# THE OUTCOME OF TIBIAL NON-UNION TREATMENT USING A REVISED DEFINITION, CLASSIFICATION SYSTEM AND MANAGEMENT STRATEGY

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**THE OUTCOME OF TIBIAL NON-UNION TREATMENT USING A REVISED**

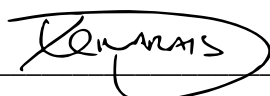**DEFINITION, CLASSIFICATION SYSTEM AND MANAGEMENT STRATEGY**

As the candidate's supervisor I have approved this thesis for submission.

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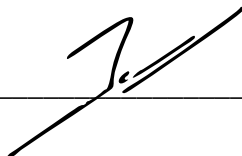Signed: _____          Date: __15 February 2016__

# Dedication

The dissertation is lovingly dedicated to Yvette, Logan and Connor. Their support and encouragement was paramount to the completion of this thesis.

# Declaration

I, Nando Ferreira declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

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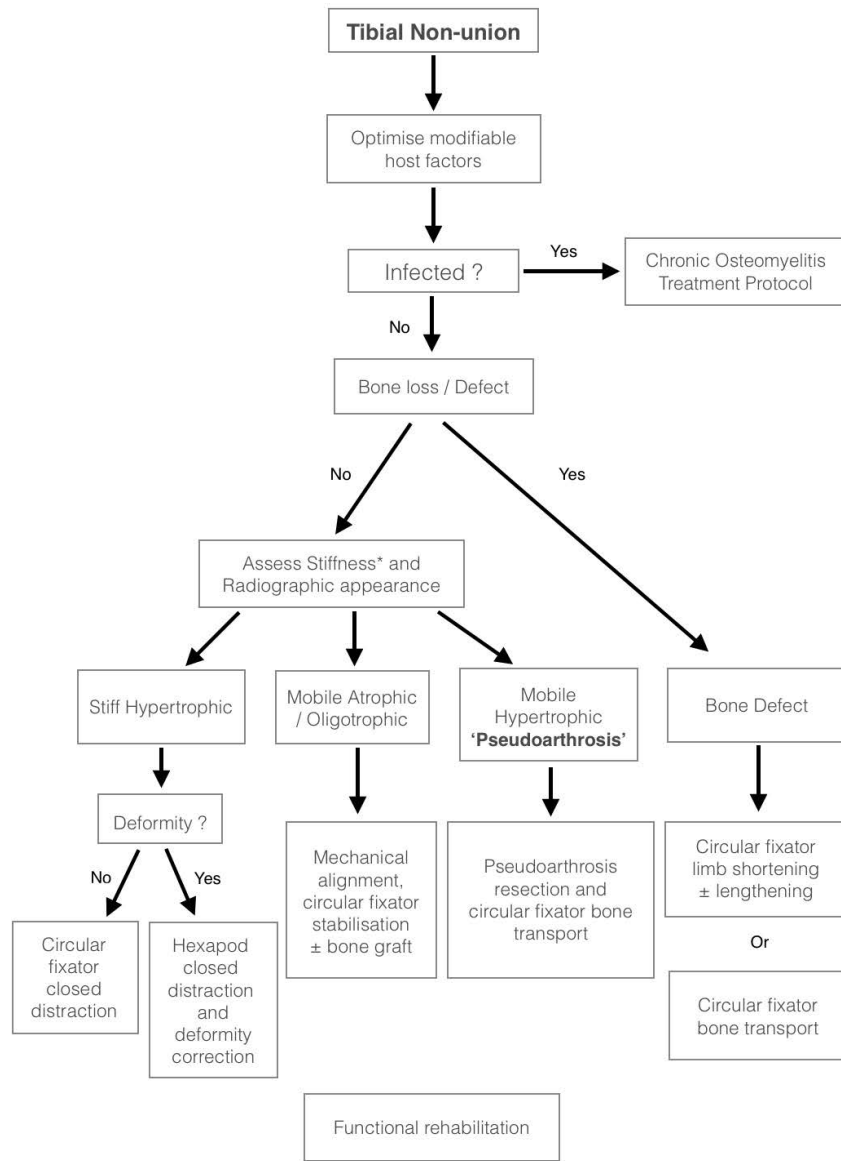
# Acknowledgements

# Summary

The management of tibial non-unions remains a challenge for orthopaedic surgeons. The treatment of tibial non-unions is historically based on small case series that frequently include a variety of non-union subtypes and infected cases. Fixation methods and treatment strategies also vary greatly between published series. This lack of uniformity in the available literature has rendered the establishment of evidence-based, reproducible protocols for the management of tibial non-unions difficult.

Controversies regarding non-union definition and classification contribute to delays in treatment and exacerbate the morbidity that is commonly associated with non-union development. In this work we propose a new definition for non-union and introduced a novel concept of 'potential non-union' to emphasise the importance of early recognition and referral.

The lack of reproducible, evidence-based treatment protocols, combined with the large volume of tibial non-union cases managed in KwaZulu-Natal, South Africa, lead to the development of a tibial non-union treatment algorithm. This algorithm was based on results from two retrospective audits of patients with tibial non-unions who were managed with circular external fixators over a four-year period. The algorithm classifies non-unions into four distinct groups, each with a specific treatment strategy. These reports also introduced the concept of mechano-biology to the management of tibial non-unions and were the first to use hexapod circular fixators for distraction of stiff hypertrophic tibial non-unions. Subsequently a prospective interventional study was undertaken aimed at evaluating the effectiveness of the proposed tibial non-union treatment algorithm.

**Figure 1.** Tibial non-union treatment algorithm



```
                         ┌─────────────────┐
                         │ Tibial Non-union │
                         └─────────────────┘
                                  │
                         ┌─────────────────┐
                         │ Optimise modifiable │
                         │   host factors    │
                         └─────────────────┘
                                  │
                         ┌─────────┐    Yes    ┌──────────────────┐
                         │ Infected ?├──────────▶│ Chronic Osteomyelitis │
                         └─────────┘           │ Treatment Protocol │
                             │ No              └──────────────────┘
                         ┌─────────────────┐
                         │ Bone loss / Defect │
                         └─────────────────┘
```

Assess Stiffness* and Radiographic appearance

Stiff Hypertrophic

Mobile Atrophic / Oligotrophic

Mobile Hypertrophic **'Pseudoarthrosis'**

Bone Defect

Deformity ?

No — Circular fixator closed distraction

Yes — Hexapod closed distraction and deformity correction

Mechanical alignment, circular fixator stabilisation ± bone graft

Pseudoarthrosis resection and circular fixator bone transport

Circular fixator limb shortening ± lengthening

Or

Circular fixator bone transport

Functional rehabilitation

\* After removal of metalware and fibula osteotomy

Preliminary results suggest that the tibial non-union treatment algorithm may produce high union rates across a diverse group of tibial non-union subtypes. Thirty-seven patients with 39 tibial non-unions were managed according to proposed algorithm. Final bony union after treatment was achieved in 38/39 (97.4%) tibias. The advantages of this algorithm include a simplified classification that divides non-unions into four clearly defined groups, each with a specific

treatment strategy that uses circular external fixators to stimulate the bodies' natural healing potential without the need for expensive adjuvant therapies. Looking beyond the scope of this thesis, we recommend that this algorithm be evaluated with larger study groups and in different study locations to assess its reproducibility.

Although these results are encouraging and appear to simplify the management of tibial non-unions, it is still recommended that these cases be referred to specialist centres that practice these advanced reconstructive techniques on a regular basis. The use of circular fixators has a steep learning curve and high volume units tend to produce better results and fewer complications. Dedicated units concentrate these complex cases resulting in better skills and infrastructure to manage them. Ancillary services are also more experienced with frame care and functional rehabilitation and patients experience a support group effect by interacting with other patients undergoing similar treatments.

**Structure of Thesis**

This document is a thesis by publication and comprises of FOUR parts. Each part consists of chapters that are composed of one publication each. These publications have either been published, been accepted for publication or are currently under review. Each publication further contains additional references that are specific to that publication.

- **Introduction:** The introduction provides background to the research, how and why it came about and briefly discusses the principles on which the thesis is based.

- **Part One:** Part one consists of two chapters that contain an overview of the literature. The first chapter explains the pathogenesis of tibial non-unions and highlights the factors that should be considered during the management of these conditions. The second chapter discusses the limitations of current non-union definitions and classifications to illustrate the need for research in this area.

- **Part Two:** Part two discusses the rationale for the development of the tibial non-union treatment algorithm. This is set out in three chapters that contain the evaluation of two retrospective reviews and a case study.

- **Part Three:** This part discusses the proposed tibial non-union treatment algorithm and consists of one chapter that includes the results of a prospective interventional study evaluating the effectiveness of the algorithm.

- **Part Four:** Three chapters discuss the most frequently experienced complication with the use of circular external fixation as a treatment method, namely pin site infection. Here we discuss the factors associated with the development and suggest simple and inexpensive strategies to limit this complication.

- **Conclusion:** This final chapter provides a summary of the thesis and highlights the limitations of the studies presented, in addition to identifying areas for possible future research.

# List of Abbreviations

| | | |
|---|---|---|
| BMP | - | Bone Morphogenic Protein |
| $CD_4$ | - | Cluster of differentiation 4 |
| COX | - | Cyclooxygenase |
| DALY | - | Disability Adjusted Life Years |
| DNA | - | Deoxyribonucleic Acid |
| HA | - | Hydroxyapatite |
| HAART | - | Highly Active Anti-Retroviral Therapy |
| HIV | - | Human Immunodeficiency Virus |
| IGF | - | Insulin-like Growth Factor |
| Il | - | Interleukin |
| KZN | - | KwaZulu-Natal |
| NHS | - | National Health System |
| NUSS | - | (Calori) Non-union Scoring System |
| NSAIDs | - | Non-steroidal Anti-Inflammatory Drugs |
| PDGF | - | Platelet Derived Growth Factor |
| RNA | - | Ribonucleic Acid |
| TL-Hex | - | Truelok-Hex |
| TNF-$\propto$ | - | Tumour Necrosis Factor $\propto$ |
| TSF | - | Taylor Spatial Frame |
| TSR Unit | - | Tumour, Sepsis and Reconstruction Unit |

# Table of Contents

# Chapter 1. Introduction

South Africa has an increased incidence of tibial non-union as a result of the high prevalence of trauma.  A 2007 WHO report identified South Africa's Road traffic mortality rates to be about double the global rate at 39.7 per 100,000. The latest WHO report on the burden of injuries in South Africa identified trauma as being responsible for approximately 2.3 million Disability Adjusted Life Years (DALYs) with interpersonal violence and road traffic injuries accounting for the second and fourth leading single causes of all DALYs in South Africa.[1] This, combined with high levels of interpersonal violence and gun related violence places significant demands on state hospitals.

In addition to the high trauma burden, UNAIDS reports South Africa to have the highest HIV infection rate in the world with more than 6 million people affected.[2] The province of KwaZulu-Natal (KZN), in particular, has the highest HIV prevalence in South Africa at 37.4%.[3] South Africa, further, has a large rural population (>19,000,000 people) with limited access to medical services and resultant delays in presentations to health facilities following trauma.

Medical services and in particular orthopaedic surgery services are under resourced in KZN and surrounding areas. Where the orthopaedic surgery workforce range between 3.1 surgeons per 100,000 population in Canada to 11 surgeons per 100,000 in the United Stated of America, the picture is drastically different in Area 2 of KZN.[4, 5] This area serves a population of approximately 3 million people with 26 qualified orthopaedic surgeons translating to 0.86 surgeons per 100,000 population.

These factors combine to create a scenario where the medical services, especially at a primary care level, is overwhelmed by the trauma burden. Many patients are treated by junior doctors without the necessary experience to identify injury patterns with high risk of impaired healing, or the expertise to alter the outcome. This results in a large population needing post-traumatic limb reconstruction including the management of long bone non-unions.

The cost associated with these non-unions is high and impacts multiple sectors of the community. The patient suffers from an inability to return to work timeously, dependency on family members and the social grant system for financial support, psychological disturbances and often narcotic dependency. In addition, non-unions harbour considerable cost for the health care system. Patients often undergo multiple surgeries with repeated hospital admissions and outpatient clinic visits. The cost of management is often further increased by the addition of adjuvant treatments including bone morphogenic proteins (BMPs), external pulsed ultrasound or electromagnetic stimulators and hyperbaric oxygen therapy, in an attempt to increase bone healing.

Most of the tibial non-unions encountered in Area 2 of KZN are eventually referred to the Tumour, Sepsis and Reconstruction (TSR) Unit at Greys Hospital in Pietermaritzburg. This unit was established in 2009 and due to the volume of tibial non-unions that are treated, is ideally placed to research the management of these post-traumatic complications. The unit has managed 122 tibial non-unions over a period of four years, representing roughly three times more patients than the largest studies published in this topic. In addition to managing post-traumatic complications the TSR unit also manages the majority of the malignant musculoskeletal tumours seen in the entire province of approximately 10 million people. The shear volume of work faced by this unit necessitated the development of cost effective management strategies with high success rates after single surgical interventions where appropriate and the ability to allow early return to function for patients.

Circular external fixators were identified as the ideal fixation devices to fulfil all our requirements for non-union management. These devices could be applied with limited iatrogenic injury to the soft tissue envelope and with preservation of the existing blood supply to the non-union site. Their mechanical characteristics also assist with creating the optimal biomechanical milieu for fracture union.

Gavril Abramovich Ilizarov popularised the use of fine wire circular external fixators in Russia during the 1950s. Introduction to the West occurred in 1981 after an Italian photojournalist, Carlo Mauri, was treated for a tibial non-union by Dr Ilizarov. In the following three decades there was a dramatic increase in the use of fine wire external fixators, with a growing number of applications in elective and trauma orthopaedic surgery. The Ilizarov system, as well as the Ilizarov principles of distraction osteogenesis, have subsequently become indispensable in limb reconstruction surgery.

Physiological loading of a fractured bone will cause deformation in three linear and three rotational dimensions. The resultant inter-fragmentary motion at the fracture site is therefore considered to be three-dimensional in nature.[6] When an external fixator is used to immobilise a fracture the resultant stability can be conceptualised as the sum of the contributions from the external fixator and bone — the concept of shared stability.[6] This overall stability will produce a degree of inter-fragmentary motion that is unique to each specific fracture-fixator configuration.

The biomechanical environment of the fracture site influences, both the pattern and rate of fracture healing.[7, 8, 9] This environment is influenced by the mechanical properties of the external fixator, and can be reported in terms of axial stiffness, translational stiffness, and resistance to bending and torsion at the fracture site.[6] Axial micromotion promotes bone regeneration while translational shear leads to the formation of fibrocartilage and predisposes to non-union.[6, 7] Bending micromotion can stimulate callus formation, but is more likely to lead to shear if the centre of rotation is not precisely at the centre of the fracture site. The optimal external fixator would therefore promote a degree of axial micromotion while preventing excessive bending and translational shear.[6]

Circular external fixators are fundamentally different from monolateral fixators.[6, 10] Through the use of tensioned fine wires as fixation elements as opposed to half-pins, ring fixators are imparted with elastic properties and a low axial stiffness, while

simultaneously preventing excessive bending and translational shear through high bending and translational rigidity.[6, 10] Tensioned fine wires also contribute to circular external fixator's ability to exhibit increased axial stiffness with higher loads.[11] This non-linear, load dependent axial stiffness is similar to the viscoelastic properties of tendons and ligaments,[11] and this biomechanical attribute has led to fine wire circular external fixators being described as the only form of 'true biological fixation'. Hexapod external fixators are recent modifications of the traditional Ilizarov type fine wire circular external fixators. It consists of two rings connected with six oblique struts in an octahedral configuration. This arrangement imparts these external fixators with six-degree-of-freedom and the ability to accurately correct three dimensional deformities. This biomechanical superiority along with their modularity and minimal invasive application make circular external fixators ideal for the management of complex trauma and limb reconstruction surgery.

The use of these fixators is however associated with specific fixator related complications, with pin site irritation and infection being the most commonly encountered complications. Despite the prolonged times that these fixators are sometimes required, the incidence and severity of pin site infection can be minimised through a good understanding of external fixation principles, meticulous surgical technique and a strict post-operative pin site care protocol.

**Study Aims**

This research aimed to develop standardised evidence based treatment protocols for the various subtypes of tibial non-unions. A tibial non-union treatment algorithm was developed following two retrospective audits of patients with tibial non-unions that were managed with circular external fixators over a four-year period. The aim of the proposed algorithm was to simplify the classification of tibial non-unions into four distinct groups, each with a specific treatment strategy. A subsequent prospective interventional study was undertaken in order to evaluate the effectiveness of the tibial non-union treatment algorithm.

**Objectives**

• Outline the pathogenesis of tibial non-union and highlight the factors associated with its development.

• Critically appraise current non-union classification systems and discern their limitations.

• Retrospectively evaluate our experience of tibial non-union management and develop a tibial non-union treatment algorithm based on these results.

• Evaluate our proposed tibial non-union treatment algorithm through a prospective interventional study.

• Investigate the incidence and severity of common complications with the use of circular fixators and provide a protocol for the prevention and management of these complications.

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# PART ONE. Overview

Long bone non-unions remain a challenge to manage regardless of advances in modern medicine. Despite the relative frequency with which non-unions are encountered, failure after surgical treatment have been reported in up to 20% of cases.[1] This poor outcome and difficulty experienced with management stem from multiple facets related to non-union development, diagnosis, classification and treatment strategy.

Normal fracture healing is a complex cascade of physiological processes that ultimately culminate in the formation of bone that is histologically indistinguishable from the original, normal bone. This fracture-healing cascade follows an organised blueprint that has arbitrarily been divided into three phases. Various factors have been identified that influence this natural healing process and can be divided into injury factors, management factors and host factors. Understanding the role and influence of each one of these variables in the development of tibial non-unions will assist reconstructive surgeons with establishing reproducible management strategies for these non-unions.

Deciding on a universally accepted definition for non-unions is an intriguingly complicated task and is the initial stumbling block for management. Most current definitions are temporal and would only designate failure of union after a set time has elapsed.[2-5] This ultimately leads to delays in referral and management and may contribute to increased complexity of eventual treatment and poor outcome. Some authors have attempted to circumvent these limitations with their own working definitions.[2, 5-7] Although pragmatic, all these attempts rely on the treating surgeon's experience to judge the natural healing process and are difficult to teach junior surgeons.

We have suggested the following definitions for non-union:

*Non unus potentia* (Potential Non-union): any fracture that when taking host factors, injury severity and management into account, has little potential to heal without further intervention.

*Non unus certus* (Established Non-union): any fracture that shows no clinical or radiological union in a reasonable time, for that specific injury, host and management strategy.

The rationale for this distinction is to facilitate early identification of potential non-unions so that they can be referred to reconstructive specialists before any additional morbidity develops. The early management of these potential non-unions will hopefully decrease treatment complexity and improve outcome.

Current non-union classifications are numerous and have limited clinical relevance. The Weber and Cech, Ilizarov, Paley and Wu classifications only address certain aspects of non-union morphology and none of the these classifications prescribes treatment for specific non-union subtypes.[8-12] The Calori Non-union Scoring System (NUSS) has been an excellent recent advance on traditional classifications.[13] This system takes various biological and mechanical factors into account to guide management. The score however, only proposes where and how these patients should be treated. The suggested treatments include 'standard treatment', 'specialised care' and 'specialised care and specialised treatment'. This provides an indication for junior orthopaedic surgeons of which patients to refer, but do not provide specific treatment guidelines as to what 'specialised treatments' should be offered.

For any classification to be useful, it should assist in diagnosis, guide treatment, indicate prognosis, and / or assist with research. Very few classifications can accomplish all of these

things and often only assist with one aspect of management. Although debatable, for the average treating surgeon a classification that prescribes treatment strategy is often the most useful.

The different approaches and focal points of these classification systems complicate treatment strategy selection and research into non-union management. Formulating standardised treatment strategies or protocols on existing classification systems is challenging, and might not take all aspects of non-union development and management into account.

The following two chapters review the factors associated with non-union development and the controversies regarding defining and classifying non-unions.

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# Chapter 2. The Pathogenesis of Tibial Non-union

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Contribution to authorship:

- N. Ferreira – Concept development, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- L.C. Marais – Concept development, contribution to literature review and revision of manuscript.
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**The pathogenesis of tibial non-union**

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**Abstract**

Bone healing is a unique and complex reparative process that results in fractures healing without scar tissue formation. Multiple factors have been implicated in altering this process. This paper reviews the factors that influence the process of bone healing and predispose to non-union development. Cognisance of these factors will assist orthopaedic surgeons in identifying fractures at risk of altered healing and guide the development of comprehensive management strategies for established non-unions.

**Introduction**

The human body has evolved the ability to spontaneously heal skeletal injuries through secondary bone healing and callus formation. This is evident from healed fractures observed in *Homo neaderthalensis* and *Homo erectus* fossils.[1,2] This healing process is unique in nature as most tissues heal with scar tissue formation, while skeletal tissue repairs with bone that is histologically indistinguishable from the original bone.

Manipulating this natural healing process in order to ensure proper alignment, maintenance of limb length and faster return to function, has been the goal of physicians throughout the ages. The Edwin Smith Papyrus from ancient Egypt is the oldest existing medical text and describes in detail the splinting of extremity fractures to preserve function.[3]

Non-union occurs when this natural healing process is hampered or disrupted and is one of the most dreaded complications of fracture management. Non-union following tibial shaft fractures represent the most common long-bone non-unions that require treatment.[4] Quoted incidences range from 4% to 48% and an established non-union signal a significant impact on a patient's function and quality of life.[4-9]

Multiple factors have been implicated in the pathogenesis of long-bone non-unions.[7, 10, 11] Recognising these factors will help refine strategies aimed at prevention of non-union and may guide the management of established non-unions. In this review we explore the factors that influence normal bone healing and predispose to non-union development after a tibial shaft fracture.

**Normal Bone Healing**

Bone healing is a complex cascade of events that results in the repair fractures without the formation of scar tissue and can be classified into two histological types, namely primary and secondary bone healing.[12, 13]

Primary bone healing ('soudure autogene') involves direct cortical remodelling through the formation of cutting cones that cross the fracture gap.[13] This type of bone healing occurs when there is a combination of anatomical reduction, stable fixation and compression of the fracture site and is only seen with open reduction and rigid internal fixation.

Secondary bone healing represents the most common type of fracture healing and occurs when there is some motion at the fracture site, which induces callus formation. During this healing process both endochondral and intramembranous ossification occurs in an ordered sequence divided into three phases.[13]

The first phase starts with a haematoma that forms after the injury. This initiates an inflammatory response with the release of cytokines, including platelet derived growth factor (PDGF), TNF-α and interleukins from macrophages, neutrophils and platelets. These cytokines are responsible for the recruitment of fibroblasts and pluripotent mesenchymal cells that migrate to the fracture site. Granulation tissue forms around the fracture ends and osteoblasts and fibroblasts proliferate. This is followed by the reparative phase when primary callus is formed. The mechanical environment drives differentiation of either osteoblastic or chondroblastic cell lines. Enchondral ossification mineralises a chondroid matrix while woven bone is generated through mineralization of an osteoid matrix. The final stage involves remodelling the healed fracture site. This process is governed by Wolff's Law in response to mechanical stresses on the bone.

**Mechano-biology**

The mechanical environment plays a major role in fracture healing and can be described in terms of inter-fragmentary motion and strain.[14, 15] While a small amount of relative deformation (strain < 2%) induces callus formation, high strain (> 10%) will lead to bone resorption and eventual non-union.[14] The amount of mobility allowed depends less on the displacement of the fragments alone than on the relation of the width of the fracture gap (L) and displacement ($\delta L$); $\delta L/L$.[15]

Mechanical stimulation also has a direct affect on the physiology of fracture healing. Ilizarov stated that functional load determines the structure, shape and volume of any limb. This is due to an increase in local blood flow during functional use that aids in tissue growth.[5] Mechanical stimulation also directly influences bone biology on a cellular level by stimulating the proliferation and differentiation of osteoblasts.[5, 16] Mechanical force application patterns, as well as loading magnitude and frequency, also effect bone healing on a biochemical level.[16] The rates of synthesis and degradation of extracellular matrix components is affected by force application patterns. Loading magnitude effects cell size through increasing amounts of intermediate filaments and glycogen particles while changes in loading frequency can alter mRNA synthesis of anabolic and catabolic genes.[16] Aggrecan gene expression is increased in response to mechanical stimulation and leads to an increased proteoglycan scaffold for type II collagen.[5]

Mechanical stimulation has further benefits in terms of union site remodelling according to "Wolff's law". This phenomenon was originally ascribed to piezo-electrical charges that are generated in response to mechanical stresses. Osteoblasts on the compressive side are stimulated by electronegative charges while osteoclasts are activated by electropositive charges on the tension side.[17, 18] This explanation is likely an oversimplification of a complex mechanism that regulates bone remodelling.[19] Current understanding of bone mechanosensation involves strain-generated potentials to explain how bone is able to respond to mechanical stresses.

**Injury Factors**

The tibia is the most commonly fractured long bone.[4] Its anatomical location exposes it to high energy trauma and its thin soft tissue envelope means that these injuries are frequently open fractures.[20] This, along with a tenuous blood supply and complex fracture patterns that are frequently seen after high energy injuries predispose tibial fractures to complications that affect fracture healing.[5, 8, 13, 20]

In an observational study of 200 patients, Bhandari *et al.* identified open fractures and transverse fracture patterns as independent variables that predict reoperation following tibial shaft fractures.

[21] In this study, reoperation was defined as any surgical procedure aimed specifically at achieving bony union. In a more recent study, Fong *et al.* identified open fractures, comminution, fracture with less than 25% cortical contact, oblique fracture pattern and segmental fractures to be associated with non-union development. After multivariable logistic regression analysis only cortical contact of less than 25% remained as a variable that was a strong predictor of non-union and reoperation.[8]

The thin soft tissue envelope of the tibia is frequently breached during high energy trauma leading to these injuries being the most common open fractures managed by orthopaedic surgeons.[20] Open fractures result in loss of the initial fracture haematoma, periosteal stripping and ischaemic bone and soft tissues.[11] These factors contribute to an increased risk of non-union development in open fractures. Gaebler *et al.* found that grade III open fractures were five times more likely to develop delayed union compared to closed, grade I and grade II fractures.[22] In a review of 104 patients, Karladani *et al.* reported a relative risk of 8.2 (95% Confidence interval) for developing non-union in open fractures.[23] Gaston *et al.* reviewed 100 patients with tibial shaft fractures. They also reported a higher risk of non-union after open fractures with a relative risk of 3.4 (95% Confidence interval).[24]

Atrophic non-unions in particular appear to be related to the extent of the initial damage sustained.[11, 25] Injuries that result in extensive soft tissue damage, severe fracture comminution and devitalisation of fracture fragments have an increased risk of atrophic non-union.[5, 25-27] Gaston *et al.* found that comminuted fractures had a higher likelihood of altered healing. They reported that Winquist and Hansen type III and IV tibial shaft fractures had 31% and 38% chance of non-union respectively compared to type I and II fractures that had an 8% chance of non-union each.[24] These high energy injuries appear to disrupt the vascularity of the fracture ends and affect the early stages of fracture healing.[11, 28, 29] In a rabbit model for atrophic non-union, the vascularity of the fracture site during the early stages of fracture healing was implicated as the driving force for atrophic non-union development. This study found that although the non-union

site appeared well vascularised at eight and 16 weeks, no vessels were seen within the inter-fragmentary gap at one week following the injury.[30]

The specific injury characteristics and damage sustained at the time of injury cannot be modified by the surgeon. Early identification of high-risk injury patterns should however prompt the treating surgeon to employ management algorithms that increase the chances of obtaining union.

**Fracture Management**

Surgical intervention may inadvertently increase the chances of fracture non-union; the choice of fixation and the way in which it is executed can contribute to the overall risk of non-union. Fractures fixed in distraction, unstable fixation and excessive soft tissue dissection all contribute to an increased risk of non-union development.[13, 25]

For fractures to heal, the mechanical environment must be appropriate.[31] Obtaining the ideal inter-fragmentary strain is of vital importance. Bhandari *et al.* identified fixation with a fracture gap as an independent risk factor for requiring additional surgery to achieve union.[21] Fracture gaps may potentially cause non-unions along two pathways. Unstable fixation coupled with small fracture gaps result in a high strain environment that favours chondroid and fibrous differentiation over osteogenesis.[25] Exposing the initial soft callus to excessive motion may disrupt the reparative phase of fracture healing and may result in a hypertrophic non-union.[27, 32] On the other hand, fractures that are rigidly fixed in distraction may result in such low inter-fragmentary strain that no callus formation is stimulated. These situations often result in atrophic non-unions and fixation failure.

The optimal mechanical environment is however not the only consideration when deciding on fixation method, as this should be offset against preserving the remaining biological potential to unite. Open reduction and internal fixation might further disrupt a tenuous blood supply, especially in tibial fractures with concomitant soft tissue injury. Excessive stripping of soft tissue and periosteum my exacerbate necrosis of bone ends and contribute to the loss of biological

potential to heal, ultimately resulting in an atrophic non-union.[25, 29] Following high energy tibial fractures it might therefore be prudent to follow management strategies that preserve the local biological environment.

**Host Factors**

Not all patients have the same fracture healing potential. Some individuals have great ability to heal fracture gaps that might proceed to non-union in another person. The factors that contribute to impaired fracture healing include age, gender and certain concomitant systemic illnesses.[7]

Age

Age has a major influence on the body's ability to heal injuries. Children have a thick periosteum and an osteogenic environment dedicated to skeletal growth. This results in large haematomas and rapid callus formation after paediatric injuries.[33] As skeletally mature individuals advance in age a significant impact on skeletal repair is observed.[34, 35] As a result, the observed healing time of fractures in the paediatric population is about half that in adults. Although there is no correlation between gender and non-union of fractures, healing problems are common among males since they have a higher incidence of high energy fractures.[31]

Concomitant systemic disease

*Anaemia.* Low haemoglobin affects aerobic metabolic processes and alters the body's ability to repair injuries following trauma. Two animal studies investigated the effect of anaemia on fracture healing. Rothman *et al.* reported that iron-deficient anaemic rats had poor mineralisation of fracture callus and a decreased rate of union.[36, 37] Heppenstall *et al.* found that hypovolaemic, anaemic rabbits showed inhibition of fracture healing but after fluid resuscitation, normovolaemic anaemic rabbits had no adverse effects.[38] Varecka *et al.* conducted a retrospective review of 734 patients and concluded that patients with a haemoglobin level below 8 g/dL had an increased risk of non-union. This was particularly significant in tibial fractures. In their series, patients that were smokers combined with anaemia had a 100% risk of non-union.[39]

*Malnutrition.* Dietary and metabolic requirements increase during fracture healing.[11, 25, 31] Brinker *et al.* found that 85% of patients who developed unexplained non-unions had an underlying, undiagnosed metabolic or endocrine abnormality. The most common of which were vitamin D deficiencies.[10] Dodds *et al.* showed that vitamin B6 deficient rats had significant delays in callus maturation.[40] Osteoblast function has further been shown to be dependent on vitamin C.[41] In order to optimise fracture healing, patients should undergo careful nutritional assessment and any identified deficiencies should be addressed.

*Diabetes.* Several clinical and experimental studies have shown that diabetes impairs bone healing.[31, 42] Multiple animal studies using either rats with streptozotocin induced diabetes or BB Wistar Type I diabetic rats have investigated the effects of diabetes on fracture healing. These rats all show decreased callus stiffness and tensile strength in the early stages of fracture healing. [43, 44] Diabetic rats was also found to have decreased cell proliferation, decreased collagen content and increased rates of cartilage resorption at the fracture site compared to controls.[43, 45-47] Follak *et al.* showed that tight glycemic control can produce normal fracture healing.[48] A study by Ghandi *et al.* further indicated that insulin might even play a direct role in healing at the fracture site.[49]

*Hypothyroidism* Urabe *et al.* investigated femur fracture healing in hypothyroid rats. They observed impaired healing as a result of deficient endochondral ossification. When these rats were treated with L-thyroxine, the healing process was returned to normal.[50]

The message from all these studies is clear; when confronted with a non-union, physicians should screen patients for these potential co-morbidities and all reversible or modifiable risk factors should be optimised during the healing process.

**Smoking**

Study data have conclusively revealed that smoking is associated with longer healing times, increased non-union rates and more wound complications after long-bone fractures.[26, 51-54] The impact of smoking appears to be particularly pronounced in open tibial fractures.[55, 56]

Several mechanisms have been proposed to explain how smoking impairs fracture healing and include alterations on a vascular, cellular and intracellular level. Smoking causes vasoconstriction and local hypoxia that could predispose the patient to atrophic non-union development.[11, 57, 58] Nicotine in tobacco prevents cellular proliferation, alters macrophage and fibroblast maturation and is directly toxic to proliferating osteoblasts.[11, 31, 59] Nicotine further inhibits TNF-α expression, required for fracture healing, through the activation of the cholinergic anti-inflammatory pathway.[60] On an intracellular level, smoking inhibits alkaline phosphatase and collagen production.[25]

Cobb *et al.* performed a case control study with patients undergoing ankle arthrodesis. They reported a relative risk of 3.74 for non-union in active smokers. When they analysed the patients without any other known risk factor for non-union development, the risk for non-union in smokers were 16 times that of non-smokers.[61] Bhandari *et al.* reported overall union rates of tibial shaft fractures to be higher in non-smokers (94%) when compared to smokers (84%).[21] Adams *et al.* showed that smokers had increased healing times after tibial fractures (32 weeks vs. 28 weeks), required more bone graft procedures (26% vs 18%) and had a higher rate of non-unions, flap breakdown and infection.[55] A recent meta-analysis by Schenker *et al.* confirmed that the mean healing time for tibia fractures was longer for smokers (32 weeks) than for non-smokers (25 weeks) and that smokers with tibia fractures or open fractures had increased rates of non-union.[62]

Cessation of smoking may not result in an immediate improvement. Castillo *et al.* investigated patients who sustained open tibia fractures and found that current smokers were 37% and previous smokers 32% less likely to achieve union than non-smokers.[63]

It is clear from the available evidence that smoking negatively impacts healing of tibia fractures. It further appears that previous smoking negatively impacts outcome but to a lesser extent than current smoking. The question that remains to be answered is the time needed for the negative affects of smoking to dissipate after cessation of smoking. It is however prudent for physicians to encourage patients with acute fractures and patients undergoing treatment for established non-unions to stop smoking.

**NSAIDS**

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used to manage post-traumatic or post-operative pain. They inhibit cyclooxygenase (COX) enzyme activity and decrease prostaglandin production, which may have a detrimental effect during the inflammatory phase of fracture healing. Conflicting evidence about their affect in clinical practice however remain.[64, 65]

Multiple clinical trials have failed to provide a definitive answer to the effect of NSAIDs on fracture healing.[66] Bhattacharyya *et al.*, Burd *et al.* and Giannoudis *et al.* all reported significant risk for non-union of long bone fractures with the use of NSAIDs.[67-69] Adolphson *et al.* and Davis *et al.*, however, failed to show any correlation between the use of NSAIDs and abnormal fracture healing.[70, 71] It is notable however that both these studies were conducted on patients who sustained Colles' fractures that generally are unlikely to develop non-unions. Studies investigating the effect of NSAIDs on spinal fusion also failed to provide conclusive answers, with some studies showing an inhibitory effect toward fusion while others contradict these findings.[72-76]

In vitro and animal studies has shown similar variations in outcome.[64, 65] The diversity in study design may have contributed to the lack of consensus, but even studies with identical study parameters sometimes report contradictory findings.

Conclusive evidence against the use of NSAIDs in acute fracture care cannot be drawn from the available evidence. The lack of evidence is however not proof of the absence of a detrimental effect and these drugs should be used with caution in patients with high-risk for abnormal fracture healing.[64]

**Other Drugs**

*Antibiotics.* Animal and in vitro evidence indicate that antibiotic therapy may have adverse effects on fracture healing.[77-79] The quinolones, ciprofloxacin, levofloxacin and trovafloxacin has been shown to decrease cellular proliferation and DNA synthesis which result in diminished healing during the early stages of fracture repair.[77, 78] The aminoglycosides gentamycin and tobramycin decrease proliferation of osteoblastic progenitors and are directly toxic to osteoblasts. [80, 81] Experimental studies have shown that osteoblast proliferation might be inhibited by rifampicin at clinical doses.[82] There is however little evidence on the effect of antibiotic therapy on fracture healing in humans.[79]

*Anticoagulants.* In vitro and in vivo evidence suggest that some anticoagulants may impair normal bone metabolism.[83-85] Several animal studies have demonstrated significant attenuation of fracture healing but no human trials are available for evaluation.[5, 31, 83, 85] A literature review by Lindner *et al.* identified strong evidence that warfarin and heparin retard fracture healing, but low molecular weight heparins appear to have a less pronounced effect.[86]

*Anticonvulsants.* There is a growing body of evidence on the adverse effects of anticonvulsants in bone metabolism. Phenytoin, phenobarbital, carbamazepine primidone and valproate have all been implicated in causing decreased bone mineral density and disorders of bone metabolism. [87-91] The extent to which these drugs affect fracture healing in humans remains to be evaluated.

*Chemotherapy.* Chemotherapeutic agents significantly affect fracture healing. Their cytotoxic and anti-proliferative properties impact neovascularisation and callus formation resulting in higher non-union rates.[31, 92] Cyclophosphamide causes diminished calcium and phosphate

deposition in callus.[93] Doxorubicin, cyclophosphamide, adriamycin and methotrexate results in decreased bone formation and these affects might last up to three weeks after administration.[93]

*Corticosteroids.* The effect of long-term corticosteroid use on bone metabolism and fracture healing is well documented.[31, 94, 95] The long term use of corticosteroids lead to osteoblast and osteocyte apoptosis and inhibition of osteoblastogenesis.[5, 13, 92] Waters *et al.* studied the effects of long-term steroid use on fracture healing in a rabbit model. They found an 85% rate of non-union in the corticosteroid group compared with 18% in the control group.[94] In contrast; Hogevold *et al.* investigated short-term corticosteroids use on fracture healing in rats and found no statistically significant difference when compared to a control group.[96]

**Alcohol**

Chronic alcohol consumption leads to osteopenia, increased risk of fracture from falls and delays in fracture healing.[97] Many of these problems have been attributed to nutritional deficiencies and biochemical derangements frequently observed in chronic alcohol abuse.

Recent research have however illustrated that excessive alcohol use may have a direct impact on bone healing. It appears that excessive doses of ethanol in the early healing period inhibits new bone formation and that the newly formed bone lacks mineralization, causing decreased stability and leading to increased incidence of delayed union.[5, 11, 31, 92]

Experimental evidence from ethanol exposed fracture healing in murine models indicates that ethanol impairs the biomechanical strength and decreases the volume of callus formation.[98-100] Chakkalakal *et al.* studied the effects of ethanol on a fracture model in rats. They found that rats that were fed ethanol as 35% of their total calorie intake had deficient bone repair that could not be attributed to nutritional deficiencies. They further found that removal of ethanol from the diet after the bone injury completely restored bone healing.[99]

A retrospective study by Askew *et al.* was consistent with these animal findings. The investigators compared the healing time of fractures in 12 alcoholics and 18 non-alcoholics and found delayed healing time in alcoholics of more than twice that of non-alcoholics.[101]

These studies indicate that alcohol might have a direct negative effect on fracture healing. It appears however that these effects could be negated by the early cessation of alcohol intake following an injury.

**Infection**

Sepsis is often cited as a cause of non-union development.[13] Infection and non-union does, however not has a simple cause-and-effect relationship. Many factors that promote infection, like open wounds with extensive devascularisation, tissue necrosis and instability, are also implicated in non-union development.[11, 25] Infection can however contribute to non-union development through bone death, creation of fracture gaps due to bone resorption and instability because of implant loosening.[25]

**Human Immunodeficiency Virus**

HIV infection has recently been disputed as a risk factor for non-union development. Initial studies showed an increased risk for non-union in certain HIV positive subgroups. Kamat and Govender evaluated the effect of HIV infection on union rates of closed ankle fractures that were managed non-operatively. They concluded that there was no difference in union rates of HIV negative and WHO clinical stage I, II and III HIV positive patients, while patients with WHO clinical stage IV HIV infection had increased non-union rates. (12.45% vs. 1.5% and 1.25%)[102] Chandanwale *et al.* compared healing rates in 80 HAART naive HIV positive patients with 80 HIV negative controls. Closed fractures had similar healing rates in the two groups when treated conservatively or operatively. Open fractures in the HIV positive group, on the other hand showed a significantly increased risk of non-union. (50% vs. 15%)[103] Aird *et al.* prospectively evaluated 133 patients (33 HIV positive) with open fractures. They reported a non-union risk of 15% in HIV positive patients compared to 4% in HIV negative patients.[104]

More recent research has contradicted these earlier findings. Gardner *et al.* prospectively evaluated union in 96 HIV positive patients. They reported that 4% of these fractures failed to unite and concluded that HIV infection did not increase the risk of non-union in surgically managed fractures. This cohort however included only five open fractures.[105]

The exact mechanisms by which HIV infection effects fracture union remain unclear although multiple pathways have been suggested. Molecular and biochemical hypotheses could explain a direct relationship between HIV and impaired fracture union. HIV infection is known to cause an altered cytokine environment that may impact bone healing. TNF-α is up regulated while IGF-1 levels are reduced and an inverse correlation between IGF-1 and IL-6 is observed when compared to HIV negative individuals.[106] HIV may further affect fracture healing by its impact on general health through malnutrition, reduced body mass and opportunistic infections.

Considering the limited and controversial evidence regarding fracture healing in HIV infected individuals, it might be well advised to take particular care to optimise bone healing in HIV positive patients. A tailored fracture management strategy, improvement of nutritional status, avoidance of NSAIDs and cessation of smoking and alcohol consumption might assist in mitigating the potential negative affects of HIV infection on bone healing.

**Genetics**

Despite the lack of any apparent risk factors, some patients still proceed to non-union development.[107] This has led to the hypothesis of a genetic predisposition to altered fracture healing.[108]

Zeckey *et al.* identified a significant correlation between polymorphisms in the PDGF gene and non-union development after femoral and tibial shaft fractures.[109] Dimitriou *et al.* investigated the impact of genetic defects in the BMP signalling cascade on non-union development. The study identified two specific single nucleotide polymorphisms on the *NOGGIN* and *SMAD6*

genes that were associated with an increased risk for atrophic non-union development.[110] Fajardo *et al.* examined RNA expression patterns of BMPs, their receptors and inhibitors in hypertrophic non-union tissue. They found substantially elevated concentrations of BMP-4 and certain BMP inhibitors (Drm/Gremlin, follistatin and Noggin) while levels of BMP-7 was lower than those seen in normal fracture healing.[111]

The extent to which these genetic components predispose to non-union formation and their role and interaction with other risk factors warrant further investigation.

## Conclusion

Non-union development has a multifactorial pathogenesis that is not well understood. The weight that each variable contributes to non-union development remains unclear and a cumulative effect to the development of a non-union is probably involved. A greater understanding of the contributing factors to non-union development will assist orthopaedic surgeons in identifying fractures at risk of altered healing, and assist in the development of multidisciplinary management strategies for established non-unions.

## Conflict of Interest

The authors declare that they have no conflict of interests and no financial support was received for this study.

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# Chapter 3. Challenges and Controversies in Defining and Classifying Tibial Non-unions

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# Challenges and controversies in defining and classifying tibial non-unions

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## Abstract

Tibial non-unions not only result in significant physical impairment but also serve as a source of considerable psychological and socio-economic stress for the patient. Unnecessary delays in recognising potential non-unions lead to treatment delays that further exacerbate the morbidities associated with non-unions. Current definitions are not universally accepted and are considered by some to be too esoteric for general use. The lack of clear defining criteria for non-union may result in delays in diagnosis and appropriate management. The most frequently used classification systems currently are more than 30 years old and do not take new knowledge of biology and modern treatment modalities into account.

**Key words**: tibia, non-union, definition, classification, healing

## Introduction

Non-unions are encountered frequently with multiple factors being implicated in their development.[1-7] These include systemic compromise of the host, local condition of the involved limb, specific injury characteristics and iatrogenic factors relating to the management of the initial injury.[1,8-11]

The management of non-unions is challenging and requires more healthcare services than the initial injury.[2,12-14] Non-unions are almost universally associated with delays in diagnosis leading to significant loss of limb function due to muscle atrophy, joint contractures and disuse osteopaenia.[10,13,15-17] These associated findings significantly complicate the management that is often protracted, expensive and may even fail in 20% of cases.[2,14,18-22]

The definition and classification of non-unions should limit the potential protracted course of diagnosis and management. To date, no consensus exists regarding the definition of non-unions and none of the current classifications has proven universally useful.[2,10,13,14,23-25] Most classifications fail to take all aspects of tibial non-union development into account, and more importantly, do not aid in the decision making as to the most appropriate treatment strategy.[12,14] This may result in non-unions being managed on anecdotal evidence that could exacerbate the existing morbidity.

*Delays in diagnosis lead to significant loss of limb function due to muscle atrophy, joint contractures and disuse osteopaenia*

The ideal definition and classification is elusive and would allow early recognition of a non-union in progress, and provide guidelines to the most effective treatment strategy.

## Defining non-unions

'Medicine is a science of uncertainty and an art of probability.'                                          Osler[26]

The existing definitions of non-union are more controversial than most other definitions in orthopaedics and medicine and are not universally accepted.[2,10,13,14,23-25] The majority are temporal systems that use time as the sole variable to define the presence of a non-union. The 1986 United States Food and Drug Administration (US FDA) definition, for example, defines non-unions as nine months having elapsed with no progression of union in the preceding three months.[2,27] This definition was not intended for clinical use, but was specifically devised for the testing and comparison of medical devices. It does however remain the most widely used definition of non-union in clinical practice. Other proposed temporal definitions use the absence of radiographic progression of healing between the third and sixth month after injury, six to eight months having elapsed without union, or double the expected union time as a definition for an established non-union.[2,24,25]

*To date, no consensus exists regarding the definition of non-unions and none of the current classifications has proven universally useful*

The reason that temporal systems are used to define non-unions is because non-unions are regarded at the extreme end of a time scale continuum, along with normal fracture healing and delayed union. The distinction between normal fracture healing and delayed union is based on the time needed to achieve union, where delayed union occurs after the arbitrary 'expected' time for union.

When non-union is seen in this frame of reference, one can understand why a time variable for the diagnosis of non-union is enforced on the definition. This approach is based on the assumption that all non-unions go through a delayed union phase. Although this might be true for some fractures, where the treating surgeon is unsure of the healing potential, there are definite fracture scenarios where union without surgical intervention is unlikely. Examples would include fractures with segmental bone loss, minimal bone contact, fractures with extensive circumferential soft tissue loss and operatively managed fracture with a fixed gap.

One obvious problem with these stipulative definitions is the erroneous implication that fractures will heal over similar time frames. Multiple factors affect normal fracture union and therefore a large variation in healing time can be expected.[23] Between individuals, for example, several host factors can affect the time to union. These include the age of the patient, where fractures in children can generally be expected to heal twice as fast as in adults.[5]

Other host factors affecting union include smoking, malnutrition, HIV infection and pre-existing pathological bone conditions.[6,28-31] Even in the same individual, a wide variation in fracture healing times is considered normal. Upper extremity fractures generally heal faster than lower extremity fractures. Injuries with severe bony and soft tissue damage may take longer to heal, and treatment strategy, aiming for either primary, direct bone healing or secondary bone healing with callus formation also influence the healing time.[6,29,32-34] An average time to union for each anatomical site, fracture configuration and method of treatment, at any given age should therefore be researched. Tibial fractures in adults, for instance, may heal from anywhere between 10 and 25 weeks, depending on the fracture severity and method of treatment.[35]

A further drawback to temporal definitions is the inevitable delay in diagnosis and treatment they cause. It is during this period where most of the morbidity associated with non-unions arises. Prolonged periods of inability to work contribute to financial hardship, which combined with chronic pain and narcotic dependency, places significant psychological stress on patients and their families.[13,20] It is also during this period that most of the muscle atrophy, joint contracture, osteopaenia and complex regional pain syndrome associated with non-unions develop.[18] Fractures treated with internal fixation also frequently lose the race between union and implant failure during this period, resulting in broken metalware or bone destruction that contribute to the surgical difficulties associated with treating non-unions. This time, waiting for a definition to be fulfilled, could be better spent achieving union and supporting functional rehabilitation.

Megas defined non-union as a cessation of all reparative processes of healing without bone union, while Marsh more specifically emphasised the cessation of both the periosteal and endosteal healing responses without bridging.[25,36] These definitions are empiricist explanations of non-unions rather than true definitions. They are teleological and descriptive in nature, and of limited value in clinical practice.

Many authors have suggested more pragmatic, working definitions. Harwood *et al*. defined non-union as symptomatic fractures with no apparent potential to heal without intervention.[2] Jones *et al*. and Brinker *et al*. defined non-union as the point normal biological healing ceases and will not continue without intervention,[9,37] while Wiss *et al*. suggested that the designation of a non-union be made once the surgeon believes the fracture has little or no potential to heal.[27] Although these definitions are not limited by temporal restrictions and more directed toward clinical use, they are however dependent on surgeon experience to predict fracture healing. This drawback often contributes to delays in diagnosis and treatment, particularly when these patients are managed by junior orthopaedic surgeons without the benefit of experience to identify potential non-unions in progress.

*Multiple factors affect normal fracture union and therefore a large variation in healing time can be expected*

## The ideal definition

The ideal non-union definition should not limit or prevent appropriate and timely intervention. The time parameter, however, should not completely be neglected from a comprehensive definition. Some fractures develop non-unions without any obvious predisposition and these non-unions also need to be addressed in the definition.

We suggest the following definitions:
- *Non unus potentia* (potential non-union): any fracture that when taking host factors, injury severity and management into account, has little potential to heal without further intervention.
- *Non unus certus* (established non-union): any fracture that shows no clinical or radiological union in a reasonable time, for that specific injury, host and management strategy.

The rationale for this distinction is the early identification of potential non-unions. Early identification, referral and treatment of these patients might achieve union with simple interventions without the need for complex, expensive surgeries – a saving that is not only monetary in terms of the healthcare system and the patient's personal finances, but also a saving in terms of morbidity, limb integrity and social dependency of the individual patient.

## Classification

Classifications in orthopaedics are useful in that they assist in diagnosis, guide treatment, indicate prognosis, and/or assist with research. Very few classifications can do all of these things and often only help with one aspect of management. Although debatable, for the average treating surgeon a classification that prescribes treatment strategy is often the most useful.

The Judet and Judet classification, modified by Weber and Cech in 1976, classified non-unions according to the vascularity of the bone ends.[38,39] The distinction between avascular and hypervascular non-unions was made and a biological cause for non-union development was underlined.[39] The diagnosis was based on strontium-85 uptake at the fracture site to delineate the viability of the bone ends. Bone scintigraphy examinations are not widely used to diagnose non-unions today and are especially difficult to perform in the resource-restricted environment of the developing world. The amount of fracture callus visible on normal radiographs is therefore currently used as a surrogate marker for fracture site vascularity, giving rise to the current terms of atrophic and hypertrophic non-unions.[11,25] Although important, the radiographic appearance of a non-union should not be the only consideration when contemplating the ideal treatment strategy.

Non-union in an avascular setting is explained by insufficient osteogenic potential to affect healing, while hypervascular non-unions are attributed to inadequate stability to allow normal fracture union.[25] Many orthopaedic surgeons use this classification as the basis of non-union management, providing stability for hypervascular (hypertrophic) non-unions, and adding biology in the form of bone-graft for avascular (atrophic) non-unions.

Although widely used, not all researchers subscribe to this aetiogenesis of non-union formation in the avascular setting,[40,41] as illustrated by the research of Sun *et al.* who hypothesised the existence of temporally quiescent mesenchymal cells in avascular bone ends.[4] This could explain why certain 'avascular' non-unions may unite in the ideal biomechanical environment without the addition of bone-graft.[42]

A further drawback to the classification proposed by Weber and Cech is the fact that bone loss, limb length discrepancy, angular deformities, rigidity of the non-union's site, previous fixation used or adequacy of fixation is not considered.[39] Each Weber and Cech group, therefore, has multiple potential treatment strategies, depending on these variables. The time required before the described bone end changes are seen on X-ray is also problematic and may lead to delays in diagnosis and management of patients who could benefit from earlier intervention.

The Ilizarov classification attempts to facilitate the selection of the appropriate surgery for a non-union. This system is based on the non-union morphology being stiff or lax, and whether stiff non-unions have any concomitant angular deformities.[43] This classification does not take the whole clinical scenario into account. Host factors, limb length discrepancy and bone loss are not considered, and non-union with internal fixation in situ is not addressed.

The Paley classification specifically addresses tibial non-union.[44,45] It considers bone loss, fracture site mobility, angular deformities and overall tibial length. Although this classification is an excellent advance on other existing classifications with regard to the mechanical attributes of a non-union, it again fails to address non-union biology and host optimisation.

An attempt to address some of these shortcomings was made by Wu *et al.* who developed their protocol to more clearly classify non-unions.[11] A novel addition to this classification was the incorporation of non-unions with internal fixation in situ. These non-unions were designated as either avascular or hypervascular depending on whether the fixation was stable or unstable. Another important aspect in non-union management was also raised, namely the possibility of these non-unions potentially being infected. The active exclusion of infection was emphasised. Management of each group was suggested, being either open bone-graft and intramedullary nailing, bone grafting alone, or bone grafting and implant exchange. The Wu classification successfully addressed the management of non-unions with failed internal fixation, but did not incorporate bone alignment or host optimisation. Automatically designating non-unions with stable fixation as avascular is also not necessarily biologically accurate as fractures fixed in distraction are not always avascular but may develop non-unions due to the healing process not being able to cross the fracture gap.

The Calori Non-union Scoring System (NUSS) has recently been developed[14] and validated[12] to assist surgeons with the complex analysis of non-union surgery. It uses the 'Diamond Concept' where multiple elements are considered in non-union management, including the cellular environment, the growth factors, the bone matrix and the mechanical stability (*Table I*). Each individual factor is scored and then added to give a final score that guides treatment.

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| Table I: Calori Non-Union Scoring System[14] | | | |
|---|---|---|---|
| **The bone** | | **Score** | **Max. score** |
| Bone quality | Good | 0 | 3 |
| | Moderate | 1 | |
| | Poor | 2 | |
| | Very poor | 3 | |
| Primary injury – open or closed fracture | Closed | 0 | 5 |
| | Open grade I | 1 | |
| | Open grade II – IIIA | 3 | |
| | Open grade IIIB and IIIC | 5 | |
| Number of previous interventions on the bone to procure healing | None | 1 | 4 |
| | <2 | 2 | |
| | 2–4 | 3 | |
| | >4 | 4 | |
| Invasiveness of previous interventions | Minimally invasive – closed surgery | 0 | 3 |
| | Internal intra-medullary nailing | 1 | |
| | Internal extra-medullary | 2 | |
| | Any osteosynthesis which include bone grafting | 3 | |
| Adequacy of primary surgery | Inadequate stability | 0 | 1 |
| | Adequate stability | 1 | |
| Weber & Cech group | Hypertrophic | 1 | 5 |
| | Oligotrophic | 3 | |
| | Atrophic | 5 | |
| Bone alignment | Non-anatomical alignment | 0 | 1 |
| | Anatomical alignment | 1 | |
| Bone defect – gap | 0.5–1 cm | 2 | 5 |
| | 1–3 cm | 3 | |
| | >3 cm | 5 | |
| **Soft tissues** | | **Score** | **Max. score** |
| Soft tissue status | Intact | 0 | 6 |
| | Minor scarring | 2 | |
| | Previous treatment of soft tissue defect | 3 | |
| | Previous free flap | 4 | |
| | Poor vascularity | 5 | |
| | Presence of skin lesion / defect | 6 | |
| **The patient** | | **Score** | **Max. score** |
| ASA grade | 1 or 2 | 0 | 1 |
| | 3 or 4 | 1 | |
| Diabetes | No | 0 | 2 |
| | Yes – well controlled | 1 | |
| | Yes – poorly controlled | 2 | |
| Blood tests: FBC, ESR, CRP | FBC: WCC > 12 | 1 | 3 |
| | ESR > 20 | 1 | |
| | CRP > 20 | 1 | |
| Clinical infection status | Clean | 0 | 4 |
| | Previously infected or suspicion of infection | 1 | |
| | Septic | 4 | |
| Drugs | Steroids | 1 | 2 |
| | NSAIDs | 1 | |
| Smoking | No | 0 | 5 |
| | Yes | 5 | |

*HIV infection and genetic predisposition has been implicated in non-union development but is omitted from the NUSS system*

The suggested treatments include 'standard treatment', 'specialised care' and 'specialised care and specialised treatment'. This provides an indication for junior orthopaedic surgeons of which patients to refer, but does not provide specific treatment guidelines as to what 'specialised treatments' should be offered.

The different approaches and focal points of these classification systems complicate treatment strategy decisions and research into non-union management.[14] Formulating standardised treatment strategies or protocols on existing classification systems is challenging, and might not take all aspects of non-union development and management into account.

## The ideal classification

EF Schumacher said that any intelligent fool can makes things bigger, more complex, but it takes a touch of genius and a lot of courage to move in the opposite direction.[48] Unfortunately, we are at a point where classifications and scoring systems for non-unions are becoming more complicated. As more variables are identified that contribute to the development and negatively impact the management of non-unions, more factors are built into classifications and scoring systems. As effective treatment will depend on addressing the host, biological and mechanical factors; all of these need to be incorporated into an encompassing classification system.

This score is an excellent starting point to improve non-union management. It does however need to be improved in terms of factors taken into account. HIV infection and genetic predisposition has been implicated in non-union development but is omitted from the NUSS system.[3,7,46,47] The weight that each factor carries towards the final score is crucial in order to guide appropriate treatment and should be devised through regression analysis. With the current NUSS score, the authors weighted each factors according to the opinions and experience of the senior authors who have tertiary referral non-union practices. Another area that needs to be addressed is the treatment strategy that the final score proposes. The present score only proposes, in broad terms, where and how these patients should be treated.

## Conclusion

Non-union management is resource intensive and technically demanding. Inadequate definitions and suboptimal classification systems often exacerbate the existing morbidities associated with non-unions and may even cause delays in diagnosis and treatment. In order to improve non-union management, definitions that allow the early identification of potential non-unions and a classification system that incorporates all factors identified in non-union development is required.

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# PART TWO. Retrospective Review and Development of the Tibial Non-union Treatment Algorithm

The Tumour, Sepsis and Reconstruction (TSR) Unit and Greys Hospital is the only dedicated limb reconstruction unit in KwaZulu-Natal and accepts referrals from the entire province. Hence, a large number of tibial non-unions are referred to this unit. Over a five year period, from January 2010 to December 2014, more than 120 tibial non-unions required treatment. In addition to these non-unions, the TSR unit also managed a large number of patients with musculoskeletal tumours, malunions, post-traumatic and congenital deformities, and chronic osteomyelitis. With only two full time orthopaedic surgeons employed in this unit and limited theatre time available, this necessitated the development of management strategies that were time efficient, cost effective and without the need for routine repeat surgeries or expensive adjuvant therapies.

During research into the most effective treatment for tibial non-unions, we were introduced to the concept of mechano-biology and its potential uses in non-union management.[1] This refers to the ability to stimulate bone formation by creating the ideal mechanical environment and forms the basis of all non-union management. This, combined with the work done on stiff non-unions by Saleh, Catagni, El-Rosasy and Kocaoğlu helped formulate treatment strategies for the two most commonly encountered non-union subtypes, namely mobile atrophic and stiff hypertrophic.[2-5]

Circular external fixators were chosen to provide fixation because of their unique characteristics of low axial stiffness combined with high bending and translational rigidity.[6, 7] The use of tensioned fine wires further imparts viscoelastic properties (non-linear, load dependent axial stiffness) to circular fixators and has been described as 'true biological fixation'.[8] These biomechanical properties along with their modularity and minimal invasive application, make circular external fixators appropriate for the management of complex trauma and limb reconstruction surgery.

The closed distraction of stiff non-unions to achieve mechanical alignment and union is a relatively new concept.[2, 3] The use of hexapod circular external fixators to accomplish this is based on the success achieved with these devices in deformity correction surgery and has to our knowledge not been published before.[9-11] We propose an explanation to the effectiveness of this strategy and have published the first report on the use of a hexapod fixator to successfully manage a stiff tibial non-union through closed distraction.

The following three chapters consist of retrospective reviews of our management of tibial non-unions. These three papers formed the framework on which the tibial non-union treatment algorithm was developed.

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# Chapter 4. Tibial Non-union Treated with the TL-Hex: a case report

Contribution to authorship:

- N. Ferreira – Concept development, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- F. Birkholtz – contribution to literature review and revision of manuscript.
- L.C. Marais – Concept development, contribution to literature review and revision of manuscript.

# Tibial non-union treated with the TL-Hex: a case report

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### Abstract

Tibial non-unions are difficult to treat, even for the experienced orthopaedic trauma surgeon. Despite being relatively common problems, controversy exists regarding their ideal management. We report a case of a stiff oligotrophic tibial non-union successfully treated with the new TL-Hex (Orthofix, Verona, Italy) circular external fixator. Closed gradual distraction was effective to correct all deformities and stimulate bone formation without the need for a tibial osteotomy or bone graft.

**Key words**: tibia, non-union, oligotrophic, hexapod, TL-Hex

## Background

The tibia in the most commonly injured long bone.[1] Due to its anatomical site and subcutaneous location the tibia is often exposed to high-energy trauma, and it is prone to a number of complications including non-union formation.[1-4] Along with the severity of injury, many other factors have been implicated in non-union development, including systemic compromise of the host and iatrogenic factors relating to the management of the initial injury.[3,5-10]

Once established, non-unions are difficult to treat.[5,7,11] For the patient, non-unions harbour significant morbidity in terms of financial and emotional compromise.[9,12-14] For the healthcare system and treating physician, non-unions demand increased resources, expensive treatment strategies and a meticulous understanding of the under-lying disease process.[14,15] The optimal management strategy promotes rapid consolidation of the non-union while simultaneously allowing functional rehabilitation of the affected limb.

We report a case of a stiff oligotrophic non-union of the distal tibia that was successfully treated with monofocal distraction with the new TL-Hex (Orthofix, Verona, Italy) circular external fixator.

## Case report

A 26-year-old woman was referred to our limb recon-struction unit after failed conservative management of a closed distal third tibia fracture. The fracture was sustained after a fall, six months prior to our consultation. Her initial management consisted of a patella-tendon bearing plaster cast and regular follow-up at her base hospital. At presentation to our unit a stiff tibial non-union with a partially correctable deformity was evident.

*Non-unions demand increased resources, expensive treatment strategies and a meticulous understanding of the underlying disease process*

Local and systemic staging confirmed the diagnosis of metabolic syndrome X. She was a type 1 diabetic, hypertensive and hypothyroid on treatment. A bone density scan done at the base hospital revealed the patient to be osteopaenic. Radiographs confirmed an oligotrophic non-union of an oblique distal third right tibia fracture with an 11° varus, 9° recurvatum and 22 mm shortening deformity (*Figure 1*). Full knee and ankle motion was possible and no vascular or neurological compromise was present. No other abnormalities were identified.

Surgical management consisted of a fibula osteotomy followed by application of a TL-Hex circular external fixator. Proximal and distal fixation consisted of two hydroxyapatite-coated half pins and one 1.8 mm tensioned transverse wire secured to a single ring for each bone segment (*Figure 2*). The non-union site was left undisturbed and in the deformed position. No bone graft was added.

After a latency period of seven days, gradual correction was achieved over 23 days at a distraction rate of 1 mm per day. During the correction and the consolidation phase functional rehabilitation was encouraged with the assistance of a physiotherapist. Full weight bearing was allowed from the first post-operative day. Pin tract care followed our standard protocol and included twice daily cleaning with an alcoholic solution of chlorhexidine.[16,17]

No complications were encountered during the treatment period, and no pin site infections developed. After 22 weeks, radiographic evaluation confirmed solid union with exuberant callus formation. Union was confirmed by the lack of tenderness at the non-union site and the ability to weight bear on a fully dynamised external fixator without pain. After clinical and radiographic confirmation of union, the external fixator was removed (*Figure 3*). Radiographic follow-up confirmed a solid union with no displacement of deformity, ten months after fixator removal.



*Figure 1. AP and lateral radiographs showing an oligotrophic non-union of the distal third tibia*
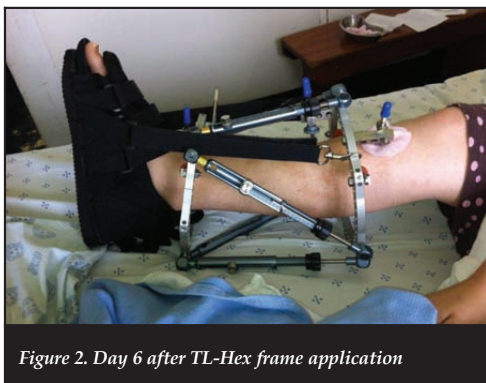


*Figure 2. Day 6 after TL-Hex frame application*



*Figure 3. AP and lateral radiographs after frame removal showing solid union with exuberant callus formation*

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## Discussion

Circular external fixators are increasingly being used for orthopaedic trauma and post-traumatic reconstruction.[18-20] These fixators exhibit a unique ability to eliminate bending and translational shear while maintaining a degree of axial micromotion.[19,21-25] This three-dimensional stability translates into a biomechanical environment that is conducive to bone healing and regenerate formation and is often exploited for limb salvage and reconstruction.[18,24,26-28]

The hexapod fixator has been a recent modification of the traditional Ilizarov-type fine wire circular external fixator.[29,30] It consists of two rings connected with six oblique struts in an octahedral configuration. Complex mathematical algorithms calculate strut length adjustments in order to manipulate the orientations of the two rings to each other.[31,32] By attaching each of these rings to a bone segment, their position and orientation can be altered, thereby facilitating the reduction of complex multiplanar deformities.

Partial fibula resection is an important step in the management of tibial non-unions.[33] Not only does the fibula osteotomy increase compressive forces across the ununited tibia, correction of tibial deformities relies on a mobile fibula.[33-37] For both these reasons a partial fibula resection was performed in our patient as it allowed correction of the tibial deformity and force transmission across the tibial non-union site.

The Orthofix TL-Hex is the latest hexapod circular external fixator that is commercially available. The first case was performed in South Africa on 12 November 2012 and since then its use has steadily increased in South Africa, Great Britain, France and Italy. The key design features of the TL-Hex include struts with both acute and gradual excursions that increase their working lengths *(Figure 4)*, struts that attach via stable ball joints on the outside of rings to open more fixation holes in the rings *(Figure 5)*, and the adjustment of struts through a user-friendly click mechanism that prevents accidental adjustments.

In stiff non-unions, the ability of the hexapod circular external fixator to provide controlled gradual distraction allows not only the correction of existing deformities, but also the stimulation of new bone formation. This 'tension-stress effect' was initially described by Ilizarov and is the biological basis of distraction histogenesis used in limb lengthening and bone transport.[38-40] It is thus possible, in low biologically active scenarios, to stimulate natural bone healing without the addition of bone graft or orthobiologics. This was demonstrated in our case, where an oligotrophic non-union healed with exuberant callus formation through gradual distraction without the addition of bone graft.

## Conclusion

Circular external fixators are extremely useful in the management of tibial non-unions. Hexapod fixators in particular provide additional management options where non-unions are associated with deformities that are not acutely correctable.
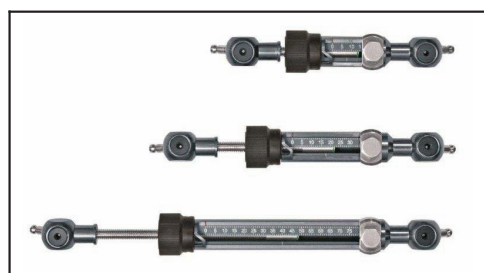


*Figure 4. TL-Hex telescopic struts that allow acute and gradual adjustments*
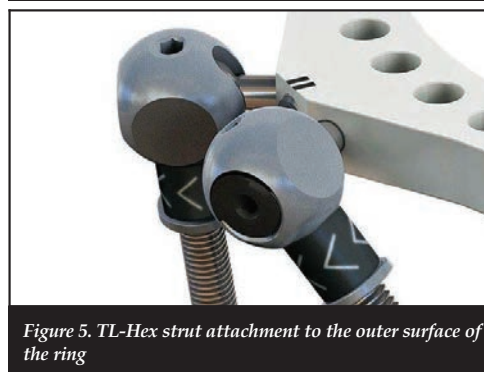


*Figure 5. TL-Hex strut attachment to the outer surface of the ring*

The TL-Hex fixator is the latest hexapod circular external fixator that is commercially available, and this case is the first report of its use in clinical practice. Its use allowed gradual reduction of a stiff non-union while also facilitating functional rehabilitation and eventual union in an acceptable position.

## Consent

Written consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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# Chapter 5. Hexapod External Fixator Closed Distraction in the Management of Stiff Hypertrophic Tibial Non-unions

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- N. Ferreira – Concept development, data collection, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- L.C. Marais – Concept development, data collection, contribution to literature review and revision of manuscript.
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■ TRAUMA

# Hexapod external fixator closed distraction in the management of stiff hypertrophic tibial nonunions

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**Tibial nonunion represents a spectrum of conditions which are challenging to treat, and optimal management remains unclear despite its high rate of incidence. We present 44 consecutive patients with 46 stiff tibial nonunions, treated with hexapod external fixators and distraction to achieve union and gradual deformity correction. There were 31 men and 13 women with a mean age of 35 years (18 to 68) and a mean follow-up of 12 months (6 to 40). No tibial osteotomies or bone graft procedures were performed. Bony union was achieved after the initial surgery in 41 (89.1%) tibias. Four persistent nonunions united after repeat treatment with closed hexapod distraction, resulting in bony union in 45 (97.8%) patients. The mean time to union was 23 weeks (11 to 49). Leg-length was restored to within 1 cm of the contralateral side in all tibias. Mechanical alignment was restored to within 5° of normal in 42 (91.3%) tibias. Closed distraction of stiff tibial nonunions can predictably lead to union without further surgery or bone graft. In addition to generating the required distraction to achieve union, hexapod circular external fixators can accurately correct concurrent deformities and limb-length discrepancies.**

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The tibia is the most commonly fractured long bone and such injuries are prone to a number of complications.[1,2] Owing to its anatomical location and minimal soft-tissue coverage, the tibia has a relatively high incidence of open fractures, which may be compromised by its tenuous blood supply. For these reasons, fracture healing can be problematic, with an incidence of tibial nonunion stated to range between 8% and 13%.[2-5] The management of such nonunion is complicated by the lack of a universally accepted definition and classification.[4,6] This may cause delays in appropriate referral and treatment, and could contribute to loss of limb function secondary to muscle atrophy, joint contractures and disuse osteopaenia.[4,7]

Despite the magnitude of this problem, the treatment of tibial nonunion has not been standardised, nor have large, randomised controlled trials been used to synthesise an evidence base. The management of these complex injuries remains one of the most challenging problems facing the orthopaedic trauma surgeon.[8]

Nonunions can be classified as hypertrophic or atrophic, stiff or mobile, with or without bone defects and as infected or uninfected.[7,9-12] This diversity in pathophysiology and presentation is reflected in a range of radically different treatment strategies.[7,12,13,14] One proposed treatment for hypertrophic nonunions is based on distraction to stimulate osteogenesis, in the process correcting any associated deformities and leg-length discrepancy.[15-20]

We report our results of closed distraction of stiff, hypertrophic, ununited fractures of the tibia with hexapod circular external fixators. In addition, we propose a mechano-biological hypothesis of the efficacy of closed distraction to achieve union of these fractures.

## Patients and Methods
Between January 2010 and January 2014, 44 consecutive patients with 46 un-infected, hypertrophic nonunion of tibial fractures were treated with closed hexapod distraction at our tertiary limb reconstruction unit. This strategy represents our current standard of care for these injuries. The cohort comprised 31 men and 13 women with a mean age of 35 years (18 to 68) (Fig. 1). In total, 45 of the 46 fractures were classified as stiff by Ilizarov's criterion[21] of < 7° of movement.

Standard physical, laboratory and radiographic evaluations were performed on all patients and any modifiable risk factors were addressed by strategies such as smoking cessation, optimal glycaemic control in diabetics and the initiation of highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) positive patients with low cluster of differentiation 4 (CD4) cell counts.
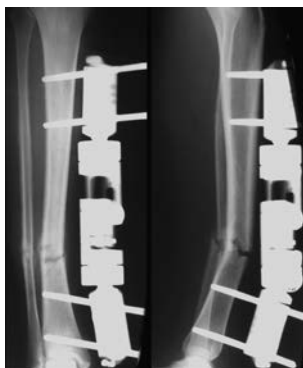
Fig. 1

Anteroposterior (left) and lateral (right) radiographs of the tibia six months after open fracture, demonstrating angulation and nonunion at the fracture site.

Table I. Identified risk factors for nonunion (more than one risk factor identified for some fractures)

| Risk factor | n |
|---|---|
| Open fracture | 36 |
| Smoker | 19 |
| HIV positive | 9 |
| Oblique distal third fracture | 2 |
| Diabetes mellitus | 1 |
| Hypothyroidism | 1 |
| Internal fixation with fracture gap | 1 |

HIV, human immunodeficiency virus

Under tourniquet control and via an approach between the peroneal and soleus muscles, 5 mm to 10 mm resection of the fibula was performed. The resection was performed at the level of the fibular deformity if one was present. Fascia and skin were then closed in layers over a drain and the tourniquet deflated for the remainder of the operation.

The hexapod external fixator was applied using the 'rings first' method,[22] entailing application of the proximal and distal rings without altering the tibial deformity, completion of the hexapod with struts and return to the ward for limb elevation without any surgical intervention at the fracture site. Pin-site management was by our standard protocol, encompassing a meticulous intra-operative insertion technique and a rigorous post-operative regime including twice-daily cleaning with alcoholic chlorhexidine.[23,24]

Post-operative radiographs were used for planning correction of the deformity, which was commenced without any latency period. Existing deformities were corrected at a rate of 1 mm per day at the apex. The initial in-hospital adjustments were undertaken by the primary author and other members of hospital staff. Where patients could cope with the adjustments themselves, they were taught how to perform the adjustments and discharged to perform them at home. Where no limb-length discrepancy existed, a minimum of 3 mm distraction was performed. During the distraction and consolidation phase, functional rehabilitation was encouraged under the guidance of a physiotherapist, with a programme based on early mobilisation and weight-bearing followed by normalisation of gait pattern and functional use.

Outpatient follow-up was scheduled at two-weekly intervals during the correction phase and until a robust rehabilitation routine was established. Thereafter, the interval between follow-up appointments was increased to four weeks. Removal of the frame was considered once tricortical consolidation was radiologically evident. At this point, a staged 'trial of union' protocol was initiated by firstly dynamising the external fixator by releasing all six struts. The site of the uniting fracture was manually stressed and if this did not cause any pain or deformity, the patient was instructed to bear weight. If the patients were able to walk without pain, they were allowed to return home with a fully dynamised frame and encouraged to mobilise, fully weight-bearing, for a period of two weeks. Repeat radiographs were then compared with those before the trial of union; if no deformity had developed, union was deemed confirmed and the external fixator removed. All patients were followed-up clinically and radiologically for a minimum of six months after removal of the frame. Any changes in angulation between visits were identified as a failure of treatment and managed accordingly.

Results

Mean follow-up after removal of the external fixator was 12 months (6 to 40). In total 36 of 46 fractures were open, comprising: 15 Gustilo-Anderson IIIB, 13 grade IIIA and eight grade II injuries.[25,26] The remaining ten were closed fractures treated with a plaster cast in nine and an intramedullary tibial nailing in the remaining fracture. The mean time elapsed before applying the hexapod frame was 21 months (6 to 84) since the initial injury.

Risk factors for nonunion were identified in 40 of 44 (90.9%) patients (Table I). The remaining four patients all had closed fractures and no identifiable risk factors for nonunion. In all, nine patients were HIV-positive (20.4%) of whom six who were on HAART had a mean CD4 count of 430 cells/mm$^3$ (124 to 600), while the remaining three, with a mean CD4 count of 506 cells/mm$^3$ (439 to 600) had not been started on treatment.

Tibial deformities after application of the frame were assessed with the aid of standardised anteroposterior and lateral radiographs (Fig. 2) and are described in Table II. All radiographic assessment was undertaken by the primary author and was performed by either line drawings on printed films or picture archiving and communications system tools. Of the 46 fractures, eight required a second programme for clinically acceptable correction. The adequacy of reduction was assessed during outpatient follow-up and
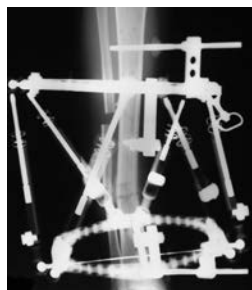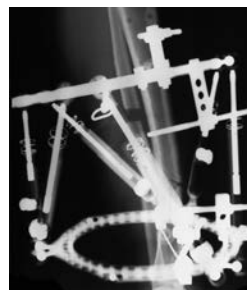
Fig. 2a                    Fig. 2b

Standardised a) anteroposterior and b) lateral radiographs after hexapod frame application and fibular osteotomy.

**Table II.** Values of measured deformities

| Deformity | Mean (range) | SD |
|---|---|---|
| Coronal plane angulation (°) | 8 (0 to 34) | 7.8 |
| Sagittal plane angulation (°) | 9 (0 to 64) | 11.6 |
| Rotation (°) | 2 (0 to 30) | 5.1 |
| Coronal plane translation (mm) | 0 (0 to 35) | 7.3 |
| Sagittal plane translation (mm) | 4 (0 to 15) | 4.4 |
| Shortening | 7 (3 to 25) | 4.4 |

SD, standard deviation



Fig. 3a                    Fig. 3b

a) Anteroposterior and b) lateral radiographs of united tibia 12 months after hexapod removal.

if it was deemed necessary, a second programme was generated and completed at home. The Taylor Spatial Frame (TSF) (Smith & Nephew, Memphis, Tennessee) was used for 24 fractures and the TrueLok-Hex (Orthofix, Verona, Italy) in 22. The mean duration of external fixator treatment was 23 weeks (11 to 49).

Bony union was achieved after initial treatment in 41 of 46 (89.1%) tibias (Fig. 3). Of the five patients whose treatment failed, four presented with progressive deformity after the external fixator was removed. Failure after initial treatment was judged to be the result of early external fixator

removal and indicates the learning curve associated with the treatment methods, as well as the difficulty with confirming union in certain cases. These patients were retreated with the same technique and progressed to union after the second treatment. This resulted in final bony union after closed hexapod distraction in 45 of 46 (97.8%) tibiae. Leg lengths were restored to within 1 cm of the contralateral side in all fractures. Alignment with deformity < 5° in all planes was achieved in 42 tibiae. The remaining three patients had 6° valgus, 8° valgus and 10° recurvatum, respectively.

Pin-tract infection was the most common complication, occurring in nine of 46 (19.5%) cases. The majority of these infections were minor according to the Checketts, Otterburn and MacEachem classification[27] and responded to local pin tract care and oral antibiotics. Hardware complications were experienced in one case; this patient sustained a fall with resultant breakage of a fine wire, which required replacement in the operating theatre without incident.

**Discussion**

Nonunion of fractures is underpinned by a spectrum of causes and the optimal management remains unclear. Several authors have outlined the principles for the generic ideal treatment of the problem. Kanellopoulus and Soucacos[15] advocated that treatment should have the ability to simultaneously address axial deviations, shortening, bone loss, poor blood supply and achieve union without further compromise of the soft-tissue envelope. It was emphasised that this should also improve, not just maintain

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functional ability. Gershuni[28] regarded the restoration of bony continuity, correction of alignment in all planes, maintenance and recovery of function, and limitation of further complications, as the ideal management strategy. Giannoudis, Einhorn and Marsh[29] recently introduced the 'diamond concept' to the management of nonunions, which attempts to address the cellular environment, growth factors, bone matrix and mechanical stability.

Circular external fixators are ideally suited to addressing complex geometrical problems while respecting the local soft-tissue environment and are increasingly being used for acute trauma and post-traumatic reconstruction.[8,30-32] They can be configured to correct deformity gradually and provide stable fixation to allow early functional rehabilitation. Their use, especially, in tibial malunion and nonunion, has gained popularity in recent years.[7,8,15,10,11,16,33] Their unique ability to eliminate bending and translational shear while maintaining a degree of axial micromovement[32,34-37] translates into a biomechanical environment that is conducive to bone healing and regenerate formation.[30,36,38-41]

Hexapod external fixators are a modification of the traditional Ilizarov-type fine wire circular fixators.[42,43] They consist of two rings connected with six oblique, variable-length struts in an octahedral configuration. Mathematical algorithms calculate strut length adjustments in order to manipulate the two rings relative to each other.[44,45] By attaching each of these rings to a bone segment, their position and orientation can similarly be altered. This allows the surgeon to correct complex multiplanar deformities without the need to alter the frame construct during the treatment process.[8,19,41,42,46-52] Such fixators have been shown to offer a much higher degree of precision for deformity correction than the traditional Ilizarov technique and hence have a clear advantage in multidimensional deformity corrections.[46,53,54] Rozbruch et al[55] reported their experience with the use of the TSF for the management of tibial nonunion. They demonstrated the TSF's ability to produce accurate deformity correction and restoration of length.

Ilizarov[56] demonstrated the ability of tissues to proliferate under controlled tension by the so-called 'tension-stress effect'. Several authors have demonstrated the effectiveness of this strategy in the management of nonunion.[16-18,20,57] Saleh and Royston[20] reported ten patients with hypertrophic nonunion who were successfully treated with distraction. Their series included femoral and tibial fractures and the use of both monolateral and circular external fixators. Catagni et al,[16] El-Rosasy[17] and Kocaoğlu et al[18] have all reported their success with the Ilizarov circular fixator in the management of hypertrophic nonunion of various fractures of long bones. Saleh and Roytson[20] and Saleh[57] concluded that nonunions could heal in distraction under the appropriate conditions and with the use of a mechanically competent external fixator, while Catagni et al[16] went on to observe that distraction osteogenesis of stiff hypertrophic nonunions offers optimal rehabilitation as the patient maintains limb function and weight-bearing status while undergoing treatment.

The mechano-biological justification for the distraction of stiff nonunions can be explained by the interfragmentary strain theory of Perren.[58,59] This states that a small amount of relative deformation (strain < 2%) is required to induce callus formation while high strain (> 10%) will lead to the resorption of bone and eventual nonunion.[59] The amount of mobility allowed depends less on the displacement of the fragments alone than on the relation of the width of the fracture gap (L) and displacement ($\delta L$); $\delta L/L$.[58]

We suggest that hexapod distraction of stiff nonunions has a dual effect on interfragmentary strain. Firstly, the tension caused by distracting an inherently stiff environment combined with stable fixation decreases interfragmentary movement ($\delta L$). Secondly, distraction increases the fracture gap (L). This results in an overall reduction of strain to within the range in which bone formation occurs. The clinical evidence for this theory appears to be supported by our results, where only one of 46 fractures failed to heal after closed distraction.

Our series is the largest in the English orthopaedic literature of tibial nonunions treated with hexapod external fixators. Two previous studies reported the use of the TSF for tibial nonunions. Feldman et al[8] reported seven patients with mal- and nonunions of hypertrophic, atrophic and infected origin, one of which failed to unite. Rozbruch et al[55] described 38 patients with nonunions associated with hypertrophic, atrophic and also infective causes, with bone loss. The treatment described comprised of a variety of methods including distraction and compression, as well as bone grafting in 25 of their patients. They reported union in 27 (71%) patients after the initial treatment and in 36 (95%) patients after re-treatment that included TSF reapplication, intramedullary nailing, fixation with a plate and amputation. Both authors concluded that the TSF is an effective strategy for treating nonunions of the tibia. Our series supports their findings and specifically indicates the value of the hexapod external fixator in the treatment of stiff hypertrophic tibial nonunions.

The reason for failure after the first treatment in our series could have been unstable fixation or early removal of the fixator, which illustrates the difficulty of confirming union in these fractures. The remaining patient who did not unite was a smoker who sustained a gunshot to the distal tibia two years earlier with a resultant nonunion. This nonunion was hypertrophic on radiographic examination and mobile with more than 7° of movement possible. In retrospect, this was an undiagnosed pseudoarthrosis and was erroneously treated with closed hexapod distraction. Pseudoarthrosis refers to the development of a 'false joint', usually after long-standing nonunion. These patients have bone ends covered in cartilage at the fracture site and a pseudo-capsule which can even produce a synovial fluid-like liquid. This is in contrast to the fibrous tissue generally seen in hypertrophic nonunions. Radiologically, these non-

unions might appear hypertrophic, but clinically they are more mobile and generally not painful on movement. Treatment by resection and bone transport was planned for this case.

Important advantages of this treatment strategy include the ability to correct mechanical alignment and leg-length discrepancy with a single admission and surgical procedure. Gradual correction is safe for neurovascular structures and the local biology around the nonunion site remains undisturbed. No additional morbidity from harvesting an autograft or additional cost of allograft or biological agents is incurred. The mechanical stability and resultant functional rehabilitation results in improved bone stock, and prevention and improvement of contractures at adjacent joints.

There are several limitations of this study including a retrospective design, single-centre cohort and lack of a control group. Controversies around the definition and classification of nonunions may have contributed to the misdiagnosis of our single failure.

In conclusion, closed distraction of stiff hypertrophic tibial nonunions can reliably produce union while accurately correcting concurrent deformities and limb-length discrepancies within a single intervention.

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# Chapter 6. Mechano-biology in the Management of Mobile Atrophic and Oligotrophic Tibial Non-unions

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Contribution to authorship:

- N. Ferreira – Concept development, data collection, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- L.C. Marais – Concept development, data collection, contribution to literature review and revision of manuscript.
- C. Aldous – Concept development and revision of manuscript.

**Original Article**

# Mechanobiology in the management of mobile atrophic and oligotrophic tibial nonunions

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## ARTICLE INFO

## ABSTRACT

*Background:* Recent research indicates that atrophic nonunions are biologically active and may heal in the optimal biomechanical environment.

*Methods:* Thirty-three patients with mobile atrophic and oligotrophic tibial nonunions were treated with circular external fixation and functional rehabilitation. Seven patients required autogenous bone graft procedures.

*Results:* Bony union was achieved after the initial surgery in 31/33 (93.9%) tibias. Two persistent nonunions were successfully treated with repeat circular external fixation without bone graft. This resulted in final bony union in 33/33 (100%) patients.

*Conclusion:* Mechanobiological stimulation of tibial nonunions can produce union even if the biological activity appears to be low.

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## 1. Introduction

The clinical entity of tibial nonunion incorporates a variety of conditions that range from mobile to stiff, hypertrophic to atrophic, with deformity or without, and even large segmental bone defects, with or without limb length discrepancy.[1–3] The proposed management of these subdivisions is almost as numerous as the variation in nonunions themselves, and even within groups, the management can be affected by host factors, condition of the surrounding soft tissues, and the nonunion morphology itself.[2,4]

The treatment of tibia nonunions is mostly based on small series of cases that frequently include a variety of nonunion subtypes and even infected cases.[2,5,6] Fixation methods vary from internal fixation, including conventional compression plating, locked plating, and reamed intramedullary nailing, to external fixation, with either monolateral fixators, circular fixators, and hybrid fixators.[2,5,7,8] Some authors have proposed cast immobilization and isolated fibula osteotomy.[9] Adjuvants to surgical management include the use of autogenous bone graft, autologous bone-marrow aspirate, bone morphogenic proteins (BMPs), low-intensity ultrasound, and hyperbaric oxygen.[10–15] This lack of uniformity in the available literature

has rendered the establishment of an evidence-based, reproducible protocol for the management of tibial nonunions difficult, if not impossible.

In this retrospective review, we focus on the management of mobile atrophic and oligotrophic tibial nonunions. We report our results of a uniform series of tibial nonunions treated by circular external fixation. In addition, we aim to show that the correct biomechanical environment can promote bone healing without the need for routine bone graft and expand on the concept of mechanobiology in the management of tibial nonunions.

## 2.    Methods

From January 2010 to January 2014, 36 patients with mobile atrophic and oligotrophic tibial nonunions were treated at our tertiary level limb reconstruction unit. Three patients were excluded because they did not complete the proposed treatment. These included a 33-year-old male and a 44-year-old female, and both died of systemic complications of chronic disease. Both these patients were HIV positive and developed nonunion following open fractures. The third patient presented to our unit three years after sustaining an open fracture. He was a chronic smoker and his previous treatment included three different external fixators, cast immobilization, internal fixation, and surgery for metalware removal. This patient was unwilling to continue reconstruction after 12 weeks in a circular external fixator and requested amputation.

Nonunions were defined as at least six months time elapsed since the fracture and union deemed unlikely without further intervention. Nonunions were classified according to radiographic appearance on preoperative radiographs. Atrophic nonunions demonstrated no callus formation or periosteal reaction while minimal callus formation designated oligotrophic nonunions. Nonunions were further classified as mobile if more than $7°$ motion was possible at the nonunion site. Motion was assessed preoperatively and then confirmed intraoperatively following fibula osteotomy. There were 22 atrophic and 11 oligotrophic nonunions as determined by preoperative radiographs.

Open fractures were the initial injury in 20 patients. Nine injuries were Gustilo-Anderson IIIB, nine Gustilo-Anderson IIIA, and two Gustilo-Anderson II open fractures.[16,17] Four patients had tibia fractures following gunshots and three of these patients had emergency fasciotomies at the time of injury. Nine patients had closed fractures; five were initially treated by closed manipulation and cast immobilization and the other four were treated by intramedullary, interlocked nails (Fig. 1). Duration of nonunion ranged from six to 192 months since the initial injury, with a mean of 25 months.

A standard physical, laboratory, and radiographic evaluation was performed on all patients as per protocol. Any modifiable risk factors that were identified were optimized. These included cessation of smoking, optimal glycemic control in diabetics, and the commencement of highly active antiretroviral therapy for HIV positive patients with low $CD_4$ counts, prior to surgical intervention. All patients with



**Fig. 1 – Antero-posterior and medio-lateral radiograph of tibial nonunion 10 months after intramedullary nail.**

infected nonunions were excluded. Screening consisted of a detailed history to exclude any previous wound drainage, sinus formation, or treatment for infection of the nonunion site. This was supplemented with clinical and laboratory evaluation that consisted of complete blood count, erythrocyte sedimentation rate, and C-reactive protein level.

Partial fibula resection prior to circular external fixator application was performed in all cases. Resection was performed under tourniquet control and at the level of the fibular deformity if present. Direct surgical approach between the peroneal and soleus muscles was made. The fibula was exposed by subperiosteal dissection and a small oscillating saw was used to resect approximately 10 mm of fibula to prevent early fibular consolidation. Fascia and skin were closed in layers over a drain. The tourniquet was deflated for the remainder of the operation.

External fixation started with a custom prebuilt frame for each patient. Standard frame construct consisted of a four-ring frame with two rings making up a ring block for each bone segment. Frame application proceeded in a stepwise approach starting with proximal and distal reference wires, followed by gradual nonunion reduction as fixation is added toward the two middle rings of the frame.[18] Frames were applied in a hybrid method, using a combination of tensioned fine wires and maximum two hydroxyapatite (HA) coated half pins. Once mechanical alignment and stable fixation were achieved, the nonunion site was compressed manually by adjusting the distance between the proximal and distal ring blocks (Fig. 2).

The nonunion site was not routinely exposed or debrided and bone graft was only used for specific indications. These
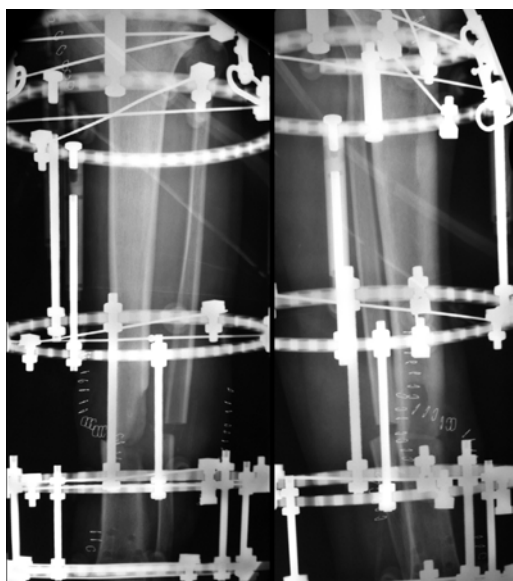
**Fig. 2 – Standardized antero-posterior and medio-lateral radiograph after fine wire circular external fixator application.**

included nonunions where the bone contact area after compression was less that 50% of the normal bone diameter. Bone graft procedures consisted of iliac crest autogenous cancellous on-lay grafting.

Functional rehabilitation was encouraged with the assistance of a physiotherapist. This entailed early joint mobilization and weight bearing followed by normalization of gait pattern and functional use. Pin track care was according to our standard protocol and included twice daily cleaning with an alcoholic solution of chlorhexidine.[19]

Outpatient follow-up was scheduled at two weekly intervals until a robust rehabilitation routine was established. Thereafter, the follow-up was increased to four weekly intervals. Fixator removal was considered once tricortical consolidation was seen. At this juncture, a staged 'trial of union' protocol was initiated. Firstly, the external fixator was completely dynamized by loosening all connections between the ring blocks and stressing the union site manually. If this did not cause any pain or deformity, the patient was instructed to bear weight. If the patient was able to walk without pain, he was allowed to return home with a fully dynamized frame and encouraged to mobilize full weight bearing for a period of two weeks. Repeat radiographs at follow-up were compared with radiographs from prior two weeks. If no deformity occurred during this trial period, union was confirmed and the external fixator was removed. All patients were followed up clinically and radiologically for a minimum of six months after frame removal. Any changes in angulation from previous visits were identified as a failure of treatment.

## 3. Results

The medical records and serial radiographs of all 33 patients were reviewed. The study population consisted of 29 men and four women with a mean age of 34 years, ranging from 18 to 73 years. Follow-up ranged from six to 43 months, with an average of 13 months, after external fixator removal (Table 1).

Risk factors for nonunion development were identified in 29 patients (87.8%). These included open fractures ($n = 19$), compartment syndrome ($n = 3$), smoking ($n = 14$), and diabetes ($n = 5$). The remaining four patients all had closed fractures with no apparent risk factor for nonunion formation. Four patients were HIV positive (12%). These patients had a mean $CD_4$ count of 369 cells/mm$^3$ (range 200–603) and were all on antiretroviral therapy.

The Ilizarov fixator (Smith & Nephew, Memphis, TN) was used in nine cases and the TrueLok fixator (Orthofix, Verona, Italy) in 24 cases. There was no statistically significant difference in union rates or complications between patients treated with the Ilizarov or TrueLok fixators. The average length of time in external fixator was 22 weeks, ranging from eight to 53 weeks.

Bony union was achieved after the initial treatment in 31 out of 33 (93.9%) tibias (Fig. 3). Two patients had failure of treatment after initial treatment. Both patients had atrophic nonunions. The first was a 34-year-old male, who sustained a closed tibia fracture that was initially treated with a locked intramedullary nail. This patient healed after repeat treatment in a fine wire circular fixator. Failure of the initial nonunion treatment was due to the erroneous early removal of the circular external fixator. The second patient sustained an open tibia fracture that was initially treated with a monolateral external fixator. After 23 weeks in the initial circular external fixator, his nonunion became hypertrophic and was successfully treated with conversion to a hexapod circular external fixator and closed distraction. Failure of the initial circular fixator treatment was probably due to unstable fixation. This resulted in final bony union in all 33 tibias (100%).

Pin track infection was the most common complication experienced and occurred in 5/33 cases (15%). The majority of these infections was minor according to the Checketts and

| Table 1 – Details of results. | |
|---|---|
| Patients | 33 |
|   Males | 29 |
|   Females | 4 |
| Mean age (years) | 34 (18–73) |
| Type of nonunion | |
|   Atrophic | 22 |
|   Oligotrophic | 11 |
| Average time to nonunion surgery (months) | 25 (6–192) |
| Fixator | |
|   Ilizarov | 9 |
|   TrueLok | 24 |
| Average healing time (weeks) | 22 (8–53) |
| Iliac autograft | 7 |

**Fig. 3 – Antero-posterior and medio-lateral radiograph of united tibia 12 months after external fixation removal.**

Otterburn classification and responded to oral antibiotics and local pin track care.[20] One patient developed a grade VI infection of a HA pin site. This pin site was debrided with the Versajet Hydrosurgery System (Smith & Nephew, Memphis, TN) and subsequently healed uneventfully.

## 4. Discussion

It is generally accepted that hypertrophic nonunions need mechanical stability to heal while atrophic nonunions need mechanical stability and biological stimulation.[21] Biological stimulation in this setting often refers to bone grafting of the nonunion site due to the perceived biological inactivity of these nonunions.[3,21,22] Biological stimulation can, however, also be provided by creating the ideal mechanical environment, the concept of mechanobiology.[8,23–25]

The biological inactivity of atrophic bone ends has been questioned by authors in recent literature.[24,26–29] Brownlow et al.[26] and Reed et al.[27] showed that the vascularity of atrophic nonunions is comparable to that seen in fresh fractures and hypertrophic nonunions. Ismail et al.[29] showed that mesenchymal stem cells were present at the site of atrophic nonunions at similar number and viability than those isolated from the iliac crest. Sun et al.[28] postulated that these mesenchymal stem cells were temporarily quiescent and could be reactivated under certain conditions. Kloen et al.[24] documented the presence of BMP-signaling components in long-standing atrophic nonunions. These studies have shown that atrophic nonunions are biologically active on a vascular,

cellular, and biochemical level. This biology could be stimulated and enhanced under the correct biological environment.[24,30] We have shown in our results that 26 out of 33 (78%) atrophic and oligotrophic nonunions healed without the need for autogenous bone graft.

The use of bone graft, however, cannot be completely abandoned. In our series, we used autograft in seven cases (21%). These involved nonunions where the bone contact area after reduction was <50% of the original bone diameter. Although these nonunions may still have united, the refracture risk after external fixator removal prompted the use of autograft to increase the diameter of the union site.

Creating the ideal mechanical environment for bone healing can be accomplished with the use of fine wire circular external fixation.[31,32] These fixators have the ability to provide stability against translation and rotation in the coronal and sagittal plane while still allowing a degree of axial micro motion to stimulate bone formation.[33,34] The circular fixator also affords the required stability to allow early rehabilitation without the need for any period of protected weight bearing.[35]

The choice and configuration of the external fixator is vitally important in the management of mobile nonunions. Unlike stiff hypertrophic nonunions that have intrinsic stability that can be manipulated, atrophic nonunions have to rely solely on the stability provided by the external fixator and compression at the nonunion site. As such, the classic Ilizarov frame design with ring blocks for each bone segment and spanning the entire length of the tibia provides the most stability and was used in all our cases.

Mechanical stimulation is the foundation of all nonunion management and can be effective in creating union even in the presence of atrophic bone ends.[24] Ilizarov stated that functional load determines the structure, shape, and volume of any limb. This is due to a local increase in blood flow during functional use that aids in tissue growth.[8] Mechanical stimulation also directly influences bone biology on a cellular level by stimulating the proliferation and differentiation of osteoblasts.[8,25] Mechanical stimulation has further benefits in terms of union site remodeling as a result of piezoelectrical charges that are generated in response to mechanical stresses. Osteoblasts on the compressive side are stimulated as a result of electronegative charges while osteoclasts are activated by electropositive charges on the tension side.[25,36] Mechanical force application patterns, loading magnitude, and frequency also affect bone healing on a biochemical level.[25] The rates of synthesis and degradation of extracellular matrix components are affected by force application patterns. Loading magnitude affects cell size through increased amounts of intermediate filaments and glycogen particles while changes in loading frequency can alter mRNA synthesis of anabolic and catabolic genes.[25] Aggrecan gene expression is increased in response to mechanical stimulation and leads to an increased proteoglycan scaffold for type II collagen.[8]

Fibula osteotomy has been shown to have low complication rates and to be effective in treating delayed union or nonunion of the tibia.[9,37] It is an important step in the management of tibial nonunions for two reasons. Firstly, a mobile fibula will allow correction on any tibial deformity, if present. Secondly, partial fibula resection will increase compressive forces across the nonunited tibia to stimulate bone healing.[37,38] Dujardyn

et al.[37] consider the fibula osteotomy as an essential part of the treatment for tibial nonunions to allow sufficient compression when used in combination with the Ilizarov frame.

There are several limitations to this study, including its retrospective design, single-center site, and lack of a control group. The series is also confined to tibial nonunions and may not necessarily be extrapolated to nonunions of other anatomical regions.

## 5. Conclusion

Mechanobiological stimulation, through the use of fine wire circular external fixation and functional rehabilitation, can predictably produce union of mobile atrophic and oligotrophic tibial nonunions. This treatment is effective without the need for routine bone graft even if the biological potential appears to be low.

## Conflict of interest

The authors have none to declare.

## Ethical statement

The study was authorized by the local ethics committee (BE 086/14) and performed in accordance with the Ethical standards of the 1964 Declaration of Helsinki as revised in 2000.

## Authors' contributions

All three authors made contributions toward the conception and design of the research, acquisition of data, and drafting of the manuscript. The final manuscript was read and approved by all the authors.

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# PART THREE. Prospective Evaluation of Treatment Algorithm

Following the publication of the two retrospective audits, the tibial non-union treatment algorithm was developed. This algorithm included the treatment strategies that were successfully used during our retrospective audits with the inclusion of two additional strategies aimed at two less frequently encountered non-union subtypes, the so-called mobile hypertrophic 'true pseudoarthrosis' and bone defect non-unions.

**Figure 1.** Tibial non-union treatment algorithm
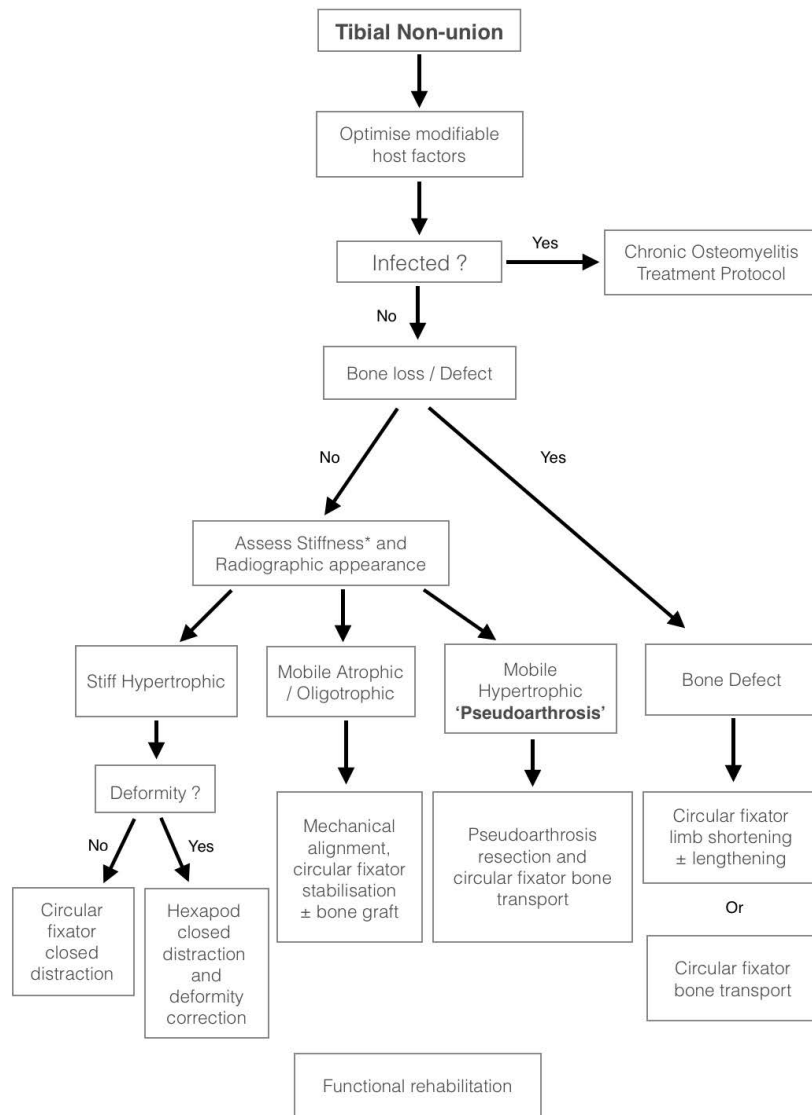


* After removal of metalware and fibula osteotomy

The advantage of the proposed treatment algorithm is the proposition of a distinct treatment strategy for each of the four non-union subtypes. The algorithm also places specific emphasis on optimisation of host factors that predispose the patient to non-union formation as well as post-operative functional rehabilitation.

Three important steps in the algorithm are:
- Diagnosis of infected cases.
- Identification of bone loss.
- Assessment of non-union mobility.

These three factors are crucial in decision making to determine which treatment strategy to follow.

The identification of infected cases is important. We consider infected non-unions to be Cierny & Mader stage IV chronic osteomyelitis and these cases are managed according to chronic osteomyelitis treatment protocols.[1, 2] (Not discussed in this thesis) A detailed history should include enquiry into the presence of prior symptoms of infection or treatment for infection. Laboratory studies including leukocyte count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein level (CRP) and ferritin:iron ratio forms part of our standard work-up for non-unions.[3] More recently interleukin-6, in combination with CRP, has increased the sensitivity and specificity of laboratory diagnosis of sepsis and can be considered where available.

Bone loss necessitates specific treatment strategies to restore leg length. These cases are often obvious, especially where defects are fixed with internal or external fixation. It can however be less conspicuous when the limb was shortened to try and establish union. It is therefore vitally important to accurately assess for any limb length inequality prior to surgical intervention. The extent of bone loss should be considered when deciding on treatment. The treatment of bone defects is complex and fall beyond the scope of this thesis.

Non-union site mobility is vitally important when deciding on treatment strategy. This can only be assessed with certainty after removal of any in situ metalware and fibula osteotomy. This means that only during definitive non-union surgery can the final decision be made on treatment strategy. The implication of getting this wrong was shown in our retrospective series on stiff hypertrophic non-unions. One patient was managed with the wrong treatment strategy resulting in treatment failure.

The following chapter evaluates the effectiveness of the tibial non-union treatment algorithm through a prospective interventional study that was undertaken over a one-year period. During this time, all patients presenting with tibial non-unions were treated according to the algorithm. The final study population consisted of 37 consecutive patients with 39 tibial non-unions. This constitutes one of the largest non-union studies available in the English literature.

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# Chapter 7. Management of Tibial Non-unions: Prospective Evaluation of a Comprehensive Treatment Algorithm

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Contribution to authorship:

- N. Ferreira – Concept development, data collection, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- L.C. Marais – Concept development, data collection, contribution to literature review and revision of manuscript.
- C. Aldous – Concept development and revision of manuscript.

**Management of tibial non-unions: Prospective evaluation of a comprehensive treatment algorithm**

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**Abstract**

Tibial non-unions represent a spectrum of conditions and are challenging to treat. The optimal management remains unclear despite the frequency with which these diagnoses are encountered. We developed a tibial non-union treatment algorithm following two retrospective audits of our patient outcomes and evaluated this algorithm in this prospective series. Thirty-seven consecutive patients with 39 uninfected tibial non-unions were treated according to our proposed treatment algorithm. There were 30 men and seven women with a mean age of 34 years. Twenty-three non-unions were classified as stiff hypertrophic, 10 mobile atrophic and four mobile oligotrophic. Two non-unions were classified as type B1 defect non-unions. Bony union was achieved after the initial treatment in 37/39 (94.8%) tibias. Two patients had failure of treatment. These patients presented with progressive deformity after the external fixator was removed. One of these patients was successfully retreated according to the tibial non-union treatment algorithm. This resulted in final bony union after treatment in 38/39 (97.4%) tibias. Our proposed treatment algorithm appears to produce high union rates across a diverse group of tibial non-unions. These conditions however, remain difficult to treat and should be referred to specialist units where advanced reconstructive techniques are practiced on a regular basis.

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## Introduction

Non-unions are frequent complications of tibial shaft fractures and their management remains a challenge for orthopaedic surgeons.[1] Quoted incidences range between 8% and 13%, but despite the frequency with which they are encountered treatment has not been standardised nor based on large randomised control trials.[2-5] As such, treatment failure rates of up to 20% have been reported in the literature.[6]

Non-unions can be classified as atrophic or hypertrophic, mobile or stiff, with or without deformity, with or without bone defects and as infected or not.[6-11] This diversity in non-union pathophysiology and presentation complicates their management, as each subgroup often requires radically different treatment strategies.[6, 11-13] The management is further complicated by delays in referral that contribute to loss of limb function secondary to muscle atrophy, joint contractures and disuse osteopenia.[3, 14] Inappropriate management may cause further delays and additional risk to limb integrity.[15] Adopting the appropriate treatment strategy is of vital importance and should promote union while simultaneously allowing functional rehabilitation.

We report the results of the management of uninfected tibial non-unions treated according to our proposed tibial non-union treatment algorithm. (Figure 1)

## Materials and Methods

Between January 2014 and December 2014, all patients who presented with uninfected tibial non-unions were treated according to our proposed tibial non-union treatment algorithm. This algorithm was developed based on results from two retrospective audits of patients with tibial non-unions who were treated at our institution between January 2010 and December 2013. Thirty-eight patients with 40 non-unions were included. One patient was excluded because his treatment was ongoing at the time of analysis. This patient had a defect non-union undergoing bone transport.

**Figure 1.** Tibial non-union treatment algorithm
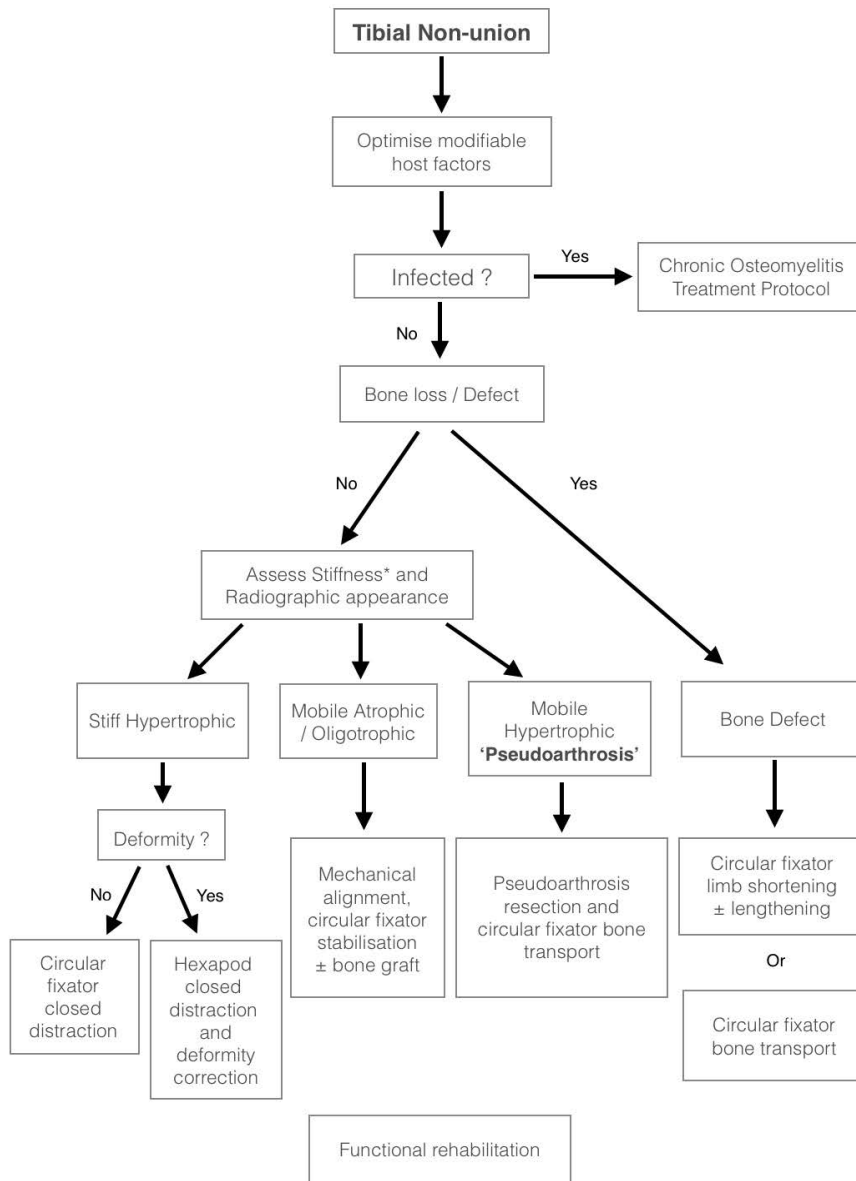


A physical, laboratory and radiographic evaluation were performed on all patients as per departmental protocol. Any modifiable risk factors that were identified were optimised prior to surgical intervention. These included cessation of smoking, optimal glycaemic control in diabetics and the commencement of highly active antiretroviral therapy (HAART) for HIV positive patients with low $CD_4$ counts.

Partial fibula resection was performed in all cases at the time of the index procedure. Resection was performed under tourniquet control and at the level of the fibular deformity if present. Direct surgical approach between the peroneal and soleus muscles was made. The fibula was exposed by sub-periosteal dissection and a small oscillating saw was used to resect approximately 1cm of fibula to prevent early fibular consolidation. Fascia and skin were closed in layers over a drain. The tourniquet was deflated for the remainder of the operation.

Mobile atrophic and oligotrophic non-unions were stabilised with Ilizarov type circular external fixation. These frames were applied using a standard 'trauma frame' construct and application technique.[16] After mechanical alignment and stable fixation, the non-union site was manually compressed and the frame statically locked. The addition of iliac crest autograft was only considered if the non-union site had a diameter less than 50% of the normal bone diameter. This was required in four patients.

Defect non-unions were treated with standard 'transport frame' constructs. These frames consisted of ring blocks proximal and distal to a fifth transport ring. The ring blocks were designed in such a way as to allow a metaphyseal osteotomy to generate a bony transport segment. After a latency period of 7 to 10 days bone transport was started at a rate and rhythm of 0.25 mm four times per day. A docking procedure in the form of a Phemister autograft was performed for all patients.[17]

Stiff hypertrophic non-unions were treated with closed gradual distraction through the use of hexapod external fixators. These fixators were applied using the 'rings first' method and the non-union site was left undisturbed. After post-operative radiographic evaluation, a correction program was generated through the online software and distraction was effected at a rate on 1 mm per day at the apex of deformity.

Pin track management occurred according to our standard protocol that encompasses a meticulous intra-operative insertion technique and a rigorous post-operative pin care regime that

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included twice daily cleaning with an alcoholic solution of chlorhexidine.[18, 19] Early functional rehabilitation was encouraged with the assistance of a physiotherapist. This entailed adjacent joint mobilisation and weight bearing followed by normalisation of gait pattern and functional use.

Outpatient follow-up was scheduled at two weekly intervals until a robust rehabilitation routine was established. Thereafter the follow-up was increased to four weekly intervals. Fixator removal was considered once tricortical consolidation was seen. At this juncture, a staged 'trial of union' protocol was initiated. Firstly the external fixator was completely dynamised and the union site manually stressed. If this did not cause any pain or deformity the patient was instructed to weight bear. If the patients were able to walk without pain, they were allowed to return home with a fully dynamised frame and encouraged to mobilise full weight bearing for a period of two weeks. Repeat radiographs at follow-up were compared with radiographs from two weeks before. If no deformity occurred during this trial period, union was confirmed and the external fixator was removed. All patients were followed-up clinically and radiologically one month after frame removal. Any changes in angulation from previous visits were identified as a failure of treatment.

**Results**

The medical records and serial radiographs of all 37 patients were reviewed. The study population consisted of 30 men and seven women with 39 tibial non-unions with a mean age of 34 years ranging from 18 to 73 years. (Table 1) Two patients were treated for bilateral tibial non-unions. Twenty-three non-unions were classified as stiff hypertrophic, 10 mobile atrophic and four mobile oligotrophic according to the Ilizarov and Weber and Cech classifications.[7, 8] The remaining two cases were type B1 defect non-unions according to the Paley classification.[9] These patients had 3cm and 6cm defects respectively.

**Table 1.** Details of results

| Type of non-union | Mobile Atrophic / Oligotrophic | Stiff Hypertrophic | Defect |
|---|---|---|---|
| Patients | 13 | 22 | 2 |
|     Males | 11* | 17* | 2 |
|     Females | 2 | 5 | - |
| Mean age (years) | 31 (18 - 59) | 38 (18 - 66) | 23 (20 - 27) |
| Average time to non-union surgery (months) | 11 (6 - 18) | 15 (6 - 48) | 7 (6 - 8) |
| Fixator | | | |
|     Ilizarov | 5 | - | - |
|     Truelok | 9 | - | 2 |
|     Taylor Spatial Frame | - | 7 | - |
|     Truelok-Hex | - | 16 | - |
| Average healing time (weeks) | 32 (13 - 53) | 25 (13 - 60) | 48 (31 - 66) |
| Treatment strategy | | | |
|     Compression | 14 | - | - |
|     Distraction | - | 23 | - |
|     Bone transport | - | - | 2 |
| Iliac autograft | 5 | 0 | 2 |

* Two patients had bilateral non-unions

Open fractures were the initial injury in the majority of cases (n=27). Fifteen fractures were initially graded as Gustilo-Anderson IIIB, 11 Gustilo-Anderson IIIA and one as a Gustilo-Anderson II open fractures.[20, 21] Two patients sustained fractures following gunshots. One patient developed a mid shaft tibial non-union following a derotation osteotomy. The remaining nine cases were closed fractures that were treated with a Plaster of Paris cast in four cases, tibial nail in four cases and a circular external fixator in the remaining case. Duration of non-union ranged from 6 to 48 months since the initial injury, with a mean of 13 months (standard deviation [SD] 9.6 months).

Risk factors for non-union development were identified in 33/37 (89%) patients. These included open fractures (n = 27), smoking (n = 17), diabetes (n = 1), hypothyroidism (n = 1), oblique distal third tibia fracture (n = 1), and internal fixation (nail) with a fixed fracture gap (n = 4). The remaining four patients all had closed fractures and no obvious risk factors for non-union formation. Seven patients were HIV positive (19%). Two of these patients had bilateral tibial

non-unions. Four HIV positive patients with a mean $CD_4$ count of 872 cells/mm$^3$ (Range 581 – 1056) were on HAART treatment while the remaining three patients with a mean $CD_4$ count of 325 cells/mm$^3$ (Range 260 – 433) were treatment naïve.

The Ilizarov external fixator (Smith & Nephew, Memphis, TN) was used for five, and the Truelok external fixator (Orthofix, Verona, Italy) for nine mobile atrophic and oligotrophic non-unions. The average time in external fixator was 32 weeks, ranging from 13 to 53 weeks. Stiff hypertrophic non-unions were treated with the Taylor Spatial Frame (TSF) (Smith & Nephew, Memphis, TN) in seven and the Truelok-Hex (TL-Hex) (Orthofix, Verona, Italy) in 16 cases. The average time in external fixator was 25 weeks, ranging from 13 to 60 weeks. Both patients with defect non-unions were treated with the Truelok external fixator (Orthofix, Verona, Italy). These patients spent 31 and 66 weeks in external fixators respectively.

Bony union was achieved after the initial treatment in 37/39 (94.8%) tibias. Two patients had failure of treatment. These patients presented with progressive deformity after the external fixator was removed. Failure after initial treatment was judged to be the result of early external fixator removal and underlines the difficulty of confirming union in certain cases. One of these patients was successfully retreated according to the tibial non-union treatment algorithm. This resulted in final bony union after treatment in 38/39 (97.4%) tibias. The remaining patient was a heavy alcohol user and smoker who sustained an open tibia fracture with a resultant non-union. Re-treatment will be considered once the patient has moderated his alcohol intake and stopped smoking.

Leg lengths after union were equalised to within 1cm of the contralateral side in 37 (94.8%) tibias. Alignment with deformity less than 5° was achieved in 36 (92.3%) tibias. The remaining three patients had 5° valgus in two patients and 8° procurvatum with 2 cm shortening in one patient.

Pin track infection was the most common complication experienced and occurred in 7/39 (17.9%) cases. The majority of these infections was minor according to the Checketts and Otterburn classification and responded to local pin track care and oral antibiotics.[22] One patient developed a grade VI infection. This patient presented with a non-healing pin site four weeks after external fixator removal. He was subsequently treated with debridement of the pin track using the Versajet Hydrosurgery system (Smith & Nephew, Memphis, TN) and healing occurred without any further complications.[23]

## Discussion

The optimal treatment of tibial non-unions remains to be established but several authors have outlined the principles for the ideal treatment. Kanellopoulus considered the ability to simultaneously address axial deviations, shortening, bone loss, poor blood supply and achieve union without further compromise of the soft-tissue envelope as the ideal treatment.[15] He emphasised that this should be achieved while simultaneously not only maintaining function, but improving it.[15] Gershuni regarded the restitution of bony continuity, correction of alignment in all planes, maintenance and recovery of function and limitation of further complications as the ideal management strategy.[24] Giannoudis recently introduced the 'Diamond concept' to the management of non-unions.[25] This approach attempts to address all factors implicated, namely the cellular environment, growth factors, bone matrix and mechanical stability. We consider the optimisation of modifiable host factors, mechanical alignment, stable fixation, biological stimulation and early functional rehabilitation the five pillars of non-union management.

Biological stimulation can be achieved in several ways. Autogenous bone graft and bone morphogenic proteins (BMPs) remains the most frequently used method to stimulate healing, especially in atrophic non-unions.[11, 12, 26] Biological stimulation can also be achieved by creating the ideal mechanical environment to support bone formation; the concept of mechano-biology. [27-32] Ilizarov further demonstrated the tension stress effect to stimulate tissue growth through distraction histogenesis.[33-35]

Mechano-biology refers to the ability of the body's physiological processes to respond to the mechanical environment and is the foundation of all non-union management.[27, 30] Ilizarov stated that functional load determines the structure, shape and volume of a limb. This is due to a local increase in blood flow during functional use that aids in tissue growth.[29] Mechanical stimulation also directly influence bone biology on a cellular level by stimulating the proliferation and differentiation of osteoblasts.[29, 31] Mechanical force application patterns, loading magnitude and frequency also affect bone healing on a biochemical level.[31] The rates of synthesis and degradation of extracellular matrix components is affected by force application patterns. Loading magnitude affect cell size through increased amounts of intermediate filaments and glycogen particles while changes in loading frequency can alter mRNA synthesis of anabolic and catabolic genes.[31] Aggrecan gene expression is increased in response to mechanical stimulation and leads to an increased proteoglycan scaffold for type II collagen.[29] Mechanical stimulation has further benefits in terms of union site remodelling as a result of piezo-electrical charges that are generated in response to mechanical stresses. Osteoblasts on the compressive side are stimulated as a result of electronegative charges while osteoclasts are activated by electropositive charges on the tension side.[31, 36] These mechano-biological processes can be exploited in non-union management to produce union even in the setting of apparent biological inactivity of atrophic non-unions. This was shown in our results where eight out of 13 (62%) atrophic and oligotrophic non-unions healed without the need for autogenous bone graft. (Image 1a, 1b, 1c)



**Image 1a**. Antero-posterior and medio-lateral radiograph of tibial non-union 10 months after intramedullary nail

**Image 1b**. Standardised antero-posterior and medio-lateral radiograph after fine wire circular external fixator application
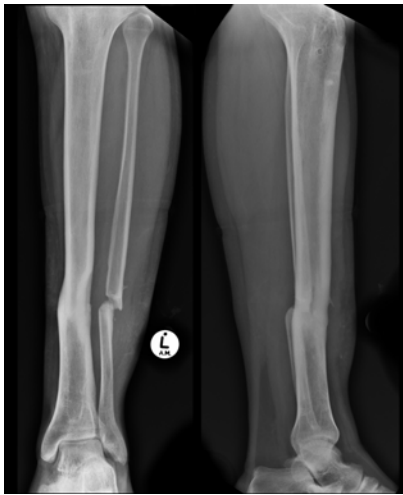


**Image 1c**. Antero-posterior and medio-lateral radiograph of united tibia 12 months after external fixation removal

The effectiveness of distracting stiff hypertrophic non-unions can be explained by the inter-fragmentary strain theory of Perren.[37, 38] This states that fracture displacement ($\delta L$) in relation to the initial fracture gap (L) produces strain ($\delta L/L$) that can either induce bone formation and union (strain $< 2\%$) or induce bone resorption with resultant non-union (strain $> 10\%$).[37] Distracting stiff non-unions has a two-fold effect on decreasing inter fragmentary strain. Firstly, the tension caused by distracting an inherently stiff environment combined with stable fixation decreases inter-fragmentary motion ($\delta L$). Secondly, distraction of the non-union increases the fracture gap (L). This results in an overall reduction of strain to within tolerable limits for bone formation in the distraction gap. The clinical implications of this theory are clearly illustrated in our series where 22 out of 23 (95.6%) stiff tibial non-unions healed after closed distraction, sometimes with exuberant callus formation. (Image 2a, 2b, 2c)
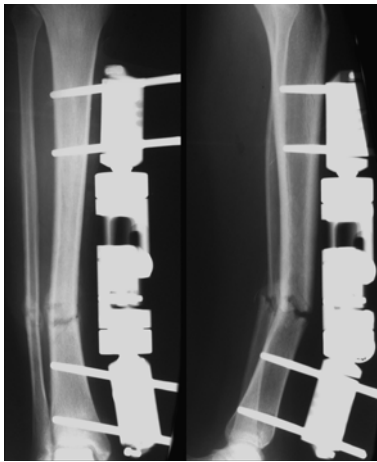
**Image 2a**. Antero-posterior and medio-lateral radiograph of tibial non-union 10 months after intramedullary nail
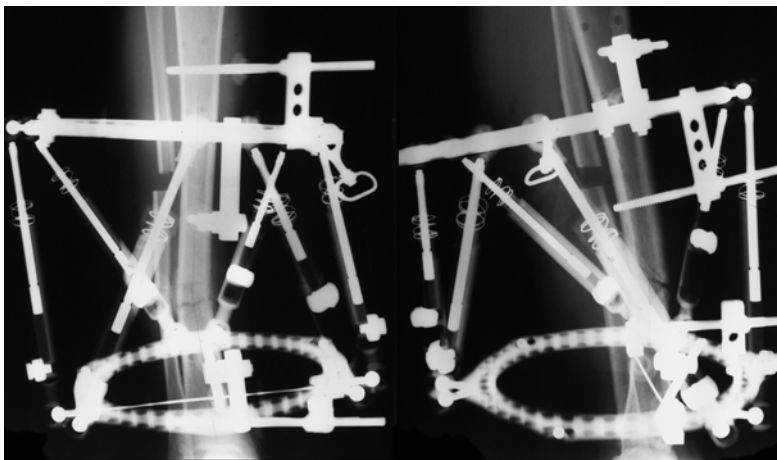


**Image 2b**. Standardised antero-posterior and medio-lateral radiograph after fine wire circular external fixator application



**Image 2c**. Antero-posterior and medio-lateral radiograph of united tibia 12 months after external fixation removal

Circular external fixators are ideally suited to provide stability for non-union management.[39, 40] Their use, especially in tibial malunions and non-unions has gained popularity in recent years.[9, 10, 14, 15, 41-44] These fixators have the ability to provide stability against translation and rotation in the coronal and sagittal planes while maintaining a degree of axial micro motion to stimulate

bone formation.[45-48] Circular fixators can also be applied with minimal iatrogenic disruption of the local biological environment and can be designed to correct mechanical alignment, either acutely or gradually, as with mobile and stiff non-unions respectively. Furthermore, the three-dimensional stability that these fixators provide allows early functional rehabilitation without the need for any period of protected weight bearing after non-union treatment.

Although 37 patients represents a large study population for tibial non-union management, the patient numbers included in each subgroup are relatively few. This research could represent a pilot study for the evaluation of our proposed treatment algorithm and future validation of this treatment with larger study groups in different study locations should be conducted. The lack of control groups for each treatment strategy is a further limitation and could be addressed in future research.

In conclusion, our proposed tibial non-union treatment algorithm appears to produce high union rates across a diverse group of tibial non-unions. Although these results are encouraging in striving for a standardised treatment strategy for tibial non-unions, we still recommend that that these cases be referred to specialist units where these advanced reconstructive techniques are practiced on a regular basis.

**Conflict of Interest**

The authors declare that they have no conflict of interests and no financial support was received for this study.

**Ethical Statement**

The study was approved by an institutional ethics committee (BE 086/14) and performed in accordance with the Ethical standards of the 1964 Declaration of Helsinki as revised in 2000.

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# PART FOUR. Complications - Pin Site Infection

Circular external fixators are important in the management of tibial non-unions. Their biomechanical attributes make them ideal for the mechano-biological stimulation needed to treat non-unions. Their use is however not without risk or complications, with pin site infection being the most frequently experienced. Quoted incidences range from 11.3% to 100% and certain authors even profess pin site infection to be an accepted certainty in the realm of external fixation.[1-5] The consequence of this infection is a gradual erosion of pin-bone interface stability that could ultimately necessitate early fixator removal and potentially lead to failure of the reconstructive process.

Multiple variables have been identified to be involved in the development of pin loosening and infection, including pre-operative, intra-operative and post-operative factors. We reviewed the available literature to identify a strategy that would be effective as well as inexpensive to satisfy the South African scenario. Ultimately we developed a comprehensive pin care protocol that encompasses a meticulous insertion technique and a rigorous post-operative pin care regime while simultaneously not placing any additional financial burden on the health services.

HIV in particular has been cited as a contra-indication for limb reconstruction with external fixators. Our research into the incidence and severity of pin site infection with the use of circular external fixators in HIV-positive and negative individuals represents the only study of its kind in the literature and refutes the belief that circular fixation is not appropriate in HIV-positive patients.

Ultimately, an overall pin site infection rate of 17% (21 out of 122 patients) was experienced across all patients treated for tibial non-unions. The majority of these were low-grade infections that responded to oral antibiotics and local pin site care. Only two patients developed high-grade infection, both of these at HA pin sites. These pin sites were debrided with the Versajet Hydrosurgery System (Smith & Nephew, Memphis, TN) and subsequently healed uneventfully. In comparison, a recent review on grade III open tibia fractures treated in circular external

fixators at our institution, found a pin site infection rate of 16% (15 out of 94 patients).[9] The difference in pin site infection rates was not statistically significant (p = 0.73), showing that comparable pin site complication rates can be expected with our approach to pin care despite the condition that is being treated.

The following three chapters explore the factors associated with pin site infection development and propose a management strategy that encompasses pre-operative, intra-operative and post-operative care. The effectiveness of this strategy and the effect of HIV infection on pin site sepsis is reported through the largest series on to our knowledge of pin site infection with the use of circular external fixators.

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# Chapter 8. Prevention and Management of External Fixator Pin Track Sepsis

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*Strat Traum Limb Recon.* 2012;**7**:67-72.

Contribution to authorship:

- N. Ferreira – Concept development, data collection, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- L.C. Marais – Concept development, data collection, contribution to literature review and revision of manuscript.

REVIEW

# Prevention and management of external fixator pin track sepsis

Nando Ferreira · Leonard Charles Marais

**Abstract**  Pin track-associated complications are almost universal findings with the use of external fixation. These complications are catastrophic if it leads to the failure of the bone–pin interface and could lead to pin loosening, fracture non-union and chronic osteomyelitis. Strategies proposed for the prevention and management of pin track complications are diverse and constantly changing. Prevention of external fixation pin track infection is a complex and ongoing task that requires attention to detail, meticulous surgical technique and constant vigilance.

**Keywords**  Pin site · Infection · Complications · External fixation

## Introduction

External fixation is an essential component of the modern orthopaedic surgeon's armamentarium and is widely used in traumatology and reconstructive surgery. This treatment modality is unfortunately associated with the almost universal complication of pin track infection [1, 2].

This article aims to highlight the factors associated with an increased risk of pin track complications, reviews the literature and proposes a protocol for effective external fixator pin track care.

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## Background

Pin track infection is almost inevitable during the long-term use of external fixators with the quoted incidence ranging from 11.3 to 100 % [3–11]. Bibbo [2] stated that 'Pin-site irritation/infection have almost become an accepted certainty in the realm of external fixation, with physicians relying heavily on the majority of those complications resolving without consequences by using appropriate pin care and antibiotic therapy'.

### Fixator pin–bone interface stability

Pin track infection decreases the stability of the pin–bone interface. Conversely, instability of the fixator pin–bone construct can lead to half-pin loosening and infection [3]. It is a common misconception that pin loosening only results from pin track infection when in actual fact pin loosening is often the initiating event resulting in pin track sepsis.

In the light of this, the external fixator construct is crucial in the prevention of pin track infection. The overall stability of the external fixator construct is the result of a complex interplay of variables. The forces transmitted through the fixator and limb is a function of the geometrical and mechanical properties of the fixator as well as the properties of the surrounding tissues and the fracture pattern [12]. There is, also, what appears to be a race between the gradual increasing loading capacity of healing bone and potential failure of the bone–pin interface [13]. For this reason, it is important to keep the fracture configuration in mind when deciding on which external fixator to use.

An unstable fixator creates an unsuitable environment for optimal bone healing and leads to increased movement at the fixator pin–bone interface, producing pin site

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irritation and infection [3, 14]. Parameswaran et al. [3] found that the type of fixator had an effect on the incidence of pin site infection, with monolateral and hybrid fixators showing a much higher incidence of pin site infection than ring fixators.

In addition to a stable fixator construct, stable pin fixation is needed to prevent the vicious cycle of pin loosening, pin site infection and further loosening [15]. Moroni et al. [16] found that deterioration of bone–pin interface strength was an inevitable phenomenon with standard, uncoated pins. This was due to fibrous tissue formation at the bone–pin interface of uncoated pins, which led to loosening [17, 18]; this was recorded as a lower extraction torque force needed during pin extraction than was the insertion torque [9]. In contrast, hydroxyapatite-coated pins show improved fixation strength, with extraction torque forces being higher than the initial insertion torque forces and 90 times higher than standard uncoated pins [9]. This improved fixation translated into significantly lower rates of osteolysis; an 18 times lower incidence of pin loosening [9] and a decrease in pin site infection when compared to uncoated pins [11, 17–25]. At our institution, we have abandoned the use of uncoated pins in long-term external fixators.

## Pin insertion

It should be emphasized that any strategy for reducing pin site complications begins in the operating theatre [10]. Wire and pin insertion should be as low energy and atraumatic as possible, with minimum damage to the skin, soft tissue and bone.

Skin incisions should be placed with care, in order to avoid tension on the skin. At the same time, the incisions should only be as large as the diameter of the pin. Large open wounds surrounding pins should be avoided, and we recommend suturing unnecessarily large wounds around pins. The aim is to facilitate rapid healing of the skin around the pin or wire, in order to create a bone–pin interface that is sealed from the external environment.

In order to prevent damage to the soft tissue envelope, wires must be pushed onto bone and not drilled through the soft tissues. The location of the pin or wire placement must also be considered. Soft tissue movement around pins and wires leads to increased risk for infection [2, 26] and any pins located in areas with considerable soft tissue, tendons and tendon sheaths are at greater risk for infection [27]. To prevent transfixing muscles in a shortened position, any muscle compartment that is traversed should be placed under stretch during the placement of the pins and wires [2].

Heat generation must be guarded against during pin or wire insertion, as this could lead to thermal necrosis of the



**Fig. 1** Cooling of drill while pre-drilling

surrounding bone, ring sequestra and pin loosening. For this reason, the anterior tibial crest must be avoided, as drilling through the thick cortical bone can generate excessive heat [2]. In order to prevent heat generation during wire insertion, cortices are breeched via drilling and the wire is then advanced through the distal soft tissues with a mallet [5].

For half-pin placement, predrilling should always be performed even when using self-drilling pins [2, 5]. Drilling should be done in a pulsed (stop–start)/metronomic fashion together with continuous irrigation with cold saline to ensure proper pin cooling [2, 10] (Fig. 1). After drilling, the pilot hole must be irrigated to remove the bone swarf that might act as sequestra and prevent optimal bone–pin fixation [10] (Figs. 2, 3).

We adhere to the recommendations by Davies, and as far as possible use a non-touch technique when inserting half-pins [10]. To ensure a non-touch technique for inserting wires, we use chlorhexidine-soaked swabs to handle and manipulate wire placement (Fig. 4).

## Peri-operative management

Pin sites should be encouraged to heal around the wires and pins, like a pierced ear heals.[1] After completion of the

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[1] Connecticut center for orthopedic surgery external fixator pin care protocol.

**Fig. 2** Irrigation of drill holes



**Fig. 3** Bone swarf rinsed from drill tract



**Fig. 4** Non-touch insertion of wire

procedure, all pin sites must be free of skin tenting and soft tissue impingement [2, 5, 26]. Sterile dressings should be placed around pin sites and held continuously in place with a small amount of pressure, to prevent skin tenting and haematoma formation [28]. Various dressings have been used, ranging from dry dressings [28], open-cell foam dressing [2], betadine-soaked gauze [5], to alcoholic solution of chlorhexidine-soaked gauze [10]. Regardless of the choice of dressings, their main purpose is to keep the pin sites clean and dry, and absorb any blood and exudates [28] and therefore we discourage the usage of paraffin gauze around the pins.

In our unit, we follow the procedure described by Davies, who found lower infection rates when pin sites were dressed immediately after pin insertion with an alcoholic solution of chlorhexidine with pressure to reduce haematoma formation around pins (Fig. 5). These dressings are then changed at the end of the procedure if they are blood stained [10]. We also cover the whole limb and external fixator with a sterile dressing at the end of the procedure, and this dressing is left in place for the first post-operative week [31] (Fig. 6).

**Pin site care**

There is no universally accepted protocol for the optimal care of pin sites [5]. In the absence of clear research evidence, consensus meetings have sought to provide guidance on pin site care. One such meeting was the Royal College of Nursing meeting held in the United Kingdom in 2010, which published their guidelines in 2011 [32]. In lieu of this, there are still a myriad of protocols available,



**Fig. 5** Pin sites dressed with chlorhexidine–alcohol solution swabs and slight pressure

**Fig. 6** Post-operative dressing of fixator

ranging from a nihilistic approach with no active pin site care [29], to twice daily cleaning and dressings plus oral antibiotics for the entire duration of the external fixator [3].

The appropriate time to commence pin track care vary greatly in the literature with published times ranging from 24 h to 10 days [2, 3, 5, 10, 27–29, 31]. The frequency of pin track cleaning also differ, with authors suggesting once daily [6, 27], twice daily [3, 4], weekly [27, 33] or 'when required' [28].

Various cleaning solutions are advocated in the literature, including soap and water, sterile water, normal saline, peroxide, polyvinylpyrrolidone iodine, isopropyl alcohol and chlorhexidine [2–6, 10, 27, 28, 30]. When comparing chlorhexidine to normal saline, W-Dahl [30] found that chlorhexidine resulted in fewer positive bacteria cultures, lower frequency of *Staphylococcus aureus* and fewer days of antibiotic use.

We have however noted a small number of cases of chlorhexidine sensitivity resulting in skin irritation and weeping pin tracks. This finding is supported by Davies who reported a 17.6 % incidence of hypersensitivity reactions to prolonged skin contact with a strong antiseptic solution [10]. Fortunately, this usually resolves through the substitution of chlorhexidine with a mild soap and water solution for pin site care.

Dressing after pin track care is also controversial. Parameswaran et al. [3] used gauze packing with one to two drops per pin of a benzolkonium chloride antiseptic solution. The Epic 2 guidelines used in an NHS hospital prescribe clear polyurethane (Allevyn™) dressings that are changed every 7 days [33]. Lee et al. [34] showed a decrease in pin site infection when comparing gauze impregnated with polyhexamethylene biguanide and plain gauze wet with saline. Davies advocates that pin sites are cleaned daily for the first 3 days, followed by alcoholic

solution of chlorhexidine dressings. After day three, an occlusive dressing is applied and changed every 5–7 days [10]. Rose [5] reported that in the presence of exudates, pins should be dressed with gauze, but left uncovered in the absence of an exudate.

At our institution, a gauze swab with an alcoholic solution of chlorhexidine dressing is applied and left undisturbed for the first 7 days, followed by twice daily cleaning with a chlorhexidine solution. No pin site dressings are used once the pin sites have healed. Twice daily pin site cleaning is continued for the entire duration of the external fixation.

Another important preventative measure involves postoperative limb elevation. We advocate limb elevation whenever the patient is not actively mobilizing. This reduces oedema around the pins and creates the optimal environment for rapid healing of the pin tracks [2].

Showering is recommended, once the pin sites have healed, but thorough drying of the skin and the external fixator is mandatory thereafter. We do not advise swimming, but if a patient does insist, swimming in a chlorinated pool is permitted. No swimming in dams or in the ocean is allowed.

**Pin site infection**

Pin site infections usually start as cellulitis around the pin or it may start as a localized form of osteitis, and most are secondary to *Staphylococcus aureus* infection, followed by *Pseudomonas aeruginosa* [9, 10]. Although there is no standardized system for classifying pin site infections [5], the Checketts-Otterburn classification is commonly used and provides valuable information regarding treatment [35] (Table 1). According to this system, pin site infections are classified into two groups, minor (Grades 1–3) and major (Grades 4–6), with the significant difference between the two groups being that the external fixation pin has to be abandoned in major infections [35].

Although pin track infection is common, very few lead to major complications [2, 5, 7, 10]. Schalamon et al. [7] found that 94 % of infections were mild and responded to local or systemic antibiotic management. Piza also reported that 75 % of their pin site infections were minor infections when using the Checketts–Otterburn classification [9, 35]. Once pin site infection has been diagnosed, limb elevation is crucial as limiting the time that the limb is spent in a dependent position may help to hasten pin site quiescence [2]. Most authors advocate oral antibiotics directed against *Staphylococcus aureus* once pin site infection is diagnosed [2, 7, 29]. Bhattacharyya [36] found that nanocrystalline silver-releasing dressings were as effective as oral antibiotics to control pin site infection.

**Table 1** Checketts–Otterburn classification

| Grade | Characteristics | Treatment |
|---|---|---|
| Minor infection | | |
| 1 | Slight redness and little discharge | Improved pin site care |
| 2 | Redness of the skin, discharge, pain and tenderness in the soft tissue | Improved pin site care and oral antibiotics |
| 3 | Grade 2 but no improvement with oral antibiotics | Affected pin or pins resited and external fixation can be continued |
| Major infection | | |
| 4 | Severe soft tissue infection involving several pins, sometimes with associated loosening of the pin | External fixation must be abandoned |
| 5 | Grade 4 but radiographic changes | External fixation must be abandoned |
| 6 | Infection after fixator removal. Pin track heals initially, but will subsequently break down and discharge in intervals. Radiographs show new bone formation and sometimes sequestra | Curettage of the pin tract |

We advocate that pin track care is restarted as soon as pin site infection is identified. This includes twice daily cleaning of the pin–skin interface with a chlorhexidine solution and absorbent dressings if excessive exudate is encountered. A course of oral antibiotics aimed at *Staphylococcal* infection is prescribed for 7–10 days. Checketts grade 3 infections are admitted for intravenous antibiotics and in-hospital pin track care and limb elevation. If these infections do not respond adequately, the involved pins or wires are removed or exchanged.

### Pin removal

Major pin track infections, Checketts grade 4 and above, should be managed in theatre in order to allow adequate debridement of the pin tracks. Morgan-Jones [37] recommends arthroscopic debridement of major pin track infection to remove all necrotic debris. Bibbo [2] on the other hand, uses the Versajet Hydrosurgery system (Smith & Nephew, Memphis, TN) to debride infected pin sites after which the wound edges are freshened and closed with nylon or polypropolene sutures.

Bibbo also identified risk factors for developing non-healing wounds after pin removal, and these include: patients with diabetes mellitus, chronic venous insufficiency, peripheral vascular disease and poor soft tissue envelope due to trauma [2]. In these cases, it may even be necessary to raise small random-pattern fasciocutaneous flaps in order to treat non-healing pin sites [2].

In cases of osteomyelitic pin tracks with a sizeable cavity following debridement, these cavities can either be treated by leaving a 2-mm antibiotic bead in the track [3] or by using antibiotic-impregnated absorbable calcium-sulphate pellets to back-fill these tracks [2].

It is important to emphasize that pin or wire removal should not destabilize the frame construct as this will result in increased movement at the fixator pin–bone interface of the remaining pins and wires, initiating loosening and infection of the remaining pins [3, 14]. Therefore, septic pins and wires should, as a rule, rather be resited than simply removed.

### Conclusion

Pin site infection is a very common complication with external fixation. In an effort to prevent or at least minimize this complication, a pin site strategy should be adopted that covers all aspects associated with pin loosening and infection. This should include understanding of external fixator biomechanics, meticulous surgical technique during pin and wire insertion and a standardized post-operative pin site care protocol.

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# Chapter 9. Pin Tract Sepsis: Incidence with the use of Circular Fixators in a Limb Reconstruction Unit

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Contribution to authorship:

- N. Ferreira – Concept development, data collection, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- L.C. Marais – Concept development, data collection, contribution to literature review and revision of manuscript.

# CLINICAL ARTICLE

# Pin tract sepsis:
# Incidence with the use of circular fixators in a limb reconstruction unit

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## Abstract

**Background**
Pin site-related problems remain one of the most common complications in the realm of limb reconstructive surgery. Several factors determine the integrity of the bone–pin interface, including the insertion technique, the mechanical forces applied through the frame and the selected pin site care protocol. Pin site complications can be catastrophic as they may lead to failure of the bone–pin interface and, possibly, osteomyelitis.

**Methods**
Between July 2008 and July 2011, 111 patients at our Limb Reconstruction Unit were treated with circular external fixators. These patients' records were reviewed with regard to pin site complications, treatment thereof and outcome.

**Results**
Eighty patients met the inclusion and exclusion criteria. Pin site infection was found in 21 patients (26.25%). One patient had a major infection, which required debridement of the pin tract. The remaining 20 cases were all minor infections that responded to local treatment and oral antibiotics.

**Conclusion**
Circular external fixation remains a safe treatment method, with the majority of pin site complications being of a minor nature that respond readily to local treatment and oral antibiotics.

**Key words:** Pin site, complications, external fixation

## Introduction

External fixation, and in particular, circular external fixation, is an essential component of contemporary limb reconstructive surgery. Pin site infection is, however, often noted as a major complication, and may act as a deterrent against the utilisation of these techniques.[1,2]

*The majority of pin site complications were of a minor nature and responded readily to local treatment and oral antibiotics*

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| Table I: Checketts-Otterburn classification | | |
|---|---|---|
| Grade | Characteristics | Treatment |
| **Minor infection** | | |
| 1 | Slight redness, little discharge | Improved pin site care |
| 2 | Redness of the skin, discharge, pain and tenderness in the soft tissue | Improved pin site care, oral antibiotics |
| 3 | Grade 2 but no improvement with oral antibiotics | Affected pin or pins resited and external fixation can be continued |
| **Major infection** | | |
| 4 | Severe soft tissue infection involving several pins, sometimes with associated loosening of the pin | External fixation must be abandoned |
| 5 | Grade 4 but radiographic changes | External fixation must be abandoned |
| 6 | Infection after fixator removal. Pin track heals initially, but will subsequently break down and discharge in intervals. Radiographs show new bone formation and sometimes sequestra | Curettage of the pin tract |

The incidence of pin site infection varies greatly, with the published figures ranging from 11.3% to 100%.[3-11] Mostafavi reported a 71% incidence of pin site infection in reconstructive surgery.[8] The high incidence of pin tract complications reported in limb reconstruction surgery may be related to the long periods of time spent in the external fixator and high demands placed on the bone–pin interface during bone transport and deformity correction.

In order to minimise the complications of pin loosening and sepsis, a protocol that includes attention to external fixator design and biomechanics,[3] intra-operative insertion technique[10] and post-operative care should be instituted.[5] The primary goal is to establish a stable bone–pin interface that will withstand the stresses transferred during the reconstruction period.[3,12]

In this article we report the incidence of pin tract complications encountered at our institution, using a pin tract protocol that is inexpensive, simple and effective.

## Materials and methods

The study population consisted of all patients who were treated with circular external fixators in a three-year period from July 2008 to July 2011. Patients were included if they had completed treatment and the external fixator had been removed. Patients were excluded if the external fixator had not been applied at our institution, or the records were insufficient with regard to the required data.

The patients' charts were reviewed and information extracted regarding patient demographics, indications for circular fixation, type of fixator used, pin tract complications and treatment of these complications. Pin site infections were graded according to the Checketts and Otterburn classification[13] (Table I).

## Results

The charts of 111 patients were reviewed. Eighty patients (59 males and 21 females) were included (Table II). The mean age was 37.7 years, ranging from 9 years to 66 years. The indications for the use of these external fixators are listed in Table III. The external fixators applied consisted of 41 Ilizarov fixators (Smith & Nephew, Memphis, TN), 20 Truelok fixators (Orthofix, Verona, Italy) and 19 Taylor Spatial Frame fixators (Smith & Nephew, Memphis, TN).

In 58 out of 80 patients (72.5%) no pin site complications occurred. The remaining 21 patients (26.25%) all had pin tract infection of at least one wire or half pin. Twenty of these infections were minor according to the Checketts-Otterburn classification, while the remaining infection was classified as major.

The minor infections were subdivided into one grade 1, 15 grade 2 and four grade 3 infections. The grade 1 infection resolved with meticulous pin site care without any further intervention. All the grade 2 infections responded to local pin site care and a course of oral antibiotics. All four grade 3 infections were managed with removal of the offending wire which led to resolution of the infection. One wire was resited elsewhere as we felt that frame stability could be compromised by the removal of the infected wire.

## Table II: Patient details

| Patient | Age | Gender | Fixator | Indication | Time in frame (Weeks) | Pin tract sepsis | Checketts & Otterburn Grade | Treatment |
|---------|-----|--------|---------|------------|----------------------|------------------|----------------------------|-----------|
| J.J. | 27 | M | Ilizarov | Bone transport tibia | 104 | Yes | 3 | Wire removed |
| P.M | 39 | F | Ilizarov | Bone transport tibia | 36 | Yes | 2 | Oral antibiotics |
| T.D. | 27 | M | Ilizarov | Bone transport tibia | 34 | No | - | - |
| T.T. | 40 | M | Truelok | Bone transport tibia | 65 | No | - | - |
| S.P. | 25 | M | Truelok | Bone transport tibia | 11 | No | - | - |
| P.M. | 44 | M | Ilizarov | Bone transport tibia | 29 | Yes | 2 | Oral antibiotics |
| N.S. | 9 | F | Truelok | Bone transport tibia | 12 | No | - | - |
| P.S. | 27 | F | Truelok | Bi-Masquelet tibia | 36 | No | - | - |
| B.M. | 49 | M | Truelok | Bi-Masquelet tibia | 24 | No | - | - |
| A.H. | 26 | M | Ilizarov | Bi-Masquelet tibia | 29 | No | - | - |
| T.J. | 34 | M | Ilizarov | Non-union tibia | 6 | No | - | - |
| H.H. | 50 | F | Truelok | Non-union tibia | 18 | No | - | - |
| N.M. | 21 | F | Ilizarov | Non-union tibia | 24 | No | - | - |
| S.D | 25 | M | Truelok | Non-union tibia | 25 | Yes | 2 | Oral antibiotics |
| B.G. | 55 | M | Truelok | Non-union tibia | 22 | No | - | - |
| N.N. | 57 | F | Truelok | Infected non-union tibia | 28 | No | - | - |
| T.N. | 24 | M | Truelok | Complex fracture tibia | 50 | No | - | - |
| M.L. | 23 | M | Truelok | Complex fracture tibia | 19 | No | - | - |
| P.S. | 27 | F | Truelok | Complex fracture tibia | 36 | No | - | - |
| L.G. | 44 | M | Ilizarov | Complex fracture tibia | 50 | No | - | - |
| M.M. | 40 | M | Ilizarov | Complex fracture tibia | 4 | No | - | - |
| M.L. | 30 | M | Truelok | Complex fracture tibia | 12 | No | - | - |
| S.M. | 18 | M | Ilizarov | Complex fracture tibia | 50 | No | - | - |
| P.S. | 50 | M | Ilizarov | Complex fracture tibia | 26 | No | - | - |
| S.M. | 59 | M | Ilizarov | Complex fracture humerus | 16 | No | - | - |
| D.N. | 36 | F | Truelok | Tumour resection tibia | 54 | Yes | 3 | Wire removed and resited |
| M.M. | 26 | M | Ilizarov | Chronic osteitis tibia | 38 | No | - | - |
| M.M. | 26 | M | Ilizarov | Chronic osteitis tibia | 38 | No | - | - |
| S.M. | 23 | M | Ilizarov | Periarticular fracture tibia | 9 | No | - | - |
| R.M. | 43 | F | Ilizarov | Periarticular fracture tibia | 12 | No | - | - |
| M.S. | 35 | M | Ilizarov | Periarticular fracture tibia | 8 | No | - | - |
| M.L. | 14 | M | Ilizarov | Periarticular fracture tibia | 11 | No | - | - |
| X.X. | 38 | M | Ilizarov | Periarticular fracture tibia | 36 | No | - | - |

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| Patient | Age | Gender | Fixator | Indication | Time in frame (Weeks) | Pin tract sepsis | Checketts & Otterburn Grade | Treatment |
|---------|-----|--------|---------|------------|-----------------------|------------------|------------------------------|-----------|
| X.B. | 29 | M | Ilizarov | Periarticular fracture tibia | 18 | No | - | - |
| M.M. | 34 | M | Ilizarov | Periarticular fracture tibia | 19 | No | - | - |
| A.N. | 40 | F | Ilizarov | Periarticular fracture tibia | 20 | Yes | 2 | Oral antibiotics |
| M.N. | 57 | M | Ilizarov | Periarticular fracture tibia | 17 | Yes | 2 | Oral antibiotics |
| E.M. | 59 | F | Ilizarov | Periarticular fracture tibia | 28 | No | - | - |
| S.N. | 19 | M | Ilizarov | Periarticular fracture tibia | 23 | No | - | - |
| N.N. | 56 | F | Ilizarov | Periarticular fracture tibia | 26 | Yes | 2 | Oral antibiotics |
| N.T. | 42 | M | Ilizarov | Periarticular fracture tibia | 20 | Yes | 2 | Oral antibiotics |
| F.M. | 37 | M | Ilizarov | Periarticular fracture tibia | 20 | No | - | - |
| N.M. | 21 | F | Ilizarov | Periarticular fracture tibia | 16 | No | - | - |
| D.N. | 41 | F | Ilizarov | Periarticular fracture tibia | 17 | No | - | - |
| P.M. | 66 | M | Ilizarov | Periarticular fracture tibia | 14 | No | - | - |
| M.K. | 40 | M | Truelok | Periarticular fracture tibia | 14 | Yes | 2 | Oral antibiotics |
| L.M. | 50 | M | Ilizarov | Periarticular fracture tibia | 12 | Yes | 3 | Wire removed |
| B.N. | 27 | M | Ilizarov | Periarticular fracture tibia | 16 | No | - | - |
| S.K. | 59 | M | Ilizarov | Periarticular fracture tibia | 10 | No | - | - |
| T.M. | 41 | F | Truelok | Periarticular fracture tibia | 21 | No | - | - |
| M.N. | 46 | M | Ilizarov | Periarticular fracture tibia | 20 | No | - | - |
| S.D. | 33 | M | Ilizarov | Periarticular fracture tibia | 13 | No | - | - |
| A.N. | 43 | F | Ilizarov | Periarticular fracture tibia | 9 | No | - | - |
| S.Z. | 57 | M | Truelok | Periarticular fracture tibia | 13 | No | - | - |
| S.Z. | 57 | M | Truelok | Periarticular fracture tibia | 13 | No | - | - |
| A.M. | 45 | M | Ilizarov | Periarticular fracture tibia | 19 | Yes | 3 | Wire removed |
| M.S. | 36 | M | Ilizarov | Periarticular fracture tibia | 15 | No | - | - |
| T.N. | 24 | M | Truelok | Periarticular fracture tibia | 50 | No | - | - |
| T.S. | 53 | F | Ilizarov | Periarticular fracture tibia | 10 | No | - | - |
| P.C. | 54 | M | Ilizarov | Periarticular fracture tibia | 32 | No | - | - |
| M.X. | 40 | M | Truelok | Periarticular fracture tibia | 16 | No | - | - |
| H.G. | 48 | F | TSF | Deformity correction tibia | 7 | No | - | - |
| K.S. | 32 | F | TSF | Deformity correction knee | 22 | Yes | 2 | Oral antibiotics |
| T.M. | 29 | M | TSF | Deformity correction tibia | 32 | No | - | - |
| J.K. | 43 | F | TSF | Deformity correction tibia | 50 | Yes | 2 | Oral antibiotics |
| S.S. | 30 | M | TSF | Deformity correction tibia | 16 | No | - | - |
| N.F. | 58 | M | TSF | Deformity correction tibia | 16 | No | - | - |
| J.K. | 53 | M | TSF | Deformity correction tibia | 14 | Yes | 1 | Pin site care |

*In 58 out of 80 patients (72.5%)*
*no pin site complications occurred*

| Patient | Age | Gender | Fixator | Indication | Time in frame (Weeks) | Pin tract sepsis | Checketts & Otterburn Grade | Treatment |
|---|---|---|---|---|---|---|---|---|
| B.K. | 57 | M | TSF | Deformity correction tibia | 33 | No | - | - |
| S.Z. | 23 | M | TSF | Deformity correction tibia | 15 | No | - | - |
| T.L. | 46 | M | TSF | Deformity correction tibia | 39 | Yes | 2 | Oral antibiotics |
| F.Z | 25 | F | TSF | Deformity correction tibia | 26 | No | - | - |
| M.M. | 15 | M | TSF | Deformity correction tibia | 12 | Yes | 2 | Oral antibiotics |
| L.C. | 14 | M | TSF | Deformity correction tibia | 14 | Yes | 6 | Pin site debridement |
| K.G. | 45 | M | TSF | Deformity correction tibia | 24 | No | - | - |
| B.K. | 57 | M | TSF | Deformity correction tibia | 36 | Yes | 2 | Oral antibiotics |
| B.K. | 57 | M | TSF | Deformity correction tibia | 18 | Yes | 2 | Oral antibiotics |
| V.J. | 53 | M | TSF | Deformity correction tibia | 12 | No | - | - |
| T.Z. | 35 | M | TSF | Deformity correction tibia | 12 | No | - | - |
| T.K. | 14 | M | TSF | Deformity correction tibia | 10 | Yes | 2 | Oral antibiotics |

*Every effort should be made to avoid or at least minimise the occurrence and severity of pin site infections*

| Table III: Circular external fixator indications | | | |
|---|---|---|---|
| **Indications** | **Fixator used (Number of cases)** | | |
| | **Ilizarov** | **Truelok** | **Taylor Spatial Frame** |
| Bone transport | 4 | 3 | |
| Bi-Masquelet | 1 | 2 | |
| Non-union tibia | 2 | 4 | |
| Periarticular fracture tibia | 28 | 6 | |
| Tumour resection tibia | | 1 | |
| Chronic osteomyelitis tibia | 3 | | |
| Complex fracture tibia | 2 | 4 | |
| Complex fracture humerus | 1 | | |
| Deformity correction tibia | | | 18 |
| Deformity correction knee | | | 1 |

The patient who developed a major infection was classified as a Checketts-Otterburn grade 6 infection. This infection occurred at the end of the treatment period after union was achieved, and the external fixators were abandoned without the need for additional stabilisation. This patient presented for follow-up 2 weeks after frame removal, and had a non-healing pin site. Radiographs revealed a small sequestrum in the pin tract that required debridement of the tract in theatre and subsequently healed without incidence.

One patient developed a hypersensitivity reaction to the alcoholic solution of chlorhexidine. The reaction was resolved by diluting the cleaning solution to half strength and continuing pin site care.

## Discussion

Pin tract infection is a very common finding,[1-11] and the potential complications can be catastrophic. These complications could ultimately lead to failure of the bone–pin interface and chronic osteomyelitis. Because of this, every effort should be made to avoid or at least minimise the occurrence and severity of pin site infections.

Instability of the external fixator–pin–bone construct leads to pin loosening and infection.[3] This infection then further contributes to the deterioration of the bone–pin interface. It is a common misconception that pin loosening results from pin tract infection, when in actual fact pin loosening is often the initiating event that leads to pin tract sepsis.

For this reason, the external fixator construct is vital in the prevention of pin site complications.[3] The overall stability of the external fixator construct is not only a function of the fixator itself, but involves a complex interplay of the geometrical and mechanical properties of the fixator, as well as the properties of the surrounding tissues and fracture pattern.[14] There also appears to be a race between the gradually increasing loading capacity of healing bone and failure of the bone–pin interface.[15] For this reason it is important to keep the fracture configuration in mind when deciding on which external fixator to use.

An unstable fixator not only provides an unsuitable environment for bone healing but also causes excessive movement at the fixator–pin-bone interface, leading to pin site irritation and infection.[3,16] Parameswaran found that the type of fixator had an effect on the incidence of pin site infection, with monolateral and hybrid fixators showing a much higher incidence when compared to ring fixators.[3] Consequently, the fixator design should always be kept in mind when embarking on limb reconstruction that will require prolonged periods of external fixation.

It is important to note that every strategy that aims to reduce pin tract infection should begin in the operating theatre.[10] We strongly advocate this approach, and recommend that every effort is made to ensure that pin and wire insertion is as atraumatic as possible, thereby minimising the iatrogenic damage to skin, soft tissue and bone.

The aim is to have pin sites heal around the wires or pins, much like a pierced earring insertion site heals.[17] We therefore recommend careful planning of any incision to ensure a snug fit of the skin around the pin, while avoiding any skin tension. These incisions should be as small as possible in order to facilitate rapid healing of the skin around the pin or wire and thereby creating a bone–pin interface that is sealed from the external environment.

The soft tissue envelope should be considered carefully during wire and pin insertion. Subcutaneous bone surfaces are preferable, while areas with considerable soft tissue bulk or tendons should be avoided as far as possible, as soft tissue movement around a wire or pin leads to an increased risk for infection.[2,18,19] Any muscle compartment that is traversed should be placed under stretch during wire insertion in order to prevent transfixing muscles in a shortened position.[2] Furthermore, wires should not be drilled through the soft tissues. Wires should rather be pushed onto the near cortex then drilled through the bone, and finally advanced through the distal soft tissues by tapping the wire with a mallet[5] (*Figure 1*). This procedure has the added advantage of decreasing the amount of heat generated through friction between the spinning wire and the bone.

The anterior tibial crest should be avoided at all cost, as drilling through the thick cortical bone can generate excessive heat that could lead to thermal necrosis of the surrounding bone, ring sequestra and pin loosening.[2]

Pre-drilling should always be performed for half-pin insertion, even when using self-drilling pins.[2,5] Drilling should be done under continuous cold saline irrigation and in a metronomic (stop-start) fashion to ensure proper cooling of the drill bit.[2,10] After drilling the pilot hole, it must be irrigated to remove the bone swarf that might act as sequestra and prevent optimal bone–pin fixation.[10] We recommend the use of a 20 ml syringe filled with cold saline together with small feeding tube in order to flush the pilot hole (*Figure 2*).

In cases where half pins are required, we routinely use hydroxyapatite-coated pins, and in our unit we have completely abandoned the use of uncoated pins. Hydroxyapatite-coated pins show increased fixation strength when compared to uncoated pins, as is evident from extraction torque forces that are higher than insertion torque forces and 90 times higher than conventional uncoated pins.[9,20-22] This improved fixation translates into lower rates of osteolysis, lower incidence of pin loosening and decreased pin site infection when compared to uncoated pins.[9,11,21-29]



**Figure 1**



**Figure 2**

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As far as possible a non-touch technique, for insertion of wires and half pins, must be used.[10] Half pins are never touched prior to insertion, and wires are handled and manipulated with chlorhexidine-soaked swabs (*Figure 3*).

Peri-operative care consists of dressing the pin sites with an alcoholic solution of chlorhexidine-soaked swab immediately after each wire or pin is inserted. These dressings are held in place with a small amount of pressure to prevent skin tenting and haematoma formation.[10,30] We generally use the rubber of a 20 ml syringe plunger in order to keep slight pressure on our dressing (*Figure 4*). These dressings are then changed at the end of the procedure if they are blood stained. Finally fluffed gauze is packed between the soft tissue and frame, and the whole extremity and external fixator is covered with a sterile dressing (*Figure 5*), which is left in place for the first 7 to 10 days post-operatively.[31]

Pin tract care is initiated following removal of the postoperative dressings at day 7 to 10 after the surgery.[31] No consensus exists regarding the optimal care of pin sites, and a myriad of pin site protocols have been advocated.[5] Protocols range from a nihilistic approach, advocating no active pin care,[32] to intensive regimens involving twice-daily cleaning, dressing and oral antibiotics for the entire duration of the external fixator.[3]

Pin tract care at our institution consists of twice-daily cleaning of the pin–skin interface with an alcoholic solution of chlorhexidine and clean gauze.[3,4,19] Chlorhexidine has been shown to have improved benefit when compared to normal saline in terms of pin site infection.[33] We advocate pin sites to be left uncovered after cleaning, and that dry, absorptive dressings only be considered in the presence of an exudate.[5] Twice-daily pin site care is continued for the entire duration of the external fixator. This extended period of pin tract cleaning, combined with a meticulous insertion technique, could explain why we encountered so few grade 1 infections in our study, as pin tract care is the suggested treatment for grade 1 infections.

Once the pin sites have healed, patients are allowed to have a daily shower, providing that the limb and external fixator is dried thoroughly thereafter. We do not recommend swimming, and swimming in dams or the ocean is definitely not allowed.

Pin tract sepsis may either start as cellulitis around a pin or a localised form of osteitis. Most cases are secondary to *Staphylococcus aureus* infection,[9,10] and antibiotic treatment should be directed at this microorganism.[2,7,32] In our series 95.2% of the infections were minor. This compares well with other studies which have reported figures ranging between 75% and 94% for minor infections.[2,5,7,9,10]

Patients who present with Checketts-Otterburn grade 2 infections are treated with a course of oral cloxacillin for seven days. If response to this treatment is inadequate the offending pin or wire is removed or exchanged. We encountered four (5.0%) patients with grade 3 infections and all three of these patients underwent removal of the infected wire or pin.
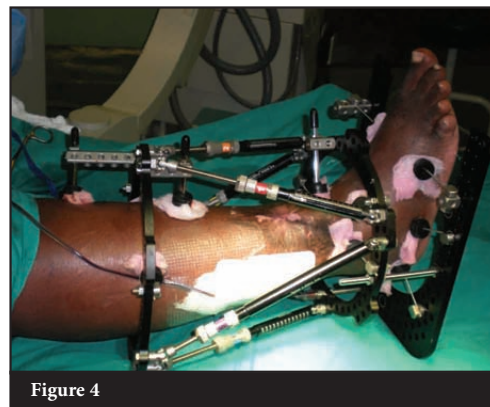

**Figure 3**


**Figure 4**


**Figure 5**

*Pin tract care at our institution consists of twice-daily cleaning of the pin–skin interface with an alcoholic solution of chlorhexidine and clean gauze*

Major infections are treated with removal of the external fixator. In our series only one (1.25%) patient required removal of his external fixator due to a major infection. This patient presented with a non-healing pin site 2 weeks after external fixator removal. He was subsequently admitted and treated with debridement of the pin tract utilising the Versajet Hydrosurgery system (Smith & Nephew, Memphis, TN).[2] After excision of the edges, the wound was closed, and healing occurred without any further complications.

Limitations of this paper include the retrospective nature of the review and the fact that the external fixators were almost exclusively used for tibial applications. We concede that external fixators used in other anatomic locations might not display similar results.

## Conclusion

Although pin tract infection is frequently found in relation to circular external fixation, the majority of these are of a minor nature and respond well to local treatment and systemic antibiotics. Furthermore, a standardised pin site protocol, encompassing insertion, peri- and post-operative care as well as removal would limit the incidence of major infections and treatment failures.

*The content of this article is the sole work of the author. No benefits of any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. The research has been approved by an ethical committee.*

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# SA ORTHOPAEDIC JOURNAL
## PEER REVIEWERS
## (PAST AND PRESENT)

# Chapter 10. The Effect of HIV Infection on the Incidence and Severity of Circular External Fixator Pin Track Sepsis: a Retrospective Comparative Study of 229 Patients

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Contribution to authorship:

- N. Ferreira – Concept development, data collection, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- L.C. Marais – Concept development, data collection, contribution to literature review and revision of manuscript.

ORIGINAL ARTICLE

# The effect of HIV infection on the incidence and severity of circular external fixator pin track sepsis: a retrospective comparative study of 229 patients

**Nando Ferreira · Leonard Charles Marais**

**Abstract** Pin track sepsis is a common complication of circular external fixation. HIV status has been implicated as an independent risk factor for the development of pin track infection and has been cited as a reason not to attempt complex limb reconstruction in HIV-positive patients. This retrospective review of patients treated with circular external fixators looked at the incidence of pin track sepsis in HIV-positive, HIV-negative and patients whose HIV status was unknown. The records of 229 patients, 40 of whom were HIV-positive, were reviewed. The overall incidence of pin track sepsis was 22.7 %. HIV infection did not affect the incidence of pin track sepsis ($p = 0.9$). The severity of pin track sepsis was not influenced by HIV status ($p = 0.9$) or $CD_4$ count ($p = 0.2$). With the employment of meticulous pin insertion techniques and an effective postoperative pin track care protocol, circular external fixation can be used safely in HIV-positive individuals.

**Keywords** HIV · Pin track sepsis · Complication · Ilizarov · Circular external fixator

## Introduction

External fixation, and circular external fixation in particular, has evolved as an indispensible component of contemporary trauma and limb reconstruction surgery. Owing to its minimally invasive nature, circular fixators are being used increasingly in the management of skeletal trauma. In injuries associated with soft tissue compromise, such as periarticular fractures of the tibia, circular fixation has been shown to decrease the incidence of deep infection [1–6]. Its use is well established in the reconstruction of post-traumatic, post-infective bone defects and congenital deformities. This treatment modality is, however, associated with its own set of complications of which the most frequent is pin track sepsis with the reported incidences ranging from 11.3 to 100 % [4, 7–15].

Pin track sepsis is often the first clinical manifestation of a vicious cycle of pin loosening and sustained pin site infection. It is a misconception that pin track sepsis result in pin loosening; pin loosening is more often the inciting event that leads to pin site infection [14, 16–19]. Failure of the pin–bone interface can have catastrophic consequences and may lead to failure of the reconstruction and, ultimately, limb ablation in some. A meticulous approach to pin and wire insertion combined with a structured protocol of pin site care has been shown to decrease the incidence of pin track sepsis [4, 20, 21]. Certain patient factors may, however, influence the incidence and severity of pin track sepsis. Poor diabetic control and HIV infection have both been implicated as independent risk factors for the development of pin track infection [7, 15, 22–24].

HIV infection was previously considered to be a relative contraindication for the use of external fixators. A recent study from Malawi investigating the use of monolateral external fixators in tibial trauma found an increased incidence and severity of pin track sepsis in HIV-positive patients [22–24]. This study is cited frequently against limb reconstruction with external fixation in HIV-positive patients. The use of circular fixators, in particular, has been avoided in HIV-positive patients due to the prolonged periods of treatment required.

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South Africa has the highest incidence of HIV infection in the world. The 2011 National Antenatal Sentinel Survey reported a national prevalence of 17.3 %, with areas like KwaZulu-Natal approaching 25 % [25]. The majority of these patients are between 20 and 50 years old. South Africa also has one of the highest incidences of road traffic accidents in the world, affecting mostly young adults [26, 27]. The HIV pandemic in South Africa, combined with the high incidence of trauma, has resulted in many HIV-positive patients requiring treatment for complex trauma or a need for post-traumatic limb reconstruction. Of note is that the overall fracture prevalence is increased in HIV-positive compared to HIV-negative patients [28–30].

This retrospective review aims to compare the rate and severity of pin track sepsis in HIV-positive and HIV-negative patients treated with circular external fixators. The research proposal was reviewed and approved by the local ethics committee. An extensive literature review revealed this current study to be the largest yet to compare the incidence of pin track sepsis in HIV-positive and HIV-negative patients. It is currently also the only study investigating the effect of HIV infection on the incidence and severity of pin track sepsis with the use of circular external fixators.

## Materials and methods

The study population consisted of all patients who were treated with circular external fixators at our institution between July 2008 and December 2012. Patients were included if they had completed treatment and had the external fixator removed. Patients were excluded if the external fixator was not applied at our institution or if the records were insufficient for the required data.

All patients were offered voluntary HIV counseling and testing. The $CD_4$ count of all HIV-positive patients was measured. Patients with $CD_4$ counts below 350 cells/mm$^3$ were started on highly active antiretroviral therapy (HAART) in accordance with South African national antiretroviral treatment guidelines.

The fixator design and application followed the general principles as outlined by Catagni with the emphasis on construction of a stable frame configuration [31–36]. Particular attention was paid to atraumatic pin and wire insertion. Recognized anatomical safe zones were used and insertion was carried out with as little heat and energy transfer as possible [31, 36, 37]. Postoperative pin track care followed the protocol previously set out by Ferreira and Marais [21]. Outpatient follow-up was scheduled at two to four weekly intervals until frame removal. At every clinic visit, the progress was assessed and any complications, including pin track sepsis, were documented. Pin site

**Table 1** Checketts–Otterburn classification

| Grade | Characteristics | Treatment |
|---|---|---|
| Minor infection | | |
| 1 | Slight redness, little discharge | Improved pin site care |
| 2 | Redness of the skin, discharge, pain and tenderness in the soft tissue | Improved pin site care, oral antibiotics |
| 3 | Grade 2 but no improvement with oral antibiotics | Affected pin or pins resited and external fixation can be continued |
| Major infection | | |
| 4 | Severe soft tissue infection involving several pins, sometimes with associated loosening of the pin | External fixation must be abandoned |
| 5 | Grade 4 but radiographic changes | External fixation must be abandoned |
| 6 | Infection after fixator removal. Pin track heals initially, but will subsequently break down and discharge in intervals. Radiographs show new bone formation and sometimes sequestra | Curettage of the pin tract |

infections were graded according the Checketts and Otterburn classification (Table 1) [38].

A retrospective review was undertaken and the variables recorded included patient demographics, HIV status, $CD_4$ count and use of antiretroviral medication, indications for circular fixation, type of external fixator used, pin track complications and treatment of these complications. Results were analyzed using the independent $t$ test, one-way ANOVA test and the Kruskal–Wallis H test to ascertain whether HIV infection had any effect on the incidence or severity on pin track sepsis.

## Results

The records of 274 patients were reviewed. Forty-five patients were excluded because the external fixators had not yet been removed. Therefore, 229 patients (163 males and 66 females) were included: The mean age was 34.5 years (standard deviation ± 15.4, range 6–71 years); mean time in external fixation was 22.9 weeks (SD ± 14.7, range 6–104 weeks).

The external fixators applied consisted of 71 Ilizarov fixators (Smith and Nephew, Memphis, TN), 91 Truelok fixators (Orthofix, Verona, Italy), 65 Taylor Spatial Frames (Smith and Nephew, Memphis, TN) and two TL-Hex fixators (Orthofix, Verona, Italy) (Table 2). The indications for the use of the external fixators are listed in Table 3.

**Table 2** External fixators applied

|                      | HIV+ | HIV− | Unknown | Total |
|----------------------|------|------|---------|-------|
| Ilizarov             | 14   | 44   | 13      | 71    |
| Truelok              | 21   | 65   | 5       | 91    |
| Taylor Spatial Frame | 5    | 57   | 3       | 65    |
| TL-Hex               | 0    | 2    | 0       | 2     |
| Total                | 40   | 168  | 21      | 229   |

**Table 3** Circular external fixator indications

| Indications          | HIV+ | HIV− | Unknown |
|----------------------|------|------|---------|
| Complex trauma       | 7    | 21   | 3       |
| Periarticular fracture | 17 | 50   | 12      |
| Non-union            | 5    | 25   | 2       |
| Bone transport       | 1    | 7    | 1       |
| Bone defect          | 2    | 3    |         |
| Limb lengthening     |      | 1    |         |
| Chronic osteomyelitis | 3   | 5    |         |
| Deformity correction | 5    | 56   | 3       |
| Total                | 40   | 168  | 21      |

The patients were divided into groups according to their HIV status. A third group was made up of patients who refused HIV testing and designated as the unknown group. The HIV-positive group consisted of 40 (17.5 %) patients. The mean age was 37.2 years (SD ± 10.2, range 8–56 years). Time in the external fixator averaged 26 weeks (SD ± 16.6, range 6–77 weeks). The HIV-negative group consisted of 168 (73.4 %) patients. The mean age was 33.2 (SD ± 16.5, range 6–71 years) and time in the external fixator averaged 33.2 weeks (SD ± 16.5, range 6–71 weeks). The group whose HIV status was unknown consisted of 21 (9.2 %) patients. Their mean age was 39.7 years (SD ± 13.1, range 17–59 years) and time in external fixation averaged 18.9 weeks (SD ± 10.2, range 7–50 weeks). There was no statistically significant difference between the three groups in terms of age ($p = 0.09$) or time in the external fixator ($p = 0.18$).

Pin track infection occurred in 52 (22.7 %) out of 229 patients. In the subgroups, nine (22.5 %) patients in the HIV-positive group ($n = 40$), 38 (22.6 %) patients in the HIV-negative group ($n = 168$) and five (23.8 %) patients in the unknown group ($n = 21$) developed pin track sepsis. Checketts and Otterburn grades for the three groups are shown in Fig. 1. There was no statistically significant difference in the incidence of pin track sepsis between the three groups ($p = 0.94$). Furthermore, the three groups had no statistically significant differences in terms of severity of pin track sepsis ($p = 0.9$).

A subgroup analysis of the HIV-positive patients ($n = 40$) was undertaken. Mean $CD_4$ count was 347.4 cells/
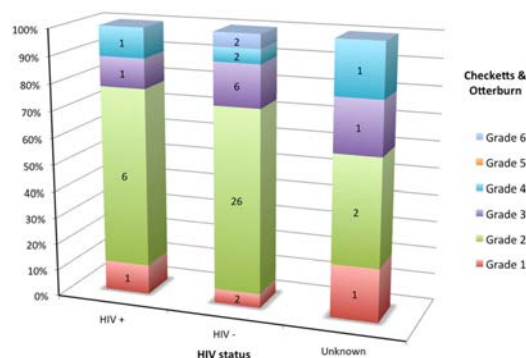


**Fig. 1** Pin track infection grades in HIV+, HIV− and Unknown groups

$mm^3$ (D ± 162.4, range 82–682 cells/$mm^3$) and 25 (62.5 %) patients were receiving HAART. Our data showed that $CD_4$ count had no influence on either the incidence ($p = 0.57$) or severity ($p = 0.21$) of pin track sepsis in the HIV-positive group.

## Discussion

Pin track sepsis remains a common complication with the use of external fixators [7, 15]. Quoted incidences range from 11.3 to 100 % [9–13]. Mostafavi reported a 71 % incidence of pin site infection in reconstructive surgery [11].

The use of meticulous pin insertion techniques and the implementation of an evidence-based pin track care protocol can reduce the incidence of pin track sepsis with circular external fixation in reconstructive surgery to approximately 25 % [4]. Our results compare favorably to previously published figures with an overall pin track sepsis incidence of 22.7 % (52 out of 229) observed in this series.

Several factors have been implicated in the development of pin track sepsis [4, 21]. They include frame design and biomechanics, pin and wire insertion techniques, point of commencement of pin track care and the specific care protocol employed [7, 8, 12, 13, 40]. Strategies to reduce pin track sepsis should include measures aimed at optimization of these factors. Some non-modifiable risk factors have also been associated with pin site infection. These include diabetes mellitus and HIV infection [7, 15, 22–24].

HIV infection has prompted many orthopedic and trauma surgeons to avoid the use of circular external fixators for the purpose of limb reconstruction in HIV-positive patients. Norrish and Harrison published the first data comparing pin track infection with the use of monolateral

external fixators in HIV-positive and HIV-negative patients [22, 24, 39]. They reported on 13 HIV-positive and 34 HIV-negative patients and found significantly more infections requiring pharmaceutical or surgical intervention in the HIV-positive group. Our results differ in that we could show no correlation between the incidence or severity of pin track sepsis and HIV status. Our results do correlate with the findings of no correlation between $CD_4$ count and the severity of pin track infection in HIV-positive patients. The low patient numbers and wide $CD_4$ range could explain the apparent lack of relationship and more research is required.

In conclusion, while pin track sepsis is a common complication with the use of circular external fixators, we did not find that the incidence or severity of pin track sepsis was influenced by HIV infection or degree of immune compromise. This finding should not preclude the use of circular external fixators for complex trauma and limb reconstruction in HIV-positive individuals.

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# Chapter 11. Conclusion

**Limitations of current definitions**

Existing definitions of fracture non-union are controversial and not universally accepted.[1, 2] The majority are temporal systems that use time as the sole variable to define the presence of a non-union. These definitions also do not take fracture morphology, anatomical location, treatment or the age of the individual into account. A further drawback to temporal definitions is the inevitable delay in diagnosis and treatment they cause. It is also during this period that most of the morbidity associated with long-bone non-unions occurs, including muscle atrophy, joint contracture, osteopenia and complex regional pain syndrome.

In an attempt to address some of the shortcomings of current definitions, we proposed the following definitions:

> *Non unus potentia* (Potential Non-union): any fracture that when taking host factors, injury severity and management into account, has little potential to heal without further intervention.

> *Non unus certus* (Established Non-union): any fracture that shows no clinical or radiological union in a reasonable time, for that specific injury, host and management strategy.

The rationale for this distinction is the early identification of potential non-unions. Early identification, referral and treatment of these patients might achieve union with simple interventions without the need for complex, expensive surgeries. A potential saving that is not only monetary in terms of the healthcare system and the patient's personal finances, but also a saving in terms of morbidity, limb integrity and social dependency of the individual patient.

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**Limitations of current classifications**

Current non-union classifications have limited clinical relevance. The Weber and Cech modification of the Judet and Judet classification distinguished between avascular and hypervascular non-unions based on the uptake of strontium-85 at the fracture site.[3, 4] The Ilizarov classification divides non-unions into stiff or lax depending on the amount of movement possible at the non-union site.[5] The Paley classification specifically addresses tibial non-union and is an advance on the existing classifications.[6, 7] All these classifications, however, have deficiencies in that they fail to take all host and non-union factors into account. Further, although dividing non-unions into various subtypes, none of these classifications prescribe treatment for specific non-union subtypes.

The classification by Wu *et al.* specifically address non-unions following failed internal fixation.[8] Non-unions are designated as either avascular or hyper-vascular depending on whether the fixation was stable or unstable. Automatically designating non-unions with stable fixation as avascular is not necessarily biologically accurate as fractures fixed in distraction are not always avascular, but may develop non-unions due to the healing process not being able to cross the fracture gap.

The Calori Non-union Scoring System (NUSS) is a recent development to assist surgeons with decision making during non-union management.[9] This system takes various biological and mechanical factors into account to guide management. The NUSS score only proposes, in broad terms, where and how these patients should be treated. The suggested treatments include 'standard treatment', 'specialised care' and 'specialised care and specialised treatment'. This provides an indication for junior orthopaedic surgeons of which patients to refer, but do not provide specific treatment guidelines as to what 'specialised treatments' should be offered.

Formulating standardised treatment strategies or protocols on existing classification systems is challenging, and might not take all aspects of non-union development and management into account.

Our research identified four distinct non-union subtypes namely, stiff hypertrophic, mobile atrophic / oligotrophic, mobile hypertrophic (true pseudoarthrosis) and defect non-unions. We propose specific treatment for each subtype according to the Tibial Non-union Treatment Algorithm:

**Figure 1.** Tibial non-union treatment algorithm
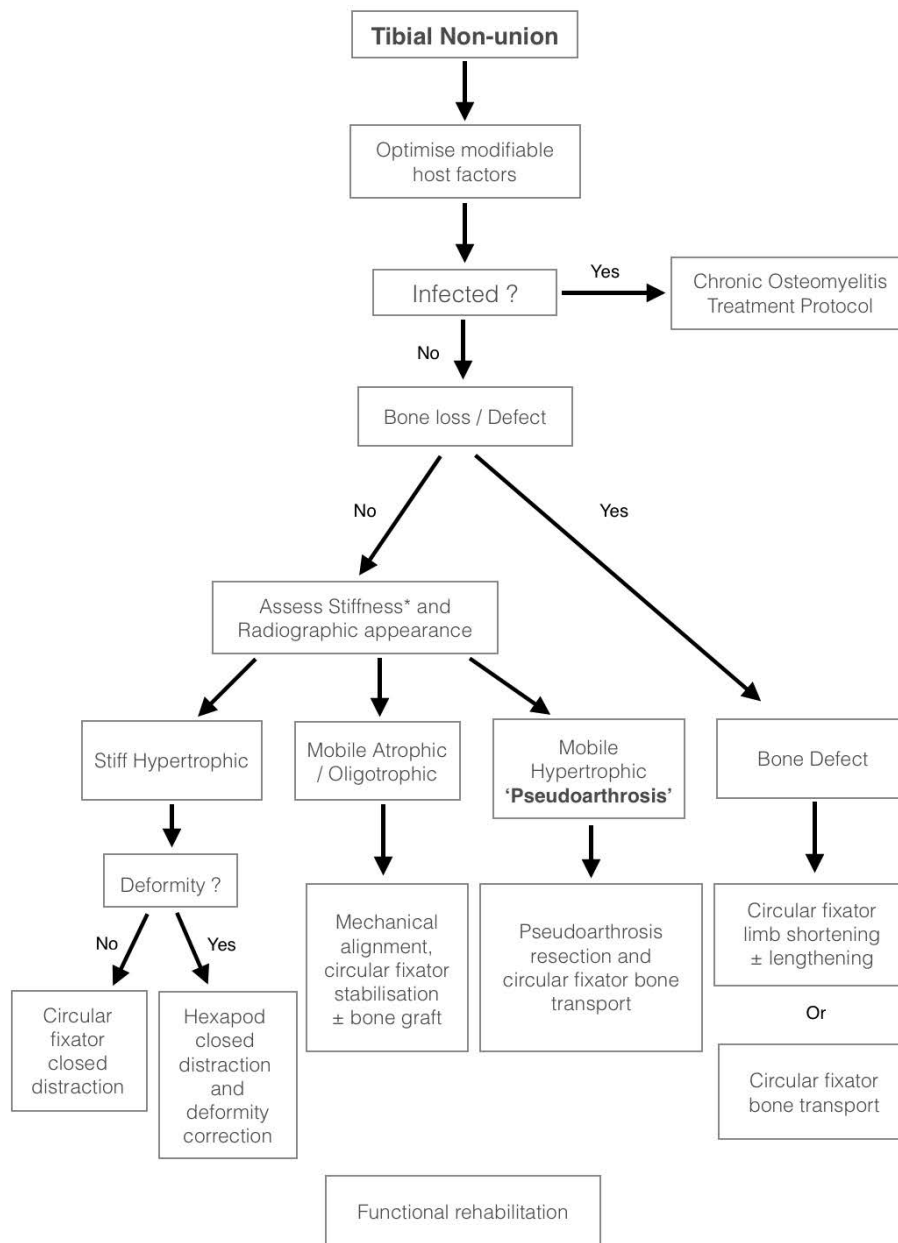


* After removal of metalware and fibula osteotomy

The proposed treatment algorithm makes specific reference to the optimisation of modifiable host factors prior to treatment and incorporates functional rehabilitation in the treatment strategy. Furthermore, infected cases are identified early and treated as separate entities according to chance osteomyelitis treatment protocols (not discussed in this thesis).

**Mechano-biology in non-union management**

Mechano-biology refers to the ability of the body's physiological processes to respond to the mechanical environment. The manipulation of these processes can be used as biological stimulation and is a novel concept in the management of tibial non-unions. To benefit from these effects however, a mechanically competent fixator must be used and applied with a good understanding of circular fixator application principles.

Functional use results in a local increase of blood flow to the limb that aids in tissue growth.[10] Mechanical stimulation directly influences bone biology on a cellular level by stimulating the proliferation and differentiation of osteoblasts.[10, 11] Mechanical force application patterns, loading magnitude and frequency also affect bone healing on a biochemical level.[11] The rates of synthesis and degradation of extracellular matrix components is affected by force application patterns. Loading magnitude affects cell size through increased amounts of intermediate filaments and glycogen particles while changes in loading frequency can alter mRNA synthesis of anabolic and catabolic genes.[11] Aggrecan gene expression is increased in response to mechanical stimulation and leads to an increased proteoglycan scaffold for type II collagen.[10] The non-linear load dependent axial stiffness of traditional fine wire circular external fixators are ideal to provide stability while allowing mechanical stimulation of the non-union site. These effects are exploited during the management of tibial non-unions allowing union even in the setting of apparent biological inactivity of atrophic non-unions. This stands in contrast with conventional thinking about non-union management where most authors would recommend bone graft to stimulate biology during atrophic non-union management. Our research was able to demonstrate the effectiveness of this strategy where 36 out of 48 (75%) atrophic and oligotrophic

tibial non-unions healed without the need for autogenous bone graft. Of the 12 patients that required autogenous bone graft, three out of 17 (23.5%) were oligotrophic non-unions and eight out of 31 (25.8%) atrophic non-unions. This meant that iliac crest autograft procedures were needed in approximately 75% of both atrophic and oligotrophic non-unions. It therefore appears that the mechano-biological effect is equally applicable to either atrophic or oligotrophic tibial non-unions.

Distraction of stiff non-unions to achieve union is a relatively new concept while the use of hexapod circular external fixators to achieve this has to our knowledge not been published.[12, 13] The mechano-biological justification for this can be explained by the interfragmentary strain theory of Perren.[14, 15] This states that a small amount of relative deformation (strain < 2%) is required to induce callus formation while high strain (> 10%) will lead to the resorption of bone and eventual non-union.[15] The amount of mobility allowed depends less on the displacement of the fragments alone than on the relation of the width of the fracture gap (L) and displacement ($\delta$L); $\delta$L/L.[14] Hexapod distraction of stiff non-unions has a dual effect on interfragmentary strain. Firstly, the tension caused by distracting an inherently stiff environment combined with stable fixation decreases interfragmentary movement ($\delta$L). Secondly, distraction increases the fracture gap (L). This results in an overall reduction of strain to within the range in which bone formation occurs. The clinical evidence for this theory appears to be supported by our results, where only one of 67 fractures failed to heal after closed distraction.

**Limitations**

The current research is largely based on two retrospective series with all the limitations associated with this study design. The 37 patients included in the prospective series represent a large study population for tibial non-union management. The patient numbers in each subgroup however, are still relatively few. The lack of a control group and the single centre where the management took place are further limitations.

The proposed treatment algorithm is specifically designed for tibial non-unions. The effectiveness of these treatment strategies at other anatomical locations remains to be investigated.

Verifying union after non-union management is difficult to judge and remains a challenge regardless of treatment strategy. The current research did not address this aspect of non-union management. We adopted a trial of union approach that clinically and radiologically evaluates union prior to fixator removal. Despite this, four failures after initial treatment still occurred due to early fixator removal.

**Future directions**

The current research could be viewed as a proof of concept for the tibial non-union treatment algorithm. Future research should be designed to include multi-centre randomised control trials that compare the proposed treatment with other published treatment methods and the application of the proposed treatment algorithm to other anatomical locations.

The difficulty with ensuring solid union prior to fixator removal remains a challenge. Non-union morphology is often in an oblique plane to standard radiographs making assessment of union difficult. The absence of pain at the non-union site is also not an indication that solid union occurred. Four patients from our series were pain free without deformity after two weeks full weight bearing on a dynamised frame. These patients all presented with progressive deformity after fixator removal and had to undergo re-treatment for persistent non-union. Research aimed at the development of a clinico-radiological scoring system to verify union would be of great benefit to surgeons managing non-unions. The incorporation of CT scans or mechanical strength testing in such a scoring system could potentially increase the accuracy of judging union in difficult cases and needs further investigation.

**Conclusion**

The proposed tibial non-union treatment algorithm appears to produce a predictable, high union rate after a single surgery without the need for expensive treatment adjuncts. One of the most important steps in deciding management is based on the mobility of the non-union site. In our experience, this is best assessed intra-operatively <u>after</u> removal of metalware and fibula osteotomy.

Furthermore, the treatment algorithm also appears effective in the re-treatment scenario where the initial treatment was unsuccessful. In these circumstances it is however, important to identify the reason for the initial treatment failure and correct this during re-treatment. In our series, failure of initial treatment was mostly the result of early fixator removal, underpinning the difficulty to confirm union with absolute confidence prior to fixator removal.

Although these results are encouraging and appear to simplify tibial non-union management, it is still recommended that these cases be referred to specialist centres that practice these advanced reconstructive techniques on a regular basis.

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# Appendices

Appendix 1: Study protocol

Appendix 2: Ethics approval

Appendix 3: Institutional approval

Appendix 4: Department of Health approval

**Appendix 1: Study Protocol**

**THE OUTCOME OF TIBIAL NON-UNIONS USING A REVISED DEFINITION, CLASSIFICATION SYSTEM AND MANAGEMENT STRATEGY**

**Degree: PhD Orthopaedics**

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## Executive summary

| Title | The outcome of tibial non-unions using a revised definition, classification system and management strategy |
|---|---|
| Aim | To design and validate a novel treatment strategy for tibial non-unions using fine wire circular external fixators, in order to assist the average orthopaedic surgeon faced with the management of diaphyseal tibial non-unions. |
| Objectives | I. Outline the pathogenesis of tibial non-union and highlight the factors associated with its development<br>II. Critically appraise current non-union classification systems and highlight their limitations<br>III. Investigate current treatment strategies for tibial non-unions<br>IV. Implement a novel classification and treatment strategy via a prospective study to address tibial non-unions with the use of fine wire circular external fixators<br>V. Investigate the incidence and severity common complications with the use of circular fixators and provide a protocol for the prevention and management of these complication |
| Methodology | Phase 1: Retrospective review and Systematic review of published literature<br>Phase 2: Prospective interventional cohort study<br>Phase 3: Retrospective review and Systemic review of published literature |
| Study centre | Grey's Hospital, Pietermaritzburg, KwaZulu-Natal, RSA |
| Study duration | Phase 1: January 2008 to December 2013<br>Phase 2: January 2014 to July 2015<br>Phase 3: January 2008 to December 2014 |
| Study population | Phase 1: Approximately 50 patients<br>Phase 2: Minimum of 30 patients<br>Phase 3: Approximately 200 patients |
| Main inclusion criteria | Patients diagnosed with tibial non-union |
| Main exclusion criteria | Infected non-unions |
| Measurements | Phase 1: Risk factors for non-union formation, treatment strategy, outcome<br>Phase 2: Classification, treatment strategy, outcome, complications<br>Phase 3: Pin track sepsis incidence and classification, treatment and outcome |

**SUMMARY**

Non-unions of long bone fractures represent a diverse group of clinical scenarios that demand specialist techniques for their optimal management. Controversies in accurately defining non-unions have contributed to delays in treatment and exacerbated the morbidity that is commonly associated with non-union development. Furthermore, treatment strategies for non-unions are not standardised, making the comparison of published outcomes and development of evidence based treatment protocols difficult.

Tibial non-unions in particular, are commonly encountered and represent the majority of cases seen in non-union and reconstruction clinics. For several reasons, the tibia is especially vulnerable to non-union development. These include anatomical factors such as a large subcutaneous border throughout its entire length and minimal muscle attachment in the distal third and injury factors such as an anatomical location predisposing the tibia to high energy injuries and open fractures.

The high cost associated with tibial non-unions impact multiple sectors of the community. Firstly, the patient suffers from an inability to work, dependency on family members and the social grant system for financial support, psychological disturbances and narcotic dependancy. In addition, non-unions harbour considerable cost for the health care system. Patients often undergo multiple surgeries with repeated hospital admissions and outpatient clinic visits.

My research aim is to standardise treatment protocols for various subtypes of tibial non-unions. A prospective interventional study will be undertaken to evaluate the outcome of tibial non-unions treated according to the new classification system and treatment protocol. Treatment will utilise fine wire circular external fixators to achieve alignment and provide stability. Along with researching the outcome of patients, the incidence and severity of the most common complications with this treatment protocol will also be investigated. Strategies to minimise these complications will be investigated and reported.

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# 1. DEFINING THE RESEARCH PROBLEM

Tibial non-unions are challenging problems to solve, demanding specialist skills and knowledge while consuming considerable time and resources. For the patient, the costs are substantial, as the development of a tibial non-union is often accompanied by prolonged morbidity, delays in return to work, psychological effects and analgesic dependence.

There are currently no practical or universally accepted definitions for fracture non-unions. This has led to difficulty in diagnosis and delays in referral and treatment of these conditions.

Research has identified multiple contributing factors to the development of non-unions, but fails to outline evidence based treatment strategies. Current classification systems are numerous and mostly descriptive in nature, focusing on a single clinical or radiological variable. Formulating a reproducible treatment strategy on these classification systems is difficult, as multiple factors would influences the treatment.

The problems with defining and classifying non-unions have made comparing research difficult. This, in turn, has led to challenges in standardising strategies for the management of these conditions. Most treatment strategies are based on anecdotal evidence and is only partly evidence based.

# 2. LITERATURE OVERVIEW AND MOTIVATION

Non-unions are encountered frequently with multiple factors being implicated in their development.[1-7] These include systemic compromise of the host, local condition of the involved limb, specific injury characteristics and iatrogenic factors relating to the management of the initial injury. [1, 8-11]

The implications of a non-union include significant long-term functional, psychological and financial consequences for the patient, and demand considerable time, resources and skill from

the treating surgeon.[1-3, 12-18] Non-unions prolong the morbidity of the initial injury and lead to extended periods of pharmacological, financial and emotional dependency.[10] Challenges and delays in diagnosis often result in significant loss of limb function with muscle atrophy, joint contractures and disuse osteopenia.[10, 13, 14, 19, 20]

The management of non-unions is challenging and requires more healthcare services than the initial injury, often necessitating treatment at specialised centres.[2, 12, 13, 21] Treatment is often protracted, expensive and may fail in up to 20% of cases.[2, 21] The treating surgeon should have good clinical judgment and a meticulous understanding of the underlying disease process,[22] as inappropriate management causes further delays and additional risk to limb integrity.[20] Adopting the appropriate treatment strategy is of vital importance and should support functional rehabilitation while simultaneously promoting union.

To limit the potential protracted course of non-union diagnosis and management, classification systems have been developed. To date, none of these has proven universally useful. Current classification systems fail to take all aspects of tibial non-union development into account, and more importantly, do not aid in the decision making as to the most appropriate treatment strategy. [12, 21] The available classifications have also failed to keep up with new developments in terms of skeletal fixation devices and our modern understanding of non-union pathophysiology. This may result in non-unions being managed on anecdotal evidence that could exacerbate existing morbidity.

The existing definitions of non-union are more controversial than most other definitions in orthopaedics and medicine and are not universally accepted.[2, 10, 13, 21, 23-25] The majority are temporal systems that use time as the sole variable to define the presence of a non-union. The 1986 United States Food and Drug Administration (US FDA) definition, for example, defines non-unions as nine months having elapsed with no progression of union in the preceding three months.[2, 26] This definition was not intended for clinical use, but was specifically devised for the testing and comparison of medical devices. It does however remain the most widely used

definition of non-union in clinical practice. Other proposed temporal definitions use the absence of radiographic progression of healing between the 3rd and 6th month after injury, six to eight months having elapsed without union, or double the expected union time as a definition for an established non-union. [2, 24, 25]

The reason that temporal systems are used to define non-unions is because non-unions are regarded at the extreme end of a time scale continuum, along with normal fracture healing and delayed union. The distinction between normal fracture healing and delayed union is based on the time needed to achieve union, where delayed union occurs after the arbitrary 'expected' time for union.

When non-union is seen in this frame of reference, one can understand why a time variable for the diagnosis of non-union is enforced on the definition. This approach is based on the assumption that all non-unions go through a delayed union phase. Although this might be true for some fractures, where the treating surgeon is unsure of the healing potential, there are definite fracture scenarios where union without surgical intervention is unlikely. Examples would include fractures with segmental bone loss, minimal bone contact, fractures with extensive circumferential soft tissue loss and operatively managed fracture with a fixed gap.

One obvious problem with these stipulative definitions is the erroneous implication that fractures will heal over similar time frames. Multiple factors affect normal fracture union and therefore a large variation in healing time can be expected.[23] Between individuals, for example, several host factors can effect the time to union. These include the age of the patient, where fractures in children can generally be expected to heal twice as fast as in adults.[5] Other host factors affecting union include smoking, malnutrition, HIV infection and pre-existing pathological bone conditions.[6, 27-30] Even in the same individual, a wide variation in fracture healing times is considered normal. Upper extremity fractures generally heal faster than lower extremity fractures. Injuries with severe bony and soft tissue damage may take longer to heal, and treatment strategy, aiming for either primary, direct bone healing or secondary bone healing with

callus formation also influence the healing time.[6, 28, 31-33] An average time to union for each anatomical site, fracture configuration and method of treatment, at any given age should therefore be researched. Tibial fractures in adults, for instance, may heal anywhere between 10 and 25 weeks, depending on the fracture severity and method of treatment.[34]

A further drawback to temporal definitions is the inevitable delay in diagnosis and treatment they cause. It is during this period where most of the morbidity associated with non-unions arises. Prolonged periods of inability to work contribute to financial hardship; combined with chronic pain and narcotic dependency, placing significant psychological stress on patients and their families.[13, 17] It is also during this period that most of the muscle atrophy, joint contracture, osteopenia and complex regional pain syndrome associated with non-unions develop.[16] Fractures treated with internal fixation also frequently lose the race between union and implant failure during this period, resulting in broken metalware or bone destruction that contribute to the surgical difficulties associated with treating non-unions. This time, waiting for a definition to be fulfilled, could be better spent achieving union and supporting functional rehabilitation.

Megas defined non-union as a cessation of all reparative processes of healing without bone union, while Marsh more specifically emphasised the cessation of both the periosteal and endosteal healing responses without bridging.[25, 35] These definitions are empiricist explanations of non-unions rather than true definitions. They are teleological and descriptive in nature, and of limited value in clinical practice.

Many authors have suggested more pragmatic, working definitions. Harwood *et al*. defined non-union as symptomatic fractures with no apparent potential to heal without intervention.[2] Brinker *et al*., and Jones *et al*. defined non-union as the point normal biological healing ceases and will not continue without intervention,[9, 36] while Wiss *et al*. suggested that the designation of a non-union be made once the surgeon believes the fracture has little or no potential to heal. [26] Although these definitions are not limited by temporal restrictions and more directed toward clinical use, they are however dependent on surgeon experience to predict fracture healing. This

drawback often contributes to delays in diagnosis and treatment, particularly when these patients are managed by junior orthopaedic surgeons without the benefit of experience to identify potential non-unions in progress.

Classifications in orthopaedics are useful in that they assist in diagnosis, guide treatment, indicate prognosis, and / or assist with research. Very few classifications can do all of these things and often only help with one aspect of management. Although debatable, for the average treating surgeon a classification that prescribes treatment strategy is often the most useful.

The Judet and Judet classification, modified by Weber and Cech in 1976, classified non-unions according to the vascularity of the bone ends.[37, 38] The distinction between avascular and hypervascular non-unions were made and a biological cause for non-union development was underlined.[38] The diagnosis was based on strontium-85 uptake at the fracture site to delineate the viability of the bone ends. Bone scintigraphy examinations are not widely used to diagnose non-unions today and are especially difficult to perform in the resource-restricted environment of the developing world. The amount of fracture callus visible on normal radiographs is therefore currently used as a surrogate marker for fracture site vascularity, giving rise to the current terms of atrophic and hypertrophic non-unions.[11, 25] Although important, the radiographic appearance of a non-union should not be the only consideration when contemplating the ideal treatment strategy.

Non-union in an avascular setting is explained by insufficient osteogenic potential to affect healing, while hypervascular non-unions are attributed to inadequate stability to allow normal fracture union.[25] Many orthopaedic surgeons use this classification as the basis of non-union management, providing stability for hypervascular (hypertrophic) non-unions, and adding biology in the form of bone-graft for avascular (atrophic) non-unions. Although widely used, not all researchers subscribe to this etiogenesis of non-union formation in the avascular setting,[39, 40] as illustrated by the research of Sun *et al*. who hypothesised the existence of temporally quiescent mesenchymal cells in avascular bone ends.[4] This could explain why certain

'avascular' non-unions may unite in the ideal biomechanical environment without the addition of bone-graft.[41] Non-union management is therefore more complex than merely designating a specific case into one of these two types.

A further drawback to the classification proposed by Weber and Cech is the fact that bone loss, limb length discrepancy, angular deformities, rigidity of the non-unions site, previous fixation used or adequacy of fixation is not considered.[38] Each Weber and Cech group therefore, has multiple potential treatment strategies, depending on these variables. The time required before the described bone end changes are seen on x-ray is also problematic and may lead to delays in diagnosis and management of patients who could benefit from earlier intervention.

The Ilizarov classification attempts to facilitate the selection of the appropriate surgery for a non-union. This system is based on the non-union morphology being stiff or lax, and whether stiff non-unions have any concomitant angular deformities.[42] This classification does not take the whole clinical scenario into account. Host factors, limb length discrepancy and bone loss are not considered and non-union with internal fixation in situ is not addressed.

The Paley classification specifically addresses tibial non-union.[43, 44] It considers bone loss, fracture site mobility, angular deformities and overall tibial length. Although this classification is an excellent advance on other existing classifications with regards to the mechanical attributes of a non-union, it again fails to address non-union biology and host optimisation.

An attempt to address some of these shortcomings was made by Wu *et al*. who developed their protocol to more clearly classify non-unions.[11] A novel addition to this classification was the incorporation of non-unions with internal fixation in situ. These non-unions were designated as either avascular or hypervascular depending on whether the fixation was stable or unstable. Another important aspect in non-union management was also raised, namely the possibility of these non-unions being potentially infected. The active exclusion of infection was emphasised. Management of each group was suggested, being both open bone-graft and intramedullary

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nailing, bone grafting alone, or bone grafting and implant exchange. The Wu classification successfully addressed the management of non-unions with failed internal fixation, but did not incorporate bone alignment or host optimisation. Automatically designating non-unions with stable fixation as avascular is also not necessarily biologically accurate as fractures fixed in distraction are not always avascular but may develop non-unions due to the healing process not being able to cross the fracture gap.

The reason that Wu *et al.* excluded infected non-unions from their protocol resulted from the evolution in the management of chronic osteomyelitis over the last 20 years. Following the modern approaches to chronic osteomyelitis management, infected non-unions are seen as Cierny and Mader IV chronic osteomyelitis and better treated according to chronic osteomyelitis treatment protocols.

The Calori Non-union Scoring System (NUSS) has recently been developed [21] and validated [12] to assist surgeons with the complex analysis of non-union surgery. It uses the 'Diamond Concept' where multiple elements are considered in non-union management, including the cellular environment, the growth factors, the bone matrix and the mechanical stability. Each individual factor is scored and then added to give a final score that guides treatment. This score is an excellent starting point to improve non-union management. It does however need to be improved in term of factors taken into account. HIV infection and genetic predisposition has been implicated in non-union development but is omitted from the NUSS system.[3, 7, 45, 46] The weight that each factor carries towards the final score is crucial in order to guide appropriate treatment and should be devised though regressional analysis. With the current NUSS score, the authors weighted each factor according to the opinions and experience of the senior authors who have tertiary referral non-union practices. Another area that needs to be addressed is the treatment strategy that the final score proposes. The present score only proposes, in broad terms, where and how these patients should be treated. The suggested treatments include 'standard treatment', 'specialised care' and 'specialised care and specialised treatment'. This provides an indication for junior orthopaedic surgeons of which patients to refer, but does not provide

specific treatment guidelines as to what 'specialised treatments' should be offered.

The different approaches and focal points of these classification systems complicate treatment strategy decisions and research into non-union management.[21] Formulating standardised treatment strategies or protocols on existing classification systems is challenging, and might not take all aspects of non-union development and management into account.

During this research, I will endeavour to redefine non-unions and suggest an additional group of non-unions not previously defined. This group will be aimed at the early identification of potential non-unions in order to allow early intervention before the traditional period of six months have elapsed. I intend to devise a treatment strategy for the different non-union subgroups, relying on circular external fixators to provide stability and address biology while simultaneously allowing functional rehabilitation of the affected limb. This treatment strategy will specifically be aimed at non-union management in the resource poor environment, where expensive biological adjuncts are not readily available

## 3. STUDY AIM AND OBJECTIVES

### 3.1 Aim
To design and validate a novel classification and treatment strategy for tibial non-unions using fine wire circular external fixators.

### 3.2 Objectives
 I. Outline the pathogenesis of non-union formation and highlight the factors associated with its development

 II. Critically appraise current non-union classification systems and highlight their limitations

 III. Investigate current treatment strategies for tibial non-unions

 IV. Undertake a retrospective review of non-unions treated at our institution

  a. Attempt to identify factors that could have predicted non-unions in these

patients and in doing so define the 'potential non-union' group of patients

    b.  Identify the type of non-union, how it was treated and the clinical outcome in order to provide a treatment algorithm / flow diagram for the management of non-unions

V.  Implement a novel classification and treatment strategy, identified during the respective phase, via a prospective study to address tibial non-unions with the use of fine wire circular external fixators

VI.  Investigate the incidence and severity common complications with the use of circular fixators and provide a protocol for the prevention and management of these complication

# 4. METHODOLOGY

## 4.1. Phase 1

### 4.1.1 Study design

A retrospective review of patients with tibial non-unions treated with circular external fixators. An additional systematic literature review of current definitions, classifications and treatment strategies will be undertaken

### 4.1.2 Study setting

This research will involve patients assessed and managed at the Tumour, Sepsis and Reconstruction Unit at Greys Hospital in Pietermaritzburg, KwaZulu-Natal, South Africa. The unit is uniquely positioned as the only dedicated tertiary unit for the management of musculoskeletal oncology, infections and limb reconstruction in the province, and receives non-union referrals from all over area 2 and beyond.

### 4.1.3 Patient selection

4.1.3.1 Study population

Patients with tibial non-unions treated at the Tumour, Sepsis and Reconstruction Unit between

January 2008 and December 2013.

## 4.1.3.2 <u>Study period</u>

To commence once BREC ethical approval is obtained. Proposed period: March 2014 to December 2014.

## 4.1.3.3 <u>Inclusion criteria</u>

    a.   Male and female patients with non-unions of the tibial diaphysis

## 4.1.3.4 <u>Exclusion criteria</u>

    a.   Congenital pseudo-arthrosis of the tibia

    b.   Infected non-unions

    c.   Non-unions following pathological fractures

    d.   Non-unions of the proximal or distal tibial metaphysis

    e.   Patients declining surgical treatment

    f.   Patients declining circular external fixation

## 4.1.4 Sample size

All patients treated for tibial non-unions during the period of January 2008 and December 2013 will be included. An approximate study population of 40 cases is expected.

## 4.1.5 Methods

### 4.1.5.1 <u>Definitions</u>

*Union:*

The physiological process that leads to the successful bridging of a fracture gap, to re-establish bony continuity in order to withstand physiological load without deformation.

*Delayed union:*

When union takes longer than expected for the specific injury, anatomical site and treatment modality

*Non-union:*

When the normal healing process ceases without the establishment of bony continuity to withstand physiological load without deformation.

*Classification of non-union according to bone end vascularity: (As described by Weber and Cech, Jupiter and Jupiter)*

These definitions rely on the outcome of bone scintigraphy examinations of non-unions.

*Avascular non-union*

No radioactive isotope uptake at the fracture site indicating no biological activity.

*Hypervascular non-union*

Increased radioactive isotope uptake at the fracture site despite the fact that the fracture has not healed.

Owing to the fact that bone scintigraphy is not a standard investigation for the evaluation of non-unions, most authors use the amount of fracture callus on plain radiographs as a surrogate marker of bone end vascularity, and this has given rise to new names used for the above non-unions:

*Atrophic non-union*

Non-unions where there is no callus formation at the fracture site.

*Hypertrophic non-union*

Fracture non-union with exuberant callus formation at the bone ends.

A third group of non-unions is added following the radiographic appearance:

*Oligotrophic non-union*

Fracture non-union where there is minimal callus formation, but the bone ends does not appear atrophic.

*Classification on non-union according fracture site mobility: (As described by Ilizarov)*

*Stiff non-union*

Non-union where there is less than 7° of motion possible at the non-union site.

*Mobile non-union*

Non-union where there is more than 7° of motion possible at the non-union site.

4.1.5.2 <u>Measurements</u>

- Patient demographics
    - o   Age
    - o   Gender
    - o   Co-morbidities

- Known risk factors for non-union formation
    - o   Initial injury characteristics – high energy vs. low energy, open vs. closed fracture
    - o   Initial treatment
    - o   Diabetes mellitus and HbA1C if indicated
    - o   Smoking status
    - o   Nutritional status
    - o   HIV status, $CD_4$ count, HAART treatment

- Non-union classification
    - o Weber and Cech: Atrophic, Oligotrophic, Hypertrophic
    - o Ilizarov: Stiff, Mobile

- Treatment variables
    - o Treatment strategy
    - o Length of hospital stay
    - o Outcome
    - o Number of surgeries to achieve union
    - o Time in external fixator
    - o Complications of management

4.1.5.3 Endpoints

4.1.5.3.1 Primary endpoints

The primary endpoint of management will be bony union (Bony continuity)

Union will be deemed to have occurred once:

a. Radiographic evidence of union (Trabecular continuity across union site) is accompanied by

b. Clinical evidence of union (No pain with manual stressing of the fracture site after removal of external support) and

c. No bony deformity occurring on follow-up after removal of the external fixator.

4.1.5.3.2 Secondary endpoints

Failure to achieve union with either

a. Amputation following failed management

b. Acceptance of a persistent non-union by the patient

**4.1.6 Statistical analysis**

Data will be captured in Microsoft Excel and analysed in SSPS version 15.0 (SSPS inc.,

Chicago, Ill, USA). Descriptive statistics such as frequency counts and percentages will be used to summarise categorical variables, while mean and standard deviation will be used for quantitative variables.

## 4.2. Phase 2

### 4.2.1 Study design

A prospective interventional cohort study of patients classified according to the proposed classification system developed in phase 1 and managed according to the newly proposed treatment strategy. All consecutive patients will be managed according to the proposed classification and treatment strategy and therefore no randomisation or blinding will be employed.

### 4.2.2 Study setting

This research will involve patients assessed and managed at the Tumour, Sepsis and Reconstruction Unit at Greys Hospital in Pietermaritzburg, KwaZulu-Natal, South Africa.

### 4.2.3 Patient selection

4.2.3.1 Study population

All consecutive patients with tibial non-unions presenting to the Tumour, Sepsis and Reconstruction Unit will be considered for inclusion.

4.2.3.2 Study period

To commence once BREC ethical approval is obtained. Proposed period: March 2014 to September 2015.

4.2.3.3 Inclusion criteria

    a.   Male and female patients with non-unions of the tibial diaphysis

4.2.3.4 Exclusion criteria

a. Congenital pseudo-arthrosis of the tibia

b. Infected non-unions

c. Non-unions following pathological fractures

d. Non-unions of the proximal or distal tibial metaphysis

e. Patients declining surgical treatment

f. Patients declining circular external fixation

**4.2.4 Sample size**

According to a meta-analysis done by Bhandari *et al.* in 2000 the incidence of lower limb long bone non-unions range from 3% – 48%. Two recent articles published in 2013 by Fong *et al.* and Mills *et al.* found similar results in the lower end of the spectrum with non-union incidences of 4% and 2% respectively.

An incidence of 3% was used to calculate a sample size of 30 cases.

**4.2.5 Methods**

4.2.5.1 <u>Definitions</u>

The same definitions used in phase 1 will also apply for phase 2.

4.2.5.2 <u>Measurements</u>

- Patient demographics
    - o Age
    - o Gender
    - o Co-morbidities

- Known risk factors for non-union formation
    - o Initial injury characteristics – high energy vs. low energy, open vs. closed fracture
    - o Initial treatment

- o Diabetes mellitus and HbA1C if indicated
- o Smoking status
- o Nutritional status
- o HIV status, $CD_4$ count, HAART treatment

- Non-union classification
  - o Potential or Established non-union
  - o Weber and Cech: Atrophic, Oligotrophic, Hypertrophic
  - o Ilizarov: Stiff, Mobile

- Treatment variables
  - o Treatment strategy
  - o Circular external fixator used
  - o Length of hospital stay
  - o Outcome
  - o Number of surgeries to achieve union
  - o Time in external fixator
  - o Complications of management

4.2.5.3 Endpoints

4.2.5.3.1 Primary endpoints

The primary endpoint of management will be bony union (Bony continuity)

Union will be deemed to have occurred once:

a. Radiographic evidence of union (Trabecular continuity across union site) is accompanied by

b. Clinical evidence of union (No pain with manual stressing of the fracture site after removal of external support) and

c. No bony deformity occurring on follow-up after removal of the external fixator.

4.2.5.3.2 Secondary endpoints

Failure to achieve union with either

    a.   Amputation following failed management

    b.   Acceptance of a persistent non-union by the patient

## 4.2.6 Statistical analysis

Data will be captured in Microsoft Excel and analysed in SSPS version 15.0 (SSPS inc., Chicago, Ill, USA). Descriptive statistics such as frequency counts and percentages will be used to summarise categorical variables, while mean and standard deviation will be used for quantitative variables.

## 4.3. Phase 3

### 4.3.1 Study design

A retrospective review of patients treated with fine circular external fixators. An additional systematic literature review of published pin site infection incidences and current treatment strategies will be undertaken.

### 4.3.2 Study setting

This research will involve patients assessed and managed at the Tumour, Sepsis and Reconstruction Unit at Greys Hospital in Pietermaritzburg, KwaZulu-Natal, South Africa.

### 4.3.3 Patient selection

4.3.3.1 Study population

Patients treated with fine wire circular external fixators at the Tumour, Sepsis and Reconstruction Unit between January 2008 and December 2014.

4.3.3.2 Study period

To commence once BREC ethical approval is obtained. Proposed period: March 2014 to December 2014.

4.3.3.3 <u>Inclusion criteria</u>

    a.   All patients who were treated with a circular fine wire external fixator

    b.   Treatment must have been concluded and the fine wire fixator must have been removed


4.3.3.4 <u>Exclusion criteria</u>

    a.   Any patient that had insufficient data collected for analysis


**4.3.4 Sample size**

All patients treated with fine wire circular external fixators during the period of January 2008 and December 2014 will be included. An approximate study population of 200 cases is expected.


**4.3.5 Methods**

4.3.5.1 <u>Definitions</u>


*Pin track infection:*

Pin track infection is defined as inflammation and suppuration around an external fixator wire or pin. The severity may vary from an infection as benign as only redness and irritation around a pin, which is easily treated with oral antibiotics and local care, to a severe infection that extends to the bone and causing osteomyelitis.


*Classification of pin track infection: (As described by Checketts and Otterburn)*

**Checketts-Otterburn Classification**

| Grade | Characteristics | Treatment |
|---|---|---|
| | **Minor Infection** | |
| 1 | Slight redness, little discharge. | Improved pin site care |
| 2 | Redness of the skin, discharge, pain and tenderness in the soft tissue | Improved pin site care, oral antibiotics |

| 3 | Grade 2 but no improvement with oral antibiotics | Affected pin or pins resited and external fixation can be continued |
| | **Major Infection** | |
| 4 | Severe soft tissue infection involving several pins, sometimes with associated loosening of the pin | External fixation must be abandoned |
| 5 | Grade 4 but radiographic changes | External fixation must be abandoned |
| 6 | Infection after fixator removal. Pin track heals initially, but will subsequently break down and discharge in intervals. Radiographs show new bone formation and sometimes sequestra | Curettage of the pin tract |

4.3.5.2 Measurements

- Patient demographics

  - o Age

  - o Gender

  - o Co-morbidities


- Known risk factors for in site infection

  - o Diabetes mellitus and HbA1C if indicated

  - o Smoking status

  - o Nutritional status

  - o HIV status, $CD_4$ count, HAART treatment


- Treatment variables

  - o Type of external fixator used

  - o Time in external fixator


- Pin site infection

  - o Checketts and Otterburn grade

  - o Treatment strategy

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   o  Outcome

### 4.3.5.3 <u>Endpoints</u>

4.3.5.3.1 Primary endpoints

The primary endpoint will be any grade of pin site infection

4.3.5.3.2 Secondary endpoints

The secondary endpoint will be treatment and outcome of pin site infections that occurred

## 4.3.6 Statistical analysis

Data will be captured in Microsoft Excel and analysed in SSPS version 15.0 (SSPS inc., Chicago, Ill, USA). Descriptive statistics such as frequency counts and percentages will be used to summarise categorical variables, while mean and standard deviation will be used for quantitative variables.

## 5. ETHICAL CONSIDERATIONS

## 5.1 Research ethics

All research will be conducted according to the ethical principles for medical research on human subjects as defined by the World Medical Association Declaration of Helsinki. (Amended at the WMA General Assembly, Seoul, October 2008)

Ethical approval for conducting this research will be obtained from the Biomedical Ethics Review Board (BREC) of UKZN.

No financial benefit will be available for anyone, either as a surgeon who performed these surgeries, a physician collecting the data, or as a patient who was treated.

## 5.2 Confidentiality

All participant information will be held strictly confidential. All data will be captured on a redacted database with unique participant identifiers and no names or file numbers will be stored in the database.

**5.3 Data capturing sheet**

The data capturing sheets (See appendix 10.1 and 10.2) will serve as the primary collection instrument of the study. Unique participant identifiers will be used for each record and no identifiable participant details will be captured on the data capturing sheets.

**5.4 Database management**

All collected data will be captured on a redacted database against unique patient identifiers that will not allow identification of individual participants. The database source file will be stored on a password-protected computer and the source file will be separately password protected. All study data will be destroyed five (5) years following completion of the research project.

## 6. BUDGET (including Funding obtained)

**6.1 Funding**

No specific funding will be sought during this research project. Any ongoing expenditure, such as printing of Data collection sheets will be funded from the UKZN Cost Centre funds of Dr Nando Ferreira.

No benefits of any form have been derived or will be derived from any commercial party related directly or indirectly to this research project.

No extra cost beyond the routine cost of treatment will be incurred by the Department of Health as a result of this research.

**6.2 Subject stipends or payments**

No stipends or payments will be offered for participation in this study.

## 7. TIME LINES AND PROJECT MANAGEMENT
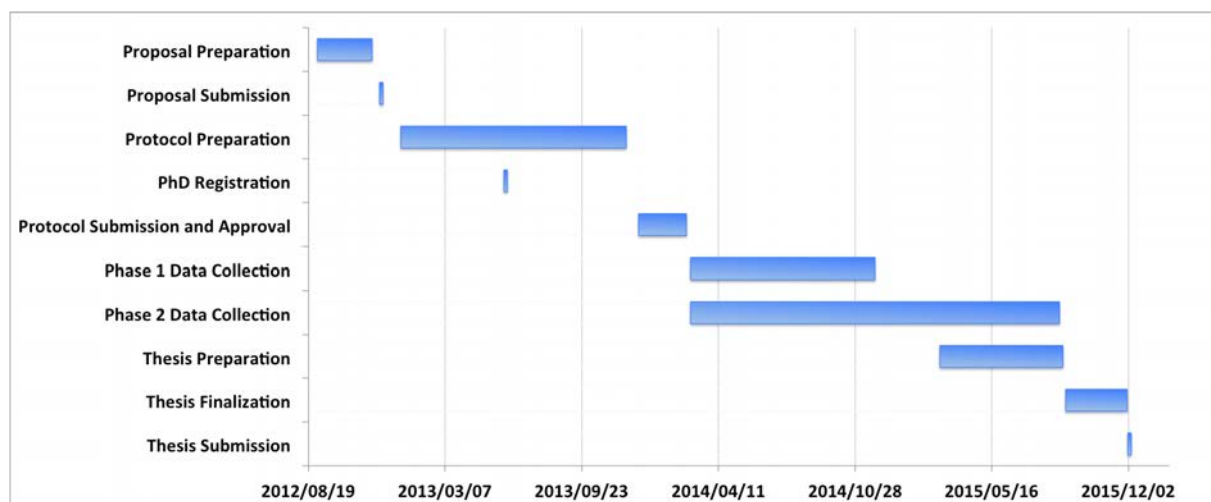


## 8. CONTRIBUTORS AND AUTHORSHIP

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| **C Aldous** | School of Clinical Medicine, UKZN | Supervisor | Author |

The results of this research project will be presented as part of the PhD (Orthopaedics) degree of Dr. Nando Ferreira at the University of KwaZulu-Natal. Results from this study will also be presented as conference presentations and submitted for publication in a peer-reviewed journal.

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## Appendix 2: Ethics Approval

**UNIVERSITY OF** ™
**KWAZULU-NATAL**
**INYUVESI**
**YAKWAZULU-NATALI**

27 May 2014

Dr Nando Ferreira
42 Oakhill Estate
31 Warwick Road
Ferncliffe, Pietermaritzburg
3201
drferreiran@gmail.com

**PROTOCOL: A systematic approach to the management of tibial non-unions. REF: BE086/14**

### EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on **25** February 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 22 May 2014 to queries raised on 30 April 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 27 May 2014.

This approval is valid for one year from **27 May 2014**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **08 July 2014**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

# Appendix 3: Institutional Approval

**health**

Department:
Health
**PROVINCE OF KWAZULU-NATAL**

**GREYS HOSPITAL**
SENIOR MANAGER: MEDICAL AND ALLIED HEALTH PROFESSIONALS
Private Bag X 9001, Pietermaritzburg, 3200
Town Bush Road, Chase Valley, Pietermaritzburg, 3201
Tel.:033 – 897 3317 Fax.: 033 - 8973398
www.kznhealth.gov.za

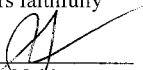| To: | Dr. Nando Ferreira |
| --- | --- |
| | Department of Orthopaedics |
| | Greys Hospital |
| From: | Dr. L. Naidoo |
| | Senior Manager – Medical Services and Acting CEO (17-20 December 2013) |
| | Greys Hospital |
| Date: | 19 December 2013 |
| Re: | Request for permission to conduct research at Grey's Hospital: A Systematic Approach to the Management of Tibial Non-unions |

Dear Dr. Ferreira

I have considered your request for permission to conduct research at Greys Hospital. However, we require ethics (BREC) approval first in order to approve your request. I hereby provisionally grant you permission, conditional to your submission of your BREC approval for this research.

Furthermore, please take note of the following:
- Permissions from Health Research Committee of the Department of Health and the District Manager would also be required;
- Confidentiality of hospital information, including patient medical and contact information, must be kept at all times;
- Informed consent must be obtained from all participants in your study.
- Policies, guidelines and protocols of the Department of Health and Grey's Hospital must be adhered to at all times;
- Professional attitude and behaviour whilst on the hospital premises must be exhibited; and
- You are required to submit to this office a summary of study findings upon completion of your research.

Yours faithfully

Dr L. Naidoo
Senior Manager: Medical Services
Greys Hospital

uMnyango Wezempilo . Departement van Gesondheid

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## Appendix 4: Department of Health Approval

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference    : HRKM 114/14
Enquiries    : Mr X Xaba
Tel    : 033 – 395 2805

Dear Dr N. Ferreira

### Subject: Approval of a Research Proposal

1. The research proposal titled **'A systematic approach to the management of tibial non-unions''** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Greys' Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

**Dr E Lutge**
Chairperson, Health Research Committee
Date: 21/05/14 .

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