Chapter 6

Treatment of Non-Union and Bone Loss of Tibial Pilon

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Abstract

Non-union is a fracture with no healing potential without a further surgical procedure. Diagnosis of non-union can be done in case of healing failure from 6 to 9 months after the first fracture. We consider appropriate to keep the attention of the reader on the relevance that more frequent traumatic mechanisms have in relationship with evolution and eventual failure of healing processes. In literature, non-union mean rate for tibial pilon fractures is around 5% independently from the synthesis technique used; as main causes we can recognize a significant fracture's comminution ad eventual bone loss, vascular damage, and local infection. Risk factors can be divided into two big groups: factors proper of the patient at the moment of injury (age, diseases, drugs, smoke, etc.) and characteristics of the trauma itself (comminution and dislocation of fragments, involvement of soft tissues, topography, distance between fragments). Tibial pilon fractures are mainly caused by high-energy trauma. This kind of dynamic determines not only more serious damage to the bone, but often cause damage of the surrounding tissues. Following important lesions of the periosteum and of the vascular network and after a suboptimal synthesis caused by comminution and dislocation of fragments is frequent with the evolution toward a bad bone healing process. Bone healing was, in the last 50 years, argument of intense research activity. The incidence of non-union is growing steadily, although principles and materials of synthesys are well standardized. Recently it has been codified the "diamond concept," which clarified different appliances mechanical and biological, these distinguished between cells, scaffolds, and growth factors. Under the mechanical profile, it must be restored the spectrum of stability that consider the set of bone and synthesis implanted. The spectrum of stability interprets Wolf's law providing indications on the need to modulate the rigidity of the synthesis in reason of the level of instability of the pseudoarthrosis itself. During the years several kinds of non-union classifications have been proposed. The most widespread until now is the one proposed by

Weber–Cech in 1976, which distinguishes vital forms (hypertrophic and oligotrophic) from non-vital forms (atrophic). In 2007 a new score classification system has been processed, which is the "Non-Union Scoring System (NUSS)," which divides patients in four big groups by score awarded based on the real non-healing risk. The NUSS represents an innovative approach to the problem because it understand the multifactorial reasons of failure, explains why in a variable percentage of cases (depending from de district affected), the healing is not obtained, even with a correct treatment and above all make possible the drafting of a therapeutic choice algorithm. Biotechnologies at our disposal are synthetic growth factors, the autologous growth factors and platelet-rich plasma, mesenchymal stem cells, and scaffolds or bone substitute. The biologic chamber represent the ideal site for bone regeneration; it is a bio-reactor in which are present all those elements at the base of the concept of diamond. The chamber needs to be aseptic, vital, mechanically stable, and sealed but selectively permeable. Thanks to the use of megaprosthesis not only in oncologic orthopaedics, but also it is now possible to avoid the amputation or long and often inconclusive treatment of lengthening or ankle arthrodesis. The new frontier in treatment of non-unions will be genetic therapy, that is, the possibility to transport to the patient those genes that con drive to the formation of good bone callus and his maturation toward strong bone.

Keywords: Tibial pilon, tibial plafond, non-union, biological chamber, biotechnologies, NUSS, megaprosthesis, stem cells, growth factor, diamond concept

1. Definition

Non-union is a fracture with no healing potential without a further surgical procedure. Diagnosis of non-union can be done in case of healing failure from 6 to 9 months after the first fracture. Time is variable between fracture types, at the level of the tibial pilon diagnosis can be done only 9 months after trauma. Between long bones, tibia is the most frequently involved by this complication.

We consider appropriate to keep the attention of the reader on the relevance that more frequent traumatic mechanism have in relationship with evolution and eventual failure of healing processes.

As known, tibial plafond fractures are mainly caused by axial overload more than torsional forces, that are, responsible more frequently of malleolus fractures.

The mechanism of axial overload presupposes a major transfer of energy which leads to a more rapid deformation of the bone tissue until resistance limit is reached. The energy released at the broken point to soft tissues surrounding causes characteristics soft tissues lesions, which are present in those kinds of fractures and make the healing more complex: associated fractures, dislocation of the astragalus; vascular and nervous lesions; muscle and skin lesions with comparison of enlarged edema.

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2. Incidence

The tibial pilon non-union incidence in the literature ranges between 2 [1] and 18% for Ruedi and Ovadia [2], and those results have been confirmed even by McFerran [3].

Studies of Havet in 2006 and Bacon and Wang in 2010 [4–6] report similar statistic data from which result in similar non-union rate independently from the kind of ostheosynthesis used.

After those premises and therapeutic compromises sometimes adopted in treatment of the tibial pilon fractures, it is easy to understand the data present in literature for which non-union mean rate is around 5% independently from the technique used, recognizing as main causes a significant fracture's comminution ad eventual bone loss, vascular damage, and local infection [4–7].

3. Risk factor

At this moment, we are able to classify risk factors, related to the establishment of non-union, in two big groups: factors proper of the patient at the moment of injury and characteristics of the trauma itself.

Between general risk factors, we can found advanced age (especially in female population penalized by hormonal imbalances resulting from the menopause); non-compensated diabetes (besides the well-known vascular and nervous disorders, it was observed a decrease in the formation of collagen and cells involved in bone callus formation and maturation); osteoporosis; muscle atrophy; lifestyle (food, smoke, alcohol); drugs as NSAD, often prescribed against pain after surgery (the reason of their bad influence on healing time is to be found in decreased macrophagic activity and prostaglandin synthesis induced by COX 1 and 2 inhibition) [8].

Local risk factors, that are inherent to the trauma itself, include

- High-energy trauma (very frequent in tibial pilon fracture) in which occurs a greater comminution and dislocation of fragments and a greater involvement of soft tissues and vascular system, with heavy impact on blood support at the fracture's site. Experimental studies have demonstrated as the physiological healing process is guided, with a peak 2 weeks after the trauma, by blood supply from the cortical bone. As a consequence, a wide lesion of soft tissues and large hematoma, narrowing blood support to the cortex itself, reduce the inflow of nutrients and osteogenic cell to the fracture site, condition that determine an increased risk of necrosis and delayed healing, with possible evolution toward atrophic pseudoarthrosis [9].
- Topography: metaphyseal and diaphyseal fractures have different healing time and a different incidence of non-union, due to the bone callus synthesis process that involve mainly spongy bone, highly vascularized, and with a faster regenerative kinetics [10].
- Interfragmentary distance: an excessive distance between bone fragments, or the presence of a third fragment, induces to the onset of non-union [11]. In this situation, a correct

anatomic reduction of fragments with the intent to preserve vascularization is a positive prognostic factor.

Tibial pilon fractures are mainly caused by high-energy trauma. This kind of dynamic determines not only more serious damage to the bone, but often cause damage of the surrounding tissues.

Following important lesions of the periosteum and of the vascular network and after a suboptimal synthesis caused by comminution and dislocation of fragments is frequent with the evolution toward a bad bone healing process.

After the end of the 1980s, thanks to statistic analysis proposed by authors as McFerran [3] and Dillin [12] and, more recently Piper et al. [13], it was possible to clarify the importance of risk factors that affect the prognosis of tibial pilon fractures.

Distal tibia is characterized by a relatively poor vascularization and skin coverage. These structures, when seriously damaged from the mechanism of injury, penalize the healing of fractures.

There are several factors to whom was charged complicity in the development of such an eventuality; among the most important, we find:

- A residual bone loss after the reduction of the fracture;
- The precariousness of the metaphyseal vascularization;
- A loss of skin coverage after injury;
- An inadequate mounting in case of external fixation synthesis;
- A wide deperiostization during synthesis with plate and screws.

Its, however, not negligible the eventuality that fractures of patients treated correctly, and with low-risk rate, could evolve toward non-union.

It seems that the population of patients affected by non-union is somehow selected toward those patients that present a higher risk of this complication. For this reason, it seems even more important to analyze and classify these patients to define better surgical program and even in some way to clarify the risk of treatment failure.

Is not a rare observation that some subject, unfortunately few in number, even if treated not correctly shows “miraculous healing.” Instead, is greater the number of patients that, although treated in a good way, under go several in effective surgical procedures.

4. Bone healing

Bone healing was, in the last 50 years, argument of intense research activity. The number of non-union is constantly growing although principles and material of synthesis are standardized. This observation finds an explanation in increase of life expectancy, in a population of female and "young" senior addicted to activities at risk of injuries and in survival to car crash deadly until few years ago. But does not clarify the feedback of those cases which, even after good cares, does not undergo to healing.

It can be reasonably supposed that the improvement of cares offered to the injured patient has in some way modified the population of patients with non-union.

In the past surgical errors, lack of knowledge of biomechanical principles that guide a good synthesis and low-quality materials created cases of non-union that need only a more correct treatment.

Recently is been codified the "diamond concept" that clarified different appliances mechanical and biological, these distinguished between cells, scaffolds, and growth factors [14].

Under the mechanical profile, it must be restored the spectrum of stability that consider the set of bone and synthesis implanted. The spectrum of stability interprets Wolf's law providing indications on the need to modulate the rigidity of the synthesis in reason of the level of instability of the pseudoarthrosis itself [15].

5. Non-union classification

To be able to encode treatment's guidelines, we must first proceed to a correct nosological assessment of the problem. During the years, it has been proposed several kinds of non-union classifications.

The most widespread until now is the one proposed by Weber–Cech in 1976, which distinguishes vital forms, hypertrophic, and oligotrophic, or rather with possible biologic response, from non-vital forms or rather non-reactive atrophic kind, frequently accompanied by osteonecrosis, and even by bone loss [16].

This classification is based on a descriptive radiological analysis of the kind of non-union evaluating only the bone, we think that a more complete classification, even from a prognostic point of view, should take into account even the quality of soft tissues and the general conditions of the patient (comorbidity, lifestyle, drugs, genetic diseases).

For this reason in 2007 have been identified through the study of international literature all possible risk factors in the healing of fractures [8].

After has been processed a score classification system, the "Non-Union Scoring System (NUSS)" [17] with double finality: not to detect a "radiographic case" but a "patient" and then detect, in relationship with the real non-healing risk, those cases in which is necessary, not only a correct surgical treatment, but even a right biotechnological approach. The NUSS represents an innovative approach to the problem because it understand the multifactorial reasons of failure, explains why in a variable percentage of cases (depending from de district affected) the healing is not obtained, even with a correct treatment and above all make possible the drafting of a therapeutic choice algorithm [18, 19].

6. The NUSS

In the new NUSS classification of 2008 are considered all the variables and all risk factors, giving to anyone a score based on clinical experience and scientific evidences and defining so a treatment guideline depending from the final score [17].

The final score, obtained by the sum of the individual score, allows to compare different patients with different non-union, making them objectively comparable according to a principle of complexity.

Atrophic forms of non-union can have better prognosis and greater chance of healing than oligotrophic reactive forms, in patients affected by impaired general health condition, as in example a non-compensated diabetes.

7. The variables considered are as follows:

- The bone (quality, kind of fracture, number of previous surgical procedures, and their invasiveness, non-union classification according to Weber–Cech, adequate first surgical procedure in order to mechanical stability, bone gap, alignment);
- Soft tissues (tissues conditions, vascurarization and possible surgical procedures on soft tissues and skin coverage);
- The patient (ASA score—American Society of Anesthesiologists—diabetes, laboratorys exams, infective condition, drugs, and smoke).

First group, score from 0 to 25, made mainly as mechanical problem, the treatment indicated is the fracture stabilization, optimizing or changing the synthesis system.

Second group, score from 26 to 50, made the problem as both mechanical and biologic, the treatment needs correction of the synthesis and biologic stimulation of the fracture site, obtained with the help of physical means (magnetic electro-pulsated fields, extracorporeal shock wave) or with the application of biotechnologies in monotherapy [20–22].

Third group with score from 51 to 75. Is a complex problem characterized by high gravity of both biological and mechanical conditions? It is almost always required the resection of the non-union site, and then, is present a bone loss that have to be restored. Next to bone transport techniques with external fixator and tibiotarsal joint arthrodesis at the docking point, there is indication to autologous bone transplant and biotechnologies (cells, scaffolds, and growth factors) applied in polytherapy according to the principles of the "Biological Chamber" [23–25] [case 1].

Fourth group with score from 76 to 100. Are non-union of such gravity to be assimilated to an almost unsolvable problem and so can require a limb amputation or the implant of megaprothesis [case 2].

There are no doubt that the third group non-union (51–75 points) are the more difficult to treat and often are those recalcitrant forms that come to experts after too many surgical procedures without outcome.

In this group, we think is appropriate the application of biotechnologies in order to avoid unnecessary use of economic resources.

8. Biotechnology

Biotechnology at our disposition are synthetic growth factors (GFs) as human bone morphogenetic recombinant proteins (rh-BMPs), autologous growth factors (AGFs) contained in platelet-enriched plasma (PRP), mesenchymal stem cells (MSCs), and scaffolds or bone substitutes.

- Growth factors (GFs)

  Since the second half of 1990s, it has been demonstrated that some growth factors act as powerful stimulators of the in vitro osteoblastic proliferation and of the in vivo bone healing, such as to turn out really useful in aiding the healing process if correctly applied at the site of the lesion [26]. Thanks to the evolution of the tissue engineering, it is been possible to produce the single growth factors with the recombinant-DNA technique, particularly the rh-BMPs. Although they have been identified at least 40 different rh-BMPs, a clear clinical demonstration of the osteoinductive potential is available only for the rh-BMP-7, also known as osteogenic protein-1 (OP-1), and for the rh-BMP-2 [27], belonging to the transforming growth factors family (TGF-β), whose receptors are expressed on chondrocytes and osteoblasts [28]. The osteoinduction phenomenon is characterized by the transformation of the perivascular mesenchymal cells in bone progenitor cells that can regenerate bone tissue. The recombinant human osteogenic protein-1 (rh-OP-1), also known as rh-BMP-7 (eptodermina-α), conveyed by type-I collagen, has been the first to be approved in the world to treat non-union of long bones and in the USA as "humanitarian device exemption" (HDE) in the treatment of spinal non-union. It allows, also, the regeneration from vascularized bone and of healthy bone surrounding toward the inside deficient area. Thanks to several preclinical and clinical studies, the efficacy of the use of rh-BMP-7 has been demonstrated reporting in some studies success percentage between 85 and 89%; at the same time, it has been found a real decrease of complications linked to the use of autologous bone, considered even at this time the "gold standard" [29–38].

- Autologous growth factors (AGFs) and platelet-rich plasma (PRP)

  The PRP is the most advanced product of the "blood management." It is a biologically active concentrate of mediators extracted from patient's plasma and is a source of non-specific autologuos growth factors [platelet-derived growth factor (PDGF), TGF-β1-β2, insulin-like growth factor type 1-2 (IGF1-2) and vascular endothelial growth factor (VEGF)] able to stimulate bone, cartilage, and soft tissues healing processes on the site of use. It is characterized by an elevate concentration of trombocytes able to degranulate releasing several growth factors and cytokines that can induce osteogenesis and angiogenesis with a chemotactic and mitogenic mechanism [39]. It can be obtained from autologous or heterologous blood. Depending from the procedure used to treat the withdrawal can be obtained final platelet concentration from 4 to 8 times higher from the initial situation. In a randomized study of 2007 on 60 long-bones non-union has been demonstrated a minor healing capabilities by the PRP (63.8%) both in comparison with BMP-7 than to the autograft [30].

The AGFs contained in the PRP, as clarified by preclinical and clinical data, are promoters of the cellular division (mitogenesis) nonspecific for the bone cells, unable to promote the differentiation of the mesenchymal cells and to induce the formation of new bone tissue. They seem to be not useful when used alone or in association with scaffold in treatment of tibial pilon non-union.

- Mesenchymal stromal cells (MSCs)

Studies based on cellular therapies are concentrated on a rare non-hematopoietic cells population, the MSCs, which are present in patient's bone marrow and can be increased in colture in an undifferentiated state [40, 41]. In addition to their pluripotent properties, the MSCs are considered osteogenic progenitor cells with demonstrated ability to repair bone defects [42]. Their concentration at bone marrow level, however, can result not ever elevated [43, 44]. The influence of this factor seems to be fundamental to the aim to obtain the healing, and there are clinical evidences that a better prognosis is obtained with a progenitor cells concentration >1500/cm^3. Recently, new techniques have become available to obviate to this problem, between these patient's bone marrow aspirate permit the mesenchymal stem cells concentration directly in the operatory room. Those new methods have demonstrated two big advantages: a reduction in costs respect to the in vitro expansion of the MSCs and a drastic decrease of the donor site morbidity compared to the traditional collection in open surgery of the iliac crest [44, 45]. The clinical use of the MSCs, especially if associated with the BMPs, it has proven effective determining the non-union healing [46].

- Scaffold

The osteoconduction mediated by the scaffold is determined by the chemical–physical characteristics of the substratum act to favor the adhesion and the growth of the cells on the surface. The mechanical characteristics of the bone graft, and their resistance to the compression and torsion, are influenced from their shape (massive, cortical splint, spongious block, morcellized), from the withdrawal modality, processing, conservation, and from the kind of synthesis meaning used.

The synthesis substitutes used are mineral structures similar to human bone kind. They have only osteoconductive power. Between synthesis substitutes you can find calcium phosphate as hydroxyapatite, coralline hydroxyapatite (absorbable), tricalcium phosphate (TCP, absorbable), and biphasic calcium phosphate (BCP = HA + TCP). For small defects, the hydroxyapatite is good filler ad favorite, thanks to their osteoconductive properties, the progressive revascularization and reossification of the treated area. All materials available have some limit. Ceramic, particularly, presents three important disadvantages: the difficulty to remain in place, the long time needed to absorption, and the complete substitution with neoformed bone and the impossibility to fill important bone gap.

The allogenic transplant from bone bank and heterologous animal origin (porcine, bovine, or equine) have demonstrate osteoconductive power but not osteoinductive. They need, then, to be revascularization and repopulated from the outside, needing a surrounding enabling environment. Con be used as filler (morcellized/granules) or as mechanical support (wedges, blocks, splints) [47, 48].

9. Biological chamber and polytherapy

The biological chamber is a concept that represents the ideal site in which to brought out the bone regeneration processes. Is a natural bio-reactor within which are present all the elements at the base of the diamond concept. It is even, physically, the site of non-union or of bone loss specially prepared from the surgeon with the aim to create the best condition for the regeneration. The chamber has to be aseptic, mechanically stable, and sealed in a selectively permeable way [25].

To use the chamber is necessary to remove completely the pathologic non-union tissue, removing all external bodies and meaning of synthesis. Is important to remove in a complete way all the necrotic tissue up to a bleeding bone resection that means vitality. The non-union tissue can be assimilated to a “meta-traumatic tumor” and as such, it must be removed entirely. In case of non-union or septic bone loss is important to do cultural withdrawal with the aim to identify the pathogen responsible of sepsis and perform targeted antibiotic therapy. Over the removal of the infected bone tissue is important to do a debridement and an accurate toilette of the soft tissues.

In septic cases is always preferable to do a two times treatment, then, once performed the removal of the pathologic tissue need to be implanted a cement spacer usually two antibiotics added (the choice of the active principle has to be done on the base of the antibiogram, when available) able to sterilize the site and create a reactive pseudo synovial membrane (described by Masquelet) extremely useful in the second reconstructive time [49].

In non-septic cases you can run a single surgical time reconstruction. Once created the biological chamber is then possible to insert within it polytherapy, or rather the simultaneous application of the three elements at the base of the diamond concept (growth factors, mesenchymal stem cells, and scaffolds). The fourth element, that is mechanical stability, will be provided by ostheosynthesis meaning (angular stability plates).

Case 1 (**Figures 1–4**)

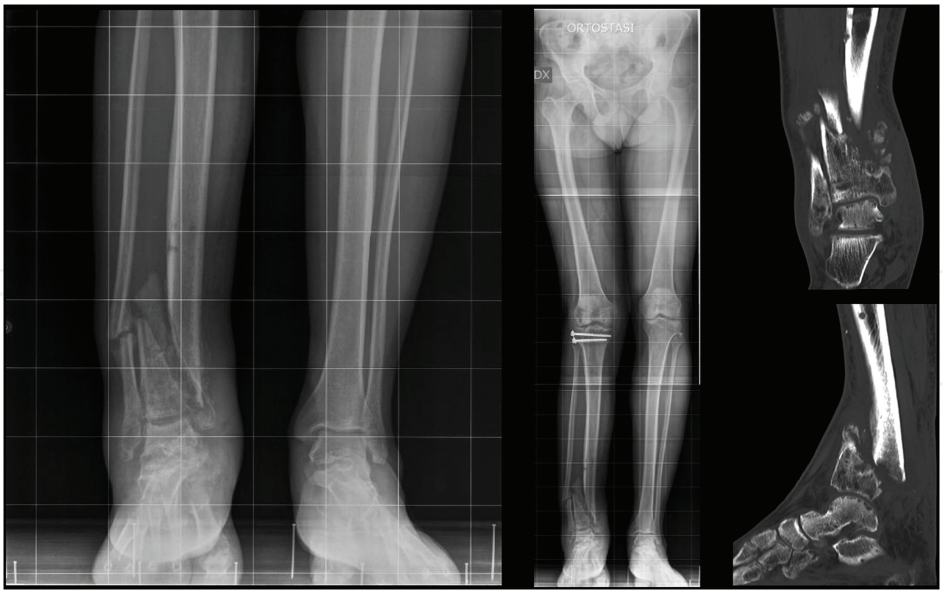

Figure 1. Clinical case 1—Man, 49 years, initial trauma following a motorcycle accident in which suffered exposed tibial pilon fracture, four ineffective treatments previously, comes to our attention (see X-rays and TC images) with a picture of septic non-union with serious bone loss and varus deformity, NUSS: 56 points.

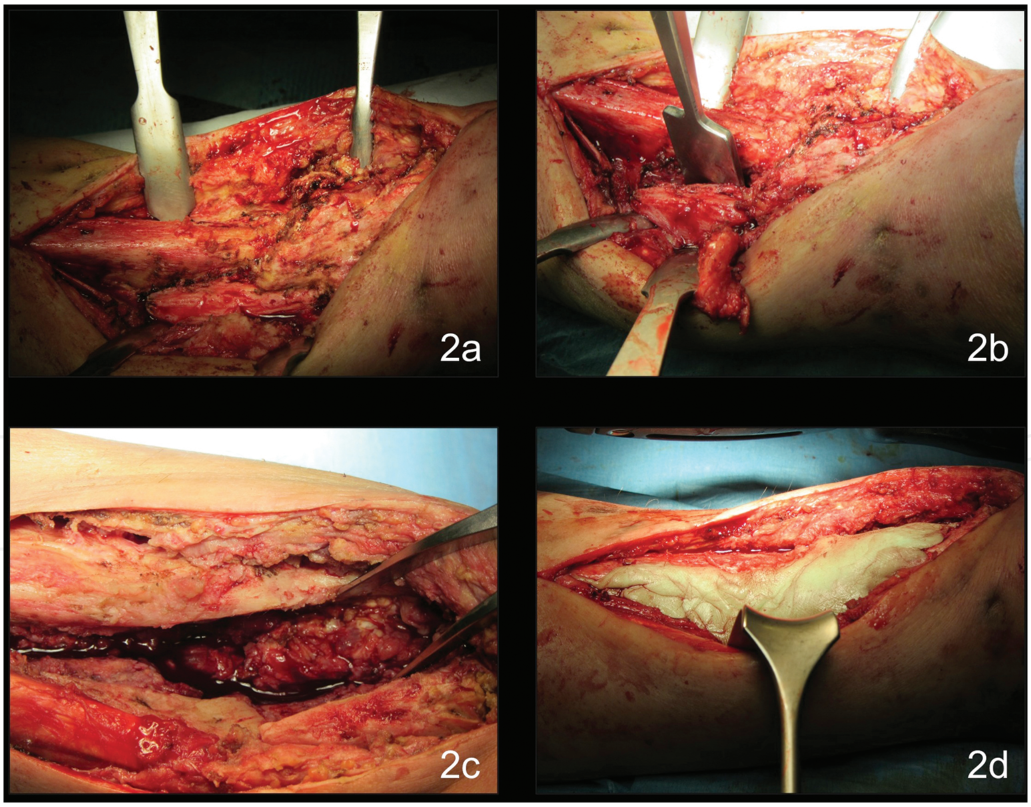

Figure 2. Intraoperative pictures that evidence: non-union site (a). Osteotomy with cruentation and removal of the pathologic tissue saving the joint surface came to healing after all previous treatments (b). The creation of the "biological chamber" (c). The implantation of antibiotic cement added with gentamicin and clindamycin (d).

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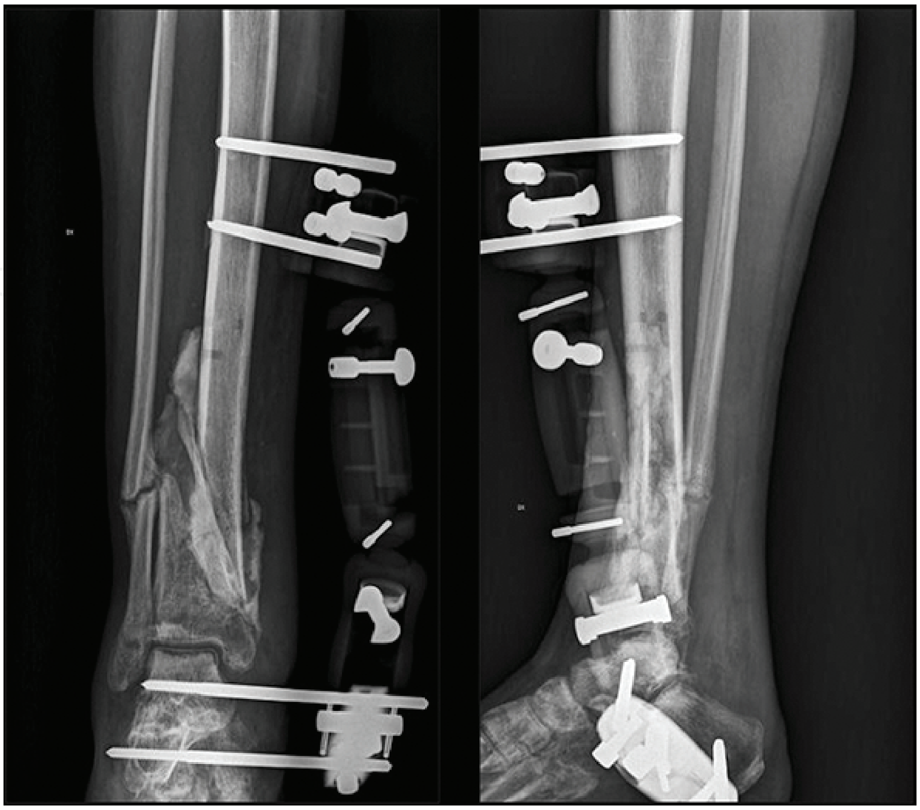

Figure 3. Radiographic post-op images that evidence the stabilization with external fixation, the positioning of the cement spacer and the deformity correction.

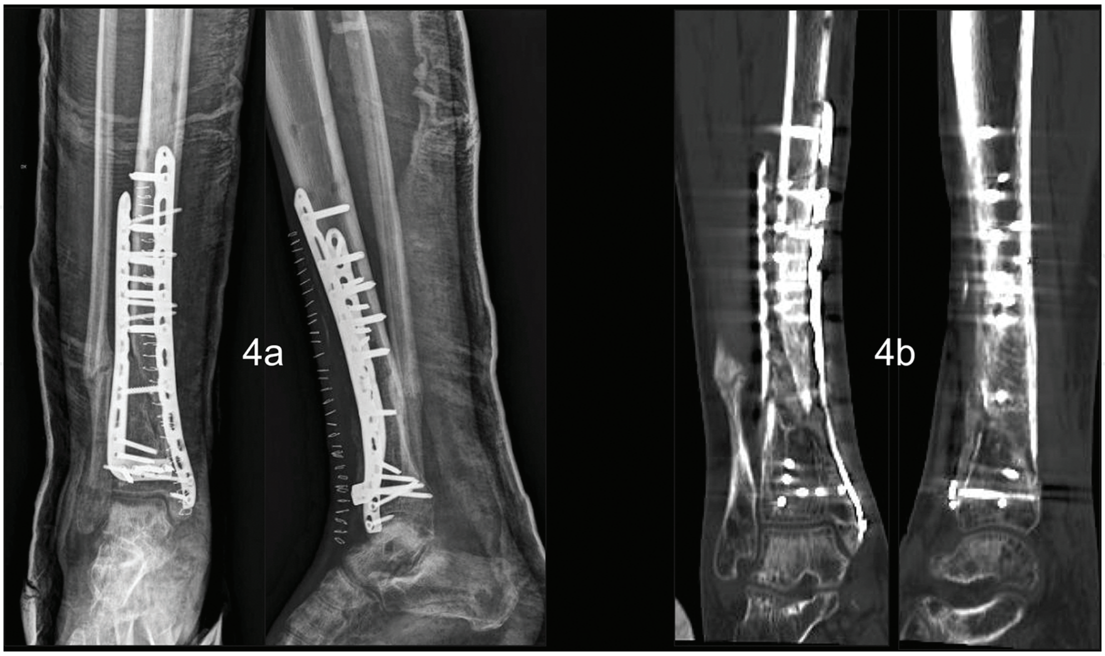

Figure 4. X-rays post-op images after the second reconstructive surgery performed by grafting biotechnologies in polytherapy and stabilization with double angular stability plate (a). CT control after 9 months (b).

10. Megaprosthesis

The development of megaprosthesis in serious segmental bon defects happened thanks to the biomedical application of the metallurgic industry on the field of surgical oncology. The development of new prosthesis for large resections offered important opportunities to oncologic orthopaedic surgeons for the substitution of skeletal segment, as long bones of the upper and lower limbs and near joints.

Our experience in treatment of non-union and serious bone loss led us, sometimes, to confront with the reality of some failure, after futile attempts to reconstruct the bone, eve with the use of advanced technologies as biotechnologies in monotherapy or polytherapy. In case of patients with a NUSS score of 76–100, the severity of the lesions and the clinical conditions usually makes sure that the surgical options of arthrodesis and amputation are implemented. In front of these drastic situations, radiologic and clinic, and to patients that have no intention to consider the amputation as a solution of their problem, we decided to apply the principles of the oncologic surgery, trying to remedy at their extreme cases with a solution of massive prosthetic [50, 51].

Actually in commerce you can find modular prosthetic system able to replace the entire femur including hip and knee joints up to the distal third of the tibia.

This surgical instrument presents peculiar characteristics:

- Custom-made realized on radiologic images,
- Stabilized with a tibial stem and a talocalcaneal stem locked with a screw,
- It allows to be stretched according to the necessity on the way to restore the correct length of the lower limbs,
- It offers the possibility to be resurfaced by silver in septic cases, exploiting the bacteriostatic action of this element.

Thanks to these new implants are now possible to avoid the amputation or long and often inconclusive treatments of lengthening and arthrodesis of the ankle with external fixators. Those patients, being part of the fourth NUSS category, cannot have benefit nor from the application of biotechnologies because the real possibilities of regeneration of the subject are too compromised. Therefore in those patients, we think more opportune to do a substitution treatment that can give back the function to the patient rapidly rather than follow again useful reconstruction attempts. More studies will be carried out to value the efficacy and the longevity of those new instruments.

Case 2 (**Figures 5–7**)

Figure 5. Clinical case 2—man, 46 years, initial injury following an accident on work in which suffered of comminuted tibial pilon fracture treated with synthesis with plate and complicated by septic condition. Comes to our attention with bone defect of the tibial distal epiphysis and severe bone loss with bone exposition and deep sepsis after the removal of the synthesis means and stabilization with external fixation. NUSS: 78 points. On the left X-rays and CT images, on the right intraoperative picture after the resection of the distal tibia, evident the severe skin loss that has been treated by covering flap.

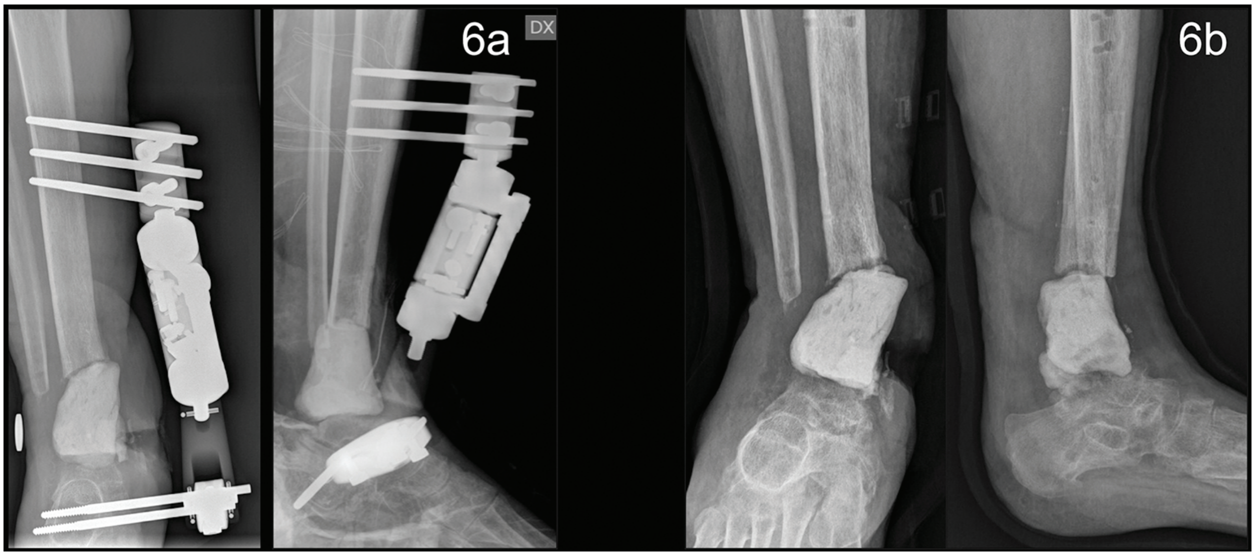

Figure 6. X-rays post-op images that evidence the stabilization with external fixator and positioning of antibiotic cement spacer with gentamicin and clindamycin (a), and after 3 months, resolved the septic condition, after the removal of the external fixator (b).

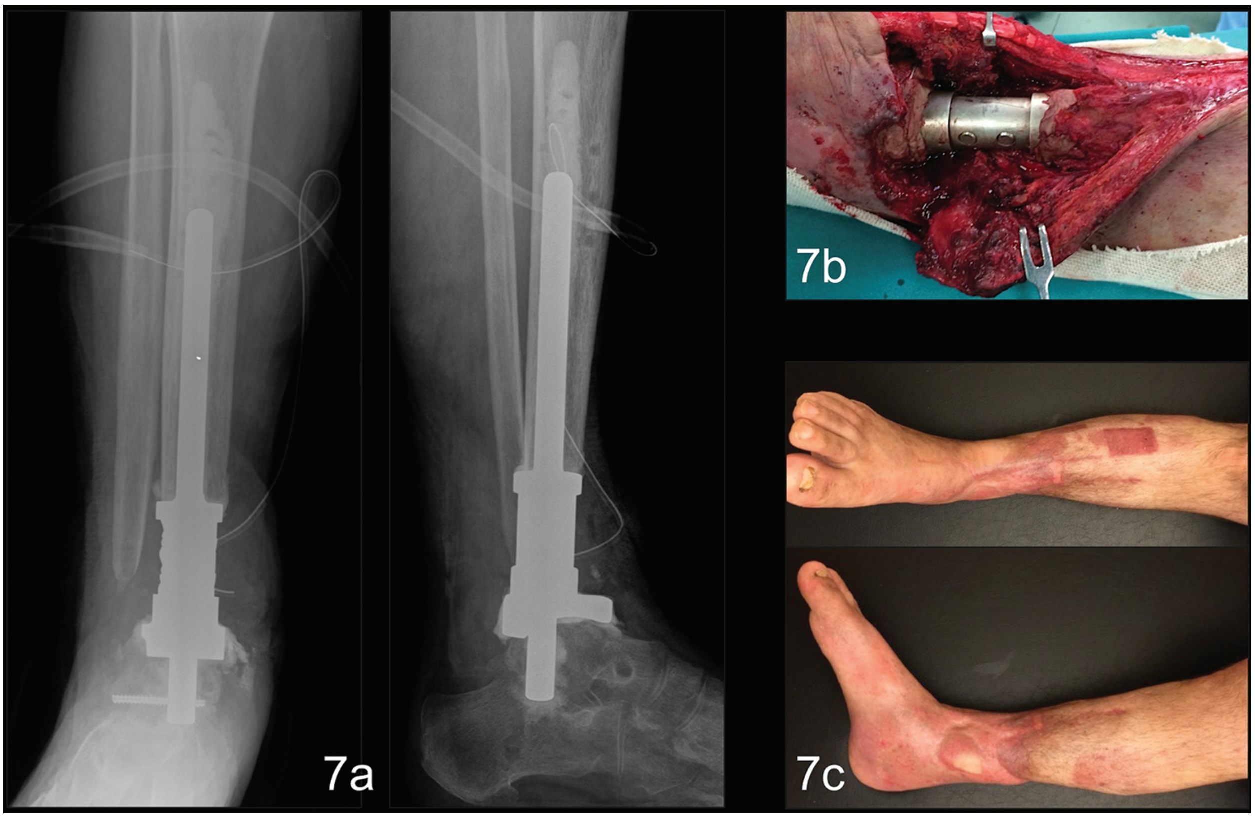

Figure 7. X-rays post-op images (a) after the implant of arthrodesing megaprosthesis of the distal leg (b) and clinical pictures (c) of the operated limb and of the skin condition.

11. Conclusions and future perspectives

The objective difficulty of those specific cases, evidenced or classified correctly by an elevated NUSS, cannot be representative in cases in which, in front of presumable mechanic necessities and correct surgical treatment, presents real biological difficulties.

This biologic difficulty is presumable to be searched in genetic expression [52, 53] but is difficult to assess in her real essential components and even more in the single clinical case.

The even more depth study of those which are the causes that can induce to non-union is today more important than ever. The new frontier will be the gene therapy or rather the possibility to transport inside the patient those genes acted to determine the succession of events that conduce to the formation of a bone callus and his maturation to strong bone.

Several studies, on animals, evidence today show that the gene therapy is viable both with the use of carrier virus [54, 55], both with the use of other non-viral carrier as for example particular pulsed electric fields (DNA electroporation) [56]. These therapies are still futuristic realities and provide an ulterior wide preclinic and clinic evaluation. A lot of road has been done until today on the ground of knowledge and of clinic treatment of non-union, and we think that in

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the near future there will be understanding of how the non-union pathology could be by herself a pathology on a vulnerable patient.

In these patients in which the regeneration possibilities are compromised, a valid solution is offered from the biological chamber and from the new mega prosthetic implants that can avoid the amputation and restoring the function to the patient.

Is today recognized the importance of a global and polyspecialists approach in the treatment of non-union and of large bone loss of the tibial pilon? Recent studies costs–benefits on the choice of the most appropriate treatment have demonstrate that the probabilities of a better outcome offered by multidisciplinary approach with biotechnology have a fewer impact on the sanitary economy compared to that expected for long-time care in case of repeated features [57].

It is therefore our opinion that the use of secure and trusted traditional techniques must be accompanied by the best is offered today by new technologies both on the respect of the quality of patient's life, both keeping in mind of the economic feasibility.

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