

# Chronic Osteomyelitis in Children Treated With Antibiotic-Laden Cement: A Preliminary Report

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## Abstract

**Introduction:** Chronic osteomyelitis and infected non-union are relatively rare conditions in pediatric patients and are more frequently observed in the developing countries. Although relatively rare, they are challenging medical and surgical issues. The current study aimed to present a novel surgical technique used to manage three patients with chronic osteomyelitis of long bones.

**Case Presentation:** Three skeletally immature patients with chronic osteomyelitis and infected non-union of the long bones were treated surgically from 2010 to 2013 through infected site debridement of bone and soft tissues, excision of sequestrum, irrigation and antibiotic-laden cement spacer, to fill the bone defect zone, were performed in all patients. All patients underwent magnetic resonance imaging (MRI), computed tomography (CT) scan and laboratory evaluation prior to surgery. Antibiotic regimen started empirically and was adjusted according to the culture and sensitivity results. Once inflammatory markers normalized, all patients were re-operated for cement removal, bone substitute graft and concomitant osteosynthesis of the affected bone. The three patients aged 14 (two patients) and 10 years (one patient) at the time of injury. All patients had at least two years follow-up (range 2-5). Clinical and laboratory evaluation had been normalized, bone healed and all patients had returned to daily life and sport activities.

**Conclusions:** Surgical debridement is the standard approach to chronic osteomyelitis. Since antibiotic therapy plays an adjunctive role, it is recommended to use antibiotic-laden cement to penetrate local infection. The cement also induces membrane formation that aids bone reconstruction.

**Keywords:** Chronic Osteomyelitis, Children, Antibiotic, Cement, Induced Membrane

## 1. Introduction

Although relatively rare in pediatric age group, chronic osteomyelitis (CO) and infected non-union are challenging medical and surgical conditions. The long duration of treatment needs patients and their family's cooperation (1-6). Needless to say that multidisciplinary approach is needed to provide satisfactory outcomes (2, 3, 6). The gold standard of surgical approach in CO is a sharp debridement of necrotic tissue, abundant lavage, sequestrectomy and removal of any hardware and/or foreign bodies (5, 6). Since antibiotic therapy plays an adjunctive role, it is recommended to use antibiotic-laden cement (ALC) to control infection locally. Moreover, cement induces a membrane formation that shows its importance for bone reconstruction (7, 8). In particular, the induced membrane technique, proposed in 1986 by Masquelet, is effective to treat bone defects, regardless of the magnitude or etiology. The technique can be performed in case of initial infection and it can control the infection before final bone reconstruction (7, 8).

The current study aimed to present a novel surgical approach used to manage three consecutive skeletally immature patients with CO and infected non-union of long bones.

Patients were treated surgically by a combination of resection of necrotic, infected bone, debridement of surrounding soft tissue and application of ALC before final bone reconstruction (Table 1). In particular, the ALC was mixed until having "dough" like consistency; the enough amount of cement was applied to fill the bone defect and it was removed before it cleaved to bone tissue. Cement piece was kept until completely solidified and finally it was applied again to the bone as "lock and key" or "cast and mold" device. The ALC was shaped to fill the bone defect contributed to the formation of a bioactive membrane and allowed diffusion of the antibiotic within the surrounding hematoma - which acts as a transporter - and bone tissue.

**Table 1.** Patients Demographic and Clinical Data at the Onset of Chronic Osteomyelitis Diagnosis

Pts.	Age/ Gender	Mechanism; Site; Location	Initial Treatment (Fixation)	Clinical and Laboratory Data	Cierny-Mader Classification	Causative Agent	Parenteral Antibiotics Duration	Oral Antibiotics Duration
1	14 y/ Male	Pushbike accident; left femur; midshaft	ESIN	Pain; Swelling; Inflammation; WBC: 10k; CRP: 127; ESR: 37	4A	Methicillin- sensitive <i>Staphylococcus</i>	Oxacillin + gentamicin four weeks	Levofloxacin + rifamycin six months
2	14 y/ Male	Motorbike accident; distal right femur; distal	Plate and screws	Limited ROM; WBC: 5.7k; CRP: 37.6; ESR: 64	4A	Methicillin- sensitive <i>Staphylococcus</i> <i>aureus</i>	Fucidin + Dalacine four weeks	Fucidine + Dalacine three months
3	10 y/ Male	Fall; distal right; humerus	ESIN	Pain; Swelling; Fever; WBC: 10k; CRP: 90; ESR: 77	4A	Methicillin- sensitive <i>Staphylococcus</i> <i>aureus</i>	Oxacillin + gentamicin three weeks	Amoxicillin three months

Abbreviations: Pts., patients; CO, chronic osteomyelitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell; ESIN, elastic stable intramedullary nailing; FU, follow-up; y, years.

## 2. Case Presentation

### 2.1. Surgical Technique: Tips and Tricks

In the first stage, a polymethyl methacrylate spacer (Palacos®R with Gentamicin, Heraeus, Wehrheim, Germany) is placed in the defect to produce a bioactive membrane, which can be considered to be biochemically and physically mature four to eight weeks after spacer placement (7, 8). To prepare ALC, the monomer catalyzer (20 mL) is added to methyl-methacrylate powder (40.8 g; gentamicin  $1 \times 0.5$  g) and mixed until having “dough” like consistency. At this phase, the enough amount of cement is applied to fill the bone defect; it should be removed before it cleaves to bone. Cement piece is kept until completely solidified and finally it is applied to the bone as “lock and key” or “cast and mold” device. As the elution of antibiotic occurs from the surface of cement, the creation of small multiple bores over the surface using K-wire can be done (1).

The ALC spacer is kept at least until normalization of infection markers occurs. The spacer is then removed in a secondary intervention. The bone defect is packed with bone substitutes (within this membrane) and concomitant osteosynthesis can be performed as needed. The membrane appears to prevent graft resorption and promote revascularization and consolidation of new bone.

Since antibiotic diffuses within the surrounding hematoma, which acts as transporter, drains application is not always recommended.

For the current series, drainage was applied when needed and the limb was immobilized in posterior splint (long arm cast or long leg cast) to protect it from pathological fractures.

### 2.2. Case 1

A fourteen-year-old male, victim of a pushbike accident sustained a closed mid-shaft fracture of left femur without neurovascular insult (Table 1). The fracture was initially fixed with two 4 mm retrograde flexible intramedullary nails (Figure 1). Bony union was achieved four months and a half after injury.

At eight-month follow-up, antero-posterior (AP) and lateral radiographs were consistent with CO of the right femur. Knee and hip ranges of movement were within normal limits although hip internal and external rotations were painful. Nails were removed and specimens sent to bacteriology. The results were positive for methicillin-sensitive *Staphylococcus aureus* (MSSA) (Table 2). Subsequently, computed tomography (CT) scan and magnetic resonance imaging (MRI) (Figure 1) confirmed infected pseudarthrosis at the fracture site, bone sequestrum, soft tissue abscess and periosteal reaction throughout the femoral diaphysis. White blood cells (WBC) of  $10 \times 10^3/\text{mm}^3$ , C-reactive protein (CRP) of 127 mg/dL and sedimentation rate (ESR) of 37 mm/hr were found.

Once all investigations were completed, the first surgical procedure was performed. It consisted of sequestrectomy, debridement of surrounding soft tissue, irrigation of bone canal and the wound using high pressure lavage, bone defect was filled with ALC as per reported technique. Intravenous oxacillin (500 mg every six hours) and gentamicin (6 mg/kg/day) were immediately started and the limb was immobilized in a long leg cast.

Four weeks later, WBC ( $< 10 \times 10^3/\text{mm}^3$ ), CRP ( $< 10$  mg/dL) and ESR ( $< 13$  mm/hr) normalized and the patient was re-operated (second procedure) to remove ALC spacer and  $\beta$ -tricalcium phosphate bone substitute was used to fill the bony defect. Osteosynthesis was achieved by a

**Table 2.** Literature Review on Chronic Osteomyelitis in Children

Work	Country	Cases	Mean Age	Surgical; Method Used	Causative Agent	FU	Results	Complications
Bassey et al., 1995	Nigeria	n = 41	11.9 y	Sequestrectomy; muscle flap	<i>Staphylococcus aureus</i> / <i>Pseudomonas aeruginosa</i>	2 y	Complete healing (all cases)	Joint stiffness; Limb shortening; pathological fractures
Kucukkaya et al., 2002	Turkey	n = 7	7.2 y	Sequestrectomy; external fixation	N/A	4.6 y	Excellent; (clinical and radiological outcomes)	-
Shrestha et al., 2005	Nepal	n = 90	2 y	Sequestrectomy; external fixation; Fibular grafting	N/A	-	-	Limb shortening (three cases); stiff knee; Pin tract infection
Unal et al., 2006	Turkey	n = 22	8 y	Debridement; secondary bone graft; (5/8 cases)	MSSA; MRSA; <i>Pseudomonas aeruginosa</i> ; <i>Proteus mirabilis</i>	4.5 y	Satisfactory; (> 50%)	-
Hoang et al., 2009	Vietnam	n = 6	9.8 y	Debridement muscle flap (gracilis)	<i>Staphylococcus aureus</i> ; <i>Escherichia coli</i>	6 y	Satisfactory; (100%)	-
Bar-On et al., 2010	Israel	n = 4	9.3 y	Debridement; lavage, reaming; ALC rods + beads	<i>Staphylococcus aureus</i> ; <i>Pseudomonas aeruginosa</i> ; <i>Streptococcus viridans</i>	3.4 y	-	Superficial abscess; soft tissue defect pathologic fracture
Mora-Rios et al., 2012	Mexico	n = 1	4 y	Debridement; application of autologous bone graft; No ALC	<i>Staphylococcus aureus</i>	-	Infection controlled; bone healed function restored	-

Abbreviations: MSSA, methicillin sensitive *Staphylococcus aureus*; MRSA, methicillin resistant *Staphylococcus aureus*; ALC, antibiotic-laden cement; FU, follow-up; N/A, not applicable.

rigid locked intramedullary nail, after having reamed the medullary canal (Figure 2). Once the inflammatory markers were stabilized, intravenous antibiotics were switched to oral regimen with levofloxacin (500 mg/day) and rifamycin (10 mg/kg/day) for six months. The patient was allowed to partial weight bear and physical therapy was started immediately after discharge.

Five years after surgery, knee and hip range of movement were within normal limits. The patient had returned to competitive cycling and inflammatory markers remained within normal range.

### 2.3. Case 2

A fourteen-year-old male involved in a motorbike accident sustained a closed intercondylar fracture of the right femur and a Salter-Harris type II injury of distal fibula fracture (Table 1). At admission, the foot was pulseless. The patient underwent open reduction and internal fixation (plate and screws) of the intercondylar right femur fracture; the epiphyseal fracture of the distal fibula was fixed with one intramedullary K-wire (Figure 3).

Eighteen months post-operatively, hardware removal was decided due to complete fracture healing (Figure 3). Inflammatory markers were not tested before surgery as follow-up measures were otherwise satisfactory and the patient had returned to daily and sport activities. During hardware removal, bone defect with pus collection around the plate and bone sequestrum, compatible with CO, were found. The first surgical procedure consisted of sequestrectomy, debridement of surrounding soft tissue, irrigation of bone canal and wound using high-pressure lavage. The bone defect was filled with ALC as per reported technique (Figure 4). Tissue samples were sent to the laboratory for bacteriological analyses and identification of MSSA positive samples (Table 1). Postoperative blood test showed CRP of 37.6 mg/dL and ESR of 64 mm/hr.

Intravenous Fucidin (500 mg three times daily) and Dalacine (15 mg/kg/day) were started immediately (Table 1).

Four weeks later, after the inflammatory markers had normalized, a second surgical procedure was performed. The ALC was removed and the bone defect filled with  $\beta$ -tricalcium phosphate bone substitute. Antibiotic treatment with Fucidin (500 mg three times daily) and Dalacine

(15 mg/kg/day) was shifted to oral regimen for 12 weeks more (Table 1).

Three years after surgery the patient had normal inflammatory markers and bone had completely healed (Figure 5). The patients returned to daily and sport activities although the range of movement of the right knee was 125 degrees compared to 135 degrees of the contralateral side.

#### 2.4. Case 3

A ten-year-old male sustained a closed fracture of the right distal humerus diaphysis without neurovascular insult. The fracture underwent closed reduction and fixation by two 3 mm anterograde flexible intramedullary nails. Three months later, the patient had sign and symptoms of inflammation of the distal scar. Six months later, the distal scar was still inflamed and blood analysis revealed WBC count of  $10 \times 10^3/\text{mm}^3$ , CRP value of 90 mg/dL and ESR of 77 mm/hr. AP and lateral radiographs showed infected non-union of the distal humerus. Infected non-union was defined as a lack of bone healing for at least six months post injury with concomitant infection of bone and surrounding tissues. Nails were removed and soft tissue sample and swap were sent to bacteriology. The results were positive for MSSA; an MRI of whole humerus was performed prior to surgery and it was consistent with infected non-union, bone sequestrum, soft tissue abscess and periosteal reaction throughout the humeral diaphysis.

Once all investigations were completed, the first surgical procedure was performed. It consisted of sequestrectomy, debridement of surrounding soft tissue, irrigation of bone canal and wound using high-pressure lavage. The bone defect was filled with ALC as per the reported technique. Intravenous oxacillin (500 mg every six hours) and gentamicin (6 mg/kg/day) were immediately started and the limb was immobilized in a long arm cast.

Three weeks later, WBC ( $<10 \times 10^3/\text{mm}^3$ ), CRP ( $<10\text{mg/dL}$ ) and ESR ( $<13\text{ mm/hr}$ ) normalized and the patient underwent a second surgical procedure. It consisted of ALC spacer removal, and  $\beta$ -tricalcium phosphate bone substitute was used to fill bony defect. Osteosynthesis was achieved by locking plate and screws. Once the inflammatory markers stabilized, intravenous antibiotics were switched to oral regimen with levofloxacin (500 mg daily) and rifamycin (10 mg/kg/day) for three months. One year after surgery, the patient had returned to full activities and right elbow range of movement was comparable to that of its contralateral side.

#### 2.5. Literature Review

Not many cases had been reported concerning CO and infected non-union in skeletally immature patients

treated by ALC. Literature search over PubMed, ScienceDirect using keywords: chronic, osteomyelitis, children, antibiotic cement, showed several cases of CO treated by several surgical techniques, but none had managed with the reported technique (Table 2).

A and B, showing antibiotic-laden cement (ALC); C, T1-weighted MRI (coronal section) showing ALC and no residual abscess collection.

### 3. Discussion

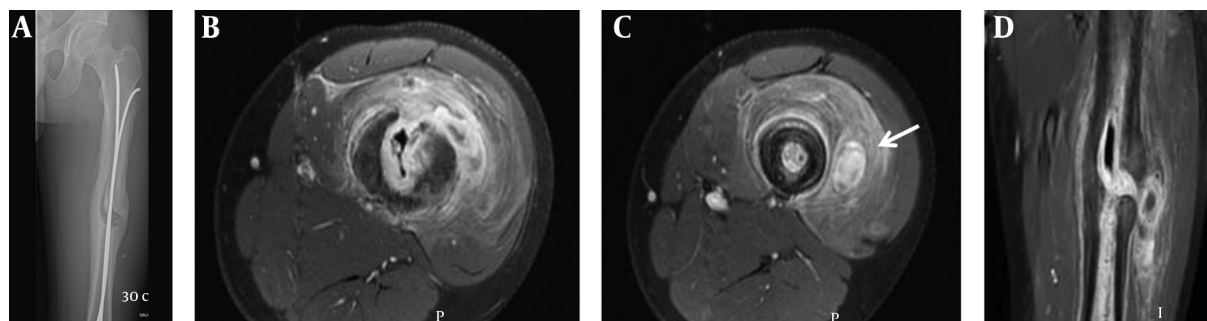
Osteomyelitis in children is primarily hematogenous in origin (2, 3) although cases secondary to open fracture, surgery and/or metastatic infection from contiguous site are also reported (4, 5). CO is frequently observed in the developing countries where medical care is not accessible (5, 8). In the developed countries, CO is most frequently traumatic or as a complication of different surgical procedures (5, 9).

The current study aimed to report three skeletally immature patients with CO and infected non-union of the long bones treated surgically by a combination of resection of necrotic, infected bone, debridement of surrounding soft tissue and application of ALC (Table 1). To the best of the authors knowledge, this is the first report on using custom-made ALC to deliver antibiotics locally and facilitate induction membrane formation, particularly important for bone healing and bone graft integration (5, 7, 8).

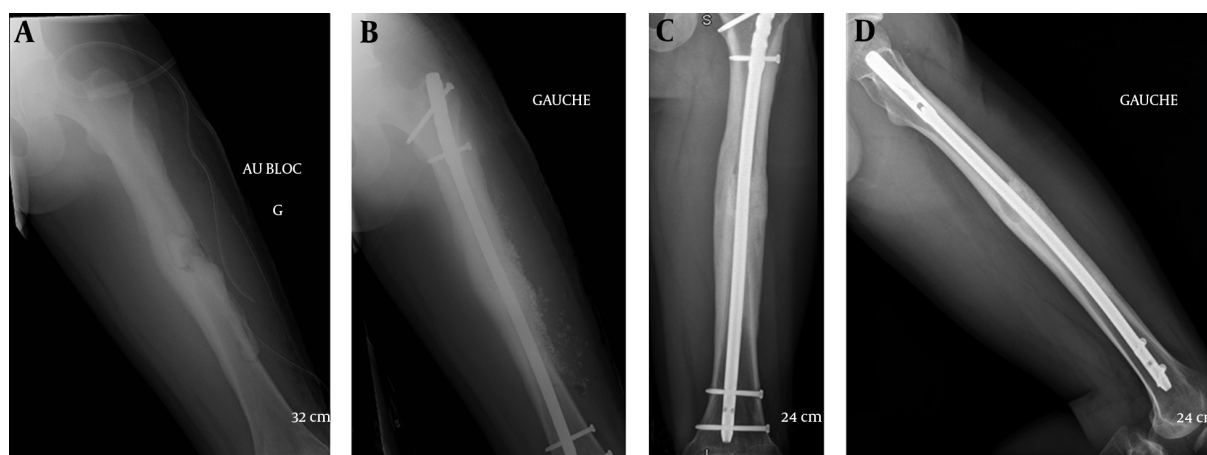
In the current series, ALC was custom-made at the time of surgery. The cement was shaped to exactly fill the bone defect and removed before it completely hardened. Once cement fully hardened, it was placed again into the bone defect to locally deliver high concentration of antibiotics. This method appears to be a relatively simple and inexpensive alternative to treat intramedullary infections and CO.

It is reported that ALC can be also used as beads either custom-made or commercially available (1, 5, 10, 11). The main disadvantage was that when removing, mutable beads were enveloped within the fibrous tissue (1, 5). However these beads were attached to the string wire. The other disadvantage was the preparation of small size beads oval ended and fed on steel wire, within a limited time before it hardened (1, 5, 6).

Buchholz et al. in the 1970s introduced the concept of local antibiotic diffusion by ALC (12-14). This idea initiated a new trend of treating musculoskeletal infection. Regardless of vascularity of the infected area, this is sometimes inaccessible by parental antibiotic; local delivery has the ability to diffuse a high concentration of antibiotic to the infected zone with less systemic toxicity (15). However, this should be handled with care in the elderly or in cases of

**Figure 1.** Six Months Post Osteosynthesis

A, Midshaft cortical destruction, periosteal reaction, sequestrum (dotted arrow); B and C, Gadolinium injection MRI shows sequestrum and abscess collection (white arrow).

**Figure 2.** Post-Operative AP X-Ray

A, Shows antibiotic-laden cement (ALC); B, After removing ACL and intramedullary nailing; C and D, Two years follow-up showing bone healing and cortical reconstruction.

renal failure (16-18). The current study patients were young and healthy, with normal renal function.

The use of ALC in form of beads or rods to treat chronic musculoskeletal infections is widely used and reported (1, 10, 19-21).

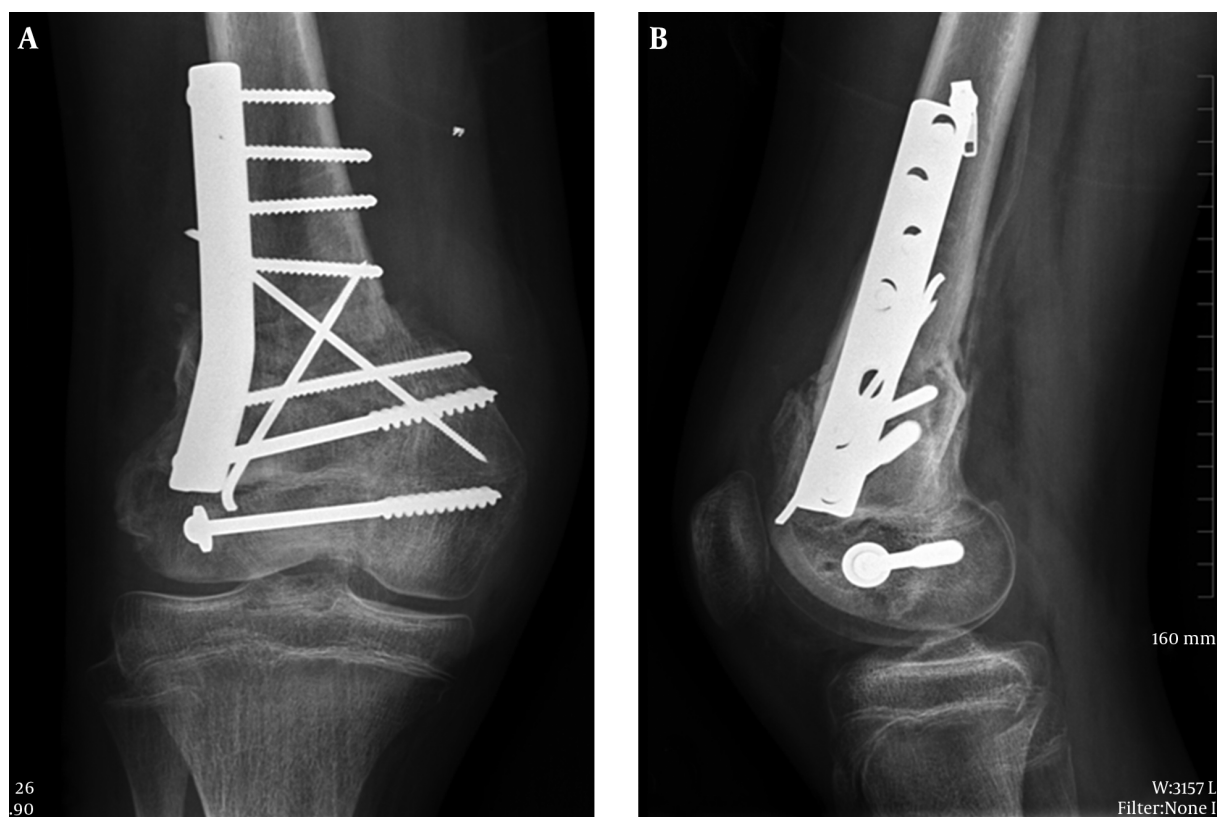
Bar-On et al. (5) reported a series of four cases of CO in skeletally immature patients with a mean age of 9.3 years. Patients were treated surgically by debridement and lavage, reaming of the intramedullary canal and insertion of gentamycin-impregnated ALC rods into the canal and beads around the infected site. All of them had been eradicated although one case had complications around the reaming site and secondary traumatic fracture most probably because of post-reaming bone fragility. In the current series, medullary canal was always reamed and the extremity was protected with a long cast in all cases; no pathological fractures occurred either before or during the reaming

process. In the current series, ALC was custom-made at the time of surgery. The cement was shaped to exactly fill the bone defect and it had to be removed before it cleaved to bone. Cement piece was kept until completely solidified and finally it was applied to the bone as a “lock and key” or “cast and mold” device.

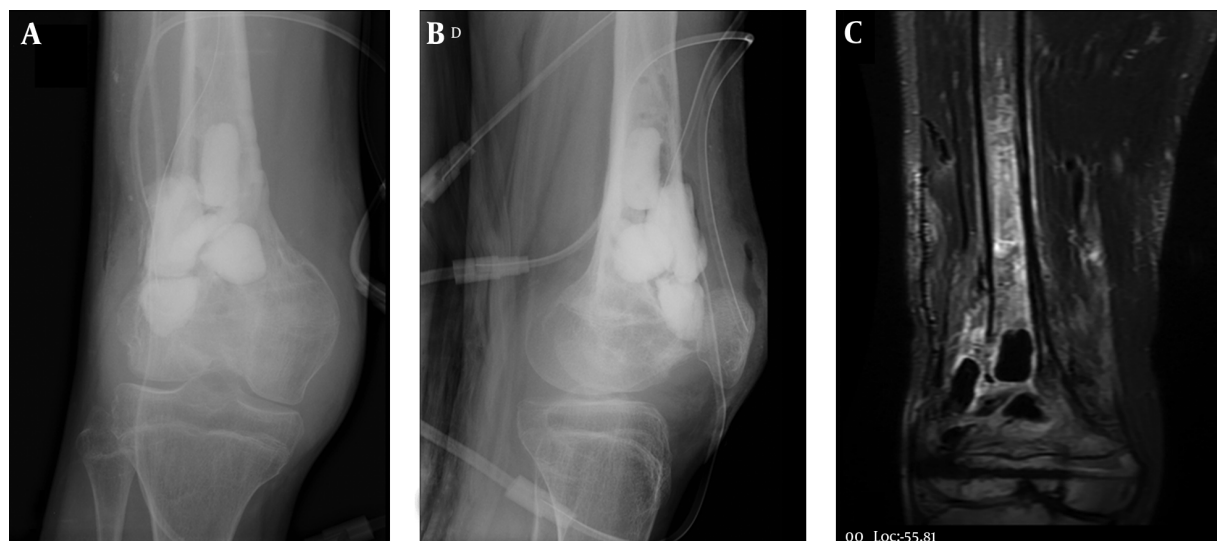
Another surgical option was to enrich the infection area by augmenting blood supply using muscle flap. Disadvantages include donor site morbidity, adjacent joint stiffness and/or long scars (22, 23).

To get more local availability, several recommendations could be considered. The elution of antibiotic occurs from the surface of cement and pores. This could be achieved by K-wire to create small pits (1). As the antibiotic diffuses within the surrounding hematoma, which acts as transporter, drain application is not recommended. Moreover, it could be a portal of germ entrance to poorly vascu-





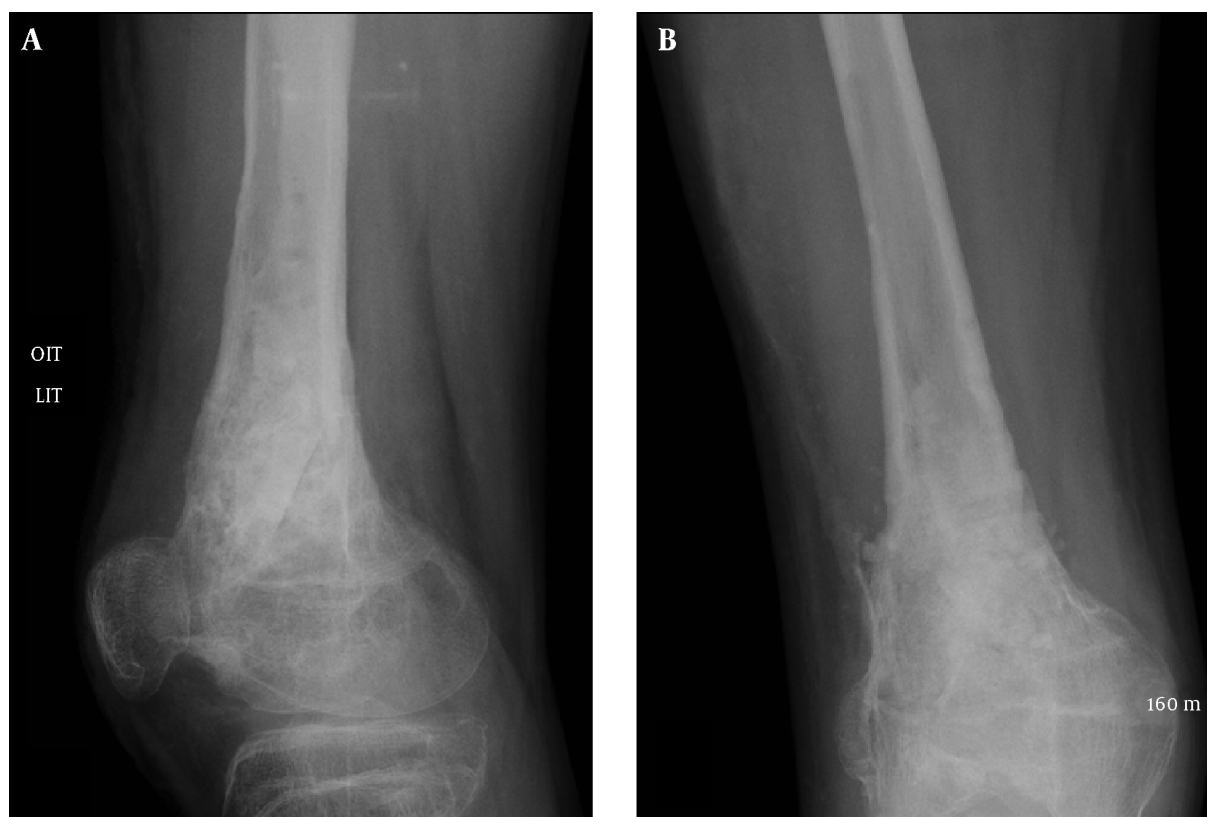
**Figure 3.** AP and Lateral X-Ray Before Hardware Removal Which Did Now Show Bone Defect Covered With the Plate (A, B)



**Figure 4.** Post-Operative AP and Lateral X-Ray

larized area. Unless the case needs a drain, e.g, risk of bleeding is suspected, the drain could be opened every six to

eight hours for fifteen minutes to allow periodic drainage of the wound and make the eluted antibiotic act locally



**Figure 5.** Three Years Follow-up AP and Lateral X-Rays Views Showing Bone Healing and Cortical Alignment

before being drained out periodically. The drain removal should be considered as soon as possible once the drainage level decreases (1, 24-27).

The appropriate choice of antibiotic therapy is set up on the results of culture and pathology testing performed on direct wound and bone samples during the first surgical step (28, 29).

Most importantly, in the current cases ALC allowed the formation of induction membrane. The formation of an induction membrane around the infected bone plays an important role in bone healing and bone graft integration due to the high vascularity of the newly formed tissue (2, 7, 8, 28, 29).

CO is a highly aggressive disease and if not treated aggressively and promptly it could end up with several complications and increased morbidity. Growth disturbance and limb discrepancy, bone and/or soft tissue loss, and deep venous thrombosis in children with CO caused by MRSA are recently reported (25-27).

Authors encountered some limitations in the analysis of the results. It was a retrospective study with preliminary results on a limited number of patients. Further investiga-

tions are needed to confirm the obtained results. However, results are encouraging and the patients formed a homogeneous group in terms of age and type of chronic infection (Tables 1 and 2).

### 3.1. Conclusion

CO and infected non-union are relatively uncommon conditions in pediatric population. Once discovered, it should be treated promptly. Debridement, sequestrectomy, and using ALC at the site of infection with parenteral and oral antibiotic treatment provide satisfactory outcomes.

The preliminary results of the surgical approach presented here were encouraging. The technique appears to be safe and effective to manage CO and infected non-union in skeletally immature patients since the induced membrane prevents graft resorption and promotes revascularization and consolidation of the new bone. Moreover the ALC cement used to exactly fill the bone defect is easily removed, provides local antibiotic delivery and avoids pathological fractures during reaming. However, the procedure

requires multiple surgeries and long periods of hospitalization.

## Footnote

**Authors' Contribution:** Federico Canavese and Ahmad Khan: designing and performing the project, writing the paper.

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