# An Integrated Approach to Adult Chronic Osteomyelitis

By

**Leonard Charles Marais**

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Department of Orthopaedics

School of Clinical Medicine

College of Health Sciences

University of KwaZulu-Natal

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

Dr C Aldous

Signed: _____ Date: 19/11/2014

Prof TLB Le Roux

Signed: _____ Date: 19/11/2014

# Dedication

This thesis is dedicated to Nadia and Luc, who had to sacrifice far more than I did.

And to my parents, for their inspiration and support.

# Declaration

I, Leonard Charles Marais declare that:

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# Abstract

No evidence-based guidelines exist on the treatment of chronic osteomyelitis of long bones in adults. Management is still largely based on expert opinion and consensus guidelines are not available. Choosing between a palliative and curative treatment strategy requires consideration of several factors. Principle amongst these is the host's physiological status, which determines the patient's ability to cope with the rigours of limb salvage surgery. This fact was recognized by Cierny and Mader, when they developed their popular staging system. The authors suggested palliative treatment in C-hosts, who will not be able to cope with the metabolic demands of an aggressive treatment plan. The problem however, is that the C-host was never accurately defined. Cierny and Mader predicted in their original paper that, as a result of the inadequate definition, the selection of surgical candidates would vary from institution to institution until there was standardization of this concept.

The limitations of existing classification systems prompted the development of a novel approach to chronic osteomyelitis for use in South Africa. This involved the establishment of an objective definition of a C-host, as well the development of a novel classification system and an algorithmic guideline to treatment strategy selection. By integrating the physiological status of the host (based on pragmatic predefined criteria) with the selection of the appropriate curative, palliative or alternative treatment strategy we were able to achieve favourable short term outcomes in both low and high risk cases and in addition reduce the rate of amputation. Furthermore, we were able to report novel data on the outcome of

palliative treatment, as well as the outcome of treatment of chronic osteomyelitis in HIV infected patients.

While the preliminary results appear promising, long term follow-up will be required in order to determine the rate of recurrence of infection. The proposed approach was designed specifically with the South African clinical environment in mind and additional development of the algorithm may be required in order to render it useful in other clinical settings. The implementation of a refined host stratification, which incorporates objective criteria for C-host classification will, however, enable the comparison of results from studies employing different therapeutic interventions in the future. In addition, selection of patient-matched treatment options closes the gap in successful outcomes between healthy and compromised patients. The major benefit of the proposed approach is therefore the fact that the integrated approach places appropriate emphasis on the importance of host factor modification prior to surgical intervention.

# Table of Contents

## List of Related Papers

**Chapter 2:** The pathophysiology of chronic osteomyelitis. Marais LC, Ferreira N, Aldous C, Le Roux TLB. *S Afr J Orthop* 2013;**12**(4):14-18.

**Chapter 3**: The classification of chronic osteomyelitis. Marais LC, Ferreira N, Aldous C, Le Roux TLB. *S Afr J Orthop* 2014;**13**(1):22-28.

**Chapter 4:** The management of chronic osteomyelitis: Part I - Diagnostic work-up and surgical principles. Marais LC, Ferreira N, Aldous C, Le Roux TLB. *S Afr J Orthop* 2014;**13**(2):42-48.

**Chapter 5:** The management of chronic osteomyelitis: Part II - Principles of post-infective reconstruction and antibiotic therapy. Marais LC, Ferreira N, Aldous C, Le Roux TLB. *S Afr J Orthop* 2014; **13**(3):32-39.

**Chapter 6:** Bone transport through an induced membrane in the management of tibial bone defects resulting from chronic osteomyelitis. Marais LC, Ferreira N. *Strat Trauma Limb Recon.* 2015*;* DOI 10.1007/s11751-015-0221-7.

**Chapter 7:** A modified staging system for chronic osteomyelitis. Marais LC, Ferreira N, Aldous C, Sartorius B, Le Roux TLB. *Journal of Orthopaedics*. 2015; http://dx.doi.org/10.1016/j.jor.2015.05.017.

**Chapter 8:** The outcome of treatment of chronic osteomyelitis following an integrated approach. Marais LC, Ferreira N, Aldous C, Le Roux TLB. (Under review).

# List of Abbreviations

| | | |
|---|---|---|
| ADL | - | Activities of daily living |
| AMA | - | American Medical Association |
| CD4 | - | CD4+ T helper cell |
| CDC | - | Centre for Disease Control |
| CI | - | Confidence interval |
| CRP | - | C-reactive protein |
| CSAT | - | Chronic suppressive antibiotic therapy |
| IDSA | - | Infectious Disease Society of America |
| HIV | - | Human immunodeficiency virus |
| Il | - | Interleukin |
| KZN | - | KwaZulu-Natal |
| MCS | - | Microscopy, culture and sensitivity |
| PCT | - | Procalcitonin |
| PMMA | - | Polymethylmethacrylate |
| PMN | - | Polymorphonuclear leukocytes |
| RANKL | - | Receptor activator of nuclear factor kappa-B ligand |
| SD | - | Standard deviation |
| SICCS | - | Seven item comprehensive classification system |
| TNF | - | Tumour necrosis factor |
| USA | - | United States of America |
| UTMB | - | University of Texas Medical Branch |
| WBC | - | White blood cell count |
| WHO | - | World Health Organization |

# Study development and rationale

## Conceptualization

In 2009 the author assumed duties at the Tumour, Sepsis and Reconstruction Unit at Grey's Hospital in Pietermaritzburg, KwaZulu-Natal, South Africa. Over a period of approximately two years several shortcomings were identified in the existing chronic osteomyelitis classification systems. In addition, it was recognized that these classifications may require adaptation in order to remain relevant in the developing world. It appeared that in a relatively under-developed region one was dealing with a higher proportion of C-hosts than authors in the USA, for example. The most popular classification system at the time (published by Cierny and Mader) recommended conservative management in C-hosts and curative treatment in A and B-hosts.[1]

When taking into account that an A-host was seen as a patient without any risk factors and that B-hosts were all patients who were neither an A or C-host, it stood to reason that the definition of a C-host had important implications in terms of treatment strategy selection. This created the need to seek clarity regarding the definition of a C-host, but existing definitions were found to be lacking and were not sufficiently concise. The lack of standardization of concepts and definitions rendered the teaching the principles of management to orthopaedic trainees particularly problematic. In addition, the lack of conformity prohibited the direct comparison of results from different studies on interventions in chronic osteomyelitis.

Our resource poor clinical environment also created other unique challenges. Owing to a lack of theatre time some patients were placed on interim chronic suppressive antibiotic therapy, in

an attempt to control symptoms while they were awaiting surgery. Many patients responded well and preferred not to undergo surgery following the initial therapy. It therefore appeared that both curative and palliative treatment strategies could deliver acceptable results, but there were still no clear guidelines in the literature regarding selection of the appropriate strategy. Apart from the lack of theatre time, plastic surgery was not readily available. This further increased the need for accurate host stratification. Without the facility for complex soft tissue reconstruction it was important to avoid aggressive surgery in cases where soft tissue cover was expected to be problematic.

In addition to the problems with host stratification, the existing classification systems did not provide for new treatment strategies. The induced membrane technique for example, popularized by Masquelet, was not included as a treatment option in the Cierny and Mader system. These shortcomings combined to identify the need for a novel approach to chronic osteomyelitis. The ideal approach would integrate patient classification with treatment strategy selection and also allow for the incorporation of contemporary concepts and management options.

**Study Setting**

This research was carried out at Grey's Hospital, which functions as a tertiary referral centre for all hospitals within the western inland region of the province of KwaZulu-Natal, South Africa. This 525 bed hospital serves a population of approximately 4 million, in a predominantly rural setting. Socio-economically underdeveloped regions, like South Africa, carry a particularly heavy burden in terms of the prevalence of osteomyelitis.[2] This may be attributed to, amongst other factors, the high incidence of osteomyelitis in childhood,

immunosuppression, malnutrition and the high incidence of trauma. The high prevalence of trauma in South Africa is clearly illustrated by the fact that interpersonal violence and road traffic accidents were the 2nd and 4th most common causes of death in South Africa in the year 2000.[3] The road traffic accident fatality rate in South Africa (39.7 per 100 000 population) is higher than in any other WHO region and almost double the world average.[4] These statistics imply a correspondingly high morbidity related to road traffic accidents, which may consequently contribute to an increased incidence in post-traumatic osteomyelitis.

In addition to a high trauma load, South Africa is faced with a critical shortage of orthopaedic surgeons. In developed countries like the USA and Canada, staffing figures range from 4.8 to 5.6 full-time equivalent orthopaedic surgeons per 100 000 population.[5,6] In contrast, during 2011 there were a mere 0.37 full-time orthopaedic surgeons per 100 000 population working in the public sector in the interior of the KwaZulu-Natal province. This shortage in qualified orthopaedic surgeons resulted in many patients with skeletal trauma, and more specifically compound fractures, not receiving timeous and/or appropriate treatment.

The final unique characteristic of the setting in which these studies was performed, was the high prevalence of HIV infection in the area. In the province of KwaZulu-Natal an estimated 21.5% of adults between the ages of 15 and 49 years have been infected with HIV.[7] The high prevalence of HIV may possibly have contributed to an increased incidence of post-traumatic chronic osteomyelitis. The main problem was however, that there were no specific guidelines available with regard to the management of chronic osteomyelitis in HIV patients.

**Study Aims**

The aim of this research project was to develop a novel approach to adult chronic osteomyelitis that, in a resource poor clinical setting, could guide selection of the appropriate treatment strategy. The resulting classification system and treatment algorithm would ideally integrate all relevant risk factors, a refined host stratification system and rationalized characterization of the pathoanatomy, as well as the realistic goal of treatment.

**Primary objectives**

- To review the pathophysiology of chronic osteomyelitis with specific reference to the immunological basis of disease.
- To compare existing classification systems and identify possible shortcomings.
- To review the contemporary treatment of chronic osteomyelitis and introduce certain additional concepts that may be relevant to the development of a novel approach.
- To establish the importance of patient selection in achieving success in curative treatment strategies.
- To evaluate the outcome of a novel approach to adult chronic osteomyelitis in South Africa. In order to achieve this objective the following was required:
    - Proposal of a new host stratification model, relevant to the South African clinical setting, which included discrete criteria that would enable the user to objectively stratify the patient's host status.
    - To propose a revised version of the pathoanatomical section of the classification of chronic osteomyelitis in order to rationalize treatment strategy selection.
    - To develop guidelines according to which the classification of patients and treatment strategy selection should be integrated. The objective was to establish

an algorithm which could guide the treating surgeon to the appropriate treatment strategy in accordance with the classification of the patient.

- To determine, both retro-and prospectively, the efficacy of the proposed integrated approach in achieving control of infection in adult chronic osteomyelitis.

**Secondary objectives**

- To determine the outcome of palliative treatment of adult chronic osteomyelitis.
- To determine the outcome of palliative treatment in patients with chronic haematogenous osteomyelitis.
- To determine the outcome of treatment in HIV positive patients.

**Structure of Thesis**

This document is a thesis by publication and comprises five parts. Each part consists of chapters containing the relevant publications. These publications have either been published, are currently under review or will be submitted for publication.

- **Introduction:** The introduction includes a single chapter, which provides the background to the research and identifies certain factors that represented obstacles to the development of an integrated approach.

- **Part One:** Here, the pathophysiology and classification of chronic osteomyelitis is reviewed. Chapter two evaluates the pathophysiology, with specific emphasis on the osteoimmunology relevant to chronic osteomyelitis. The immunological basis of the

disease not only has implications for the definition of the clinical entity, but also emphasizes the importance of the host's immunological competency in the treatment of the disease. Chapter three assesses existing classification systems, illustrating their limitations and identifying areas requiring improvement.

- **Part Two:** Two chapters are in included that deal with the management of chronic osteomyelitis. Chapter four and five review all treatment modalities available and attempt to discern areas were existing treatment guidelines fail to consider all relevant concepts or treatment options.

- **Part Three:** Here we illustrate the importance of accurate host stratification in treatment strategy selection. This part focuses on the implementation of a curative treatment strategy involving wide resection and bone transport through an induced membrane. Patient selection is identified as an important factor in ensuring a successful outcome of this complex procedure.

- **Part Four:** This part consists of a retrospective evaluation of the efficacy of the proposed integrated approach. The paper which makes up this chapter is the first to report the outcome of palliative treatment strategies in conjunction with curative treatment outcomes. It allows for the development of a more comprehensive picture of the validity of the proposed approach, in contrast to previous reports which focused on the outcome of curative strategies. Novel information is garnered regarding the management of chronic osteomyelitis in HIV positive patients and the outcome of palliative treatment in patients with chronic haematogenous osteomyelitis.

- **Part Five:** The final part of the thesis consists of a prospective assessment of the outcome of treatment according to the proposed integrated approach.

- **Conclusion:** This chapter provides a summary of the entire thesis, highlights the limitations of the studies presented and identifies areas for possible future research.

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# Chapter 1: Introduction

## 1.1. Background

Despite the numerous advances in antibiotic therapy and operative intervention, chronic osteomyelitis remains challenging to treat.[1] In fact, absolute cure from the disease is considered to be an unrealistic goal and most authors prefer to use terms like "arrest" or "remission" rather than "cure" or eradication" .[2] When analyzed at its most elementary level, the management of adult chronic osteomyelitis is based on a choice between either a palliative or curative approach.[3] Curative treatment, aimed at remission of disease, typically involves a combination of complex surgical procedures and tailored adjuvant antibiotic therapy.[4] Palliative treatment, on the other hand, is less invasive and typically involves to the use of chronic suppressive antibiotic therapy.[5] Although the decision to operate or alternatively to select a non-operative treatment strategy is a dilemma frequently faced by orthopeadic surgeons, it is particularly problematic in chronic osteomyelitis. Selecting the incorrect strategy may have devastating consequences. Embarking on a curative limb salvage protocol which involves extensive debridement resulting in a large bone defect, for example, may result in an unwanted amputation if the patient is unable to withstand the rigours of the reconstructive process.

No evidence-based guidelines have previously been published in terms of the selection of the appropriate treatment strategy in patients with chronic osteomyelitis.[3] The treatment of osteomyelitis remains largely based on expert opinion and no consensus guidelines are available.[6] Choosing between a palliative and curative treatment strategy requires consideration of several factors, principle amongst which is the host's physiological status.

This was recognized by Cierny and Mader when they included the physiological status of the host in their staging system which was aimed at guiding treatment selection.[7] The authors suggested palliative strategies involving observation, antibiotic therapy, orthosis and/or compressive garments in C-hosts.[7] The problem however, is that the C-host was never accurately defined. Cierny and Mader predicted in their original paper that, as a result of the inadequate definition, the selection of surgical candidates would vary from institution to institution until there was standardization of this concept.[7]

With a lack of clear guidelines the selection of the appropriate treatment strategy remains difficult, especially amongst training doctors who are inexperienced in the management of chronic osteomyelitis. This is a result of the fact that treatment selection, according to the Cierny and Mader system, is based on the physician's ability to predict the patient's capacity to cope with the metabolic demands of an aggressive treatment plan. In addition, the lack of standardization has prohibited the comparison of results of studies investigating different therapeutic interventions. Many studies focussing on antibiotic therapy included patients with and without surgical implants, as well as cases which did and did not have surgical debridement. This lack of uniformity makes comparison of results difficult and illustrates the need for the establishment of standardized nomenclature and definitions.

### 1.2. Obstacles to the development of an integrated approach

Taking the above-mentioned limitations into account, it would be ideal to establish a standardized, unified approach which integrates the realistic goals of treatment, all relevant risk factors (psychosocial, physiological and local), the anatomic nature of the disease, and

allows selection of the appropriate treatment strategy through a rational algorithmic process. Such an integrated approach could serve as a useful treatment guideline for surgeons less experienced in managing chronic osteomyelitis. In addition, standardization of host staging and treatment selection would enable the comparison of results from interventional studies. There were however, several obstacles to the development of such an integrated approach:

### 1.2.1. The definition of chronic osteomyelitis in adults

There is currently no uniform clinical definition (in the English language) for the diagnosis of chronic osteomyelitis and most authors are left to define their own diagnostic criteria.[8] In order to propose a universally applicable definition, the pathogenesis as well as the bacteriological and immunological basis of the disease has to be considered.

Chronic osteomyelitis is characterized by the progressive inflammatory destruction of bone, followed by the apposition of new bone as part of the reparative process. Traditionally, chronic osteomyelitis was therefore defined by the presence of sequestrum and involucrum. Although this definition remains applicable in terms of chronic haematogenous osteomyelitis, it fails to address certain clinical scenarios found in contiguous post-operative, post-traumatic and implant-related infections. As a result, Cierny proposed a definition more appropriate in the setting of contemporary orthopaedics.[9] He defined chronic osteomyelitis as a biofilm-based infection where the majority of pathogens are sessile-based and are resiliently attached to necrotic bone, surgical implants or foreign material. This definition is not restricted to the cause, the presence of surgical implants, nor to the anatomic nature or duration of the disease, but rather defines it by the presence of a universally applicable pathogenesis. The concept of chronic osteomyelitis is thus currently understood to include a wide variety of clinical

scenarios, including haematogenous, contiguous, post-traumatic and post-operative infections. Certain aspects of this definition can however be explored further.

Taking the pathogenesis of arthroplasty-related periprosthetic infections into account, it could (when applying Cierny's definition) be classified as a type of chronic osteomyelitis. In this thesis, periprosthetic infections have been excluded from the discussion, based on the current trend of classifying and treating arthroplasty-related infections as a separate entity.[10]

Another question which arises from the definition proposed by Cierny relates to the entity known as minimal necrosis osteomyelitis.[7] Although Cierny and Mader recognized this entity in their original publication, they did not include it in their classification system and furthermore, the concept does not fit into the definition proposed by Cierny in 2011.[9] In the case of minimal necrosis osteomyelitis, the absence of necrotic bone makes the definition proposed by Cierny less relevant. In these cases, the pathophysiology of the infection may also involve other characteristics of the causative organisms, including the ability of small colony variants to persist intra-cellularly for extended periods of time. A definition based on the duration of infection may therefore also be relevant as it would remain applicable, irrespective of the cause of infection or presence of a sequestrum or implant. However, this raises questions regarding the timescale of biofilm formation, which will be explored further in Chapter 9.

The final issue surrounding the definition of chronic osteomyelitis relates to the age of the patient. Paediatric chronic osteomyelitis is seen as a separate entity and Cierny and Mader recognized this when developing their classification for use in adults.[7] One notable difference

in the management of chronic osteomyelitis in children is that in certain instances sequestra are left in place in order to allow for adequate new bone formation prior to surgical intervention.[11,12] This strategy may be successful in the paediatric population because children have a much greater potential to resorb sequestra and to form adequate involucrum, but it is unlikely to be successful in adult cases. Owing to these differences the author has adopted the same approach as most authors on the topic, by excluding paediatric patients (below the age of 14 years) from the study.

### 1.2.2. The indications for surgery

Factors which have previously been recognized to have an influence in the selection of treatment in adults with chronic osteomyelitis, include the functional impairment caused by the disease, the anatomical nature of the pathology, the reconstruction options available and the metabolic consequences of aggressive therapy.[7] Other factors may however also need to be considered, for example the social circumstances of the patient (which may influence their ability to comply with the requirements of a specific treatment protocol), the presence of psychiatric illness and the realistic goal of treatment.

A draining sinus associated with minimal pain or dysfunction is not, in itself, an indication for surgical treatment.[9] At times, procedures aimed at achieving arrest of the disease are of such magnitude that the consequences can prove to be more disabling than the disease itself and the treatment can lead to loss of function, limb, or life.[7] The decision to pursue a curative treatment strategy is thus based on the assessment of the risk/benefit ratio in each patient. Curative treatment must offer distinct advantages over palliative care and the risk profile of

the proposed surgical treatment should be low.[9] Ultimately, quality of life remains the priority.[7]

While surgical intervention in a patient who is unable to cope with the physical and physiological demands of the reconstructive procedure should be avoided, leaving chronic osteomyelitis untreated may (in rare cases) also have serious consequences. Secondary amyloidosis has been reported in 10% of patients with long standing suppurating osteomyelitis.[13] Secondary (Amyloid A) amyloidosis most commonly results in proteinuria, renal insufficiency, or nephrotic syndrome. [14] Amyloid deposits may also cause hepatomegaly, splenomegaly and gastrointestinal manifestations including motility disturbances, malabsorption, bleeding or perforation. In approximately 5% of patients with secondary amyloidosis, cardiac involvement may cause heart failure. Secondary amyloidosis however, typically only develops when the causative chronic infection or inflammatory disease has been present for a long time; a median period of 17 years in one series.[15] In addition the amyloid deposits are absorbed when the suppuration is controlled or removed.[13]

The second life-threatening condition that may result from long-standing uncontrolled chronic osteomyelitis is the development of a Marjolin's ulcer or squamous cell carcinoma.[16] Other malignancies, fibrosarcoma for example, have also been reported in the vicinity of long-standing chronic osteomyelitic lesions.[17,18] The development of these cancers is however a slow process. Typically chronic discharging osteomyelitis has to be present for at least 12 to 35 years prior to the development of a malignancy.[19] Furthermore, this serious complication can be prevented by adequate wound coverage or wound healing.[16]

Although the above-mentioned complications are serious and even life threatening, it appears that they only develop in cases involving long-standing periods of uncontrolled infection. Therefore the risk of these complications can be minimized by achieving suppression of the disease through a successful palliative strategy and is therefore not necessarily an indication for surgery in patients with chronic osteomyelitis.

Clearly the decision to embark on a curative or palliative strategy is a difficult one, with many factors to consider. The Cierny and Mader classification system was aimed at facilitating this process and recommended curative (surgical) treatment in A and B-hosts and palliative treatment in C-hosts. The definition of the C-hosts is therefore critical as it forms the basis of treatment strategy selection. As stated previously, the main problem faced (in terms of treatment selection) was the absence of pragmatic diagnostic criteria defining a C-host.

### 1.2.3. The definition of a C-host

While bacterial infection may initiate the disease, the majority of the clinical and radiological sequelae of chronic osteomyelitis are the result of a patient's immune response to the infection.[20] The patient's immune response is also an important role-player in effecting remission of the disease. Without a competent immune response or the necessary healing potential, any attempt at the eradication of infection may be compromised.[21] The patient's immunological and physiological status is, therefore, a critical factor to consider when contemplating a curative treatment strategy.

In 1985 the Cierny and Mader classification system (also known as the University of Texas Medical Branch or UTMB classification) recommended curative treatment in A and B-hosts

and suppressive or no treatment in C-hosts.[7] In 2011 Cierny again recommended that C-hosts be palliated or simply treated expectantly.[9] Walter and co-workers also recognized the validity of both curative and palliative treatment pathways.[3] They however did not provide guidelines in terms of how a specific treatment strategy should be selected.

The definition of a C-host (i.e., the patient who should be palliated) is critical as it forms the basis of treatment strategy selection. Objective and discreet diagnostic criteria, defining a C-host, has not previously been established. Cierny and Mader defined a C-host as a patient in whom treatment or results of treatment are more compromising than the disability caused by the disease itself.[7] Their definition encompasses a large group of patients, which includes patients with minimal disability as well as patients who are not suitable candidates for complex bone and/or soft tissue reconstruction. The main shortcoming in this definition remains the fact that it is susceptible to widely varying interpretation depending on the surgeon's experience. Cierny and Mader recognized the limitations of their definition of a C-host and predicted that the selection of surgical candidates would vary from institution to institution until there was standardization of the concept.[7] Therefore, in order to develop an integrated approach to adult chronic osteomyelitis, which incorporates treatment strategy selection guidelines, the definition of a C-host would have to be refined.

### 1.2.4. The definition of cure

Another obstacle to the comparison of results of previous studies and the development of an integrated approach, was the lack of a consensus definition of cure in chronic osteomyelitis.[22] Lazzarini *et al.* came to a similar conclusion when they reviewed the outcome of antibiotic therapy in osteomyelitis.[6] They were obliged to adopt their own definition of cure because

different definitions of a successful outcome were used in the 93 studies included in their review.

While clinical evidence of osteomyelitis may be relieved (in certain cases) by antibiotic therapy alone, symptoms and signs are likely to recur in many patients if the source of the infection is not surgically addressed. The surgical margin elected by the surgeon also has important implications in terms of the outcome. Cure, in the strictest sense of the word, can theoretically only be attained through wide resection of all necrotic, ischemic and infected tissue.[21]

Marginal debridement involving direct or indirect unroofing, avoids compromising skeletal stability but may leave infected bone behind. The offending bacteria may evade host defences or antibacterial agents by persisting intracellularly or by entering a metabolically inactive state within the biofilm.[23] As a result, clinically evident infection may recur years later, in certain cases more than 50 years after the initial episode.[24,25] In cases where marginal debridement is employed, “cure” is therefore an unrealistic expectation and “remission”, “arrest” or “quiescence” would be more appropriate terminology.[3] In order to allow better comparison of studies in chronic osteomyelitis, standardization of the concept of a successful outcome thus need to be established.

Different criteria may be required in respect of the definition of a successful outcome in cases treated palliatively and curatively. While arrest or remission would be a reasonable goal for a curative treatment strategy, the same outcome cannot be expected of a palliative protocol.

Palliative treatment strategies aim to suppress the disease.[26,27] Successful suppression has however, not yet been defined.

### 1.3. Other unresolved issues

An integrated approach to chronic osteomyelitis, which incorporates a rationalized host stratification system, could be of benefit to orthopaedic surgeons inexperienced in the management of chronic osteomyelitis. An algorithm-like approach would be especially useful in underdeveloped regions where surgeons frequently do not have access to specialized infection units or multi-disciplinary teams. Furthermore, surgeons working in resource-poor clinical environments are frequently faced with additional challenges like a high prevalence of HIV infection or other risk factors which might result in C-host classification. The development of an integrated approach to chronic osteomyelitis, aimed at assisting decision making in a developing country, would therefore require consideration of the outcome of treatment in C-hosts or in patients living with HIV. Unfortunately there has, to date, been very little information published regarding chronic osteomyelitis in HIV positive patients. In addition, the outcome of palliative treatment has not been established.

#### 1.3.1. The results of palliative treatment strategies

Chronic osteomyelitis in adults is particularly challenging to treat. In specialized bone infection units success rates of curative treatment strategies varies from 70% to 90%.[3,28] Cierny reported an 85% success rate of curative treatment at two year follow-up, with 96% success in A-hosts and 74% in B-hosts.[9] Ten percent of cases in his series were managed by primary amputation. The Bone Infection Unit in the United Kingdom reported an excellent

cure rate of 90% at five years follow-up (though the amputation rate was not mentioned).[29] Both of these articles are review articles and the authors reported only briefly on their outcomes as an illustration of the potential prognosis. Neither reported the outcome of treatment in the palliative group. In fact, there are very few reports of the outcome of palliative treatment in chronic osteomyelitis. The paucity in the literature, in terms of the outcome of palliative treatment, is particularly prominent in the case of chronic haematogenous osteomyelitis. Lazzarini *et al.* have previously drawn attention to the fact that the efficacy of suppressive treatment of long-bone osteomyelitis, without an implant in place, has not been determined.[26]

The majority of studies looking at the outcome of chronic suppressive antibiotic therapy (CSAT) involved patients with periprosthetic joint infections and not chronic osteomyelitis of long bones.[30-33] Some of the earlier reports investigating the efficacy of CSAT in periprosthetic infections included patients with infected osteosynthesis implants. Stein *et al*. reported a "cure" rate of 60% in patients treated with antibiotics without surgical removal of the implants.[34] The authors did not distinguish between joint replacement and osteosynthesis implant-related sepsis when reporting these results. An earlier study from the same authors reported "cure" in six of the nine patients with osteosynthesis implant related sepsis who were treated with antibiotics alone for a period of six months.[35]

Other studies investigating the efficacy of certain antibiotics, also included patients treated palliatively. These articles were, however, written mostly from an infectious disease viewpoint and often did not report on how patient classification or treatment strategy selection was performed. This was clearly illustrated by Spellberg and Lipsky, who found that only two

of the 17 non-randomized trials investigating cure rates of parenteral antibiotic agents in chronic osteomyelitis, reported specifically on the use of concomitant surgical debridement.[22] In the first of these studies, four out of the eight patients who did not receive surgery were "cured".[36] Thirteen of the 34 patients enrolled in the second study (involving intravenous imipenem/cilastatin therapy) were managed without surgical debridement.[37] The authors however did not specifically report the outcome in patients who did not receive surgery. Spellberg and Lipsky also found that none of the 18 studies looking at the efficacy of fluoroquinolones reported cure rates in patients who did and did not undergo debridement.[22] Saengnipanthkul *et al*. reported a 45% cure rate using trimethoprim-sulfamethoxazole to treat 66 patients with chronic osteomyelitis, only 55% of whom underwent surgical debridement. Cure rates in patients who did not receive debridement were not reported independently.[38] Similarly, Javaloyas de Morlius and Monreal Portella did not report the outcome separately in the six patients who did not receive surgery in their series.[39] Lazzarini *et al*. reviewed the outcome of antibiotic therapy in paediatric and adult osteomyelitis by analysing the results of all clinical trials performed over the preceding 30 years.[6] However, the authors excluded all patients with surgical implants from the start. In addition, the authors were unable to analyse the outcome by treatment duration as only a small number of the studies involved prolonged treatment.[6]

There is therefore very little data available on the outcome of palliative treatment (in the form of chronic suppressive antibiotic therapy) in chronic osteomyelitis and none of the studies available investigated this issue specifically. Furthermore, none of the above-mentioned studies explained how patients were selected for palliative treatment instead of curative treatment. In addition, none of the previous authors apart from Cierny and McNally, reported

their results with reference to accepted orthopaedic host classification systems.[9,29] To justify the validity of a classification system, the outcomes of both curative and palliative treatment, as well as the amputation rate, would have to be reported. The ideal treatment guidelines for adult chronic osteomyelitis should preferably result in comparatively high success rates in both the curative and palliative treatment arms, while maintaining a low amputation rate.

### 1.3.2. HIV infection and chronic osteomyelitis

The association between HIV infection and chronic osteomyelitis has not been clearly defined. Several conflicting studies have been published. Initial reports noted an increased risk of post-operative infection, while more recent studies failed to show an increase in infection.

In 1991 Hoekman *et al.* found an increase in the risk of post-operative infection following surgical fracture fixation in symptomatic (defined as CDC stage III or IV) HIV infected individuals.[40] Jellis subsequently reported a 33% infection rate following internal fixation of closed fractures and a 72% infection rate in open fractures.[41] Noteworthy is the fact that Jellis noticed an increase in adult haematogenous osteomyelitis and late implant-related infections, as patients' immune competency decreased. In 2002 Harrison *et al.* found a significant increase in early wound infection following open fractures in HIV positive patients.[42] The incidence of early wound sepsis following internal fixation of closed fractures was however not increased in this series. Harrison *et al.* then investigated the prevalence of late infection and found no implant related infection in 26 HIV positive patients at one year follow-up.[43] A subsequent study from the same center in Malawi again failed to show an increased risk of early wound infection following clean surgery, but found that the infection rate had doubled in

contaminated wounds.[44] Contrary to the findings of Jellis, this study did not show an increase in chronic infections in HIV positive patients. Two further studies from KwaZulu-Natal, South Africa, added to the controversy. The first noted an increased risk of infection in open fractures in patients with advanced HIV disease (CD4 < 350 cells/μl).[45] The second study failed to show an increase in early wound infection in HIV positive patients with open tibia fractures.[46]

The evidence available appears to be contradictory in terms of the development of infection in both open and closed fractures. However, most of these studies were designed to look at HIV as a risk factor for early wound infection rather than the development chronic osteomyelitis. Moreover, it is not known if HIV infection resulted in an increased risk of reactivation of chronic haematogenous osteomyelitis. Most significantly there is little data available on the outcome of treatment of chronic osteomyelitis in HIV positive patients. Some of the aforementioned articles simply mentioned the fact that patients who did develop infection responded well to standard treatment.[40,41]

### 1.4. Summary

In conclusion, we have elucidated several issues in the literature which require further investigation. These include the absence of standardized definitions, the outcome of palliative treatment strategies, as well as the clinical characteristics and results of treatment of chronic osteomyelitis in HIV positive patients. In addition the need for the establishment of a comprehensive treatment algorithm has been identified. This would however, require refinement of existing host stratification and classifications systems in order to ensure

objective risk-factor assessment and treatment strategy selection.

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# PART 1

# The pathophysiology and classification of chronic osteomyelitis

The clinical manifestations of chronic osteomyelitis result from the complex interplay between the host's immune defence system and the pathogen attempting to establish a biofilm-based colony on a sequestrum or surgical implant.[1] Although bacterial infection may initiate the patient's symptoms, there are strong indications that the immune system may actually be the strongest contributor to disease and pathology of chronic infections.[2] The host's physiological status therefore, not only determines the clinical course of the disease but also serves as the primary indicator of the patient's ability to effect healing of bone and soft tissues, as well as their ability to launch an effective immune response in conjunction with antibiotic therapy and surgery. Without a competent immune response from the host, any attempt at eradication of the infection may be futile.[3]

The first paper (Chapter 2) provides an overview of the definition of chronic osteomyelitis, the biological behaviour of the causative organisms and the immunological basis of the disease. The relatively new field of osteoimmunology sheds light on the importance of the host's immune system in the pathophysiology of the disease. The role of biofilm is also discussed as it may have important implications for the definition of the disease, as well as the definition of cure.

Chronic osteomyelitis includes a wide variety of clinical scenarios, including haematogenous, post-operative and post-traumatic infections. An accurate definition of the disease entity is

required in order to identify cases in whom the proposed algorithm could be deemed appropriate. Haematogenous osteomyelitis , although still common in the developing world, has been surpassed by post-traumatic or post-operative infection as the leading cause of chronic osteomyelitis in adults. The changing face of chronic osteomyelitis has necessitated an evolution in the definition of the disease to one that is based on a universally applicable pathogenesis. Some questions regarding the suitability of existing definitions remain and these issues will be discussed further in Chapter 9.

The second paper (Chapter 3) provides a critical review of existing classification systems and identifies areas that require further development. It highlights the need for accurate host stratification and the fact that existing classification systems fail to consider certain contemporary reconstructive options.

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# Chapter 2: The pathophysiology of chronic osteomyelitis

**Marais LC**, Ferreira N, Aldous C, Le Roux TLB.

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Contribution to authorship:

- LC Marais – Concept, literature review, drafting of manuscript, revision of manuscript, corresponding author.
- N Ferreira – Contribution to literature review and revision of manuscript.
- C Aldous – Concept development and revision of manuscript.
- TLB Le Roux − Concept development and revision of manuscript.

# The pathophysiology of chronic osteomyelitis

**LC Marais MBChB, FCS Orth(SA), MMed(Ortho)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics,
Grey's Hospital, University of KwaZulu-Natal
**N Ferreira BSc, MBChB, FC Orth(SA), MMed(Orth)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics,
Grey's Hospital, University of KwaZulu-Natal
**C Aldous BSc, BSc (Hons), MSc, PhD**
Medical Research Scientist, School of Clinical Medicine
College of Health Sciences, University of KwaZulu-Natal
**TLB le Roux MBChB, FCS Orth(SA), MMed(Ortho)**
Professor and Head of Department, Department of Orthopaedics,
I Military Hospital, University of Pretoria

**Correspondence:**
Dr LC Marais
Department of Orthopaedic Surgery
Grey's Hospital
School of Clinical Medicine
University of KwaZulu-Natal
Private Bag X9001
Pietermaritzburg
3201
Email: Leonard.Marais@kznhealth.gov.za
Tel: +27 033 897 3424
Fax: +27 33 897 3409

## Abstract

Chronic osteomyelitis is a biofilm-based infection of bone where the majority of causative microorganisms are sessile in nature, rendering them less sensitive to systemic antibiotic agents and making routine culture techniques unreliable. Biofilms are the characteristic growth pattern for most bacteria and are now understood to consist of interactive communities with the ability to alter their gene expression in order to ensure survival. Our knowledge of the host's response to infection is also rapidly expanding. The discovery that osteoclastic and osteoblastic cells play a central role in the immune response of bone has resulted in a better understanding of osteo-immunology. This expansion of knowledge has created new opportunities in terms of the development of novel treatment strategies in the management of chronic osteomyelitis and periprosthetic infections.

**Key words:** osteomyelitis, chronic, pathogenesis, osteo-immunology, biofilm

## Introduction

Chronic osteomyelitis remains a daunting challenge to orthopaedic surgeons. It is often described as a disease that can never truly be cured, particularly when the biological characteristics of the causative organism are taken into account.[1]

The two main routes of infection in osteomyelitis are through either haematogenous or contiguous bacterial inoculation. It is estimated that approximately 10 to 30% of acute haematogenous osteomyelitis may become chronic in nature. Chronic haematogenous osteomyelitis is an age-old problem, illustrated by the fact that the palaeopathological analysis of an *Australopithecus africanus* hominid skeleton, from Sterkfontein, South Africa, revealed evidence of chronic infectious disease of the skeleton.[2] The oldest medical text, known as the Edwin Smith Papyrus from the sixteenth century BC also describes cases of 'pus pouring from bone', probably in reference to osteomyeilits.[3] Despite the advent of antibiotic therapy and advances in the management of acute haematogenous osteomyelitis, the incidence of chronic osteomyelitis has steadily climbed, particularly during the past century. This is likely as a result of the increased incidence of high velocity skeletal trauma, as well as the increased use of surgical implants.

Open fractures can lead to the development of contiguous osteomyelitis in 3–50% of cases, depending on the severity of the injury and quality of the subsequent management.[4] The surgical management of closed fractures may result in post-operative osteomyelitis in 1–5% of cases, while the estimated risk of infection complicating an elective primary hip or knee replacement is in the region of 0.5–2%.[5] This risk is, however, significantly higher in revision surgery (5%) and, in the case of second stage revision for periprosthetic infection, the infection rate climbs to approximately 20%. Overall, infectious complications occur in approximately 5% of orthopaedic cases during the life-time of the prosthesis or implant.[5]

Socio-economically underdeveloped regions carry a particularly heavy burden in terms the prevalence of osteomyelitis.[6] This may be attributed to, among other factors, the high incidence of osteomyelitis in childhood, immunosuppression, malnutrition and the high incidence of trauma. The high prevalence of trauma in South Africa is clearly illustrated by the fact that interpersonal violence and road traffic accidents were the second and fourth most common causes of death in South Africa in the year 2000.[7] The road traffic accident fatality rate in South Africa (39.7 per 100 000 population) is higher than for any other WHO region and almost double the world average.[8] This implies a correspondingly high morbidity related to road traffic accidents, which contributes to an increased incidence of post-traumatic osteomyelitis.

In addition to a high trauma load, South Africa is faced with a severe shortage of qualified orthopaedic surgeons. In developed countries, like the USA and Canada, figures range from 4.8–5.6 full-time equivalent orthopaedic surgeons per 100 000 population.[9,10] In contrast, in 2011, public sector medical services in the interior of the KwaZulu-Natal province in South Africa served a population of approximately 3.5 million people with only 0.37 full-time orthopaedic surgeons per 100 000 population. This shortage results in many patients with skeletal trauma, and more specifically compound fractures, not receiving appropriate treatment, contributing to a further increase in the chronic osteomyelitis disease burden.

Although the association between HIV infection and chronic osteomyelitis has not been clearly defined, previous research has shown an increased risk of post-operative infection following surgical fracture fixation in HIV-infected individuals.[11] The prevalence of HIV infection in Southern Africa has reached epidemic proportions. Mid-year estimates for 2011 approximates the national prevalence of HIV infection in adults at 10.6%.[12] In KwaZulu-Natal the situation is worse, with an estimated 21.5% of adults between the ages of 15 and 49 years being infected with HIV.[13]

The problem of high disease prevalence is compounded by the financial implications of the treatment of chronic osteomyelitis. The direct medical cost associated with the management of osteomyelitis, in the USA in 1999, was estimated at $35 000 per episode.[14] In Southern Africa the high cost of treatment is multiplied by the much higher burden of disease, posing a significant challenge to our resource-restricted health systems.

*In addition to a high trauma load, South Africa is faced with a severe shortage of qualified orthopaedic surgeons*

## Definition

Osteomyelitis is characterised by the progressive inflammatory destruction of bone followed by the apposition of new bone as part of the reparative process. Classically chronic osteomyelitis was therefore defined by the presence of either sequestrum or involucrum as a result of an infective process involving bone. This definition originated from the observation that acute haematogenous osteomyelitis, if left untreated, may result in the formation of necrotic segments of bone, which would then serve as a source of on-going or chronic infection.

As orthopaedics evolved into a primarily surgical field and the use of surgical implants increased, the incidence of contiguous post-operative osteomyelitis dramatically increased, necessitating revision of our definition. No longer was haematogenous spread considered to be the major cause and the emphasis shifted towards the duration of the disease. The duration of infection that defined chronicity gradually decreased over time and in 1997 it was defined as symptoms remaining for longer than ten days.[15] An alternative, more philosophical approach was to define chronic osteomyelitis according to the response to therapy, where chronicity was defined as infection unresponsive to multiple therapeutic attempts to eradicate infection.[16]

As our understanding of the pathophysiology has grown, the definition of chronic osteomyelitis has been refined even further. Cierny proposed a definition more appropriate to the setting of contemporary orthopaedics.[17] He defined chronic osteomyelitis as a biofilm-based infection where only a minor fraction of the causative microorganisms are planktonic (free-swimming). The majority of pathogens are sessile-based, resiliently attached to necrotic bone, surgical implants or foreign material and embedded within a glycocalyx slime (biofilm). This renders them less sensitive to systemic antibiotic agents and makes routine culture techniques less reliable. With time the bacterial toxins and by-products of the host's immune system accumulate to result in the local and systemic manifestations of chronic osteomyelitis. Cierny's definition is not restricted to the cause, the presence of surgical implants, nor to the anatomic nature or duration of the disease, but rather defines it by the presence of a universally applicable pathogenesis.

## The pathogen

Normal bone is highly resistant to infection. Osteomyelitis typically occurs in the setting of a large bacterial inoculation in combination with trauma, necrosis or ischaemia of tissue and/or the presence of foreign material. Large strides have been made over the past few decades in our understanding of the disease process underlying chronic infections of bone. Central to this understanding lies the concept of bacterial biofilm. In 1987 Gristina *et al*. coined the phrase 'the race for the surface'.[18] The host cells strive to establish an integrated protective cellular layer with functional defence mechanisms (including opsonification, phagocytosis and complement mediated lysis), while the invading bacteria enter their default growth pattern and establish a biofilm. This is a layer-like aggregation of microbial cells and extracellular polymeric substances attached to a substrate which provides an environment for the exchange of genetic material between bacterial cells.[19]

The presence of a foreign body has been shown to significantly increase susceptibility to infection. For example, the minimal infecting dose of *Staphylococcus aureus* is more than 100 000-fold lower in the vicinity of subcutaneous devices than in skin without an implant.[20] This increased susceptibility to infection is partially due to a locally acquired granulocyte defect.[21]

Biofilm formation occurs in five stages, namely adhesion, production of the extra-cellular matrix, colonisation, maturation and finally dispersion of bacteria. The first stage involves adhesion of the bacteria to the substrate through specific and non-specific mechanisms.[22] Specific mechanisms involve the expression of adhesion molecules known as adhesins or MSCRAMM (microbial surface components recognising adhesive matrix molecules) specific to certain host proteins like fibronectin, laminin, sialoglycoproteins, fibrinogen and collagen. Non-specific mechanisms involve surface tension gradients, hydrophobicity and electrostatic forces. Once contact is made with the substrate, bacteria migrate (with the aid of flagella) until other bacteria are encountered, thus establishing micro-colonies. Once the microbial density reaches a critical point, the volume of cell-to-cell signal molecules released is sufficient to activate genes involved in the production of an exocellular polysaccharide or glycocalyx. The ability of a microbial colony to sense its size and respond by altering its gene expression is referred to as quorum sensing. This phase of biofilm formation is being investigated as a target for the prevention of biofilm formation on orthopaedic implants. Animal models have shown that the quorum-sensing inhibitor RNA III-inhibiting peptide can help prevent staphylococcal biofilm formation and infection.[23]

Contrary to popular belief bacteria do not differentiate during the colonisation phase of biofilm formation but rather they alter their pattern of gene expression and should therefore be seen as interactive communities, rather than a multicellular organism.[19] A sub-population of bacteria may evolve into a phenotypically resistant state and express biofilm-specific antimicrobial resistance genes. Other bacteria within the biofilm may produce hydrolase enzymes and exotoxins, resulting in local tissue invasion. Biofilm-based bacteria have up to a 1000 times greater resistance against antimicrobials and host immune defences. This derives from a combination of phenotypic, mechanical and metabolic mechanisms. Antibiotics face mechanical and osmotic challenges in penetrating a biofilm, while the reduced growth rate of bacteria due to incomplete penetration of metabolic substrates and accumulation of waste product, makes the biofilm-based bacteria even more resilient.[24] These so-called small colony variants are characterised by slow growth, decreased pigment formation, low coagulase activity, reduced haemolytic activity, and resistance to antibiotics.[25] Small colony variant bacteria are able to persist within host cells and it has been suggested that the intracellular location of this subpopulation might shield them from host defences and antibiotics, thus providing one explanation why chronic osteomyelitis is able to reactivate years after the initial infection.[26] The final stage in the evolution of a biofilm involves the dispersion of planktonic bacteria. Through quorum sensing, gene expression may alter the bacterial phenotype from colonising to invasive and as environmental conditions deteriorate within the biofilm, bacteria disperse to find a surface with a more favourable environment.

## The host response

The innate immune response is critical in the early phase of bacterial colonisation. It is triggered at the site of bacterial infection by the production of cytokines like interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF). These cytokines recruit and activate phagocytic cells such as polymorphonuclear (PMN) leukocytes and macrophages to produce bacteriolytic free radicals.[27] Neutrophils, which engulf bacteria, die at the site of infection and comprise much of the material we see as pus draining from a sinus. Macrophages are critical for the phagocytosis of planktonic bacteria and necrotic material. This process is facilitated by opsonisation (the binding of an antibody to a bacterial antigen), which anchors the bacteria to the Fc-receptors on phagocytic cells and activates intracellular signalling pathways to produce free radicals like superoxide and nitrous oxide.

*Antibiotics face mechanical and osmotic challenges in penetrating a biofilm*

Acquired or adaptive immunity is responsible for the eradication of chronic or persistent infections and also plays an important role in the prevention of recurrence. The first component of the adaptive immune response is the cellular response in which cytotoxic $CD8^+$ T cells lyse infected host cells. The second component is the humoral response involving the production of antibodies by B lymphocytes. Centrally positioned within the adaptive immune response are macrophages which produce TH1 lymphokines (IL-12 and interferon-$\gamma$) which drive cell-mediated immunity, as well as TH2 lymphokines (IL-3 and -4) regulating the humoral response. Most cases of chronic osteomyelitis involve extracellular organisms and therefore the humeral immune response, incorporating antibody opsonisation and phagocytosis of bacteria, plays a central role. Animal studies have identified several bacterial antigenic proteins in antibody-mediated immunity in *Staphylococcus aureus* biofilm-based infections, including cell-surface-associated beta-lactamase, lipoprotein, lipase, autolysin and ABC transporter lipoprotein.[28] Some of these antigens are currently being investigated as possible targets for vaccination.[29] Anti-autolysin monoclonal antibodies (mAbs), for example, may have a protective effect through the inhibition of adhesion and growth of *Staphylococcus sp*.

## Osteo-immunology

Chronic osteomyelitis is characterised by osteolysis in combination with reparative osteosclerosis, which aims to confine the inflammatory process. Bacterial components and toxins have a strong stimulatory effect on osteoclastic activity through indirect (RANKL and other osteoclastogenic factors) and direct mechanisms.[30] As is the case with TNF, bacterial surface-associated material (SAM) can induce the formation of osteoclasts from monocytes independent of the RANKL mechanism. Other bacterial products such as lipopolysaccharide (LPS) and endotoxin induce the expression of osteoclastogenic cytokines including RANKL, TNF, IL-1, and IL-6 by osteoblasts and

other cells.[31] These cytokines, not only stimulate osteoclasts, but also inhibit bone formation through impairment of osteoblast differentiation, proliferation, activity and survival, resulting in net resorption of bone at the site of chronic infection. Although it is well known that bacteria that cause chronic osteomyelitis can be found intracellularly, within osteoblasts, it is not known if these bacteria have a direct inhibitory effect on osteoblasts or inhibit bone formation through mechanisms involving the known inhibitory cytokines like sclerostin, DKK1 or noggin.[27]

## The role of osteoclasts

Receptor activator of nuclear factor kappa-B ligand (RANKL) is a potent activator of osteoclasts and is produced by bone marrow stromal cells under normal conditions. However, in osteomyelitis certain bacterial components, such as lipopolysaccharide (LPS), result in the production of RANKL by a variety of cells (including activated T-cells) ultimately causing abnormal bone loss.[32] Dendritic cells (DCs) are monocyte-derived antigen-presenting cells which play an important role in both innate and adaptive immunity. Migrating dendritic cells (mo-DCs) transport antigens from the site of infection to lymphoid organs in order to initiate T-cell responses, including $CD4^+$ activation. Dendritic cells also affect osteoclasts through the stimulation of RANKL production by T cells.[33] A subset of resident dendritic cells, called Tip-DCs, present at the site of infection also have strong anti-microbial effects through the production of TNF-alpha and inducible nitric oxide synthase (iNOS). Although these products are beneficial in terms of eliminating pathogens they also contribute to tissue damage.

*Staphylococcus aureus* directly activates dendritic cells through the production of an exotoxin called leukocidin which triggers a Toll-like receptor (TLR-4) dependent signalling pathway.[34] *Staphylococcus aureus* enterotoxin B induces maturation of dendritic cells and stimulates them to produce high levels of IL-2. A third mechanism whereby *Staphylococcus aureus* up-regulates dendritic cell function is through the production of the protease staphopain B, which, through a complex mechanism results in the formation of chemerin. Chemerin, in turn, has been suggested to act as a potent chemoattractant to immune-regulatory dendritic cells. It is also interesting to note that upon activation by microbial antigens, $CD11c^+$ dendritic cells can differentiate into functional osteoclasts in the presence of macrophage colony-stimulating factor (M-CSF) and RANKL expressed by activated $CD4^+$ T cells.[35]

## The role of osteoblasts

Although our understanding is still cursory, osteoblasts are seen as the last line of defence in the fight against bacterial infection and biofilm formation. They express a wide array of immune-stimulatory cytokines in response to ligation of bacterial products, like LPS and DNA, to the Toll-like receptors (TLR-2, 4 and 9) on their surface. These cytokines include anti-microbial peptides (beta-defensin-3), chemokines (CCL-2, CCL-5, CXCL-8, CXCL-10), nflammatory cytokines (IL-6), co-stimulatory molecules (CD40) and MHC II.[27,36,37] The secretion of these chemokines suggests that osteoblasts do not only play an important role in the innate immune response but also in the cellular immune response. Cells expressing MHC II molecules typically present exogenous antigens to T-helper cells. The fact that osteoblasts express MHC II may explain why osteoblasts internalise bacteria like *Staphyloccus aureus*. This process has been investigated further and *Staphylococcus aureus* sigma B regulon has been shown to be the key mediator of the internalisation of bacteria by osteoblasts, and is thus a possible target for therapeutic intervention.[38]

## Conclusion

The physiological status of the host determines not only the clinical extent of the disease, but also the treating physician's ability to effect cure. Without a competent immune response from the host, any attempt at surgical eradication of the infection may well be futile. The importance of the host's ability to launch an effective immune response is clearly illustrated in the principles behind the Cierny and Mader classification, which incorporates assessment of local and systemic factors affecting the hosts immune competency.[39] Studies using the Cierny and Mader classification have confirmed that the host status is the most important predictor of treatment failure.[40]

The discovery that osteoclastic and osteoblastic cells play a central role in the immune response of bone has resulted in better understanding in the relatively new field of osteo-immunology. As is the case with bacterial biofilms, our knowledge of the host's response to infection is also rapidly expanding. This knowledge creates new opportunities in terms of the development of novel treatment strategies in the management of chronic osteomyelitis and periprosthetic infections.

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# Chapter 3: The classification of chronic osteomyelitis

**Marais LC**, Ferreira N, Aldous C, Le Roux TLB.

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Contribution to authorship:

LC Marais – Concept, literature review, drafting of manuscript, revision of manuscript, corresponding author.

N Ferreira – Literature review and revision of manuscript.

C Aldous – Concept development and revision of manuscript.

TLB Le Roux − Concept development and revision of manuscript.

# The classification of chronic osteomyelitis

**LC Marais MBChB, FCS Orth (SA), MMed (Orth)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics, Grey's Hospital, University of KwaZulu-Natal
**N Ferreira BSc, MBChB, FC Orth (SA), MMed (Orth)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics, Grey's Hospital, University of KwaZulu-Natal
**C Aldous BSc, BSc (Hons), MSc, PhD**
Medical Research Scientist, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal
**TLB le Roux MBChB, FCS Orth (SA), MMed (Orth)**
Professor and Head of Department, Department of Orthopaedics, I Military Hospital, University of Pretoria

**Correspondence:**
Dr LC Marais
Department of Orthopaedic Surgery
Grey's Hospital
School of Clinical Medicine
University of KwaZulu-Natal
Private bag X9001
Pietermaritzburg
3201
Email: Leonard.Marais@kznhealth.gov.za
Tel: +27 33 897 3299
Fax: +27 33 897 3409

## Abstract

As a result of the heterogeneous nature of chronic osteomyelitis and the complexity of management strategy formulation, more than ten classification systems have been published over the past 40 years. Historical systems, used in the classification of chronic osteomyelitis, remain useful in terms of the description of the nature and origin of the disease. They fail, however, to provide the user with sufficient information in order to select the appropriate treatment strategy. As a result, more comprehensive classifications have subsequently been proposed. Accurate host stratification, in particular, is considered to be essential. The physiological status of the host serves as the primary indicator of the patient's ability to effect healing of bone and soft tissues, as well as their ability to launch an effective immune response in conjunction with antibiotic therapy. Despite the development of more comprehensive classification systems, many shortcomings remain within the domain of disease classification and host stratification.

**Key words:** osteomyelitis, chronic, classification

## Introduction

Chronic osteomyelitis, as a clinical entity, encompasses a wide array of clinical scenarios, including chronic haematogenous osteomyelitis, post-traumatic osteomyelitis, periprosthetic infections and contiguous osteomyelitis. Owing to the heterogeneous nature of disease, the wide variety of patients affected and the multitude of factors that need to be considered during the formulation of a treatment strategy, more than ten classification systems of chronic osteomyelitis have been published over the past 40 years. None of these classifications is universally accepted. Some of the systems simply classify the nature of the disease while others attempt to guide the treating surgeon on certain aspects of the management of chronic osteomyelitis or enable comparison of the outcome of different treatment strategies.[1]

Formulating the appropriate management strategy, albeit palliative or curative, is a complex task. The decision-making process requires consideration of multiple factors including the impairment resulting from the disease, the patient's functional requirements, local and systemic risk factors, the anatomic nature of the disease and the realistic goals of therapy. When considering the risk–benefit ratio of any proposed management strategy, the host's physiological status remains the main determinant of the risk involved with a specific intervention. This is illustrated by previous studies which have identified the physiological status of the host as the most important predictor of treatment failure.[2] The significant impact of inadequate or incorrect host stratification and risk assessment is epitomised by the fact that failure of a curative (limb reconstruction) strategy often results in the inevitable amputation of the involved limb.

This article aims to review the available classification systems for chronic osteomyelitis and highlight some of their shortcomings. Furthermore we will evaluate how the existing classification systems relate to new and evolving principles and techniques utilised in the management of chronic osteomyelitis.

## Historical perspectives

Traditionally, osteomyelitis has been classified according to the system described by Waldvogel in 1970.[3] This was a descriptive classification system incorporating the source of the infection (haematogenous or contiguous), the presence of generalised vascular disease and the duration of the infection (acute, sub-acute and chronic). Haematogenous chronic osteomyelitis of long bones typically presents as recurrence at a previous site of acute haematogenous osteomyelitis, while haematogenous periprosthetic infections involve seeding from a distant infective focus. Contiguous osteomyelitis may be the result of either direct inoculation (as is the case in post-traumatic and post-operative infections) or, alternatively, continuous spread from an adjacent septic focus (pressure sore or vascular ulcer, for example). As the frequency of surgical intervention increased, so did our need to classify contiguous osteomyelitis. Kelly subsequently published an aetiological classification which distinguished haematogenous from post-surgical and post-traumatic causes (with or without the presence of non-union).[4]

Ger's classification, published in 1977, recognised that the condition of the soft tissues plays an important role in the surgical decision-making process. According to this system the condition of the soft tissue is classified as a simple sinus, chronic superficial ulcer, multiple sinuses or multiple skin-lined sinuses.[5] In 1984 Weiland *et al*. introduced an anatomical classification system based on the nature of skeletal involvement in order to guide the utilisation of free tissue transfers during the reconstruction process. Type I lesions were defined as soft tissue infection with exposed bone. Type II lesions were characterised as circumferential endosteal and cortical infection, while type III lesions involved endosteal and cortical infection in the presence of a segmental bone defect.

Although the abovementioned classification systems are useful in terms of describing the nature and origin of the disease, they fail to provide the treating physician with guidance regarding the management of the patient. May and Jupiter addressed these shortcomings in 1989 through the publication of their classification system, which focused on the status of the tibia and ipsilateral fibula as a guide during the selection of the appropriate reconstruction procedure (*Table I*).[6]

Gordon *et al*. simplified the approach to post-infective reconstruction by condensing the classification of tibial defects into three groups, namely, no significant bone loss, <3 cm of bone loss and >3 cm bone loss.[7] This classification system was, however, specifically designed to prognosticate patients following free muscle transfers. Romanò *et al*. subsequently proposed a more extensive classification system for bone defects, which included defects frequently seen following periprosthetic infections. According to this system, type 1 lesions were defined as cavitatory defects within a stable bone segment, type 2 lesions represented epiphyseal lesions with joint involvement and type 3 lesions involved a segmental bone defect. Type 3 bone defects were sub-classified as either less than 1cm, between 1 and 3 cm, or more than 3 cm.[8]

Prior to 2006 there was no published classification for infections following osteosynthesis. Romanò *et al*. responded to this omission with the publication of the ICS (Infection, Callus, Stability) classification. According to this system, type I infection occurs in the presence of stable internal fixation and progression of union on serial X-rays. In terms of the management of type I infections, they suggested conservative measures until union was achieved. Type II infections were defined as infections in the presence of stable osteosynthesis without the progression of callus. The authors suggested managing this type of infection with control of the infection (as for type I), acceleration of bone healing through physical stimulation (low-intensity pulsed ultrasound, for example), biological factors (bone morphogenetic protein, platelet-rich plasma, etc.) and limited surgical procedures (e.g. dynamisation of intra-medullary nail fixation). For type III infections, involving unstable fixation and the absence of callus formation, revision surgery was recommended.

***Table I: Classification and reconstruction options as suggested by May and Jupiter[6]***

| Type | Characteristics | Reconstructive options |
|---|---|---|
| I | Intact tibia capable of withstanding functional loads | None required |
| II | Intact tibia requiring bone graft for structural support | Anterior bone graft and flap<br>Posterolateral bone graft<br>Papineau open bone graft |
| III | Tibial defect <6 cm, intact fibula | Posterolateral bone graft and tibio-fibular synostosis<br>Distraction osteogenesis |
| IV | Tibial defect >6 cm, intact fibula | Posterolateral bone graft and tibio-fibular synostosis<br>Distraction osteogenesis<br>Fibula-pro-tibia (ipsilateral fibula transfer)<br>Free vascularised bone graft<br>Allograft replacement |
| V | Tibial defect >6 cm | As for type IV<br>Consider amputation |

The abovementioned classification systems are all useful, especially in terms of the description of the nature and origin of the disease. With exception of the ICS classification system they fail, however, to provide the user with sufficient information to formulate a treatment strategy. The need had thus arisen to develop a more comprehensive classification system which incorporated several criteria and was able to guide the treating orthopaedic surgeon towards the correct management strategy.

## Comprehensive classification systems

Cierny and Mader revolutionised our approach to osteomyelitis in 1984 through the publication of a classification system which emphasised a more holistic approach to the patient, recognising the importance of immune competency and the physiological ability of the host to effect healing.[9] This system involved classification according to the host's physiological status and the anatomic nature of the disease (*Table II*).

***Table II: Cierny and Mader classification system[9]***

| **Anatomic type** | |
|---|---|
| **Type** | **Characteristics** |
| I | Medullary osteomyelitis |
| II | Superficial osteomyelitis |
| III | Localised osteomyelitis |
| IV | Diffuse osteomyelitis |

| **Physiological class** | |
|---|---|
| **Class** | **Characteristics** |
| A | Good immune system and delivery |
| B | Compromised locally ($B^L$) or systemically ($B^S$) |
| C | Requires suppressive or no treatment;<br>Minimal disability;<br>Treatment worse than disease;<br>Not a surgical candidate |

| **Factors affecting physiological class** | |
|---|---|
| **Systemic factors ($^S$)** | **Local factors ($^L$)** |
| Malnutrition | |
| Renal, liver failure | |
| Alcohol abuse | Chronic lymphedema |
| Immune deficiency | Venous stasis |
| Chronic hypoxia | Major vessel compromise |
| Malignancy | Arteritis |
| Diabetes mellitus | Extensive scarring |
| Extremes of age | Radiation fibrosis |
| Steroid therapy | |
| Tobacco abuse | |

*Cierny and Mader in 1984 published a classification system which emphasised a more holistic approach to the patient*

The importance of the consideration of the physiological host status of patients with osteomyelitis was validated through Cierny and Mader's study involving 189 patients. The host classification facilitated the decision-making process in terms of offering the patient the alternatives of amputation or limb salvage surgery. Forty-six patients required amputation in order to achieve cure, while arrest of disease was achieved in 93.6% of patients in the limb salvage group.[10]

In our opinion the anatomical sub-section of the Cierny and Mader classification remains applicable today, although the definition of the subtypes has been refined over the years. Type I lesions imply infection limited to the medulla, while type II lesions refer to infection limited to the cortex. Type III and IV infections involve both medullary and cortical bone, with type IV being differentiated by the presence of instability prior to or following the debridement. Although initially included as an anatomic type IV infection, peri-prosthetic infection has subsequently also been allocated its own classification system.[11]

The Cierny and Mader classification however failed to provide specific, objective criteria according to which the C-host, whom they deemed unsuitable for surgery, should be defined. McPherson *et al*. attempted to address the shortcomings of the Cierny and Mader host classification system by modifying it to include specific objective criteria (*Table III*).[12]

The McPherson system divides patients into three classes, A, B or C, based on the number of comorbid conditions that a patient has in common with a list of 14 immune-compromising factors. Patients with no compromising factors are in class A, while patients in class B have fewer than three compromising factors. Patients in class C have three or more compromising factors and/or one of the following conditions: an absolute neutrophil count less than 1 000; a CD4 count less than 100; intravenous drug abuse; chronic active infection of another site; or dysplasia or a neoplasm of the immune system. This classification system was, however, developed specifically for use in terms of planning for second stage revision arthroplasty in patients with infection following total hip replacement. The criteria suggested by them are conservative in terms of their numerical values and may not be appropriate when applied to chronic osteomyelitis in the South African clinical setting. Several criteria have been omitted, with specific reference to physical impairment, the state of the soft tissue, arterial and venous sufficiency, age, diabetic control (HbA1c), albumin and haemoglobin values, which may play a critical role in the decision-making process in the case of chronic osteomyelitis. The McPherson modification of the Cierny and Mader host classification system has, nevertheless, also been used in other clinical settings. Bowen and Widmaier looked at the incidence of infection following open fractures in three cohorts of patients, who were classified according to the McPherson modification.[13] They found that type B hosts were 2.86 times, and type C hosts 5.72 times more likely than type A hosts to develop infection following open fractures.

Lautenbach developed a staging system that integrates clinical, laboratory and radiological features in an incremental manner.[14] This classification is based on the severity of the disease and describes certain characteristic laboratory abnormalities which may be utilised to confirm the presence underlying infection in equivocal cases.

*In our opinion the anatomical sub-section of the Cierny and Mader classification remains applicable today*

***Table III: Systemic and local compromising factors according to the McPherson classification of infected total hip arthroplasty[12]***

| Systemic factors | Local factors |
|---|---|
| Age >80 years | |
| Immunosuppressive medication | |
| Alcoholism | Active infection >3–4 months |
| Malignancy | Multiple previous incisions with skin bridge |
| Pulmonary insufficiency | Soft tissue loss from prior trauma |
| Chronic indwelling catheter | Subcutaneous abscess >8 $cm^3$ |
| Renal failure requiring dialysis | Synovial cutaneous fistula |
| Chronic malnutrition | Prior peri-articular fracture |
| Systemic inflammatory disease | Prior local irradiation |
| Current nicotine use | Vascular insufficiency |
| Systemic immune compromise | |
| Diabetes | |
| Hepatic insufficiency | |

***Table IV: The Lautenbach classification system[14]***

| Grade | Characteristic |
|---|---|
| **Clinical grades** | |
| Acute | |
| Grade 1 | Acute fulminating |
| Grade 2 | Sub-acute |
| Grade 3(a) | Acute with insidious onset |
| Grade 3(b) | Acute exacerbation of chronic |
| Chronic | |
| Grade 4 | Chronic overwhelming |
| Grade 5 | Chronic diffuse with inflammation |
| Grade 6 | Chronic low grade extensive without inflammation |
| Grade 7 | Chronic localised lesion |
| Grade 8 | Non-infective pathology |
| **Laboratory findings** | |
| Chronic | |
| Grade 4 | Increased WBC, neutrophilia, left shift and toxic granulation, decreased transferrin, procalcitonin >2, increased platelets, abnormal RBC corpuscles |
| Grade 5 | Decreased Hb MCV and MCH, rouleaux formation |
| Grade 6 | Increased ferritin, decreased iron, decreased iron saturation, increased ESR |
| Grade 7 | Ferritin:iron ratio >7 |
| Grade 8 | Normal |
| **Radiological features** | Definite infection<br>Probable infection<br>Equivocal<br>Probable cure or absence of infection<br>Definite cure or absence of infection<br>New bone lysis or sequestrum<br>New periosteal reaction<br>No change<br>Sclerosis only<br>Normal bone architecture |

The classification system consists of eight escalating grades of severity (three grades of acute and five grades of chronic osteomyelitis), which are each defined by characteristic clinical and laboratory features (*Table IV*). As the grades of chronic osteomyelitis increase in intensity we see progressive abnormalities of the laboratory findings, especially in terms of iron studies, which may then be utilised in the diagnosis and stratification of disease severity.

Recently Romanò *et al*. again highlighted the shortcomings of the Cierny and Mader host stratification system as a subjective evaluation of the host's physiological ability to deal with infection.[15] Their Seven-Item Comprehensive Classification System (SICCS) of bone and joint infections for adults is based on the clinical presentation, aetiopathogenesis, anatomo-pathological characteristics (incorporating the Cierny and Mader anatomical sub-section for long bones), the McPherson modification of host classification (further subdivided according to age as less than 2 years, less than 14 years and more than 14 years of age), causative microorganism, the bone defect (in accordance with Romanò's earlier classification system), as well the state of the soft tissues (*Table V*).

The SICCS is descriptive in nature, incorporating existing classification systems. In contrast with the Cierny and Mader classification system it was not designed to guide management, but is rather intended for didactic and scientific purposes in order to compare results from different clinical trials.

## Importance of accurate host stratification

The clinical manifestations of osteomyelitis are the result of the complex interplay between the host's immune defence system and the causative organisms' attempts to establish a biofilm-based colony on a sequestrum, surgical implant or foreign body. The host's physiological status in particular, has been identified as a crucial factor, determining the course and clinical manifestations of the disease. The host status also serves as the primary indicator of the patient's ability to effect healing of bone and soft tissues, as well as their ability to launch an effective immune response in conjunction with antibiotic therapy. Without a competent immune response from the host, any attempt at surgical eradication of the infection may be futile.

The physiological host status does not only determine the suitability of a treatment strategy for the patient, be it curative or palliative, it also guides the surgeon in terms of the appropriate surgical margin during debridement. Traditional teaching regarding the surgical management of chronic osteomyelitis advocates the excision of all necrotic and ischaemic bone and soft tissue, to a clean, well-perfused surgical margin.[16] The importance of the extent of debridement has been investigated in both normal and compromised hosts. Compromised patients (B-hosts) treated with marginal resection (clearance margin of <5 mm) had a higher rate of recurrence than normal patients (A-hosts), whereas a marginal resection may be acceptable in normal hosts.[17] Thus, compromised hosts are theoretically best treated with a wide resection and subsequent limb reconstruction. These reconstruction procedures, involving bone transport or extensive bone grafts, are however fraught with danger, and failure invariably results in the amputation of the limb.

*Table V: The Seven-Item Comprehensive Classification System proposed by Romanò, et al.*[15]

| Item | Characteristic |
|---|---|
| Clinical presentation | Acute/sub-acute/chronic<br>Early/delayed/late |
| Aetiopathogenesis | Haematogenous<br>Vasculopathy/neuropathy<br>Temporary implant<br>ICS classification<br>Type I<br>Type II<br>Type III<br>Permanent implant |
| Anatomo-pathology | Rachis<br>Hand<br>Long bones<br>Type 1<br>Type 2<br>Type 3<br>Type 4<br>Foot<br>Joint |
| Host type/age | A/B/C<br><2 yr/<14 yr/>14 yr |
| Microorganism | Gram +<br>Gram −<br>Mixed or multi-resistant<br>Mycobacterium<br>Negative |
| Bone defect | Type I<br>Type II<br>Type III A/B/C |
| Soft tissue defect | No soft tissue defect<br>Soft tissue defect ($cm^3$)<br>With or without exposed bone |

The decision-making process is further complicated by that fact that many patients should not receive surgery because the risk of surgery may outweigh the benefit thereof. For example, patients may have little pain and minimal disability, with only intermittent drainage from a sinus. Embarking on major limb reconstruction surgery may be inappropriate in such a case, due to the risk of ablation. Thus, further consideration should also be given to the patient's current functional status and the realistically achievable goals of treatment.

*Many patients should not receive surgery because the risk of surgery may outweigh the benefit thereof*

In South Africa the high prevalence of immune compromise, malnutrition and other risk factors present unique challenges during host stratification. Classifications previously devised in developed countries have been found to be either inadequate or inappropriate in a resource-poor clinical setting.

In stark contrast with the South African public sector, where approximately one-third of patients are classified as C-hosts, developed countries deal with a much lower percentage. In a review of 2 207 patients seen over approximately 30 years, Cierny reported an incidence of only 4% type C-hosts in his American practice.[18] Clinical experience in South Africa has therefore revealed the need for accurate and objective host stratification to enable the selection of a safe, appropriate and patient-specific treatment plan. Ultimately the patient's physiological status should be considered as a critical factor during the formulation of the appropriate treatment strategy for an individual.

## Shortcomings of existing classification systems

The first major shortcoming of existing classification systems relates to host stratification. The stratification strategies currently available have failed to determine specific objective criteria whereby which patients who are unsuitable for a curative management strategy (a type C-host) can be identified. According to Cierny type C-hosts should not be offered definitive care, but rather palliated or simply treated expectantly.[18] The type C-host, as defined by Cierny and Mader, is a patient in whom the risk or morbidity of treatment outweigh the benefits thereof or, in other words, the treatment or results of treatment of chronic osteomyelitis are more compromising to the patient than the disability caused by the disease itself. This definition encompasses a large group of patients, including patients with minimal disability as a result of the disease as well as patients who are not suitable candidates for complex bone and/or soft tissue reconstruction. The limitation of this definition is the fact that it is subjective (with a poor inter-observer reliability), case dependent and susceptible to widely varying interpretation depending on the surgeon's experience.

The second limitation of existing chronic osteomyelitis classification systems lies in the patho-anatomical characterisation of lesions. There is currently no universally accepted classification system for either bone or soft tissue defects. The problem is further confounded by the fact that the magnitude of a bone defect that should be considered as critical and thus not manageable with cancellous bone graft, remains controversial.[19] Older classifications systems have failed to keep up with contemporary reconstruction techniques. The classifications proposed by May and Jupiter, for example, fail to mention the induced-membrane technique popularised by Masquelet.[20] Furthermore, the classification of bone defects varies widely in terms of cut-off points and each system reflects the unique preferences and abilities of the authors. While some surgeons, for example, feel comfortable transporting bone for a defect in excess of 6 cm, others would prefer the use of a vascularised fibula graft.

A problematic decision commonly faced when utilising the Cierny and Mader classification's anatomical subsection, is whether a specific lesion should be graded as a type III or type IV lesion. This decision is complicated by the fact that the distinction between the two grades is defined as instability following debridement.

The classification of a lesion as either type III or IV is, therefore, completely subjective and arbitrary, depending on the surgeon's choice of resection margin. If an infected section of bone is critical for axial stability, the surgeon has two choices: either resection of the bone with subsequent destabilisation of the limb (which will require complex reconstruction procedures), or leaving the infected bone behind and attempting to suppress the infection. The former type of wide resection with 'clear' margins (resecting any avascular material) remains the ideal, but it is frequently unachievable as it may involve resecting bone or soft tissue that is vital to the survival and function of the limb. On the other hand marginal resections may leave behind soft tissue or bone which contains bacteria and may serve as a nidus for recurrence of infection. The major limitation of the Cierny and Mader system is that it unfortunately does not provide any guidelines regarding the selection of the appropriate surgical margin.

The most prominent inadequacy of existing classification systems rests in the fact that they fail to guide the user in selecting the appropriate treatment strategy from the myriad of contemporary treatment options available. Although the Seven-Item Comprehensive Classification System, proposed by Romanò *et al*., is useful when describing the nature of the infection, it is complex and does not offer any guidelines for the selection of the applicable treatment strategy. In fact, the authors conclude that the classification system should find application in the comparison of outcomes, rather than being used as a guide to management. This problem is not unique to the SICCS and is a feature common to the other classification systems. The treatment guidelines offered by Cierny and Mader have failed to keep up with modern trends in the surgical management of chronic osteomyelitis.[10] Although the basic premise remains sound, some of the modalities suggested in the original publication has fallen out of favour. The use of open-sky (Papineau) bone grafting, for example, has been all but abandoned. This point is further illustrated by the fact that Cierny abandoned the original guidelines in a more recent publication, opting for a more generic approach to management.[21]

*The most prominent inadequacy of existing classification systems rests in the fact that they fail to guide the user in selecting the appropriate treatment strategy from the myriad of contemporary treatment options available*

The final limitation of existing classification systems lies in the structure of the decision-making process. While there are three host types described there are only two major treatment options, namely cure or palliation.[22] In order to appear logical and aid in the therapeutic decision-making process each host group should ideally be matched with its own unique management strategy. This will require revision of existing systems and the establishment of a new unified classification which incorporates all the relevant selection criteria, as well as all contemporary interventional strategies and techniques.

## Conclusion

As stated by Cierny, the selection of patient-matched treatment options (for example low risk treatment in high risk patients) closes the gap in successful outcomes between health-compromised patients (B- or C-hosts) and patients without compromise (A-hosts).[23] Ultimately the patient's physiological status is considered to be the single most important factor that needs to be considered when stratifying patients and during the formulation of the appropriate treatment strategy for any individual.

Despite the development of comprehensive classification systems, many shortcomings remain within the domain of disease classification and host stratification. The failure of existing classification systems to keep pace with contemporary management philosophies and modern reconstructive techniques has resulted in the need for the development of a new classification system which allows integration of host factors with the oncological-oriented approach which is currently being popularised in the surgical management of chronic osteomyelitis.

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# PART 2

# The management of adult chronic osteomyelitis

This section provides an overview of the current concepts pertaining to the management of chronic osteomyelitis. The lack of evidence-based or consensus guidelines has resulted in the fact that the management of adult chronic osteomyelitis is currently mainly based on expert opinion.[1,2] Although both curative and palliative treatment options are recognized, the way in which the appropriate treatment strategy should be selected remains unclear.

The treatment philosophy involving the application of certain surgical concepts typically applied in orthopaedic oncology surgery is explored. This oncologically orientated approach reinforces certain important notions, principally the fact that a wide resection is required to achieve eradication of the disease.[3] A previous report has suggested that the host status may be an important consideration when selecting the appropriate surgical margin.[4] Simpson *et al*. defined a wide resection as excision of all necrotic and infected bone with ≥5 mm clear margin.[4] Taking the pathogenesis of the disease into account, specifically the invasive nature of the infection, a wide excision may frequently equate to segmental resection. While wide resection and limb reconstruction may be advisable to achieve cure in a compromised host; the reconstruction procedures required, typically involving bone transport or extensive bone grafts, are fraught with danger in the poor host and failure frequently results in the amputation of the limb. The issue of wide resection and the maintenance of stability will be discussed further in Chapter 7.

As is the case with surgical margins, antibiotic therapy in chronic osteomyelitis can also be thought of in oncological terms. Directed antibiotic treatment therapy as part of a curative treatment strategy can be considered as adjuvant therapy and preoperative antibiotic therapy, in cases with abscess formation or cellulitis, can be likened to neo-adjuvant therapy. Chronic suppressive antibiotic therapy (CSAT) on the other hand, is used in a similar fashion as palliative chemotherapy in the oncology setting.

Apart from the oncologically orientated approach, several other aspects relating to the treatment of adult chronic osteomyelitis will be discussed. Previous classification systems failed to consider certain novel therapeutic strategies, for example the Masquelet (induced membrane) technique.[5,6] The aim of this section was to develop contemporary treatment guidelines which incorporate all available options.

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# Chapter 4: The management of chronic osteomyelitis - Diagnostic work-up and surgical principles

**Marais LC**, Ferreira N, Aldous C, Le Roux TLB.

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Contribution to authorship:

LC Marais – Concept, literature review, drafting of manuscript, revision of manuscript, corresponding author.

N Ferreira – Literature review, treatment protocol development and revision of manuscript.

C Aldous – Concept development and revision of manuscript.

TLB Le Roux − Concept development and revision of manuscript

# The management of chronic osteomyelitis:
## Part I – Diagnostic work-up and surgical principles

**LC Marais MBChB, FCS Orth(SA), MMed(Ortho)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics, Grey's Hospital, University of KwaZulu-Natal
**N Ferreira BSc, MBChB, FC Orth(SA), MMed(Orth)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics, Grey's Hospital, University of KwaZulu-Natal
**C Aldous BSc, BSc(Hons), MSc, PhD**
Medical Research Scientist, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal
**TLB le Roux MBChB, FCS Orth(SA), MMed(Ortho)**
Professor and Head of Department, Department of Orthopaedics, I Military Hospital, University of Pretoria

**Correspondence:**
Dr LC Marais
Department of Orthopaedic Surgery
Grey's Hospital
School of Clinical Medicine
University of KwaZulu-Natal
Private Bag X9001
Pietermaritzburg 3201
Email: Leonard.Marais@kznhealth.gov.za
Tel: +27 033 897 3299
Fax: +27 33 897 3409

### Abstract

To date, no evidence-based guidelines for the treatment of chronic osteomyelitis exist. Owing to certain similarities, treatment philosophies applicable to musculoskeletal tumour surgery may be applied in the management of chronic osteomyelitis. This novel approach not only reinforces certain important treatment principles, but may also allow for improved patient selection as surgical margins may be customised according to relevant host factors. When distilled to its most elementary level, management is based on a choice between either a palliative or curative approach. Unfortunately there are currently no objective criteria to guide selection of the most appropriate treatment pathway.

The pre-operative diagnostic work-up should be tailored according to the relevant objective, albeit confirming the clinical suspicion of the presence of infection, host stratification, anatomical disease classification, pre-operative planning or post-operative follow-up. MRI and PET-CT are emerging as the imaging modalities of choice. Interleukin-6, in combination with CRP, has been shown to have excellent sensitivity in the diagnosis of implant-associated infection. Molecular methods are growing rapidly as the method of choice in pathogen detection.

Chronic osteomyelitis, as is the case with musculoskeletal tumours, can only be eradicated through complete resection of all infected bone. Chemotherapy, in the form of antibiotics, only plays an adjuvant role. Dead space management is essential following debridement, and the appropriate strategy should be selected according to the anatomical nature of the disease. Provision of adequate bony stability is crucial as it promotes revascularisation and maximisation of the host's immune response. Although there is currently a variety of fixation options available, external fixation is generally preferred.

**Key words**: osteomyelitis, chronic, management, review

### Introduction

When contemplating open fractures Hippocrates stated that 'One should especially avoid such cases if one has reasonable excuse, for the risks are great and rewards are few'.[1] This statement still rings true today for chronic osteomyelitis. Prior to the implementation of contemporary classifications systems poor results were universally reported in the management of chronic osteomyelitis. The Mayo Clinic, for example, reported a failure rate of 20% and this figure deteriorated to failure in over 60% of patients in the presence of mixed aerobic and anaerobic infections.[2]

*Chronic osteomyelitis can only be eradicated through complete resection of all infected bone*

The poor outcome of treatment in chronic bone infections has inspired many changes in our management strategy over the past few decades. The 1970s can be seen as the era of secondary healing. During this period sequential debridement, healing by secondary intention and long-term antibiotic treatment were the order of the day. Reconstruction options were often limited to open sky techniques (Papineau grafting) or bypass grafting. As a result of these limitations the extent of surgical debridement was restricted and residual fibrotic and ischaemic tissue was often left behind, impairing the host's ability to launch an effective defence against bacterial persistence. In the 1980s wound revitalisation, involving thorough wound debridement with excision of all ischaemic tissue, became the mainstay of treatment. In conjunction with systemic and local antibiotic therapy, wound revitalisation allowed early closure of wounds following the debridement.[3] The era of revascularisation followed as a result of this new-found ability. In the 1990s free tissue transfer involving microvascular anastomosis became an integral part of the post-infective reconstruction process. The advances in soft tissue management culminated in the creation of a wound bed that was able to withstand the metabolic demands of more complex limb reconstruction procedures. In the past two decades, the potential for skeletal reconstruction has reached new heights. Salvage protocols for peri-prosthetic infection, incorporating staged endo-prosthetic replacement, have grown in popularity. The propagation of the science of distraction osteogenesis and Ilizarov techniques outside of Russia has allowed surgeons the opportunity to reconstruct much larger bone defects than before. Most recently the induced membrane technique, popularised by Masquelet, has emerged as a useful adjunct in the management of large bone defects following debridement.

In Part I of this two-part series we will discuss the management strategies currently available for the management of chronic osteomyelitis. Certain novel concepts, key to the decision-making process, will also be introduced. The different diagnostic modalities, which may be employed in the conformation of the presence of infection or during the pre-operative workup of the patient, will also be explored. Finally we will discuss the surgical management strategies that may be implemented during the first stage of treatment, with specific reference to debridement techniques, pathogen detection, dead space management and skeletal stabilisation. In Part II of this series on the management of chronic osteomyelitis, which will be published in the next issue of this journal, we will review antibiotic therapy, as well as soft tissue and skeletal reconstruction following debridement.

## Management strategies

To date, no evidence-based guidelines exist in terms of the treatment of chronic osteomyelitis.[4] When distilled to its most elementary level, management is based on a choice between either a palliative or curative approach. Management strategies, aimed at eradication of infection and limb reconstruction, incorporate a wide array of surgical procedures and techniques in terms of debridement, dead space management, soft tissue cover and skeletal reconstruction. While curative management strategies usually involve multiple surgical procedures, palliative treatment strategies, on the other hand, are much less invasive and typically involve the use of chronic suppressive antibiotic therapy. Thus the most important decision a surgeon faces is whether to embark on either a curative or a palliative treatment strategy.

This decision regarding cure or palliation requires consideration of several factors, foremost of which is the host's physiological status. As described by Cierny, a C-host should be palliated, whereas A- and B-hosts may be considered for a curative treatment protocol. The main risk involved in certain curative treatment strategies, is the fact that treatment failure may result in unplanned amputation of the limb. If, for example, wide resection and limb reconstruction through bone transport is embarked upon in a patient who is unable to cope with the physical or physiological demands of the process, failure of the reconstruction process may result in amputation. To justify the morbidity and risk of limb salvage, the expected outcome must offer distinct advantages over an amputation or palliation alone. If treatment aimed at cure is contraindicated or excessive, as a result of the risk it entails, the patient should be classified as a C-host and offered palliation (incision and drainage, oral antibiotics, ambulatory aides, and pain medication). Amputation may be indicated when limb salvage and palliation are neither safe nor feasible.[5] The main problem we currently face, however, is the absence of objective criteria according to which a C-host should be defined.

Owing to various similarities, principle among which is the high recurrence rate following incomplete excision, certain treatment philosophies applicable to musculoskeletal tumour surgery may also be applied when formulating a treatment plan for chronic osteomyelitis. Excision margins, for example, may be thought of in oncological terms with a simple sequestrectomy representing an intralesional excision, direct or indirect unroofing a marginal excision, and finally a complete resection can be seen as a wide excision. Similarly antibiotic therapy can be thought of as chemotherapy which may be instituted in a neo-adjuvant, adjuvant and palliative setting. This novel approach to chronic osteomyelitis not only reinforces certain important treatment principles, but may also allow for improved patient selection as surgical margins may be customised according to relevant host factors.

## Pre-operative considerations

### Clinical evaluation

Patient evaluation should include a meticulous history taking and careful examination.

Information should be gathered regarding the main complaint, associated problems, medical history, previous surgical history and prior therapeutic interventions. Examination should include a systemic evaluation as well as a thorough assessment of the local pathology, skeletal stability, the condition of the soft tissues, vascularity and neurological status.

### Imaging

Imaging modalities should be tailored to the relevant objective, albeit confirming the clinical suspicion of the presence of infection, anatomical disease classification, pre-operative planning or post-operative follow-up.

Ultrasonic waves do not cross cortical bone but ultrasound is still useful in the assessment of the presence of periosteal reaction or purulent collections. Ultrasound may also be utilised as a guide during deep aspiration of fluid collections for culture and sensitivity. X-rays and CT scanning are useful in localising sequestra or cloacae and also aid in the assessment of skeletal integrity and stability (*Figure 1*).

MRI has evolved as the modality of choice, especially in light of the modern oncologically oriented approach. It provides the most accurate information on extent of disease in bone and soft tissue and is therefore especially useful when planning a marginal or wide resection[6] (*Figure 2*).

Positron emission tomography (PET) scanning has also gained popularity and has surpassed MRI as the most sensitive and specific imaging modality to diagnose the presence of infection.[7] It has also been shown that $^{18}$F-FDG PET/CT is a highly sensitive and specific method in the evaluation of chronic post-traumatic infection. PET/CT allows precise anatomical localisation and characterisation, demonstrating the extent of involvement with a high degree of accuracy.[8]

**Laboratory investigations**

As is the case with imaging modalities, laboratory investigations may be used in several contexts. In all patients a comprehensive haematological and biochemical profile, including a full blood count, renal and liver function tests, as well as an electrolyte and nutritional profile is required in order to stratify the host's physiological status. In addition, supplementary tests may be required to ascertain the degree of systemic compromise as a result of certain specific disorders. Examples include $HbA_1C$ assessment in the case of diabetes mellitus, creatinine clearance in patients with chronic renal failure, and $CD_4$ counts and viral loads in HIV-infected individuals.

The second capacity in which laboratory studies can be utilised is as a diagnostic tool in the confirmation of the presence of sepsis. In this respect Lautenbach has shown that iron studies are particularly useful with an increased ferritin:iron ratio (in excess of 7), a decrease in iron saturation, as well as a decrease in mean cell volume and mean cell haemoglobin, all pointing to the presence of underlying infection.[9] Routine infection markers, including the leukocyte count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein level (CRP) may be used in both the diagnosis of the presence of infection as well as the follow-up of the patient. It should however be kept in mind that the WBC and ESR may be normal in extensive non-inflamed, and localised lesions (grade 6 and 7 infections according to the Lautenbach classification system). Pro-calcitonin (PCT) is currently routinely used in the diagnosis of the presence of severe infections in critically ill patients.[10] Pro-calcitonin however has a limited role in the diagnosis of the presence of osteoarticular infection, with a sensitivity of only 16.6% in osteomyelitis and 33% in peri-prosthetic infections.[11,12] In addition PCT does not appear to be superior to CRP in the post-operative follow-up of patients.[13] In contrast to pro-calcitonin, the combination of abnormal CRP and inteleukin-6 has been shown to be 100% sensitive in the diagnosis of deep infection in the presence of an implant.[10]

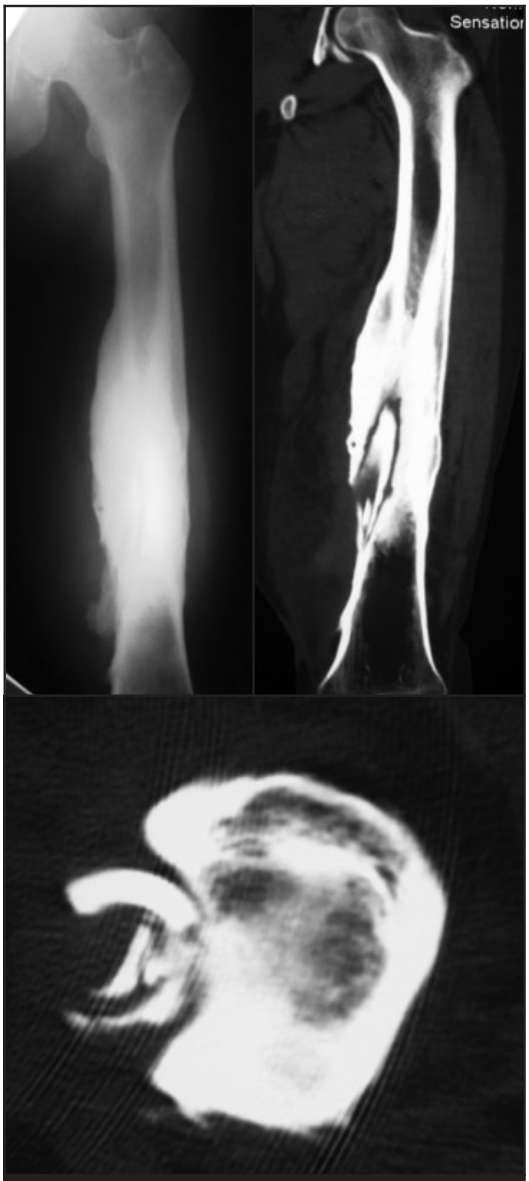

***Figure 1. X-ray and CT scan images illustrating cortical sequestration as a result of chronic haematogenous osteomyelitis***

On the other hand tumour necrosis factor and interleukin-8 have been shown to be elevated in acute, but not in chronic post-traumatic osteomyelitis.[14] These pro-inflammatory cytokines have unfortunately not been studied in the setting of chronic haematogenous osteomyelitis.

*Positron emission tomography (PET) scanning has also gained popularity and has surpassed MRI as the most sensitive and specific imaging modality to diagnose the presence of infection*

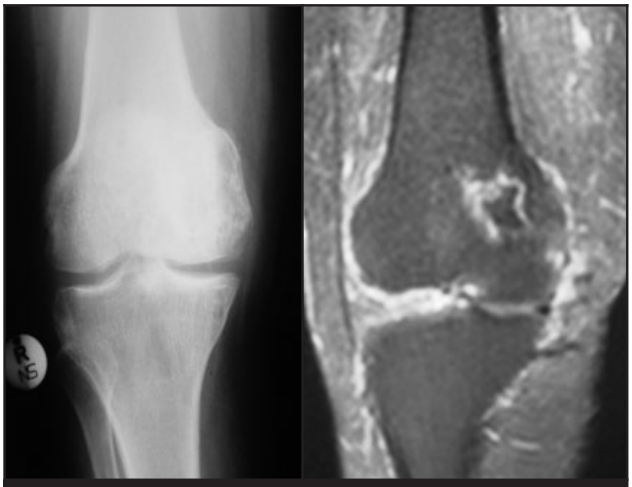

*Figure 2. X-ray and MRI images indicating cancellous sequestration in the metaphysis of the distal femur*

**Host stratification and optimisation**

Following the confirmation of the presence of infection and determination of the severity of the disease, attention should shift towards accurate anatomical and physiological classification. Numerous classification systems have been described. The Cierny and Mader system remains the most popular classification system in use today. The most important decision is to embark on either a curative or palliative treatment strategy. Once a curative management option is selected emphasis should be placed on host optimisation, and modifiable risk factors should be addressed. Reversal of these risk factors will improve the outcomes in B-hosts to more closely resemble the results seen in A-hosts.[15] Cessation of smoking, tight glycaemic control and dietary supplementation, for example, take precedence over any surgical intervention.

**Pathogen identification**

Cierny has previously recommended that attempts be made to identify the pathogen prior to the first formal surgical debridement through biopsy of deep granulation tissue.[16] This view is not uniformly held and not routinely implemented. In cases without significant local or systemic septic complications, pathogen detection may be delayed to after the primary debridement procedure. In certain scenarios pre-operative ('neo-adjuvant') antibiotics may be mandatory, for example in patients with significant local (cellulitis in the region of the incision) or systemic compromise (systemic sepsis or septic shock). In such cases pre-operative identification of the causative organism is essential and samples for microscopy, culture and sensitivity (MCS) should be obtained either through open biopsy or deep aspiration under ultrasound guidance, prior to definitive surgery.

Contrary to popular belief swab culture from a sinus may offer some diagnostic benefit. Firstly, the identification of methicillin-resistant *S. aureus* (MRSA) or vancomycin-resistant enterococcus necessitates the implementation of stringent infection control measures during hospitalisation. Secondly, isolation of *S. aureus* from a superficial culture has a high degree of correlation with deep cultures.[17]

In cases without significant local or systemic septic complications, pathogen detection may be delayed to after the primary debridement procedure.

## Surgical management

**Debridement techniques**

As is the case with musculoskeletal tumours, eradication of chronic osteomyelitis can only be achieved through adequate resection. Chemotherapy only plays an adjuvant role. Unless a palliative treatment pathway has been chosen, all necrotic or ischaemic tissues should be excised.[16] All foreign bodies and surgical implants need to be removed, with the exception of early infection following osteosynthesis where union is expected to occur. Soft tissues, and especially scar tissue, should be resected to a supple, well-perfused margin.[18] In terms of the bony debridement several techniques are currently available including simple sequestrectomy, intra-medullary reaming (indirect unroofing), tangential excision (direct unroofing), segmental resection and amputation. Despite the fact that several techniques have been described in order to determine the viability of bone, 'point-of-care testing' (POCT) remains the most trustworthy tool.[19] This technique involves intra-operative assessment of bone colour, bone sound, bone texture, as well as the quality of the cancellous bone and surrounding soft tissues in order to distinguish vital bone from vital-affected bone or devitalised bone. Devitalised bone should be excised to the point where punctate bleeding, also known as the 'paprika sign', is noted.[20]

Schmidt *et al*. illustrated that osteitis can only truly be eradicated through complete resection of all infected bone, and that remaining infected or devitalised bone segments may act as a source for persistent infection or result in late reactivation. On the other hand, the authors pointed out that affected bone may recover when it is surrounded by vital, healthy soft tissue.[21] When contemplating the extent of the debridement the anatomic nature of the disease, the physiological condition of the host and the proposed skeletal reconstruction technique should be considered. Compromised hosts, for example, are theoretically best treated with a wide resection of all infected tissues and subsequent limb reconstruction.[22] But herein resides one of the main problems a surgeon faces when dealing with a compromised host. Wide resection and limb reconstruction is advised to achieve cure, but the reconstruction procedures required, typically involving bone transport or extensive bone grafts, are fraught with danger in the poor host and failure frequently results in the amputation of the limb.

**Pathogen detection**

Routine microscopy, culture and sensitivity (MCS) of tissue, bone and exudates taken under aseptic condition in the absence of antibiotic therapy in the preceding ten days, still serves as the primary diagnostic modality in order to confirm the presence of infection.[23] Multiple samples should be acquired early in the procedure from fluid collections, soft tissue, bone and foreign materials or sequestra.

Samples should undergo aerobic and anaerobic incubation for prolonged periods, at least seven days, in order to increase detection of fastidious organisms.

Owing to the fact that only a minor fraction of biofilm-based micro-organisms is planktonic in nature (and thus available for culture) and small colony variants may enter a latent metabolic state, traditional culture techniques are frequently unreliable in the identification of the causative pathogen embedded in the biofilm covering implants or necrotic bone. Culture yield from implants or sequestra can be enhanced through sonication, a process utilising ultrasound to shear organisms from the biofilm on the substrate.[24] This technique may be especially valuable in low-grade periprosthetic infections.

Molecular methods have, however, grown rapidly as the method of choice in pathogen detection. These techniques are based on characterisation of the causative organism's genome. Polymerase chain reaction (PCR) pyrosequencing is currently the most popular technique. It can be performed on any specimen and is able to reliably identify the micro-organism involved, irrespective of its phenotype (culturability), prior antibiotic therapy or metabolic state.[18]

## Dead space management

Several alternatives are available to deal with the dead space resulting from the excision of necrotic and devitalised tissue. Contemporary techniques include gentamycin-impregnated polymethylmethacrylate (PMMA) beads, Lautenbach irrigation systems, physician-directed antibiotic-impregnated PMMA spacers or intramedullary nails, as well as antibiotic-loaded calcium sulphate pellets. All of these methods incorporate local adjuvant antibiotics, aimed at eradicating persistent bacterial contamination. The choice of dead space management is generally determined by the patho-anatomical nature of the disease and the volume of the dead space. Continuous irrigation, as popularised by Lautenbach, remains a versatile dead space management technique and is commonly utilised in Cierny and Mader type I post-operative infections.[25,26] Alternatively, antibiotic-impregnated PMMA intramedullary nails may be used in type I infections, especially in the setting of post-operative sepsis.[27] Dead space following debridement of type II lesions are typically dealt with through local or free soft tissue transfer procedures. Gentamycin-impregnated PMMA beads remain useful in type III lesions despite the fact that they require removal at a subsequent procedure. This disadvantage has prompted the use of several alternative, absorbable products including antibiotic-impregnated lyophilised collagen sponge, calcium sulphate pellets and bioactive glass.[28,29] Concerns have, however, been raised regarding the occurrence of aseptic wound dehiscence with the use of calcium sulphate pellets.[30] Antibiotic-impregnated PMMA spacers, commonly utilised in the setting of peri-prosthetic infection, have gained much popularity in the management of other Cierny and Mader anatomical type IV infections following the encouraging results with the induced-membrane technique reported by Masquelet[31] (*Figure 3*).

The optimal composition of physician-directed antibiotic-impregnated PMMA spacers has been investigated. Using a combination of antibiotic agents improves antibiotic release and inhibition of bacterial growth.[32] Gentamicin/vancomycin-loaded spacers were most effective against *S.epidermidis* and MRSA, while gentamicin/teicoplanin-combination spacers showed the best results against *E. faecalis* and *S. aureus*. Proportional weights of up to approximately 5 weight/weight % (2 g vancomycin per 40 g cement powder) have a negligible influence on the mechanical strength of the cement.[33] When mechanical strength is not a consideration, the antibiotic content may be increased to 10%, although concentrations as high as 20% have been used.[34,35] As a result of the formation of a richly vascularised membrane around the PMMA spacer, this form of dead space management has become known as the induced membrane or Masquelet technique.[31] This technique offers several mechanical and biological advantages. The first is the fact that the induced membrane, which can be likened to an artificial periosteum, secretes several growth factors including VEGF and BMP-2.[36] Furthermore extracts from the membrane have been shown to stimulate bone marrow cell proliferation and differentiation to osteoblastic lineage. These factors combine to result in reduced resorption of cancellous bone graft inside the membrane.[31] Secondly, as illustrated in an animal model, the induced membrane prevents adjacent soft tissue from protruding into the defect, adheres to the resected bone edges and does not collapse following removal of the spacer, thus delineating a cavity corresponding to the volume of the retrieved cement spacer.[37]

*Figure 3. Antibiotic-impregnated spacer following a wide resection. Stability was achieved with the aid of a circular external fixator*

This so-called 'spacer effect' has proven very useful in the reconstruction of bone defects, where the resulting cylinder forms a stable receptacle for bone graft and also serve as a framework through which a bone segment may be transported.

**Skeletal stabilisation**

It is has been shown that skeletal stability results in a statistically significant reduction in the incidence of infection following open fractures.[38] This principle also applies to skeletal reconstruction following debridement of infected bone. In an animal model it was found that the union of an infected fracture is directly related to the degree of bony stability.[39] The theory is that stability promotes revascularisation, resulting in enhanced perfusion and maximisation of the host's immune response.[40]

A variety of fixation options is currently available, although external fixation is generally preferred. Intramedullary PMMA nails do provide some stability, but cannot achieve the level of stability provided by external fixation. Curtis and colleagues found, in an experimental model, that infected osteotomies stabilised with external fixation had fewer and less severe infections than those stabilised with either a reamed or unreamed intramedullary nail.[41] Circular external fixators have gained much popularity in the field of post-infective reconstruction as a result of their modularity, minimally invasive nature and ability to effect bone transport and deformity correction.

*Stability promotes revascularisation, resulting in enhanced perfusion and maximisation of the host's immune response*

The attributes of fine wire fixators, in particular, are commonly used in the setting of septic non-unions and post-infective skeletal reconstruction. When dealing with a bone transport docking site, for example, the aim is to create the optimal biological milieu through the use of osteo-inductive materials in combination with the ideal mechanical environment. External fixation cannot achieve the level of stability required for primary bone healing, and union is therefore generally achieved through enchondral ossification. As predicted by the inter-fragmentary strain theory this can only be achieved under conditions resulting in inter-fragmentary strain of 2 to 10%.[42] This mechanical environment can reliably be created through the use of fine wire circular fixators. Tensioned fine wires exhibit increased axial stiffness with higher loads.[43] This non-linear, load-dependent axial stiffness is similar to the viscoelastic properties of tendons and ligaments. As result of these biomechanical attributes fine wire circular external fixators can be described as the only true form of true biological fixation.[44]

## Conclusion

Many questions regarding the management of chronic osteomyelitis remain unanswered. The wide variety of treatment options currently available, combined with the advances in our surgical reconstruction abilities, makes disease classification and accurate host stratification now more important than ever.

A dilemma commonly encountered is whether to embark on a palliative or curative treatment pathway. Although existing classification systems do offer some guidelines, the lack of objective selection criteria makes the decision a subjective one. The critical significance of correct patient selection is epitomised by the fact that failure of a curative (limb reconstruction) strategy invariably results in amputation of the involved limb.

Surgical debridement offers definite advantages in terms of achieving eradication of infection. However, not all cases require surgical intervention in order to achieve quiescence and certain patients may be successfully treated with antibiotics alone. In the second part of this series on the management of chronic osteomyelitis, the principles of antibiotic therapy, as well as the current concepts in post-debridement reconstruction, will be explored.

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# Chapter 5: The management of chronic osteomyelitis - Principles of post-infective reconstruction and antibiotic therapy

**Marais LC**, Ferreira N, Aldous C, Le Roux TLB.

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Contribution to authorship:

LC Marais – Concept, literature review, drafting of manuscript, revision of manuscript, corresponding author.

N Ferreira – Literature review, contributed to development of protocol for reconstruction of post-infective bone defects and revision of manuscript.

C Aldous – Concept development and revision of manuscript.

TLB Le Roux − Concept development and revision of manuscript.

# The management of chronic osteomyelitis: Part II – Principles of post-infective reconstruction and antibiotic therapy

**Dr LC Marais MBChB, FCS Orth(SA), MMed(Ortho)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics, Grey's Hospital, University of KwaZulu-Natal
**Dr N Ferreira BSc, MBChB, FC Orth(SA), MMed(Orth)**
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics, Grey's Hospital, University of KwaZulu-Natal
**Dr C Aldous BSc, BSc(Hons), MSc, PhD**
Medical Research Scientist, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal
**Prof TLB le Roux MBChB, FCS Orth(SA), MMed(Ortho)**
Professor and Head of Department, Department of Orthopaedics, I Military Hospital, University of Pretoria

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**Correspondence:**
Dr LC Marais
Department of Orthopaedic Surgery
Grey's Hospital
School of Clinical Medicine
University of KwaZulu-Natal
Private Bag X9001
Pietermaritzburg 3201
Email: Leonard.Marais@kznhealth.gov.za
Tel: +27 033 897 3299
Fax: +27 33 897 3409

## Abstract

Over the past few decades considerable progress has been made in terms of our ability to reconstruct post-infective soft tissue and bone defects. Soft tissue reconstruction is not always required and it is frequently possible to achieve a tension-free closure of well-perfused tissue following debridement. It is now generally accepted that primary closure of the wound, be it by direct suturing or tissue transfer, may be performed at the same sitting as the debridement. In cases were debridement has resulted in tissue loss, muscle or musculocutaneous flaps appear to be superior to random-pattern flaps in achieving resolution of infection. The management of bone defects is dependent on several factors including the host's physiological status, the size of the defect, duration of the defect, quality of the surrounding soft tissue, the presence of deformity, joint contracture/instability or limb length discrepancy, as well as the experience of the surgeon.

Surgery remains the mainstay of treatment when a curative treatment strategy is selected. As is the case with chemotherapy for bone tumours, antibiotic therapy fulfils an adjuvant role in curative management strategies. The choice of antibiotic, in this setting, remains a very difficult one and there are many problems with the interpretation of 'cure rate' data. The controversy surrounding the optimal duration and route of antibiotic therapy has not been resolved. The second role of antibiotics in the management of chronic osteomyelitis is disease suppression as part of a palliative treatment strategy. Further studies are required to clarify which patients may successfully be treated with antibiotics alone.

**Key words**: osteomyelitis, chronic, management, review

## Introduction

The complex and heterogeneous nature of chronic osteomyelitis necessitates a multi-disciplinary approach, involving experts in the field of orthopaedic tumour, infection and limb reconstruction surgery, plastic surgery, microbiology, nursing, physiotherapy and psychology. Numerous surgical techniques and adjuvant therapies have been developed during the past three decades in order to deal with the wide spectrum of pathology that falls under the heading of chronic osteomyelitis. Despite these developments, the outcome of current treatment protocols remains unsatisfactory, with failure of therapy reported in up to 20% of cases.[1]

The preceding article in this series aimed to elucidate current concepts in the diagnostic work-up and surgical management of chronic osteomyelitis. In this paper post-infective soft tissue and skeletal reconstruction, as well as the principles of antibiotic therapy, will be addressed. There are several controversial issues related to these subjects. The optimal choice for soft tissue cover following debridement, for example, remains controversial. Although several techniques have been described to deal with bone defects, a comprehensive contemporary strategy has not yet been described. In terms of antibiotic therapy, clear evidence-based guidelines are also lacking, especially in terms of the selection of the appropriate antibiotic agents, the optimal duration of treatment and the ideal route of administration.

## Post-debridement reconstruction

### Soft tissue reconstruction

In many cases it is possible to achieve a tension-free closure of well-perfused tissue following debridement. Unfortunately the excision of ischaemic tissue and sinuses frequently result in a soft tissue defect. It is now generally accepted that primary closure of the wound, be it by direct suturing or tissue transfer, may be performed at the same sitting as the debridement.[2,3] Cierny, however, emphasises the importance of systemic and local antibiotics, as well as a double setup in case of a single stage procedure. This involves re-scrubbing of all staff members, repeat preparation and draping of the patient, as well as the use of new instruments for the reconstructive part of the procedure.[4] Delayed primary closures may still be required in certain cases where, for example, a second look at the viability of remaining tissue is required, soft tissues are not amenable to closure due to swelling or induration, or where a second team is required to perform a complex free flap.

In the past post-debridement soft tissue defects were often left to heal by secondary intention or dealt with through the use of open-sky techniques like Papineau bone grafting. These methods have subsequently fallen out of favour, and authors like Ger have promoted the principle of muscle flap coverage in order to achieve improved cure rates.[5,6] This approach was justified through animal studies which showed that muscle or musculocutaneous flaps were superior to random-pattern flaps (i.e., local flaps) in achieving resolution of infection.[7] In an experimental model, Feng and colleagues were able to explain this phenomenon by showing increased blood flow and more consistent leukocyte mobilisation in musculocutaneous flaps when compared to random flaps. In addition, the oxygen tension in soft tissue defects covered by muscle flaps was shown to be higher than those covered through random-pattern flaps. The advantages of muscle flaps have also been illustrated in the clinical setting, although a recent review still questioned the clinical validity of the theoretical advances of muscle flaps in the setting of infection.[8,9]

With the advances in microsurgical techniques in the recent past, free tissue transfer has become more accessible. The success achieved with free flaps in the management of open fractures has prompted utilisation of these techniques in the management of chronic osteomyelitis. The excellent results, in terms of bony union and eradication of infection, with free muscle transfer in chronic osteomyelitis, have also been attributed to the dramatic increase in the local blood supply.[10] In addition, performing a debridement and free flap in a single sitting has been shown to be reliable in achieving cure.[3] Recently, perforator free flaps have gained much popularity in the management of open fracture and have been suggested to be superior in the management of tibial osteomyelitis.[11] Although free anterolateral thigh fasciocutaneous flaps have been shown to be effective in the management of open tibia fractures, it is technically challenging and free muscle- or musculocutaneous flaps are still considered the method of choice in coverage of lower leg defects.[12]

Several other salvage techniques have emerged in the recent past. Negative pressure dressing has been employed successfully in the management of many soft tissue defects. It has, however, a limited role in the management of chronic osteomyelitis as it results in the formation of dense and poorly vascularised scar tissue. The application of vacuum dressings to draining sinuses in particular is discouraged as it significantly complicates subsequent surgery.[4] Vacuum dressing may occasionally be considered in severely compromised hosts where tissue transfer is deemed impossible. More recently negative pressure wound therapy combined with the instillation of solution in the local area (VAC instil therapy) has been proposed as a viable alternative in the management of osteomyelitis-associated soft tissue defects.[13] This form of therapy is attractive as it offers the theoretical advantages of both the Lautenbach technique and negative pressure wound therapy. As a last resort, in certain cases where the local soft tissue condition does not permit flap coverage, open skeletal transport (in accordance with Ilizarov principles) may be considered.

### Skeletal reconstruction

Cierny and Mader type I, II and III lesions are, per definition, stable and generally do not require reconstruction of the defect left by the debridement. Type IV lesions, on the other hand, are characterised by instability and routinely require stabilisation and reconstruction of osseous defects resulting from the debridement. Existing classification systems for post-osteomyelitis bone defects, including those suggested by May and Gordon, have failed to keep up with the modern trends in limb reconstruction surgery and have therefore lost some of their value.[14,15]

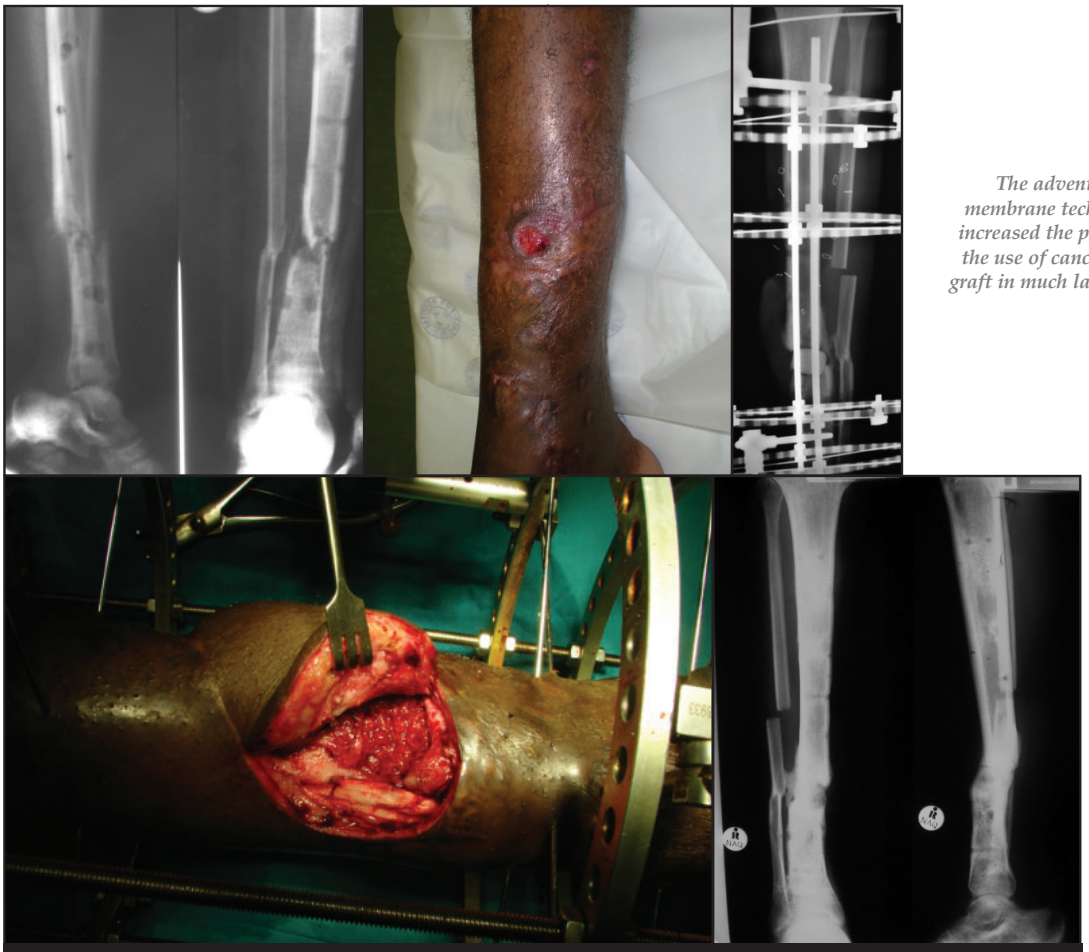

*Figure 1. Post-traumatic, contiguous chronic osteomyelitis of the tibia. Following marginal resection of the necrotic bone the resulting bone defect was treated with cancellous bone graft into an induced membrane (classic Masquelet technique).*[21]

Acute shortening, with primary docking of the bone ends, of up to 4 cm has been advocated for post-traumatic bone loss.[16] Unfortunately the soft tissue scarring associated with chronic osteomyelitis rarely permits acute shortening beyond 2 cm. Not only does acute shortening in the presence of significant scar tissue present technical difficulties with wound closure, it also carries a particular risk of vascular compromise as a result of kinking of blood vessels which are immobilised by rigid soft tissues. Acute shortening of 1–2 cm can, however, be used as part of a combined strategy, which may include the induced membrane technique along with bone grafting or bone transport.

*Unfortunately the soft tissue scarring associated with chronic osteomyelitis rarely permits acute shortening beyond 2 cm*

The size of a segmental bone defect which should be considered critical, and thus not suitable for autologous cancellous bone grafting, remains controversial. Traditionally approximately 4 cm has been recommended as the cut-off point.[17,18] The first problem with cancellous bone grafting is its dependence on the surrounding soft tissues for nourishment. Large grafts may undergo central necrosis in the absence of an excellent soft tissue envelope (bone bed).[19] Secondly the regenerated segment is often weak and prone to fracture as a result of partial graft resorption.[20] As a result, Tiemann *et al*. recommended 2 cm as the maximum size of a segmental diaphyseal tibial defect that can be managed with autologous cancellous grafting.[19]

The advent of induced membrane techniques has, however, increased the potential for the use of cancellous bone graft in much larger defects. Masquelet reported the successful use of this technique in 35 cases, with defects ranging from 4–25 cm.[21] Others have been able to reproduce these results.

*The advent of induced membrane techniques has increased the potential for the use of cancellous bone graft in much larger defects*

Stafford reported a 90% union rate of defects ranging from 1–25 cm (average 5.8 cm) with the use of reamer-irrigation-aspiration graft.[22] Although the induced membrane technique offers several theoretical and practical advantages, caution should be applied in the use of cancellous bone graft in tibial defects exceeding 4 cm, especially in the absence of periosteal new bone formation (*Figure 1*).[19]

Distraction osteogenesis, in accordance with the Ilizarov method, remains the gold standard in the management of post-debridement bone defects of 4 cm or more.[16,23] This may take the form of acute shortening with subsequent lengthening or, more commonly, bone transport into the defect. Distraction osteogenesis offers several advantages in the management of chronic osteomyelitis, including the increase of regional blood flow for a period of up to 17 weeks following the corticotomy.[24] Large defects can be dealt with through simultaneous multifocal transport, sequential transport or cable-transport techniques. The upper limit of the size of defects which may be dealt with through distraction osteogenesis is, however, highly dependent on the surgeon's experience with the technique (*Figure 2*).

*Circular fixation and bone transport is associated with its own subset of complications and a second procedure involving cancellous grafting of the docking site is generally recommended*

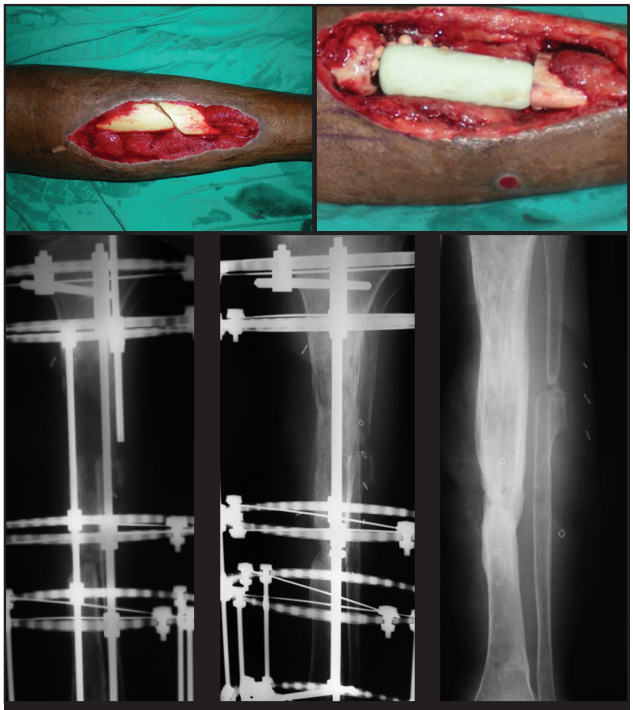

***Figure 2. Contiguous chronic osteomyelitis following a failed open reduction of a tibial shaft fracture. Wide resection of the necrotic bone segments was performed and an antibiotic-impregnated PMMA spacer inserted. Following removal of the spacer the resulting 8 cm bone defect was addressed with distraction osteogenesis. Union was achieved after a formal docking procedure.***

Circular fixation and bone transport is associated with its own subset of complications and a second procedure involving cancellous grafting of the docking site (formal docking) is generally recommended.[25] Following a comparative study, El-Gammal and colleagues suggested that defects smaller than 12 cm should be reconstructed with Ilizarov bone transport while free vascularised fibula grafts performed better in defects larger than 12 cm.[26] Although vascularised fibula grafts, fibula-pro-tibia (fibula centralisation) or fibula bypass grafting remain options for defects in excess of 12 cm these procedures involve donor site morbidity and is often complicated by non-union or fracture of the graft during the period of hypertrophy (*Figure 3*).[27]

A combination of techniques is commonly used. Ultimately the management of bone defects is dependent on several factors including the host's physiological status, the size of the defect, duration of the defect (i.e. acute or chronic), quality of the surrounding soft tissue, the presence of deformity, joint contracture/instability or limb length discrepancy, as well as the experience of the surgeon.

## Antibiotic therapy

It is important to note that surgery remains the mainstay of treatment when a curative treatment strategy is selected. As is the case with chemotherapy for bone tumours, antibiotics fulfil an adjuvant role in curative management strategies. Curative surgery should ideally involve a wide resection with clear margins. This goal is however frequently unachievable as it may result in unreconstructable loss of bone that is vital to the survival and function of the limb. Marginal resection may, on the other hand, leave behind colonised bone or soft tissue that may serve as a nidus for recurrent infection.[28] Even in wide resections the remaining bone and soft tissue bed should also be considered contaminated. Antibiotics are, therefore, used in wide and marginal resections (curative surgical strategies) in an attempt to sterilise the remaining bone and soft tissues. In the curative setting empirical adjuvant antibiotics are typically started immediately following the debridement, and the regimen is modified once the culture and sensitivity results become available.

The first role of antibiotics in the management of chronic osteomyelitis, is adjuvant therapy as part of a curative treatment strategy. The choice of antibiotic, in this setting, remains a very difficult one and there are many problems with the interpretation of 'cure rate' data. Firstly there are no standardised definitions for cure or failure of treatment and no universally accepted host stratification system. In addition, many of the historical studies evaluated the efficacy of antibiotics in the absence of surgical debridement or surgical implants. Studies often include a heterogeneous group of patients in terms of their physiological status, the aetiological source of the infection and the anatomical/pathological nature of the disease. Finally, *in vivo* effect does not always mirror the high degree of efficacy predicted by *in vitro* investigations. Empirical antibiotics should be selected on the basis of the aetiology of the infection as well as local pathogen profiles. β-lactams and vancomycin are the most commonly used antimicrobials in the medical management of osteomyelitis.[29]

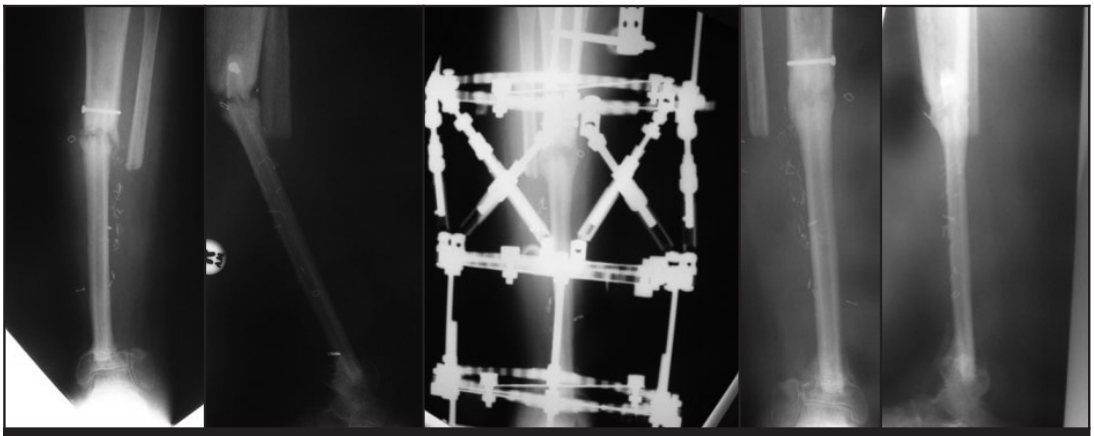

***Figure 3. Fracture of a vascularised fibula graft which was used to manage a 20 cm bone defect. Union of the fracture was achieved following gradual correction of the mechanical axis with the use of a hexapod external fixator.***

In terms of contiguous infections, The Bone Infection Unit in the United Kingdom recommends empirical parenteral vancomycin and meropenem.[2] Although this protocol covers a broad range of pathogens there are some potential concerns. Vancomycin offers excellent activity against MRSA and ampicillin-resistant enterococci. Unfortunately it has several drawbacks including poor bone penetration, increased minimal inhibitory concentrations among many *S. aureus* strains and has been shown to have increased recurrence rate when compared with cefazolin or ceftriaxone.[30,31] β-lactam antibiotics (penicillins, cephalosporins and carbapenems) exhibit poor bone penetration, with levels reaching only approximately 5–20% of serum concentrations. Fortunately serum levels of parenteral β-lactams are so high that the resulting bone levels most likely exceed the necessary minimum inhibitory concentration (MIC).[32] Cefepime appears to be a reasonable alternative to meropenem, offering good activity against Gram-negative organisms, and it has been shown to have excellent bone penetration, with bone concentration reaching 97–100% of serum levels.[33]

In terms of the route of administration, oral antibiotic agents which exhibit high bioavailibility are an acceptable alternative to parenteral therapy.[32] Several randomised clinical trials have found similar cure rates in patients treated with oral and parenteral antibiotic therapy.[34,35] In addition parenteral antibiotics are associated with an increased incidence of moderate or severe side-effects.[30] Preferred oral agents, based on clinical and pharmacokinetic data, include fluoroquinolones and trimethoprim-sulfamethoxazole (cotrimoxazole).[32] Studies involving fluoroquinolones have found high cure rates, although failure of treatment may occur in *Pseudomonas* or *S.aureus* infections, especially when used as monotherapy.[36] In addition, it is a matter of concern that fluoroquinolones have been associated with impaired bone healing and these agents may need to be avoided in cases of septic non-union or in the setting of post-infective reconstruction.[37]

Cotrimoxazole exhibits concentration-dependent killing, therefore higher than usual doses (7–8 mg/kg/day trimethoprim) are recommended in the treatment of chronic osteomyelitis.[38] De Barros *et al*. reported an impressive 98% cure rate with 6 months of cotrimoxazole therapy following surgical debridement, although it may be argued that the extended duration of therapy may have resulted in disease quiescence through suppression.[39] Rifampicin achieves bone levels equivalent to serum concentrations and when used in conjunction with other agents there appears to be a clear benefit in terms of cure rates.[40,41] It should however never be used as monotherapy due to the risk of the development of resistance. Sanchez *et al.* reported a 100% cure rate in staphylococcal infections with surgical debridement in conjunction with double the standard dose of cotrimoxazole combined with rifampicin for a mean of five weeks.[42] Similarly, cotrimoxazole combined with rifampicin achieved similar cure rates to both linezolid with rifampicin, as well as eight weeks of intravenous cloxacillin monotherapy, in the treatment of chronic osteomyelitis and infections associated with surgical implants.[43,44] It is important to note that oral dosing of β-lactam antibiotics results in serum levels of less than 10% of parenteral administration. This pharmacokinetic characteristic raises concern regarding the ability of β-lactams to reach adequate MIC in bone, despite the fact that their penetration is better in infected than in uninfected bone.[45] Clindamycin exhibits good bone penetration and many methicillin-resistant *S. aureus* strains are susceptible to the agent. Despite these characteristics there are no recent studies investigating the use of clindamycin in the management of osteomyelitis.

*In terms of the route of administration, oral antibiotic agents which exhibit high bioavailibility are an acceptable alternative to parenteral therapy*

Linezolid, the first antimicrobial in the new oxazolidinone class, was initially received with much enthusiasm as a result of its high bioavailability following oral administration and excellent activity against staphylococci, streptococci and vancomycin-resistant enterococci. Unfortunately clinical studies have shown cure rates of only 60% and prolonged used has been associated with pancytopaenia, peripheral neuropathy and optic neuritis.[46,47] The use of linezolid is therefore typically limited to patients with osteomyelitis resulting from vancomycin-resistant enterococci or patients who are intolerant of vancomycin.[46] Daptomycin, a new lipopeptide antimicrobial agent, exhibits good activity against Gram-positive bacteria including methicillin-resistant *S. aureus* and glycopeptide-resistant enterococci. It has been studied extensively in the management of osteomyelitis and has been shown to be a good salvage option in cases which failed to respond to standard therapy.[48]

The optimal duration of antimicrobial therapy following surgical debridement remains unknown. The traditional duration of treatment is four to six weeks. This is based on experience with the management of acute osteomyelitis in children, where extended periods of antibiotics are required, as well as the results of animal studies which illustrated that six weeks of antibiotics was effective in sterilising diseased bone.[49] This traditional recommendation is also derived from the assumption that revascularisation of bone following debridement takes about four weeks.[50] Several studies have failed to demonstrate increased efficacy of extended duration antibiotic therapy.[51] Furthermore, the absence of standardised treatment algorithms makes interpretation of the data very difficult. Many studies did not include surgical debridement or removal of surgical implants, and thus this form of treatment should rather be viewed as palliative intervention. Because of the historical absence of standardised definitions and treatment strategies, older antibiotic treatment protocols are inconsistent with our current way of thinking. The duration of antibiotic treatment should rather be based on the treatment strategy selected, the realistic aim of treatment and the extent of the surgical margin. In theory, curative management strategies involving wide resection would only require a short period of antibiotics in order to sterilise the remaining soft tissue. In practice truly wide margins are, however, very difficult to achieve. Traditional thinking dictates a minimum of six weeks treatment in curative treatment protocols involving marginal debridement. Unfortunately there is insufficient evidence to make definitive recommendations and further studies are required in this respect.[32] In palliative treatment strategies or in cases treated with intra-lesional debridement extended periods of antibiotics appear to remain appropriate.

The second role of antibiotics in the management of chronic osteomyelitis is disease suppression as part of a palliative treatment strategy. This form of treatment appears to be justified by the successful use of suppressive antibiotics in peri-prosthetic infections of hip or knee replacements.[52,53] Success rates of between 60 and 75% have also been reported in cases of infection associated with osteosynthesis through the use of long-term antibiotics without surgical removal of the implants.[38,54] The efficacy of suppressive treatment in chronic osteomyelitis without an implant has, however, not been determined. In addition many of the older studies looking at long-term antibiotic therapy included patients with and without surgical implants as well as surgically and non-surgically managed patients. This lack of uniformity made comparison of results impossible and, again, illustrates the urgent need for the establishment of standardised nomenclature and treatment strategies in the management of chronic osteomyelitis.

Chronic suppressive antibiotic therapy forms the cornerstone of palliative management in C-hosts. This form of treatment typically involves antibiotics that are prescribed for a period six months. If quiescence or sufficient suppression is achieved the antibiotics can be stopped. If the infection recurs after discontinuation of the therapy, a lifelong suppressive regimen should be considered.[50] Various antibiotic regimens have been investigated. Due to the inferior results reported with single agents, and the efficacy shown with the addition of a second agent in the setting of implant-related infections, most chronic suppressive regimens generally involve the combination of two agents.[55,56] Antibiotics used in suppressive regimens include cotrimoxazole, rifampicin, ciprofloxacin, cloxacillin, fusidic acid and clindamycin.[38,45,57,58] Although directed therapy according to culture and sensitivity results is the ideal, this is frequently not practical and possibly not necessary in order to achieve clinical quiescence. The available literature suggests that cotrimoxazole and rifampicin can be considered as first line chronic suppressive antibiotic therapy.[33] If these agents fail to achieve clinical suppression during the first six months, second line therapy may be instituted in the form of clindamycin or cloxacillin in combination with rifampicin, ciprofloxacin or fusidic acid.

## Conclusion

Over the past few decades considerable progress has been made in terms of our ability to reconstruct post-infective soft tissue and bone defects. Muscle or musculocutaneous flaps appear to be superior to random-pattern flaps (i.e. local flaps) in achieving resolution of infection and it is now generally accepted that primary closure of the wound may be performed at the same sitting as the debridement. Several factors need to be considered when dealing with post-infective bone defects, and the size of the defect serves as a useful guideline when selecting the appropriate treatment strategy. The soft tissue scarring associated with chronic osteomyelitis rarely permits acute shortening beyond 2 cm. Good results have been reported with cancellous grafting into an induced membrane and the Masquelet technique may be utilised in cases with bone loss of more than 2 cm. For bone defects larger than 4 cm distraction osteogenesis may be appropriate, while free vascularised fibula grafts may have to be considered for defects in excess of 12 cm.

In terms of antibiotic therapy clear evidence-based guidelines are lacking, especially in terms of the selection of the appropriate antibiotic agents, the optimal duration of treatment and the ideal route of administration. Oral antibiotic agents that exhibit high bioavailability appear to be an acceptable alternative to parenteral therapy.

*Over the past few decades considerable progress has been made in terms of our ability to reconstruct post-infective soft tissue and bone defects*

Preferred oral agents, based on clinical and pharmacokinetic data, include fluoroquinolones, rifampicin and trimethoprim-sulfamethoxazole. In theory, curative management strategies involving wide resection would only require a short period of antibiotics in order to sterilise the remaining soft tissue. Traditional thinking dictates a minimum of six weeks of treatment in curative treatment protocols involving marginal debridement. In palliative treatment strategies and in cases treated with intra-lesional debridement, extended periods of antibiotics remain appropriate.

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# PART 3

# The importance of patient selection in curative management strategies

Part 3 of this thesis investigates the outcome of a curative treatment strategy involving bone transport through an induced membrane with the aid of circular external fixation. Although the number of cases presented in this series was small, there were certain noteworthy findings.

Despite the fact that antibiotic-impregnated PMMA spacers offer several theoretical biological advantages, their use did not translate into a clinically relevant improvement in the external fixation index. In actual fact, the procedure resulted in a considerable increase in external fixation time when compared with the more traditional Ilizarov methods.[1] The theoretical mechanical advantages of the spacer however, appeared to be clinically relevant. Not only did the spacer act as a useful dead space management tool, it also facilitated the bone transport process by preventing soft tissue entrapment. It was not possible in this series to determine if local antibiotic elution was beneficial as a control group was not included. Despite the limitations of the study, the technique appears to be effective and we were able to achieve remission of infection in all cases.

Our success in achieving resolution of infection was however, most likely not a result of therapeutic prowess. It is more likely that our success was the result of prudent patient selection. The patients included in this series of cases were selected according to the same host stratification system proposed in Part 4 of this thesis. This study therefore indicates that

patient selection is key in ensuring a successful outcome of curative treatment. In addition, this study also shows that once segmental resection and bone transport is embarked on it has to be carried through to completion, as the only alternative may be amputation. One patient was poorly motivated, non-compliant with rehabilitation and eventually requested amputation. This suggests that patient compliance and motivation should be included as a risk factor, that needs to be assessed during host stratification.

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# Chapter 6: Bone transport through an induced membrane in the management of tibial bone defects resulting from chronic osteomyelitis

**Marais LC**, Ferreira N.

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LC Marais – Concept, literature review, data collection and analysis, drafting of manuscript, revision of manuscript, corresponding author.

N Ferreira – Concept, literature review, data collection, revision of manuscript.

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ORIGINAL ARTICLE

# Bone transport through an induced membrane in the management of tibial bone defects resulting from chronic osteomyelitis

**Leonard Charles Marais**[1] · **Nando Ferreira**[1]

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**Abstract** Wide resection of infected bone improves the odds of achieving remission of infection in patients with chronic osteomyelitis. Aggressive debridement is followed by the creation of large bone defects. The use of antibiotic-impregnated PMMA spacers, as a customized dead space management tool, has grown in popularity. In addition to certain biological advantages, the spacer offers a therapeutic benefit by serving as a vehicle for delivery of local adjuvant antibiotics. In this study, we investigate the efficacy of physician-directed antibiotic-impregnated PMMA spacers in achieving remission of chronic tibial osteomyelitis. This retrospective case series involves eight patients with chronic osteomyelitis of the tibial diaphysis managed with bone transport through an induced membrane using circular external fixation. All patients were treated according to a standardized treatment protocol. A review of the anatomical nature of the disease, the physiological status of the host and the outcome of treatment in terms of remission of infection, time to union and the complications that occurred was carried out. Seven patients, with a mean bone defect of 7 cm (range 5–8 cm), were included in the study. At a mean follow-up of 28 months (range 18–45 months), clinical eradication of osteomyelitis was achieved in all patients without the need for further reoperation. The mean total external fixation time was 77 weeks (range 52–104 weeks), which equated to a mean external fixation index of 81 days/cm (range 45–107). Failure of the skeletal reconstruction occurred in one patient who was not prepared to continue with further reconstructive surgery and requested amputation. Four major and four minor complications occurred. The temporary insertion of antibiotic-impregnated PMMA appears to be a useful dead space management technique in the treatment of post-infective tibial bone defects. Although the technique does not appear to offer an advantage in terms of the external fixation index, it may serve as a useful adjunct in order to achieve resolution of infection.

**Keywords** Chronic osteomyelitis · Bone transport · Distraction osteogenesis · Induced membrane · Masquelet technique · Circular external fixation

## Introduction

Wide resection of infected bone improves the odds of relapse-free periods in patients with chronic osteomyelitis. Aggressive debridement creates segmental bone defects. While small defects may be managed with acute shortening or cancellous bone grafting, larger segmental bone defects typically require bone transport with regeneration of the deficient bone segment through distraction osteogenesis [1]. The size of critical bone defect which by definition cannot be managed with cancellous bone graft remains controversial. Tiemann et al. [2] recommended 2 cm as the maximum size of a segmental diaphyseal tibial defect that should be managed with autologous cancellous grafting alone.

The induced membrane (Masquelet) technique, involving the placement of a polymethylmethacrylate (PMMA) spacer in the defect with subsequent bone grafting, has emerged as a useful adjunct in the management of large

✉ Leonard Charles Marais
Leonard.Marais@kznhealth.gov.za

[1] Tumor, Sepsis and Reconstruction Unit, Department of Orthopaedic Surgery, Greys Hospital, University of KwaZulu-Natal, Private bag X9001, Pietermaritzburg 3201, South Africa

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defects. The induced membrane is highly vascularized and secretes several growth factors, including VEGF and BMP-2 [3]. Furthermore, extracts from the membrane have been shown to stimulate bone marrow cell proliferation and differentiation of progenitor cells to the osteoblast lineage [4]. These factors combine to facilitate successful consolidation of cancellous bone graft within an induced membrane in segmental tibial defects of up to 25 cm in length [5].

Distraction osteogenesis remains a method of choice for the management of bone defects in excess of 4 cm [6, 7]. The procedure offers several advantages in the scenario of post-osteomyelitis skeletal reconstruction, including the increase in regional blood flow for a period up to 17 weeks following the corticotomy [8]. Although bone transport can be achieved with various devices, circular external fixation in accordance with Ilizarov principles remains foremost due to its reliability, modularity and safety in the presence of infection.

The use of antibiotic-impregnated PMMA spacers, as a customized dead space management tool after debridement for chronic osteomyelitis, has grown in popularity [9, 10]. Apart from the biological advantages illustrated by Masquelet et al., the spacer offers potential therapeutic benefit as a vehicle for delivery of local adjuvant antibiotics. Physician-directed antibiotic-impregnated PMMA spacers have been shown to effectively elute antibiotics at the site of infection for up to several months following implantation [11]. This characteristic has been used to good effect in periprosthetic infections where staged reconstruction has been shown to be safe after removal of the spacer [12]. The biological, mechanical and therapeutic advantages offered by the Masquelet technique have prompted the use of antibiotic-impregnated PMMA spacers in larger segmental defects requiring bone transport.

The aim of this study was to determine whether the use of antibiotic-impregnated PMMA spacers followed by bone transport with circular external fixation is effective in achieving remission of infection following segmental resection in chronic tibial osteomyelitis. A secondary objective was to determine the external fixation index of these cases and to compare it to those of other authors using traditional Ilizarov methods.

## Materials and methods

A retrospective review was conducted of all patients treated by bone transport through an induced membrane at our tertiary level limb reconstruction unit over a 4-year period between June 2009 and June 2013. All adult patients treated for a diaphyseal tibial bone defect by bone transport were included in the study. Patients were excluded if the standard treatment protocol was not completed. The subjects' charts were reviewed and data extracted in order to describe the patient demographics, cause of the bone defect, physiological status of the host in accordance with the Cierny and Mader classification system, relevant local and systemic risk factors, the number and nature of surgical procedures performed, time to union and, finally, the complications that occurred.

All patients were treated according to a standardized treatment protocol. Following comprehensive clinical, biochemical and radiological evaluation, patients were classified according to the Cierny and Mader classification system [13]. The initial surgical procedure included a wide resection of all necrotic and ischemic tissue to a well-perfused margin, insertion of an antibiotic-impregnated PMMA spacers in the resulting bone defect, reconstruction of the soft tissue defect with a local flap and application of a standard five ring circular fine wire external fixator capable of effecting bone transport (Fig. 1). The PMMA spacers were constructed from Palacos R+G® bone cement (Heraeus Medical, Hanau, Germany) containing 500 mg gentamicin per 40 mg of PMMA powder, mixed with 2 g of vancomycin powder per 40 mg of PMMA. In the majority of cases, the spacer was shaped outside the body and only inserted into the defect once it had hardened and most of the heat had dissipated. In later cases, the PMMA spacer was inserted before the cement had completely hardened, in order to allow the ends of the cement to overlap the bone ends.

Post-operatively, all patients were treated with generic parenteral antibiotics, in the form of vancomycin and meropenem, until results from 7-day microscopy, cultures and microbial antibiotic sensitivity (MCS) became available. Oral antibiotic therapy, tailored according to the results of culture and sensitivity, was then commenced and continued for a period of 6 weeks. During this initial period, the patient was allowed to mobilize partial weight-bearing in order to curtail disuse osteopenia. The second-stage procedure was performed after a minimum of 6 weeks from the index procedure and only if there was no clinical or biochemical evidence of ongoing infection as indicated by normal white blood cell count, C-reactive protein and erythrocyte sedimentation rate. The second-stage procedure involved removal of the spacer through an incision at the edge of the flap, debridement of the bone edges, as well as suturing of the incision made in the induced membrane. At the same sitting, a metaphyseal osteotomy was performed, according to the technique described by De Bastiani, in preparation for bone transport [14]. A latency period of 7 days was observed prior to commencement of bone transport which was performed according to standard Ilizarov principles of 0.25 mm distraction increments, four times per day [15]. During this

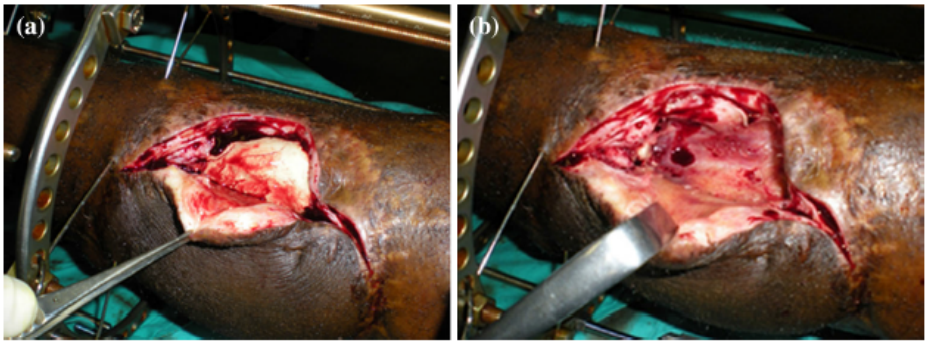


**Fig. 1** **a** Antibiotic-impregnated PMMA spacer, which was inserted into the bone defect prior to soft tissue cover and stabilization. **b** Induced membrane at time of removal of the spacer

stage of the treatment protocol, full weight-bearing, with no more than a single crutch, was advocated.

Once the bone ends were brought into close apposition through bone transport, a formal docking procedure was performed in the form of a cancellous and Phemister-type bone graft [16]. No internal fixation of docking sites or regenerated segments was performed. Pin track care was performed according to a previously published protocol [17]. When three out of the four cortices of the regenerate were judged well formed on AP and lateral X-rays and the docking site had united, the circular fixator was removed. The external fixation index was defined as the total time of external fixation per centimetre of bone transport.

Ethical approval was obtained from the relevant ethics review board prior to commencement, and the study was performed in accordance with the pertinent ethical guidelines.

## Results

The records of eight patients, who were referred to our unit with Cierny and Mader anatomical type IV chronic osteomyelitis of the tibial diaphysis, were reviewed. One patient, who did not complete the standard treatment protocol, was excluded from the study. The follow-up period for this case was <18 months. Of the remaining seven patients, chronic osteomyelitis occurred after treatment for open tibia fractures in six and the final patient developed contiguous osteomyelitis following an open reduction and intramedullary nail for failed non-operative management of a closed fracture of the tibia shaft.

The mean age of patients was 29 years (range 28–44 years), and the mean time from injury to referral to our unit was 3 months (ranging from 1 to 14 months). Systemic risk factors, namely hypoalbuminemia, substance-induced psychiatric disorder and cigarette smoking, were identified in five of the patients (Table 1). The mean follow-up period in this series of patients was 28 months (range 18–45 months). The mean interval between the index (first stage) procedure and removal of the spacer and tibial osteotomy (second stage) was 12 weeks (range 9–28 weeks), and the mean time from the second-stage procedure to bone grafting of the docking site was 17 weeks (8–39 weeks).

Clinical resolution of infection was achieved in all patients as indicated by normal clinical and biochemical findings at last follow-up. The mean magnitude of the bone defect following debridement was 7 cm (range 5–8 cm). Leg length was restored to within 1 cm of the contralateral side in all of the cases. Union of the docking site and consolidation of the regenerated segment was achieved in all but one of the cases. This patient was poorly compliant with the follow-up, rehabilitation and circular fixator care programs; he requested an amputation 17 months after presentation. The median value of the total time spent in the circular external fixator was 77 weeks (ranging from 52 to 104 weeks), and the mean external fixation index was 81 days/cm (range 45–107).

Complications were common and occurred in six of the seven cases. Unplanned additional surgeries were required in two patients, and the circular external fixator of one patient was revised at the time of the formal docking procedure in order to create the optimal biomechanical environment for union at the docking site (Table 1). Four major complications occurred. Despite the fact that all soft tissue flaps were performed by a plastic surgeon, flap dehiscence occurred in two cases. A flexion contracture of the knee combined with an equinus contracture of the ankle occurred in one patient (who had an associated substance-induced psychotic disorder). These deformities necessitated extension of the circular external fixator frame across the knee and ankle joints to allow gradual correction (Fig. 2). In one patient, a fracture of the docking site occurred 1 year following removal of the circular fixator. This fracture was treated successfully with a second

**Table 1** Risk factors, magnitude of bone defect, treatment intervals, follow-up duration and complications

| Patient | Age | Systemic risk factors | Post-debridement bone defect (cm) | First to second stage (weeks) | Time in frame (weeks) | Fixator index (days/cm) | Follow-up period (months) | Complications |
|---|---|---|---|---|---|---|---|---|
| 1 | 30 | Substance-induced psychotic disorder | 8 | 14 | 52 | 45 | 28 | Knee flexion and ankle equinus contractures requiring unplanned reoperation |
| 2 | 28 | Hypoalbuminemia | 5 | 28 | 77 | 107 | 30 | Flap dehiscence, fracture of docking site requiring second external fixator |
| 3 | 28 | Smoking | 7 | 11 | 104 | 104 | 45 | Pin track sepsis necessitating removal of one wire (Checketts and Otterburn grade 3), 5° equinus contracture |
| 4 | 39 | None | 8 | 13 | 80 | 70 | 41 | None |
| 5 | 29 | None | 6 | 12 | 58 | 67 | 21 | New circular fixator with acute compression of docking site at formal docking |
| 6 | 44 | Poor compliance, smoking | 8 | n/a | n/a | n/a | 21 | Flap dehiscence, pin track sepsis (Checketts and Otterburn grade 2), patient eventually requested amputation |
| 7 | 30 | Smoking | 5 | 9 | 58 | 81 | 18 | Pin track sepsis (Checketts and Otterburn grade 2) |

circular fixator combined with a fibula osteotomy; union occurred after 21 weeks in external fixation.

Four minor complications occurred. A functional range of motion of the adjacent joints was achieved in all but one patient with a residual equinus contracture of five degrees. Minor pin track infection (Checketts and Otterburn grade 2 and 3) was experienced in three cases and necessitated the removal of the offending wire in one of these patients [18]. The incidence of pin track sepsis did not appear to differ from a previous study involving circular fixation [19].

## Discussion

Surgical resection of avascular bone should be considered a mainstay of treatment when embarking on a curative treatment strategy aimed at eradication of infection in patients with chronic osteomyelitis [6]. Systemic and local antibiotic therapy is considered to play an adjunctive role in this setting. The resection margin, which can be thought of in oncological terms as being either marginal or wide, has been shown to affect the outcome. Wide resection margins, in comparison with marginal resection, have been shown to decrease the recurrence of infection and improve cure rates [20–22]. Wide resection of all avascular bone creates large bone defects and necessitates the implementation of an appropriate dead space management strategy [23].

The management of post-infective bone defects is dependent on several factors including the host's physiological status, the size of the defect, duration of the defect (i.e. acute or chronic), quality of the surrounding soft tissue, the presence of deformity, joint contracture/instability or limb length discrepancy, as well as the experience of the surgeon. Smaller defects may be treated by autologous bone graft [24]. The size of a segmental bone defect that should be considered critical, and thus not suitable for autologous cancellous bone grafting, remains controversial. Traditionally, 4 cm has been recommended as the cut-off point [1, 25]. The main concern with cancellous bone grafting of larger bone defects is its dependence on the surrounding soft tissues for incorporation. Large grafts may undergo central necrosis in the absence of an excellent soft tissue envelope [2]. Secondly, the regenerated segment may be weak and prone to fracture as a result of partial graft resorption [26]. As a result, it has been recommended that the length of a segmental diaphyseal tibial defect that can be managed with autologous cancellous grafting should not exceed 2 cm [14].

Masquelet et al. redefined the role of cancellous bone grafting in limb reconstruction by taking advantage of the mechanical and biological characteristics of the induced membrane. They reported the successful use of this technique in 35 cases, with defects ranging from 4 to 25 cm [3]. These results appear to be reproducible, with others reporting 90 % union rates of large defects (average size 5.8 cm) through the use of reamer–irrigation–aspiration graft [27]. Richards et al. [28] also utilized a modification of this technique in the management of bone loss following open fractures. Through the use of form-fitting spacers and

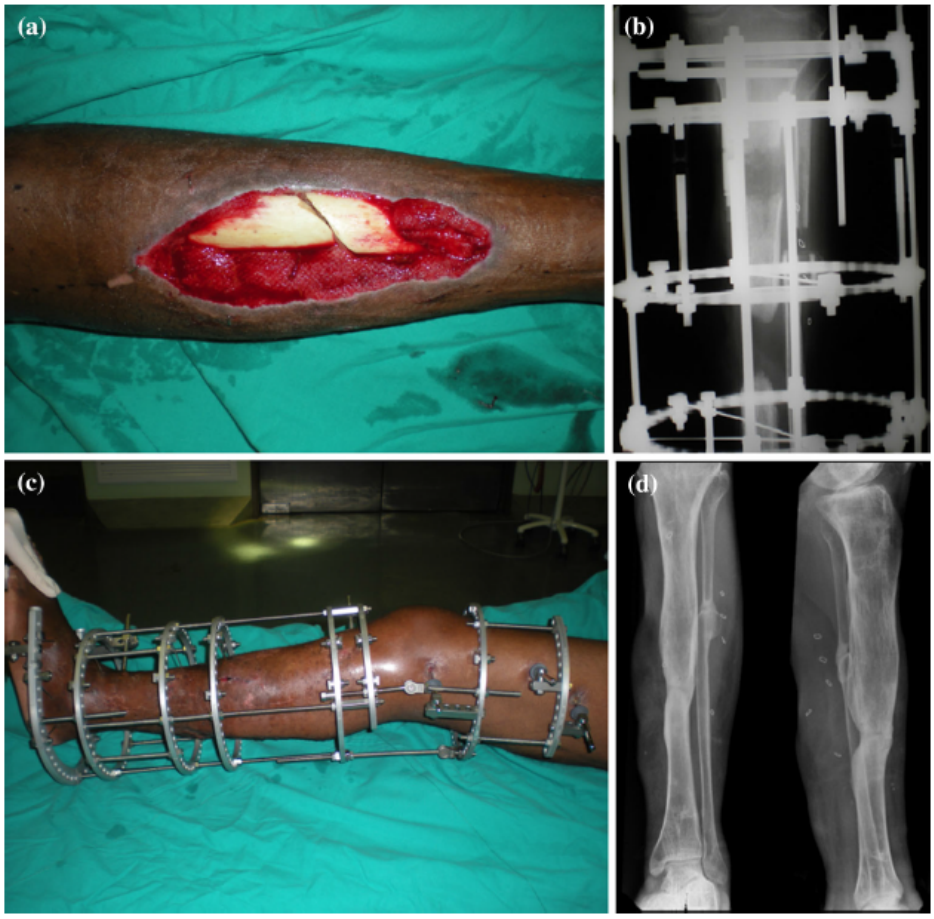


**Fig. 2** Clinical and radiological features of a case complicated by knee flexion and equinus contractures. **a** Wound dehiscence following open reduction and intramedullary nailing of a neglected tibia fracture. **b** Distraction osteogenesis following removal of the PMMA spacer. **c** Gradual correction of the knee and ankle deformities. **d** Final radiographs showing satisfactory consolidation of the regenerate and union at docking site

subsequent autogenous bone grafting, the authors were able to achieve union in 18 out of 18 patients with bone defects involving a minimum of 50 % of the circumference of the tibia, ranging in size from 2 to 16 cm (average 4 cm).

Although the induced membrane technique offers several theoretical and practical advantages, caution should be applied in the use of cancellous bone graft in defects exceeding 4 cm [14]. Furthermore, the classic Masquelet technique, involving cancellous grafting onto the induced membrane, appears to deliver more predictable results in the presence of pre-existing periosteal new bone formation at the margins of the defect. In their original series, Masquelet et al. [3] reported that some of the patients required repeated bone grafts and that fracture occurred in four of the 35 cases. In their subsequent, prospective series that involved the adjunctive use of BMP-7, three of the eight patients with segmental defects developed deformities and another patient required amputation. Although Stafford et al. reported a high union rate, 80 % of their patients received BMP in addition to bone graft, only nail or plate fixation was used and seventeen of the 25 defects were $\leq$4 cm in size [18]. Richards et al. reported excellent results with the use of form-fitting spacers in the management of post-traumatic bone loss, but only two of their eighteen patients had circumferential bone loss and all fractures were treated with nail and plate fixation.

PMMA spacers offer several potential advantages in the setting of post-infective reconstruction. Bone transport through scar tissue, using more traditional Ilizarov techniques, can be particularly problematic. The use of temporary PMMA spacers prevents soft tissue impingement between the leading edge of the transport segment and the target segment. As illustrated in an animal model, the induced membrane prevents protrusion of adjacent soft tissue and neurovascular structures into the defect and adheres to the resected bone edges without collapse despite removal of the spacer, thus delineating a cavity corresponding to the volume of the retrieved cement spacer [6, 29]. This so-

called spacer effect can be utilized in the reconstruction of bone defects where the resulting cylindrical cavity forms a stable envelope through which a bone segment may be transported.

As a result of the biological, therapeutic and mechanical advantages offered, and supported by the positive results reported in periprosthetic infections, antibiotic-impregnated PMMA spacers appear to be an attractive option in the management of other Cierny and Mader anatomical type IV infections associated with a bone defect. A case report where a similar technique, involving the use of a PMMA spacer with subsequent distraction osteogenesis, was used in the management of an infected open fracture is published [10]. The authors made use of a monolateral external fixator for bone transport. Circular external fixation was preferred in our series due to its modularity, minimally invasive nature and ability to effect bone transport and deformity correction (as illustrated in the case which developed joint contractures). The attributes of fine wire external fixators may also offer theoretical advantages in terms of bone healing. This stems from the three-dimensional stability combined with the low axial stiffness exhibited by fine wire circular external fixators [30, 31]. In addition, meta-analysis has shown that the Ilizarov method of distraction osteogenesis significantly reduces the risk of deep infection in infected osseous lesions [32].

Spiegl et al. [9] have published a series of cases where segmental bone defects as a result of chronic tibial osteitis were managed with PMMA spacers and subsequent distraction osteogenesis. The authors report an average overall treatment time of 93 weeks. Complications were common, and infection requiring reoperation occurred in 28 % of cases at 2-year follow-up. In our series of cases, the technique of bone transport through an induced membrane was confirmed to be a useful option for reconstruction of post-infective tibial defects in excess of 4 cm. Remission of infection was achieved in all cases without the need for reoperation for infection. This is, however, also a function of patient selection, and only Cierny and Mader type A and B hosts were considered suitable candidates for this procedure. The improved cure rates in our series may be the result of judicious patient selection rather than technical prowess. Union of the docking site and consolidation of the regenerated segment was achieved in all but one of the cases (who elected to have an amputation). Traditional Ilizarov methods, involving monofocal strategies without spacers, have been noted to produce external fixation indices of up to 50 days/cm [33, 34]. Considering the high external fixation index in our series (mean 81 days/cm), as well as the 57 days/cm reported by Speigl et al. [9], it appears that the use of PMMA spacers necessitate an increased period of external fixation. This may partly be explained by the time spent awaiting the formation of the induced membrane prior to initiation of bone transport.

There was a high rate of complications in our series. Spiegl et al. [9] had a similar experience with this technique, reporting 22 minor and 13 major complications (including one amputation) in their series of 19 cases. Interestingly, internal fixation of the docking site was performed in 16 of their 25 patients. The authors emphasized the challenging nature of the technique and stated that the procedure places considerable physical and emotional stress on the patient. The frequency of complications may be a reflection of the complexity of the cases involved but may also be related to the technical demands of the procedure.

There are several limitations to this study: its retrospective nature; a small sample size and short follow-up period; as well as the lack of a control group involving traditional Ilizarov-type bone transport. The Masquelet technique is still relatively new and many questions remain. Further investigation is required regarding the possibility of improved union at the docking site related to the biological advantages offered by the induced membrane. This will require a control group of cases managed without PMMA spacers. Our knowledge of certain technical aspects is still evolving. The optimal time for removal of the spacer and initiation of bone transport remains unclear. Internal fixation of the docking site may possibly also offer additional benefit [9].

## Conclusion

The temporary insertion of a PMMA appears to be a useful dead space management technique in the treatment of post-infective tibial bone defects. Although the technique does not appear to offer an advantage in terms of the external fixation index, it may serve as a useful adjunct in achieving resolution of infection. Patient selection, however, appears to be a crucial step in ensuring a remission of tibial osteomyelitis.

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**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standard** This retrospective human study conforms to the declaration of Helsinki and has received approval from the relevant Ethical Review Board with waiver of informed consent.

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# PART 4

# Development of an integrated approach

In parts 1 and 2 of this thesis the limitations of existing classification systems and the lack of evidence-based treatment guidelines were highlighted. Part 3 illustrated the importance of patient selection in curative surgical treatment. Part 4 introduces a novel approach to adult chronic osteomyelitis which integrates a modified host stratification system with treatment strategy selection.

The first step in developing this approach, involved refinement of the Cierny and Mader classification system.[1] The aim was to remove ambiguity and apply pragmatic criteria during the classification process [Table 4.1]. In order to achieve this, modification of the criteria defining both the physiological class and anatomic type was required.

The physiological classification of the host, as proposed by Cierny and Mader, was modified in order to standardize and improve objectivity of the stratification process. Although Cierny and Mader recognized the need for standardization in their original publication, no method was proposed.[1] In the following study C-hosts were defined according to presence or absence of certain predetermined major and minor risk factors [Table 4.2]. The selection of these criteria was based on existing evidence and classification systems, as well as prior experience.

**Table 4.1:** Modified classification system for adult long bone chronic osteomyelitis.

| Classification | Characteristic |
|---|---|
| **Physiology:** | |
| Type A host | No risk factors |
| Type B host | Less than three minor risk factors |
| Type C host | One major and/or three or more minor risk factors |
| **Pathoanatomy**: | |
| I - Medullary | No cortical sequestration |
| II - Cortical | Direct contiguous involvement of cortex only |
| III - Combined (stable) | Both cortex and medullary regions involved |
| IV - Combined (unstable) | As for III plus unstable prior to debridement |

In terms of CD4 count in HIV infected patients, 350 cells/mm$^3$ was selected as the cut-off between B and C-host classification. This value, which coincides with the WHO immunological definition of advanced HIV infection, was selected on the basis of practical considerations.[2] Current treatment guidelines in South Africa dictate that retroviral therapy is instituted once the patient's CD4 count falls below 350 cells/mm$^3$.[3] Although evidence remains scanty, it appears reasonable to institute antiretroviral treatment in patients with advanced HIV infection in an attempt to reduce the complication rate in non-emergent surgery.[4,5] In addition, Aird *et al*. found an increased infection rate in open fractures in HIV positive individuals with a CD4 count below 350 cells/mm$^3$.[6] The incidence of postoperative infection has also been shown to be increased in patients with a CD4 count below 350 cells/mm$^3$.[7,8] Likewise, an albumin level of less than 30g/L has been associated with an increase in postoperative complications and infections.[9-11] Hyperglycemia has been associated with increased post-operative infection in both trauma and elective orthopaedic surgery and a HbA1c of 8% translates to an average blood glucose level of 10 mmol/L over the preceding

three months.[12,13] Cellulitis and abscess formation compromises the soft tissue envelope and temporarily precludes the performance of definitive surgery. [Table 4.2]

**Table 4.2:** Risk factors assessed during host status determination

| **Major Risk factors** | **Minor systemic risk factors** | **Minor local risk factors** |
|---|---|---|
| $CD_4$ count < 350 cells/$mm^3$ | HIV infection | Poor soft tissues requiring flap |
| Albumin < 30 g/L | Anaemia | Chronic venous insufficiency |
| HbA1C ≥8% | Smoking | Peripheral vascular disease |
| Cellulitis or abscess formation | Diabetes mellitus | Previous radiation therapy |
| Malignancy at site of infection | Rheumatoid arthritis | Instability expected after surgery |
| Pathological fracture | Chronic lung disease | Adjacent joint stiff / arthritic |
| | Chronic cardiac failure | Heterotopic ossification |
| | Common variable Immune deficiency | Segmental resection of >6cm required to achieve cure |
| | Paraplegia / Quadriplegia | |
| | Drug or substance abuse | |
| | Chronic corticosteroid use | |
| | Active tuberculosis | |
| | Ischemic heart disease | |
| | Cerebrovascular disease | |

With this classification system we aimed to address the element of uncertainty which may occasionally arise during the anatomical classification of the disease. In the original Cierny and Mader classification system, the differentiation between localized (type III) and diffuse (type IV) disease was based on the surgeon's estimation of stability *following* debridement.[1] This estimation can however be problematic, especially for training orthopaedic surgeons, as there are many factors that determine the extent of the debridement. Cierny and Mader did not provide specific guidelines regarding which cases required segmental resection.[1] In theory compromised hosts are best treated with wide resection.[14] Wide resection may however result

in segmental bone loss, requiring complex reconstruction procedures like bone transport or extensive bone grafts. These techniques are fraught with danger, especially in the compromised host and failure may result in unplanned amputation. The fact that the anatomic type of the infection and the extent of debridement was (according to the original Cierny and Mader classification system) not defined prior to surgery, created uncertainty during the pre-operative counselling of patients. The modification of the anatomic staging which was used in this series relied on classification of the anatomic nature of the disease *prior* to debridement. The approach followed in our study involved maintenance of stability when present and therefore it was known in advance if reconstruction of a segmental bone defect would be required. A notable implication of this approach is that all septic non-unions were classified and treated as type IV chronic osteomyelitis.

The final step of the proposed approach involved integrating the modified classification system with selection of the appropriate treatment strategy. This required the development of a treatment algorithm which incorporated the physiological status of the host, the presence of skeletal instability, the severity of impairment, as well as the concept of minimal necrosis osteomyelitis.

In order to assess the efficacy of the proposed approach, the outcome of treatment (in terms of the resolution of infection) was retrospectively assessed. While previous studies focused on the outcome of curative treatment, we also report the outcome of palliative treatment strategies.[1,15-17] To the best of our knowledge this study is the first to report the outcomes in all treatment groups. This allowed evaluation of the approach as a whole, which provided insight into the relevance of the proposed treatment strategy selection process.

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# Chapter 7: A modified staging system for chronic osteomyelitis

**Marais LC**, Ferreira N, Sartorius B, Aldous C, Le Roux TLB.

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Contribution to authorship:

LC Marais – Concept, study design, literature review, classification development, algorithm development, data collection, data analysis and interpretation, drafting of manuscript, revision of manuscript, corresponding author.

N Ferreira – Algorithm development, data collection and revision of manuscript.

B Sartorius – Study design, statistical analysis and interpretation, drafting of manuscript .

C Aldous – Study design, concept development and revision of manuscript.

TLB Le Roux – Study design, concept development, algorithm development and revision of manuscript.

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Original Article

# A modified staging system for chronic osteomyelitis

*Leonard Charles Marais* [a,*], *Nando Ferreira* [a], *Colleen Aldous* [b], *Benn Sartorius* [c], *Theo Le Roux* [d]

[a] *Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics, School of Clinical Medicine, University of KwaZulu-Natal, Grey's Hospital, Pietermaritzburg, 3201, South Africa*
[b] *School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, 4013, South Africa*
[c] *Public Health Medicine, School of Nursing and Public Health, College of Health Sciences, University of KwaZulu-Natal, Howard College Campus, Durban, 4041, South Africa*
[d] *Department of Orthopaedics, University of Pretoria, 1 Military Hospital, Pretoria, 0187, South Africa*

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ABSTRACT

*Aims:* To investigate the short-term outcome of treatment of chronic osteomyelitis where management was based on a refined host stratification system.
*Methods:* A retrospective review of 109 adult patients with chronic osteomyelitis.
*Results:* At a minimum follow-up of 12 months (range 12–36) we observed an overall success rate of 89.9% (95% CI: 82.7–94.9%). There was no statistically significant difference in success rates by host status (p-value = 0.201).
*Conclusion:* By integrating the redefined host status and treatment strategy, we were able to achieve comparable short-term outcomes in both low and high-risk cases while maintaining a low rate of amputation.



## 1. Introduction

There are currently no evidence-based guidelines in terms of the treatment of chronic osteomyelitis.[1] Achieving remission is notoriously difficult, with some studies reporting failure rates of 20–60%.[2,3] In essence the aim is to improve quality of life through either a curative or a palliative treatment strategy. Curative management strategies, aimed at limb salvage, usually comprise of a combination of complex surgical procedures and tailored adjuvant antibiotic therapy.[4] On the other hand, palliative treatment strategies are less invasive and typically involve to the use of chronic suppressive antibiotic therapy.[5] The decision to embark on either a curative or palliative treatment strategy requires consideration of several factors, principle amongst which is the host's physiological status. Furthermore, in cases where a curative treatment strategy is employed the host status also influences the

* *Corresponding author*. Department of Orthopaedic Surgery, Greys Hospital, Private bag X9001, Pietermaritzburg, 3201, KwaZulu-Natal, South Africa. Tel.: +27 33 897 3424; fax: +27 33 897 3409.
E-mail address: maraisl@ukzn.ac.za (L.C. Marais).
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clearance margin that is required during surgical debridement.[6]

Recognizing the importance of considering the host's physiological status during formulation of a treatment plan, Cierny and Mader revolutionized our approach to chronic osteomyelitis through the publication of their clinical staging system in 1985 (Table 1).[7] According to this classification system A- and B-hosts could be considered for a curative treatment protocol. To justify the considerable demands and risks associated with limb salvage, the expected outcome should, however, offer distinct advantages over an amputation or palliation. In cases where treatment aimed at remission is contraindicated or deemed excessive, as a result of the risks it entails, a patient should be classified as a C-host and offered palliation.[8,9] Amputation should be considered in cases where limb salvage or palliation is deemed to be neither safe nor feasible.[10]

The choice between curative or palliative treatment strategies may however be particularly problematic. This results from the absence of precisely defined criteria according to which a C-host should be defined. Unfortunately no discreet objective criteria exist to guide the decision-making process. Originally, Cierny and Mader defined a C-host as any patient in whom treatment or the result of treatment will be more compromising to the patient than the disability caused by the disease itself.[7] The main shortcoming of this definition is that it is subjective in nature and susceptible to widely varying interpretation depending on the experience of the surgeon.

In this study we set out to determine the short term outcome of treatment in a cohort of adult patients with chronic osteomyelitis where management strategy selection was based on a modified classification system.

## 2. Patients and methods

A retrospective review was performed of patients with chronic osteomyelitis treated at our tertiary referral center from 2011 to 2013. Patient notes, blood tests and radiographs were reviewed pre- or post-treatment. For the purposes of this study chronic osteomyelitis was defined as a bone infection characterized by the presence of necrotic bone (sequestrum) or host reparative reaction (involucrum) and/or duration of at least 6 weeks.[1] All patients, 18 years or older, treated for chronic osteomyelitis with a minimum follow-up of twelve months were included in the study. Cases involving atypical organisms, acute postoperative infection where the fracture was expected to unite, periprosthetic joint infection with retained implants and hand sepsis were excluded from the study.

Following clinical, radiological and biochemical evaluation, patients were classified according to a modified version of the Cierny and Mader classification system (Table 2).[7] The characterization of the host's physiological status was modified in order to provide a more pragmatic definition of a C-host. A patient was classified as a C-host if one major risk factor or three (or more) minor risk factors were present (Table 3). Risk factors were selected following systematic review of existing data and consideration of previously published classification systems.[11–25] One of the aims of the modified classification system was to emphasize host optimization prior to surgical intervention. Resultantly the majority of major risk factors are modifiable which places appropriate emphasis on risk factor modification prior to surgery.

Palliative treatment was instituted in all C-hosts without skeletal instability. A- or B-hosts with minimal impairment, no sequestrum and no skeletal instability, were also managed palliatively (Fig. 1). All remaining A- and B-hosts were treated curatively. C-hosts with skeletal instability were managed through the implementation of alternative treatment strategies that involved either amputation (if union was unlikely to occur) or chronic suppressive antibiotic therapy in combination with external fixation, with or without debridement.

Curative treatment involved debridement, dead space management, provision of bony stability, soft tissue reconstruction and/or skeletal reconstruction, in conjunction with pathogen directed adjuvant antibiotics for a period of six weeks. The extent of the debridement was determined by the host status and the anatomic nature of the infection. Resection margins were defined according to the guidelines previously published by Simpson et al.[6] In B-hosts we strived to obtain a wide clearance margin, as long is it did not compromise skeletal stability. In type I, II and III lesions this was achieved by direct debridement (tangential excision with high speed burr) and/or indirect debridement (medullary reaming). In cases with pre-operative skeletal instability (type IV lesions)

**Table 1 – Cierny and Mader clinical staging system for adult chronic osteomyelitis.[7]**

| | |
|---|---|
| Anatomic type | |
| I | Medullary osteomyelitis |
| II | Superficial osteomyelitis |
| III | Localized osteomyelitis |
| IV | Diffuse osteomyelitis |
| Physiological Class | |
| A | Good immune system and delivery |
| B | Compromised locally ($B^L$) or systemically ($B^S$) |
| C | Requires suppressive or no treatment; minimal disability; treatment worse than disease; not a surgical candidate |
| Clinical Stage | |
| | Type + Class = Clinical stage |

**Table 2 – Modified classification system.**

| | |
|---|---|
| Physiology | |
| Type A host | No risk factors |
| Type B host | Less than three minor risk factors |
| Type C host | One major and/or three or more minor risk factors |
| Pathoanatomy | |
| I - Medullary (stable) | No cortical sequestration |
| II - Cortical (stable) | Direct contiguous involvement of cortex only |
| III - Combined (stable) | Both cortex and medullary regions involved |
| IV - Combined (unstable) | As for III plus unstable prior to debridement |

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**Table 3 – Major and minor risk factors used during host stratification. A patient with one major or three (or more) minor risk factors was considered to be a C-host.**

| Major risk factors | Minor systemic risk factors | Minor local risk factors |
|---|---|---|
| $CD_4$ count <350 cells/mm$^3$ | HIV infection | Poor soft tissues requiring flap |
| Albumin <30 g/L | Anemia | Chronic venous insufficiency |
| HbA1C ≥ 8% | Smoking | Peripheral vascular disease |
| Cellulitis or abscess formation | Diabetes mellitus | Previous radiation therapy |
| Malignancy at site of infection | Rheumatoid Arthritis | Surgery will result in instability |
| Pathological fracture | Chronic lung disease | Adjacent joint stiff/arthritic |
| | Chronic cardiac failure | Heterotopic ossification |
| | Common variable immune deficiency | Segmental resection of ≥6 cm required to achieve cure |
| | Paraplegia/Quadriplegia | |
| | Drug or substance abuse | |
| | Chronic corticosteroid use | |
| | Active tuberculosis | |
| | Ischemic heart disease | |
| | Cerebrovascular disease | |

segmental resection was performed and stability provided by circular external fixation. Dead space management techniques were also tailored to anatomic nature of the pathology [Table 2]. Continuous irrigation, as popularized by Lautenbach, was used in type I (medullary) post-operative infections.[26,27] Dead space management in type II lesions was achieved through soft tissue flaps. In type III lesions gentamycin impregnated polymethylmethacrylate (PMMA) beads (Septopal® Merck, Darmstadt Germany) were utilized and removed at six to eight weeks. Dead space following debridement of type IV lesions were dealt with through the use of physician-directed antibiotic-impregnated PMMA spacers, as described by Masquelet.[28] The PMMA spacers were constructed from Palacos R + G® bone cement (Heraeus Medical, Hanau Germany) containing 500 mg Gentamycin per 40 mg of PMMA powder, mixed with 2 g of Vancomycin powder per 40 mg of PMMA. Post-operatively all patients were treated with generic parenteral antibiotics, in the form of Vancomycin and Meropenem, until the seven day microscopy, culture and sensitivity (MCS) results became available. Oral antibiotic therapy, tailored according to the culture and sensitivity, was then commenced and continued for a period of six weeks. Following this period, reconstruction of segmental bone defects in Cierny and Mader type IV lesions were undertaken; if clinical and biochemical evaluation confirmed the absence of active infection. The size of the bone defect determined the nature of the skeletal reconstruction procedure. Defects less than 1–2 cm in magnitude were managed by acute shortening. Defects between 2 and 4 cm in size were managed utilizing the Masquelet technique,

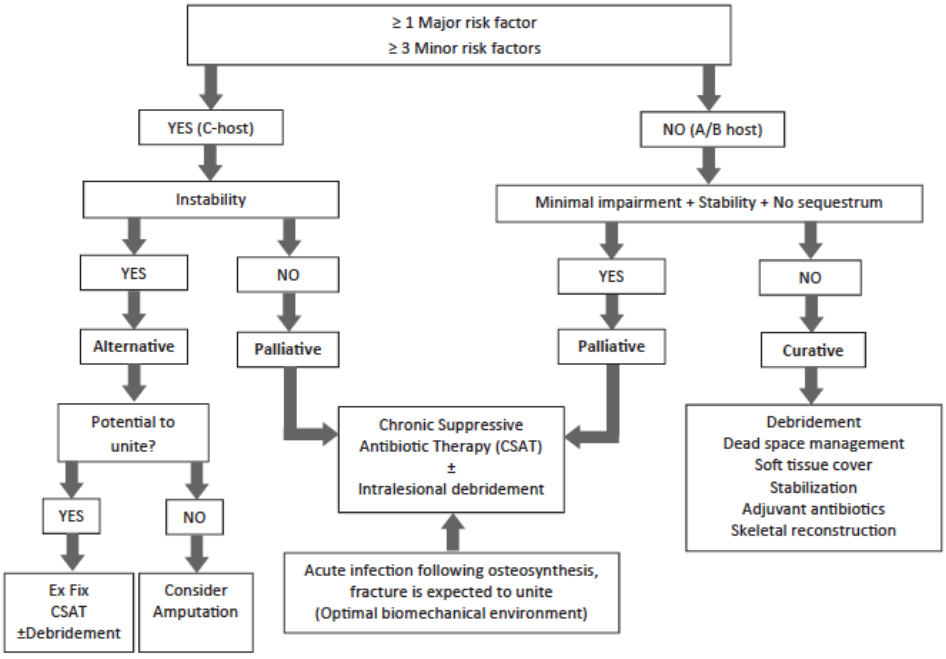


**Fig. 1 – Treatment selection algorithm. (i) CSAT: Chronic suppressive antibiotic therapy; (ii) Ex Fix: Circular External Fixation.**

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involving autogenous bone grafting into an induced membrane. Gaps in excess of 4 cm were treated through the use of bone transport through the induced membrane.

Palliative treatment, aimed at suppression of infection, was provided as a three to six months course of chronic suppressive antibiotic therapy (CSAT) in the form of trimethoprim-sulfamethoxazole (800 mg/160 mg twice daily) and rifampicin (600 mg daily). If suppression was successfully achieved following three to six months of therapy the treatment was stopped and the patient followed-up for recurrence. In the case of recurrence CSAT was restarted and continued for a further 6 months before cessation. If symptoms of infection again returned following 12 months of treatment, permanent CSAT was instituted.[29] Patients with cellulitis or abscess formation received culture directed pre-operative antibiotic therapy. In this scenario palliation was aimed at resolution of the local compromising factors that prohibited the performance of definitive surgical procedures. Alternative treatment strategies involved either amputation of the limb or antibiotic therapy combined with external fixation and/or intralesional debridement (minimally invasive surgical procedure involving drainage of abscess and/or removal of large sequestra/obviously necrotic bone). Patients refusing amputation where managed with long term CSAT.

Following a minimum follow-up period of 12 months the outcome was determined in respect of the success or failure of the treatment of infection. Success was defined as achievement of remission through a curative treatment strategy or suppression (or better) in patients treated palliatively. Remission was defined as the absence of clinical evidence of infection.[30] Suppression was defined as resolution of symptoms and signs of infection to the extent that it did not interfere with activities of daily living (ADL). For the purposes of this study failure of treatment was defined by failure of the initial treatment plan to achieve the predetermined goal (remission or suppression); recurrence of infection; the necessity for unplanned reoperation; and/or failure to achieve patient satisfaction with the outcome of treatment. If suppression was not successfully achieved following six months of CSAT the case was classified as a treatment failure.

Data were process and analyzed using Stata 13.0 SE (StataCorp, 2013). Standard t-tests were used to identify significant mean differences in continuous explanatory variables. For non-normal distributed continuous data the Wilcoxon rank-sum test was used. Categorical explanatory variables were cross-tabulated against C-host status or treatment failure and significant association was identified using the standard Pearson's chi-square ($\chi^2$) test. If an expected cell count in the cross tabulation was less than 5 (sparse numbers) then the Fishers exact test was preferred. Ninety-five percent confidence intervals (CI) were constructed around proportions using binomial exact limits.

Ethical approval was obtained from a national level ethics review board prior to commencement of the study.

## 3. Results

A total number of 123 cases were enrolled. Fourteen patients were excluded from the study: nine patients were lost to follow-up before 12 months; two cases were excluded on the basis of the involvement of atypical organisms (*Cryptococcus neoformans* and *Actinomyces israelii*) and three patients, who presented with acute post-operative infection, were also excluded. The final sample utilised in this analysis thus comprised 109 patients. The mean follow-up period was 18.6 months (standard deviation [SD]: 6.8; range: 12–36 months). The mean age was 39.8 years (SD: 13.8; range: 18–78 years).

### 3.1. Pathology

Post-traumatic infection (following compound fractures) was the most common cause of chronic osteomyelitis, involving 53% (n = 58) of cases. Contiguous post-operative infection involved 30% (n = 33), while hematogenous chronic osteomyelitis accounted for 15% (n = 16) of cases. In two cases chronic osteomyelitis resulted from direct contiguous spread from ulcers on the lower leg. In terms of the causative organisms, methicillin-sensitive *Staphyllococcus aureus* was the most commonly isolated organism in patients with hematogenous chronic osteomyelitis. *Enterococcus*, *Serratia*, *Proteus*, *Pseudomonas*, *Enterobacter* and *Klebsiella* spp., as well as methicillin-resistant *S. aureus* where identified as to most prevalent pathogens in the chronic post-traumatic group. Multiple organisms were involved in 31% of contiguous (post-operative or post-traumatic) cases. In 15% of cases the causative organism could not be isolated using routine culturing techniques. The tibia was to most commonly affected bone, involving 52% of cases (n = 57). The femur was the second most common site at 23% (n = 25), followed by the foot (5%), pelvis and forearm (4% each). The remainder of infections involved the ankle, knee, hip, fibula, humerus and clavicle.

### 3.2. Host stratification

The majority of patients in this study were classified as C-hosts (46.8%; n = 51), followed by B-host classification in 41.3% of cases (n = 45) (Table 4). The mean albumin and haemoglobin levels were 35.8 g/L (SD: 5.5) and 13.0 g/dL (SD: 2.0) respectively. HIV infection was present in 30% (n = 33) of cases, with a median CD4 count of 336 cells/mm$^3$ (Interquartile range [IQR]: 307–507; min–max 13–1034).Fifty five percent of these patients were not on antiretroviral therapy at the onset of treatment. These patients were either newly diagnosed cases or did not qualify for treatment according to the national guidelines.[31] Antiretroviral treatment was initiated in all patients with a CD4 count below 350 cells/mm$^3$ as prescribed by the national policy. With regards to the C-hosts, 45% (n = 23) were designated on the basis of the presence of a major risk factor, while 55% (n = 28) were classified as C-hosts on the basis of the presence three or more minor risk factors.

### 3.3. Treatment strategies

A curative management strategy was employed in 42% (n = 46) of patients, while a palliative strategy was selected in 43% (n = 47) of cases. In the palliative group two patients required additional intralesional debridement involving simple sequestrectomy and/or drainage of an abscess.[6] The specific therapeutic interventions employed in the curative group are

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**Table 4 – Descriptive statistics of the most common risk factors, the host classification according to the modified classification system and treatment strategies employed.**

| Variable | n | Summary measure | Range |
|---|---|---|---|
| Risk factors | | | |
| Age: Mean (SD[a]) | 109 | 39.8 (13.8) | 18–78 |
| HIV positive | 33 | 30% | |
| $CD_4$ count: Median (IQR[b]) | 33 | 336 (307–509) | 13–1034 |
| Albumin: Mean (SD[a]) | 109 | 35.8 (5.5) | 22–48 |
| Hemoglobin: Mean (SD[a]) | 109 | 13.0 (2.0) | 6.6–18.6 |
| Poor soft tissue necessitating flap | 48 | 44.0% | |
| Current smoker | 42 | 38.5% | |
| Diabetes mellitus | 10 | 9.2% | |
| Anemia | 9 | 8.3% | |
| Final host status | | | |
| A | 13 | 11.9% | |
| B | 45 | 41.3% | |
| C | 51 | 46.8% | |
| Palliative treatment | 47 | 43.1% | |
| Chronic suppressive antibiotic therapy (CSAT) | 45 | | |
| Intralesional debridement plus CSAT | 2 | | |
| Curative treatment | 46 | 42.2% | |
| Stable lesions | | | |
| Direct debridement (high speed burr) | 15 | | |
| Indirect debridement (medullary reaming) | 5 | | |
| Unstable lesions | | | |
| Debridement without reconstruction | 6 | | |
| Debridement and external fixation | 3 | | |
| Segmental resection, acute shortening | 2 | | |
| Segmental resection, Masquelet bonegraft | 5 | | |
| Segmental resection, bone transport | 10 | | |
| Alternative treatment | 16 | 14.7% | |
| Amputation | 6 | | |
| Debridement, external fixation, CSAT | 10 | | |

[a] Standard deviation;
[b] Interquartile range.

listed listed in Table 4. An alternative treatment strategy was required in 15% (n = 16) of patients. This involved debridement and/or circular external fixation followed by CSAT in ten cases. Primary amputation was performed in the 5% (n = 6) of patients.

### 3.4. *Success rate*

We observed an overall success rate of 89.9% (95% CI: 82.7–94.9%). There was no statistically significant difference in failure rates by host status (Fishers exact p-value = 0.201) (Table 5). Zero failures occurred among A-hosts, with a possible one sided 97.5% CI for the success rate in this group of 81.5–100%. The success rate among B-hosts was 93.3% (95% CI: 81.7–98.6%) and 84.3% (95% CI: 71.4–93.0%) among C-hosts. In terms of the management strategy, success was achieved in 93.5% of patients treated curatively, 87.2% of patients treated palliatively and 87.5% in the alternative treatment group. Remission was achieved in 62% of patients in whom the aim of treatment was disease suppression, through the use of CSAT as part of a palliative (n = 47) or an alternative treatment strategy (n = 16). Fifty three percent (n = 25) of patients treated palliatively required more than six months of antibiotic treatment in order to achieve suppression. Approximately half (52%, n = 13) of these patients required chronic suppressive antibiotic therapy on a permanent basis.

Overall, the success rate in HIV positive patients was 84.8% or 28/33 (95%CI: 68.1–94.9%) compared to 92.1% or 70/76 among HIV negative patients (95%CI: 83.6–97.0). The success rate did not significantly vary by HIV status (p-value = 0.248). All treatment failures, in the HIV positive group, occurred in patients who fulfilled the World Health Organization immunological criteria for advanced HIV infection ($CD_4$ count < 350 cells/$mm^3$).[32] It is important to note that the majority of HIV positive patients were treated through either a palliative or alternative treatment strategy. Curative treatment was however successful in all four of the HIV positive patients in whom it was employed.

Eight of the eleven treatment failures occurred in C-hosts (Table 6). Several additional risk factors, which were not considered during initial host stratification, were identified in the failure group. These include prior attempts at limb reconstruction, poor motivation and compliance, age, involvement of the adjacent joint, and foot or pelvic involvement.

## 4. Discussion

The complex nature of the disease necessitates an individualized approach to a patient with chronic osteomyelitis. Selecting low risk treatment options in high-risk patients

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**Table 5 – Host status versus treatment outcome.**

| Host status | Treatment strategy (n) | Success | Failure | p-value[a] |
|---|---|---|---|---|
| A | | 100% (n = 13) | 0% (n = 0) | 0.201 |
| Curative | 12 | | | |
| Palliative | 1 | | | |
| Alternative | – | | | |
| B | | 93.3% (n = 42) | 6.7% (n = 3) | |
| Curative | 34 | | | |
| Palliative | 11 | | | |
| Alternative | – | | | |
| C | | 84.3% (n = 43) | 15.7% (n = 8) | |
| Curative | – | | | |
| Palliative | 35 | | | |
| Alternative | 16 | | | |

[a] Fishers Exact test.

reduces the risk of complications. Embarking on a curative protocol in a host who is unable to withstand the metabolic and immunological demands of complex limb reconstructive process may result in therapeutic failure and amputation. In such patients (C-hosts) unnecessary or unwanted limb ablation may be avoided by the institution of a palliative treatment strategy, that does not involve high-risk reconstructive surgical procedures. Existing classification systems however fails to provide discreet objective criteria that allow reproducible identification of C-hosts. This shortcoming prompted the implementation of a refined host stratification system, which incorporated a more pragmatic definition of C-hosts. By integrating the resulting host status with the appropriate curative, palliative or alternative treatment strategy we were able to achieve acceptable short-term outcomes in both low and high-risk cases while maintaining a low rate of amputation.

The reported success rates of the management of adult chronic osteomyelitis vary widely, with figures ranging from 40 to 95%.[1,33,34] A recent Cochrane review, comparing the efficacy of oral and intravenous antibiotics following surgical debridement, found an overall remission rate of 78.8% at 12 months.[35] In the original article by Cierny and Mader the success rate of limb-salvage procedures was reported to be 93.6%.[6] Primary amputation was performed in 46 of the 189 (24%) of patients who received definitive treatment in their series. More recently, Cierny reported an 85% success rate of curative treatment, with 96% success in A-hosts and 74% in B-hosts.[7] Ten percent of cases in this series were managed by primary amputation. The Bone Infection Unit in the United Kingdom reported an excellent cure rate of 90% at 5 years follow-up.[34] Treatment strategy selection and host status were, however, not specifically discussed in this report of their outcomes. In comparison to these results we were able to achieve an overall success rate of 89.9% at a mean follow-up of 18 months, with 100% and 93% success in A- and B-hosts respectively. A success rate of 93.5% was achieved in patients treated curatively and through the judicious implementation of palliative treatment strategies we were able to achieve a primary amputation rate of only 5%. Lack of uniformity in the literature on chronic osteomyelitis, in terms of definition, classification and treatment protocols makes comparison of results problematic. Authors reviewing trials involving antibiotic therapy in chronic osteomyelitis came to a similar conclusion, citing the heterogeneous nature of the patients, classification systems and treatment strategies used as a stumbling block in making evidence based recommendations.[30,33] Similarly our results cannot be directly compared to those of Cierny, who excluded C-hosts in whom a much higher failure rate can be expected when calculating outcome figures.[6,7]

The successful use of suppressive antibiotics in periprosthetic infections of hip or knee replacements has prompted implementation of similar strategies in patient with chronic osteomyelitis.[5,36] To the best of our knowledge this is the first series to specifically look at the outcome of the use of chronic suppressive antibiotic therapy in chronic osteomyelitis. Success have however been reported in isolated cases involving infection associated with osteosynthesis through the use of long-term antibiotics without surgical removal of the implants.[37,38] In our series we were able to achieve successful suppression in 87.2% of patients treated palliatively. Remission of disease was achieved in 62% of patient treated with chronic suppressive antibiotic therapy (CSAT). The efficacy of CSAT in chronic hematogenous osteomyelitis in adults has also not previously been reported.[30] Successful suppression of disease was achieved in all of the five patients with hematogenous osteomyelitis treated palliatively. This finding suggests that chronic osteomyelitis without the presence of surgical implants can successfully be treated palliatively, in appropriately selected patients.

The overall success rate in this series is most likely related to host stratification and treatment selection, rather than therapeutic or surgical prowess. The selection of patient-matched treatment options may close the gap in successful outcomes between compromised and healthy patients. Our strategy involving C-host classification in accordance with certain predefined major and minor criteria, resulted in comparable success rate in both the palliative and curative treatment groups. The fact that there was no statistical difference in success rate between high and low risk patients (p-value = 0.201) suggests that the proposed decision tree may be relevant, at least in a developing world clinical environment. The majority of the suggested major criteria are modifiable. This implies that, in certain cases, palliative treatment can be utilized as a temporary measure while the patient is optimized for curative management.

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**Table 6 – Description of cases in which treatment failure occurred.**

| Age | Host status | Etiology | Site | Anatomic nature | Risk factors | Management strategy | Treatment |
|---|---|---|---|---|---|---|---|
| 44 | B | Contiguous post-traumatic | Tibia | IV | Compliance and motivation | Curative | Wide resection, Masquelet bone transport |
| 34 | C | Contiguous post-traumatic | Ankle | IV | HIV infection (CD4 <350 cells/mm$^3$), smoking, joint involved | Alternative | Patient refused amputation, marginal debridement and acute shortening |
| 25 | C | Contiguous post-traumatic | Tibia | IV | HIV infection (CD4 <350 cells/mm$^3$) | Alternative | Circular fixation, fibula osteotomy, CSAT* |
| 30 | C | Contiguous post-traumatic | Midfoot | IV | Poor soft tissue, joint involved, foot, local extent | Palliative | CSAT* |
| 49 | C | Contiguous post-traumatic | Tibia | III | HIV infection (CD4 <350 cells/mm$^3$), poor soft tissue, local extent, debridement will result in instability | Palliative | CSAT* |
| 26 | B | Contiguous post-traumatic | Proximal tibia | IV | Failed reconstruction elsewhere, joint involved, poor soft tissues | Curative | Wide resection, classic Masquelet |
| 45 | C | Contiguous post-operative | Proximal femur | III | Chronic venous insufficiency, joint involved, local extent, debridement will result in instability | Palliative | CSAT* |
| 65 | C | Contiguous post-operative | Femur | III | Ischemic heart disease, smoker, diabetes mellitus (HbA1c > 8), age | Palliative | CSAT* |
| 46 | B | Hematogenous | Pelvis | III | Smoking, local extent, pelvis | Curative | Marginal resection, PMMA beads |
| 38 | C | Contiguous post-operative | Humerus | IV | HIV infection (CD4<350cells/mm$^3$), adjacent joint stiffness, local extent, diabetes mellitus | Palliative | CSAT* |
| 48 | C | Contiguous post-traumatic | Proximal tibia | III | HIV infection (CD4 <350 cells/mm$^3$), smoking, local extent, poor soft tissues | Palliative | CSAT* |

* Chronic suppressive antibiotic therapy.

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There are several shortcomings to this study. Due to the short follow-up our results are likely to deteriorate over time due to the recurrence of infection. A minimum follow-up of 12 months, as applied by Simpson et al and Conterno et al, may however be reasonable as 95% of recurrences can be expected within the first year.[6,30,35,39] In the palliative treatment group in particular recurrence can be expected. The lack of a control group and randomization are further shortcomings. The lack of randomization could however be difficult to overcome. Exposing all patients, including the most compromised hosts, to the rigors of limb salvage surgery in order to see which risk factors is associated with treatment failure (which frequently would involve amputation) represents an ethical dilemma. The fact that we defined success differently in the curative and palliative also resulted in an apparent improvement in our results. However, it would be unrealistic to expect cure (clinical, biochemical and radiological absence of infection) in patients treated palliatively and thus the definition of success or failure of treatment is intimately bound to the management strategy selected. The final shortcoming of this study its retrospective nature and we have embarked on a prospective study in order to validate these results.

Many questions remain and while this approach may prove to be useful in the developing world, it may not be applicable in all clinical scenarios. Our hope is that the introduction of the concept of a pragmatically defined C-host will spark further research, which could lead to uniformity in host classification and ultimately treatment strategy selection. This may in turn facilitate comparison of different treatment protocols or interventions.

## Conflicts of interest

All authors have none to declare.

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# PART 5

# Assessment of integrated approach

The major limitation of the preceding study was the retrospective study design. In order to address this limitation, a prospective study was undertaken to assess the outcomes of treatment according to the proposed integrated approach. Data analysis from the retrospective series (Chapter 7) identified the need for further development of both the classification system and the treatment selection algorithm. In order to facilitate the treatment strategy selection process the classification system was modified to include impairment severity and the presence of an infection nidus [Table 5.1].

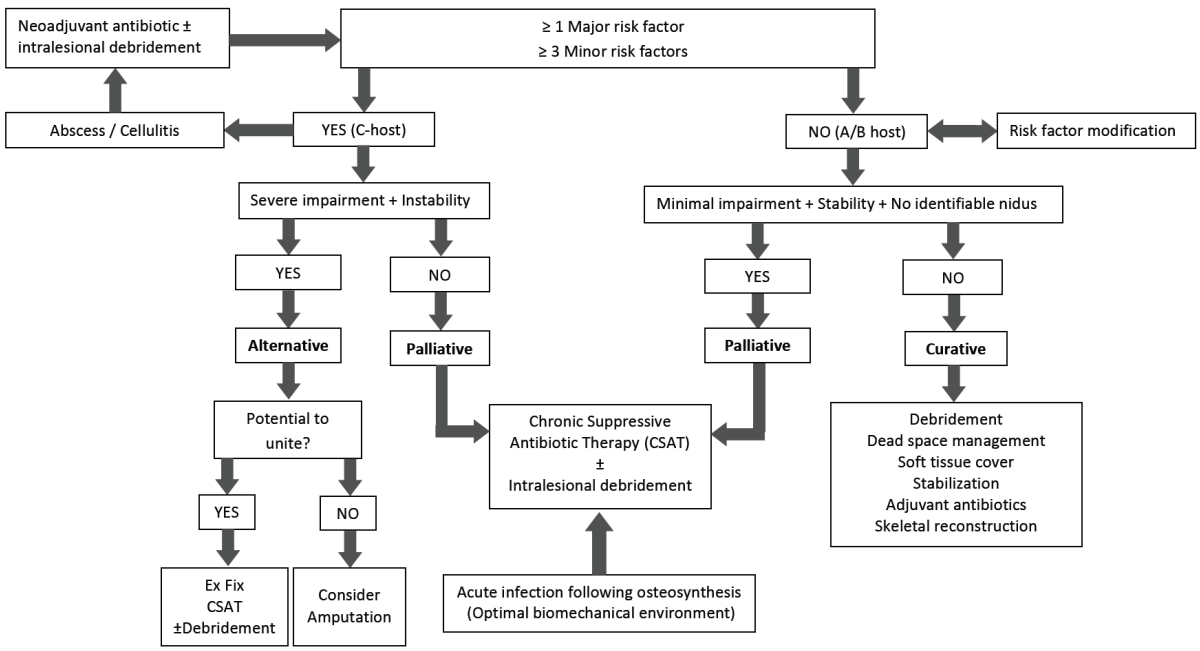
**Table 5.1:** Classification system used in the prospective series.

| Classification | Characteristic |
|---|---|
| **Physiological:** | |
| Type A host | No risk factors |
| Type B host | Less than three minor risk factors |
| Type C host | One major and/or three or more minor risk factors |
| **Pathoanatomy:** | |
| I - Medullary | No cortical sequestration |
| II - Cortical | Direct contiguous involvement of cortex only |
| III - Combined (stable) | Both cortex and medullary regions involved |
| IV - Combined (unstable) | Same as III plus unstable prior to debridement |
| **Nidus:** | |
| Sequestrum | Cortical sequestrum present |
| Implant | Biofilm-based infection in the presence of an implant |
| No identifiable nidus | Minimal necrosis osteomyelitis |
| **Impairment:** | |
| Minimal | Patient able to perform ADL |
| Severe | Unable to perform ADL |

For the treatment selection algorithm to remain relevant in both haematogenous and post-operative infection, the concept of minimal necrosis osteomyelitis required further expansion. Minimal necrosis osteomyelitis was defined as chronic infection in the absence of an identifiable nidus of infection, albeit a sequestrum or orthopaedic implant. This definition therefore also catered for the scenario of an infected tibial nail in the presence of a united tibial fracture, where removal of the nail is required as part of a curative treatment strategy.

The second item added to the proposed classification system was the extent of impairment as a result of the disease. This step was required in order to clarify the decision making process during treatment strategy selection [Figure 5.1].

**Figure 5.1:** Treatment selection algorithm.



In addition to the changes that were made in the classification system, certain additional risk factors were added to the list of host-defining criteria [Table 5.2]. These were identified in the retrospective series (Chapter 7) amongst patients in whom the initial treatment plan failed.

**Table 5.2:** Major and minor host-defining criteria used in prospective series.

| **Major risk factors** | **Minor systemic risk factors** | **Minor local risk factors** |
|---|---|---|
| $CD_4$ count < 350 cells/$mm^3$ | HIV infection | Poor soft tissues requiring flap |
| Albumin < 30 g/L | Anaemia | Chronic venous insufficiency |
| HbA1C ≥ 8% | Smoking | Peripheral vascular disease |
| Cellulitis or abscess formation | Diabetes mellitus | Previous radiation therapy |
| Malignancy at site of infection | Rheumatoid arthritis | Instability expected after surgery |
| Pathological fracture | Chronic lung disease | Adjacent joint stiff / arthritic |
| | Chronic cardiac failure | Heterotopic ossification |
| | Common variable Immune deficiency | Segmental resection of >6cm required to achieve cure |
| | Paraplegia / Quadriplegia | Failed reconstruction elsewhere * |
| | Drug or substance abuse | Foot involvement * |
| | Chronic corticosteroid use | Pelvic involvement * |
| | Active tuberculosis | Adjacent joint involved * |
| | Ischemic heart disease | |
| | Cerebrovascular disease | |
| | Compliance and motivation * | |
| | Age > 65 * | |

* Risk factors identified in retrospective series

The final treatment algorithm, implemented in the prospective series, incorporated the physiological status of the host, the presence of skeletal instability, the severity of impairment,

as well as the concept of minimal necrosis osteomyelitis. Furthermore, additional emphasis was placed on risk factor modification [Figure 5.1].

# Chapter 8: The outcome of treatment of chronic osteomyelitis following an integrated approach

**Marais LC**, Ferreira N, Aldous C, Le Roux TLB.

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Contribution to authorship:

LC Marais – Concept, study design, literature review, algorithm development, data collection, data analysis and interpretation, drafting of manuscript, revision of manuscript, corresponding author.

N Ferreira – Algorithm development, data collection and revision of manuscript.

C Aldous – Study design, concept development and revision of manuscript.

TLB Le Roux – Study design, concept development, algorithm development and revision of manuscript.

# The outcome of treatment of chronic osteomyelitis following an integrated approach

LC Marais MBChB, FC Orth (SA), MMed (Ortho)
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics,
Grey's Hospital, University of KwaZulu-Natal

N Ferreira BSc, MBChB, FC Orth (SA), MMed (Orth)
Tumour, Sepsis and Reconstruction Unit, Department of Orthopaedics,
Grey's Hospital, University of KwaZulu-Natal

C Aldous BSc, BSc (Hons), MSc, PhD
Medical Research Scientist, School of Clinical Medicine
College of Health Sciences, University of KwaZulu-Natal

TLB Le Roux MBChB, FC Orth (SA), MMed (Ortho)
Professor and Head of Department, Department of Orthopaedics,
I Military Hospital, University of Pretoria

Corresponding author:
Dr LC Marais
Department of Orthopaedic Surgery
Greys Hospital
School of Clinical Medicine
University of KwaZulu-Natal
Private Bag X9001
Pietermaritzburg
3201

Email: Leonard.Marais@kznhealth.gov.za
Tel: +27 033 897 3424

## The outcome of treatment of chronic osteomyelitis following an integrated approach


### Abstract

Chronic osteomyelitis of long bones can be particularly challenging to treat in adult patients. While several classification systems have been proposed, none has been universally accepted. Popular classifications have failed to provide objective and pragmatic guidelines for selection of the appropriate treatment strategy. In this study we investigate the short-term treatment outcome in adult patients with long bone chronic osteomyelitis, where a modified host classification system was integrated with treatment strategy selection through a novel management algorithm. Prospective evaluation was performed of adult cases with chronic long bone osteomyelitis treated at a tertiary level tumour, sepsis and reconstruction unit. Following clinical, radiological and biochemical evaluation, patients were classified using a modified version of the original Cierny and Mader classification system. The physiological host status was modified to provide a more pragmatic and objective C-host definition. This classification system was integrated with treatment strategy selection using a novel management algorithm. Twenty-six of the 28 enrolled patients were available for follow-up. The median patient age of was 36.5 years (range 15-72 years). Three patients (12%) were classified as A-hosts, eleven patients (42%) as B-hosts and twelve (46%) as C-hosts. Seven patients (27%) were HIV positive with a mean $CD_4$ count of 401cells/$mm^3$ (range 220-986 cells/$mm^3$). Nine patients (35%) were smokers and three patients (12%) had hypoalbuminemia. Fourteen patients (54%) were managed palliatively and 11 patients (42%) were managed through the implementation of a curative treatment strategy. One patient

required alternative treatment in the form of an amputation. The overall success rate was 92.3% (95%CI: 74.9-99.1%) at a minimum of 6 months follow-up. Remission was achieved in all [11/11] patients treated curatively (one sided 95% CI: 73.5-100.0%). Palliative treatment was successful in 86% [12/14] of cases (95% CI: 57.2-98.2%). In patients with lower limb involvement there was a statistically significant improvement of 28.3 (95% CI:21.0-35.7; SD 17.0) in the AAOS Lower Limb Outcomes Instrument score (p-value<0.001). The integrated approach proposed in this study appears to hold some promise in serving as a useful guideline to the management of chronic osteomyelitis of long bones in adult patients in the developing world. Further investigation is required to validate the approach and additional development of the algorithm may be required in order to render it useful in other clinical environments.

**Keywords**

Osteomyelitis, Chronic, Classification, Outcome, Management.

## Introduction

Long bone chronic osteomyelitis can be particularly challenging to treat in adult patients. The typical causative organisms possess characteristics which render them more resistant to the host's immune response and antibiotic therapy. Bacteria may persist in a biofilm-based colony or intracellular, concealed within osteoblasts.[1,2] While chronic haematogenous osteomyelitis is typically not associated with skeletal instability, it frequently involves a large segment of bone. Post-traumatic contiguous osteomyelitis is often complicated by the presence of instability or a compromised soft tissue envelope. Lastly, there are frequently systemic risk factors present in the host which compromise their immune system's ability to effectively combat the infection.

Several classification systems have been proposed, but none has been universally accepted.[3,4] Although the Cierny and Mader classification has been the most popular, the stratification of the physiological status of the host remains problematic.[5,6] The definition of a C-host, according to this classification, is subjective in nature and is dependent on the treating surgeon's ability to predict the patient's response to a therapeutic intervention.[7] The differentiation between a B and C-host is important as it identifies patients who should be treated curatively or palliatively.[3] In addition, the lack of standardization in host classification has made comparison of results from different studies challenging.[8]

No evidence-based guidelines exist on the treatment of chronic osteomyelitis in adults.[3] There is no single treatment regimen or surgical procedure which is appropriate for all patients.[9] Essentially the choice is between a curative, a palliative or an alternative approach. Curative

treatment usually involves surgical debridement with or without complex reconstructive procedures and short-term pathogen-directed antimicrobial therapy.[10] Palliative treatment on the other hand typically involves long-term chronic suppressive antibiotic therapy (CSAT) and, rarely, intra-lesional or minimally invasive surgical intervention.[11] An alternative treatment strategy is occasionally indicated and may comprise either amputation of the limb or a combination of surgical intervention and chronic suppressive antibiotic therapy. The main difficulty lies in choosing the correct treatment strategy in each patient. This process is further complicated by the aforementioned lack of standardization in host stratification.

The limitations of existing classification systems, as well as the lack of evidence based guidelines, prompted us to develop a classification system and treatment algorithm which would assist in treatment strategy selection in a developing country. In this study we investigate the short-term outcome of treatment in adult patients with long bone chronic osteomyelitis, where a modified host classification system was integrated with treatment strategy selection through a novel management algorithm.

**Materials and Methods**

A prospective study was performed on 28 consecutive patients with long bone chronic osteomyelitis treated by the Tumour, Sepsis and Reconstruction Unit at Grey's Hospital in Pietermaritzburg, South Africa. All adult patients older than 13 years of age and with a minimum follow-up of six months were included in the series. Patients with infections involving the foot or hand, atypical organisms (including tuberculosis and fungal infections)

and arthroplasty-related periprosthetic infection were excluded from the study. Data were collected with regard to patient demographics, the cause and site of infection, the initial and final impairment, causative organisms, management strategy employed, follow-up period and outcome of treatment in terms of remission or suppression of infection. Impairment was assessed by means of the quickDASH scoring system for upper limbs or AAOS Lower Limb Outcomes Instrument (version 2.0) in the case of lower limb involvement.[12,13]

For the purposes of this study chronic osteomyelitis was defined as an infection involving bone, with a duration of at least ten days, where the causative organisms were thought to have persisted either intracellularly or in interactive biofilm-based colonies. Periprosthetic infections were excluded from the study based on the current trend of classifying and treating arthroplasty related infections as a separate entity.[14] Following clinical, radiological and biochemical evaluation, patients were classified according to a modified version of the original Cierny and Mader classification system [Table 1].[7] In terms of the physiological status of the host, the Cierny and Mader classification system was modified in order to provide a more pragmatic and objective definition of a C-host. A patient was classified as a C-host if one major or more than two minor risk factors were present [Table 2]. In order to remove any ambiguity during classification of the anatomical nature of the disease this was performed prior to, rather than following, the debridement. The impairment resulting from the disease and the nidus of infection was added to the classification as these factors were to be considered during the treatment selection process.

**Table 1:** Modified version of the original Cierny and Mader classification system that served to guide treatment strategy selection.

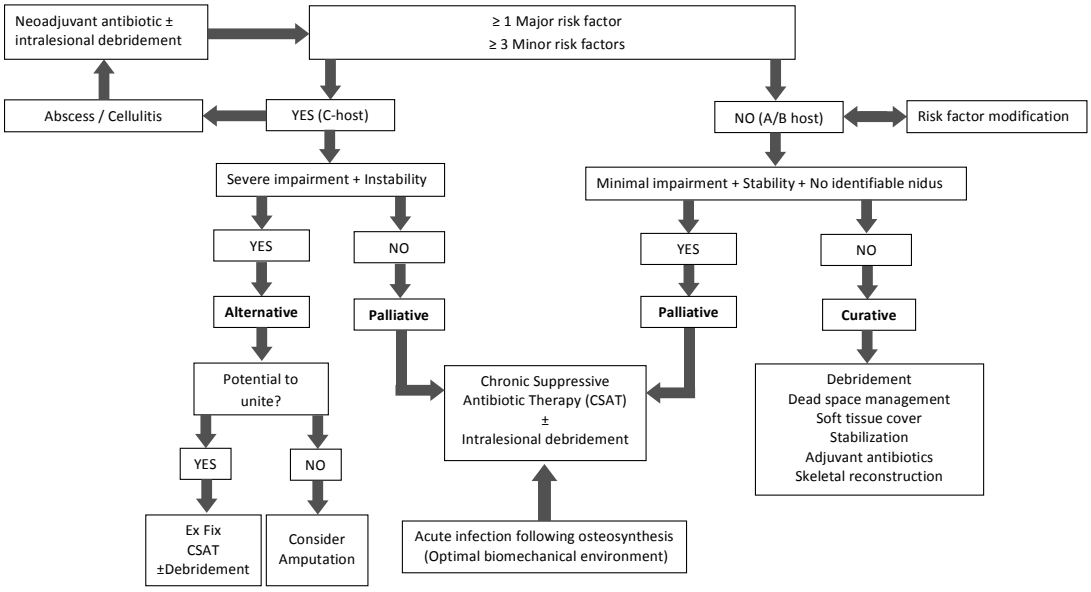
| Classification | Characteristic |
|---|---|
| **Physiological:** | |
| Type A host | No risk factors |
| Type B host | Less than three minor risk factors |
| Type C host | One major and/or three or more minor risk factors |
| **Pathoanatomy**: | |
| I - Medullary | No cortical sequestration |
| II - Cortical | Direct contiguous involvement of cortex only |
| III - Combined (stable) | Both cortex and medullary regions involved |
| IV - Combined (unstable) | As for III plus unstable prior to debridement |
| **Nidus:** | |
| Sequestrum | Cortical sequestrum present |
| Implant | Biofilm-based infection in the presence of an implant |
| No identifiable nidus | Minimal necrosis osteomyelitis |
| **Impairment:** | |
| Minimal | Patient able to perform ADL (activities of daily living) |
| Severe | Unable to perform ADL |

**Table 2:** Risk factors used to stratify the physiological status of the host.

| Major risk factors | Minor systemic risk factors | Minor local risk factors |
|---|---|---|
| $CD_4$ count < 350 cells/$mm^3$ | HIV infection | Poor soft tissues requiring flap |
| Albumin < 30 g/L | Anaemia | Chronic venous insufficiency |
| HbA1C ≥ 8% | Smoking | Peripheral vascular disease |
| Cellulitis or abscess formation | Diabetes mellitus | Previous radiation therapy |
| Malignancy at site of infection | Rheumatoid arthritis | Instability expected after surgery |
| Pathological fracture | Chronic lung disease | Adjacent joint stiff / arthritic |
| | Chronic cardiac failure | Heterotopic ossification |
| | Common variable Immune deficiency | Segmental resection of >6cm required to achieve cure |
| | Paraplegia / Quadriplegia | Failed reconstruction elsewhere |
| | Drug or substance abuse | Foot involvement |
| | Chronic corticosteroid use | Pelvic involvement |
| | Active tuberculosis | Adjacent joint involved |
| | Ischemic heart disease | |
| | Cerebrovascular disease | |
| | Compliance and motivation | |
| | Age > 65 | |

The modified classification system was integrated with treatment strategy selection through the implementation of a novel management algorithm [Figure 1]. C-hosts, as well as A or B-hosts with minimal impairment, no identifiable source and no skeletal instability, were managed palliatively. All remaining A and B-hosts were treated curatively. C-hosts with severe impairment combined with skeletal instability were managed through the implementation of an alternative treatment strategy. This involved either amputation or chronic suppressive antibiotic therapy in combination with external fixation with or without intralesional debridement.

**Figure 1:** Treatment selection algorithm



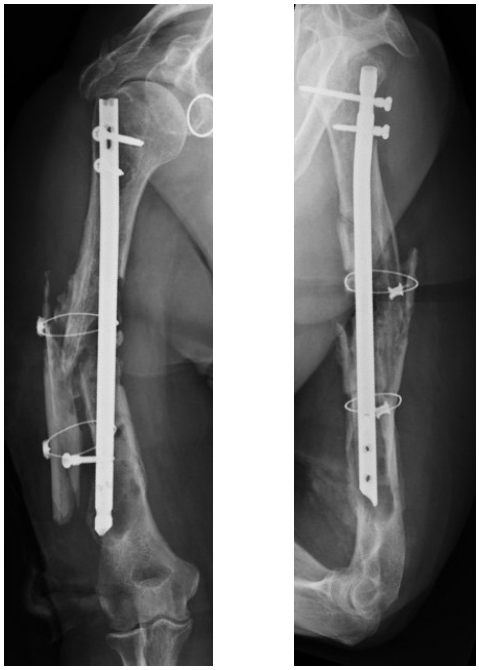

Curative treatment involved marginal or wide resection, dead space management, provision of bony stability, soft tissue reconstruction and/or skeletal reconstruction, in conjunction with pathogen directed adjuvant antibiotics for a period if six weeks. In cases without skeletal instability (Cierny and Mader anatomic type I, II and III lesions) the aim was to maintain stability through the performance of marginal debridement involving direct unroofing (tangential excision with high speed burr) and/or indirect unroofing (medullary reaming). In cases involving skeletal instability, wide (segmental) resection was performed and stability provided by circular external fixation. Dead space management techniques were tailored to the anatomic nature of the pathology. Continuous irrigation, as proposed by Lautenbach, was used in type I (medullary) post-operative infections.[15,16] In type III lesions (stable combined medullary and cortical lesions), gentamycin impregnated polymethylmethacrylate (PMMA)

beads (Septopal® Merck, Darmstadt Germany) were used and removed at six to eight weeks. Post-operatively, all patients were treated with generic parenteral antibiotics in the form of Cefazolin and Imipenem until the seven day microscopy, culture and sensitivity (MCS) results became available. Oral antibiotic therapy, in the form of two agents which were tailored to the culture and sensitivity, was subsequently commenced and continued for a period of six weeks.

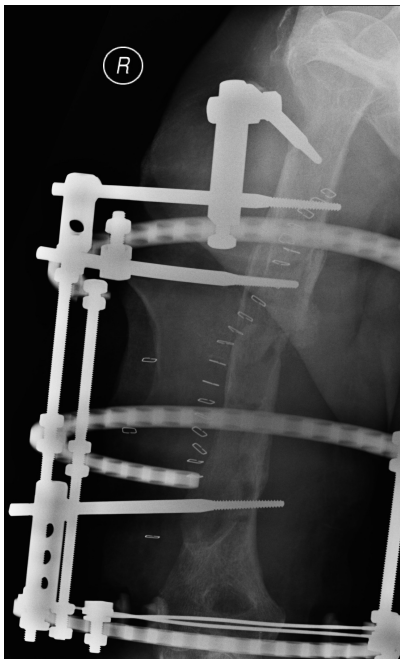
Following this period, reconstruction of segmental bone defects in Cierny and Mader type IV lesions were undertaken if clinical and biochemical evaluation confirmed the absence of active infection. The treatment protocol dictated that the size of the bone defect would determine the nature of the subsequent skeletal reconstruction procedure. Defects less than 1-2cm in magnitude were managed by acute shortening [Fig. 2]. In long bones other than the tibia, defects between 2 and 4 cm in size were managed using the Masquelet technique, involving autogenous bone grafting into an induced membrane. Tibial defects larger than 2 cm and other gaps in excess of 4 cm were treated through the use of bone transport.

Palliative treatment involved the use of chronic suppressive antibiotic therapy (CSAT) in the form of trimethoprim-sulfamethoxazole (800mg/160mg twice daily) and rifampicin (600mg daily). In cases where the general condition of the patient and local soft tissues allowed, an intralesional excision of discreet exposed sequestra was performed. In this series, all cases treated by an alternative treatment strategy required amputation of the limb.

(a)



(b)




(c)

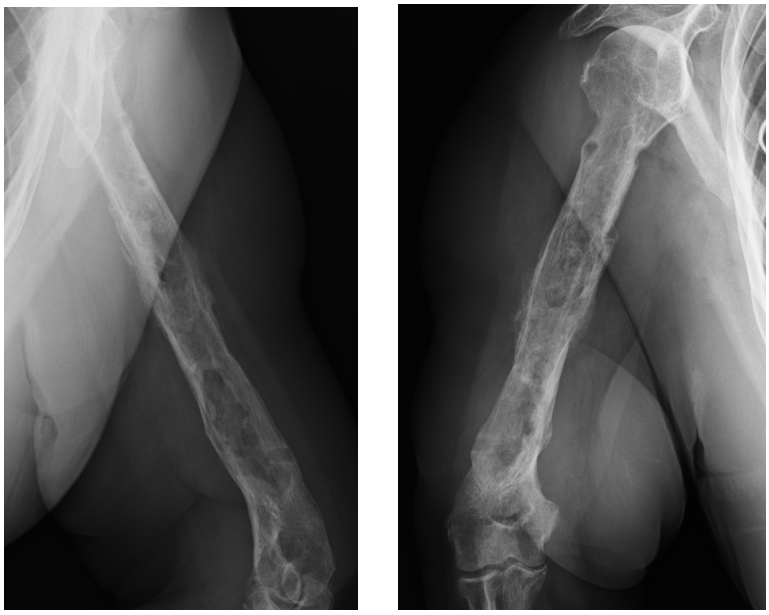


**Figure 2:** X-ray images of a case involving pre-operative instability (anatomic type IV infection). (a) This 72 year old diabetic patient presented with a septic non-union of the humerus following multiple previous surgeries. (b) Post-debridement reconstruction involved acute shortening, bone graft and circular external fixation. (c) Radiological images following external fixator removal.

Following a minimum six month follow-up period treatment success or failure was determined. Success was defined as achievement of remission through a curative treatment strategy or attainment of suppression in patients treated palliatively. Remission was defined as the absence of clinical signs of infection.[8] Suppression was defined as subjective resolution of infection symptoms and signs, from the patient point of view, to the extent that the patient required no additional treatment. Treatment failure was defined as the failure to achieve the predetermined goal (remission or suppression). The outcome was also reported as failure if unplanned re-operation was required or if the patient was dissatisfied with the outcome.

Data were analyzed using Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Continuous variables were summarized using mean and standard deviation values. If the variable was skewed or outlying values were present, then the median and interquartile range was used instead. Category variables were summarized using frequency tables. 95% confidence intervals were constructed around sample point estimates. Change in AAOS Lower Limb Outcomes Instrument score from initial assessment to final assessment was compared using a paired t-test. A p-value of $<0.05$ was considered statistically significant for all tests.

Ethical approval was obtained from the relevant ethics review boards prior to commencement of the study.

## Results

Twenty-six of the 28 enrolled patients were available for follow-up at six months. The median patient age was 36.5 years (range 15-72 years; interquartile range 24 years). Seven patients had chronic haematogenous osteomyelitis, eight had post-operative infections, nine developed chronic osteomyelitis after open fractures and two patients developed contiguous chronic osteomyelitis as a result of direct local extension. The tibia diaphysis was the most commonly involved site [Table 3].

**Table 3:** Infection site.

| Infection site | Number of patients |
|---|---|
| Tibia diaphysis | 12 (46%) |
| Femur diaphysis | 8 (30%) |
| Tibial plateau | 2 (8%) |
| Humerus diaphysis | 2 (8%) |
| Tibial plafond | 1 (4%) |
| Ulna shaft | 1 (4%) |

Culture results, from tissue samples taken at the time of debridement in patients who were treated curatively, revealed a variety of causative organisms [Table 4]

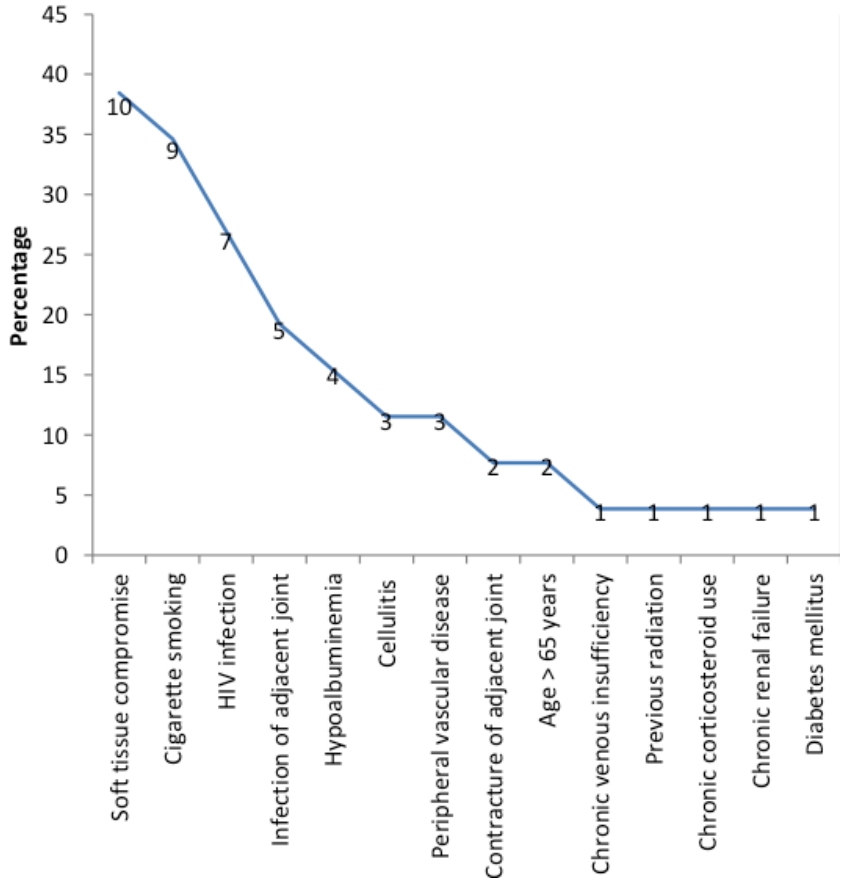
**Table 4:** Microorganism cultured from tissue samples taken during debridement in patients treated curatively.

| Microorganisms | Number of patients |
|---|---|
| Staphylococcus aureus | 3 |
| Staphylococcus epidermidis | 1 |
| Entrobacter sp. | 1 |
| Streptococcus infantarius | 1 |
| Pseudomonas auriginosa | 1 |
| Aeromonas hydrophila | 1 |
| Serratia sp. | 1 |
| Proteus Mirabilis | 1 |
| Pantoea sp. | 1 |
| No growth | 1 |
| Multiple organisms | 1 |

*Classification*

Three patients (12%) were classified as A-hosts, eleven patients (42%) as B-hosts and twelve (46%) as C-hosts. Six patients were classified as C-hosts due to the presence of one major risk factor and six patients on the basis of the presence of three or more minor risk factors. Of the twelve C-hosts, six had both a major and more than 2 minor risk factors present. Seven patients (27%) were HIV positive with a mean $CD_4$ count of 401cells/$mm^3$ (range 220-986 cells/$mm^3$; standard deviation (SD) 238 cells/$mm^3$). A variety of additional risk factors were identified amongst the patients enrolled [Fig. 3].

**Figure 3:** Risk factors identified.




Nine patients (35%) were smokers and three patients (12%) had hypoalbuminemia. The soft tissues were considered to represent a significant risk factor for the development of complications following surgery, if not addressed by flap or other means, in ten patients. Cellulitis and abscess formation, precluding the performance of definitive surgery was present in three patients. Peripheral vascular disease or chronic venous insufficiency with lipodermatosclerosis was present in three patients. The infection involved the adjacent joint in five cases and there was significant loss in range of motion of the adjacent joint in an additional two patients. Other risk factors included previous radiation, chronic renal failure

requiring dialysis and chronic corticosteroid use in one patient, diabetes mellitus in one patient and age over 65 years in two patients. In terms of the anatomic nature of the disease, twenty patients had type III infection, five patients had pre-operative instability and in one patient the infection was confined to the medullary cavity. The mean initial AAOS Lower Limb Outcomes score in patients with lower limb involvement was 58.2 (range 21-100; SD 22.9). In three cases the upper limb was involved, with a mean initial quickDASH score of 18.2 (range 2.3-29.5) [Table 5].

*Management*

Fourteen patients (54%) were managed palliatively and 11 patients (42%) were managed through the implementation of a curative treatment strategy. One patient required alternative treatment in the form of an amputation. This patient had infection and bone loss following a neglected open fracture and was classified as a C-host on the basis of the presence of two major and two minor risk factors. The palliative treatment group consisted of eleven C-hosts and three B-hosts who had stable lesions with minimal impairment and no identifiable sequestra. All patients in the palliative treatment group received chronic suppressive antibiotic therapy - trimethoprim-sulfamethoxazole (800mg/160mg twice daily) and rifampicin (600mg daily) - for a period of three to six months. One patient, who had an exposed sequestrum in the region of the tibial plateau, required an additional intralesional excision (simple sequestrectomy).

In the curative treatment group, surgical intervention involved marginal debridement (direct and/or indirect unroofing) in ten patients. Wide (segmental) resection of the ulna diaphysis, without subsequent reconstruction, was performed in one patient. Dead space management

involved a modified Lautenbach continuous irrigation system in six cases, PMMA beads in four patients and local muscle flap in one case. Primary soft tissue closure was obtained in all curative cases. In the two patients, in whom skeletal stabilization and reconstruction was required, acute shortening and Ilizarov circular external fixation was performed. Union was achieved in both of these cases. All patients treated curatively received a combination of two oral antibiotics for a period of six weeks.

*Outcome*

The overall success rate was 92.3% (95%CI: 74.9-99.1%) after a minimum of six months follow-up. Remission was achieved in all [11/11] patients treated curatively (one sided 95% CI: 73.5-100.0%). Palliative treatment was successful in 86% [12/14] of cases (95% CI: 57.2-98.2%), with suppression in 36% and remission in the remaining 64% of these patients. The overall mean final AAOS Lower Limb Outcomes score was 86.6 (range 51-100; SD 14.5). This equated to a statistically significant (p-value<0.001) mean improvement of 28.3 (95% CI:21.0-35.7, SD 17.0). In the upper limb the mean final overall quickDASH score was 75 (range 72.5-86.4), with a mean improvement of 54.3 (range 45.5-84.1). There was comparable improvement of the functional outcome scores in the palliative and curative treatment groups [Table 5].

**Table 5:** Functional outcome.

| Category | n | Mean | Range | SD | 95% CI | p-value [iii] |
|---|---|---|---|---|---|---|
| **Overall lower extremity** [i] | 23 | | | | | |
| Initial | | 58.2 | 21 - 100 | 22.9 | 48.2 - 68.1 | |
| Final | | 86.6 | 51 - 100 | 14.5 | 80.3 - 92.9 | |
| Improvement | | 28.3 | 0 - 49 | 17.0 | 21.0 - 35.7 | <0.001 |
| **Overall upper extremity** [ii] | 3 | | | | | |
| Initial | | 18.2 | 2.3 - 29.5 | | | |
| Final | | 75 | 72.5 - 86.4 | | | |
| Improvement | | 54.3 | 45.5 – 84.1 | | | |
| **Palliative group** [i] | 14 | | | | | |
| Initial | | 51.1 | 28 - 100 | | | |
| Final | | 92.5 | 51 - 100 | | | |
| Improvement | | 25.5 | 0-54 | | | |
| **Curative group** [i] | 8 | | | | | |
| Initial | | 61 | 34 - 94 | | | |
| Final | | 91 | 74-100 | | | |
| Improvement | | 27.5 | 6-48 | | | |

(i) AAOS Lower Limb Outcomes Instrument, (ii) quickDASH, (iii) paired t-test

Both treatment failures occurred in the palliative treatment group. One failure occurred in a patient who required regular dialysis as a result of Goodpasture syndrome. This patient had extensive involvement of the entire femoral diaphysis following prior irradiation, with peripheral vascular disease and avascular necrosis of the femoral head. A hip disarticulation was required following abandonment of the palliative treatment protocol. The second failure occurred in a patient who developed post-traumatic osteomyelitis following an open tibial

fracture with compartment syndrome. Palliative treatment was instituted in this patient as a result of the presence of multiple risk factors which included HIV infection (CD4 count 518 cells/$mm^{3)}$, cigarette smoking, poor soft tissue condition and age >65 years.

**Discussion**

Chronic osteomyelitis management continues to pose a major challenge to orthopaedic surgeons.[11] The Mayo Clinic previously reported a 20% failure rate in the management of chronic infections.[17] Twenty years later the disease remains difficult to cure, as was recently illustrated in a Cochrane review on the topic of antibiotic therapy in chronic osteomyelitis.[18] The combined remission rate, in this analysis of four randomized controlled trails, was 78.8% at 12 months. Specialized units have, however, been able to achieve superior results. Cierny for example, achieved success in 84% of patients managed curatively at two year follow-up.[10] The Bone Infection Unit in the United Kingdom reported an impressive cure rate of 90% at 5 years follow-up.[9] While the multidisciplinary nature of the service offered by these specialized units is bound to improve outcomes, appropriate surgical candidate selection may also play a role.

Without a pragmatic and objective definition of a C-host (who should be palliated) the selection of a curative (surgical) treatment strategy, according to the Cierny and Mader classification system, is essentially based on prior clinical experience.[7] According to this approach the expected outcome of a curative strategy should offer a distinct advantage over symptomatic treatment or amputation, in order to justify the potential morbidity and risks involved in limb salvage surgery.[7,10] Selecting candidates for surgery on this basis clearly

requires considerable experience, as it is based on a prediction of the patient's response to treatment. The experience gained in specialized units will therefore improve the success rate of curative treatment strategies due to, amongst other factors, improved surgical candidate selection. The approach followed in our study, was developed to serve as a guideline for treatment of chronic osteomyelitis in a resource-poor clinical environment, where treatment by specialized units is not always easily accessible.

In a previous retrospective series of 116 cases we were able to achieve an overall success rate of 91% at 18 months follow-up, through the application of an approach which involved integration of pragmatic host stratification with treatment strategy selection (unpublished data). With this study we aimed to perform a preliminary validation of a similar approach, in a prospective fashion. After a minimum of 6 months follow-up we were able to achieve an overall success rate of 92%, with 100% remission in the curative group and 86% suppression (or better) in the palliative group. These results are comparable to those achieved in our retrospective series, where curative and palliative treatment was successful in 92% and 89%, respectively.

Although these results appear promising, caution is still advisable with regard to the widespread implementation of this approach. It should be kept in mind that the proposed classification system and treatment algorithm was designed for use in the developing world. It is therefore unlikely to be suitable in the developed world without further improvement or modification. Apart from the high incidence of HIV infection and hypoalbuminemia in our series, the pattern of causative organisms identified in our cases appears to differ somewhat from that seen in the developed world.[19]

Additional problems may also arise when the algorithm is tested in a wider range of patients. In one case in this series, the treatment algorithm was deemed to be inadequate as it prescribed chronic suppressive antibiotic therapy (CSAT) in a C-host (on the basis of the presence of skeletal stability), where amputation was going to be inevitable. This algorithm error was however on the conservative side and in many C-hosts without skeletal instability CSAT may suppress the disease to the extent that amputation may not be required. Furthermore, the proposed host stratification criteria could result in the initiation of palliative care in patients who may possibly have been able to cope with curative treatment. This approach may however, hold some benefit as it emphasises the importance of host factor modification prior to surgical intervention. Many high risk cases ,who may initially be classified as C-hosts, will become candidates for curative treatment (B-hosts) following implementation of the appropriate interventions aimed at risk factor reduction.

There are further limitations to this study. The heterogeneous nature of the disease demands a much larger series of cases to determine if the algorithm is truly appropriate. The follow-up period in this series is too short to determine the ultimate success rate and our results are likely to deteriorate over time due to infection recurrence. While deterioration can be expected in both groups, it is bound to be more pronounced in the palliative group. Long term follow-up will be required to shed more light on this subject. The lack of a control group represents a further limitation. Randomizing high risk patients to high or low risk interventions, in order to identify which factors are associated failure (amputation), presents obvious ethical concerns. Future comparative studies will, however, be facilitated by the fact that we have provided a standardized host stratification system.

Despite these limitations, preliminary results suggest that our proposed approach may be useful in certain clinical environments. Our modified classification system may be more relevant to clinicians inexperienced in the management of chronic osteomyelitis, as it is less dependent on estimation of the response to treatment or the prediction of instability following debridement.[7] Another important potential benefit of this approach is that standardized host stratification may enable the comparison of results from future studies. It may thus become possible to compare the outcome of different interventions or strategies,if the physiological host status was classified using the same pre-defined pragmatic criteria. This may in turn allow us to answer many of the questions that remain regarding the management of adult chronic osteomyelitis.[8]

**Conclusion**

The integrated approach proposed in this study appears to hold promise in the management of chronic long bone osteomyelitis in adult patients in the developing world. Further investigation is required to validate the approach and additional algorithm development may be required in order to render it useful in other clinical settings.

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# Chapter 9: Conclusion

## 9.1. Limitations of previous classification systems

The absence of evidence-based guidelines for chronic osteomyelitis treatment in adult patients has been highlighted in the recent literature.[1] Although both curative and palliative management options have been advocated, selection of the appropriate treatment strategy can be challenging. Embarking on a curative protocol, for example, in a compromised host who is unable to withstand the metabolic and immunological demands of complex limb reconstructive process may result in therapeutic failure. Failure of a curative treatment strategy, especially if it involves bone transport, can in some cases be impossible to salvage and result in unplanned amputation. This point was illustrated in Chapter 6, where the failure of a curative treatment strategy resulted in limb amputation.

The clinical manifestations of chronic osteomyelitis result from the complex interplay of the host's immune defense system and the biofilm-based bacterial colony on a sequestrum or surgical implant.[2] The host's physiological status not only determines the clinical course of the disease, but also serves as the primary indicator of the patient's ability to effect healing of bone and soft tissues, as well as their ability to launch an effective immune response in conjunction with antibiotic therapy. Without a competent immune response from the host an attempt at eradication of the infection may be futile.[3]

Cierny and Mader recognized the physiological status of the host as a crucial factor in the decision-making process, during the development of their UTMB classification system.[4] The authors recommended palliative treatment in C-hosts, but failed to provide discreet or

pragmatic criteria by which to define a C-host. They acknowledge this fact by stating that there would be a wide variation in surgical candidate selection until there was standardization of this concept. The absence of such criteria has not only made treatment strategy selection problematic, it has also made teaching the subject to students and trainees challenging. Cierny and Mader's definition of a C-host, as a patient in whom treatment or the results of treatment are expected to be worse than the disease itself, required an accurate estimation of a patient's response to any particular intervention.[4] Selection of the appropriate treatment strategy based on this definition clearly required considerable experience, which made treatment selection difficult for students or inexperienced clinicians.

Romanò *et al.* also recognized the shortcomings of Cierny and Mader's host classification during the compilation of their classification system.[5] Their seven item comprehensive classification system (SICCS) is descriptive in nature and incorporates several existing classification systems. In contrast with the Cierny and Mader classification system it was not designed to guide management, but is rather intended for didactic and scientific purposes. In an attempt to circumvent the problems associated with the Cierny and Mader host classification, the authors preferred to use the McPherson host classification system and subdivided patients according to age (less than 2 years, less than 14 years and more than 14 years of age). The McPherson system divides patients into three classes, A, B, or C, based on the number of co-morbid conditions that a patient has in common with a list of 14 immune-compromising factors.[6] Patients with no compromising factors were placed in class A, while patients in class B had less than 3 compromising factors. Class C patients were defined as having three or more compromising factors and/or one of the following conditions: an absolute neutrophil count less than 1000/$mm^3$, a CD4 count less than 100 cells/$mm^3$,

intravenous drug abuse, chronic active infection at another site or dysplasia/neoplasm of the immune system. In our retrospective series we noted a poor agreement between the McPherson classification and our modification of the Cierny and Mader system in terms of C-host classification. This was most likely due to the fact that McPherson system was developed specifically for use in the planning of 2nd stage revision arthroplasty in patients with periprosthetic joint infection following total hip replacement. In addition, the list of criteria proposed by McPherson is conservative and may not be appropriate when applied to chronic osteomyelitis in general. Several criteria have been omitted, with specific reference to patient impairment, the state of the soft tissue envelope, arterial and venous sufficiency, age, diabetic control and nutritional status. All of these factors may however need to be considered during the decision making process in chronic osteomyelitis.

In order to the address the limitations of the aforementioned classification systems the development of a novel approach to chronic osteomyelitis was required. However, in order to remain clinically relevant a new classification system would need to poses the potential to guide patient management. The ideal approach would therefore integrate patient classification with appropriate treatment strategy selection in a logical and reproducible manner.

### 9.2. Developing an integrated approach to adult chronic osteomyelitis

The lack of standardization in host classification, and therefore treatment strategy selection, has made the interpretation and comparison of previously published results problematic.[1,2,7,8] The provision of standardized, pragmatic definitions would, firstly, enable the validation (or invalidation) of the results of the studies contained in this thesis. Secondly, if these definitions

were adopted by future researchers in the field of adult chronic osteomyelitis, it would enable direct comparison of different treatment interventions. In order to increase objectivity and standardize host stratification, as well as treatment strategy selection, the definition of the disease itself, the characterization of the C-host and the definition of cure, required clarification.

### 9.2.1. Defining chronic osteomyelitis

Chronic osteomyelitis is not a homogenous entity but consists of various clinical conditions with multiple causes.[9] Numerous definitions have been proposed, but controversy remains and the inconsistent definition of the disease has made it difficult to compare different investigation and treatment methods.[1] A standardized definition was required to clarify which clinical scenarios should be termed chronic osteomyelitis and thus treated according to the proposed treatment algorithm.

The definition proffered by Cierny, where the disease is characterized by the presence of biofilm, appears relevant as it is based on a universally applicable pathogenesis.[2] This definition however, has certain practical limitations. By defining chronic osteomyelitis as a biofilm-based infection it becomes necessary to determine the timescale of biofilm formation in order to distinguish acute from chronic osteomyelitis. The answer may have important clinical implications: At what stage, for example, should an open fracture with devitalized bone be classified as chronically infected and thus chronic osteomyelitis treatment protocols implemented?

Biofilm formation is a complex process which is modulated by several factors including nutritional and environmental conditions.[10] In addition, the process is possibly genetically programmed within the offending bacteria.[11] Our knowledge of biofilms, though, is mostly based on the results of *in vitro* experimentation. *In vivo* biofilms exhibit several characteristics that differ significantly from what is predicted by our current *in vitro* models. Key differences include their smaller size and the fact that *in vivo* biofilm matrix does not necessarily need to be produced by the bacteria themselves.[12] An obvious reason for these differences is the absence of immunological defence mechanisms in *in vitro* models. *In vitro* studies suggest that staphylococcal biofilm formation can occur within 24 to 48 hours of bacterial contamination.[13] The question arises whether i*n vivo* biofilm formation occurs at the same pace.

Through the use of variable-pressure scanning electron microscopy, *S. aureus* biofilm formation has been illustrated within 7 days of infection in an animal model.[14] The process is however continuous and the influence of the hosts immune response needs to be considered. Li and co-workers eloquently illustrated that, although *in vivo* biofilm formation is initiated within 48 hours after inoculation, the resulting acquired immune response starts limiting bacterial growth to a biofilm growth pattern from day 11.[15]

It therefore appears that the temporal definition proposed in 1997 by Lew and Waldvogel, who defined chronic osteomyelitis as infection remaining for longer than ten days, also remains relevant.[16] We therefore adopted a combination of the definitions suggested by Cierny and Waldvogel, in the studies contained within this thesis. Chronic osteomyelitis was thus defined as an infection involving bone, with a duration of at least ten days, where the

causative organisms is thought to have persisted either intracellularly or in interactive biofilm-based colonies. This definition was thought to be specific enough to be reproducible, while still recognizing the importance of the underlying pathogenesis.

Two additional clinical scenarios required special consideration. The first of these was "early post-operative infection following osteosynthesis". Romano *et al.* have proposed a separate classification system and treatment approach to this entity.[5,17] According to this classification system, conservative management was suggested for infection following osteosynthesis, *if* the construct was estimated to be stable. Stability is, however, not the only determinant of bony union. Although a fractured tibia with bone loss which was nailed with a fracture gap might be considered stable, it may still go on to septic non-union. In order to deal with this contingency, we propose that the potential for fracture union should rather be assessed. If the fracture fixation is deemed unstable or inadequate and union of the fracture is considered unlikely the diagnosis of chronic osteomyelitis should be deemed appropriate. When the fracture is however considered to be in the optimal bio-mechanical environment, and union is likely to occur, the standard chronic osteomyelitis algorithm should be deemed inappropriate and chronic suppressive antibiotic instituted until union. Once union is achieved in these patients, the chronic osteomyelitis protocol can implemented in order to manage on-going infection.

The second clinical scenario which required special consideration was so-called "minimal necrosis osteomyelitis". Although Cierny and Mader recognized this entity, they did not provide specific guidelines regarding its management.[4] In this thesis we attempted to incorporate the treatment of this clinical scenario in our proposed algorithm. Thus our

definition of chronic osteomyelitis included the entity known as “minimal necrosis osteomyelitis”.

### 9.2.2. Indications for surgery

The indication for surgery, according to the approach proposed in this thesis, is based on the treatment aim. While surgery was always employed in cases receiving curative treatment, palliative treatment rarely involved surgery. Furthermore, when surgery was employed in the palliative treatment group it was always intralesional (minimally invasive) in nature.[18] In order to develop a comprehensive treatment algorithm a third therapeutic option, namely alternative treatment, was required. This treatment arm dealt specifically with septic non-unions in C-hosts and included amputation as a treatment option. Prior experience identified the need to also include an intermediate treatment option in the alternative treatment arm, involving chronic suppressive antibiotic therapy combined with circular external fixation with or without minimal debridement. Only a small number of patients in our retrospective series (10% of cases), were subjected to this treatment option (Chapter 7).

The selection of the appropriate surgical intervention (curative, palliative or alternative) was primarily based on the physiological status of the host. Because only A and B-hosts were treated curatively there was an obvious need to accurately define the C-host. When taking into account that an A-host is a patient without any risk factors and that B-hosts are all the patients who are not an A or C-host, it stands to reason that by accurately defining the C-host, standardization of host stratification would be achieved across the entire spectrum of patients with chronic osteomyelitis.

### 9.2.3. Defining the C-host

The provision of a pragmatic and objective C-host definition was central to the research idea, as the differentiation between A/B and C-hosts was integral to treatment strategy selection. The provision of such a definition necessitated the refinement of the Cierny and Mader host stratification system. According to the integrated approach, a C-host was defined as a patient with either one major and/or three or more minor risk factors (Chapter 8).

The selection of these criteria was based on existing evidence, prior experience and the list of factors previously suggested by Cierny and Mader.[4] While these criteria were developed with the South African clinical setting in mind, the principle of objective host stratification could also be beneficial in other clinical environments as it would enable the comparison of studies. In order to allow comparison of future results it would, however, also be necessary to standardize the definition of successful outcome.

### 9.2.4. Defining a successful outcome

In the studies contained within this thesis, success of a curative treatment strategy was defined in line with the definition proposed by Lazzarini *et al*. and the Infectious Disease Society of America (IDSA).[19] Successful outcome of curative treatment was thus defined as the absence of signs of infection, from an objective (the treating physician's) point of view.

The outcome of palliative treatment strategies has not been studied previously, which would explain the absence of a successful outcome definition with palliative management. As is the case in oncology, a similar outcome cannot be expected from a curative and palliative strategy. The aim of palliative treatment is typically to provide symptomatic relief or

improvement. Therefore, it appeared reasonable to define palliative treatment success from a subjective (the patient's) point of view. We therefore defined success as symptom improvement to the extent that the patient was satisfied with the outcome and requested no additional treatment.

### 9.3.Treatment outcomes using an integrated therapeutic approach

Chronic osteomyelitis in adults is notoriously difficult to treat. A recent Cochrane review, comparing the efficacy of oral and intravenous antibiotics following surgical debridement, found an overall remission rate of 78.8% at 12 months.[7] Dedicated units and experts in the field of chronic osteomyelitis have, however, been able to achieve superior results. Cierny and Mader, through the application of their classification system, were able to achieve success in 93.6% of patients who underwent limb-salvage procedures.[1] Primary amputation was performed in 46 of the 189 (24%) patients who received definitive treatment in their series. Although the authors stated that 15% of their patients were classified as C-hosts, they did not report the outcome or prognosis in these patients. More recently, Cierny reported an overall success rate of 85% in curative treatment strategies at two year follow-up, with 96% success in A-hosts and 74% in B-hosts.[2] Ten percent of cases in this series were managed by primary amputation. Again, C-host outcomes were not reported. The Bone Infection Unit in the United Kingdom reported that they were able to achieve a cure rate of 90% at 5 years follow-up, in a review article on chronic osteomyelitis.[8] Treatment strategy selection and host stratification were, however, not discussed in this brief report of their outcomes. In addition the authors did not indicate what fraction of these cases was managed by amputation, which would have obviously improved cure rates.

Through the integration of a new classification and host stratification system with a treatment strategy selection algorithm we were able to achieve favourable outcomes in both high and low risk patients and, in addition, reduce the rate of amputation. At a minimum follow-up of 12 months an overall success rate of 89.9% was achieved in our retrospective series (Chapter 7). There was significant difference in outcome according to host status ($p = 0.201$) in this series, with no treatment failures in A-hosts, 6.7% failure in B-hosts and 15.7% failure in C-hosts. In terms of the different treatment strategies, 93.5% success was achieved in the curative group, 87.2% in the palliative group and 87.5% in the alternative group (including amputations). Through the judicious implementation of palliative treatment strategies we were able to reduce the rate of primary amputation to 5%. In the South African clinical setting a low amputation rate is particularly relevant due to the limited availability of prosthesis. In addition, amputation is not accepted as a viable treatment option by many patients as a result of cultural or religious beliefs.

A prospective study (Chapter 8), was subsequently undertaken in an attempt to validate the results of the retrospective series. The overall success rate was 92.3% at a minimum of 6 months follow-up. Remission was achieved in all of the patients treated curatively. Palliative treatment was successful in 86% of cases, with suppression in 36% and remission in 64% of these patients. Due to the small patient numbers and short follow-up period, definitive conclusions could not be made. These results however, appeared comparable to those achieved in our retrospective series, with no significant difference in the success rate when comparing the prospective and retrospective series (two-sample test p-value=0.877).

Through the selection of patient-matched treatment options we were able to close the gap in successful outcomes between healthy and compromised patients.[19] The success we achieved in these studies was therefore probably not the result of surgical or therapeutic prowess, but most likely due to appropriate treatment strategy selection. In addition the integrated approach places particular emphasis on risk factor modification and host optimization.

### 9.4. Other findings and contributions in the field

Secondary aims of the study included the assessment of the outcome of palliative treatment, as well as the outcome of treatment of adult chronic osteomyelitis in HIV positive patients.

#### 9.4.1. Palliative care outcomes

There is very little data available on the outcome of palliative treatment in chronic osteomyelitis. While promising results have been reported in patients with periprosthetic joint infections, no studies have looked specifically at the outcome of palliative treatment in non-arthroplasty related infections.[21] Drancourt *et al.* reported "cure" in six out of the nine patients with osteosynthesis implant related sepsis that were treated with antibiotics alone for a period of six months.[22] Stein *et al.* reported "cure" in 60% of patients treated with antibiotics without surgical removal of the implants.[23] The authors, however, did not distinguish between joint replacement and osteosynthesis implant related sepsis in their study.

In our retrospective series (Chapter 7), successful palliation (defined as the resolution of infection to the extent that the patient was satisfied with the outcome and required no further treatment) was achieved in 87% of patients (n=48). Of these patients, 25% were A or B-hosts

who had minimal impairment and no sequestrum or implant present. Remission (defined as the absence of any signs of infection) was achieved in 62% of patients in the palliative group, which is similar to the rate of "cure" that was reported by Stein *et al*.[23] The majority of patients received only chronic suppressive antibiotic therapy, in the form of co-trimoxazole and rifampicin, for a period of three to twelve months. A small number of patients (4%) received intralesional debridement in addition to chronic suppressive antibiotic therapy in order to successfully achieve suppression.

These findings suggest that successful palliation can be achieved in a large proportion of appropriately selected cases. Chronic suppressive antibiotic therapy may tip the scale in favour of the patient, allowing the immune system to suppress the infection in certain compromised hosts. Furthermore, many of the risk factors, defining a patient as a C-host, are modifiable. Instituting a palliative treatment strategy in these patients may thus buy sufficient time for risk factor modification and host optimization to allow subsequent curative intervention. In cases were curative surgery is not feasible, chronic suppressive antibiotics may also be a useful alternative to ablative surgery.

With the potential for the recurrence of infection up to 50 years later, our study did not have a sufficiently long follow-up period to detect all possibly recurrences and it is likely that there will be an increase in the incidence of recurrence on the long term. Patients are counselled regarding this eventuality at completion of treatment and antibiotic therapy is re-instituted in the case of recurrence. Fifty-three percent of patients treated palliatively in our retrospective series required continuation of antibiotic therapy for longer than six months, due to the recurrence or persistence of infection. Approximately half of these patients required 12

months of treatment and the other half were placed on chronic suppressive antibiotic therapy on a permanent basis. This illustrates that, if host modification is unable to change the host status to the extent that curative treatment becomes possible, long-term suppressive antibiotic therapy may be required in order to achieve and maintain suppression. It is noteworthy that only two patients, in the prospective and retrospective series combined, required alteration of the chronic suppressive antibiotic therapy regime due to gastrointestinal side effects, which suggests that it is well tolerated in the majority of patients

### 9.4.2. The outcome of palliative treatment in chronic haematogenous osteomyelitis

The appropriate treatment of acute haematogenous osteomyelitis has resulted in a drastic decrease in the incidence of chronic osteomyelitis of haematogenous origin in the developed world.[1,18] It is however, still common in under-developed regions and the outcome of palliative treatment in compromised hosts with chronic haematogenous osteomyelitis have not previously been reported.[24]

In our retrospective series we were able to achieve successful suppression of the disease in all patients with haematogenous osteomyelitis treated palliatively (n=5). This finding suggests that chronic osteomyelitis without the presence of surgical implants can successfully be treated palliatively in appropriately selected patients. Again, there is likely to be a high recurrence rate and long-term studies will be required to determine the incidence and frequency of recurrence of symptomatic infection.

### 9.4.3. The outcome of treatment in patients living with HIV

To the best of our knowledge the outcome of treatment in patients with HIV/AIDS has not previously been investigated. In Chapter 7 we report the outcome of treatment in 33 adult HIV positive patients with chronic osteomyelitis. Overall, the success rate in HIV positive patients was 84.8% or 28/33 (95%CI: 68.1-94.9% ).There was no statistically significant difference in outcome of treatment (i.e. failure rate) between HIV positive and negative patients (Pearson chi-square p-value=0.248).There was a trend towards treatment failure in patients with a CD4 count below 350 cells/$mm^3$ (Fishers exact p-value=0.083).

All treatment failures, in the HIV positive group, occurred in patients who fulfilled the World Health Organization immunological criteria for advanced disease ($CD_4$ count < 350 cells/ $mm^3$).[25] It is, however, also important to note that the majority of HIV positive patients were treated through either a palliative or alternative treatment strategy. Curative treatment was successful in three out of the four HIV positive patients in whom it was employed.

These findings suggest that palliative treatment may be successful in appropriately selected HIV positive patients. Because of the small patient numbers, firm conclusions could not be made in terms of the outcome of curative treatment. Failure occurred in only one of the four patients that were treated curatively. In this case, failure was not the result of recurrence of infection, but the result of the patient's unwillingness to complete the bone transport process (opting rather for amputation). Taking the aforementioned into account, it appears that curative treatment may also be successful and should not be excluded as an option purely on the basis of HIV infection alone.

### 9.5. Limitations

While the proposed integrated approach may offer several advantages and appears to have delivered promising results, there are several limitations to the studies contained within this thesis. The most apparent of these relate to the short follow-up periods in the three clinical studies (Chapters 6-8). Owing to the unique characteristics of the causative organisms, reactivation of chronic osteomyelitis may occur as much as 65 years following the initial infection.[26,27] Our results are therefore likely to deteriorate over time due to the recurrence of infection. In the palliative treatment group in particular, recurrence can be expected. Our current treatment protocol is to inform patients of the likelihood of recurrence and to reinstate chronic suppressive antibiotics when needed. Longer follow-up will be require to determine the frequency of recurrence in the respective treatment groups.

There are several potential advantages to the use of PMMA spacers as dead space management tool in patients with large post-infective bone defects. The small sample size and lack of control group of the study in Chapter 6 however, prohibited drawing firm conclusions in this regard. No clear advantage could be shown in terms of the external fixation index, which in actual fact appeared to be higher than in other studies using traditional Ilizarov techniques. The findings of this study did however emphasize the importance of surgical candidate selection and the fact that failure of complex reconstructive procedures (involving bone transport) may result in amputation.

Other limitations of the retrospective study investigating the outcome of treatment according to an integrated approach (Chapter 7) include the absence of a control group and lack of randomization. The lack of randomization would however, be difficult to overcome. Exposing

all patients, including the most compromised hosts, to the rigours of limb salvage surgery in order to see which risk factors are associated with treatment failure (which may involve amputation) would represent an ethical dilemma. The fact that we defined success differently in the curative and palliative groups resulted in an apparent improvement in results. However, it would be unrealistic to expect cure (clinical, biochemical and radiological absence of infection) in palliated patients and thus the definition of success or failure of treatment is intimately bound to the management strategy selected. The final shortcoming of this study was its retrospective nature, which prompted the design of a prospective study to validate the results.

The main limitation of the prospective series, investigating the outcome of treatment according to the integrated approach (Chapter 8), was again the short follow-up period. Deterioration of results is likely to occur with longer follow-up. The lack of a control group and randomization presented similar difficulties to those found in the retrospective series. The use of standardized host stratification criteria may, however, enable the comparison of our results with those of future studies. The final limitation is the small sample size. Due to the heterogenous nature of the disease and patient profile a larger series would be required to determine if the algorithm is truly appropriate in all possible clinical scenarios.

### 9.6. Future directions

The primary aim of this project was to introduce the concept of pragmatic host stratification, which could potentially facilitate and standardize treatment pathway selection. The ideas introduced in this thesis still require additional validation and development. A large multi-

centre prospective trial would provide further validation of the suggested approach. In accordance with these results the treatment algorithm may have to be adapted to include all possible clinical presentations and treatment options. Proposals for the management of cases where the initial treatment strategy failed may also need to be added.

A particular problem group is the C-host with unstable (type IV) chronic osteomyelitis. The distinction between a patient who requires amputation or alternative treatment strategy needs to be clarified. According to our approach, this decision was based on the physician assessment of the potential to achieve union. This guideline however lacks sufficient objectivity to be reproducible and further criteria will need to be developed to guide treatment strategy selection in C-hosts with septic non-union.

A second area of ambiguity in the proposed treatment algorithm relates to the rating of impairment. Diagnosis-based impairment rating according to the American Medical Association (AMA) Guides to the Evaluation of Permanent Impairment (6th edition) was found not to be sufficiently specific, as most infections were rated as class 4 (very severe) impairment.[28] The functional history adjustment ratings proposed by the AMA Guides however, appeared to be more appropriate as a guide to treatment selection. As suggested by the AMA Guides , the AAOS Lower Limb Outcomes Instrument and quickDASH was used to perform functional symptom assessment in the lower and upper limbs respectively. While these objective scoring systems were used to determine impairment in our prospective series, the small sample size prohibited the establishment of discreet cut-off points.

The list of risk factors may also need to be expanded and further stratification of individual risk factors may be required in order to render the approach valid in all patients. Several additional risk factors were, for example, identified in the retrospective series (Chapter 7). The weighting of each risk factor, or a combination of certain risk factors, will also need further consideration. In one case in our prospective series (Chapter 8) the treatment algorithm may have been too conservative by prescribing chronic suppressive antibiotic therapy in a case where amputation was probably inevitable.

It also remains unclear if the suggested approach will be applicable beyond South Africa. Although preliminary results appear promising, caution is still advisable with regard to the widespread implementation of this approach. The treatment selection pathways were developed and tested in the developing world. Extrapolation to regions with a lower number of C-hosts may require further improvement or modification of the approach

In principle there are several potential advantages to pragmatic treatment strategy selection. The most relevant of these is the fact that standardized host stratification may enable the comparison of results from future studies. It may thus become possible to compare the outcome of different interventions or strategies, if the physiological status of the host was classified according to same pre-defined pragmatic criteria. In turn this may allow us to answer many of the questions that remain in the management of adult chronic osteomyelitis.[19]

### 9.7. Conclusion

Through the integration of a modified host stratification system with treatment strategy selection, in an algorithmic approach, we achieved favourable outcomes in both high and low risk patients. In addition we were able to maintain a relatively low amputation rate, which is particularly relevant to our resource-poor clinical environment.

Although this approach was specifically designed for use in the South African setting, the principle of defining the host status according to pragmatic diagnostic criteria may also be useful elsewhere, as it would enable the comparison of results of different therapeutic interventions.

Finally, instituting a palliative treatment strategy in high-risk patients creates an opportunity for risk factor modification and host optimization, which may allow subsequent curative intervention. While our preliminary results are promising, further prospective research and follow-up is required in order to assess long-term outcomes and validity of the suggested treatment algorithm.

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# Appendices

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

17 December 2013

Dr LC Marais
P.O Box 13375
Cascades
3202
Leonard.Marais@kznhealth.gov.za

**PROTOCOL: An Integrated Approach to Adult Chronic Osteomyelitis. REF: BF285/13.**

The Biomedical Research Ethics Committee (BREC) has considered the abovementioned application.

The study was provisionally approved by a quorate meeting of BREC on 10 September 2013 pending appropriate responses to queries raised. Your responses dated 10 October 2013 to queries raised on 02 October 2013 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 **17 December 2013.**

This approval is valid for one year from **17 December 2013.** 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 hpp://research.ukzn.ac.za/ResearchEthics11415.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).

**Professor D Wassenaar (Chair)**
**Biomedical Research Ethics Committee**
**Westville Campus, Govan Mbeki Building**
**Postal Address:** Private Bag X54001, Durban, 4000, South Africa
**Telephone:** +27 (0)31 260 2384 **Facsimile:** +27 (0)31 260 4609 **Email:** brec@ukzn.ac.za
**Website:** http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx
Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

The following Committee members were present at the meeting that took place on 10 September 2013:

| | |
|---|---|
| Prof D Wassenaar | Chair |
| Prof V Rambiritch | Pharmacology |
| Prof R Bhimma | Paediatrics & Child Health |
| Prof A Coutsoudis | Paediatrics & Child Health |
| Dr T Crankshaw | External - Public Health |
| Dr R Govender | Family Medicine |
| Dr U Govind | Private Pract - Gen. Practitioner |
| Dr T Hardcastle | Surgery - Trauma |
| Dr Z Khumalo | KZN Health (External) General Medicine |
| Dr K Naidoo | Family Medicine |
| Prof C Rout | Anaesthetics |
| Dr A Sathar | External |
| Dr D Singh | Critical Care |
| Dr S Singh | Dentistry |

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

Yours sincerely

**Professor D Wassenaar**
**Chair: Biomedical Research Ethics Committee**

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 04/14**
**Enquiries : Mr X Xaba**
**Tel : 033 – 395 2805**

Dear Dr LC Marais

**Subject: Approval of a Research Proposal**

1. The research proposal titled **'An integrated approach to adult chronic osteomyelitis'** 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

Lutge

**Dr E Lutge**
Chairperson, Health Research Committee
Date: 24/01/2014.

## PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

**This must be completed and submitted to the Medical Superintendent/s / Hospital Manager for signature.**

**For King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH) studies please submit together with the following:**

i) **Two copies of the final, approved protocol**
ii) **Letter giving provisional ethical approval**
iii) **Details of other research presently being performed by yourself (individually or as a collaborator)**
iv) **Details of any financial or human resource implications to King Edward VIII Hospital**
v) **If a clinical trial, please produce proof of payment or intention thereof to KEH**

**Once the document has been signed it should be returned to this office so that full ethical approval can be granted.**

**To: Hospital Manager**

**PROTOCOL: An Integrated Approach to Adult Chronic Osteomyelitis (BREC Ref: BF285/13)**

Permission is requested to conduct the above research study at the hospital/s indicated below:

**Site 1 address: Investigator/s:**

Grey's Hospital
Townbush Road
Pietermaritzburg

**Principal:** Dr LC Marais
**Co-investigator:** Dr C Aldous
**Co-Investigator:** Prof TLB Le Roux

**Signature of Hospital Manager:** Dr K B Bilenge
Chief Executive Officer
Grey's Hospital
**Date:** 09/10/2013.