

# Non-unions

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## Summary

**Non-union of long bones is a significant consequence of fracture treatment. Bone regeneration is a complex physiological process of bone formation which can be seen during normal fracture healing. An improved understanding of the molecular and cellular events that occur during bone repair and remodelling has led to the development of biologic agents that can augment the biological microenvironment and enhance bone repair. Currently, there are different strategies to augment the impaired or "insufficient" bone-regeneration process, including the "gold standard" autologous bone graft, free fibula vascularised graft, allograft implantation, and use of growth factors, osteoconductive scaffolds, osteoprogenitor cells and distraction osteogenesis. A lack of standardized outcome measures for comparison of biologic agents in clinical fracture repair trials, frequent off-label use and a limited understanding of the biological activity of these agents at the bone repair site have limited their efficacy in clinical applications.**

*KEY WORDS:* non union; bone defect; regenerative medicine; bone regeneration; megaprosthesis.

## Introduction

Fracture non-union is a chronic condition characterised by pain and functional disability. These cases are often difficult to manage, because patients reply differently to various stresses and have various impact on the patient's family (relationships, income and job). About 90 to 95% of all fractures

heal without problems. Non-unions are that small percentage of cases in which the biological process of fracture repair cannot overcome the local biology and mechanics of the bony injury. This leads to a large number of procedures to treat non-healing fractures, increasing morbidity for patients and costs. The U.S. Food and Drug Administration (FDA) defines a non-union as a fracture that is at least 9 months old and has not shown any signs of healing for 3 consecutive months. We define non-union a fracture that, in the opinion of the treating physician, has no possibility of healing without further intervention. We define delayed union a fracture that shows slower progression to healing than anticipated and it's at risk of non-union without further intervention.

## Etiology and new trend in the classification of non-unions

Fracture repair is a process that involves spontaneous structured regeneration of bony tissue and restores mechanical stability. The early biological response at the fracture site is an inflammatory reaction with bleeding and the formation of a fracture hematoma. The repair response occurs rapidly in the presence of osteoprogenitor cells from the periosteum and endosteum and hematopoietic cells that are capable of secreting growth factors. Following fracture healing, bony remodelling progresses according to Wolff's law. The repair process, involving both intramembranous and endochondral bone formation, needs basic requirements for fracture healing. To address all the factors that may be implicated in fracture non-union, several elements need to be considered, including the cellular environment, growth factors, bone matrix and mechanical stability; these comprise "the diamond concept", which has further evolved into "the regenerative pentagon" when vascularisation is also considered (1-3). The absence of one or more of these factors predisposes the fracture to the development of a non-union. Recently we defined different risk factors that are implicated in the pathogenesis of fracture non-union. These risk factors can be separated into general factors (sex, age, diet, diabetes, osteoporosis, muscular mass, smoking, alcohol, drugs) and local factors (fracture personality, type of fracture, exposure, infection, multiple trauma/fractures) (4, 5). The goals of the evaluation are to discover the etiology of the non-union and form a plan for healing the non-union. In 2008, we published a new classification for non-unions: the Non-Union Scoring System (NUSS) (6, 7). With our new classification, we have attributed precise clinical and radiographic values to compare the outcomes of patients with fractures of similar complexity. The NUSS considers the bone quality, typology of primary injury, number and invasiveness of previous interventions, adequacy of previous surgery, Weber-Cech classification, bone alignment, presence of bone defect, state of the soft tissues, American Society of Anaesthesiologists (ASA) grade of the patient, and specific clinical characteris-

tics of the patient, including clinical infection status, smoking status, use of drugs, parameters of specific blood tests (white cell count, erythrocyte sedimentation rate, C-reactive protein) and diabetes. The total score is multiplied by two. All the factors included in the scoring system have an impact on the complexity and difficulty of treatment of any non-union. The NUSS recognises four groups according to severity.

### Evaluation of non-unions

Evaluation begins with a thorough history, including the date and mechanism of injury of the initial fracture. Preinjury medical problems, disabilities, or associated injuries must be noted. The patient's pain and functional limitations related to the non-union should be known, with the specific details of each prior surgical procedure to treat the fracture and fracture non-union. The prior treating surgeons and a review of all medical records since the time of the initial fracture are necessary. The history should also include details regarding prior wound infections. Intravenous and oral antibiotic use should be documented, particularly if the patient uses antibiotics at the time of presentation. Problems with wound healing and episodes of soft tissue breakdown should be documented. Finally, the patient should be investigated regarding other possible risk factors for non-union.

Following the history, a physical examination must be performed. The skin and soft tissues in the fracture zone should be inspected. The presence of active drainage, sinus formation and deformity should be noted. The non-union site should be manually stressed to evaluate motion and pain. A neurovascular examination should be performed to document vascular insufficiency and motor or sensory dysfunction. Active and passive motion of the joints adjacent to the non-union, both proximal and distal, should be performed.

A review of the original fracture films reveals the character and severity of the initial bony injury. They can also show the progress or lack of progress toward healing when compared with the most recent plain radiographs. The non-union is evaluated with radiographs, through an anteroposterior (AP) and lateral projections of the involved bone, including the proximal and distal joints. AP, lateral and two oblique views of the non-union site on small cassette films, which improve magnification and resolution are useful with bilateral AP and lateral alignment radiographs for lower extremity non-unions (for assessing length discrepancies and deformities). Flexion/extension lateral radiographs to determine the arc of motion and to assess the relative contributions of the joint and the non-union site to that arc of motion must be performed. The current plain films help to evaluate the following radiographic characteristics of a non-union: anatomic location, healing effort, bone quality, surface characteristics, status of previously implanted hardware and deformities.

Plain radiographs are not always sufficient regarding the status of fracture healing. Sclerotic bone and orthopaedic hardware may obscure the fracture site, particularly in stiff non-unions or those well-stabilized by hardware. CT scans and tomography are useful in such cases. CT scans help to estimate the percentage of the cross-sectional area that shows bridging bone. Non-unions typically show bone bridging of less than 5 percent of the cross-sectional area at the fracture surfaces. Healed or healing fracture non-unions typically show bone bridging of greater than 25% of the cross-sectional area. Serial CT scans may be followed to evaluate the

progression of fracture consolidation. CT scans are also useful for assessing intra-articular non-unions for articular step-off and joint incongruence. Plain tomography helps evaluate the extent of bony union when hardware artefact compromises CT images. Rotational deformities may be accurately quantified using CT by comparing the relative orientations of the proximal and distal segments of the involved bone to the contralateral normal bone. An evaluation of the septic activity and the residual vitality of the bone affected are essential information in order to decide if it's necessary a surgical treatment in 1 or 2 steps (first step: bone resection and placement of an antibiotic spacer, second step: spacer removal and reconstruction Vs mega-prosthesis implantation) and to evaluate at which level perform the resection removing the whole necrotic and septic bone. FDG PET CT could be an important tool to better analyse this kind of pathologies. FDG PET CT is able to confirm the presence of a septic state and to assess the residual bone vitality. Patients, in the event of a positive result for infection, were treated by bone resection at the level indicated by the exam (all necrotic bone was removed), explantation of devices and antibiotic spacer implantation.

Routine laboratory work, including electrolytes and a CBC are useful for screening general health. The sedimentation rate and C-reactive protein are useful to monitor the course of infection.

When infection is suspected, the non-union site may be aspirated or biopsied under fluoroscopic guidance. The material is sent for a cell count and gram staining and cultures are done for aerobic, anaerobic, fungal, and acid-fast bacillus organisms. To encourage the highest yield possible, all antibiotics should be stopped at least 2 weeks prior to aspiration.

### From the classification to the development of a ladder strategy

Algorithm of choice of treatment for non-union and bone defect based on the Non-Union Scoring System (NUSS), which recognises four groups of severity. This treatment algorithm is based on the concept of a "ladder strategy": for a simple problem there should be a simple answer, whereas a more serious problem corresponds to a more complex solution.

Score from 0 to 25 should be considered a straightforward non-union and should respond well to standard treatments; usually the problem is mainly mechanical. The common aim of treatment is to improve stability, usually choosing a different system of fixation.

Score from 26 to 50 should require more specialised care; usually the problem is both biological and mechanical. The treatment requires the correction of the fixation associated with a biological stimulation obtained with pulsed electromagnetic fields (PEMF), extracorporeal shock wave therapy (ESWT) or biotechnologies, such as mesenchymal stromal cells, growth factors or scaffold, in monorail therapy.

Score from 51 to 75 requires specialised care and specific treatments. The problem is complex and is characterised by impairment of both biological and mechanic conditions. Resection of the non-union is usually required and consequently a bone defect must be treated. Traditional treatments may be used, such as bone transport with external fixator, autologous iliac crest grafts, microvascular fibula grafts, RIA system (Reamer / Irrigator / Aspirator); however, also indicated are biotechnological products, including cells, scaffold and

growth factors, according to the principles of the “biological chamber” and “polytherapy” (8-16).

Score from 76 to 100 may indicate the need for primary amputation, arthrodesis, prosthesis or mega-prosthesis implantation depending on the patient’s condition, the severity of the bone loss and the anatomical localisation (17, 18).

## Conclusion

Development of treatment strategies to provide viable solutions to an impaired fracture healing response has been a subject of intense scientific activity. Both researchers and clinicians have been working to understand better the physiological events influencing the host responses to injury and bone loss at the molecular level (molecular mediators, cellular chemotaxis and cell interactions, systemic and local signals, gene expression, induction of angiogenesis). Current trends therefore in bone repair include the application of philosophies and techniques that have been developed and practised in reconstruction centers based on the experience and intuition acquired over the years by the clinicians. While several case series have been published utilising innovative techniques, the lack of control groups and randomisation makes the findings of these studies weak in terms of the level of scientific evidence. The best way to address this issue is to support the designation and operation of some clinical units and a national and international level to operate as centers of application of advanced biological based therapies utilising tissue engineering techniques. Such strategy will allow these units to develop the necessary experience to refine techniques and develop standardised protocols (19-21).

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