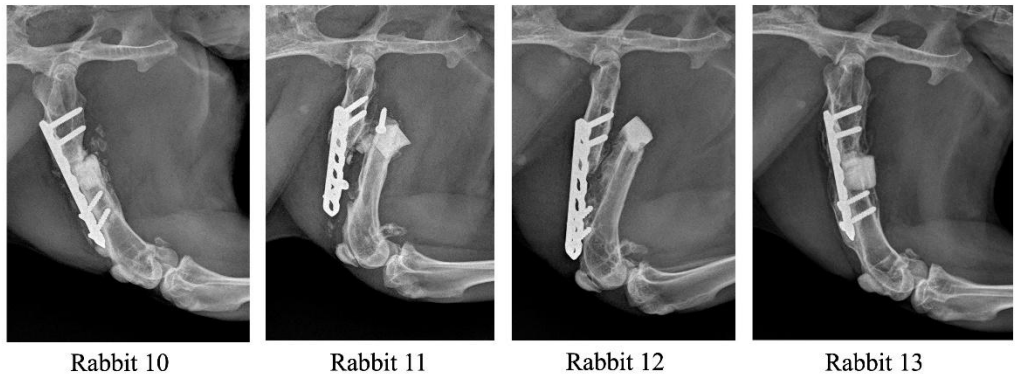
Mechanical *complications*

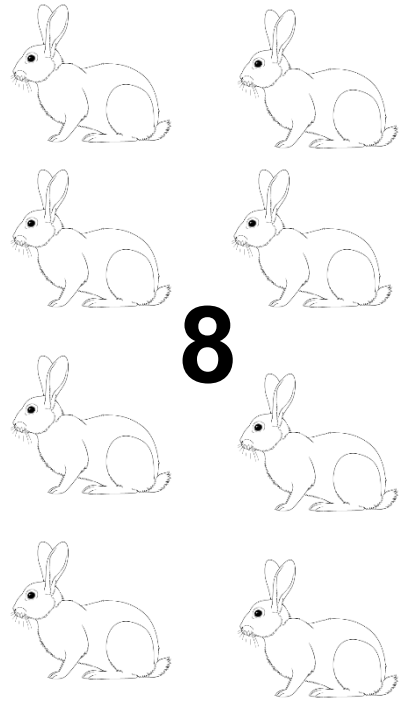
Cortex screws were inserted eccentrically in compression mode, to stabilize the plate to the distal fragment and further compress the scaffold in the defect.

87.5% developed non-union (vs 31.8%; *p* = 0.007)

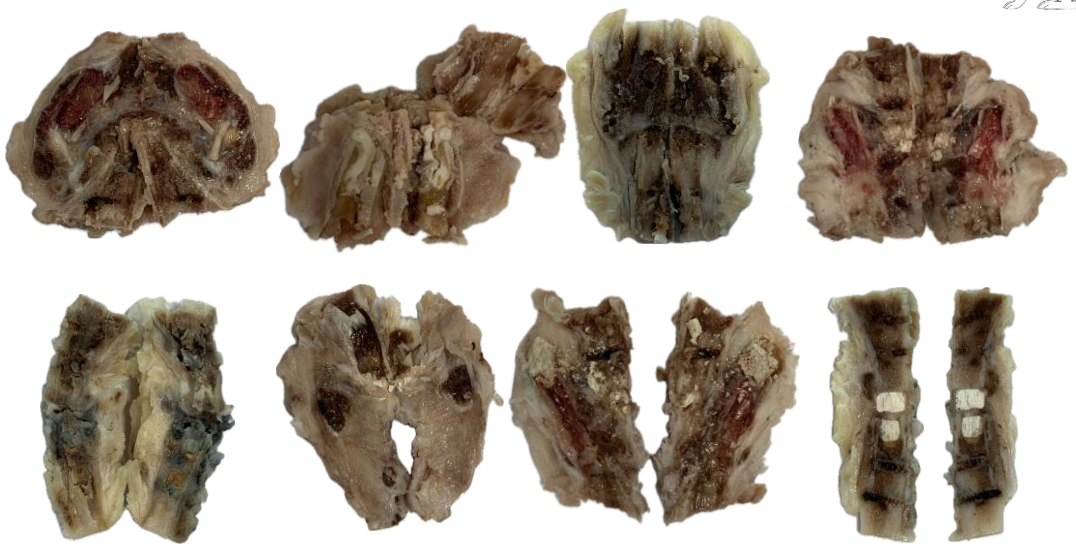
100% developed osteomyelitis, (vs 72.7%; p = 0.099)







Drop-out



Unbalanced fixation, characterized by a rigid proximal construct (locking screws) paired with a more flexible distal fixation (conventional screws)

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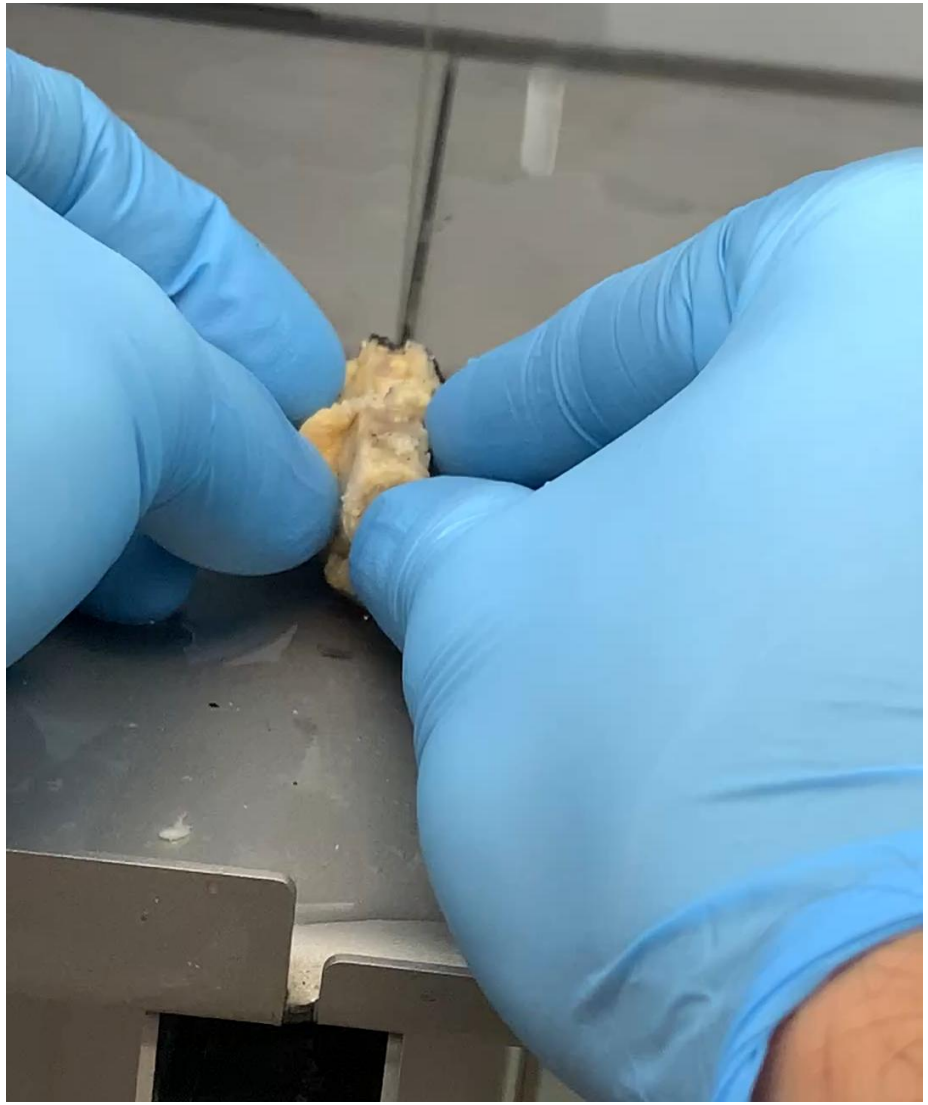
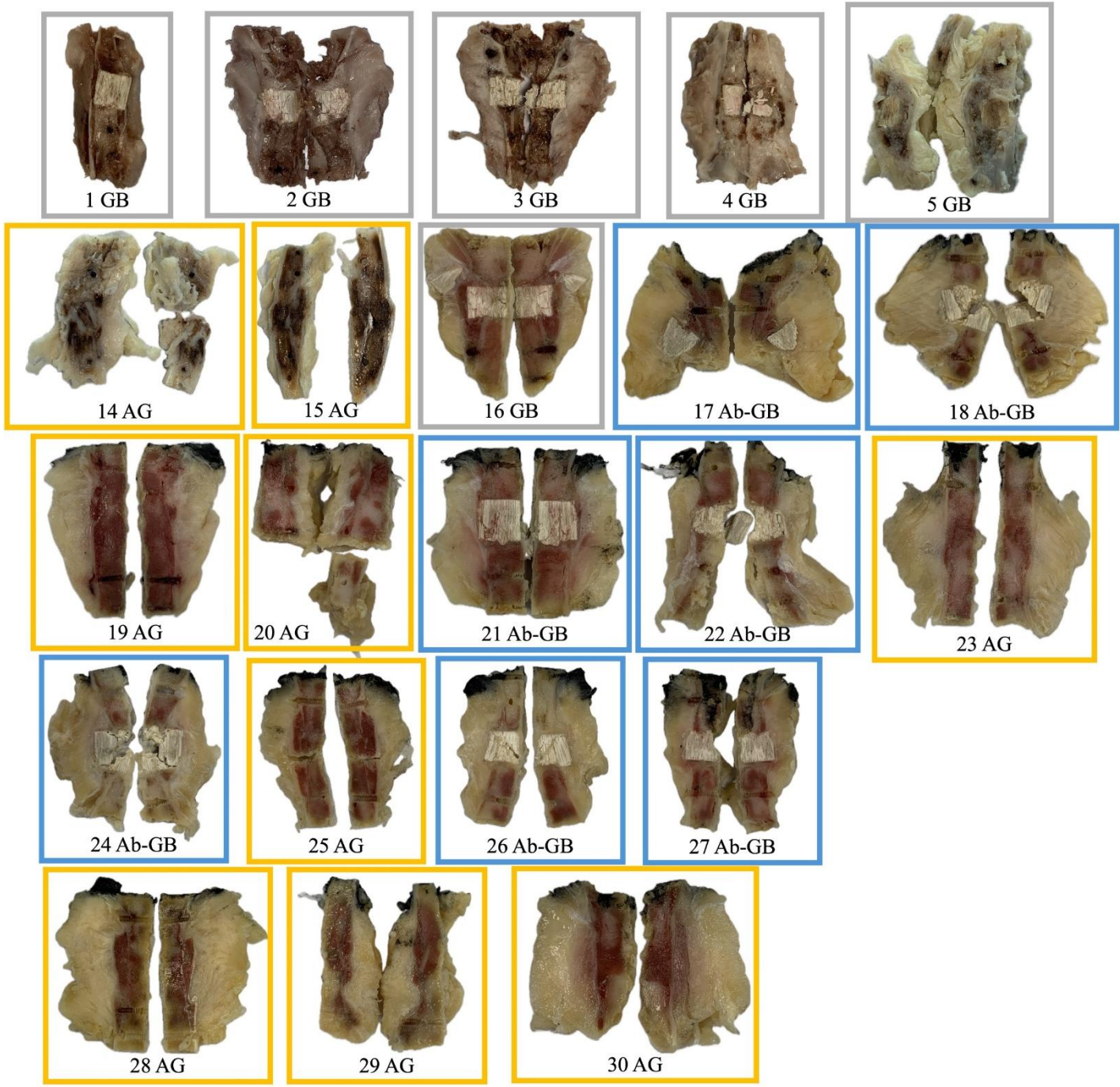
RESULTS





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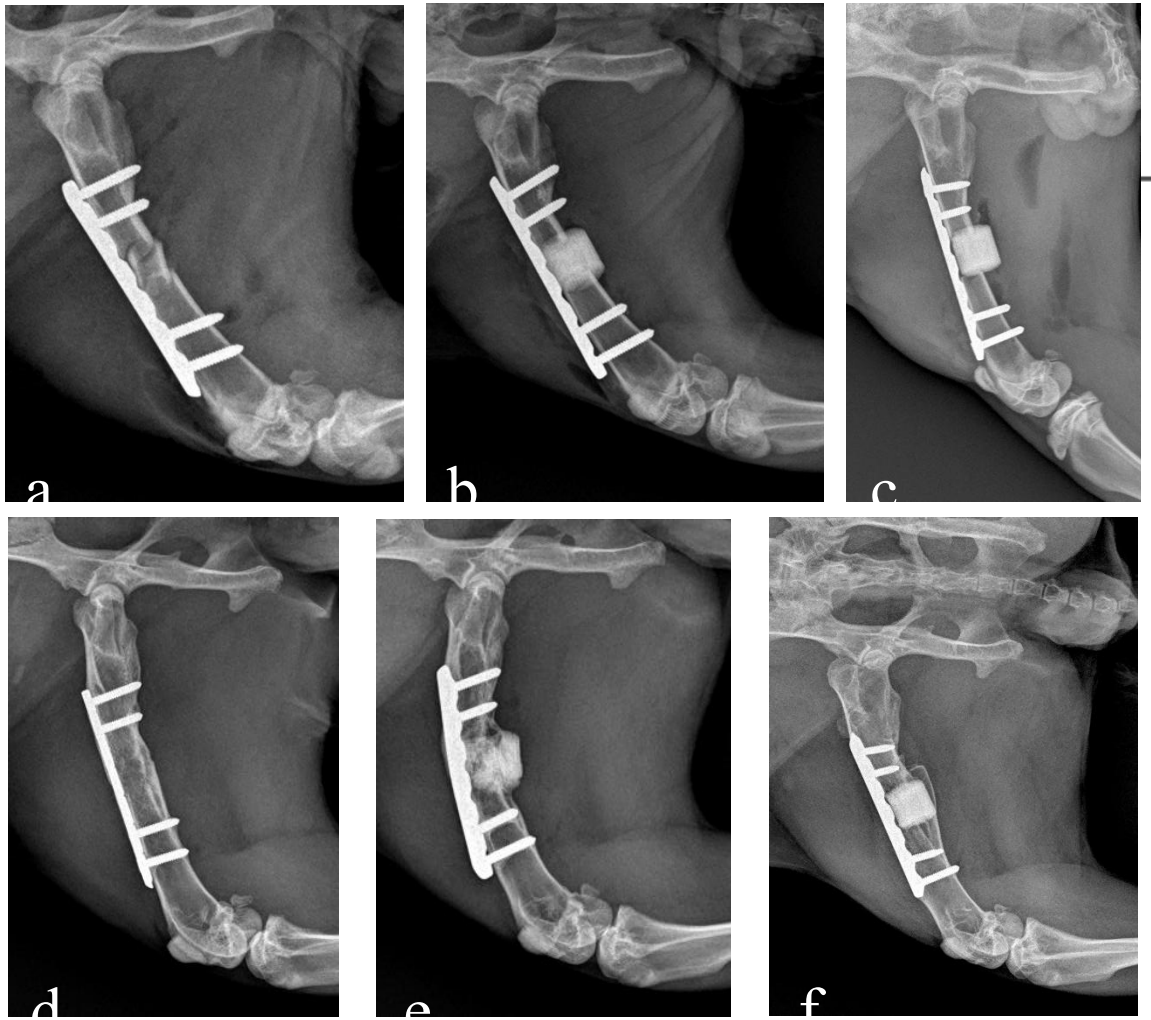
RESULTS

		Ab-GB ($n = 7$)	GB ($n = 6$)	AG ($n = 9$)
Bone union	Non-union	5	0	2
	Union	2	6	7
	Chronic OM	6	1	4
	Subsided OM	1	1	1
	Chronically florid OM	0	2	0
	No signs of OM	0	2	4



The **bone union rate** was significantly lower in the antibiotic-loaded group (28.6%) compared to the non-antibiotic-loaded groups (86.7%; p = 0.006).

There were no statistically significant differences in bone union rate between animals treated with the non-loaded scaffold and those treated with the allograft (p = 0.215)

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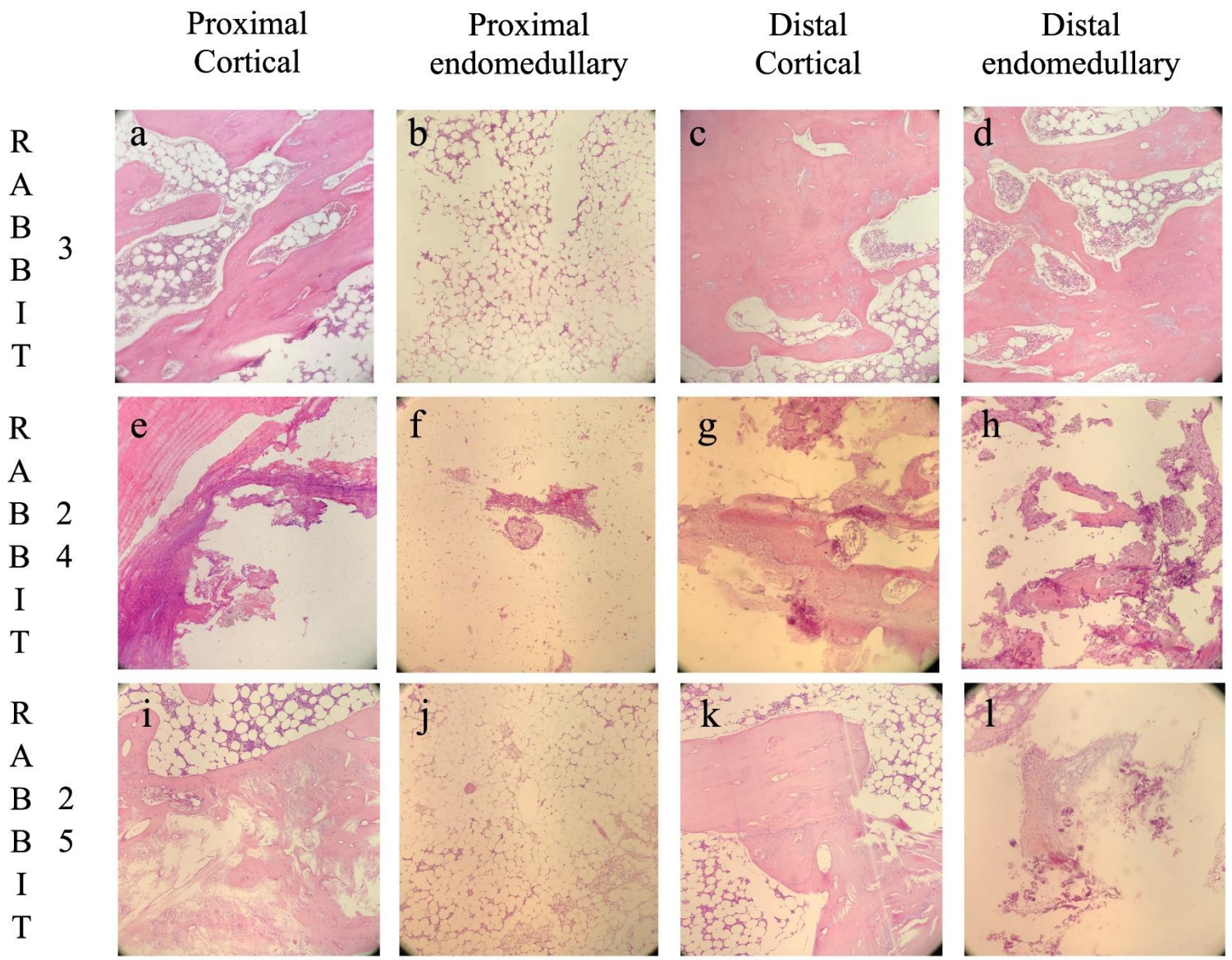
In the group of rabbits with antibiotic-loaded implants, we observed a higher **rate of osteomyelitis** (100%) compared to the rabbits with non-antibiotic- loaded implants (60%; $p < 0.05$).

No statistically significant differences were detected in the infection rate between the non-loaded scaffold group and the allograft group ($p = 0.667$).



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RESULTS

		Ab-GB ($n = 7$)	GB ($n = 6$)	AG ($n = 9$)
Bone maturation *	0	7	1	1
	1	6	0	0
	2a	3	0	0
	2b	1	1	1
	2c	4	9	5
	3a	0	3	0
	3b	6	9	29
	N/A	1	1	0

* $n > 22$ because every sample was analyzed in four different quadrants: proximal cortical area, proximal intramedullary area, distal cortical area, and distal intramedullary area. OM: osteomyelitis; AbGB: antibiotic-loaded GreenBone scaffold; GB: GreenBone scaffold; AG: allograft.

In the group of rabbits with antibiotic-loaded implants, we observed a lower **degree of bone callus maturation** (22.2% of HOES grade 3) compared to the rabbits with non-antibiotic-loaded implants (69.5% of HOES grade 3; $p < 0.001$)

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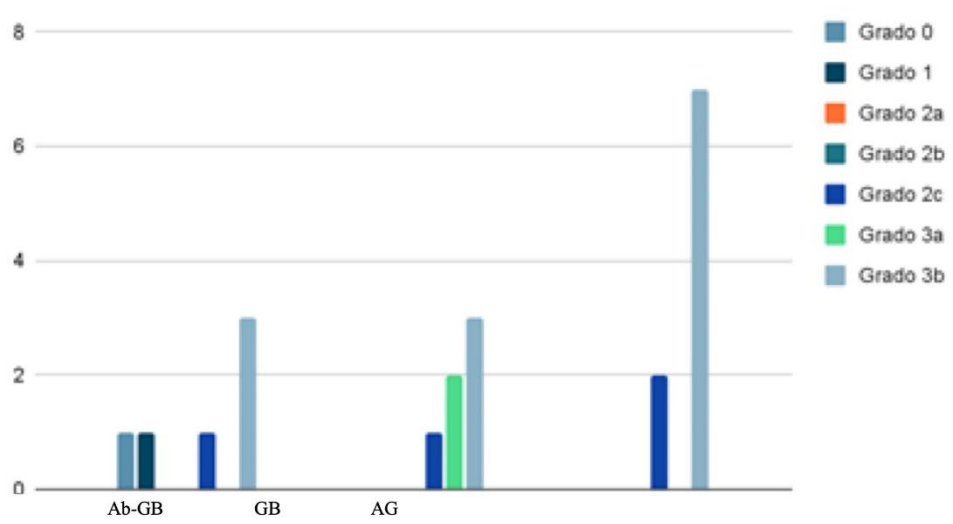
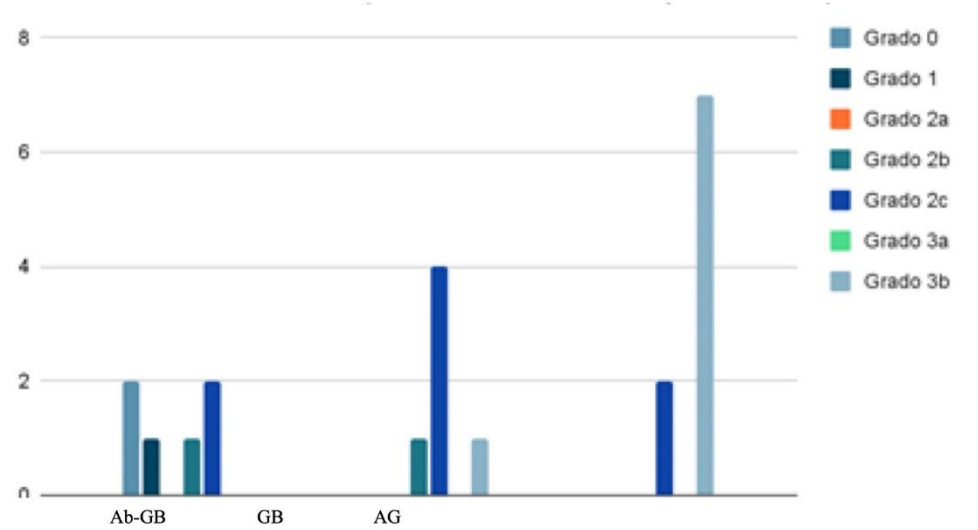
a



b



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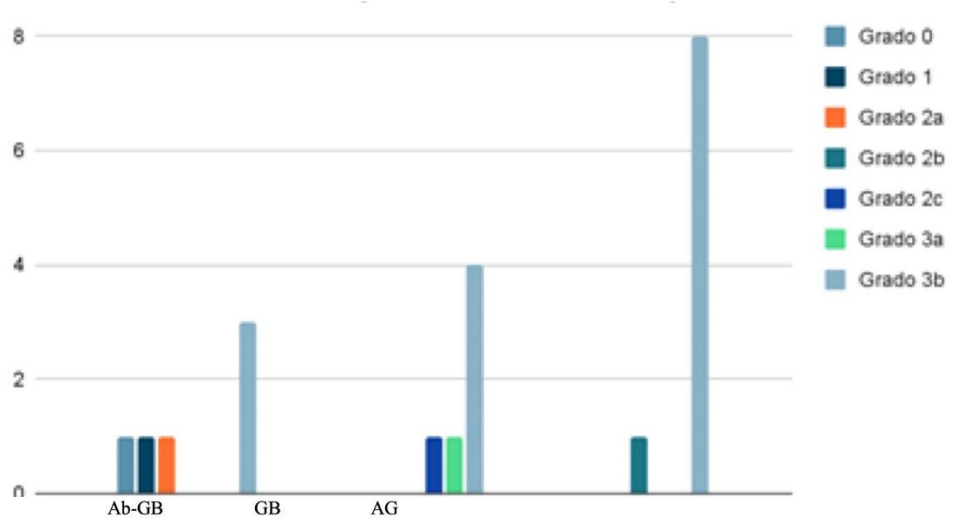
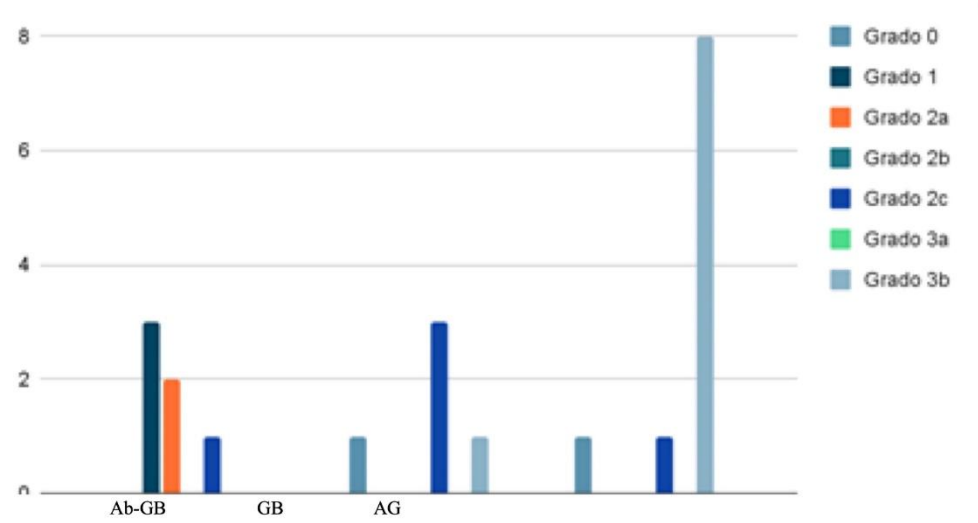


d



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RESULTS

		Ab-GB (n = 7)	GB+AG (n = 15)
Bone union	**Non-union, n = 7 (31.8%)**	5 (71.4%)	2 (13.3%)
p = 0.006	**Union, n = 15 (68.2%)**	2 (28.6%)	13 (86.7%)
Infection	**Chronic OM—n = 16 (72.7%)**	7 (100%)	9 (60%)
p < 0.05	**No signs of OM—n = 6 (27.3%)**	0	6 (40%)
Bone maturation *	**0–1**	13	2
p < 0.001	**2**	8	16
	3	6	41

* n > 22 because every sample was analyzed in four different quadrants: proximal cortical area, proximal intramedullary area, distal cortical area, and distal intramedullary area. OM: osteomyelitis; AbGB: antibiotic-loaded GreenBone scaffold; GB: GreenBone scaffold; AG: allograft.

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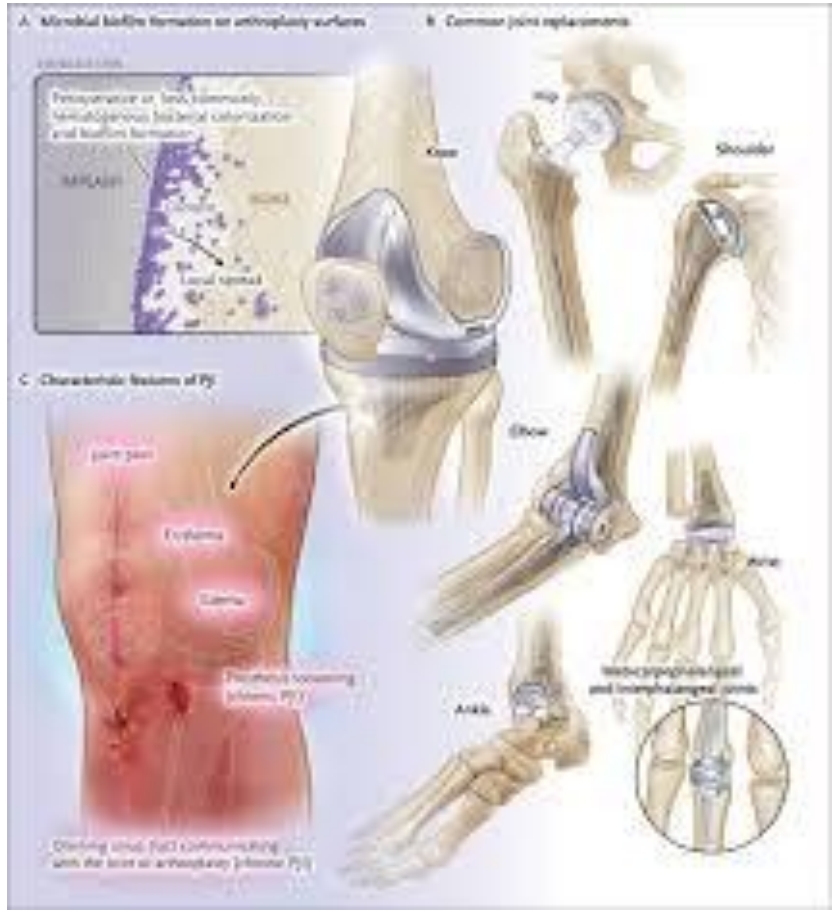
DISCUSSION

Many related studies have primarily focused on periprosthetic joint infection (PJI), and few investigations have addressed the specific problem of fracture-related infections (FRIs) where bone union is the priority.



Second INTERNATIONAL CONSENSUS MEETING (ICM) on MUSCULOSKELETAL INFECTION

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DISCUSSION

Expert Opinion

1. Introduction
2. Methods [107]
3. Results
4. Conclusion
5. Expert opinion

Review

In vitro and *in vivo* effects of antibiotics on bone cell metabolism and fracture healing

Rami Kallala, Simon Matthew Graham, Dariush Nikkhah, Margaritis Kyrkos, Manolis Heliotis, Athanassios Mantalaris & Eleftherios Tsiridis[†]

[†]*Aristotle University Medical School, Academic Department of Orthopaedics and Trauma, Thessaloniki, Greece*

Article highlights.

- At therapeutic concentrations seen with topical use of antibiotics in quinolones, aminoglycosides, cephalosporins and tetracyclines all interfere with bone cell function in animal and human models.
- Quinolones exhibit negative effects on fracture repair and bone strength in animal models and inhibit human bone cells *in vivo*. Cartilage and chondrocytes are particularly vulnerable, with implications for secondary bone healing via endochondral ossification.
- Tetracyclines (TCs) exhibit diverse effects on bone cells, improving bone density in osteoporotic animal models but exhibiting inhibitory effects on osteoclast function and in higher doses inducing apoptosis.
- Fracture callus resorption and bone remodelling in later stages of fracture healing rely on intact osteoclast populations; therefore, inhibition of osteoclast function or decrease in osteoclast number by TCs could prolong bone healing.

This box summarises key points contained in the article.

There is substantial evidence both in vitro and in vivo that antibiotics have several deleterious effects on bone healing and the mechanism of this effect varies depending on the class of antibiotic.

Kallala 2011 Expert Opin. Drug Saf

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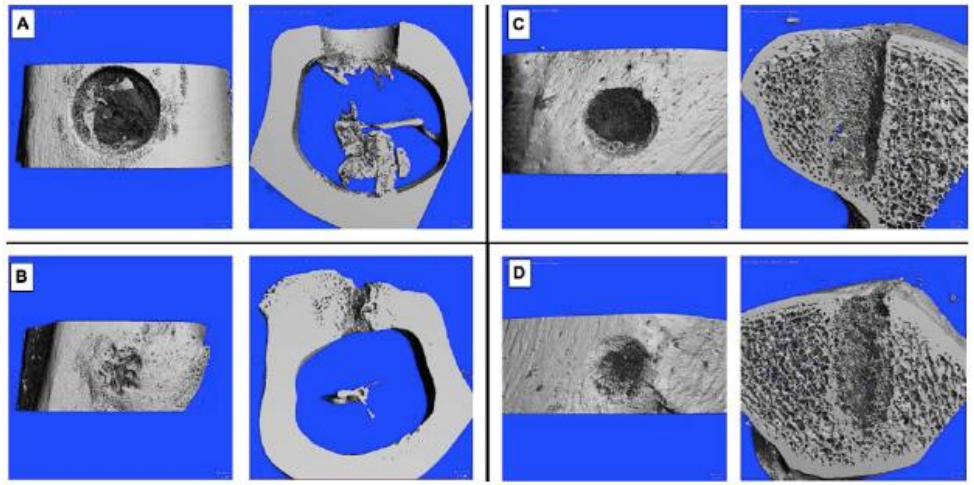
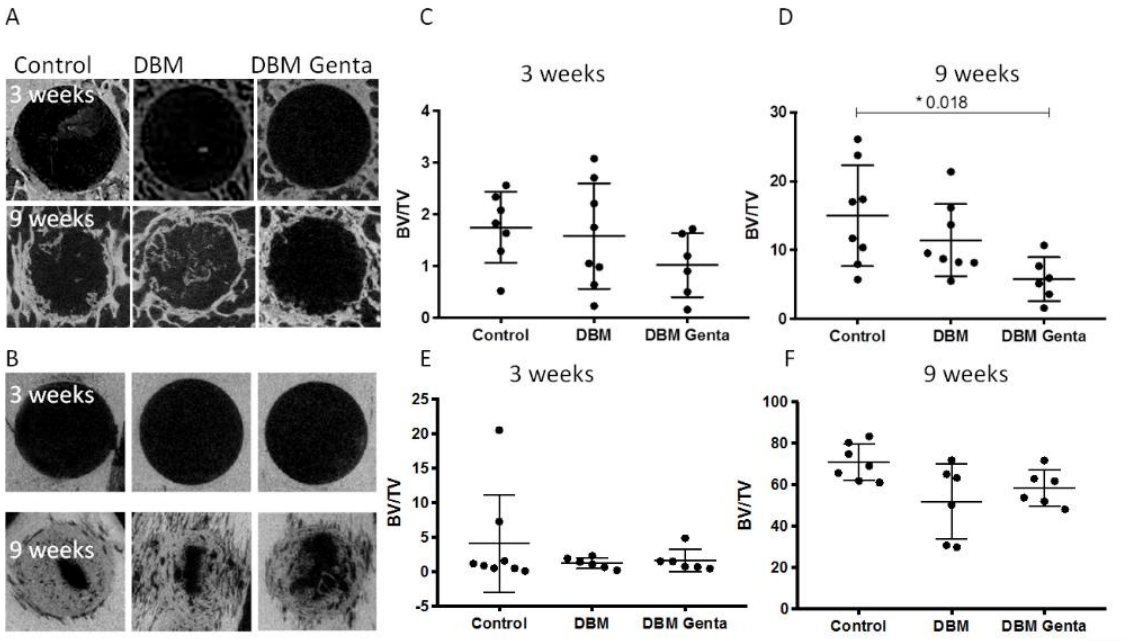
DISCUSSION





Impact of Gentamicin-Loaded Bone Graft on Defect Healing in a Sheep Model

Elisabeth Beuttel [1], Nicole Bormann [1], Anne-Marie Pobloth [1], Georg N. Duda [1] and Britt Wildemann [1,2,*]

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2 Experimental Trauma Surgery, University Hospital Jena, 07740 Jena, Germany

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Received: 7 March 2019; Accepted: 2 April 2019; Published: 4 April 2019

Abstract: Infections of bone are severe complications, and an optimization of grafting material with antimicrobial drugs might be useful for prevention and treatment. This study aimed to investigate the influence of gentamicin-loaded bone graft on the healing of bone defects in a sheep model. Metaphyseal and diaphyseal drill hole defects (diameter: 6 mm, depth: 15 mm) were filled with graft or gentamicin-loaded graft (50 mg/g graft) or were left untreated. Analysis of regeneration after three and nine weeks, micro-computed tomography (μCT), and histology revealed a significant increase in bone formation in the drill hole defects, which began at the edges of the holes and grew over time into the defect center. The amount of graft decreased over time due to active resorption by osteoclasts, while osteoblasts formed new bone. No difference between the groups was seen after three weeks. After nine weeks, significantly less mineralized tissue was formed in the gentamicin-loaded graft group. Signs of inflammatory reactions were seen in all three groups. Even though the applied gentamicin concentration was based on the concentration of gentamicin mixed with cement, the healing process was impaired. When using local gentamicin, a dose-dependent, compromising effect on bone healing should be considered.

materials

Beuttel 2019 Materials

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THE BONE & JOINT JOURNAL

■ GENERAL ORTHOPAEDICS

The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis

A SERIES OF 195 CASES

J. Y. Ferguson,
M. Dudareva,
N. D. Riley,
D. Stubbs,
B. L. Atkins,
M. A. McNally

From The Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford, United Kingdom

We report our experience using a biodegradable calcium sulphate antibiotic carrier containing tobramycin in the surgical management of patients with chronic osteomyelitis. The patients were reviewed to determine the rate of recurrent infection, the filling of bony defects, and any problems with wound healing. A total of 193 patients (195 cases) with a mean age of 46.1 years (16.1 to 82.0) underwent surgery. According to the Cierny–Mader classification of osteomyelitis there were 12 type I, 1 type II, 144 type III and 38 type IV cases. The mean follow-up was 3.7 years (1.3 to 7.1) with recurrent infection occurring in 18 cases (9.2%) at a mean of 10.3 months post-operatively (1 to 25.0). After further treatment the infection resolved in 191 cases (97.9%). Prolonged wound ooze (longer than two weeks post-operatively) occurred in 30 cases (15.4%) in which there were no recurrent infection. Radiographic assessment at final follow-up showed no filling of the defect with bone in 67 (36.6%), partial filling in 108 (59.0%) and complete filling in eight (4.4%). A fracture occurred in nine (4.6%) of the treated osteomyelitic segments at a mean of 1.9 years (0.4 to 4.9) after operation.

We conclude that Osteoset T is helpful in the management of patients with chronic osteomyelitis, but the filling of the defect in bone is variable. Prolonged wound ooze is usually self-limiting and not associated with recurrent infection.

Cite this article: ***Bone Joint J*** **2014; 96-B:829–36**

J. Y. Ferguson, MRCS, MEd, Specialist Registrar
N. D. Riley, FRCS Orth,

variable.[38,39] There was no filling of the defect in 67 cases (36.6%) at final follow-up. This is similar to that reported by Chang et al,[29] who found bony ingrowth in only 40% one year post-operatively.[29] This may be due to the relatively quick dissolution of the calcium sulphate, not allowing sufficient time for new bone to form before it is absorbed. Also, there is concern that the high levels of tobramycin may inhibit mesenchymal stem cells, thereby preventing osteogenesis.[40]

Ferguson 2014 Bone Jt J

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biomedicines

MDPI

Article

"Anti-Bios": Can Local Antibiotics Affect Bone Union in Infected Bone Defects Treated with Degradable Bone Substitutes

Filippo Vandenbulcke [1,2,*], Salvatore Lorenzo Renne [1,2], Giuseppe Anzillotti [1,2], Pietro Conte [1,2], Giuliano Ravasio [3,4], Gabriele Meroni [5], Federica Riva [6] and Elizaveta Kon [1,2]

Preliminary osteogenic and antibacterial investigations of wood derived antibiotic-loaded bone substitute for the treatment of infected bone defects

Francesca Salamanna[1], Angela De Luca[1]*, Filippo Vandenbulcke[2,3], Berardo Di Matteo[2,3,4], Elizaveta Kon[2,3], Alberto Grassi[5], Alberto Ballardini[6], Giacomo Morozzi[6], Lavinia Raimondi[1], Daniele Bellavia[1], Viviana Costa[1], Stefano Zaffagnini[5], Milena Fini[7] and Gianluca Giavaresi[1]

[1]Surgical Science and Technologies, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy, [2]Department of Biomedical Sciences, Humanitas University, Milan, Italy, [3]IRCCS Humanitas Research Hospital, Milan, Italy, [4]Department of Traumatology, Orthopaedics and Disaster Surgery, Sechenov University, Moscow, Russia, [5]2nd Orthopedic and Traumatologic Clinic, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy, [6]GreenBone Ortho SpA, Faenza, Italy, [7]Scientific Direction, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

JEO Journal of Experimental Orthopaedics — Open Access — THE OFFICIAL OPEN ACCESS JOURNAL OF ESSKA

Vandenbulcke *et al.*
Journal of Experimental Orthopaedics (2023) 10:77
https://doi.org/10.1186/s40634-023-00644-6

Journal of Experimental Orthopaedics

ORIGINAL PAPER — Open Access

External fixator-assisted plating osteosynthesis in a rabbit model of femoral bone defects appears to be a feasible and reproducible surgical technique: preliminary insights from a bone substitute study

F. Vandenbulcke[1,2*], G. Anzillotti[1,2], G. Ravasio[3,4], E. Malagoli[2], P. Conte[1,2], B. Balzarini[1,2], A. Kirienko[2] and E. Kon[1,2]

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Ethics Statement

The animal study protocol was approved by the Institutional Review Board “University of Milan Animal Welfare Organisation” (OPBA n. 17/2019-UT). The animals were regularly checked by a certified veterinarian responsible for health monitoring and animal wellbeing supervision. All surgical procedures were performed under general anesthesia, and all efforts were made to minimize suffering.

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