

## ORIGINAL PAPER

**ROLE OF PROSTAGLANDINS AND ULTRASOUND DEBRIDEMENT IN HEALING OF SEPTIC ULCERS AND FISTULA - COMPLICATION OF PROSTHESES IN OSTEOMYELITIS INFECTED KNEE**

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**Abstract**

Implant of devices in patients affected by serious osteoporosis following chronic inflammatory diseases like rheumatoid arthritis represent a great clinic and surgical challenge, especially when associated with bacterial infections. Here we report a case of a 75 years old woman who developed recidivism of infection, after prosthesis' implantation. Although repeated treatments with both topical antibiotics and systemic ones, knee edema and purulent secretion were constant. Conventional treatment based on topical and systemic antibiotics' administration was replaced with a vascular rehabilitative medical therapy. Furthermore, the patient has undergone surgery for ulcers and fistulas debridement at the knee, the lower third of thigh and the upper third of leg. The analyzed case suggested that the experimental protocol we used to treat implant – derived osteomyelitis with cutaneous fistulization could reduce the healing time between the primary lesion and osteomyelitis complication, but only if patient presents an acceptable condition of his immune system.

**Key words:**

osteomyelitis, prostaglandins, implants, immune system

**Introduction**

Implant of devices in patients affected by serious osteoporosis following chronic inflammatory diseases like rheumatoid arthritis represent a great clinic and surgical challenge, in particular when associated with bacterial infections [1]. Implant – derived inflammatory process involving bone and bone marrow, are known as osteomyelitis [2]. Incidence is estimated to be about 1 – 3% of total lower limbs after arthroplasty treatments and around 2 – 27% for post – traumatic cases [3]. Osteomyelitis leads to bone destruction and necrosis, and it has infectious etiology [4]. Bone necrosis results from acute inflammatory reaction and subsequent periosteum involvement. Following bone resorption is an event of chronic stage, due to cytokines released by inflammatory cells [5]. Infection leads to a biofilm's formation with consequent development of prosperous microenvironment for bacterial growth [6]. Today, *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*) are considered the most frequent aetiological agents responsible of about 90% of the cases of pyogenic osteomyelitis, even in the absence of clinical signs of infection [7]. However, infections caused by other Gram-negative bacteria, especially Enterobacteriaceae, were also reported due to vascular insufficiency [8]. Therefore, understanding

the molecular mechanisms involved in biofilm formation and the interaction between the microenvironment and the host in device-related infection could lead to improve surgical implant techniques, reducing patients' postoperative negative consequences [9]. Recent studies have shown that treatment with a mix of vasodilator prostaglandins, such as prostaglandin E1 (PGE1) and prostaglandin E2 (PGE2), and antibiotics can lead to a rapid recovery from osteomyelitis, without the need to remove implanted devices [10]. Prostaglandins appear to reduce biofilm formation and chronicization of the infection, and stimulate a rapid and effective clearance of the infecting microorganism [11]. Nevertheless, it is still unknown the real mechanisms by which PGEs realize it. Here we report a case of recovery from implant – derived osteomyelitis after management with antibiotics, anti-thrombotics and PGE1 vasodilator in a patient with previous tibial plateau fracture repaired with internal fixation devices.

### Case presentation

Here we report a case of a 75 years old woman who developed recidivism of infection, after prosthesis' implantation. Due to post-menopausal osteoporosis, prostheses at both knees were implanted. Particularly, twenty years ago, she had implanted prosthesis at the right one and no rejection events were reported. Also revision surgery was well tolerated. However, two years ago prosthesis was also implanted at the left knee, with consequent recurrent infectious episodes. Basing on computed axial tomography (CAT), osteomyelitis was, then, diagnosed. Early inflammatory symptoms began one week after

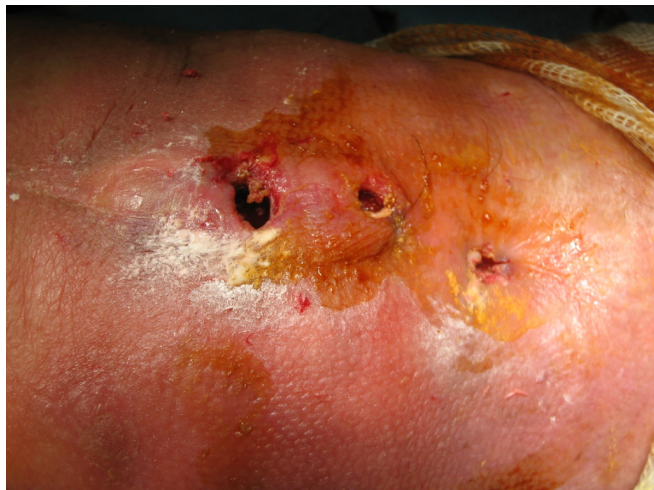


Fig.1. Limb before treatment. It is clearly evidenced a huge infection with secreting fistula.

surgery until they become chronic. Two months later prosthesis was removed and replaced with an antibiotic spacer. Microbiological analysis performed on tissue revealed a double infection by Methicillin-Resistant Staphylococcus Aureus (MRSA) particularly, Staphylococcus epidermidis, and Pseudomonas aeruginosa. Then, five months later, a novel prosthesis was implanted. However, limitation of joint functions continued and, three months later, a secreting fistula was diagnosed (Fig. 1). Although repeated treatments with both topical antibiotics (Ceftriaxone) and systemic ones (quinolones), knee edema and purulent secretion were constant.

### Materials and methods

Due to repeated failures in healing following conventional therapeutic treatments, the patient was hospitalized at Vascular Surgery Department of "Orestano" Nursing Home, in Palermo. On admission, she showed the left knee site of fistulas and cutaneous ulcers together with purulent secretion. Conventional treatment based on topical and systemic antibiotics' administration was replaced with a vascular rehabilitative medical therapy, as follows:

- Prostaglandins: one 60 ml vial diluted in 250 ml of physiological solution, intravenous slow-release;
- Propyl-carnitine: one intravenous vial diluted in 100 ml of physiological solution;
- Antithrombotics: one 0,3 subcutaneous vial, twice daily;
- Cephalosporin: one gram per day;
- Teicoplanin: one 200 mg intravenous vial;
- Anti-edema: two tablets for day;
- Interleukin 10: twenty drops, three times per day;
- Medications and advanced bandage with iodoformic gauze, soaked by amikacin.

The entire described therapeutic protocol was followed for a period of 11 days of treatment.

Moreover, the patient has undergone surgery for ulcers and fistulas debridement at the knee, the lower third of thigh and the upper third of leg. The intervention was performed by a "Bisonic" instrument, with 27 mhz probe and by a bacterial killing with 35 mhz probe.

At post-operative control, the wound swab showed no bacterial development. Moreover, after the 11 days of medical treatment and the ultrasound debridement, reduction of edema's volume, reepithelization of ulcers and cessation

of purulent secretion were observed, thanks to eradication of microbial growth.

At discharge, the ensuing domestic therapy was prescribed to follow for a period of 20 days:

- Levofloxacin: a 500 mg tablet, twice per day, for a period of 7 days;
- Antithrombotics: one 0,6 subcutaneous vial;
- Interleukin 10: 20 drops, three times per day;
- Capillaries-protector: one tablet, three times per day;
- Propionyl-carnitine: one tablet, twice per day.

## Results and discussions

Postoperative infections and osteomyelitis are plenty described in detailed protocols of international Orthopedic Trauma Societies [12]. Today, as for most relevant and complex pathologies, a personalized approach is applied in orthopedic surgery, evaluating characteristics of the initial trauma, the patient's risk factors and follow-up rehabilitation [13]. We propose an innovative protocol for infectious complications management of devices implant. After close examination of the literature, we maintain that this is the first clinical case of rapid recovery from osteomyelitis with ulceration due to bone fistulization in an immune-competent patient with no risk factors (e.g., diabetes), following a treatment protocol for potential post-fracture infection complications that included PGE1.

As evidenced by recent studies, prostaglandins derivatives act as powerful stimulators of adenylate cyclase enzymes, increasing cyclic adenosine monophosphate (cAMP) levels and inhibiting hemostasis [14]. These molecules induce vasodilatation directly on vascular smooth muscle, and indirectly by reducing oxygen request and reactive oxygen species (ROS) production in



Fig. 2. Limb after treatment. Scenario is totally changed, showing an important closure of fistula.

injured organs [15]. Our case seems to confirm the recent results published by Lovati et al. [16] which suggest that a mix of antibiotics and vasodilators might prevent bone infections in animal models. Nevertheless, it was only when we combined antibiotic therapy with vascular-active molecules that we saw a rapid improvement in the clinical scenario (Fig. 2). It is possible that similar changes can occur after PGE1 administration in the bone vessels, where alprostadil associated with nadroparin calcium may contribute to intraosseous hyperperfusion and block toxic osteonecrosis associated with osteomyelitis. Basing on this case report and other research on organ transplants and animals [17], the authors suggest that PGEs could play a favorable role in bone infections evolutions. Our hypothesis is based on the assumptions that the creation of biofilms could determine the development of an anoxic microenvironment, in which many Gram negative bacteria are able to enforce it and proliferate. Due to the characteristic anaerobiosis, probably caused by biofilm encapsulation, the interruption of blood flow inhibits antibiotics to reach infected areas, inducing necrosis in the involved tissue. Thus, delivery of a mix made of antibiotic and PGEs, due to a renewed vascularization, could permit the drug to act in the affected areas (Fig. 3).



Fig. 3. Limb at the final stage of treatment. Fistula is near to be totally closed, with no relevant signs of infection.

Nevertheless, the correct functionality of immune system is fundamental to resolve the infection. We want highlight that previously described treatment, in immunodeficient patients, could be less incisive or even useless, probably due to lack of the ability to fight bacteria proliferation, especially during first stages of infection. The direct consequence of such scenario could be that the remarkable bacterial load might be



very difficult to challenge, even if in presence of antibiotics.

## Conclusions

Although the clinical-surgical treatment applied to the patient did not foresee the removal of infected prosthesis, infection has been eradicated together with the reduction of knee's edema and ache. Therefore, the innovative therapeutic methods that forecasts prostaglandins' use, combined with targeted antibiotic therapy and surgical ultrasound debridement treatment has been proven innovative and effective, and it can be used as good practice, before deprosthesis.

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