Antibiotic cement-coated rods to control infection in infected nonunion of the humerus

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ABSTRACT

Objective: To evaluate the efficiency of antibiotic cement-coated rods (ACCR) to eradicate infections in infected nonunion of the humerus (INH). **Materials and methods:** We included 11 patients with INH with a mean age of 48 years. The time from fracture to surgery was 25 months. The ACCR was impregnated with vancomycin in 9 of 11 cases. Follow-up was 54 months. **Results:** Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in 5 cases. All patients received systemic antibiotic treatment for 7 weeks. Vancomycin was the most commonly used antibiotic. Time from ACCR placement to reconstructive surgery averaged 56 days [confidence interval range (CIR) 47-98]. After debridement and implant removal, the residual deformity of the nonunion was measured with dichotomous variables and classified into two groups: group 1, <2 cm (7 patients) and group 2, ≥2 cm (4 patients). No significant differences were observed between the number of days from placement of the ACCR to the development of the MRSA infection, compared to other pathogens [48 days (CIR 45-75) vs. 73 days (CIR 56-149) p = 0.2002, Mann-Whitney U test], nor were differences observed in the size of the defect in those who developed a MRSA infection or by any other pathogen (p = 0.242, Fisher's exact test). Reconstruction was performed with different techniques. Laboratory parameters were normal, and cultures were negative. Fractures achieved consolidation without recurrence of the infection. **Conclusions:** ACCRs are an adequate treatment option for patients with an INH. The infection was controlled in all cases, which allowed for the secondary reconstruction of the nonunion.

Key words: Nonunion; humerus fracture; antibiotic rod; infection; intramedullary rod; reconstruction.
Level of evidence: IV

Clavo endomedular recubierto con antibiótico para controlar la infección en una seudoartrosis infectada de húmero

RESUMEN

Objetivo: Comunicar la eficacia del clavo endomedular recubierto con antibiótico (CERA) para erradicar la infección en la seudoartrosis infectada de húmero (SIH). **Materiales y Métodos:** Once pacientes (edad promedio 48 años). El tiempo entre la fractura y la cirugía fue 25 meses. El CERA se impregnó con vancomicina en 9 pacientes. El seguimiento promedio fue de 54 meses. **Resultados:** Se aisló *S. aureus* resistente a meticilina (SARM) en 5 pacientes. Todos recibieron antibióticos sistémicos por 7 semanas. El antibiótico más utilizado fue vancomicina. La mediana entre el primer tiempo quirúrgico y la reconstrucción fue 56 días (RIC 47-98). Luego del desbridamiento quirúrgico del primer tiempo, se midió el defecto óseo remanente y se lo dividió con variables dicotómicas: grupo con defectos <2 cm (7 pacientes) y grupo con defectos ≥2 cm (4 pacientes). No se observaron diferencias significativas entre la mediana de días entre el primero y segundo tiempo quirúrgico comparando el desarrollo de SARM con el de otros gérmenes (48 días [RIC 45-75] vs. 73,5 días [RIC 56-149], p = 0,2002 Mann-Whitney), ni en la proporción del tamaño del defecto óseo según el desarrollo de SARM o de otro germen (60% vs. 17%, p = 0,242 Fisher). Todos los cultivos fueron negativos y se logró la consolidación del foco fracturario, sin recurrencia de la infección. **Conclusiones:** El CERA es una buena opción terapéutica en el primer tiempo quirúrgico para un paciente con SIH. Se pudo controlar la infección, lo que permitió la reconstrucción secundaria de la seudoartrosis.

Palabras clave: Seudoartrosis; fractura de húmero; espaciador de cemento; infección; clavo endomedular; reconstrucción.
Nivel de Evidencia: IV

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INTRODUCTION

Treatment of infected long-bone nonunions represents a critical situation for orthopedists.

The combination of mechanical instability and infection of the nonunion site creates an unfavorable setting for fracture consolidation.[1,2] In addition, this condition is related to limited fixation options, poor functional results and increased morbidity.

Therefore, from a multidisciplinary approach, the treatment requires a balance between fixation method, adequate management of soft tissues and specific antibiotic treatment with the purpose of eradicating infection and achieving fracture consolidation.[3]

Treatment of infected nonunions usually involves a two-stage procedure.[4,5] The first stage is the removal of the osteosynthesis material, surgical debridement—in many cases, with local antibiotic treatment—, and administration of specific systemic antibiotics to turn an infected nonunion into an aseptic one. The second stage includes reconstruction and mechanical stabilization with the ultimate goal of fracture consolidation.

Different authors have promoted the use of antibiotic cement-coated intramedullary rods (ACCR) as a simple, low-cost and effective treatment, since they fill the dead space, provide a high local concentration of the antibiotic agents, and allows mechanical stability on the fracture site.[4,5]

Several studies have reported the results of this approach in the lower limb, but there are few publications on the treatment of infected nonunion of the humerus (INHs).[6]

The aim of this study is to report the effectiveness of ACCRs in eradicating infection in INHs.

MATERIALS AND METHODS

We retrospectively evaluated patients with shaft INHs operated on in our Department. Inclusion criteria were as follows: shaft nonunion of the humerus initially treated with surgical placement of an ACCR, without radiologic evidence of consolidation six months after surgery, presence of fracture site pain, abnormal acute phase reactants (C-reactive protein, erythrocyte sedimentation rate and white cell count) on lab tests, positive nonunion site cultures (performed by biopsy), and a minimum follow-up of one year. The exclusion criteria were a follow-up <1 year and lack of compliance to treatment.

Eleven patients were included (6 men and 5 women, average age 48 years [range 23-66]). None was lost to follow-up. Seven patients had a left humerus fracture, and the dominant limb was affected in six cases. Table 1 provides patient details.

Table 1. Patient details

Patient	Sex	Age	High/low energy	Comorbidities	Original fixation	Cierny-Mader classification system
1	M	38	H	None	External fixator	4A
2	F	59	L	Smoking, diabetes, hypothyroidism	Intramedullary rod	4B
3	M	42	H	Smoking	Plate	4B
4	M	48	H	No	Plate	4A
5	M	23	H	Smoking, obesity, marijuana use	Intramedullary rod	4B
6	F	58	L	Smoking, obesity, high blood pressure	Plate	4B
7	F	39	L	Diabetes, obesity	Intramedullary rod	4B
8	M	36	H	Smoking	Intramedullary rod	4B
9	F	66	L	Smoking, Parkinson's disease	Plate	4B
10	F	57	L	Renal artery stenosis	Plate	4B
11	M	61	L	No	Intramedullary rod	4A

M: male; F: female.

The average time between fracture and surgery was 25 months (range 6-120), and the average number of previous surgeries was 1.6 (range 1-4). The initial fracture had been fixed by different approaches (Table 1). All nonunions were atrophic.

Patients were classified according to the clinical and radiologic Cierny-Mader classification of osteomyelitis[7] (Table 2): 8 patients were IVB and 3 were IVA.

All were operated on by the same surgeon (GG) and the average follow-up was 54 months (range 12-145). A statistical analysis of the results was performed.

Table 2. Cierny-Mader classification of osteomyelitis.

Anatomic type		
1	Medullary	Limited to the medullary canal
2	Superficial	Superficial cortical bone infection due to poor coverage
3	Localised	Cortical bone sequestrum that can be debrided without compromising stability
4	Diffuse	Any of the above combined with mechanical instability (before or after debridement)
Physiological class (host)		
A	Normal	Good immune system
B	Compromised	Local or systemic factors compromising immunity
C	Suppressive	Minimal disability or surgical contraindication

Type + class: clinical stage.

Surgical approach

With the patient in the dorsal decubitus position, under general and local anesthesia, the osteosynthesis material and necrotic tissue were removed, after which the medullary canal was progressively milled and a thorough washout was performed. Finally, the ACCR was placed by an antegrade (7 cases), a retrograde (3 cases) and a nonunion site (1 case) approach.

Rod preparation was previously reported.[8] A 40 French plastic chest tube (Atrium Medical Corp, Hudson, NH, USA) was used and cut to the length of the rod to be inserted. The antibiotic agent was mixed with a dose of polymethylmethacrylate powder (DePuy Inc., Warsow, IN, USA). With the help of a bone cement gun, cement was introduced into the tube. Then a 4.5 mm. Ender rod was introduced into the tube, allowing the cement to wrap around it. After cement setting, the tube was cut longitudinally and the rod was introduced into the medullary canal (Figure 1).

RESULTS

The most frequently isolated pathogen (5 cases) was methicillin-resistant *Staphylococcus aureus* (MRSA). The antibiotic agent introduced in the cement in most cases was vancomycin (9 cases). All patients received specific systemic antibiotic treatment, depending on the isolated pathogen, for an average of 7 weeks (range 4-12). The most commonly used antibiotic was catheter-delivered vancomycin (8 patients).

The median interval between the first surgical stage and the reconstruction procedure was 56 days (interquartile range [IQR] 47-98). After the first-stage surgical debridement, the residual bone defect was measured and divided by dichotomous variables: a first group comprised by defects measuring <2 cm (7 patients) and a second group comprised by defects measuring ≥2 cm (4 patients) (Table 3).

Patients kept the rod for an average of 3 months (range 1-13). No significant differences were observed between the median interval of days elapsed between the first and second surgical stage comparing the development of MRSA with that of infections by other pathogens (48 days [IQR 45-75] vs. 73.5 days [IQR 56-149]; p = 0.2002, Mann-Whitney U test). No significant differences were found on bone defect size related to the development of MRSA or infections by other pathogens (60% vs. 17%, p = 0.242, Fisher's exact test).

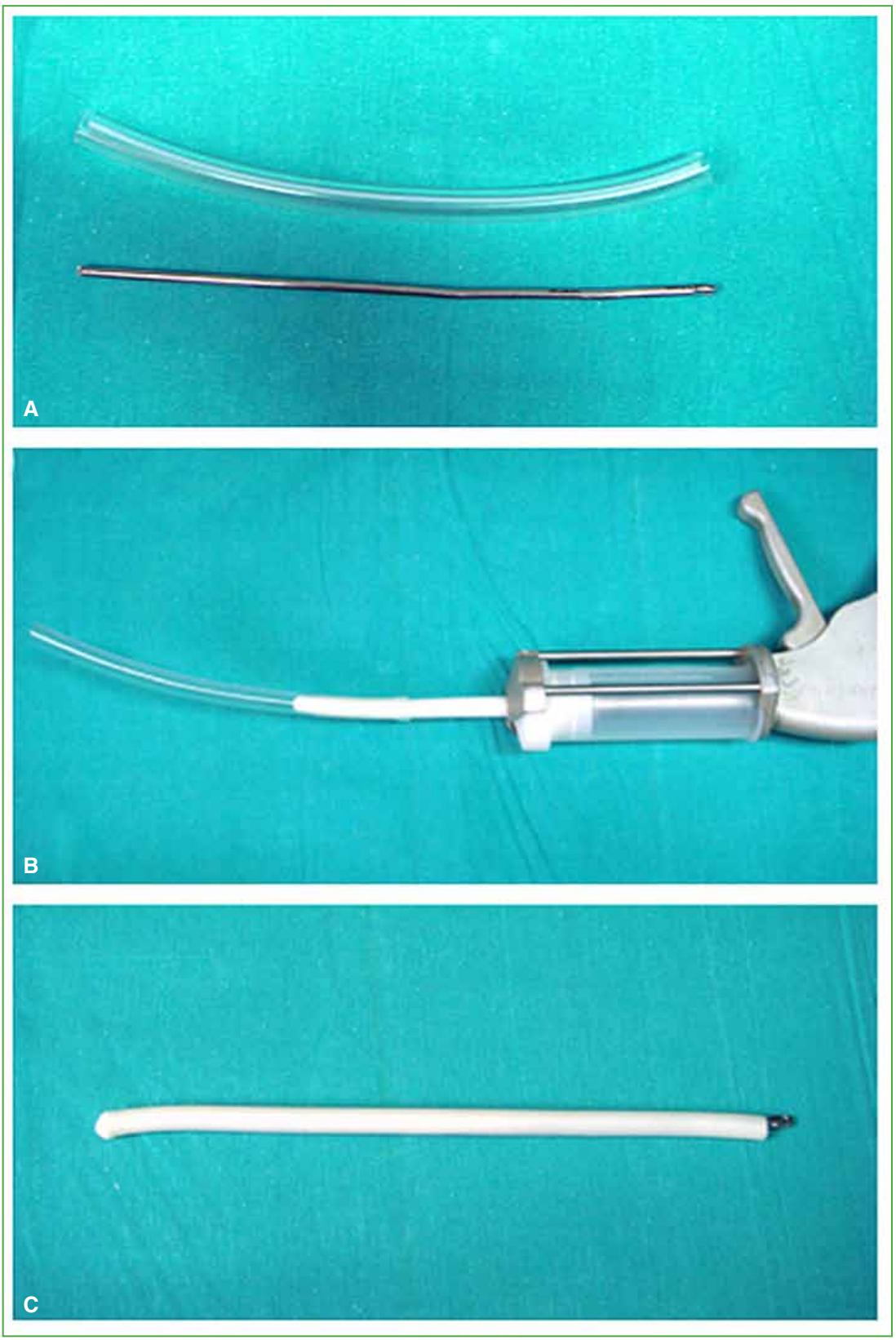

Figure 1. **A.** 40 French plastic tube, cut to the size of the rod. **B.** A gun was used to introduce the cement into the tube. **C.** Once the cement set, the tube was removed by cutting it longitudinally.

Table 3. Results

Patient	Pathogen	Antibiotic mixed with cement	Residual bone defect	Post-operative antibiotic agent	Time between first and second surgical stage (days)
1	MSSA	Vancomycin	<1 cm	Cefalotin for 4 weeks	47
2	Coagulase-negative *Staphylococcus*	Gentamicin	<1 cm	Vancomycin-rifampin for 12 weeks	91
3	MRSA	Teicoplanin-vancomycin	<1 cm	Vancomicina-rifampicina x 12 semanas	98
4	MRSA	Vancomycin	2 cm	Teicoplanin for 8 weeks	33
5	MSSA	Gentamicin-vancomycin	<1 cm	Ceprofloxacin-ciprofloxacin for 6 weeks	56
6	*Staphylococcus epidermidis*	Vancomycin	3	Vancomycin for 6 weeks	411
7	*Enterobacter cloacae*	Vancomycin	<1 cm	Vancomycin-ciprofloxacin for 8 weeks	149
8	MRSA	Teicoplanin	3	Vancomycin-rifampin for 6 weeks	75
9	MRSA	Vancomycin	5	Vancomycin-ciprofloxacin for 4 weeks	45
10	*Staphylococcus epidermidis*	Vancomycin	<1 cm	Vancomycin-ciprofloxacin for 6 weeks	56
11	MRSA	Vancomycin	<1 cm	Vancomycin for 12 weeks	48

MSSA: methicillin-sensitive *Staphylococcus aureus*, MRSA: methicillin-resistant *Staphylococcus aureus.*

During follow-up, X-rays, clinical signs and laboratory tests were assessed.

All infections were eradicated by the second surgical stage. After finishing the specific antibiotic treatment, the patients had no clinical signs of infection and none of the acute phase reactants were altered in the lab tests (Table 4).

Table 4. Lab tests results

Test	Before first surgical stage	Second surgical stage
C-reactive protein	13.26 (5-55)	4.6 (2.6-6.5)
Erythrocyte sedimentation rate	39.7 (9-78)	10.5 (1-15)
White blood cell count	12.479 (5736-30.230)	6653 (5620-11.620)
Intraoperative frozen section	Positive	Negative
Site culture	Positive	Negative

The second surgical stage of shaft reconstruction was performed according to the residual defect of each patient. In all cases, screw plates with different types of bone grafts were used. All cultures obtained during the reconstruction procedure were negative, and consolidation of the fracture site was achieved in all cases, without recurrent infection (Figures 2 and 3).

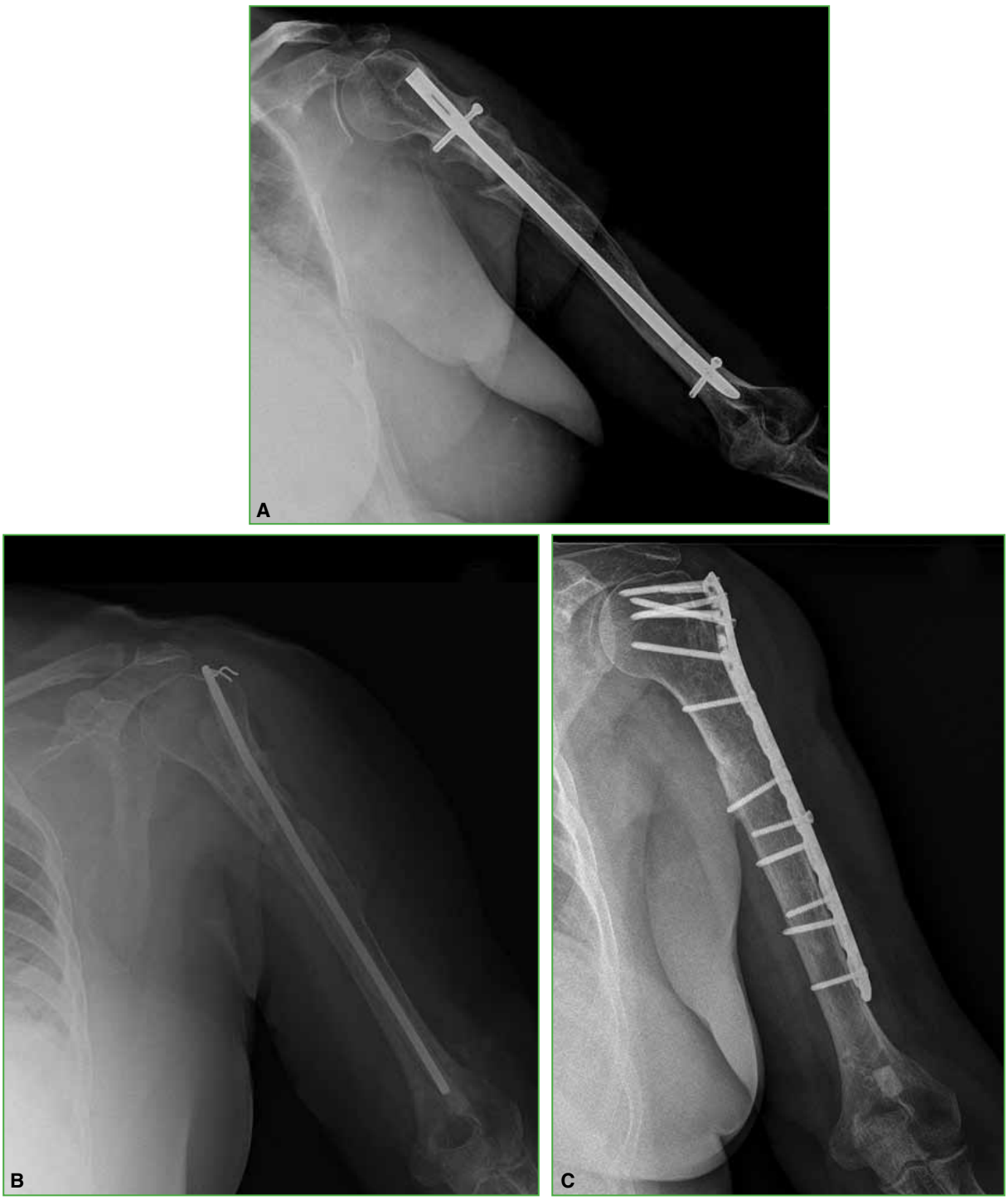

Figure 2. A. X-ray of a 59-year-old woman, smoker, with type 2 diabetes and infected nonunion of the humerus. **B.** X-ray of the first surgical stage—removal of osteosynthesis and placement of the antibiotic cement-coated intramedullary rod. **C.** X-ray one year after the second surgical stage. Consolidation of the nonunion site can be observed.

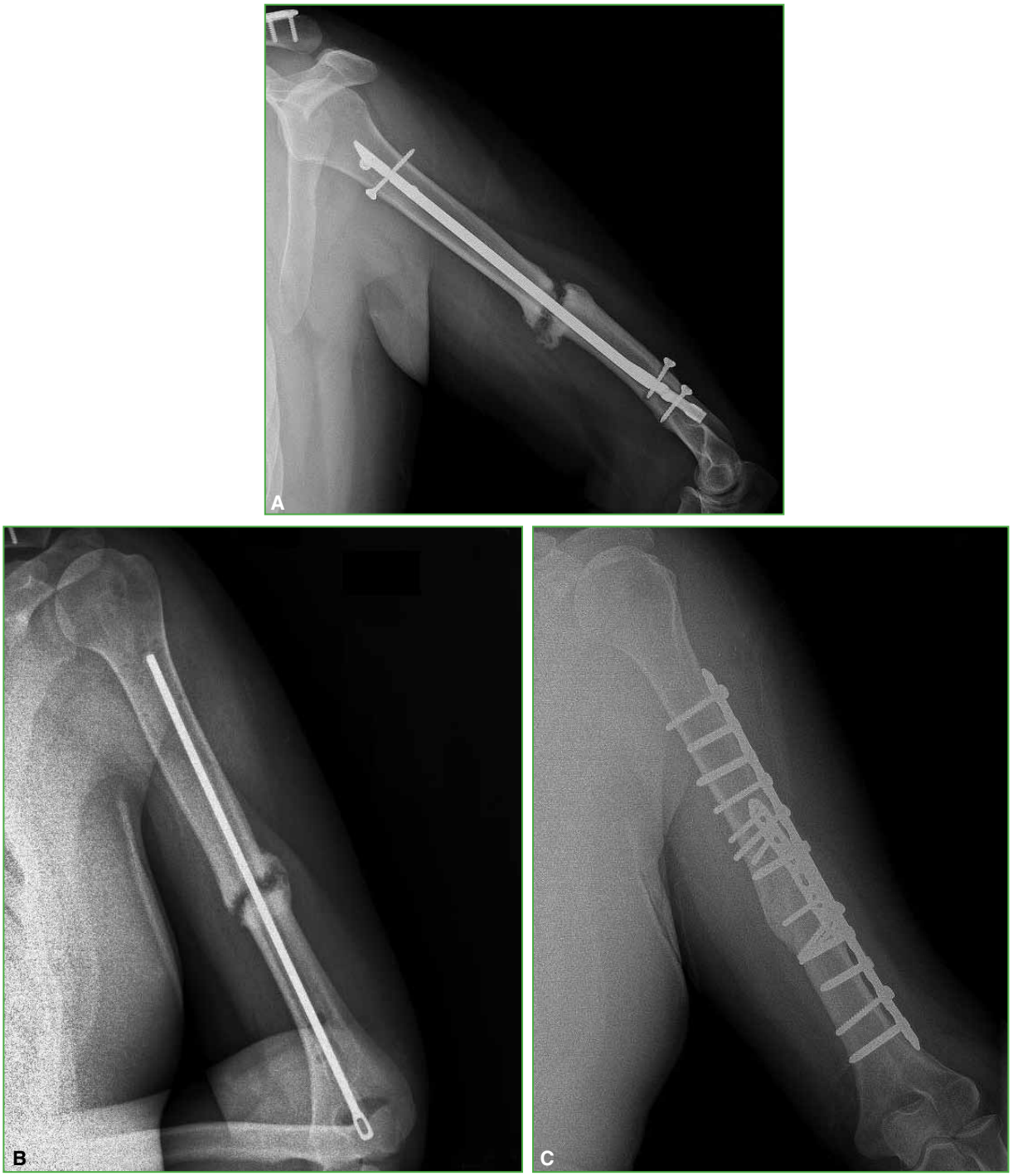

Figure 3. A. X-ray of a 23-year-old man, obese and smoker, with infected nonunion of the humerus. **B.** X-ray of the first surgical stage—removal of osteosynthesis and placement of the ACCR. **C.** X-ray two years and six months after surgery. Consolidation of the nonunion site can be observed.

DISCUSSION

Infected nonunions are a complex condition and require an aggressive surgical approach; otherwise, treatment success is difficult to achieve.

Infected nonunions usually compromise the medullary canal and are surrounded by a highly thickened fibrous tissue including the muscles and, often, the cellular subcutaneous tissue. This creates an avascular environment that often renders systemic antibiotic treatment ineffective, which explains the high number of positive cultures of the nonunion site, although many patients had received previous systemic antibiotic treatment.

Therefore, complete resection of all scar tissue and milling of the canal are critical steps of surgical treatment.

ACCRs also allow for local release of the antibiotic agent and partial site stability. It is a viable alternative to treat infected long-bone nonunions. In a recent review, Koury *et al.*[9] reported success rates of between 80% and 100%. Selhi *et al.*[10] evaluated 16 patients (15 cases in the lower limb and one in the humerus) and, in 14 of them, they achieved eradication of the infection and bone consolidation. Conway *et al.*[4] reported 43 cases of infected long-bone nonunions of the lower limb with consolidation and remission of infection in all patients. Kanakaris *et al.*[11] and Bharti *et al.*[12] reached the same results.

As is clear from the literature, this treatment has been widely reported in the femur and tibia, but there are few reports in the humerus. The use of external fixators in the upper limb to treat INHs has been described. Ferreira *et al.*[13] evaluated 8 patients with INHs initially treated by debridement and placement of a circular external fixator, and in a second stage, with the addition of an autologous bone graft, achieving eradication of the infection in all cases.

Bassiony *et al.*[14] also reported the use of an Orthofix external fixator in 8 patients, eradicating infection and achieving bone consolidation in all of them. The time of use was, on average, 38 weeks in the first series and 6.5 months in the second series. Although the final results show a high percentage of infection eradication and bone consolidation, the long-term use of an external fixator requires strict hygiene protocols, which makes it an extremely uncomfortable treatment for the patient.

The advantages of using an ACCR, in addition to achieving similar final results, are that it does not require daily hygiene and it is better tolerated by the patient.

The size of the residual bone defect can be important in defining the best method to eradicate infection. Sancheti *et al.*[5] evaluated residual bone defects after surgical debridement, combining the classifications of May *et al.*[15] (defects measuring <6 cm and >6 cm) and of Jain and Sinha[16] (defects measuring <4 cm and >4 cm). The authors divided their patients into three groups: defects measuring <4 cm (average of 2.2 cm), 4 to 6 cm (average of 4.4 cm) and >6 cm (average of 6.6 cm), and concluded that ACCRs are effective to control infection in the first two groups and that the eradication time is longer in patients with defects measuring <4 cm, and do not recommend its use in defects measuring >6 cm, since, in these cases, they did not achieve a correct infection control nor an adequate fracture stability. In these cases, they suggest using an external Ilizarov external fixator.

In our series, the largest defect measured 5 cm, so it was decided to divide the patients into those with defects measuring <2 cm (7 cases) and ≥2 cm (4 cases). This classification allowed a statistical analysis of the results (although we know that the number of patients is low and does not allow evident conclusions to be drawn). In any case, no differences were found in the eradication of infection between the two groups.

As in most studies, the most frequent isolated pathogen was MRSA, and the antibiotic used in most cases for preparation of the rod and for systemic treatment was vancomycin.

In our series, all bone defects were, for the most part, small, the largest measuring 3.5 cm, and infection eradication and fracture consolidation were achieved in all patients, regardless of the size of the defect and the isolated pathogen.

This study has several limitations: mainly its retrospective nature and the small number of patients; however, it dealt with a condition of the humerus about which very little has been published, which makes it interesting.

CONCLUSIONS

The use of ACCRs is an adequate treatment option for the first surgical stage in patients with INHs. It is a simple and low-cost method that allows partial site stabilization and releases antibiotic agents into the area, both critical factors to eradicate infection. After removing the rod and administering the appropriate antibiotic treatment, we managed to perform shaft reconstruction by different approaches and achieved nonunion consolidation.

Conflict of interests: Authors claim they do not have any conflict of interests.

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