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Hyperbaric oxygen therapy in the management of post-traumatic osteomyelitis: A case series of 11 patients and long-term outcomes

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ABSTRACT

Aim: Osteomyelitis is a rare but serious complication of bone fractures, often requiring complex and prolonged treatment. If not properly managed, it can lead to severe disability and chronic infection. This study evaluates the effectiveness of adjunctive hyperbaric oxygen therapy (HBOT) in chronic post-traumatic osteomyelitis, including refractory cases (6/11) and chronic non-refractory cases (5/11) with relevant comorbidities.

Materials and Methods: We conducted a single-center case series of 11 consecutive patients with chronic post-traumatic osteomyelitis treated with combined surgical debridement, antibiotic therapy and adjunctive HBOT between 2014 and 2024. Five cases (N. 5, 6, 7, 9, 11) did not fulfill criteria for "refractory" disease (no documented failure after ≥6 weeks of targeted antibiotics plus indicated debridement) and were classified as chronic, non-refractory osteomyelitis at baseline. Patients were selected based on clinical urgency and comorbidities. Outcomes were assessed based on infection resolution, wound healing, and absence of recurrence during a minimum follow-up of 12 months.

Results: All 11 patients achieved complete infection resolution and wound healing without recurrence. The adjunctive use of HBOT was well tolerated and appeared particularly effective in patients with diabetes or cardiovascular disease. These results may be attributed to HBOT's known mechanisms: enhanced oxygen delivery to hypoxic tissue, improved neutrophil-mediated bacterial clearance, and disruption of biofilms. Conclusions: HBOT, when integrated into a multidisciplinary treatment strategy, may significantly improve outcomes in patients with complex osteomyelitis. In this mixed cohort of chronic (refractory and non-refractory) post-traumatic osteomyelitis, adjunctive HBOT within a multidisciplinary strategy was associated with infection control at ≥12-month follow-up, with benefits particularly evident in patients with comorbidities. Its benefits were most evident in patients with systemic comorbidities, suggesting a valuable role for HBOT in high-risk clinical scenarios. All patients achieved clinical healing without recurrence, suggesting a possible association between HBOT and favorable outcomes.

Abbreviations: ATA, atmospheres absolute; CO, carbon monoxide; DNA, deoxyribonucleic acid; ED, emergency department; EF, external fixation; EGF, epidermal growth factor; ERK1/2, extracellular signal-regulated kinases 1/2; HBOT, hyperbaric oxygen therapy; Hb, hemoglobin; HIF, hypoxia-inducible factor; IL-6, interleukin-6; kPa, kilopascals; K wires, kirschner wires; mmHg, millimeters of mercury; MRSA, methicillin-resistant staphylococcus aureus; NO, nitric oxide; NOS, nitric oxide synthase; Nrf2, nuclear factor erythroid 2–related factor 2; O2, oxygen; PET-CT, positron emission tomography/computed tomography; RIA, reamer-irrigator-aspirator; RNS, reactive nitrogen species; ROS, reactive oxygen species; RX, radiography; SIMSI, italian society of underwater and hyperbaric medicine; SPCs, stem/progenitor cells; TC, computed tomography; TIMP-1, tissue inhibitor of metalloproteinases-1; TNF-a, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

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1. Introduction

Osteomyelitis is a bone infection typically caused by bacteria, including anaerobes such as clostridia; fungi (and, less commonly, mycobacteria) can also be involved. Infection can reach the bone through the bloodstream, direct exposure via wounds, or spread from nearby infected areas [1–3]. Osteomyelitis is categorized clinically as:

- acute (e.g., hematogenous or post-traumatic, often from direct or nearby inoculation)
- chronic (either progressing slowly from the start or as a complication of acute osteomyelitis). In most definitions, the condition is considered "chronic" if it persists for more than four weeks after onset, although alternative definitions not based solely on a time threshold are also used.
- chronic refractory osteomyelitis, a subset of chronic osteomyelitis characterized by persistent or recurrent infection despite at least one full course (≥6 weeks) of appropriate culture-directed antibiotic therapy combined with indicated surgical debridement. This form is often associated with poor vascular supply, comorbidities such as diabetes, or infection by multidrug-resistant organisms.

Diagnosis involves clinical evaluation supported by imaging, lab tests, bone biopsy and microbial cultures to identify the causative pathogen.

1.1. Management overview

Standard management consists of culture-directed antibiotic therapy and indicated surgical debridement; adjunctive therapies such as HBOT may be considered in selected cases. Risk-factor staging guides surgical planning and, when needed, reconstructive procedures [4]. Antibiotic therapy is the primary treatment, customized to the patient's specific pathogen and clinical condition. Patient staging by risk factors can aid in planning surgical interventions, which often involve bone debridement. Additional surgical procedures may be needed to restore bone function or fill gaps, depending on the severity of disease. Conditions like diabetes and cardiovascular disease increase the risk of both acute and chronic osteomyelitis, along with recurrence [5]. Adjunctive HBOT has gained attention in recent years for its potential to support infection resolution and tissue regeneration. Its proposed mechanisms include improved oxygenation of ischemic tissues, enhancement of leukocyte function, and modulation of inflammation [6,7]. These effects may be particularly useful in patients with diabetes or vascular compromise, where chronic hypoxia and impaired immune response contribute to poor outcomes. Its management is challenging due to poor antibiotic penetration into bone tissue, particularly in chronic or refractory forms. Standard treatment includes antibiotic therapy and surgical debridement. However, adjunctive therapies such as HBOT have been proposed to improve clinical outcomes, particularly in refractory or diabetic cases [8–13].

Globally, antibiotic resistance, particularly in Methicillin-Resistant *Staphylococcus aureus* (MRSA), has risen sharply due to bacterial evolution and antibiotic overuse. This trend has complicated treatment for MRSA, as the bacterium has developed resistance to many antibiotics, posing significant challenges for infection control [14,15]. Osteomyelitis linked with vascular insufficiency, particularly in diabetes, presents unique diagnostic and therapeutic challenges [16–18]. Patients often exhibit localized symptoms like pain, swelling, and long-standing ulcers, such as those common in diabetic neuropathy, making osteomyelitis progression difficult to diagnose and often requiring surgical intervention or amputation [19,20].

HBOT has shown promising results in selected patient populations, though robust clinical evidence remains limited [21–25]. In patients with chronic osteomyelitis, particularly those with diabetes or vascular comorbidities, HBOT may enhance infection control through three main mechanisms: increased oxygen delivery to ischemic tissue, improved bactericidal activity of neutrophils and disruption of bacterial biofilm formation, especially by pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. These effects are especially relevant in individuals with impaired peripheral circulation or compromised immune responses [26–29].

This study aims to report a 10-year single-center case series involving 11 patients with post-traumatic osteomyelitis (6 chronic refractory and 5 chronic non-refractory) treated with combined surgical, antibiotic, and adjunctive HBOT therapy, and to assess the clinical outcomes of this multidisciplinary approach.

2. Materials and methods

Between July 2014 and July 2024, a total of 70 patients presenting to our center met the study's predefined criteria for chronic or chronic refractory osteomyelitis. Of these, 11 patients were included in this report, as they fulfilled all inclusion criteria and completed at least one year of follow-up. No additional exclusion criteria were applied beyond the inability to complete the minimum follow-up period. Patients were enrolled consecutively during the study period at Vito Fazzi Hospital in Lecce, Italy, a tertiary referral center for orthopedic infections and trauma.

Patients enrolled in the study were required to meet the following three criteria at the time of study enrollment, prior to initiation of the treatment protocol:

1. Clinical and/or imaging-confirmed diagnosis of bone infection.
2. Indication for, and subsequent performance of, surgical debridement aimed at infection eradication, followed by personalized reconstructive surgery.
3. Administration of parenteral antibiotic therapy.
4. Post-traumatic etiology of osteomyelitis (patients with hematogenous, diabetic foot-related, or other non-traumatic forms were excluded).

These criteria were assessed before inclusion in the study; however, criteria 2 and 3 were fulfilled as part of the standardized treatment approach applied at our center after enrollment.

The 11 patients with post-traumatic osteomyelitis, including 6 chronic refractory and 5 chronic non-refractory cases, involving various anatomical regions, were treated with personalized surgical and antibiotic therapy, alongside adjunctive HBOT. The cohort consisted of 9 men and 2 women, with a mean age of 54.4 years (range 26–78 years). In addition to the main inclusion criteria listed below, priority was given to patients presenting with clinical urgency and/or comorbid conditions such as diabetes or cardiovascular disease. The initial assessment included a thorough medical history, laboratory data and culture-based microbiological testing with antibiotic sensitivity profiling. Imaging studies always included standard radiographs and, when indicated, second-level imaging such as computed tomography (CT), magnetic resonance imaging (MRI), labeled leukocyte scintigraphy, or Positron Emission Tomography/Computed Tomography (PET-CT).

Chronic osteomyelitis, in the enrolled patients, was classified using the Cierny-Mader classification system. All cases were categorized as either anatomical type III or IV osteomyelitis. Of the 11 cases, 9 were associated with closed fractures, 2 with open fractures. Antibiotic selection was guided by the most recent culture and sensitivity testing. Parenteral antibiotic therapy was typically administered for 2 weeks post-surgery, followed by an additional 2–4 weeks of oral antibiotics. In addition to surgical debridement and parenteral antibiotics, all patients underwent adjunctive HBOT in a hyperbaric chamber (specific brand unknown). The treatment protocol was designed according to the guidelines of the Undersea and Hyperbaric Medical Society (UHMS). In the hyperbaric chamber, 100 % oxygen was delivered via a mask system at a pressure of 2.5 absolute atmospheres (ATA). Each session lasted 2 h

and followed an intermittent schedule of 25 min of 100 % oxygen breathing alternated with 5 min of air breathing, conducted once daily, 5 days per week.

In this series, expressions such as "accelerated healing" or "greatest benefits" refer to observed improvements in each patient when comparing their post-HBOT clinical course to their pre-HBOT status, rather than to a concurrent control group. Where noted, comparative statements also draw from outcome trends described in previous literature on HBOT in chronic osteomyelitis.

3. Clinical cases

Case 1 – Male, 29 years, type 1 diabetes (Fig. 1)

Classifiation at presentation.

Type: Chronic refractory osteomyelitis

Justification: Persistent clavicular osteomyelitis with draining fistula 4 months after fracture fixation; failed 8-week course of targeted antibiotic therapy and prior surgical debridement before referral.

Location: Clavicle

Pathogen: *Staphylococcus aureus* (from culture)

1. Pre-HBOT management

The patient sustained a clavicle fracture in a motorcycle accident, treated at another hospital with open reduction and percutaneous Kirschner wire fixation. Four months later, he presented to our center with a draining fistula and signs of osteomyelitis. Previous management included wire removal and an 8-week course of targeted antibiotic therapy (amoxicillin–clavulanate) based on culture results, without resolution.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

The patient underwent 45 HBOT sessions in a monoplace chamber at 2.5 ATA, breathing 100 % oxygen for 25 min alternating with 5 min of air, for a total of 2 h per session, 5 days per week. Antibiotic therapy (amoxicillin–clavulanate) continued during HBOT. Surgical intervention during this phase included pseudotumor resection (removal of chronic inflammatory granulation tissue and necrotic bone) and placement of an antibiotic-loaded cement spacer.

3. Post-osteomyelitis reconstructive management

Approximately 60 days after initial surgery, the cement spacer was removed, and definitive fixation was achieved using a plate and screws with bank bone graft.

Follow-up: 12 months

Outcome: Complete clinical and radiographic healing, no recurrence of infection, no HBOT-related complications.

Case 2 – Male, 56 years, type 2 diabetes (Fig. 2).

Classification at presentation

Type: Chronic refractory osteomyelitis

Justification: Tibial pilon fracture with persistent wound dehiscence and infection 4 months after initial fixation; prior implant removal and antibiotic therapy failed to achieve healing.

Location: Distal tibia (pilon)

Pathogen: *Pseudomonas aeruginosa*.

1. Pre-HBOT management

The patient sustained a tibial pilon fracture treated at another hospital with open reduction and internal fixation (plate and screws). Due to wound dehiscence and infection, the hardware was removed. Despite local wound care and systemic antibiotics, the surgical wound remained dehiscent after 4 months, with clinical and radiographic evidence of osteomyelitis.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT was initiated with parameters of 2.5 ATA, 100 % oxygen breathing in 25-minute cycles alternated with 5 min of air, 2 h total per session, for a total of 60 sessions, 5 days per week. Antibiotic therapy continued during HBOT. Surgical management included pseudotumor resection and reconstruction using the Ilizarov technique with segmental bone transport for new bone generation.

3. Post-osteomyelitis reconstructive management

Over ~4–5 months, proximal corticotomy and bone transport achieved docking-site consolidation. The patient underwent revision surgery at the docking site to ensure stability.

Follow-up: 12 months

Outcome: Complete wound closure, radiographic union, no infection recurrence, functional limb preservation.

Case 3 – Male, 26 years, type 1 diabetes (Fig. 3).

Classification at presentation

Type: Chronic refractory osteomyelitis

Justification: Proximal tibia fracture with severe wound dehiscence and infection 3 months post-fixation; failed prior surgical management and antibiotics; contralateral leg amputation for unrelated injury.

Location: Proximal tibia

Pathogen: *Staphylococcus aureus*.

1. Pre-HBOT management

Following a motorcycle accident, the patient was treated at another hospital for a proximal tibia fracture with dual plate fixation; the contralateral leg required amputation. At 3 months, he presented severe wound dehiscence and confirmed osteomyelitis despite prior antibiotic therapy and surgical care.

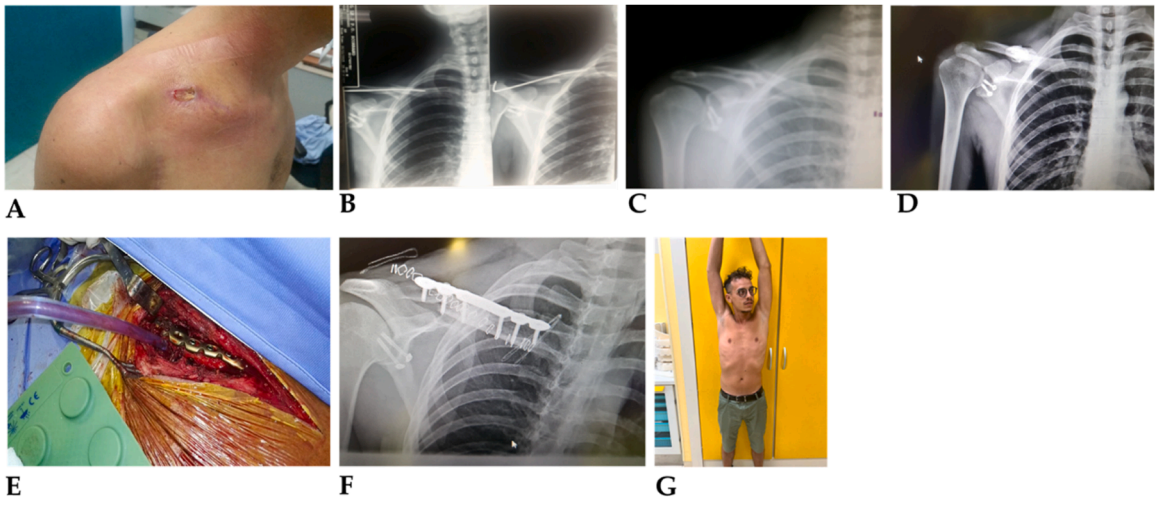

Fig. 1. A: clinical presentation under our observation; B: RX at our observation; C: X-ray after removal of the Kirschner wire; D: X-ray after surgical toilet and interposition of antibiotic cement; E: intraoperative images: surgical toilet and preparation of fracture heads for reduction and synthesis with plate and screws and opposing bank bone splint; F: post-operative x-rays; G: 1-year clinical follow-up.

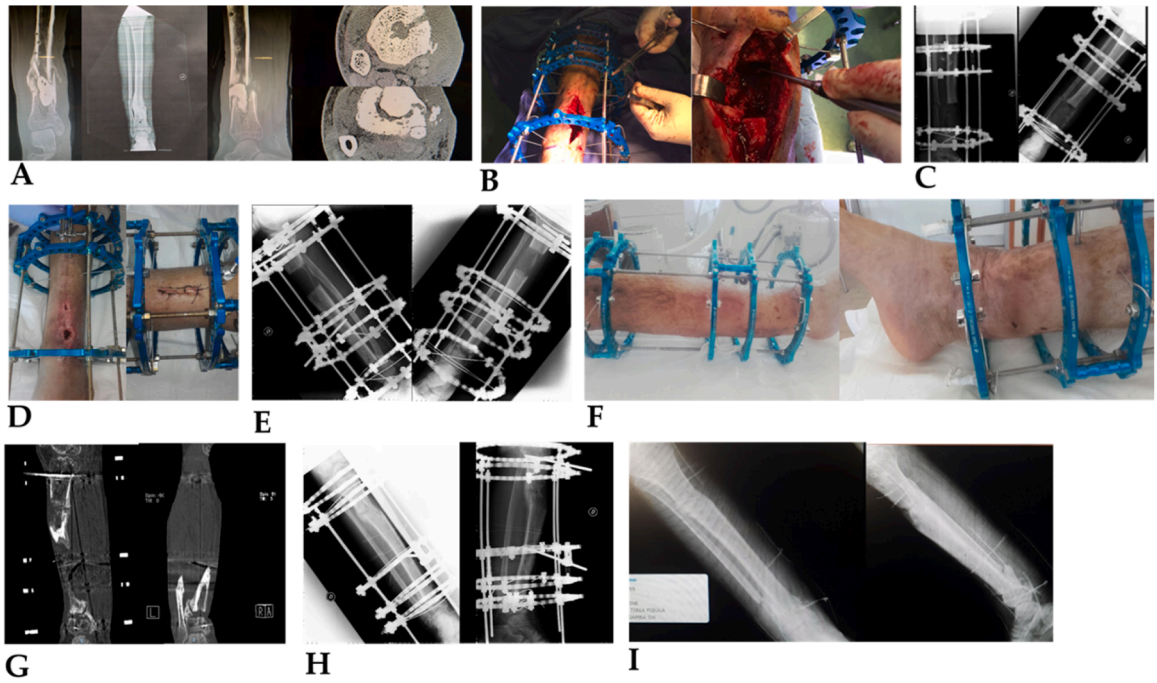

Fig. 2. (A): post-surgical osteomyelitis for reduction and synthesis of distal fracture III of leg with synthetic means removed and secreting fistula; (B): intraoperative: pseudotumoral resection of necrotic bone and implantation of circular external fixator (EF) according to ilizarov technique; (C): postoperative radiography (X-ray); (D): clinic during osteo-myocutaneous proximal-distal carriage) proximal corticotomy); (E): X-ray after about 4 months after commencement of carriage; (F): clinic at about 5 months (wound closure); (G): Computed Tomography (CT) of the docking-site; (H): revision in docking-site compaction; (I): rx and clinic at 1 year after lengthening.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT was delivered at 2.5 ATA, 25-minute oxygen/5-minute air cycles, 2 h per session, for 65 sessions, 5 days per week. Antibiotics were continued during HBOT. Targeted antibiotic: vancomycin. Surgical treatment involved pseudotumor resection and Ilizarov bone transport following distal corticotomy.

3. Post-osteomyelitis reconstructive management

Bone transport continued for ~7 months, achieving docking-site re-epithelialization and consolidation.

Follow-up: 12 months

Outcome: Functional limb with solid bone union, healed soft tissues, and no recurrence.

Case 4 – Female, 76 years, smoker, cardiac comorbidity (Fig. 4).

Classification at presentation

Type: Chronic refractory osteomyelitis

Justification: Periprosthetic femur fracture treated with fixation. Ten months later, the patient developed a purulent fistula with MRSA-positive cultures. Before HBOT, she had completed ≥6 weeks of culture-directed antibiotic therapy (linezolid) without clinical or microbiological resolution, and nuclear medicine imaging confirmed prosthesis involvement. These features meet our definition of chronic refractory osteomyelitis.

Location: Femur (periprosthetic)

Pathogen: MRSA

1. Pre-HBOT management

The patient presented with persistent drainage and severe soft-tissue compromise after completing $a \geq$ 6-week course of linezolid directed at MRSA, without infection control. Scintigraphy confirmed involvement of the prosthesis. Due to comorbidities, soft-tissue coverage was not feasible.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT at 2.5 ATA, oxygen/air cycling, 5 days/week, for 50 sessions. Targeted antibiotic: linezolid (continued per Infectious Diseases guidance). Concurrent antibiotics targeted MRSA. Surgery included methylene blue–guided removal of the prosthesis, plate, and screws, followed by arthrodesis with an Ilizarov circular fixator.

3. Post-osteomyelitis reconstructive management.

Gradual consolidation achieved with EF.

Follow-up: 12 months.

Outcome: Stable limb with arthrodesis, no recurrent infection.

Case 5 – Male, 65 years, smoker, type 2 diabetes (Fig. 5).

Classification at presentation

Type: Chronic osteomyelitis

Justification: Distal tibia fracture with small wound dehiscence 5 months post-fixation; infection persisted but did not meet the ≥6 weeks failed antibiotic + debridement criteria for refractory classification.

Location: Distal tibia (pilon)

Pathogen: *Staphylococcus aureus* (from culture swabs)

1. Pre-HBOT management

Treated at another hospital for a tibial pilon fracture with plate and screws. After 5 months, the patient presented with minimal wound dehiscence and radiographic evidence of anterior bone sequestration. Local culture confirmed S. aureus. Prior antibiotic treatment had been given but without prolonged documented failure after 6 weeks.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT protocol: 2.5 ATA, oxygen/air cycling, 2 h per session, 5 days/week, for 40 sessions. Targeted antibiotic: cefazolin. Concurrent targeted antibiotics administered. Surgical treatment included removal of plate and screws, anterior hemidiaphysectomy, drilling, and placement of Stimulan beads loaded with specific antibiotics.

3. Post-osteomyelitis reconstructive management

Progressive healing documented over ~6 months.

Follow-up: 12 months

Outcome: Complete healing, no infection recurrence, preserved function.

Case 6 – Male, 50 years, type 1 diabetes (Fig. 6).

Classification at presentation

Type: Chronic osteomyelitis

Justification: Pilon fracture with wound dehiscence and osteomyelitis 4 months post-fixation; no documented prior ≥6 weeks failed

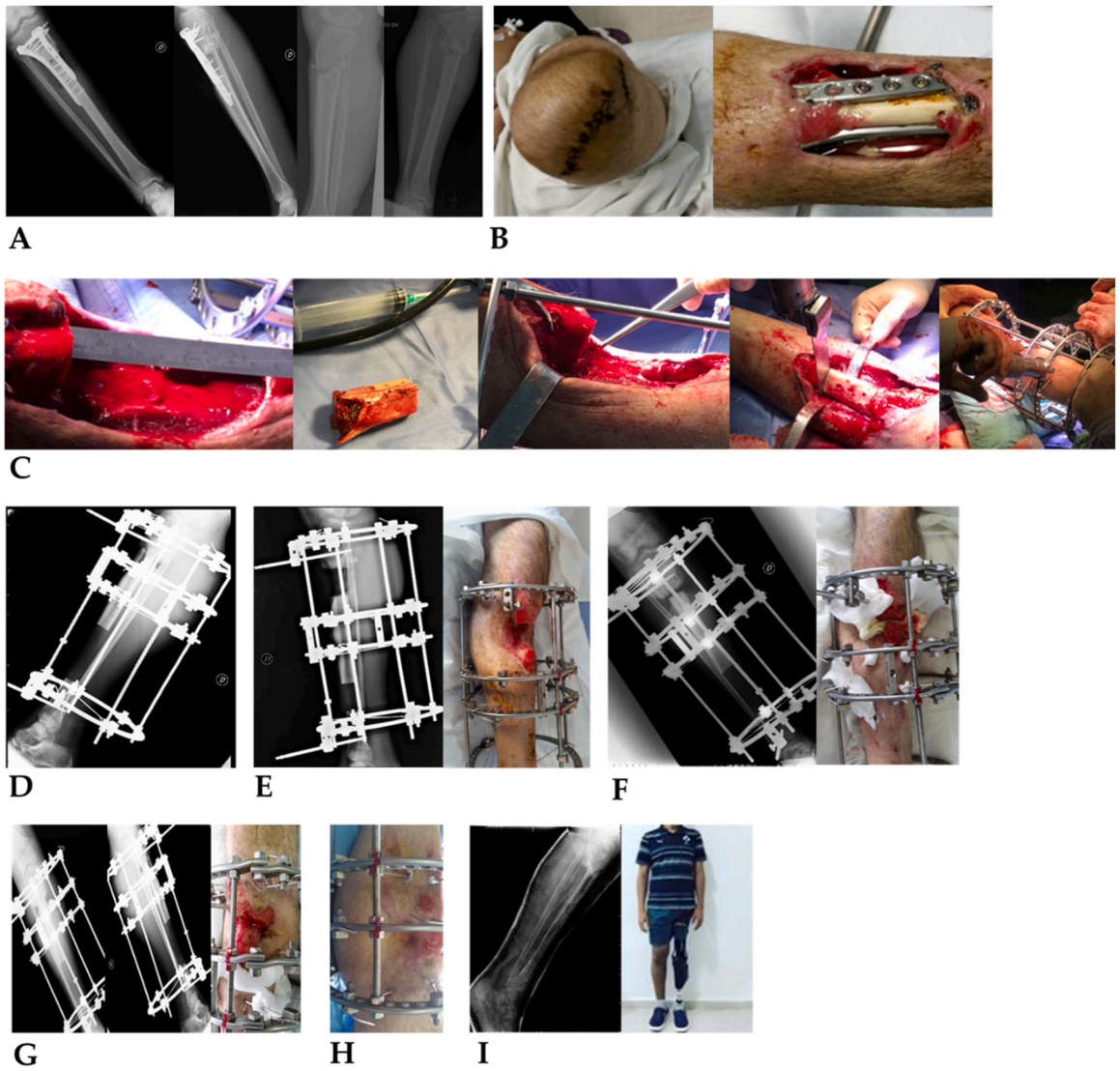

Fig. 3. (A): reduction and synthesis with plates and screws at the proximal right tibia; (B): proximal III amputation of sinus leg at another hospital; (C): intra-operatively: pseudotumoral resection of necrotic bone and soft tissue and implantation of circular EF according to Ilizarov technique; (D): postoperative x-ray; (E): x-ray and clinical images during disto-proximal osteo-myotendinous transport (distal corticotomy); (F): x-ray after 6 months from the start of osteo-myotendinous transport; (G): x-ray after7 months from the start of osteo-myotendinous transport; (H): re-epithelialization after docking-site compression; (I): x-ray and clinical re-evaluation after 1 year.

antibiotic + debridement.

Location: Distal tibia (pilon)

Pathogen: *Pseudomonas aeruginosa*.

1. Pre-HBOT management

Initially treated with open reduction and fixation using plate and screws after pilon fracture. At 4 months, I presented wound dehiscence and Pseudomonas superinfection.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT: 2.5 ATA, oxygen/air cycling, 5 days/week, for 35 sessions. Targeted antibiotic: piperacillin-tazobactam, administered during HBOT. Surgical intervention: superficial curettage and vacuum-assisted closure (VAC) therapy.

3. Post-osteomyelitis reconstructive management

Radiographic and clinical control showed healing at 8 months.

Follow-up: 12 months

Outcome: Wound closure, no recurrence.

Case 7 – Male, 61 years, cardiac comorbidity (Fig. 7).

Classification at presentation

Type: Chronic osteomyelitis, non-refractory (post-traumatic; early presentation)

Justification: Severe open distal femur fracture with bifocal tibia fracture; femoral osteomyelitis diagnosed ~1 month post-trauma. No prior ≥6-week course of targeted antibiotics combined with indicated debridement had failed; operative findings of devitalized bone required debridement and placement of an antibiotic-loaded cement spacer (Cierny–Mader type III/IV).

Location: Femur and tibia

Pathogen: *Staphylococcus epidermidis*.

1. Pre-HBOT management

Polytrauma with severe open fractures treated with damage control (temporary EF). At 1 month, femoral osteomyelitis developed despite prior surgical interventions.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT was initiated soon after diagnosis during the index admission within 10 days of diagnosis.

HBOT as per standard protocol (2.5 ATA), for 55 sessions. Targeted antibiotic: cefepime, that continued during HBOT. Surgical steps included pseudotumor resection and implantation of antibiotic cement,

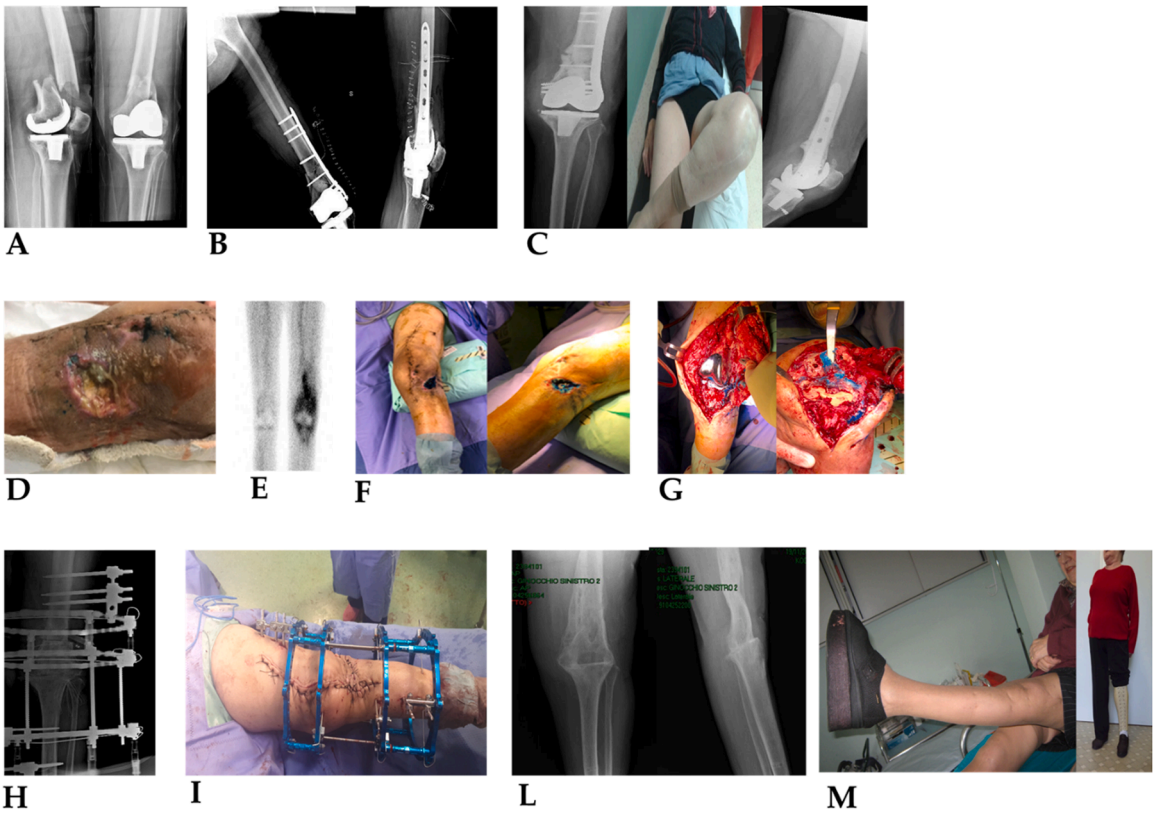

Fig. 4. (A): periprosthetic fracture type II according to Rorabeck's classification; (B): reduction and synthesis with plate and screws; (C): RX after 10 months; (D): clinic after 10 months with purulent fistula positive for MRSA; (E): scintigraphy + for ostea and prosthetic infection; (F): in view of soft tissue distress, MRSA positivity, scintigraphic involvement of the prosthesis, no possibility of coverage, and the patient's age, removal of the prosthesis after instillation of methylene blue is performed; (G): intraoperatively with the tracer reaching the prosthesis and bone, visible even after removal of the prosthesis and the plate and screws; (H): RX after compaction and arthrodesis with circular EF; (I): clinic with fixator; (L): RX after 1 year; (M): clinic after 1 year.

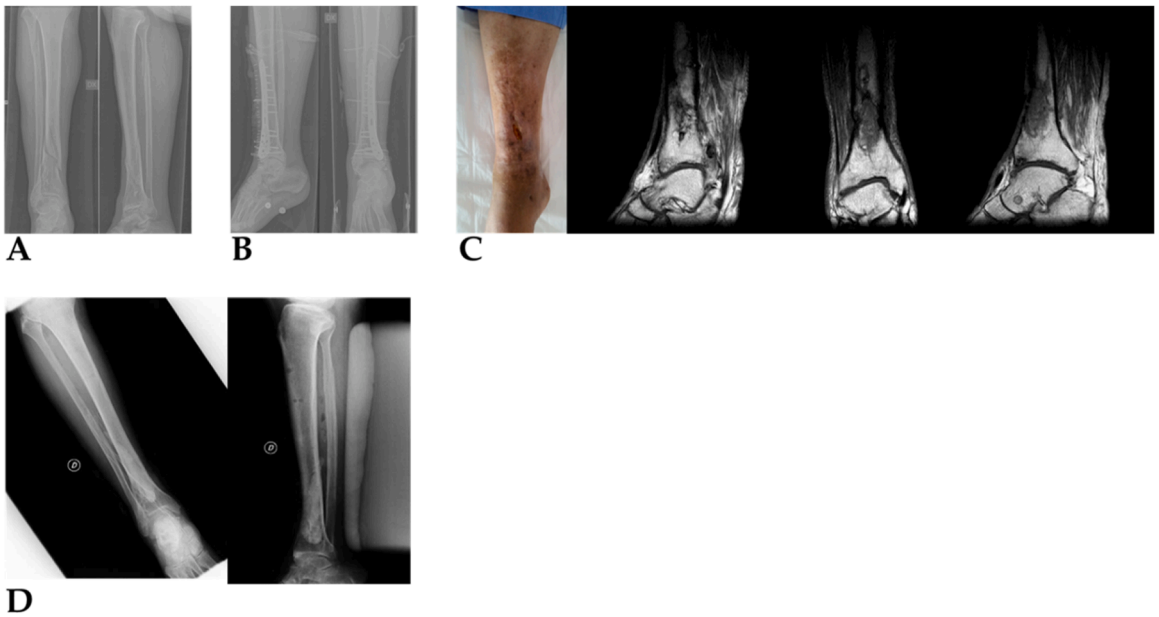

Fig. 5. Before surgery (A) and after surgery (B). (C): At 5 months, a fistula with regenerative medicine for anterior bone sequestration, culture swabs positive for *Staphylococcus aureus*. (D): X-ray at about 6 months after anterior hemidiaphysectomy and drilling with Stimulan, medicated with specific antibiotics.

followed later by removal of cement and custom large resection prosthesis with tibial stem fixation. A "biological chamber" was created by the antibiotic cement spacer, inducing a vascularized membrane that provides a biologically active environment and supports subsequent reconstructive surgery.

3. Post-osteomyelitis reconstructive management

Stable limb achieved, good prosthesis function.

Follow-up: 12 months

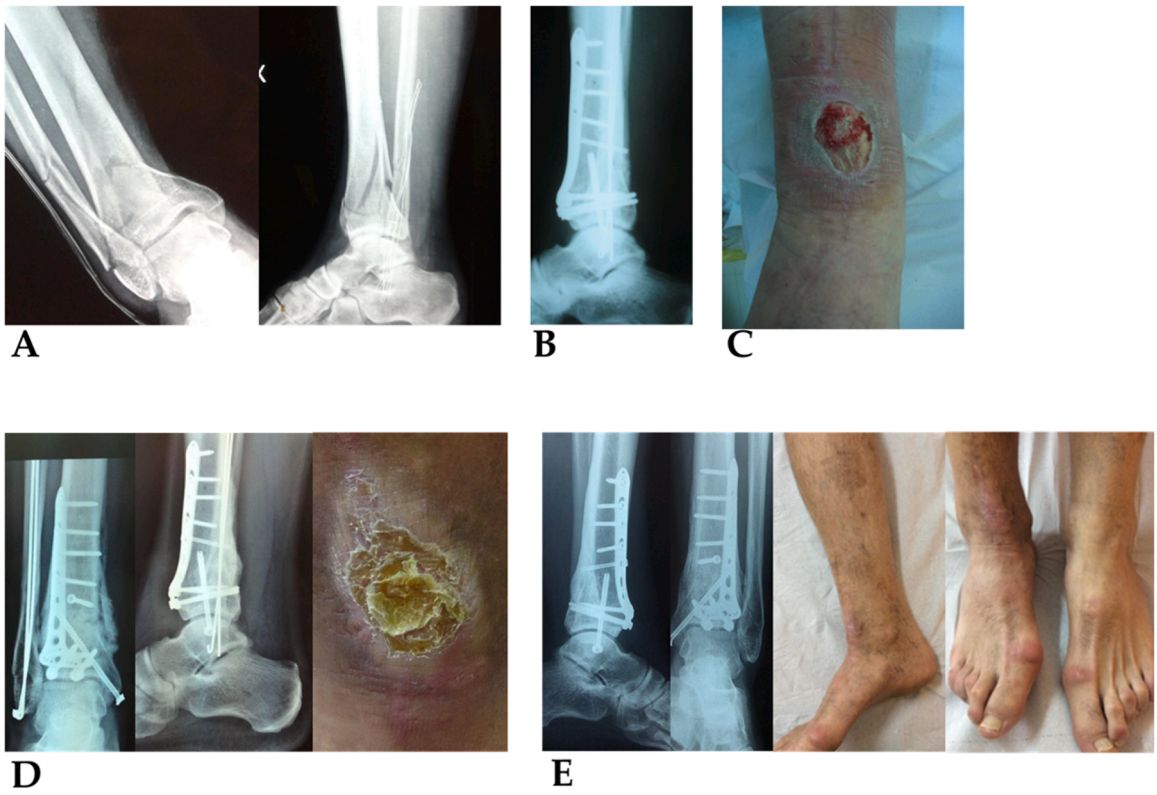

Fig. 6. (A): Tibial pylon fracture. (B): After damage control with temporary EF and CT view following reduction and fixation with plates, screws, and definitive Kirschner wires (K). (C): At 4 months, soft tissue distress with *Pseudomonas aeruginosa* superinfection. (D): X-ray and clinical control at 2 months. (E): Clinical and X-ray control at approximately 8 months.

Outcome: No recurrence, satisfactory mobility.

Case 8 – Male, 29 years, type 1 diabetes (Fig. 8).

Classification at presentation

Type: Chronic refractory osteomyelitis

Justification: Distal femur fracture with severe comminution; osteomyelitis confirmed 6 months after fixation with a circular external fixator. Before HBOT, the patient completed ≥6 weeks of culture-directed antibiotic therapy (ceftriaxone + metronidazole) without clinical or microbiological resolution, despite local/instrumental measures. These features meet our definition of chronic refractory osteomyelitis.

Location: Distal femur.

Pathogen: *Flora polimicrobica.*

1. Pre-HBOT management

Managed with a circular external fixator after the index fracture. At ~6 months, there was no callus formation and nuclear imaging confirmed bone infection. Despite *a* ≥ 6-week course of targeted antibiotics (ceftriaxone + metronidazole) prior to HBOT, infection control was not achieved. Local/instrumental measures had been undertaken, but signs of infection persisted.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT at 2.5 ATA, for 60 sessions. Targeted antibiotic: ceftriaxone + metronidazole (continued per Infectious Diseases guidance). Antibiotic therapy combined with pseudotumor resection and antibiotic cement spacer with intramedullary nail core. Continued until normalization of inflammatory markers.

3. Post-osteomyelitis reconstructive management

At ~4 months, custom prosthesis implanted.

Follow-up: 5 months

Outcome: Stable prosthesis, no recurrence.

Case 9 – Male, 64 years, type 2 diabetes (Fig. 9).

Classification at presentation

Type: Chronic osteomyelitis

Justification: Internal malleolar fracture treated with cast; osteomyelitis at 45 days; no prior ≥6 weeks failed therapy.

Location: Ankle/malleolus

Pathogen: *Staphylococcus aureus.*

1. Pre-HBOT management

Fracture managed conservatively in cast. Osteomyelitis developed within 45 days.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT at 2.5 ATA, for 48 sessions. Targeted antibiotic: levofloxacin. Pseudotumor resection, antibiotic cement placement, targeted antibiotics.

3. Post-osteomyelitis reconstructive management

After 2 months, cement removed, intramedullary nail and bank bone graft inserted using RIA technique.

Follow-up: 8 months

Outcome: Solid union, no recurrence.

Case 10 – Female, 53 years, type 2 diabetes, cardiac comorbidity (Fig. 10).

Classification at presentation

Type: Chronic refractory osteomyelitis

Justification: Pelvic fracture with fixation; perioperative infection and osteomyelitis despite prior surgical care and antibiotics.

Location: Pelvis

Pathogen: *Escherichia coli.*

1. Pre-HBOT management

Vertical shear pelvic injury treated with anterior fixation. Posterior fixation not performed due to perioperative infection and dehiscence with pus. Devices removed, cultures obtained.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT at 2.5 ATA (25 min/5 min), for 52 sessions. Targeted antibiotic: meropenem. Temporary EF applied.

3. Post-osteomyelitis reconstructive management

Gradual functional recovery.

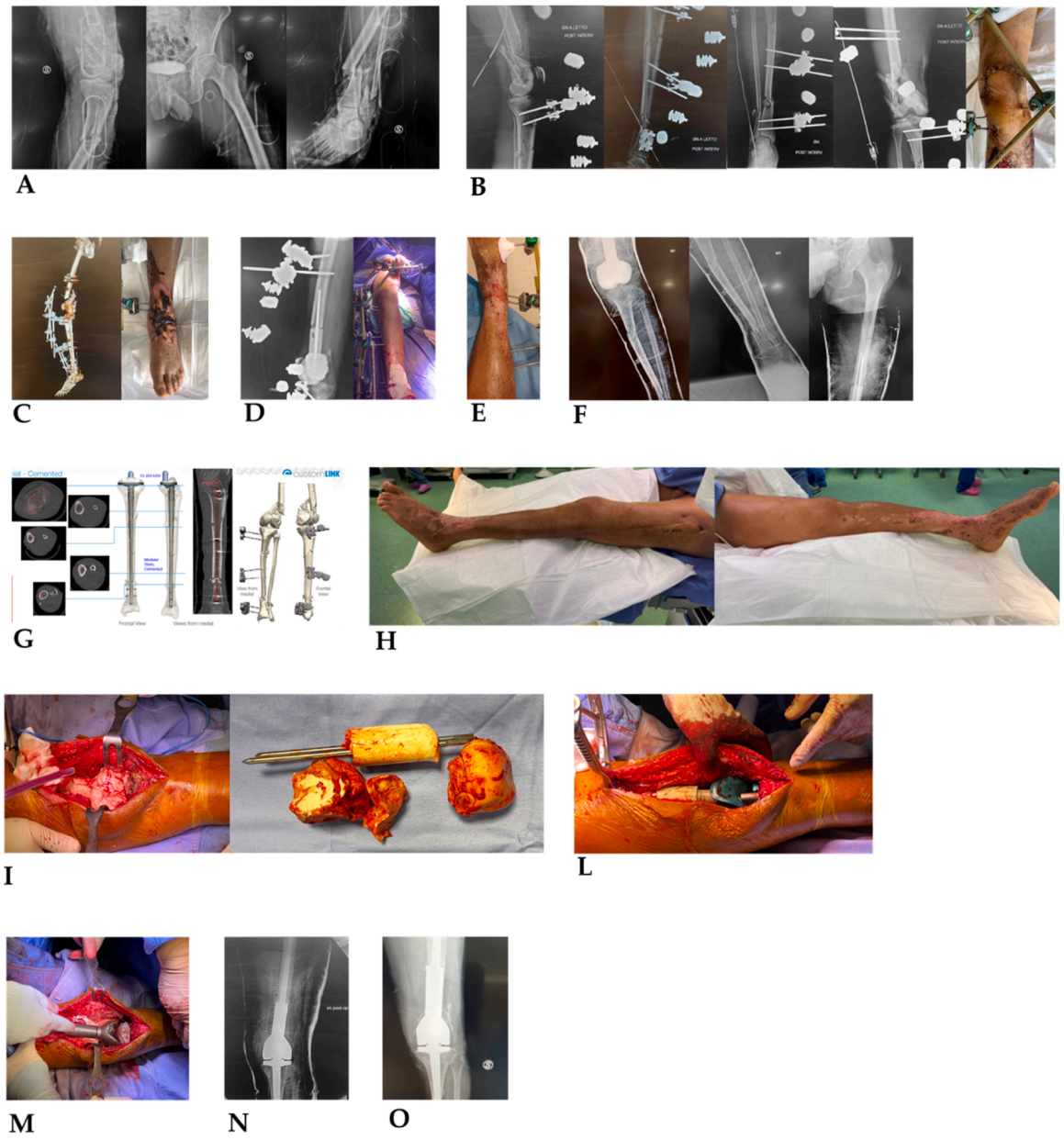

Fig. 7. (A): Exposed multifragmentary supra-intercondylar fracture of the left femur, bifocal fracture of the left tibia with medio-distal exposure and associated fibula fracture, loss of skin substance on the dorsal region of the left foot with extensive injury to the extensor tendons of the 2nd, 3rd, and 4th toes.
(B): Damage control and urgent management of soft tissues. (C): CT control – evolution of soft tissues.
(D): First surgery 30 days after trauma: Removal of the EF lateral access to the left thigh. Non-reducible femoral fracture, markedly osteomalacic bone. Removal of bone fragments. Femoral corticotomy. Antibiotic spacer implantation. Stabilization with EF in a bridging configuration with the foot in equinus. (E): Evolution of soft tissues at 40 days. (F): Second surgery: Removal of fixators and casting. (G): Customized surgical planning. (H): Pre-operative skin conditions before definitive surgery with custom-made mega prosthesis. (I): Removal of the spacer. (L): Biological chamber created by the antibiotic cement spacer, consisting of an induced vascularized membrane that promotes bone healing and facilitates later prosthetic reconstruction. (M): Custom-made tumor resection prosthesis for managing femoral bone loss and bilateral tibial fractures. (N): Post-operative X-ray. (O): X-ray after 1 year.

Follow-up: 12 months

Outcome: Stable pelvis, acceptable mobility.

Case 11– Male, 78 years, cardiac comorbidity, type 2 diabetes (Fig. 11).

Classification at presentation.

Type: Chronic osteomyelitis.

Justification: Post-traumatic femur osteomyelitis decades after initial fracture; chronic fistula; no documented recent ≥6 weeks failed therapy.

Location: Femur.

Pathogen: MRSA.

1. Pre-HBOT management.

Fracture treated with nail 20 years prior, nail removed after 10 years. Chronic draining fistula developed.

2. Active Treatment (Surgery, Antibiotics, and HBOT)

HBOT at 2.5 ATA (25 min/5 min), for 46 sessions. Targeted antibiotic: clindamycin, with targeted antibiotics. Pseudotumor resection, modular EF fixation, antibiotic cement spacer.

3. Post-osteomyelitis reconstructive management.

Following antibiotic therapy and HBOT, the patient was scheduled for a second surgery to remove the spacer and implant a wide resection prosthesis. However, considering his functional needs and ambulatory

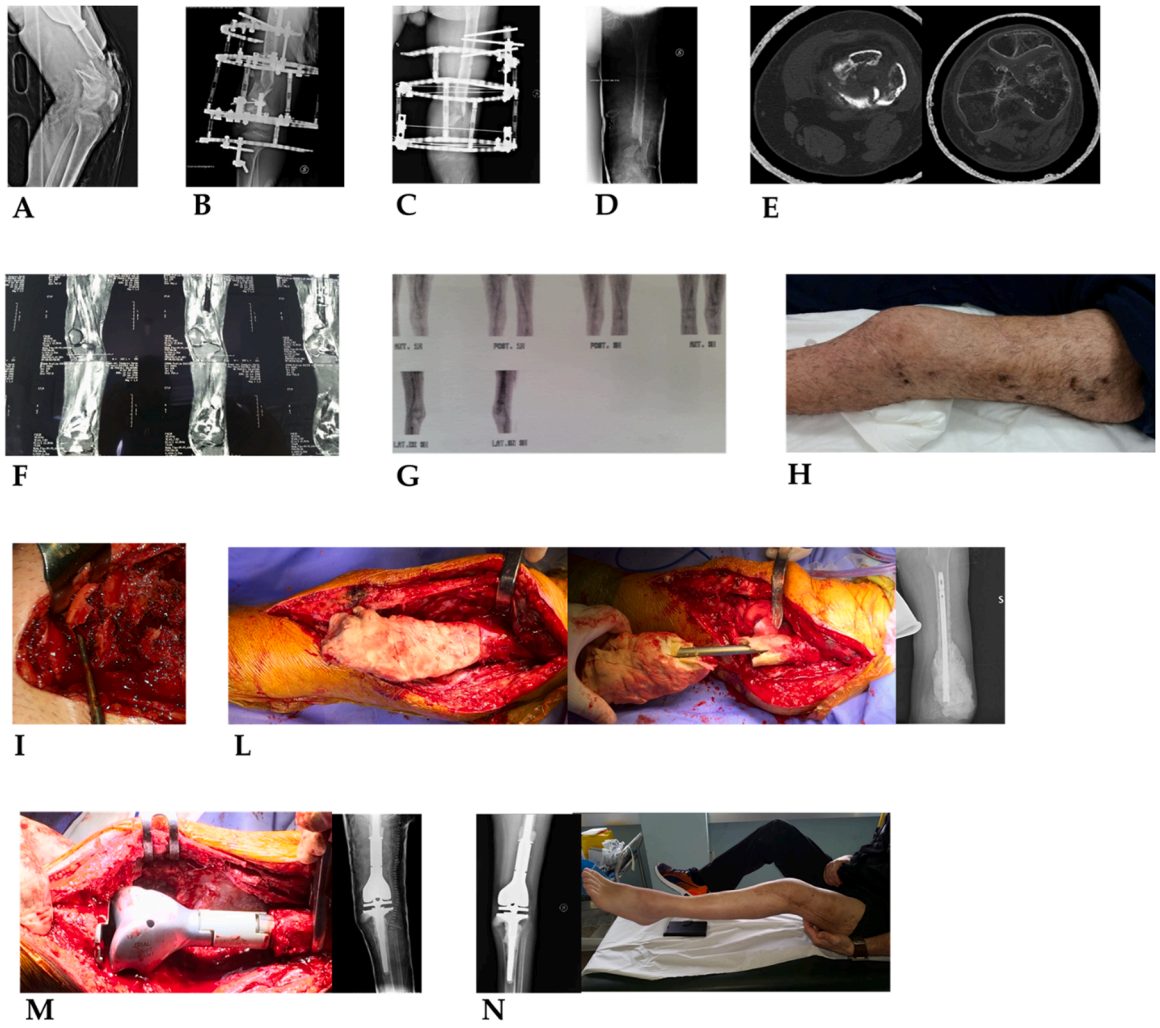

Fig. 8. (A): X-ray in the emergency department (ED). (B): X-ray after reduction and stabilization with a circular EF. (C): X-ray after 6 months, showing no evident callus formation. (D): X-ray after removal of the FE. (E): CT scan: osteomalacia. (F): MRI: magnetic resonance imaging. (G): Scintigraphy: positive for bone infection. (H): Clinical examination without fistulas. (I): Severe intra-operative osteomalacia. (L): Pseudotumoral resection and implantation of an antibiotic-loaded spacer with an intramedullary nail core. (M): Implantation of a prosthesis following extensive resection at about 4 months (after antibiotic therapy, HBOT and normalization of inflammatory markers). (N): X-ray and clinical follow-up after 5 months.

ability, the patient declined the second surgery and expressed satisfaction with the outcome.

At 6 months, patient declined planned prosthesis, satisfied with semi-rigid knee and cane-assisted walking.

Follow-up: 8 months.

Outcome: Ambulatory with stable joint, no infection recurrence.

4. Results

All patients were followed for a minimum of 1 year, with a mean follow-up duration of 15 months (range 12–18 months). Treatment success was defined as patients achieving adequate wound healing without discharge and no recurrence of infection during the follow-up period after HBOT.

In this case series, all 11 patients with post-traumatic osteomyelitis (6 chronic refractory / 5 chronic non-refractory) treated with adjunctive HBOT achieved infection resolution and wound healing, with no recurrence over a mean follow-up of 15 months (range 12–18). No major adverse events related to HBOT were reported. Clinical improvements were confirmed both radiographically and microbiologically. A detailed overview of each patient's clinical characteristics, including the number of HBOT sessions, pathogens identified in cultures, preoperative antibiotic regimens, comorbidities, and HBOT tolerability, is summarized in Table 1.

5. Discussion

5.1. Mechanistic rationale and clinical considerations for HBOT in osteomyelitis

HBOT increases dissolved oxygen in plasma and tissue oxygen tension (typically at 2.0–2.5 ATA), thereby improving host defense and wound biology through: (1) augmentation of neutrophil oxidative killing and macrophage function; (2) inhibition of anaerobic growth and disruption of biofilm architecture; (3) pro-angiogenic and osteogenic signaling (e.g., HIF-1α/VEGF) supporting neovascularization and bone repair; (4) edema reduction and modulation of inflammation and (5) potentiation of certain antibiotics in hypoxic microenvironments [30–34]. Because benefits derive from reversing local hypoxia and improving perfusion, HBOT is used adjunctively with meticulous debridement and culture-directed antibiotics, rather than as stand-alone therapy. Appropriate dosing and monitoring aim to balance therapeutic reactive oxygen species (ROS) / reactive nitrogen species (RNS) signaling with the risk of oxidative stress and barotrauma [35,36]. From

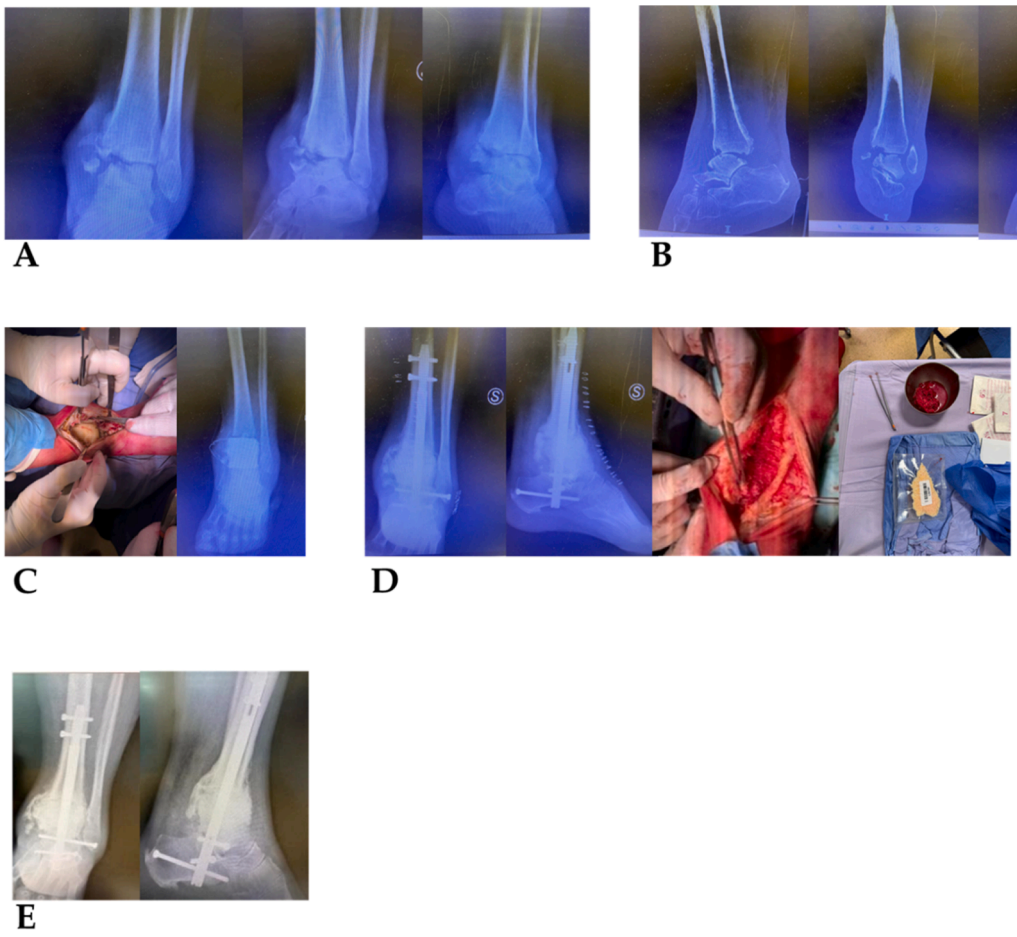

Fig. 9. (A): X-ray of chronic ankle osteomyelitis with bone exposure and secernent malleolar fistula; (B): CT view; (C): intraoperative image and X-ray after pseudotumor resection and interposition of antibiotic cement; (D): surgical toilet and preparation of site heads for reduction and arthrodesis with intramidullary nail and RIA (reamer-irrigator-aspirator) and spongy bone of bank; (E): X-ray control at approximately 8 months.

a physics standpoint, HBOT relies on two primary mechanisms: (1) increased dissolved oxygen content in blood and tissues due to elevated ambient oxygen partial pressure (Henry's law); and (2) reduction of intravascular and tissue gas bubble volume at higher ambient pressure (Boyle–Mariotte's law). The increased diffusion gradient from capillaries to hypoxic tissues is a direct consequence of mechanism (1), rather than a separate primary mechanism [37–40].

It is critical to balance these effects to optimize HBOT's benefits and minimize risks in clinical use (Table 2).

5.2. *Evidence synthesis and alignment with the present series*

Observational cohorts and case series on HBOT for chronic osteomyelitis have mainly included adults with post-traumatic long-bone disease (tibia/femur), peri-/post-surgical infections (including sternal osteomyelitis after cardiothoracic surgery), and diabetic foot/vasculopathic infections. *Staphylococcus aureus* is the most frequent pathogen, with Gram-negatives, especially *Pseudomonas aeruginosa*—often reported in lower-limb and implant-associated infections. Many prior reports did not stratify patients as refractory vs non-refractory at baseline, limiting cross-study comparisons [41–47].

Across studies, HBOT is almost invariably delivered as an adjunct to meticulous surgical debridement and culture-directed antibiotics (IV followed by PO). Typical chamber parameters range from 2.0 to 2.5 ATA for 90–120 min once daily, 5 days/week, over ~20–60 sessions; timing varies (pre-/peri-/post-operative), with some programs adding sessions after reconstruction (e.g., flaps, Ilizarov bone transport). Guideline documents (UHMS/ECHM; SIMSI) describe similar dosing and positioning HBOT as an adjunct for chronic/refractory osteomyelitis [48–51].

Aggregated chronic osteomyelitis (mixed etiologies): a 2018 systematic review (419 patients) concluded HBOT is a safe, potentially useful adjunct; pooled success/"infection controlled" rates reported across included series generally clustered ~60–85 % [52–56]. Clinical series in post-traumatic long-bone osteomyelitis report high rates of infection control when HBOT is integrated into aggressive surgical strategies and staged reconstruction. Diabetic foot/vasculopathic infections show more variable outcomes, largely influenced by perfusion status and off-loading quality. In sternal osteomyelitis/mediastinitis, retrospective comparative studies suggest a more favorable clinical course with adjunctive HBOT. Overall, HBOT is generally well tolerated; the most frequent adverse events are reversible middle-ear barotrauma and transient visual/myopic shifts, with serious events uncommon [57–59].

Unlike many prior reports, the current post-traumatic cohort explicitly differentiates refractory (6/11) from chronic non-refractory osteomyelitis (5/11) at baseline. All patients received standardized debridement plus culture-directed IV antibiotics (~2 weeks) followed by oral therapy (2–4 weeks) and a uniform HBOT protocol at 2.5 ATA (25-min O_2/5-min air cycles; 2 h/session; 5 days/week). At ≥12-month follow-up (mean 15; range 12–18 months), all 11 patients achieved infection resolution and wound healing without recurrence, a rate at the favorable end of the spectrum reported for comparable long-bone, post-traumatic cohorts using aggressive debridement and staged

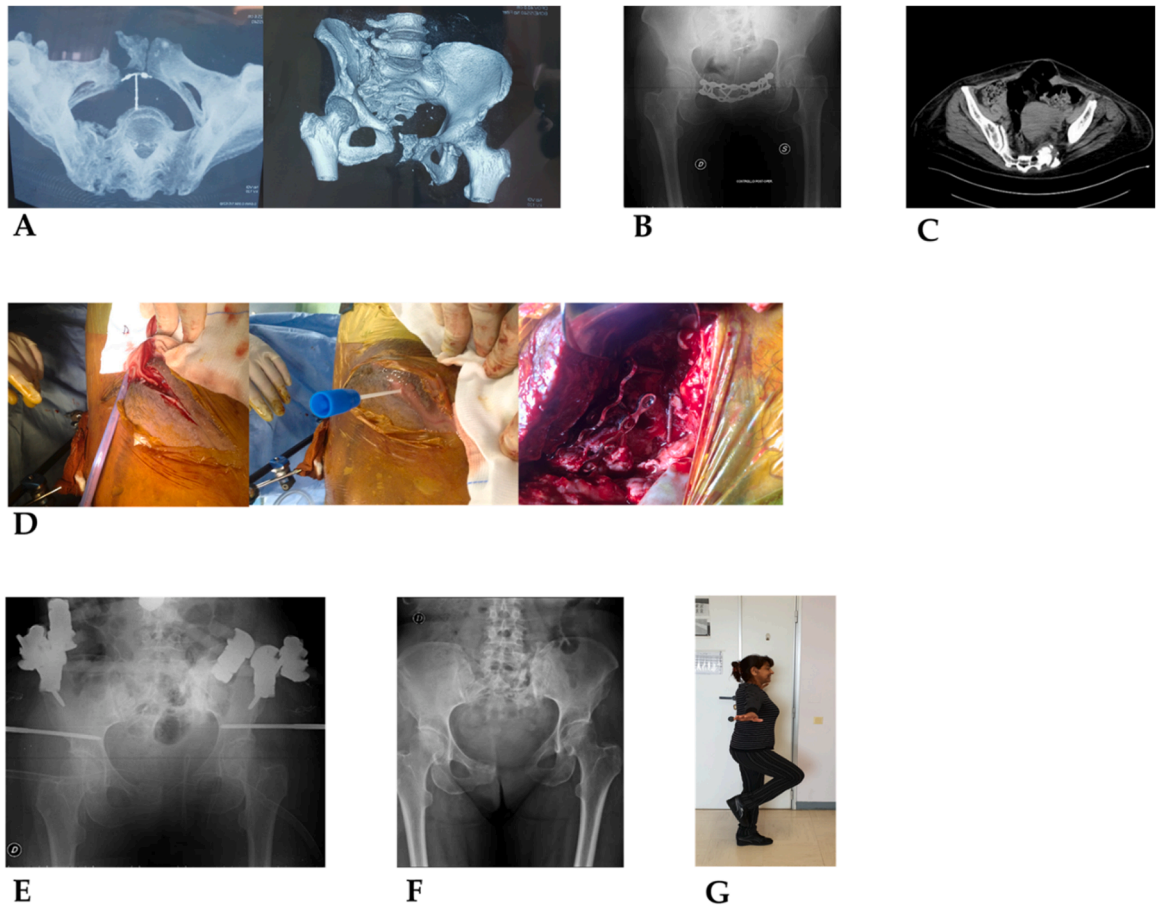

Fig. 10. A: CT scan in the ED. B: Post-operative: plates and screws in open reduction and internal fixation. C: CT scan at 25 days due to pain and swelling with fistula: extensive purulent collection. D: Abundant pus, removal of fixation devices. E: Stabilization with EF, antibiotic therapy and HBOT. F: Follow-up X-ray and clinical examination at approximately 12 months. G: Clinical mobility of the leg.

reconstruction. Differences in case-mix, extent of debridement, reconstructive strategy (e.g., Ilizarov transport vs resection arthroplasty), and outcome definitions still limit direct head-to-head comparison.

Guidelines from SIMSI recommend 2.4–2.5 ATA for 30–60 sessions, often split around surgical debridement (e.g., ~30–40 pre-op and ~20–30 post-op), aligning with UHMS/ECHM practice statements that position HBOT as an adjunct to surgery and antibiotics in chronic/refractory disease [60–65]. Taken together, prior cohorts in post-traumatic long-bone, peri-prosthetic, and diabetic foot osteomyelitis—treated with debridement plus antibiotics and adjunctive HBOT, report infection-control and limb-salvage outcomes within the ranges detailed above. Within this context, our series (explicitly stratified as refractory vs non-refractory) achieved complete infection resolution without recurrence at 12–18 months, positioning these results at the upper bound of reported ranges for comparable post-traumatic long-bone disease. Differences in case mix, surgical strategy, and outcome definitions remain important when interpreting cross-study comparisons [66–68].

5.3. Strengths and limitations of the present case series

5.3.1. This case series has several strengths

First, it describes a consecutive cohort of patients with chronic or refractory osteomyelitis, many of whom presented with complex comorbidities such as diabetes and cardiovascular disease, reflecting real-world clinical scenarios. Second, all patients were treated with a standardized multimodal protocol combining surgical debridement, targeted antibiotics, and adjunctive HBOT, and all underwent at least 12 months of follow-up, which allowed reliable assessment of recurrence. The uniform documentation of clinical, radiological, and microbiological findings further strengthens the validity of the reported outcomes.

5.3.2. Nevertheless, important limitations must be acknowledged

The absence of a control group and the small sample size (11 patients) limit the ability to establish causal inferences, generalize the results, and draw firm conclusions on the independent contribution of HBOT to infection eradication. As a single-center experience, the results may also be influenced by institutional expertise and local protocols. In addition, patient selection was not randomized: individuals with more severe or urgent conditions and comorbidities were prioritized, which may introduce selection bias. Another limitation is the heterogeneity of infection sites and pathogens, which complicates direct comparison across cases. Finally, while short-term and mid-term outcomes were favorable, longer follow-up would be necessary to confirm the durability of the results.

When compared with other published case series, our findings are consistent with the beneficial role of HBOT in refractory osteomyelitis, particularly in diabetic or vascular-compromised patients. However, similar studies also highlight the need for randomized controlled trials and standardized HBOT protocols to establish stronger evidence for its efficacy and cost-effectiveness [69,70].

6. Conclusions

The study underscores the potential of HBOT as a valuable tool in managing osteomyelitis, particularly in patients with diabetes and

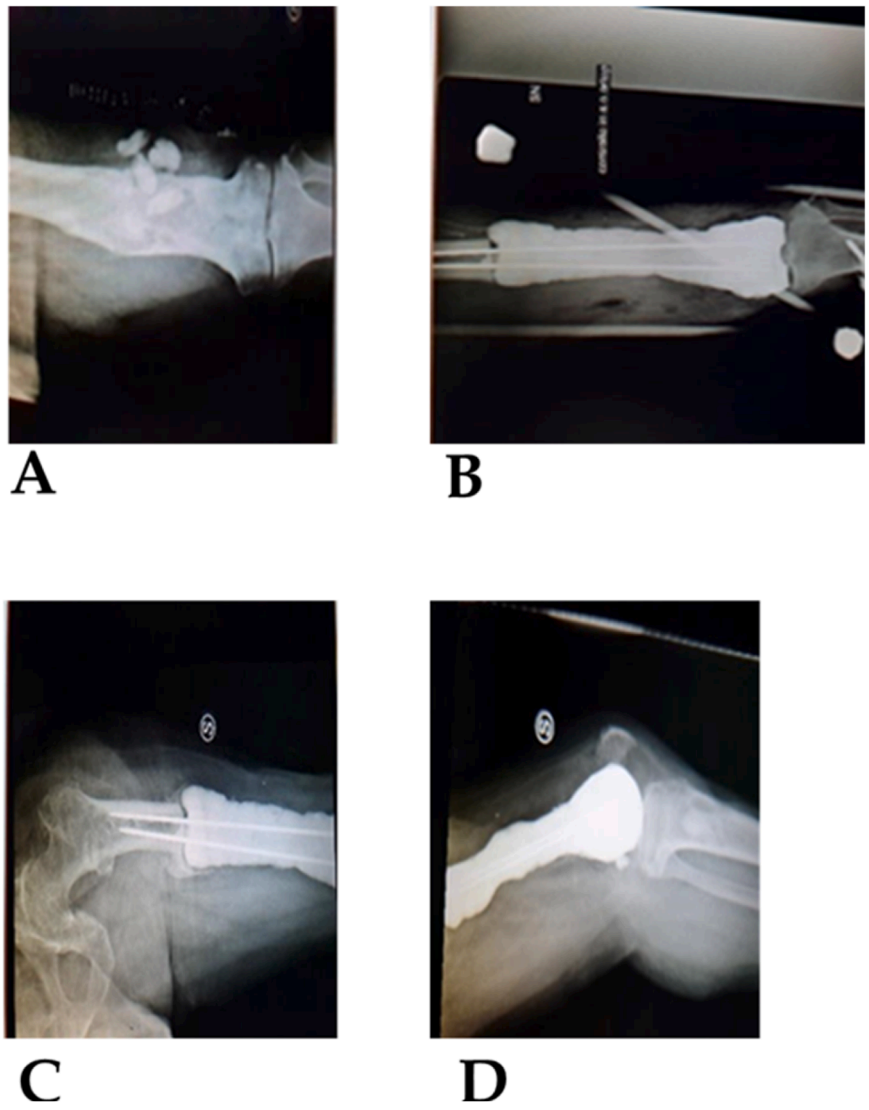

Fig. 11. (A): X-ray imaging at the time of initial presentation. (B): Pseudotumoral resection and implantation of an antibiotic-loaded cement spacer with a metallic core, stabilized using a knee-bridging EF. (C): X-ray imaging after 8 months: The patient is ambulatory with knee stiffness. (D): X-ray imaging after 8 months, sagittal projection of the knee.

cardiovascular disease, which complicate infection treatment and elevate amputation risk. HBOT increases tissue oxygen levels, supports blood vessel growth, and boosts immune response, directly combating infection and improving wound healing in challenging cases. Our experience suggests that adjunctive HBOT, when combined with standard surgical and antibiotic therapy, may contribute to successful management of chronic refractory osteomyelitis. In this single-center case series, combined treatment with culture-directed antibiotics, indicated surgical debridement, and adjunctive HBOT was associated with clinical eradication of osteomyelitis in all 11 patients, with no recurrences identified over a mean follow-up period of 15 months. In sum, while osteomyelitis is difficult to treat, integrating HBOT into treatment protocols offers promising benefits for infection management and patient quality of life.

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Ethics committee

Bari oncology ethics committee code:" Prot.n 502 of 16.07. 10lh Local Ethics Committee Secretariat Prot. 1737 /CEL.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT (OpenAI) in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full

Table 1
Clinical summary of the 11 patients treated with adjunctive HBOT, including microbiological findings, antibiotic therapies, number of hyperbaric sessions, comorbidities, and side effects.

Patient ID	Age (years)	Comorbidities	Infection Site	Time from injury to osteomyelitis diagnosis	Microorganisms Identified	Previous Antibiotic Therapy	HBOT Sessions	HBOT Completed	Side Effects
Case 1	29	Type 1 Diabetes	Clavicle	≈4 months	Staphylococcus aureus	Amoxicillin-clavulanate (≥6 weeks, pre-HBOT)	45	Yes	None
Case 2	56	Type 2 Diabetes	Distal Tibia	≈4 months	Pseudomonas aeruginosa	Ceftriaxone (≥6 weeks, pre-HBOT)	60	Yes	Mild ear barotrauma
Case 3	26	Type 1 Diabetes	Proximal Tibia	≈3 months	Staphylococcus aureus	Vancomycin (≥6 weeks, pre-HBOT)	65	Yes	None
Case 4	76	Cardiopathy, Smoking	Femur (Periprosthetic)	≈10 months	MRSA	Linezolid (≥6 weeks, pre-HBOT)	50	Yes	None
Case 5	65	Type 2 Diabetes, Smoking	Distal Tibia	≈5 months	Staphylococcus aureus	Cefazolin	40	Yes	None
Case 6	50	Type 1 Diabetes	Tibial Pilon	≈4 months	Pseudomonas aeruginosa	Piperacillin-tazobactam	35	Yes	Mild vision changes
Case 7	61	Cardiopathy	Femur	≈4 months	Staphylococcus epidermidis	Cefepime	55	Yes	None
Case 8	29	Type 1 Diabetes	Distal Femur	≈6 months	Polymicrobial flora	Ceftriaxone + Metronidazole (≥6 weeks, pre-HBOT)	60	Yes	None
Case 9	64	Type 2 Diabetes	Medial Malleolus	45 days	Staphylococcus aureus	Levofloxacin	48	Yes	None
Case 10	53	Type 2 Diabetes, Cardiopathy	Pelvis	≈25 days	*E. coli*	Meropenem (≥6 weeks, pre-HBOT)	52	Yes	None
Case 11	78	Type 2 Diabetes, Cardiopathy	Femur (Post-traumatic)	≈20 years (late chronic)	MRSA	Clindamycin	46	Yes	Mild ear discomfort

Table 2
Summary of the key features and physiological effects of HBOT using a single-seat hyperbaric chamber. The table highlights session parameters, mechanisms of action, and clinical benefits.

Concept	Explanation
Hyperbaric Chamber	A single-seat chamber used to deliver 100 % oxygen under 2–3 atmospheres of pressure.
Duration of Treatment	Sessions last 1.5–2 h, up to three times daily, with a total of 20–60 sessions depending on clinical needs.
Mechanism	Two primary physical mechanisms: (1) increased dissolved O_2 (Henry's law) → higher tissue O_2 tension; (2) bubble size reduction (Boyle–Mariotte's law). Biological effects (e.g., leukocyte function, angiogenesis, biofilm modulation) derive mainly from (1)
Physiological Benefits	1. Resolves tissue hypoxia and reduces edema (hyperoxia-induced vasoconstriction with preserved oxygen delivery). 2. Anti-inflammatory modulation: ↓ pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), attenuation of NF-κB signaling, ↓ leukocyte–endothelium adhesion, promotion of macrophage M2 polarization. 3. Controlled ROS/RNS signaling with upregulation of antioxidant defenses (e.g., SOD, catalase, HO-1). 4. Enhances growth-factor expression and stem/progenitor cell mobilization and stimulates angiogenesis/osteogenesis and tissue regeneration; may increase antibiotic efficacy within biofilm-rich microenvironments.
Clinical Outcomes	Improves oxygen delivery to tissues, supports wound healing, boosts immune function, and modulates inflammation.

responsibility for the content of the published article.

CRediT authorship contribution statement

Marco Filipponi: Writing – review & editing, Resources, Conceptualization. **Gianna Dipalma:** Software, Resources, Methodology. **Laura Ferrante:** Writing – original draft, Methodology, Conceptualization. **Giuseppe Rollo:** Writing – review & editing, Resources, Conceptualization. **Luigi Valentino:** Writing – review & editing, Formal analysis, Data curation. **Francesco Inchingolo:** Software, Resources, Methodology. **Giacomo Farì:** Supervision, Formal analysis. **Luciano Allegretti:** Validation, Supervision, Software. **Andrea Palermo:** Visualization, Supervision, Formal analysis. **Angelo Michele Inchingolo:** Validation, Methodology, Data curation. **Alessio Danilo Inchingolo:** Software, Resources, Methodology.

Declaration of competing interest

Authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nexres.2025.100830.

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