The Classification of Long Bone Osteomyelitis



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Abstract

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This thesis investigates the classification of long bone osteomyelitis in adults and aims to develop a new classification system for the guidance of management and prognosis.

Osteomyelitis can be complex and carry a significant burden for patients and healthcare services. Recent developments in treatment options and the multi-disciplinary approach to management have resulted in improved outcomes over the last 40 years. However, currently there is no evidence based or validated method of stratifying these patients into those that require specialist management or defining disease prognosis.

Systematic review of the literature highlighted 13 classification systems that have been presented in the medical literature ranging from 1970 to 2015. Detailed analysis highlighted the important variables that may be included in a new classification system. Combining these with the multi-disciplinary approach to management, the four most important variables were presented. These were: the bone involvement, the microbiology (anti-microbial options), the coverage of the soft tissues and the host status. This was incorporated into the acronym of BACH.

Version 1 of the BACH classification system was applied retrospectively to 96 cases of long bone osteomyelitis. The classification successfully correlated with clinical and patient reported outcome measures, demonstrating that a higher BACH score increases the chance of a poor prognosis. However, there were limitations demonstrated in the application of the classification system. These issues related to the use of certain terminology, the application of the ESCMID criteria for anti-microbial resistance patterns and the definition of host status. Further analysis of the microbiology demonstrated that isolates with $\geq$4 resistant or $<$80% sensitive susceptibility tests had a 96.6%-100% likelihood of being multi-drug resistant.

Version 2 of the BACH classification system was assessed using an inter-user assessment which included 30 clinicians from around the world who were asked to classify 20 cases of long bone osteomyelitis. Users consisted of orthopaedic surgeons, plastic surgeons, infectious disease physicians, microbiologists and anaesthetists.

The overall accuracy of BACH classification was 86.2% (SD6.2% [95% CI 83.9-88.6%]). The anti-microbial options variable scored the highest Fleiss' κ ($F\kappa$) (0.815 [95% CI 0.811 - 0.819], almost perfect agreement) but as the complexity of the isolate increased, the classification became less accurate. It was hypothesised that this was due to the application of the ESCMID criteria. The bone involvement variable had the lowest accuracy (77.0% [95% CI 71.2-82.8%]) and agreement amongst users (0.479 [95% CI 0.475-0.483], fair agreement). This was thought to be secondary to the presentation of the CT and MRI series as single slices, thus not allowing a 3-dimensional visualisation to the user. Further assessment of this variable was conducted by asking 9 users to classify the bone involvement variable using a webPACS as in real-world clinical practice. This demonstrated a significantly higher accuracy ($p<0.01$, *ANOVA with Dunnett's post hoc test*) in the group who used the webPACS compared to those who did not.

On the basis of these assessments, version 3 of the classification was presented. To assess its application, use in management and ability to offer prognosis, a prospective analysis has been planned. In this assessment, three end points will be assessed. These are (i) the ability of BACH to guide need for referral, (ii) the application of individual variables and (iii) the ability of BACH to offer prognosis in terms of clinical and health related outcome measures. A pilot of 40 cases is included to assess the feasibility of implementation.

The BACH classification has been developed using a number of analyses that are presented as part of this thesis. The development of the BACH classification system has led to a simple, non-invasive intervention that can be used in clinical practice and ultimately improve the care that is offered to patients who have long bone osteomyelitis.

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List of Abbreviations

ANOVA	Analysis of Variance
ASA	American Society of Anaesthesiologists
AUC	Area Under the Curve
BIU	Bone Infection Unit
BSAC	British Society of Antimicrobial Chemotherapy
CABG	Coronary artery bypass graft
CI	Confidence Interval
CM	Cierny and Mader classification system
CRP	C-Reactive Protein
CSAT	Chronic suppressive antibiotic therapy
CT	Computerised Tomography
CTRG	Clinical Trials Research Group (University of Oxford)
E. Coli	*Escherichia coli*
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
ESR	Erythrocyte Sedimetation Rate
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GCP	Good Clinical Practice
H. Influenzae	*Haemophilus influenzae*
HAART	Highly Active Anti-Retrovial Therapy
HbA1c	Haemoglobin A1c
HIV	Human Immunodeficiency Virus
IL	Interleukin
IV	Intra-venous

K. Kingae	*Kingella kingae*
MDR	Multi-drug resistant
MDT	Multi-disciplinary team
MRI	Magentic Resonance Imaging
MRSA	Methicillin Resistant *Staphylococcus aureus*
MSSA	Methicillin Sensitive *Staphylococcus aureus*
NICE	The National Institute of health and Care Excellence
NHS	National Health Service
NYHA	New York Heart Association
OPAT	Outpatient Antibiotic Therapy
OVIVA	Oral Versus Intra-Venous Antibiotics for Bone and Joint Infection
PACS	Picture Archiving and Communication System
PDF	Portable Document Format
PDR	Pan drug resistant
PET	Positive Emission Tomography
PET-CT	Positive Emission Tomography Computerised Tomography
PJI	Prosthetic joint infection
PMN	Polymorphonuclear neutrophils
PTCA	Percutaneous coronary angiography
ROC	Receiver Operator Characteristic
S. aureus	*Staphylococcus aureus*
S. epidermidis	*Staphylococcus epidermidis*
SD	Standard deviation
Spa	*Staphylococcus aureus* protein A
spp.	Species
SVT	Supra-ventricular tachycardia
TIA	Transient Ischaemic Attack
TNF	Tumour Necrosis Factor
TMN	Tumour Node Metastasis

UK . . . . . United Kingdom

US . . . . . United States of America

VAS . . . . . Visual Analogue Score

XDR . . . . . Extensively drug resistant

1 Introduction

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1.1 Introduction

Osteomyelitis is a term that has been in use since the middle of the nineteenth century for describing the infection and inflammation of bone (Nelaton, 1844; Chassaignac, 1852). Since, the combination of surgical therapy (Orr, 2006; Trueta, 1942), antibiotics (Buchman and Blair, 1945) and soft tissue coverage (Stark, 1946) have been integral to achieving remission. Ultimately, this has resulted in a specialist multi-disciplinary approach to diagnosis, treatment and long-term management (Ziran et al., 2003; Salvana et al., 2005). The complexity and

challenges of osteomyelitis have resulted in difficulty unifying a classification system or distinction between chronic and acute forms of the disease (Levine et al., 1993; Parsons and Strauss, 2004; Romanò et al., 2011).

The aim of this thesis is to develop and validate a novel approach to the classification of long bone osteomyelitis in adults. The classification system will aim to have the following features: (i) reproducibility between centres, (ii) aid decision making both in terms of where and how to best manage the patient and (iii) enable prognostic information to be given to the patient, assisting in the informed and patient centred management of osteomyelitis.

1.2 Epidemiology and Aetiology

Osteomyelitis is defined as an inflammation of bone secondary to infective processes (McNally and Nagarajah, 2010). A recent epidemiological study demonstrated that between 1969 and 2009 the overall age and sex-adjusted incidence of osteomyelitis was 21.8 cases per 100,000 person-years in the US (Kremers et al., 2015). In both adults and children, the most commonly isolated organism was *Staphylococcus aureus* (*S. aureus*) (44%), followed by *Staphylococcus epidermidis* (*S. epidermidis*) (17%) and *Streprococci* species (spp.) (16%) (Kremers et al., 2015). In the younger age groups, after *S. aureus* and *S. epidermidis*, *Haemophilus influenzae (H. Influenzae)* is the next most common causative organism (Song and Sloboda, 2001). However, the incidence of *H. Influenzae* infection is decreasing since the introduction of the vaccine (Blyth et al., 2001). One explanation for the changing microbiology is the improvement of bacterial culture mediums and laboratory techniques. As a result, uncommon pathogens have an increased detection rate for example, there has been an increase in the detection of *Kingella kingae (K. kingae)* for childhood osteo-articular infections (Yagupsky et al., 2011; Levy et al., 2013).

Osteomyelitis can arise following bone exposure to a pathogen. This can be through blood borne infection (the haematogenous route), or through direct pathogen exposure either through open trauma, soft tissue infection or following a surgical procedure (Waldvogel et al., 1970a,b,c). Each of these aetiological

types of osteomyelitis have a variable physiology, but there are some similarities. Implant associated osteomyelitis has been described in a similar way as exogenous, contiguous or haematogenous (McNally and Sendi, 2015).

Haematogenous osteomyelitis is most common in the paediatric patient and can follow systemic illness. This is thought to be due to the highly vascular nature of immature and growing bone that permits the seeding of infection following septicaemia (Yeo and Ramachandran, 2014). Haematogenous seeding to bone can follow either silent or symptomatic bacteraemia in all children although, children with sickle cell disease, chronic granulomatous diseases and diabetes mellitus are at an increased risk (Epps et al., 1991; Moutschen et al., 1992).

Exogenous osteomyelitis occurs when a pathogen is introduced to the bone from outside the body or from an adjacent infected structure (for example a muscle abscess). In adults, infection following trauma or orthopaedic surgical procedures comprise the majority of osteomyelitis (McNally and Nagarajah, 2010). Furthermore, open fractures are more likely to have infective outcomes compared to closed fractures (Gustilo and Anderson, 2002). Up to 80% of osteomyelitis are comprised of post-operative or post-traumatic aetiology, an increasing figure due to growing numbers of orthopaedic procedures (Walter et al., 2012). Patients who have poor vascular supply and peripheral neurology secondary to diabetes mellitus are also at an increased risk of osteomyelitis affecting the foot, presenting as diabetic foot syndrome (Lindbloom et al., 2014; Senneville and Nguyen, 2014).

1.3 Pathophysiology

The wide spectrum of clinical presentation accompanying osteomyelitis is secondary to the complexity and the variation in the pathophysiology of the disease. There are three phases to the development of a bone infection.

1.3.1 Stage 1: Formation of biofilm

The first stage in the development of osteomyelitis is microbial invasion and, without successful treatment, proliferation of the biofilm. Following introduction

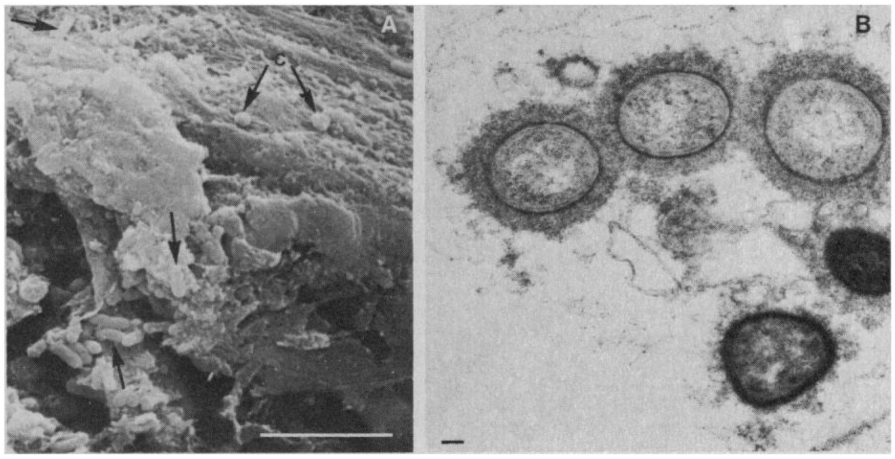


Figure 1.1: A. Scanning electron microscopy demonstrating the biofilm taken from a piece of infected tibia. B. Scraping of tibial cortex demonstrating micro-colonies of gram positive bacteria. From (Gristina et al., 1985).

of a micro-organism to bone or implant, adhesins mediate attachment to the surface. When attached, bacteria will produce a polysaccharide extra-cellular matrix and nutrient trapping ion exchange material. The biofilm is a survival strategy that enables bacteria to survive in a hostile environment (Costerton et al., 1999), allowing propagation and establishment of a bacterial colony (Costerton et al., 1978). It is beyond the scope of this thesis to compare and discuss biofilm adherence to foreign bodies (i.e. metal work) and biofilm forming on native bone. In osteomyelitis, biofilms were first observed using transmission electronic microscopy and scanning electron microscopy in compromised, sequestered or dead bone, figure 1.1 Gristina et al. (1985). The formation of the biofilm compounds the treatment of osteomyelitis because they are relatively impermeable to antibiotics thus highlighting the importance of surgical intervention (Stoodley et al., 2011).

1.3.2 Stage 2: Immune response to biofilm

The second stage in the pathogenesis of osteomyelitis is the immune response to the biofilm propagation. The immune system recognises the biofilm as a foreign body and recruits immune cells including polymorphonuclear neutrophils (PMNs). This in turn promotes a host immune response involving pro-inflammatory cytokines and leukotrienes which are produced by macrophages and leukocytes (Günther

et al., 2009). *In vitro*, it was observed that a PMN immune response was more effective at targeting the infection in the 'young' biofilm compared to the 'mature' biofilm (Günther et al., 2009). Cytokines typically produced within the acute phase include TNF (tumour necrosis factor)-α, TNF-β and interleukins (IL-) 1β, 6 and 8. However, in chronic disease, levels remain similar to that of healthy controls (Klosterhalfen et al., 1996). IL-6 mediates acute phase proteins including the c-reactive protein (CRP) which is commonly measured in clinical practice as a marker of the inflammatory process (Geiger et al., 1992). The presence of the acute inflammatory cascade is supported by a longitudinal series of 29 patients where CRP was shown to be elevated above normal levels in acute disease but not in healthy controls or in chronic osteomyelitis (Klosterhalfen et al., 1996). As part of the systemic inflammatory response, IL-6 is responsible for promotion of osteoclastic activity and prevention of osteoblastic activity, thus causing an increase in the resorption of bone, allowing bacteria to propagate further (Tilakaratne and Soory, 2014). In the presence of ongoing biofilm formation, the bacteria are able to propagate and evade the host immune response, despite a prominent leukocyte infiltration (Wagner et al., 2003). Neutrophils that are recruited to the area of infection still attempt to irradicate the bacteria (Bergstrand, 1990). It is hypothesised that granulocyte function is impaired by their interaction with the non-phagocytosable biofilm (Zimmerli and Sendi, 2011). Furthermore, granulocytes around a subcutaneous implant are unable to efficiently kill *Staphylococci*, despite their adequate opsonisation (Zimmerli et al., 1982). In these situations where opsonised material is inadequately ingested, the granulocytes are partially degranulated and have a decreased production of oxygen free radicals (Zimmerli et al., 1984). This oxidative burst is ineffective and the phenomenon is known as frustrated phagocytosis (Gardiner et al., 1994).

1.3.3 Stage 3: Prolonged inflammatory response

The third phase is the impact of bacterial invasion on bone and tissue components. This prolonged inflammatory response is responsible for osteolytic and tissue

damaging processes (Bergstrand, 1990; Wagner et al., 2005; Sanchez et al., 2013). The bacterial protein Staphylococcus aureus protein A (SpA), has been shown to be capable of binding directly to osteoblasts, reducing proliferation and mineralisation of bone resulting in apoptosis *in vitro* (Claro et al., 2011; Widaa et al., 2012). Furthermore, TNF-α and TNF-β have direct effects on osteoblastic activity in the presence of osteoclasts resulting in increased bone reabsorption (Thomson et al., 1987). This inflammatory response results in further necrotic bone and bacterial propagation. In chronic osteomyelitis, it has been reported that bacteria can reside in osteoblasts which may be involved in the reactivation of the disease after many years (Bosse et al., 2005).

1.4 Clinical Diagnosis

The diagnosis of both acute and chronic osteomyelitis is made based on a combination of clinical, laboratory and radiological investigations. Acute osteomyelitis, can present clinically with pain, swelling and fever in a fulminant infection (Song and Sloboda, 2001). Often it is accompanied by oedema, vascular congestion and small-vessel thrombosis that can result in compromise of the medullary and periosteal blood supply causing areas of necrosis (Emslie et al., 1983). Blood tests can show a rise in the inflammatory markers including the CRP, white blood cell count, in particular neutrophils, or erythrocyte sedimentation rate (ESR). Imaging is important in both the diagnosis and management of osteomyelitis. Modalities available include x-ray, ultrasound, computerised tomography (CT) and magnetic resonance imaging (MRI). X-ray is readily available but changes within the bone are not commonly seen in the acute phase of an infection (Jacob et al., 1985). Ultrasound is becoming increasingly available and therefore may have a role in the diagnosis of acute presentation osteomyelitis in children. Here, subperiosteal bone reaction and increased vascular flow in or around the periosteum may be seen early in the disease (Zam et al., 2005). The gold standard imaging for osteomyelitis is MRI, although this can be difficult to achieve in acute disease. Treatment of acute osteomyelitis starts by ensuring that the patient is haemodynamically stable.

Antibiotics are usually given after microbiological sampling (i.e. blood cultures in a septic patient) and emergency surgery may need to be performed.

The history and clinical examination of chronic bone infection can include, pain, low grade fever, and tenderness on palpation over the affected area. In chronic osteomyelitis symptoms and signs may be subtle compared to the acute form of the disease (McNally and Nagarajah, 2010). Chronic osteomyelitis may be complicated with episodes or flares of acute relapse. Blood tests can be helpful in the diagnosis although inflammatory markers are commonly in the normal range (Lew and Waldvogel, 2004). X-rays characteristically show osteolysis, destruction and periosteal reaction. MRI is the gold standard imaging modality in clinical practice but computerised tomography (CT) can be used if MRI is contraindicated. Microbiological sampling should be performed under sterile conditions. Emergency antimicrobial treatment is rarely indicated and usually can be administered once a pathogen has been identified. Treatment combines bone resection, antibiotic therapy and soft tissue management, optimally performed as part of a multidisciplinary team (Ziran et al., 2003; Salvana et al., 2005).

1.5 Acute and Chronic Osteomyelitis

There is no generally accepted transition point between the acute and chronic forms of osteomyelitis (Cierny and Mader, 1984; Riise et al., 2008). However, persistence of acute disease gives a greater chance of transformation to chronic disease which is thought to be due to biofilm formation and the presence of necrotic bone (Jacob et al., 1985; Norden et al., 1992). Necrotic bone is the hallmark of chronic disease and highlights the importance of early treatment to prevent the transition from acute to chronic disease states (Ciampolini and Harding, 2000). The clinical timescale of the disease is difficult to define due to the indiscernible starting point of the infection. Moreover, there is significant heterogeneity in the clinical course of the disease, adding to the challenge of differentiating acute and chronic osteomyelitis.

Despite the difficulties in defining the time course in osteomyelitis, a useful clinical distinction of implant associated infections has been proposed. It is based

on the theory that a micro-organism is exogenously introduced to the bone in the early pre- or post-operative period. These infections can present as either early, delayed or late. The presentation is related to the time interval from surgery to clinical symptoms, causative pathogen and the virulence of these pathogens, table 1.1 McNally and Sendi (2015).

Time scale	Typical organism
Early	Often high virulent pathogens: *Staphylococcus aureus* Group A *Streptococcus* Gram negative bacilli
Delayed (2-10 weeks after implant insertion)	Low virulence pathogens Coagulase negative *Staphylococci* Mixed skin flora (sinus tract)
Late (>10 weeks after implant insertion)	Acute haematogenous *Staphylococcus aureus* *Escherichia coli* Chronic 'silent' infection Any microbial infection

Table 1.1: The timescale of Implant associated infections. Timescale of implant associated infections and the resultant isolated organism adapted from (McNally and Sendi, 2015).

Early infection occurs within 2 weeks of insertion of the implant. It will present with pain and fever and commonly be secondary to highly virulent pathogens such as *S. aureus* or group A *Streptococcus*. Delayed infection will present within 2 and 10 weeks of insertion of the implant. Typically, this will be caused by less virulent pathogens and the symptoms are less specific than during early infection. These symptoms can include low grade fever and discomfort around the implant. A late infection presents more than 10 weeks after insertion of the implant either by haematogenous seeding or by a silent ongoing infection McNally and Sendi (2015). However, this method of classification differs from native osteomyelitis because it includes a specific time point when the bone has been exposed to a pathogen.

1.6 Multidisciplinary Management

Due to the complexity of osteomyelitis, a multidisciplinary approach is essential in order to achieve a successful outcome (Salvana et al., 2005). The multidisciplinary team may include orthopaedic surgeons, plastic surgeons, vascular surgeons or angiologists, musculoskeletal radiologists, infectious disease specialists and nurse practitioners (for example, outpatient antibiotic therapy (OPAT) nurses or Ilizarov nurses). Each member of the team has a specific role, particularly in chronic osteomyelitis.

The orthopaedic surgeon is responsible for debridement, bone resection, bone stabilisation and for the sampling of infected tissues (McNally and Nagarajah, 2010). The importance of resection of dead bone until it bleeds has been documented since the Roman times (Jackson, 1988). This debridement is to remove infective bone and disrupt any potential biofilm (McNally and Nagarajah, 2010). At the time of surgery, antibiotic carriers can be applied that release high concentrations of local antibiotic and manage dead space (Patzakis et al., 1993).

The role of the plastic surgeon in osteomyelitis is for the management of the soft tissues by performing microvascular free tissue transfer. The importance of these procedures in the management of soft tissue defects has been documented for over 40 years (Burri et al., 1973). The soft tissue coverage can include direct closure, application of skin grafts, local muscle transfer and free muscle transfer. These techniques ensure that all infected tissue is removed and the vascular supply is optimised to the site of the infection, maximising the chances of a successful outcome (Anthony et al., 1991).

The role of the infectious disease physician in osteomyelitis is to offer appropriate antimicrobial options that consider the presented microbiology and susceptibility testing. Anti-biotic choices are made based on appropriateness for use in bone infection (i.e. bone penetration) and patient factors. Patient factors can include allergy and other medications that may interact with the proposed anti-microbial (Conterno and Turchi, 2013). Anti-biotics have been combined with surgical debridement with good effect since the early part of the 20th century (Clawson and

Dunn, 1967). This role is becoming increasingly important with the emergence of multi-drug resistance strains of bacteria and improved laboratory detection yielding rarer pathogens. The infectious disease physician is responsible for recommending the duration and nature of the antibiotic treatment which is decided by a combination of clinical features and isolate susceptibility panels.

The musculoskeletal radiologist has an important role in defining the extent of the disease and communicating this with the other members of the multidisciplinary team. Radiology enables the visualisation of infection and surgical planning. Appropriate imaging will ensure that the maximal amount of infected bone is debrided and relevant stabilisation procedures are performed. The plastic surgeons need to be made aware of any soft tissue compromise (such as sinus formation or abscesses) that may interfere with healthy soft tissue cover of the infected bone. Furthermore, plastic surgeons may require angiography for the assessment of vascular disease in the planning of soft tissue procedures.

Vascular surgeons are experts in ensuring that there is adequate blood supply to the infected bone and the surrounding tissues. Osteomyelitis is a disease of ischaemia, with poor blood supply mediating initiation of the disease and also outcomes (Lew and Waldvogel, 2004). Success with soft tissue techniques such as free or local flap coverage, require an adequate blood supply. If there is compromise in the vascularity of the infected area, the vascular surgeons are responsible for ensuring that blood flow is adequate prior to any curative surgical intervention.

Although, in theory and as presented here, this task appears clearly defined. However, this is not the case in clinical practice. In multidisciplinary management, there is both knowledge and task overlap, allowing for efficient treatment strategies.

1.7 Summary of problem

Osteomyelitis is a complex disease with a variety of clinical presentations. The pathophysiology is not well understood but bacterial biofilms and the host immune system have been shown to be key players in disease progression. Developments in surgical techniques, imaging and microbiological techniques have resulted in

the improvement of outcomes in osteomyelitis. Furthermore, the importance of multidisciplinary working, involving specialist physicians, surgeons and radiologists can maximise the possibility of a successful outcome. However, in view of these advances, there is currently no accepted method for stratifying patients by complexity in osteomyelitis to help guide where patients are treated nor way of offering a prognosis.

1.8 Aims of Thesis

The aim of this thesis is to propose a novel classification system for long bone osteomyelitis in adults. This will be for guiding management and prognosis. The thesis will have 3 parts which are listed below.

1. Perform a systematic review of the literature to discuss the present classification systems for long bone osteomyelitis (chapter 2). Use the information from this systematic review to propose a new classification system for osteomyelitis (chapter 3).

2. Optimise this classification system using a retrospective cohort (chapter 4) and with multiple users (chapter 6). Address the limitations that were presented as a result of these analyses (chapters 5 and 7).

3. Present a protocol for the prospective application, assessment and validation of this classification so that it can successfully be applied in clinical practice (chapter 8).

2

Systematic Review: The Classification of Long Bone Osteomyelitis

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2.1 Introduction

The complexity of osteomyelitis has resulted in difficulty in the unifying of a classification system or distinguishing between acute and chronic forms of the disease (Romanò et al., 2011; Parsons and Strauss, 2004; Levine et al., 1993). The most commonly used classification systems for osteomyelitis are the Cierny and Mader (Cierny and Mader, 1984), and the Waldvogel (Waldvogel et al., 1970a,b,c). These are over 40 years old and are not commonly used due to their complexity and recent development in treatment strategies. Without a globally accepted classification method, remission rates and prognosis are not easily comparable between studies or centres. Furthermore, patients are unable to be stratified according to the complexity of their disease.

2.1.1 Objectives

This chapter evaluates the current classification systems present in the literature for long bone osteomyelitis. This will allow a framework for a new classification of osteomyelitis to be built. This chapter will highlight the potential variables that will be included in the new classification system.

2.2 Methods

2.2.1 Electronic resources

MEDLINE, EMBASE, Ovid and the Cochrane databases were searched from their date of development until 29 October 2015. Preliminary searches were performed using a combination of the terms “bone infection”, “osteomyelitis”, “classification”, “staging” and “scoring”. The final search strategy is presented in appendix A.

The review was registered on the PROSPERO database and can be found at the following web address (Hotchen et al., 2016a). This chapter has been published in truncated form as a systematic review (Hotchen et al., 2017).

2.2.2 Selection Criteria

Eligible studies were those presenting a new classification system for long bone osteomyelitis that has been validated in a patient cohort. Records returned from the search were screened for eligibility using the PRIMSA guidelines. All levels of evidence above case report were included for review. Previous literature reviews were excluded after the search had been performed. The references of the results were then reviewed for any further classification systems that were omitted by the search. All original articles involving human subjects written in English were reviewed.

2.2.3 Types of Osteomyelitis Included

Any classification systems relating to long bone osteomyelitis were included. All aetiological subtypes of osteomyelitis were included. Classification systems which focused on vertebral osteomyelitis, maxillofacial osteomyelitis or diabetic foot disease were excluded. These were excluded because they are generally regarded as a separate entity to long bone osteomyelitis and managed by specialists such as maxillofacial, spinal or foot surgeons. Scoring systems that indicated the probability of diagnosis of osteomyelitis were excluded.

2.2.4 Classification Systems Included

Data was collected on classification systems of long bone osteomyelitis in both adults and children. Classification systems were included if they used new approaches to classify osteomyelitis.

2.2.5 Data Extraction

Demographic data extracted from the studies included number of patients in the validation, follow up details and patient age ranges. The classification systems were assessed for the variables used and the outcome measures that were performed.

2.3 Results

2.3.1 Study Selection

Through the Medline and EMBase / Ovid search databases, a comprehensive search of the medical literature was performed. This returned a total of 336 studies. Through further reading and references, a further 6 studies were included. There were 144 duplicate studies that were removed from the results. Then, 145 publications that did not meet the inclusion criteria (either not relevant to osteomyelitis, spinal, maxillofacial or diabetic foot) were excluded based on abstract or title. The reviews and case reports were then excluded based on the title and the abstract. Full text was retrieved for 26 studies. Of these, 8 were studies using previous classification systems, and 5 were for diagnostic purposes. Thus, 13 studies met the inclusion criteria and were reviewed. This process is shown in appendix A. Within the literature, there was one classification system that was referenced which proved difficult to obtain. This classification was presented at the American Academy of Orthopaedic Surgeons in 1982, and has not been entered onto the EMBase / Ovid search databases. The reference was included in the Romano 2011 paper (Romanò et al., 2011). After evaluating the benefit-versus-effort balance, the author and supervisors decided to exclude the single publication (Ger, 1982).

2.3.2 Study Demographics

A summary of the studies included are shown in table 2.1. All of the reported studies had their classification systems described in patient cohorts either prospectively or retrospectively. The mean number of patients used to validate the classification systems was 158 (range 14 – 425, SD 131). Of the 13 studies, four were intended for prognostic purposes (May et al., 1982; Weiland et al., 1984; Gordon and Chiu, 1988; May et al., 1989), four for guiding management strategy (Lauschke and Frey, 1994; Solagberu, 2003; Jones et al., 2009; Yang et al., 2013) and two were for prognosis and guiding management (Cierny and Mader, 1984; Marais et al., 2015). Three classifications were not intended for clinical use and did not report outcomes.

Author	Year	n	Age range	Follow-up	Aetiology	Primary variable	Analysis
Waldvogel	1970	248	-	-	All	Aetiology	Descriptive
May	1982	22	11-66y (mean 29.4)	6-47m	Post-traumatic Long bone	Time course	Prognosis
Weiland	1984	33	16-52y (mean 29.8)	24-59m (mean 41.1m)	Post-traumatic Long bone	Bone	Prognosis
Cierny	1984	189	-	Min. 2y	Long bone	Bone Host status	Prognosis Management
Gordon	1988	14	7-39y (median 32)	7-39m (median 32)	Post-traumatic Non-union	Bone	Prognosis
May	1989	250	-	-	Post-traumatic Tibial	Bone	Prognosis
Kelly	1990	425	-	-	All Tibial / femoral	Aetiology	Descriptive
Lauschke	1994	55	0-14y	89% followed 2 years	Haematogenous	Time course	Management
Solagberu	2003	271	2-48y (mean 29.4y)	-	All	Clinical course	Management
Jones	2009	87	<16y	-	Haematogenous	Bone	Management
Romano	2011	300	-	-	All	Multiple	Descriptive
Yang	2013	51	-	6-41m (mean 26.3m)	Post-traumatic	Soft tissues Bone	Management
Marais	2015	109	18-78y (mean 39.8y)	12-36m (mean 18.6m)	All Long bone	Bone Host status	Management Prognosis

Table 2.1: A summary of the retrieved and included classification systems of long bone osteomyelitis. Classification systems were put into groups dependent on the aspect of osteomyelitis that they were evaluating. These groups were (i) descriptive (whether the classification system was for descriptive purposes only), (ii) prognostic (whether the classification could measure prognosis) and (iii) management (whether the classification could guide management strategy).

Hence, they were for descriptive purposes only (Waldvogel et al., 1970a,b,c; Kelly et al., 1990; Romanò et al., 2011). Seven studies gave the exact time scales of patient follow-up (between 6 and 41 months) (May et al., 1982; Weiland et al., 1984; Cierny and Mader, 1984; Gordon and Chiu, 1988; Lauschke and Frey, 1994; Yang et al., 2013; Marais et al., 2015).

2.3.3 Aetiological Types

Six of the classification systems attempted to classify all aetiological types of osteomyelitis (Waldvogel et al., 1970a,b,c; Cierny and Mader, 1984; Kelly et al., 1990; Solagberu, 2003; Romanò et al., 2011; Marais et al., 2015). Of these, two included all long bones (Cierny and Mader, 1984; Marais et al., 2015) and one was limited to the tibia (Kelly et al., 1990). Five classification systems were for post-traumatic osteomyelitis only (May et al., 1982; Weiland et al., 1984; Gordon and Chiu, 1988; May et al., 1989; Yang et al., 2013). Of these five classification systems, one was limited to infected tibial non-union (Gordon and Chiu, 1988). The remaining two classification systems were for haematogenous osteomyelitis in children (Lauschke and Frey, 1994; Jones et al., 2009).

2.3.4 Approach to Classification

Table 2.1 summarises the approaches of the retrieved classification systems.

- **Aeitology**: Of the 13 classification systems, two used aetiology as a primary approach to classifying osteomyelitis and both of these were for descriptive purposes only.

- **Bone**: Seven classification systems used bone as the main variable for classification, two of which were dedicated to post-traumatic osteomyelitis in patients who required free tissue transfer. Bone was classified by the pattern of involvement, stability, extent of involvement or radiological presence of abscesses, sequestrum or sclerosis. One classification system defined that the bone should have a >3cm defect present.

- **Soft tissue**: Two of the 13 classification systems used the soft tissue as the primary variable for classification (May et al., 1989; Yang et al., 2013). However, 3 classification systems (all for post-traumatic osteomyelitis), specified the presence of either a draining sinus (May et al., 1989) or a defect that necessitated free tissue transfer (Weiland et al., 1984; Gordon and Chiu, 1988).

- **Duration of disease**: Two classifications used the duration of the clinical picture to classify the infection (May et al., 1982; Lauschke and Frey, 1994).

- **Miscellaneous**: One classification system was based on radiological criteria to classify haematogenous osteomyelitis in children (Jones et al., 2009). One classification system incorporated multiple aspects of osteomyelitis but due to complexity was not intended for clinical use but for descriptive purposes only (Romanò et al., 2011).

2.3.5 Definitions of Acute and Chronic Osteomyelitis

Of the 13 studies, 6 gave a definition of acute and chronic osteomyelitis, table 2.2. The classification systems used a number of terms to describe the time course. These were acute, subacute, early acute, late acute and chronic. In non-haematogenous osteomyelitis, the transition between acute and chronic disease ranged from 2 weeks to 6 months. One classification system defined chronic osteomyelitis as being present when there was a previous admission for the same disease (Waldvogel et al., 1970a,b,c). Two classification systems, both of which were classification of the soft tissue status, used the duration of a draining sinus as a marker for acute and chronic disease (May et al., 1982; Gordon and Chiu, 1988). The two classification systems for acute and chronic haematogenous osteomyelitis used definitions that varied from days (Lauschke and Frey, 1994) to months (Jones et al., 2009).

2.4 Individual classification systems

Each classification system will be analysed in turn. They are placed in the following order: (A) classification systems for all types of osteomyelitis (B) classification of the soft tissues (C) classification of the bone involvement and (D) classification of haematogenous osteomyelitis.

Author, year	Acute / chronic definition
Waldvogel, 1970	Acute <1 admission for disease Chronic ≥2 admissions for disease
May, 1982	Acute <6 weeks draining sinus Chronic >6 weeks draining sinus
Gordon, 1988	Acute <6 months draining sinus Chronic >6 months draining sinus
Lauschke, 1994	Early acute ≤3 days following commencement of symptoms: fever, raised white blood cell count or moderate pain in the affected extremity. Late acute 4 – 5 days following commencement of symptoms: high fever, a high white blood-cell count, severe pain in the affected extremity with swelling and restriction of motion or effusion. Chronic >5 days following commencement of symptoms: fever or sepsis, moderate to very high white blood-cell count, pain and swelling with or without deformity, draining sinuses or presence of abscesses.
Jones, 2009	Acute <6 months of radiographic evidence Chronic >6 months of radiographic evidence
Romano, 2011	Acute <2 weeks after onset of symptoms Sub-acute >2 weeks after onset of symptoms Chronic – several months after onset of symptoms

Table 2.2: A summary of the different approaches to classifying acute and chronic osteomyelitis.

2.4.1 (A) Classification of All Aetiological Types

Waldvogel, 1970

Waldvogel classified osteomyelitis by aetiology based on experience in 248 patients. He classified the disease by aetiology into haematogenous, contiguous or vascular, figure 2.1.

Haematogenous osteomyelitis
Osteomyelitis secondary to a contiguous focus
Osteomyelitis associated with vascular insufficiency

Figure 2.1: Waldvogel classification of osteomyelitis.

Haematogenous osteomyelitis was secondary to a blood borne infection following seeding into bone and comprised 19% of the cohort. It was most commonly seen in the 11 to 20-year age group and predominantly affected the long bones. However, in adults, haematogenous vertebral disease was more common than long bone haematogenous disease. Haematogenous osteomyelitis responded well to antibiotics alone with only 15% of patients requiring surgery (Waldvogel et al., 1970a).

Contiguous osteomyelitis is infection that arises from exogenous sources such as surgery, post-traumatic or secondary to soft tissue infection. This group was predominantly comprised of post-operative infections (62%) and infections following open trauma (38%). Most cases of contiguous osteomyelitis were seen in patients aged over 50 years, and the onset of the infection commonly occurred less than one month following the initial insult. The femur or tibia were the most commonly affected bones and the most common isolate was *S. aureus*, seen in more than 60% of the cases (Waldvogel et al., 1970b).

The osteomyelitis secondary to vascular insufficiency included 31 patients and was attributable to diabetes mellitus, atherosclerosis or vasculitis. In this group, patients were more likely to have a concurrent cellulitis on admission (>50%), deep ulceration (23%) or a combination of both. Patients who had end stage renal disease, polyneuropathy or retinopathy were noted to have a poorer prognosis compared to those who did not (Waldvogel et al., 1970c).

Cierny and Mader, 1984

The extent of bone involvement was first classified by Cierny and Mader in 1984 (Cierny and Mader, 1984). This classification system used the anatomical pattern of infection to classify long bone osteomyelitis. This categorised osteomyelitis into medullary, superficial, localised and diffuse, see figure 2.2 (Cierny and Mader, 1984). This was first reported using a series of 189 patients treated over 13 years. The number of operations that were performed in this cohort was 357 at an average of 3.9 operations per patient, which is more than the single stage technique that is used today (McNally et al., 1993). Twenty-seven years later (2011), the cohort

was increased to 2,207 cases. In the cases that were eligible for curative surgery, 6% were classified as medullary, 13% as superficial, 16% as localised and 66% as diffuse (Cierny, 2011). The anatomical subtype proposed by Cierny and Mader was designed to be able to guide treatment strategies with comprehensive and detailed algorithms produced for each of the individual subgroups. More recently, type III and type IV have been grouped together with the presence of stability following resection distinguishing the two types (Marais et al., 2014, 2015).

Type I	Medullary osteomyelitis
Type II	Superficial osteomyelitis
Type III	Localised osteomyelitis
Type IV	Diffuse osteomyelitis
A Host	Good immune system delivery
B^L Host	Local compromise
B^S Host	Systemic compromise
C Host	Requires suppressive or no treatment;
	Minimal disability;
	Treatment worse than the disease;
	Not a surgical candidate;

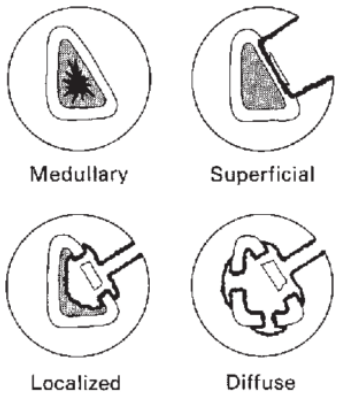


Figure 2.2: The Cierny Mader classification of long bone osteomyelitis. Image from (Cierny et al., 2003).

In addition to the classification of the pattern of bone involvement, Cierny and Mader suggested a host categorisation dependent on the accompanying degree of patient co-morbidity, figure 2.2 (Cierny and Mader, 1984). These co-morbidities were divided depending on their proximity to the area of the body affected by osteomyelitis into local and systemic. Patients who are fit and well were classed as A hosts, those compromised locally or systemically were classed as B hosts and those who were not fit for curative surgery were classed as C hosts. However, patients are able to move categories with changes in co-morbid status. It has been demonstrated that patients who had increased co-morbidities had a poorer outcome and increased rate of recurrence (Cierny, 2011).

Kelly, 1990

Twenty years following the Waldvogel classification system, Kelly presented a series of 425 patients with tibial or femoral osteomyelitis based on aetiology, figure 2.3 (Kelly et al., 1990). This classification built on Waldvogel's from 1970, figure 2.1. Successful outcome was defined as union of fracture and cessation of signs of infection at a minimum of 2-year follow-up. However, the classification system has not been correlated with the presented outcomes. Despite this, the outcomes of remission in osteomyelitis over a 15-year study period were reported to have improved from 50% in 1971 to 84% in 1985. It was concluded that this substantial improvement was secondary to advances in sampling techniques, culture techniques and more attention being given to soft tissue management.

Haematogenous osteomyelitis
Osteomyelitis in a united fracture
Osteomyelitis in a non-united fracture
Osteomyelitis with no fracture but post-operative or post-traumatic

Figure 2.3: Kelly's classification of osteomyelitis.

Solagberu, 2003

Stage	Description	Management
0	Pre-invasion	Prophylactic antibiotics
I	Early osteomyelitis	Culture driven antibiotics
II	Intermediate osteomyelitis	Multiple drill holes Parental and oral antibiotics
III:	Late / chronic osteomyelitis	Excision of bone Curretage of periosteum in a child
IIIa	Curable	
IIIb	Controllable	
IIIc	Complicated	
IV	Compound chronic osteomyelitis	Soft tissue management Bone grafting Open arthrotomy and appropriate procedure

When presenting the stage, the haemoglobin status should be presented if known: HbSS (sickle cell trait), HbAA (no sickle cell trait), HbSC (sickle cell carrier).

Figure 2.4: Solagberu's classification of osteomyelitis for developing countries.

Solagberu presented a classification system of osteomyelitis for developing countries in 2003, figure 2.4 (Solagberu, 2003). The classification was for the guidance of

broad treatment options for hospitals that had limited access to advanced medical technology. It had five progressive stages and was validated in 271 patients, most of whom (n=184) had stage 0 (pre-invasive) disease. This indicated open fracture or open reduction surgery, requiring prophylactic antibiotics. The main aim of this classification system was to guide treatment strategy although outcomes relating to these approaches were not reported.

Romano, 2006 and 2011

Romano presented a classification in 2006 and 2011. This included an alternative strategy for classification of bone defect by combining site of infection with the nature of the defect which could either be cavitational, epiphyseal or segmental, figure 2.5 (Romanò et al., 2011). Segmental defects were classified further based on size with the largest, type 3C, being unstable (Romano, 2006). These are two parts of the seven item classification system that incorporates many aspects of osteomyelitis for descriptive purposes only. The other categories in this classification system were clinical presentation, aetiopathogenesis, host type and micro-organism, which are shown in figure 2.5. It is intended for osteomyelitis, septic arthritis and osteosynthesis infection (Romanò et al., 2011). Evaluation showed that the 300 patients were able to be successfully classified into each of the individual categories, although due to complexity, it is not intended for clinical use.

Marais 2015

The most recent classification system has been proposed by Marais in 2015 (Marais et al., 2015). This classification system is for all long bone osteomyelitis and is built on the Cierny and Mader classification system presented in 1984 (Cierny and Mader, 1984). This classification system attempted to update the 'pathoanatomy' model for bone involvement, along with further classifying the host status, figure 2.6.

The modified approach to classification of bone involvement used the stability of the bone, removing the localised and diffuse definitions from this section. An algorithm was produced to guide treatment which placed patients into three groups dependent on their host status. These three treatment groups were termed curative,

Site of infection:

- Spine
- Hand
- Long bones – according to Cierny and Mader, 1984
- Foot
- Joint – according to Gächter, 1985

Bone defect:

- Type 1 – small cavity ranging from a few millimetres to a few centimetres with no loss of stability
- Type 2 – is an epiphyseal defect which features bone loss at the level of the joint
- Type 3 – is a segmental defect and can be further divided:
- 3A – less than 1cm
- 3B – between 1cm and 3cm
- 3C – greater than 3cm

Clinical presentation:

- Early / acute
- Subacute / delayed
- Chronic / late

Host Type / Age (a=adults, c=children<14 y, i=infants<2yrs)

- $A_{a,c,i}$
- $B_{a,c,i}$
- $C_{a,c,i}$

Etiopathogenesis:

- Hematogenous
- Vasculopathy / neuropathy
- Trauma
- Temporary implant
- ICS classification
  - Type I
  - Type II
  - Type III
- Permanent implant

Microorganism:

- Gram+
- Gram-
- Mixed flora and/or multiresistant
- Mycobacterium
- Fungi
- Negative

Soft tissue defect:

- No soft tissue defect
- Size of defect in cm^2 +/- bone defect

Figure 2.5: Romano's seven item, comprehensive classification of bone and joint infection.

palliative and alternative. The curative group (only A and B hosts) were for debridement and for curative management of the infection. The palliative group (either A, B or C hosts) received chronic suppressive antibiotic therapy (CSAT) or 'intra-lesional' debridement. The alternative group were for C hosts who would be left with an unstable defect. These patients would either have CSAT with circular frame or amputation without antibiotic therapy. Marais presented a retrospective

Physiology	
Type A host	No risk factors
Type B host	<3 minor risk factors
Type C host	One major and/or ≥3 minor risk factors
Pathoanatomy	
I - Medullary (stable)	No cortical sequestration
II - Cortical (stable)	Direct contiguous invovlemnet of cortex only
III - Combined (stable)	Both cortex and medullary regions involved
IV - Combined (unstable)	As for III plus unstable prior to debridement
Major risk factors	
CD4 count <350 cells/mm3	Cellulitis or abscess formation
Albumin <30g/L	Malignancy at the site of infection
HbA1c ≥8%	Pathological fracture
Minor 'systemic' risk factors	
HIV infection	Common variable immune deficiency
Anaemia	Paraplegia / quadraplegia
Smoking	Drug of substance abuse
Diabetes mellitus	Chronic corticosteroid use
Rheumatoid arthritis	Active tuberculosis
Chronic lung disease	Ischaemic heart disease
Chronic cardiac failure	Cerebrovascular disease
Minor 'local' risk factors	
Poor soft tissues requiring flap	Adjacent joint stiff / arthritic
Chronic venous insufficiency	Heterotopic ossification
Peripheral vascular disease	Segmental resection ≥6cm
Surgery will result in instability	

Figure 2.6: Marais' classification for long bone osteomyelitis. This stated that an A host was defined by no risk factors, a B host was defined by <3 minor factors and a type C host was defined as ≥3 minor risk factors. The bone involvement was classified using the pathoanatomy modification to the Ceirny and Mader classification.

series of 109 adult patients with chronic osteomyelitis. In this series, a successful outcome was defined as remission or suppression of disease. At follow up of one year, 100% of A hosts had a successful outcome although there were only 13 patients in this group. The B hosts had a 93.3% successful outcome and the C hosts had a successful outcome in 84.3% of cases. Using the treatment algorithm Marais proposed, most (57.8%), patients were not suitable for curative treatments, but for palliative or alternative treatments instead.

2.4.2 (B) Classification of the Soft Tissue

May, 1982

May used the duration of a draining sinus to classify osteomyelitis with local soft

tissue compromise necessitating free flap cover, 2.7 (May et al., 1982).

Sinus draining for <6 weeks - acute
Sinus draining for >6 weeks - chronic

Figure 2.7: May's 1982 classification of osteomyelitis.

In May's original report which consisted of 22 patients, 18 patients had a chronic sinus draining for more than 6 weeks and the remaining four patients had a sinus draining for less than 6 weeks. At long term follow-up which averaged 19.3 months for chronic and 16.3 months for those with acutely draining sinuses, all patients had successful soft tissue reconstruction regardless of duration of the draining sinus May et al. (1982). In 1991, May built on this by publishing a 13 year series of 91 patients using free muscle transfer (May et al., 1991). However, clinical outcomes were not correlated with the original classification system. The reported long-term outcomes included recurrence of the draining sinus (4.2%), amputation (5.2%), death (3.1%) and tibial non-union (2.1%). It was also reported that ambulatory status without assistance was achieved in 89.6% of patients who had lower limb disease (May et al., 1982, 1991).

Yang, 2013

In 2013, a classification system for massive tibial bone defects was proposed with the aim of guiding a single staged management strategy (Yang, 2013). This incorporated the soft tissue status with limb shortening in addition to a bone defect, figure 2.8. During the study period, 51 patients were classified using this system with a follow up of between 6 – 41 months (mean 26.3 months). All patients underwent debridement and the bone defects were repaired in the same operation according to the protocols for each subtype, figure 2.8. In this study, 12 cases were type A, 33 cases were type B, 4 cases were type C and 2 cases were type D. Results were evaluated using the Johner-Wruhs method with regard to fracture union, neurovascular disturbance, deformity and mobility (Johner and Wruhs, 1983). Using this method, 20 cases had an excellent outcome, 22 had a good outcome, 4 cases were fair and 5 were poor. However, the outcome corresponding to each individual classification group was not

reported. Using this classification and treatment algorithm, two cases progressed to a long-standing osteomyelitis and two had amputation of the affected limb.

Type A	Bone defect >3cm Without soft tissue defect	Vascularised fibular graft
Type B	With soft tissue defect of 10x20cm or less	Vascularised fibular osteoseptocutaneous graft
Type C	With soft tissue defects of 10x20cm or more	Vascularised fibular graft and anterior lateral thigh flap
Type D	With limb shortening >3cm	Limb lengthening in addition to either protocol A, B or C

Figure 2.8: The classification of post-traumatic tibial osteomyelitis by Yang in 2013.

2.4.3 (C) Classification of the Bone Involvement

Weiland, 1984

Type I	Open, exposed bone without evidence of osseous infection but with evidence of soft tissue infection.
Type II	Circumferential, cortical or endosteal infection: Roengenograms showing a diffuse inflammatory reaction, increased density and spindle-shaped thickening of the cortex in addition to areas of bone reabsorption; and often an involucrum surrounding sequestrum.
Type III	Cortical and endosteal infection associated with segmental defects.

Figure 2.9: The Weiland classification of osteomyelitis with a large soft tissue defect.

Weiland's 1984 classification incorporated the extent of bone involvement with the nature of the soft tissue defect, figure 2.9. This aimed to distinguish patients who would require amputation from those who would not. All patients in this cohort had a draining sinus for greater than 6 months and necessitated free microvascular tissue transfer. The osseous involvement was categorised into 3 separate subgroups. These ranged from no obvious osseous involvement to bone involvement resulting in instability, figure 2.9 (Weiland et al., 1984). Of the 33 patients in the validation of this classification system, four were type I, six were type II and 23 were type

III. The type III group had the largest failure of free muscle transfer resulting in four amputations. Patient mobility was one of the reported outcome measures, defined as the ability to walk without the aid of a stick. It was observed that type III patients had poorer outcomes, both in 'flap failure' and in mobility, when compared to the other 2 groups. The importance of good vascular supply was highlighted for the success of free muscle transfer procedures, where all of the failed muscles had a poor vascular supply.

Gordon, 1988

A classification for patients who required free muscle flaps was proposed by Gordon in 1988 based on the extent of the bone defect (Gordon and Chiu, 1988). Three subtypes were used to classify infected tibial non-union based on the size of segmental bone defect and the presence of an intact fibula, figure 2.10. This was in attempt to classify the severity of the disease and demonstrate good prognosis with adequate soft tissue coverage. The series included 14 patients, and the outcome measures were (i) survival of the transplanted muscle, (ii) soft tissue drainage and (iii) ability to weight bear. These categories of bone defect were correlated with the prognosis. Type A defects had the best prognosis and type C the worst.

Type A	A tibial defect and non-union without significant segmental loss
Type B	A tibial defect that is >3cm long with an intact fibula
Type C	A tibial defect that is >3cm long without an intact fibula

Figure 2.10: The classification of long bone osteomyelitis according to Gordon, 1988.

May and Jupiter, 1989

In addition to the original classification from 1982 for the duration of the draining sinus, May also proposed a classification system that involved the bone defect, figure 2.11 (May et al., 1989). This classification system was for post-traumatic tibial osteomyelitis. The size of the tibial defect was measured in addition to whether the fibula was intact, acting as a marker of stability. Using these markers, the severity could be graded from least to most severe, thus being able to approximate

the rehabilitation time. Although this classification system was based on an experience of 250 patients over a 10-year period, detailed data analysis of this cohort was not published.

Type	Description	Rehab. time
1	Intact tibia and fibula capable of withstanding functional loads	6-12w
2	Intact tibia, with bone graft needed for structural support	3-6m
3	Tibial defect <6cm long with intact fibula	6-12m
4	Tibial defect >6cm long with intact fibula	12-18m
5	Tibial defect >6cm with no usable fibula	>18m

Figure 2.11: The classification of long bone osteomyelitis according to May and Jupiter.

2.4.4 (D) Classification of Haematogenous Osteomyelitis

Lauschke, 1994

	Timescale	**Treatment**	**Surgery**
Early acute (n=7)	$>\geq$ days since commencement of symptoms	IV antibiotics 1-2 weeks PO antibiotics 1-2 weeks	No
Late acute (n=18)	4-5 days since commencement of symptoms	IV antibiotics 2-3 weeks PO antibiotics 3-4 weeks	Usually
Chronic (n=30)	>5 days since commencement of symptoms	IV antibiotics 3-4 weeks PO antibiotics 1-2 months	Yes

Figure 2.12: The classification of paediatric osteomyelitis according to Lauschke.

A classification of haematogenous osteomyelitis in children was proposed in 1994 by Lauschke who classified the condition according to time scale following the commencement of symptoms (Lauschke and Frey, 1994). This time scale, shown in figure 2.12, was over a number of days and the presence of infection was confirmed by bone cultures, clinical findings and radiological findings. All 7 patients in the 'early acute' group were successfully treated with antibiotics. Of the 18 patients who were 'late acute', 4 were successfully treated with antibiotics alone and the remaining 14

required surgery. All of the 30 patients in the chronic group required surgery. The duration of antibiotic treatment was also estimated by this classification, see figure 2.12 (Lauschke and Frey, 1994). Follow up of these patients at 2-years demonstrated absence of disease in 19 of the 23 who had either acute form of the disease and 15 of 26 patients who had the chronic form.

Jones, 2009

In 2009, a radiological classification for chronic haematogenous osteomyelitis in children was proposed (Jones et al., 2009). This classification system divided the disease on x-ray appearance, categorising the presence of abscesses, sequestrum and sclerotic bone. Each of these had their own category with the sequestrum type being divided into 4 sections, figure 2.13. Physeal damage was also suffixed as either proximal (P) or distal (D). Any patient who did not fall into these categories was deemed as unclassifiable. The classification system was originally based on 87 children who were under the age of 16 years. In all patients, osteomyelitis was present for greater than 6 months and no previous surgery had been performed. The outcomes of this classification system were not presented with regard to the three groups in the original paper but were published in two subsequent publications (Beckles et al., 2010; Stevenson et al., 2015). Intra-observer and inter-observer reliability was measured across 2 rounds with 5 observers (intra-observer: 95% and inter-observer: 96% round 1 and 95% round 2) (Jones et al., 2009). This classification has been termed the Beit-CURE classification by the authors in subsequent articles (Beckles et al., 2010; Stevenson et al., 2015). The first paper reported that none of the patients returned with recurrent infection, although with regard to individual classification, specific outcomes were not reported (Beckles et al., 2010). The second was a 167 patient series where 4% were classified as type A, 68% were type B (1% B1, 17% B2, 34% B3 and 16% B4) and 6% were type C. Almost a quarter of patients, 22%, were unable to be classified either because they did not have x-ray changes, or they did not meet the criteria. The length of hospital admission was related to the type, with type A and B1 patients having

Type A	Broadie's abscess
Type B	Sequestrum involcrum
B1	Localised cortical sequestrum
B2	Sequestrum with structural involcrum
B3	Sequestrum with sclerotic involcrum
B4	Sequestrum without structural involcrum
Type C	Sclerotic
Unclassifiable	
(P) - proximal; (D) - distal	

Figure 2.13: The radiological classification of paediatric osteomyelitis according to Jones, 2009.

the shortest admission (mean 11 days), followed by B2, B3 and C types (mean 26 days, 28 days and 32 days respectively). The longest hospital admission was observed in type B4 patients at 87 days (Stevenson et al., 2015).

2.5 Discussion

Over the past 45 years, multiple classification systems for long bone osteomyelitis have been proposed within the literature. As of yet, none are uniformly accepted or wildly used clinically. Using a comprehensive literature search, 13 individual classification systems were retrieved, all of which use a different approach to the classification of osteomyelitis.

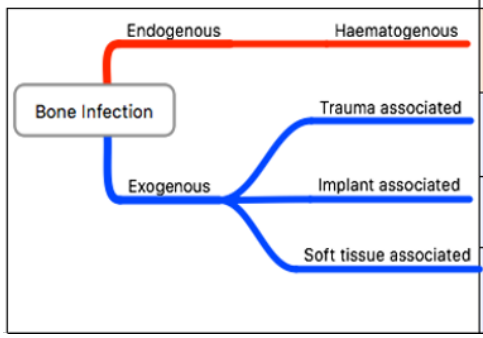
2.5.1 Aetiological Approach to Classification

Describing the osteomyelitis by aetiology can offer information on the likely treatment approaches, the age of the patients and the likely bones involved. However, classification by aetiology alone is unable to offer detailed information on prognosis or management. In the literature, osteomyelitis is naturally classified by aetiology as either haematogenous, post-traumatic, implant-associated or secondary to co-morbidity associated soft-tissue defects (for example ulcers in diabetic foot syndrome). Using this as a basis, the most simplistic method for describing osteomyelitis by aetiology is either as exogenous (referring to post-traumatic, post-operative or following bone exposure to a non-sterile environment) or endogenous

(haematogenous). Within these categories the patient cohorts differ with regards to age as well as response of the osteomyelitis to conservative or surgical management.

The three aetiological types Waldvogel proposed had different characteristics including the frequency of each causative organism and the clinical course of the infection (Waldvogel et al., 1970a,b,c). Waldvogel realised the importance of vascular supply and today, the importance of involving a vascular surgeon if the blood supply is poor is well recognised. However, as with every classification system, there are limitations when using this system alone. By grouping all patients regardless of extent of disease, it is unable to be specific to the individual severity or complexity.

Both the Waldvogel and the Kelly classification systems are over 25 years old and both presented observations about osteomyelitis that are generally accepted today (Waldvogel et al., 1970a,b,c; Kelly et al., 1990). Since the presentation of the classification system, management strategies, including soft tissue cover and antibiotics, have advanced. Bacterial aetiology and epidemiology has also evolved with an increase in the number of resistant organisms and an improvement in culture techniques (Conterno and Turchi, 2013; Kremers et al., 2015). Improvement in diagnostic techniques such as the introduction of Magnetic Resonance Imaging (MRI) has resulted in a greater sensitivity for detection of the disease that may change the pattern observed today. More recently, the importance of neuropathy has been proposed in the development of diabetic foot syndrome, with vascular insufficiency often co-existing with neuropathy in diabetic patients (Berendt and Lipsky, 2004). Although Waldvogel proposed three aetiological categories, there is little distinction between the vascular category and the contiguous category and when blood supply is restored, they behave in similar ways (Walter et al., 2012). The Waldvogel classification also does not distinguish between location or type of bone that is infected. In contrast, Kelly classified only tibial and femoral disease. Both authors defined haematogenous osteomyelitis as a separate entity to osteomyelitis arising from external sources. Kelly divided the latter group into three distinct subcategories dependent on the state or presence of a fracture. The outcomes for categorising patients in this manner were not reported in their patient series



	Bone extent	Soft tissue	Infectious Agent	Host status
Endogenous Haematogenous	Variable	Variable	Single-organism	Variable
Exogenous Trauma associated	Related to fracture	Disturbed	Multi-organism	Variable
Exogenous Implant associated	Variable	Variable	Variable	Variable
Exogenous Soft tissue associated	Variable	Disturbed	Multi-organism	Variable

Figure 2.14: Variation in the different aetiological types of osteomyelitis. The aetiological types of osteomyelitis and the likely involvement of bone, soft tissues, infectious agent and the host status.

and therefore the classification system may not have had a bearing on outcome or clinical application (Kelly et al., 1990).

In terms of aetiology, osteomyelitis encompasses a broad range of conditions that can be summarised as either endogenous (haematogenous) or exogenous (arising from a route other than the blood) (Walter et al., 2012). This distinction between the different subtypes of endogenous and exogenous osteomyelitis can result in a variable clinical picture, figure 2.14. This variation makes applying aetiology to a classification system difficult due to the degree of contributing aspects. Therefore, classification of osteomyelitis by aetiology alone is useful in describing the disease, but it is unlikely to be able to guide treatment or give information on prognosis.

2.5.2 Classification of Haematogenous Osteomyelitis

Classification of haematogenous osteomyelitis (or endogenous osteomyelitis) has either been based on the timescale of the clinical presentation or by the pattern of disease observed. Lauschke proposed a method based on timing. As previously suggested in the Waldvogel classification, only 15% of patients required surgery for their osteomyelitis which was much less than the figure demonstrated by Lauschke which was 76% (Waldvogel et al., 1970a). The use of timescale in this cohort, was applied to predict the likelihood of requiring surgery for successful management. Despite this, in a cohort of similar size (44 patients), surgery was reserved for cases

that did not respond to antibiotics alone (Hamdy et al., 1996). The Lauschke classification is limited by the narrow time window between groups and for patients whose disease has progressed past 6 days, the classification system has limited clinical use (Lauschke and Frey, 1994).

A second method of classifying haematogenous osteomyelitis in children was by using radiological criteria (Jones et al., 2009). The original paper only quoted figures for the intra and interobserver reliability. Following the original article, the authors used the Beit-CURE classification to classify two subsequent patient cohorts (Beckles et al., 2010; Stevenson et al., 2015). It is based on a simple diagnostic method using plain radiographs which are easily available in the developing world. It is the only classification system of the included 13, that reported inter- and intra-observer reliability. However, 22% of patients were deemed as unclassifiable, which suggests that the reliability has been improved by excluding the difficult cases. This could also be due to the limitations of correlating plain radiographs to the exact clinical syndrome (Jacob et al., 1985). Furthermore, a range of sites in the body were classified which could lead to a variation in the radiographic appearance and reliability (Jones et al., 2009). The classification systems for endogenous osteomyelitis are predominantly designed for use in children, where the acute disease is most prevalent. The methods of classifying endogenous osteomyelitis have been either using clinical course or based on simple radiology. The wide variety of clinical presentation and lack of reliability in the clinical measures are limitations to these approaches.

2.5.3 Classification of the Bone Involvement

Classifying bone involvement can assist in giving information regarding the extent of disease for both endogenous and exogenous osteomyelitis. Patterns of bone defect can be described largely as segmental or cavitary. A segmental defect is defined as any loss in the supporting shell of the bone. A cavitary defect is defined as a contained lesion that represents an excavation of cancellous or endosteal cortical bone with no breech in stability (Malizos and Poultsides, 2007). The different

methods of classifying bone deficit can be either by anatomical pattern, deficit size or the stability of the bone. Assessment of each of these bone defects can only be performed either following detailed imaging (either CT or MRI) or during surgery. Classification of the bone involvement is important in planning surgery and deciding on the need for bone stabilisation.

In the Cierny and Mader classification, the pattern of bone involvement was used to guide surgical treatment strategy. In clinical practice, assigning the different anatomical patterns to patients reliably without modern imaging and during surgery can be difficult (Cierny and Mader, 1984). This process can be subjective and may result in variation between surgeons. Interestingly, this pattern of bone involvement had little correlation with prognosis at 2-year-follow-up amongst surgical candidates (Cierny, 2011). Although the Cierny and Mader anatomical classification did not have a bearing on prognosis, the location within the length bone may play a role. One study demonstrated the importance of the site of infection in relation to the phases in children. In metaepiphyseal disease 53% (8/15) had relapse compared to none of the 72 children who had non-metaepiphseal involvement (Mantero et al., 2011). However, a similar study with adults has not yet been reported within the literature (Cierny, 2011).

In addition to the pattern of infection, the critical size of the bone defect to define stability was described by Gordon (Gordon and Chiu, 1988) and Romano (Romanò et al., 2011) as >3cm and by May / Jupiter (May et al., 1989) as >6cm. These classification systems aim to predict rehabilitation and prognosis, with the larger defect correlating with poorer outcomes. This was based on instability or the presence of a segmental defect. It follows that because segmental defects encompass the whole width of the bone, they are less likely to be stable, thus stability and type of defect are closely related. The literature is yet to compare the outcomes of segmental defects with cavitational defects. Although, infected segmental defects are thought to carry a worse prognosis than cavitation defects. This is supported by a series of 66 infected non-union patients who were followed up for an average of 52 months (22 months to 97 months)(Bose et al., 2015). These patients had a high

proportion of complications in their management including persistent infection, pin site infections and frequent surgeries with 1 in 3 patients requiring more than one operation. Amputation was the end outcome in seven of the patients, either for chronic pain (4/7) or for failure of eradiation of infection (3/7).

Bone involvement in osteomyelitis can be classified either by stability, type of defect (segmental versus cavitary), location of infection in the bone (relation to the physis), the anatomical pattern of infection (medullary, superficial, localised or diffuse), or by defining the amount of bone that has been debrided. The stability and therefore the nature of either cavitary and segmental defects is correlated with prognosis in terms of mobility, recurrence and rehabilitation.

2.5.4 Classification of the Soft Tissues

The extent of soft tissue defect in osteomyelitis has been classified using duration and extent of skin sinuses. The importance of defining the management of the soft tissues in osteomyelitis is essential to achieve remission and an optimal outcome (Ger, 1982; May et al., 1991; McNally et al., 1993). In light of the historical perspective that osteomyelitis was considered as a limb debilitating disease, the success of both the Ger and the May techniques were impressive and underlined the importance of soft tissue coverage (Ger, 1977; May et al., 1982). The success of soft tissue restoration techniques relies on the state of surrounding soft tissues and this will dictate the need for direct closure, local or free microvascular transfer. However, not all cases that are treated with debridement require complex soft tissue reconstruction (McNally et al., 1993; Ferguson et al., 2014).

The Ger and May classifications were aimed at predicting failure of the soft tissue flap rather than the successful treatment of the bone infection. For larger defects, Yang demonstrated a method to define management type (Yang et al., 2013). These classification systems demonstrate that with appropriate orthopaedic debridement and antimicrobial management, complex soft tissue reconstruction can be successfully performed. However, risk factors for unfavourable outcomes for soft tissue procedures have not been classified within the literature with regard

to osteomyelitis. In non-infected orthopaedic cases, factors such as Gustilo grade IIIc fractures, need for interpositional vein grafts and anastomotic revision at index operation were associated with poor outcomes (Gupta et al., 2015). This retrospective study included 238 cases and did not investigate factors related to patient co-morbidity. In non-orthopaedic head and neck cancer, a large study including 2,846 patients demonstrated that co-morbidity such as diabetes mellitus, peripheral vascular disease, renal failure, radiotherapy and a duration of anaesthesia that was longer than 18 hours were associated with poor outcomes for free soft tissue transfer procedures (Ishimaru et al., 2016). It is likely that these patient factors will also apply to flaps used for management of the soft tissues in osteomyelitis.

The soft tissue compromise present in osteomyelitis will vary on an individual basis. If managed correctly, using appropriate soft tissue reconstruction techniques, the prognosis in osteomyelitis be optimised.

2.5.5 Classification of Micro-organism

There is little evidence within the literature regarding correlation between causative organism and prognosis in osteomyelitis, although there have been changes in the most prevalent organisms in recent years (Kremers et al., 2015). Romano's 2011 classification is the only classification system to incorporate causative organism, where isolates were classified into five different categories. These were Gram positive, Gram negative, fungal, mycobacterium and mixed flora. The rationale for using these five groups is unclear. However, the authors suggest that different organisms result in different clinical approaches (Romanò et al., 2011). The value of classifying the micro-organism in this way was not demonstrated. Other publications have demonstrated that type of organism does not have a bearing on the outcome of treatment (Cierny and Mader, 1984) except in mycobacterial osteomyelitis where the samples may need specific culture mediums (Gardam and Lim, 2005), and can be treated with antibiotic therapy alone (Bi et al., 2015). However, the importance of microbiology management is supported by improved outcomes when involving a specialist musculoskeletal infectious disease physician (Ziran et al., 2003).

2.5.6 Other Factors: Host Status and Co-morbidity

Patient co-morbidity is thought to play a role in both guiding appropriate surgical strategies as well as giving an indication of prognosis to patients (Cierny, 2011). Cierny and Mader first categorised host status in 1984 using a subjective A – C classification. Long-term follow up showed that increasing medical co-morbidity correlated with increased recurrence of infection and need for further treatment (Cierny, 2011). This was supported in a 50 patient series which observed longer hospital admissions (12.3 days versus 7.1 days) for B hosts when compared to C hosts (Leung et al., 2015). However, there were no differences in recurrence at mean follow up of 3.2 years. This difference could be due to the subjective nature of host stratification. In an attempt to remove this subjectivity, a different approach to host status classification was proposed in 2002 for use in prosthetic joint infection (PJI) (McPherson et al., 2002). McPherson built on the Cierny and Mader classification by defining criteria for each A, B and C hosts, figure 2.15. These criteria were designed for implant associated infection rather than osteomyelitis, although it is thought to be applicable to osteomyelitis (Romanò et al., 2011). Using this method, a series of 50 patients with implant related infections were followed up over an average of 23.28 months. All of the post-operative deaths were in those designated as C hosts (5/50). There was a correlation between systemic host grade and having one or more complication, amputation or re-implantation.

In addition to McPherson, Marais proposed a modification to the Cierny and Mader host status. Here, the definition for A, B and C hosts were dependent on the number of major and minor risk factors, see figure 2.6 (Marais et al., 2015). In contrast to the Cierny and Mader classification system where host status may predict outcome and define suitability for surgery, the Marais classification was unable to predict prognosis in the cohort used, with none of the groups achieving statistical significance (Marais et al., 2015).

The correlation between co-morbidity and outcomes in osteomyelitis has been presented but the degree to which these factors predict poor outcomes has not been reported. Cierny and Mader highlighted the separation of local and systemic

Systemic factors:	Local extremity grade (wound) compromising factors:
- Age $\geq$ 80	- Active infection present >3-4 months
- Alcoholism	- Multiple incisions (creating skin bridges)
- Chronic active dermatitis or cellulitis	- Soft tissue loss from prior trauma
- Chronic indwelling catheter	- Subcutaneous abscess >8cm^2
- Chronic malnutrition albumin <3.0g/dl	- Synovial cutaneous fistula
- Diabetes mellitus (requiring oral agents and / or insulin)	- Prior periarticular fracture or trauma about joint (especially crush injury)
- Hepatic insufficiency (cirrhosis)	- Prior local irritation to wound area
- Immunosuppressive drugs (methotrexate, prednisolone, cyclosporine)	- Vascular insufficiency to extremity (absent extremity pulses, chronic venous stasis, significant calcific arterial disease
- Systemic immunocompromise from infection or disease (e.g. HIV)	

A Uncompromised
B 1-2 Compromising factors
C (Medical and immune status) >2 compromising factors and one of the following:
- Absolute neutrophil count <1,000
- CD4 T cell count <100
- IV drug abuse
- Chronic active infection from another site
- Dysplasia or neoplasm of immune system

C (local) >compromising factors

Figure 2.15: Classification of host status for prosthetic joint infection. From (McPherson et al., 2002).

host factors (Cierny and Mader, 1984). The local host factors include the vascular supply to the limb and the soft tissue status surrounding the infection. The local vascularity of the limb is of such importance that Waldovgel described it as a separate entity to osteomyelitis without vascular insufficiency (Waldvogel et al., 1970c). Factors that were highlighted to cause vascular insufficiency have included diabetes mellitus, atherosclerosis and vasculitis. Those with end stage microvascular disease, such as end stage kidney disease and retinopathy, had worse prognosis with regard to their osteomyelitis. Other local co-morbidity that impairs wound healing is previous radiotherapy (O'Sullivan et al., 2002). This is thought to be due to damaging local soft tissues and the local blood supply (radiation-induced vascular disease). This overlap in soft tissue and vascular factors is also evident in local wound management where an adequate blood supply can contribute to the success of soft tissue transfer procedures and ultimately wound healing (Weiland et al., 1984). These local factors further draw on the importance of the multidisciplinary team approach with vascular and plastic surgical expertise. Systemic diseases can indirectly play a role in the local host status. Diabetes mellitus predisposes to atherosclerosis and therefore can cause impaired blood supply which can influence

the ability for soft tissues to heal (Ger, 1977). Advances in medical therapies has resulted in compromising factors that would have limited surgery are better controlled today. One example of this is the improvement of outcomes in PJI before and after the introduction of highly active anti-retroviral therapy (HAART) in patients with Human Immunodeficiency Virus (HIV) (Falakassa et al., 2014).

In the development of infection, host factors can play a role in predicting infective outcomes following trauma. In a retrospective study undertaken in 2005, patients who had between 1 and 2 medical co-morbidities were at increased risk of bone infection by almost 3 times compared to those who had none (Bowen and Widmaier, 2005). Those who had 3 or more medical co-morbidities were between 5 and 6 times more likely to develop a bone infection compared to those who had less. Castillo *et al.* investigated the rate of smoking in patients who presented with tibial fractures (Castillo et al., 2005). These were divided into 3 categories: (i) those who had never smoked (n=81), (ii) those who had smoked previously (n=82) and (iii) those who were current smokers (n=105). Patients who smoked were more than twice as likely to acquire an infection of any sort and 3.7 times more likely to have osteomyelitis following their fracture. Those that had previously smoked were 2.8 times more likely to develop osteomyelitis but were not at increased risk of other infections. The association of smoking with delayed union, non-union and other complications following fractures is well documented but the precise mechanisms for this are unclear (Al-Hadithy et al., 2012; Patel et al., 2013; Bose et al., 2015).

Host status has been used to guide management (Cierny and Mader, 1984; Marais et al., 2015) in addition to predicting the rate of recurrence and prognosis in patients with osteomyelitis (Cierny, 2011). Clearly, the consideration of host status is important, although advances in clinical practice will mean that the definition of the host has changed over the past 40 years.

2.5.7 Factors Not Currently Classified

It is conceivable that with an increasing polymorbid population with polypharmacy that there are factors yet to be incorporated into an osteomyelitis classification

system. Advances in the availability of radiological techniques have resulted in more detailed radiological assessment. This aids diagnosis and helps define the surgical approach. In chronic osteomyelitis, non-enhanced and gadolinium enhanced MRI are important to locate areas of sequestrum that will need to be debrided surgically (Jennin et al., 2011). Prior to MRI and CT imaging, plain x-ray, tomography and isotope bone scanning were the main imaging modalities and these have limitations. On x-ray, osteomyelitis appears as an area of irregular bone with destruction and periosteal reaction (Jennin et al., 2011). X-ray appearance lags behind clinical findings at surgical exploration and is an unreliable marker of disease (Jacob et al., 1985). Tomography and bone scanning have poor localisation and are non-specific. Although MRI and CT are more reliable when compared to x-ray, they do have shortfalls. Images can be distorted if there is an implant in situ and they can overestimate the extent of the osteomyelitis (McNally and Sendi, 2015). Recent increased availability of MRI imaging could potentially render a reliable method to assess extent of disease prior to surgical resection. If the baseline imaging shows complex disease then early referral to specialist centre would be appropriate to ensure optimisation of treatment at an early stage.

Another potential factor to consider is the original clinical presentation of the patient, which could influence prognosis. If the patient presents as systemically unwell (i.e. Septic) and surgery needs to be performed urgently, then they may possibly be at higher risk of poor outcome (Gaieski et al., 2010). This hypothesis has not been fully investigated and none of the current classifications include this factor. Nevertheless, there is evidence from other surgical specialities that urgent surgery carries greater risk than elective surgery, for example in surgery for aortic aneurysms. When the patient is prepared in an elective manner, then they can be worked up thoroughly and the resulting 1-year post-operative mortality following an aortic aneurysm is between 1-6% (Greenhalgh, 2004). When the procedure is performed as an emergency for a ruptured aneurysm then the mortality is significantly higher at between 46-50% (Bown et al., 2002). Although these

are clearly different patient cohorts, failing to urgently treat a septic patient may also adversely affect the outcome.

2.5.8 Strengths and Weaknesses of this Literature Review

This review adds to the literature by demonstrating the variability in the approaches to classification of osteomyelitis. It has highlighted both the values and the limitations of these classification systems. They all consist of factors that were important during their evolution, and hence reflect the spirit of the time. However, this review has served to reveal why they may not commonly be used in clinical practice. The reasons for this observation may include complexity, classification systems that are too broad and those that have no definitive aim for clinical use. To propose a new classification system, these issues need to be addressed with a practical and clinical focus. By discussing these individually, we can learn from previous experiences. This review has also demonstrated the lack of consensus in defining acute and chronic osteomyelitis.

Although this review has included systematic searches of different medical publication databases, it is always possible to have omitted other classification systems. To minimise omission of important articles, any references that were not returned in searches but found within an article were eligible for inclusion. Paediatric studies were included within this review because the pathogenesis and clinical presentation may add relevant factors for a classification system in adults. Furthermore, owing to the factor that this is a thesis, the literature review was undertaken by the main author. For a systematic review, this process should be performed separately by two reviewers and any discrepancies resolved by a third reviewer.

2.5.9 Summary

This review of the literature has shown that there are multiple approaches to the classification of osteomyelitis, with a varying degree of success and clinical importance.

- **Timescale**: One of the most frequent methods of osteomyelitis classification is by using the timescale over which the symptoms arise. This can be defined as acute or chronic, although the literature has no accepted definition of either of these time points. The difficulty remains in determining the true time point of bone inoculation. It is often impossible to determine when an acute episode becomes a chronic condition. The pathological definition of the presence of dead bone may be defined at operation but is not useful clinically. Therefore, it may be prudent to abandon a definition of acute and chronic infection on the basis of a timescale in disease classification. The importance of defining the clinical status of the patient is, nevertheless essential for guiding the clinician to how urgently treatment needs to be performed.

- **Aetiology**: The aetiology of osteomyelitis can either be defined as endogenous or exogenous. By using these terms, it can be easily distinguishable where the infection has arisen. This may have a clinical use owing to the variation that is seen in clinical presentation with different aetiological subtypes. This differentiation can sometimes help to guide management with endogenous osteomyelitis more likely to be treated with antibiotics alone rather than surgery. Also, it is unknown how this differentiation affects outcome. Therefore, it is uncertain whether or not aetiology should be part of a new classification.

- **Bone**: Bone involvement can be classified in a way that can guide the most appropriate surgical approach. The presence of instability may also change treatment and affect outcome. Thus, extent of bone involvement and stability must be part of the classification.

- **Soft tissues**: The decision to involve a plastic surgeon in the treatment for osteomyelitis is essential in the multidisciplinary approach to osteomyelitis. Given the consequence for the management of the disease, it is meaningful to include soft-tissue involvement in a classification system.

- **Microbiology**: The antimicrobial treatment of the causative organism is best managed by a specialist infectious disease physician, suggesting that it contributes to a positive outcome (Salvana et al., 2005). Correct surgical treatment without adequate anti-microbial treatment is as insufficient as adequate anti-microbial treatment without surgery. This is especially true in the presence of a foreign body. Thus, a classification for the micro-biology should be included.

- **Host status**: The host status is also likely to guide management, with patients who are not fit for curative surgery undergoing palliative procedures (Marais et al., 2015). The host status does seem to have a bearing on outcome being able to predict the likelihood of recurrence in curative surgery. As with previous classification systems, it is meaningful to include host status in patient assessment. The presence of acute sepsis with a systemically unwell patient has not previously been evaluated in a classification system but does affect the urgency of treatment. It is therefore proposed that this should be part of a new classification.

By incorporating easily defined clinical elements of the disease, a classification system can be produced to guide the multi-disciplinary team, with regard to timing, location, method and options for treatment. Validation of this classification may give information on outcome for each patient group.

3

Proposal of New Classification for Long Bone Osteomyelitis

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3.1 Introduction

Many different classification systems exist within the medical literature. They can have a number of uses, which include academic purposes, confirming diagnosis, guiding management and predicting disease outcome. Despite use across all medical specialities, the most widely used and successful classification systems have a number of features in common. These include being memorable, being reproducible across healthcare providers and having a clinical purpose. In this section, established classification designs will firstly be explored, highlighting important examples of successful classification systems. With these attributes in mind combined with the conclusions from the systematic review (chapter 2), the aims of an osteomyelitis classification system will then be discussed. Lastly, this chapter will explore the purpose and scope of the newly proposed osteomyelitis classification system.

3.2 Examples of classification systems

3.2.1 Objective Classification Systems

Objective classification systems use criteria that can be definitively measured and do not rely on a degree of subjective interpretation. This can allow weighting of elements of a disease corresponding to their clinical importance which may be useful in giving information to both the clinician and the patient. One example of this type is weight classification via the body mass index (BMI) (World Health Organization, 1995). This classification gives an estimate of whether a patient is underweight or overweight dependent on weight and height. In this case, the weight and height, which are objective variables, are entered into an equation to give an objective outcome measure. Each grade is associated with a certain risk for morbidity and mortality. As this example shows, this type of classification can be easily and reliably reproducible. It can be applied by those who are not experts in the disease allowing patients to be easily grouped for comparison between centres.

3.2.2 Subjective Classification Systems

Subjective classification systems allow room for clinical judgement. An example a subjective classification system is the American Society of Anaesthesiologists (ASA) score which grades the risk of giving a general anaesthetic. The ASA score grades patients from 1 (no systemic disease) to 5 (moribund, not expected to survive more than 24 hours) or 6 (braindead patient for organ harvesting) (Dripps, 1963). There are no defined criteria for each category, making this classification subjective. The subjectivity relies on the clinician and therefore can give variable results (Stonelake et al., 2015). Another example where the symptoms reported by the patient are used to classify disease status is in the New York Heart Association grading of heart failure (NYHA) (The Criteria Committee of the New York Heart and Association, 1994). Here, the patient's level of dyspnoea is measured from 'no limitation of physical activity' (NYHA I) to 'symptoms of heart failure at rest' (NYHA IV). In this example, the subjective assessment is made by the patient based on their perceived level of symptoms. Due to the nature of subjective classification systems there may be a large amount of variation between patients depending on patient or clinical opinion.

Specific Example: TMN Classification System One widely adopted classification system is the TNM staging system for malignancy. Malignancy is an example of one disease that can affect multiple organs and this is reflected in this classification system. TNM is an abbreviation that stands for tumour (the extent of tumour invasion into a mucosa or beyond), node (lymph node involvement) and metastasis (presence and extent of distant metastases). The TMN system was introduced in 1960 and is used for a number of cancers, for example colorectal, oesophagus and lung (Sellers, 1960). When this information is combined it can help to give both prognostic information and guide management for an individual cancer. For malignancy, the grade of the tumour present on histological specimens is commonly used as an adjunct to the TNM classification system.

Specific Example: Diabetic Foot Infection Classification System Similar to osteomyelitis, diabetic foot infections have also posed a problem for classification and multiple systems have been suggested. Diabetic foot infection is an example of many diseased organs producing one outcome (i.e. vascular, neurology and endocrinology diseases resulting in foot disease). In 2004, a new four-part diabetic foot infection classification was proposed based on the clinical features of the infection into four groups. These were no infection, mild, moderate or severely infected (Lipsky et al., 2004). The aim of the classification system was to aid decision making regarding hospital admission, extent of diagnostic efforts, type of antibiotic therapy and urgency of surgery. The lesions in this study were classified with regard to wound depth as full thickness (soft tissue), fascia-tendon, bone-joint or bone only. In a validation of this classification system including 1,666 patients, it was found that increased severity of infection correlated with deeper infections and more frequent lower-extremity co-morbidities such as peripheral neuropathy and arterial vascular disease (Lavery et al., 2007).

3.2.3 Aims of a new classification system in Osteomyelitis

Successful classification systems focus on the salient points of the disease which are relevant to the vast majority of patients. Ideally, a classification system should be objective, thus minimising inter-user error. Depending on the nature of the content of the classification system, this may not be possible and a subjective degree of interpretation may be required. With respect to classification systems, long bone osteomyelitis may be more in line with the classification of diabetic foot infection (i.e. many variables affecting one organ) than malignancy (i.e. one disease affecting many organs).

In the following sections of this chapter, the rationale for including and excluding specific variables into the new classification system will be discussed. First, we remove the "classic" variables that have been used previously. These variables are often cited by previous classification systems, but they have limited clinical

use. Following this, the proposed variables for a new classification system will be discussed.

3.2.4 Removal of Classic Variables

Two variables that have frequently been included in previous classification systems will be removed. These are the time course (acute versus chronic) and the aetiology which will now be discussed in turn below.

3.2.4.1 Acute and Chronic

Multiple definitions between acute and chronic osteomyelitis exist although these vary between authors demonstrating the difficulty in making this distinction (Waldvogel et al., 1970a; May et al., 1982; Gordon and Chiu, 1988; Lauschke and Frey, 1994; Jones et al., 2009; Romanò et al., 2011). Knowing the exact starting point of the infection is impossible except in some cases when infection presents shortly after injury or surgery. More importantly, the terms acute and chronic do not have a strong influence on the diagnostic work-up or the principles of medical or surgical management. Necrotic bone has to be removed surgically irrespective of whether the disease is 'acute' or 'chronic'. Furthermore, whether osteomyelitis is 'acute' or 'chronic' does not alter the duration or choice of antimicrobial treatment. Traditionally, it was thought that acute bone infections should be treated for 6 weeks or less, and chronic infections for 3 months (Lim et al., 2003; Walter et al., 2012). This recommendation is not based on results of clinical trial and does not allow for the consideration of the surgical procedure. For example, patients not fit for surgery can be treated for a long period without cure (e.g. suppressive treatment). On the other hand, chronic osteomyelitis without systemic upset, may not require antimicrobials (e.g., in the presence of a sinus tract, dormant bacteria, low grade clinical presentation). Thus, using the term 'chronic' does not determine the need for or duration of antimicrobial treatment. On the basis of these arguments, the terms 'acute' and 'chronic' will not be included in the new classification system.

3.2.4.2 Aetiology

Waldovgel and Kelly are the main authors to have classified osteomyelitis by its origin (Waldvogel et al., 1970a; Kelly et al., 1990). In both systems, osteomyelitis of haematogenous origin is defined as one class that responds well to antibiotic therapy alone and surgery is reserved for cases where medical management has failed (Carmody et al., 2014). The remainder of the cases are comprised of infections that have arisen either through trauma (contiguous focus osteomyelitis) or from peripheral vascular disease, usually secondary to diabetes. Once blood flow is improved to the affected limb, it is seen that patients will behave in a similar manner to the contiguous group of patients (Walter et al., 2012). Knowing this, it can be concluded that in fact, there are two main aetiological types of osteomyelitis; haematogenous (endogenous) or contiguous (exogenous). This exogenous group has a number of subdivisions which can be either iatrogenic, trauma related, implant related or from concomitant, adjacent soft tissue infections. Given the aim of the new classification system is for planning treatment and predicting prognosis, the aetiology plays a minor role in long bone osteomyelitis.

Regardless of aetiology, osteomyelitis can progress to an equivalent disease state which does not define the treatment plan or the prognosis. Other factors, such as stability, soft tissue coverage and anti-microbials may offer a better method of stratifying the disease. Therefore, aetiology will not be included in the new classification system.

3.2.5 Variables to be Included

The most common classification system referred to within the literature is the Cierny & Mader, first described in 1984 (Cierny and Mader, 1984). Since the introduction of this classification system, there have been considerable developments in diagnostic procedures and management of osteomyelitis. One of the most important advances in the management of osteomyelitis is the use of the multidisciplinary team. By using a multidisciplinary approach to classification, the most important features will

be highlighted with an aim to guiding treatment strategy and offer prognostic information to patients.

The variables to be included represent the key clinical teams involved in the multi-disciplinary management of osteomyelitis. These are:

(i) the orthopaedic surgeon: to define how the bone in infected,

(ii) the plastic surgeon: to ensure there are healthy soft tissues,

(iii) the infectious disease physician: to manage the microbiology,

(iv) the health of the patient (who is involved in all aspects of treatment).

In addition to these key specialities, other specialists, for example vascular surgeons and musculoskeletal radiologists, may be required for their expertise. Although, it is reasonable to focus on the key players first. The host status of the patient (iv) is important in osteomyelitis treatment and therefore is included. This largely determines 'when' and 'if at all' osteomyelitis can be curatively treated.

Thus, these four categories are selected for the proposed classification system. They comprise the main multidisciplinary teams that are included for the optimum management of osteomyelitis (Pittenger et al., 1999; Salvana et al., 2005; McNally et al., 2016). By approaching the classification system in this way, the need for each treatment team can be assessed. This will allow centres to offer an appropriate level of management on a case by case basis. It will also be able to gauge the disease severity enabling the expected duration of treatment and potential prognostic information.

Within these management categories, a simple approach to the disease can be taken, scoring each section with regard to its severity. Broadly, each category can be stratified into tiers ranging from least severe (for example B1A1C1H1) to most severe (B3A3C2H3). Deciding on exactly how to classify each category will be discussed further below.

3.3 Osteomyelitis Classification System Proposal

3.3.1 B: Bone Involvement

Previously, bone involvement has been classified in osteomyelitis either by extent of infection (Cierny and Mader, 1984; Romanò et al., 2011; Marais et al., 2015) or stability of bone following surgery (Weiland et al., 1984; Marais et al., 2015). These classification systems can be applied at different times during the clinical course.

The amount of bone removal and stability following surgery may influence functional outcomes, either over a defined period or indefinitely (Weiland et al., 1984). For any bone to heal, it must be alive with good blood supply and good fixation, which promotes callus formation and healing (Bizzarro and Regazzoni). The extent of debridement (often correlated with the extent of infection) will have a bearing on fixation and therefore overall stability of the defect. Thus, making all of these features related. Segmental defects have a poorer prognosis when compared to non-segmental or cavitary defects and may need extensive procedures to fill the gap, for example bone transport or external fixation (Dumic-Cule et al., 2015). Segmental defects are unstable, which is a contributing factor to their poor ability to heal (Bose et al., 2015). Conversely, a cavitary defect will usually be stable, potentially offering a better prognosis. One further aspect that may complicate osteomyelitis surgery is the involvement of a joint. When attempting to achieve stability in a defect that is near to a joint, special measures may need to be employed, such as frame fixation, which complicates and prolongs management.

The bone defect will be classified following surgical debridement of infection. This can be a cavitary defect (stable, either requiring stabilisation or not) or a segmental defect (unstable and requiring external fixation). The final category adds in the presence of osteomyelitis with adjacent joint involvement. This gives three different types of bone involvement which are as follows: (B1) cavitary defect following surgery without joint involvement, (B2) segmental defect following surgery without joint involvement or (B3) either segemnetal or cavitary defect following surgery in addition to having joint involvement. It is hypothesised that the bone

involvement variable will be optimally applied during debridement surgery as this gives the most objective assessment of necrotic bone and stability. However, it may be estimated prior to surgery following appropriate imaging such as MRI.

3.3.2 A: Antimicrobial options

Previously, classifications of osteomyelitis have not included any consideration of infective micro-organism, with the exception of the descriptive Romano classification where five categories were used (Romanò et al., 2011). The importance and benefit of involving infectious disease physicians in the multidisciplinary approach to osteomyelitis has been demonstrated (Ziran et al., 2003). Furthermore, the improvement of outcomes when using a specialist musculoskeletal infectious diseases physician is also evident (Salvana et al., 2005). Musculoskeletal infectious disease physicians are often limited to teaching hospitals and bone infection units. Due to limited access to these services, it may not be feasible that a specialist musculoskeletal infectious disease physician could be involved in every case of osteomyelitis. However, every institution commonly works with a microbiology laboratory and therefore uses already accepted methods of classifying bacteria. Furthermore, it is meaningful that micro-organisms are classified by the availability of treatment options and that the availability corresponds to resistance patterns. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) has established definitions for multi-drug resistant (MDR), extensively drug resistant bacteria (XDR) and pan-drug resistant bacteria (PDR) (Magiorakos et al., 2012). The advantages of referring to an existing categorisation for micro-organisms is the timely adaption by a professional society and its applicability by every microbiologist.

The first classification of the anti-microbial options variable is Ax. This denotes that either no tissue samples are available or the presence of culture negative osteomyelitis. This is followed by the A1 category where 'treatment options are available'. This includes osteomyelitis case of implant-associated infections caused by organisms which are susceptible to antibiofilm antibiotics (for example,

staphylococci that are susceptible to rifampacin and gram-negative rods that are susceptible to fluoroquinolones).

If fewer treatment options are available, the presence or absence of a foreign body becomes relevant. Limited treatment options include resistance to anti-biofilm antibiotics such as rifampicin resistance against staphylococci and fluoroquinolone resistance against gram-negative rods. In the presence of an implant, resistant to an anti-bioiflm compound is classified as A2, even when criteria for MDR are not fulfilled. Intolerance to these compounds, or multiple allergies or intolerance leading to a limited choice that is comparable to MDR are also classified as A2, even when the micro-organsim is tested as susceptible. The second category is therefore 'limited treatment options caused by MDR organisms' (A2).

In rare cases, and with growing resistance patterns, the final group (A3) should include isolates with available antibiotic treatment options, caused by either PDR or XDR bacteria. Surgically, this is important because, if known pre-operatively, it can govern the amount of bone debridement that is required.

3.3.3 C: Coverage by Soft Tissues

The soft tissue status in osteomyelitis has been categorised with differing objectives. Firstly, for prediction of flap failure (May et al., 1982) and secondly for the actual type of soft tissue cover required (Yang et al., 2013). As previously mentioned in chapter 2, the two main methods of classifying soft tissues are by the extent of involvement or by the duration of a draining sinus. However, neither of these issues has been shown to determine treatment or outcome. The ability to predict flap failure are present by co-morbidity defined in the 'host status' variable, although these are not necessarily applicable to osteomyelitis (Gupta et al., 2015; Ishimaru et al., 2016). It is important to note that patients who have good soft tissue cover will have a favourable prognosis regardless of the underlying disease (Ger, 1977; May et al., 1982).

The purpose of classifying the soft tissues will be to dictate whether a plastic surgeon is required to provide adequate soft tissue coverage, or whether they can

be closed directly by the orthopaedic surgeon. Therefore, the proposed categories for the coverage of the soft tissues are either (C1) direct closure possible or (C2) direct closure not possible; plastic surgery expertise required.

3.3.4 H: Host status

Host status has previously been used in the Cierny Mader, Romano and Marais classification systems (Cierny and Mader, 1984; Romanò et al., 2011; Marais et al., 2015). Medical co-morbidities are an important measure of how patients will fair after any operation (Smith et al., 2014) and is applicable to osteomyelitis (Cierny, 2011). However, it should only be viewed as one component of a total procedural risk as other factors will play a role in influencing outcome too. These include, the nature of the procedure itself, the current status of the patient, experience of surgeon and experience of the anaesthetist (Fitz-Henry, 2011). In osteomyelitis, these features need to be considered. As previously discussed, pre-operative scoring systems such as the ASA grade, give variable prognosis on the outcome of surgical procedures (Stonelake et al., 2015).

One method of classification of host co-morbidity is the Charlson co-morbidity index which predicts mortality dependent on their past medical history (Charlson et al., 1987). It scores co-morbidity weighted dependent on their severity as 1, 2, 3 or 6. A total score is calculated from the number of co-morbidities. It has been validated in both medical (Melfi et al., 1995) and surgical cohorts (Klabunde et al., 2007; Radley et al., 2008). Charlson's original study was performed on breast cancer patients to predict one-year mortality (Charlson et al., 1987). Since, there have been multiple modifications dependent on patient population (Romano et al., 1993; Quan et al., 2011). In 2010, a large study used coding data from over 35 million patients to correlate the odds ratio for individual conditions to a base line measure of in-patient mortality (Sessler et al., 2010). This study demonstrated the complexity of host classification and the shortfalls of using host scoring systems such as the ASA and the Charlson co-morbidity index.

In osteomyelitis, co-morbidities are important for determining whether patients are fit for curative surgery and govern the chances of treatment success (Cierny, 2011). In terms of fitness for surgery, patients can have reversible or irreversible systemic co-morbidities. Irreversible co-morbidities are present regardless of patient optimisation, for example disseminated malignancy. Reversible co-morbidities, for example malnutrition or tobacco smoking, can and should be reversed prior to surgery, if the patient is able to wait for definitive treatment. However, reversal in some cases may only be partial. Finally, certain co-morbidity previously associated with poor outcome can now be optimised due to the advancement in medical research (e.g. in HIV infection). Therefore, with this constant evolution of medical treatment, it may not be useful to list specific diseases in the host variable of a classification system.

In the new classification system there will be three categories for host status. These are (H1) fit for curative surgery without the need for optimisation, (H2) fit for definitive surgery with specialist optimisation and (H3) not fit for surgery even after optimisation or patient does not wish to have surgery.

3.4 BACH version 1

Version 1 of the BACH classification of long bone osteomyelitis is presented in figure 3.1. This summarises how the variables will be applied to patients for stratification in terms of management and prognosis. This can either be uncomplicated, complex (specialist intervention required) and palliative (not for definitive surgery).

3.5 Reproducibility of BACH version 1

Any classification should be reproducible between centres. This will allow patient outcomes and treatment strategies to be compared reliably. Ultimately, this will provide improved information for researchers, clinicians and patients. These parameters could include remission rates, prognosis and rehabilitation times.

The BACH classification system is designed so that all patients are able to be classified. Furthermore, it should stand the test of time as the specific details of each

	Bone involvement (B):	**Antimicrobial options (A):**	**Coverage by soft tissue (C):**	**Host status (H):**
Uncomplicated	B_1: Cavitary defect without joint involvement	A_1: treatment options available OR A_X: unknown / no anti-microbial growth	C_1: Direct closure possible	H_1: fit for definitive surgery without specialist intervention
Complex: Specialist intervention needed	B_2: Segmental defect without joint involvement	A_2: limited treatment options (MDR) or resistance to anti-biofilm antibiotics in presence of an implant	C_2: Direct closure not possible; plastic surgery expertise required	H_2: fit for definitive surgery with specialist intervention
	B_3: Any osteomyelitis with associated joint involvement	A_3: no treatment options (XDR / PDR)		
Palliative: Not for definitive surgery				H_3: unfit for definitive surgery after specialist intervention / patient refusal for surgery

Figure 3.1: Summary of the BACH classification system, version 1. The colours represent the complexity of cases and requirement for specialist management: Green = uncomplicated; Amber = complex and Red = Paliative. MDR, XDR and PDR as defined by the ESCMID criteria (Magiorakos et al., 2012).

part of the classification system may be altered over time as medicine progresses and bacterial resistance patterns change. Progress in treatment and better understanding of osteomyelitis may better inform the classification of individual patients, but will not change the definition of each of the categories.

It is hypothesised that all cases of long bone osteomyelitis are able to be scored as either B1, B2 or B3 and with adequate imaging, be reproducible between centres.

Changes in bacterial resistance patterns, make the classification of microbiology difficult. Defining the exact bacteria in each category would result in the classification system being complex and rapidly outdated. However, the title of the groups is based on the availability of antimicrobial treatment options which are more specific to each patient. The criteria for each section of the antimicrobial classification will be based on an already defined classification, namely MDR, XDR and PDR (as defined by ESCMID) (Magiorakos et al., 2012). With reproducibility in mind, the microbiology should fit into each of these defined categories. Furthermore, as the ESCMID criteria are updated with resistance patterns, the antimicrobial variable in the classification system will remain up to date.

The coverage of the soft tissues can be divided into two simple groups that define the need for a plastic surgeon. The classification defines whether specialist management is required and not the requirements for specialist management. This will allow the classification to remain applicable with advances in soft tissue management techniques.

Defining the host status can be difficult to reliably reproduce for different reasons as previously demonstrated by the complexity of the Charlson co-morbidity index and the subjective nature of the ASA grading system (Dalton et al., 2011; Han et al., 2004; Davenport et al., 2006). In the proposed classification system, the host is defined based on their fitness for surgery (H3 versus H1 / H2) or by their need for optimisation by a specialist (H1 versus H2). This method of classification has moved away from defining precise variables that put patients into distinctive groups that will encompass advances in medical therapy over time. This is because each patient has an individual set of circumstances and disease status can change over time.

3.6 When to Apply BACH

The clinical presentation of the patient is important in determining the appropriateness for classification. Patients who do not require emergency treatment can be classified using the proposed BACH system. A haemodynamically unstable patient will require admission for anti-microbial therapy, blood cultures and potentially emergency surgery. Patients who attend as an emergency may be classified using the BACH system after urgent treatment and stabilisation. Therefore, it may not be appropriate to classify long bone osteomyelitis in a haemodynamically unstable patient and the priority should be in stabilisation of the patient.

Following resuscitation, the most appropriate time to classify a patient may be at different times. This could be (i) when the patient is seen in clinic (finalisation of H), (ii) prior to surgery (for planning), (iii) directly post-operatively (finalisation of B and C) and (iv) 10 days following antimicrobial culture (finalisation of A). In reality, it may be sensible to classify the patient at all of these time points as it should be able to guide where a patient is treated.

3.7 BACH version 1 in Management

One of the aims of this classification system is for guiding patient management. During the first consultation, all of the information required for complete classification may be unavailable. For example, the antimicrobial status will not be known if bone biopsy or deep tissue biopsy have not been performed. The patient in this case will be designated as an Ax denoting that there is not enough information to classify antimicrobial status. The bone status may also not be known, but can be predicted by using pre-operative imaging. With regards to management, all H2 patients should have their co-morbidities optimised if possible. H3 patients should be informed that reconstructive surgery cannot be performed without putting them at significant risk. The patients who are suspected to need soft tissue coverage (C2) should also be consulted by a plastic surgeon to review the need for soft tissue reconstruction or referred to a specialist bone and joint infection centre where a plastic surgeon is available. The bone involvement should be classified either after surgery or after detailed imaging (ideally MRI or nuclear imaging). This will give information on requirement for bone debridement (B1 or B2) and whether the case involves management of an infected joint (B3).

Following biopsy and sterile cultures, the antimicrobial status will be obtained and can influence management in two possible ways. Firstly, resistant bacteria may require a longer duration of anti-microbial therapy. Secondly, in the case of the most severe category, an A3 with no treatment options, larger surgical debridement may be necessary to irradicate the infection due to the absence of antimicrobials availability.

It is important to realise that all of the categories in the BACH classification system can influence management. This can theoretically be demonstrated by using the most severe outcome for each category. A B3 patient may need surgery to the joint, an A3 may need further surgical resection or amputation with a long course of broad spectrum or antibiotics in combination, a C2 will need the involvement of a centre with access to plastic surgeons and an H3 patient may only be fit for suppressive or non-reconstructive treatment, whereas H1 / H2 are able to undergo reconstructive surgery.

3.8 BACH version 1 in Prognosis

It is hypothesised that the BACH classification system should be able to predict the prognosis of patients with osteomyelitis, with the higher scores in each category equating to a poorer prognosis. Regarding the bone involvement, a B1 patient has potentially the best prognosis regarding remission and rehabilitation following surgery. A B3 patient could have a longer rehabilitation time due to the involvement of a joint which would potentially slow progress and increase the chance of the patient's infection relapsing. Soft tissue coverage is a factor that can influence the duration of the hospital stay, due to the need to undergo 'flap training' which may further slow the rehabilitation process. Good antimicrobial treatment options (A1) will carry an improved prognosis for remission and shorter hospital stay compared to a patient who has no treatment options (A3), which may require a long course of antibiotics and carry a worse prognosis. The host status can play a role in prognosis, with those who have increased co-morbidity having poorer outcomes (Cierny, 2011; Hotchen et al., 2016b). The BACH classification system highlights the importance of optimising the patient's medical co-morbidity before surgery. A patient who is deemed H3 is unlikely to be cured from the osteomyelitis unless radical surgery is performed (for example amputation).

It is important to realise the close interplay between the four variables that have been included. A patient who is classified in the most severe group for each variable has a poor prognosis. However, the contribution of each variable to clinical and functional outcomes are yet to be determined.

3.9 Summary

The classification for adult long bone osteomyelitis contains four sections. These are (i) bone involvement, (ii) anti-microbial options (iii) coverage by soft tissues and (iv) host status. Version 1 of the BACH classification system is provided in figure 3.1. Within each of these categories there can be two or three options; either

compromised or not compromised. The simplicity of this system is attractive as each component is easily assessed by clinicians regardless of speciality.

4

Retrospective analysis of BACH version 1

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4.1 Introduction

Version 1 of the BACH classification was proposed in chapter 3, figure 3.1. It comprised the following variables: bone, antimicrobial susceptibility, coverage of the soft tissue and the host status. The aim of this classification system was stratification of specialist management. Furthermore, it is proposed that each category could play a role in predicting the prognosis for each patient and used as a comparison for research studies. This chapter reports the application of BACH in a retrospective case series. It first analyses the application of the individual variables of the classification and then discusses how BACH version 1 can guide management and predict prognosis.

4.2 Patients

4.2.1 Patient selection

The retrospective analysis included 100 patients who received an operation for osteomyelitis in the Bone Infection Unit (BIU) at the Nuffield Orthopaedic Centre, Oxford, UK between March 2013 and April 2015. Each patient had the diagnosis of osteomyelitis confirmed using a composite protocol including clinical (symptoms for a minimum of 6 months, with radiological features), microbiological (intra-operative pus or draining sinus) or histological features (two or more cultures with indistinguishable organisms) (Sheehy et al., 2010). Details extracted from the patient's notes included the age at the time of surgery, the bone involved, patient gender, allergy status and the aetiology of the infection. Patients were followed-up either in the clinic or by telephone consultation. Any medical complication, further surgery or complication occurring during follow-up was recorded.

4.2.2 Patient Demographics and Infection Details

The average patient age was 57.1 years (range 21.3 – 88.6; SD 15.6). There were 63 males and 37 females.

From an anatomical perspective, there were nine different bones that were involved. These were the tibia (n=41), femur (n=25), humerus (n=17), radius (n=8), clavicle (n=2), ulna (n=2), calcaneum (n=3), fibula (n=1) and sacrum (n=1). Non-long bone infections comprised 4.0% of the total cohort (4/100, 3 calcaneum and 1 sacrum) and were analysed separately. The most commonly infected bone was the tibia (41/100) and the least common was the sacrum and fibula, which both included one case. Two thirds of patients had either a femoral or tibial osteomyelitis (66/100).

The cohort was divided into four aetiological types of osteomyelitis. These were post-traumatic (n=71), haematogenous (n=19), related to an orthopaedic procedure (n=6) and secondary to soft tissue infection (n=4). As proposed in chapter 2, these can be denoted as endogenous (n=19) and exogenous osteomyelitis (n=81). All aetiological types of osteomyelitis were included for BACH classification as proposed in chapter 3.

4.3 Application of BACH version 1

4.3.1 Bone Defect Analysis (B)

The bone defect was classified by a combination of pre-operative imaging (MRI, CT and PET-CT), radiology report and operation note. Each bone deficit was also classified using the Cierny and Mader classification system at the time of surgery by the operative surgeon (Cierny and Mader, 1984).

Using the BACH classification system, most bone defects were classified as B1 (71/96, 74.0%). Fourteen patients were classified as B2 (14/96, 14.6%) and eleven were classified as B3 (11/96, 11.5%). Of note, a significantly higher proportion of patients with humeral osteomyelitis were deemed a B3 when compared to other sites of infection (6/17, 35.3%, $p<0.05$ χ^2 test).

4.3.1.1 Comparison to the Cierny Mader classification system

Using the Cierny and Mader classification system (CM), all patients were classified as either a grade III (localised) or IV (diffuse) osteomyelitis (Cierny and Mader, 1984). This is due to the nature of the cohort available; all patients received a

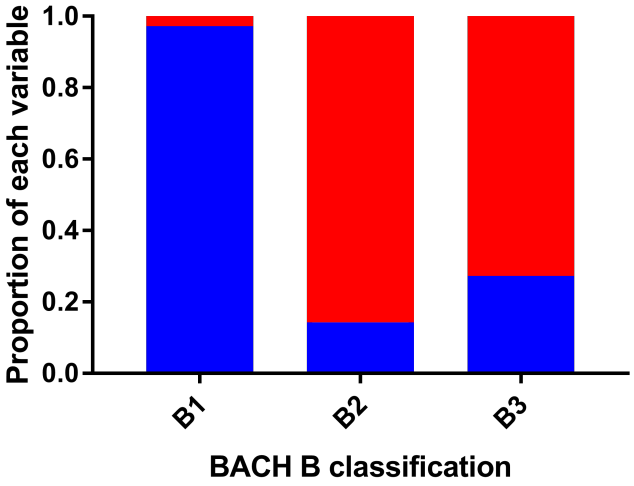


Figure 4.1: Proportion of Cierny Mader classification that comprises each 'B' variable. The B1 variable was comprised predominantly of CMIII osteomyelitis (blue bar) and B2 was comprised predominantly of CMIV osteomyelitis (red bar). B3 osteomyelitis was comprised of a mixture of CMIII (blue) and CMIV (red).

gentamicin loaded Calcium Sulphate carrier which would not be appropriate for CM I (superficial) or CM II (medullary) osteomyelitis. Within the cohort, there were 74 CM type III and 22 CM type IV patients.

Predominantly, patients classified as CM III were placed in the B1 group and those classified as CMIV were placed in the B2 group, figure 4.1. Aside from the eleven cases of B3 osteomyelitis, four cases did not follow this rule (two Cierny Mader IV were classified as B1 and two Cierny Mader III were classified as B2). These four patients are shown and discussed in table 4.1. Two patients were difficult to classify because the infection was of an amputation stump. This was classified as B2 because it required segmental resection but classified as a CMIII because it was a 'localised' infection (patients 1 and 90). Two further patients (patients 23 and 41) were difficult to classify because they had a CM IV osteomyelitis but it was difficult to distinguish whether they should be a B1 or B2 because they had a cavitational debridement. When reviewing these specific cases, these patients received an intra-lesional debridement due to the epiphyseal site of the infection, table 4.1.

Patient ID	CM classification	BACH classification	Site of infection	Aetiology	Comment
1	III	2	Femur	Exogenous	Post above knee amputation.
90	III	2	Tibia	Exogenous	Complete segmental debridement.
23	IV	1	Distal radius	Endogenous	Intra-lesional debridement.
41	IV	1	Distal femur	Exogenous	

Table 4.1: Discrepancies between the CM classification and the BACH classification of the Bone. Patient ID represents the patient's anonymised study number.

4.3.1.2 Limitations of the bone defect variable

This retrospective analysis demonstrated a limitation with the terminology and definitions used in the 'B' variable. This was the inclusion of the term 'defect' implying the surgical approach was being classified and not the pattern of infection. In addition to allowing this to be scored pre-operatively using imaging, it is likely that intra-lesional resections (non-curative) may carry a worse prognosis than a complete debridement. On the basis of this change, the above cases that were difficult to classify (patients 1, 90, 23 and 40) would have been in different 'B' categories (patients 1 and 90 would have been B1 and 23 and 40 would have been B2). A second limitation in the application of the classification system was the definition of a segmental infection. To minimise ambiguity, a circumferential soft tissue reaction should be present to make the diagnosis of a segmental infection. This information should be included with the key that accompanies the classification system.

4.3.2 Antimicrobial Options Analysis (A)

The antimicrobial options were assessed using the full microbiology susceptibility panel of bone and tissue culture that were retrieved at the time of surgery. Only culture results from the primary surgery performed in the BIU were analysed and susceptibility testing obtained from previous sampling were not included. Similarly, any microbiology culture results from subsequent operations were also not included in the classification of the antimicrobial availability.

All patients were classifiable using the four antimicrobial option categories that were defined. Most patients were classified as A1 (43/96, 44.8%) and only one patient met the requirements of A3 (1/96, 1.0%). The 37 patients (37/96, 38.5%) who had a culture negative osteomyelitis were classified as Ax. The remainder of patients were classified as A2 and having limited treatment options (15/96, 15.6%).

4.3.2.1 Per isolate Analysis

Combining mono- and poly-microbial growth, there was a total of 94 isolates returned from microbiology culture. The complete list of isolates from microbiology culture are shown in table 4.2. The most commonly isolated organism was *S. aureus* (31/94, 33.0%). The ESCMID criteria were applied to the isolate susceptibility panels to determine MDR, XDR and PDR status. The results from these were then applied to version 1 of the BACH classification, table 4.2. Sixty-nine isolates could be classified according to ESCMID (69/94; 73.4%) and 25 (26.6%) could not. BACH classification was possible in 6 non-ESCMID classifiable isolates (6/25, 24.0%) because all susceptibility tests performed were sensitive and therefore the isolate must have been classified as an A1. In the remainder of the non-ESCMID classifiable group (19/25, 76.0%), advice was sought from a specialist musculoskeletal infectious disease physician (supervisor PS) who advised on the complexity of treatment options and BACH classification. The details of these cases are shown in table 4.2. Using a 'per isolate' analysis, 76.6% (72/94) isolates were classified as A1, 22.3% (21/94) as A2 and 1.1% (1/94) as A3.

4.3.2.2 Per patient analysis

Of the 96 patients included, 59 patients had a positive bacterial culture (61.5%) and 37 (38.5%) had a culture negative osteomyelitis. Of the cases with a positive bacterial culture, 66.1% (39/59) were able to be classified completely by ESCMID. 20 cases (20/59, 33.9%) had at least 1 isolate that was unclassifiable by ESCMID. Two scenarios existed that allowed the application of the BACH classification to non-ESCMID classifiable isolates. The first scenario applies to cases where non-ESCMID classifiable isolate are 100% sensitive to all susceptibility tests performed,

	Isolate	ESCMID low resistant	MDR	XDR	PDR	Total	A1	A2	A3
ESCMID classifiable	*Acinetobacter spp.*	0	0	0	0	0	0	0	0
	Enterobacteriacae:								
	Citrobacter spp.	2	0	0	0	2	2	0	0
	Enterobacter spp.	4	1	0	0	5	4	1	0
	E. Coli	5	2	0	0	7	5	2	0
	Klebsiella spp.	2	1	0	0	3	2	1	0
	Morganella morgagnii	0	2	1	0	3	0	2	1
	Proteus mirabilis	3	1	0	0	4	3	1	0
	Salmonella spp.	1	0	0	0	1	1	0	0
	Serratia marcescens	0	1	0	0	1	0	1	0
	Enterococcus spp.	7	0	0	0	7	7	0	0
	Pseudomonas aeruginosa	5	0	0	0	5	5	0	0
	S. aureus	23	8	0	0	31	23	8	0
Non-ESCMID classifiable	*Bacteroides fragilis*	-	-	-	-	-	1	0	0
	Dermobacter hominis	-	-	-	-	-	1	0	0
	Pseudomonas monteilii	-	-	-	-	-	1	0	0
	Pseudomonas stutzeri	-	-	-	-	-	1	0	0
	Staphylococcus epidermidis	-	-	-	-	-	1	0	0
	Streptococcus anginosus	-	-	-	-	-	1	0	0
Non-ESCMID classifiable (advice required)	*Achromobacter*	-	-	-	-	-	0	2	0
	Bacillus spp.	-	-	-	-	-	1	0	0
	Clostridium difficle	-	-	-	-	-	1	0	0
	Corynebacterium spp.	-	-	-	-	-	3	1	0
	Propionibacterium acnes	-	-	-	-	-	1	0	0
	Pseudomonas otitidis	-	-	-	-	-	1	0	0
	Staphylococcus epidermidis	-	-	-	-	-	4	1	0
	Staphylococcus lugdunensis	-	-	-	-	-	1	0	0
	Streptococcus agalactae	-	-	-	-	-	1	0	0
	Streptococcus gordonii	-	-	-	-	-	1	0	0
	Streptococcus oralis	-	-	-	-	-	0	1	0
						Total:	72	21	1

Table 4.2: A summary of how each of the isolates in the retrospective analysis were able to be classified. Isolates were grouped according to how they were able to be classified. These were (i) using the ESCMID criteria for MDR / XDR and PDR, (ii) Non-ESCMID classifiable isolates that were 100% sensitive to all susceptibility tests performed and (iii) Non-ESCMID classifiable isolates that required specialist advice to make the classification. The ESCMID classification is shown, where applicable, alongside the corresponding BACH classification scores. The totals for each of the BACH classification scores are also shown.

resulting in an A1 classification. This occurred in 5 of the non-ESCMID classifiable cases (5/20, 25.0%). The second scenario applies to cases of polymicrobial growth with an ESCMID MDR, XDR or PDR isolate. In this situation, the case will be classified as either an A2 or A3 dependent on the results of the susceptibility testing. This occurred in 1 of the non-ESCMID classifiable cases (1/20, 5.0%). The remaining 14 patients required expertise from an infectious diseases physician (supervisor, PS) to make the classification. Therefore, without specialist expertise, a total of 82 patients (82/96, 85.4%) were classifiable by BACH.

4.3.2.3 Mono- versus poly-microbial culture

Monomicrobial culture was present in 61.0% (36/59) with the remainder (23/59, 39.0%) having a poly-microbial culture of $\geq$2 distinguishable isolates. Patients who had poly-microbial culture, were statistically more likely to be classified within the A2 or A3 category $p<0.01$ χ^2 test). Microbiology from nine of the 21 patients classified as A2 gave a *S. aureus* on culture (8/21, 38.1%), eight of which were methicillin resistant *S. aureus* (MRSA). The A2 patient where a methicillin sensitive *S. aureus* (MSSA) was isolated, was classified as A2 category due to a multi-drug resistant *Escherichia Coli* (*E. Coli*). The patient who was classified as A3 had a poly-microbial culture including *Citrobacter* spp., *E. Coli*, *Enterococcus faecalis* and *Morganella morgagnii*. Here, the *E. Coli* was resistant to all susceptibility tests performed, hence the patient being classified as A3.

4.3.2.4 Allergy

As discussed in chapter 3, patient allergies to antimicrobials can limit the number of medical treatments that are available. Patient allergy to antibiotic was collected from the medical notes. Of all the patients, 19/96 (19.8%) had an allergy to at least one antibiotic which did not alter the classification of the 'A' variable in any of the cases. However, it may have had an influence on the management of the patient, but this could not be demonstrated using the retrospective analysis. In addition to allergy, other medical co-morbidity (for example malabsorption syndromes and drug interactions with concomitant medications) that reduce the available antimicrobial options. However, the inclusion of this in the classification system may increase the complexity.

4.3.2.5 Difficulty with classification

The classification of the anti-microbial options was applicable in 85.4% of patients. The remaining 14.6% patients required consultation with a specialist musculoskeletal disease physician (supervisor PS). Furthermore, 7 cases that were able to be

classified by ESCMID were originally classified incorrectly (7/69, 10.1%) and were reclassified following specialist review.

One explanation for the difficulty in classification is due to the complexity of the ESCMID criteria. These criteria provide detailed advice whether bacteria should be classified as MDR, PDR and XDR. However, they only apply to five specific bacterial classes making less common isolates unclassifiable by a non-specialist. Hence, an infectious diseases physician was required for application in 21 cases. On the basis of this, the groups should be modified to make the classification simpler and usable by non-specialist clinicians. It therefore should be specified that if there is doubt in the classification of the anti-microbial options, the patient should be placed in the A2 category. Following discussion with an infectious disease physician, the patient may then be placed into the A1 category if the bacteria is deemed to have good treatment options.

4.3.3 Coverage of the Soft Tissues Analysis (C)

To classify the coverage of the soft tissues, patients were grouped into those who required plastic surgical expertise and those who did not. If plastic surgical expertise was needed, the nature of the surgical procedure was recorded.

The C1 group included the majority of the patients (73/96; 76.0%). These patients had the surgical site closed directly by the orthopaedic surgeons who performed the debridement operation. In the remaining 23 patients (24.0%), soft tissue procedures were required to close the surgical wound. The muscle donor site for the tissue transfer included gracilis (n=10), latissimus dorsi (n=6), gastrocnemius (n=4), anterio-lateral thigh (n=1) and vastus lateralis (n=1). One patient received a free fibular graft. All soft tissue procedures were performed at the time of bone debridement in a one-stage operation (McNally et al., 1993). Tibial osteomyelitis most frequently necessitated plastic surgical expertise (19/41, 46.3%) and all of these cases were (post-traumatic) exogenous osteomyelitis.

The classification of the coverage of the soft tissue variable was made retrospectively after surgical debridement. Therefore, the application of this variable prior to

debridement surgery has not been evaluated. It is hypothesised that this variable will become more difficult to apply before debridement as this is dependent on individual expertise of the surgeon. Furthermore, it could not be determined retrospectively whether this cohort contained patients who had been referred to a Plastic surgeon and specialist soft tissue management had not been performed. In this situation, where a plastic surgery opinion is sought but no surgical expertise is required, these patients should be placed in the C1 group. The definition of the groups or the classification user key may need to be altered to encompass this scenario.

4.3.4 Host Status Analysis (H)

For classification of the host, the medical notes were reviewed from the first clinic appointment. Any specialist optimisation of the host required was classified as H2. If optimisation was not required and the patient did not require specialist intervention prior to the primary operation, this was designated as H1.

At the outpatient clinic, 20 patients did not need medical optimisation prior to surgery and were designated as H1 (20/96; 20.8%). The remainder required medical optimisation either by anaesthetist, specialist physician or general practitioner and were deemed as H2 (76/96; 79.2%). There were no cases of H3 osteomyelitis as all patients received debridement operations.

All patients were classifiable by host status and using criteria that specified whether the patient needed to be optimised prior to surgery ensured simplicity for classification. Despite this, the amount of optimisation that patients receive prior to surgery is a subjective factor. For example, a patient may have a number of medical co-morbidities but may not need to see a physician prior to surgery because they are 'optimised' for them. In this scenario, they would be scored as an H1 using the BACH system. There are no criteria that are used to specify to which group a patient should be placed, thus increasing the subjective nature of the classification, a factor that we were attempting to avoid. Being H2 did not change the management of the patient, as all H2 patients received an operation. Based solely on host status, it is unlikely that all 76 H2 patients would have required

debridement surgery in a specialist bone infection centre. Therefore, the criteria for being classified as H1 may be too strict and should be altered. One method of achieving this could be to define the criteria for H2 to include specific irreversible co-morbidity that can complicate the treatment of osteomyelitis and necessitate treatment in a specialist bone infection centre.

One limitation of this retrospective analysis is that none of the patients were deemed as H3. This is because this retrospective cohort originated from a database of patients who had all received surgery for their osteomyelitis. The patients who decline surgery or are not fit for surgery may move from being in the H3 to the H2 group and would need appropriate assessment and optimisation. This will be best addressed in the prospective analysis.

4.3.5 'Uncomplicated', 'Complex' and 'Palliative'

BACH version 1 classified osteomyelitis as 'uncomplicated', 'complex' or 'palliative'. 'Uncomplicated' osteomyelitis occurred in 16 (16.7%) of patients as they scored 1 point in each category. 'Complex' osteomyelitis occurred in 80 of the patients as they scored at least one option that put them in the 'complex' group. In this cohort, there were no 'palliative' patients.

4.4 Reproducibility of BACH version 1

One of the aims of the BACH classification system was to ensure reproducibility between centres and between clinicians. This was not officially performed during this retrospective analysis. However, for the bone defect variable and anti-microbial options variable the cases were reviewed with the supervisors to ensure that they had been classified accurately. To test for reliability of the application of the classification, an inter-user analysis will be presented in chapter 5.

4.5 When to use the BACH classification system

As specified in chapter 3, it was stated that the BACH classification system should not be used for a septic, unwell osteomyelitis patient, rather when the patient is

Time point		Variable	Status
1.	Clinic appointment	B	Can be defined based on imaging
		A	Unknown or available from previous samples or biopsy
		C	Can be classified: referral to plastic surgeons if required
		H	Referral to physicians if patients classified as H2
2.	Pre-operative Admission	B	Pre-operative planning
		A	As in (1)
		C	Pre-operative planning
		H	Defined at (1)
3.	Inter-operatively or Immediately post-operatively	B	Confirmed by operating surgeon
		A	Unknown (started on broad spectrum antibiotics)
		C	Confirmed by operating surgeon
		H	Defined at (1)
4.	10 days post-operatively*	B	Defined at (1), confirmed at (3)
		A	Known and classified at (4)
		C	Defined at (1) and (2), confirmed at (3)
		H	Defined at (1)

Table 4.3: Different time points in the application of BACH. Four important time points in the management of osteomyelitis are specified. Clinical information varies at each of these different time points which varies how the BACH classification system can be applied. **=the time point at which the retrospective analysis was performed.*

stable and can be operated on in an elective manner. Each of the patients in this retrospective cohort met these criteria. It was also stated in chapter 3 that there could be four potential time points to use the BACH classification system. These were in the outpatient clinic, pre-operatively, immediately post-operatively and 10 days post-operatively (when antimicrobial growth is available). Table 4.3 shows how the four variables can be classified at each of the time points.

The primary function of the BACH classification was to determine the type of centre in which the patient could be best managed. Pre-operatively, this is possible in three out of four of the variables (B, C and H). The only variable that may not be determined pre-operatively is the antimicrobial options and it is unlikely that this variable would influence the surgical debridement. Therefore, if the osteomyelitis is deemed uncomplicated (B1, C1 and H1) then the patient can receive surgical debridement in a non-specialist centre with referral to a specialist medical team if classified as either A2 or A3.

The secondary function of the BACH classification system is for research purposes, to compare different patient cohorts. For this, the BACH score can

be used, which can be fully completed at 10 days following surgery as performed in this retrospective cohort.

4.6 Use of the BACH classification in management

Initially, if the patient is classified as B2 or B3, then referral to a specialist unit should be sought early. Both osteomyelitis with segmental defect and osteomyelitis that involves a joint may require complex limb and joint reconstruction, managed in a specialist unit. It was hypothesised that the B2 and B3 cases may require more frequent plastic surgeon expertise when compared to B1 cases. This was not demonstrated by the retrospective cohort where similar numbers of soft tissue procedures were performed for across all B variables. It is possible that B2 and B3 patients may be more likely to require consultation with a plastic surgeon at the pre-operative clinic. Furthermore, having their operation in a centre where plastic surgical expertise is available may be an important back-up option if required. This will be assessed using the prospective analysis.

The antimicrobial options classification guides the complexity of treatment and the degree of antibiotic choice available. Patients who are classified as A1 or Ax have multiple treatment options and management should be according to first line therapies, taking into account bacterial sensitivities. In both A2 and A3 cases, discussion with a specialist infectious diseases physician is advised. One limitation of using the antimicrobial options in the classification system is that it is only available in its entirety following complete culture results. The cases in the present analysis have been isolated from a specialist bone infection unit and this may self-select rare or resistant pathogens. Therefore, it is unlikely that these cases represent the microbiology from all cases of osteomyelitis from around the UK. In this retrospective series, a specialist musculoskeletal infectious disease physician (supervisor PS) was needed to classify 14.6% of the patients. These cases were not listed as part of the ESCMID criteria for MDR, XDR and PDR. This inadequacy may be able to be incorporated into the classification system and any bacteria that

are either not part of the ESCMID guidelines or sensitive to all antibiotics tested should have consultation with an infectious disease physician (classed as A2 / A3).

The soft tissue management is defined based on the requirement for a plastic surgeon. This allows a less experienced surgeon to make a referral to a specialist centre if required. Although this is based on individual expertise, it will ensure the primary aim of this classification system, the early referral where it is necessitated, is fulfilled.

In this retrospective cohort, both H1 and H2 patients received a curative operation. When using the classification system prospectively, at the outpatient clinic appointment, the host status may be used to determine the patient management. It is important to score the patient pre-operatively either to decide the intent of surgical intervention (for example amputation versus debridement) and to ensure that the patient is optimised before surgery if required.

In summary, each of the BACH variables is useful for patient management and can be applied at various times during the course of treatment. They can be used to guide both how the patient is managed and where the patient receives treatment.

4.7 Use of the BACH classification for prognosis

One of the aims of the BACH classification system is to stratify patients within the four categories by severity for prognosis. For example, a B3 osteomyelitis may have a worse prognosis when compared to a B2, which may have a worse prognosis than a B1. Theoretically, this will apply to all of the BACH variables, with higher score predicting a poorer prognosis. Defining prognosis can be either by clinical outcome (i.e. the presence of medical or surgical complications), or by how the surgery affects the patient quality of life. Both will be discussed in the following section.

4.7.1 BACH version 1 and clinical outcome

All patients in this cohort were followed-up for an average of 20.2 months (range: 10.6 – 40.6; SD 0.6 months). Complications included those related directly to the osteomyelitis (recurrence, fracture, non-union, mal-union), soft tissues (flap failure

or soft tissue abscess) or medical complications (cardiac arrhythmia, pulmonary embolism), table 4.4. A complication was defined as a further need for treatment (either medical or surgical) as a direct relation to the original osteomyelitis surgery. The most common complication was recurrence (n=4). One patient died 5-months following the surgery from a drug overdose and a second died of unrelated causes. Both of these outcomes were not included as a complication.

'B'	'A'	'C'	'H'	Type of osteomyelitis	Complication
1	x	1	1	Uncomplicated	Fracture (following a fall whilst drunk)
1	2	1	2	Complex	Recurrence
1	1	2	2	Complex	Recurrence
2	x	1	1	Complex	Mal-union
2	1	1	2	Complex	Non-union
2	1	1	2	Complex	Non-union
2	1	1	2	Complex	Recurrence
2	1	1	2	Complex	Recurrence
3	x	1	2	Complex	Fracture
1	x	1	1	Uncomplicated	Soft tissue abscess
1	3	2	2	Complex	Flap failure
1	1	2	2	Complex	Flap failure
3	2	2	2	Complex	Flap failure
1	1	2	2	Complex	Pulmonary embolism
1	3	2	2	Complex	Pulmonary embolism
3	1	2	2	Complex	Arrhythmia (SVT)

Table 4.4: Summary of the complications for each of the patients in the retrospective cohort. These have been divided into those that are associated with the bone (top), those associated with the soft tissues (middle row) and those not directly associated with the osteomyelitis (bottom row). *SVT=Sinus Ventricular Tachycardia.*

Eight of the patients who were scored as B1 had complications (8/71, 11.2%). Three complications were directly attributable to the bone resection and included recurrence (n=2) and fracture at the site (n=1). There were two patients who developed a PE which could have been indirectly related to the surgery, especially as both of these cases received soft tissue procedures which would have prolonged hospital stay and reduced mobility. Five patients who were classified as B2 had a complication (5/14, 35.7%). All five complications could be attributed to the bone with two non-unions, two recurrences and one mal-union. Three of those who were scored as B3 had complications (3/11, 27.3%) that included one fracture. However, other complications in this group could not be directly attributable to the bone

defect. Although the numbers are small, the complex 'B2' or 'B3' osteomyelitis had an increase number of complications compared to the B1 category (B1 11.2%; B2 35.7%; B3 27.3%). The 'B2' osteomyelitis was more likely to produce a non-union or a mal-union which is common in segmental defects.

In terms of the antimicrobial options classification, eight patients who were in the A1 category (8/51, 15.7%) had a complication of which three were recurrence and two were non-union. The Ax group had four complications (4/33, 12.1%). Interestingly, both soft tissue abscesses occurred in this group. Two patients in the A2 group had complications (2/11, 18.0%), one of which was recurrence. The one patient who was classified as A3 had a flap failure.

The complications that involved the coverage of the soft tissues directly were either soft tissue abscesses (n=2) or failure of the tissue transfer (n=3). All flap failures occurred in C2 patients as patients with flaps were ineligible to be deemed as a C1. Both soft tissue abscesses occurred in C1 patients which may have been a consequence of not managing the soft tissues optimally. Plastic surgical procedures such as soft tissue transfer can be long (>5 hours) and the rehabilitation can be difficult, commonly resulting in prolonged hospital stay and reduced mobility. Both patients who developed a PE occurred in the C2 group patients which could have been an indirectly causative factor for development of a thrombus.

The twenty patients who were classified as H1 overall had three complications (3/20, 15.0%). Twelve patients had complications in the H2 group (12/76, 15.8%). These proportions are similar, however, all medical complications (pulmonary embolus and arrhythmia) occurred in the H2 population.

4.7.2 BACH version 1 in the prediction of health-related outcome measures

The cohort of 96 patients were cross referenced with health-related outcome scores that were recorded as part of parallel prospective study (OVIVA). Permission was sought to release these data in an anonymised manner according to the ethics of the OVIVA trial. To do this, a common identifier to both cohorts (NHS number) was

provided with correlated BACH classification score. The returned data contained each of the 5 EQ-5D-3L domains at baseline (post-debridement surgery), 14 days, 6 weeks (42 days), 4 months (120 days) and 12 months. The EQ-5D-3L is a validated measure of anxiety, pain, mobility, self-care and ability to perform usual daily activities. These scores can be weighted to give an overall EQ-5D-3L index that is scored from -0.543 to 1.00 (Dolan, 1997). In addition to this, it includes a visual analogue score (VAS) which rates the health of an individual at that specific point in time on a scale of 0 to 100.

Of the 96 cases included in the retrospective cohort, data was available for a total of 40 respondents who completed the EQ-5D-3L score at each time point, table 4.5. This included data for the VAS and each of the 5 domains of the EQ-5D-3L score. From the 5 individual domains, the EQ-5D-3L index scores were calculated.

Classification variable	Baseline (% of total cohort)	14 day (% of total cohort)	6 weeks (% of total cohort)	4 months (% of total cohort)	12 months (% of total cohort)
B1	32 (45.1%)	21 (29.6%)	27 (38.0%)	24 (33.8%)	25 (35.2%)
B2	3 (21.4%)	1 (7.1%)	3 (21.4%)	0 (0%)	2 (14.3%)
B3	5 (45.5%)	5 (45.5%)	5 (45.5%)	4 (36.4%)	4 (36.4%)
Ax	16 (43.2%)	11 (29.7%)	14 (37.8%)	11 (29.7%)	13 (35.1%)
A1	15 (34.9%)	10 (23.3%)	12 (27.9%)	11 (25.6%)	9 (20.9%)
A2	9 (60.0%)	6 (40.0%)	9 (60.0%)	6 (40.0%)	9 (60.0%)
A3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
C1	31 (42.5%)	20 (27.4%)	28 (38.4%)	22 (30.1%)	24 (32.9%)
C2	9 (39.1%)	7 (30.4%)	7 (30.4%)	6 (26.1%)	7 (30.4%)
H1	12 (60.0%)	8 (40.0%)	11 (55.0%)	9 (45.0%)	11 (55.0%)
H2	28 (36.8%)	19 (25.0%)	24 (31.6%)	19 (25.0%)	20 (26.3%)

Table 4.5: Summary of the number of patients who returned an EQ-5D score compared to the total from the retrospective cohort. Time points were baseline, 14 days, 6 weeks, 4 months and 12 months. Percentage of original retrospective cohort are denoted in brackets.

There was an overall improvement of VAS from 60.8 (95% CI 53.6 - 68.1) at baseline to 77.7 (95% CI 69.7 - 85.7) at the 1 year follow-up. The variable that gave the greatest distinction between 'uncomplicated' and 'complex' osteomyelitis was the bone involvement variable, figure 4.2. The average scores for each variable are presented in table 4.6.

The individual domains of the EQ-5D-3L scores were translated into the EQ-5D-3L index score. There was a general improvement of the EQ-5D-3L index from a baseline of 0.283 to 0.727 at 1 year follow up. The trend of the EQ-5D-3L index

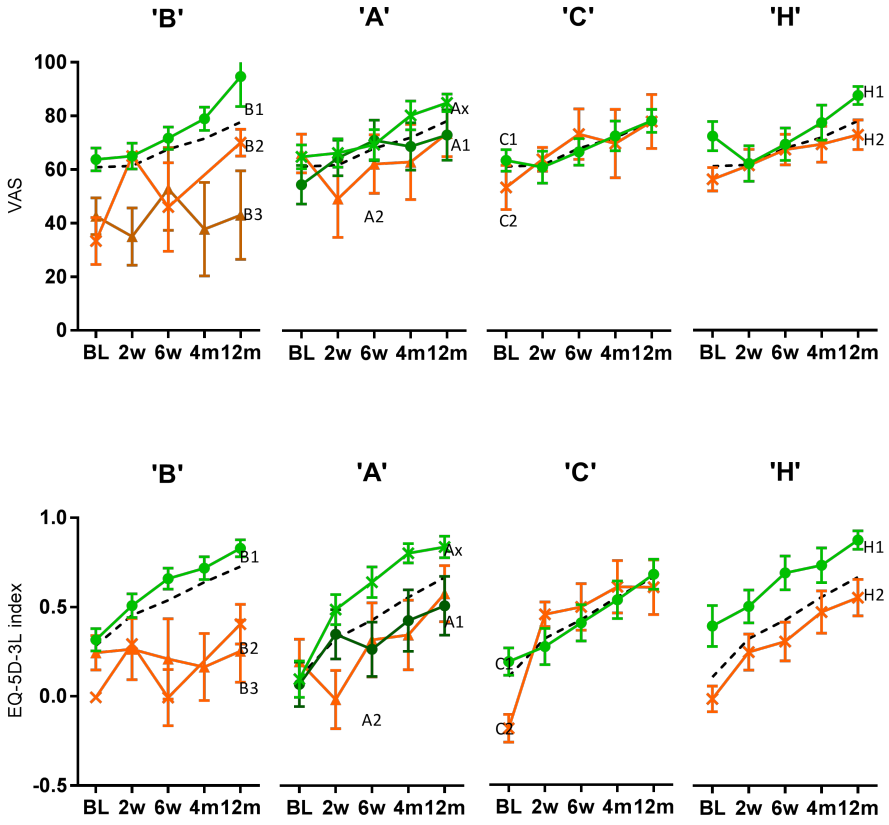


Figure 4.2: Distribution of the results of the VAS and EQ-5D-3L index score correlated to the individual variables of the BACH classification. The corresponding time points are BL = baseline, 2w = 2 weeks, 6w = 6 weeks, 4m = 4 months and 12m = 12 months. Green lines denote 'uncomplicated' osteomyelitis and orange lines denote 'complex' osteomyelitis. Dotted line = mean VAS across all variables at the specific time point. Error bars are the standard error of the mean.

were similar to that of the VAS where the cases classified as 'uncomplicated' had better outcomes when compared to those classified as 'complex', figure 4.2. The lowest overall average scores for the EQ-5D-3L were both in the bone involvement variables with B2 and B3 scoring 0.199 and 0.220 respectively.

Correlating VAS and EQ-5D-3L, a range of outcomes were reported on both the VAS and EQ-5D-3L index score. Predominantly the patients who were classified as 'uncomplicated' had VAS and EQ-5D-3L index scores that represented the better outcomes, figure 4.3. The patients who were classified as 'complex' reported outcomes that ranged from low to the best outcome achievable, figure 4.3.

Variable	**VAS** (95% CI)	**EQ-5D-3L index** (95% CI)
Bone		
B1	73.3 (69.7-76.9)	0.594 (0.532-0.656)
B2	49.2 (31.9-66.5)	0.118 (-0.0669-0.302)
B3	42.4 (30.8-54.0)	0.228 (0.0799-0.378)
Anti-microbial options		
Ax	72.3 (67.6-76.9)	0.632 (0.553-0.714)
A1	64.9 (57.9-72.0)	0.433 (0.325-0.542)
A2	63.4 (54.1-72.8)	0.437 (0.309-0.566)
A3	-	-
Coverage of the soft tissues		
C1	67.8 (63.5-72.2)	0.524 (0.454-0.594)
C2	66.4 (58.1-74.8)	0.485 (0.367-0.603)
Host status		
H1	73.9 (68.5-79.3)	0.706 (0.630-0.782)
H2	64.6 (59.6-69.5)	0.427 (0.352-0.502)
H3	-	-

Table 4.6: Summary of the average VAS and EQ-5D-3L scores across all time points for each variable. Standard deviation (SD) is denoted in brackets).

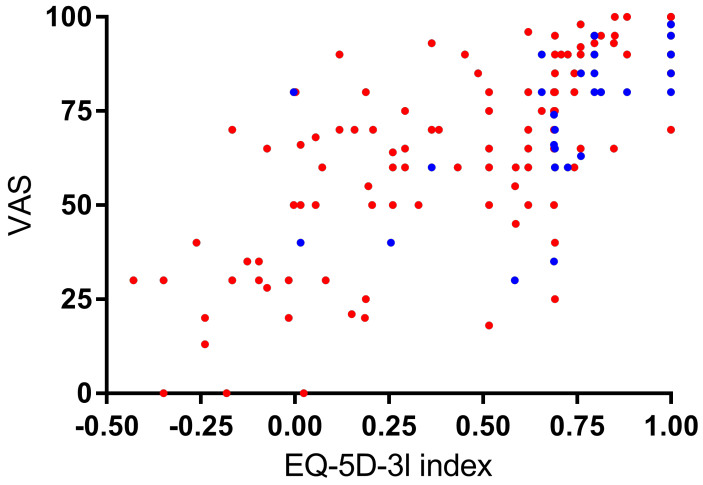


Figure 4.3: Correlation of VAS and EQ-5D-3L across the retrospective cohort. Blue dots = 'uncomplicated' osteomyelitis and red dots = 'complex' osteomyelitis.

This observational data has demonstrated that there is a correlation with the BACH classification variable and the resultant health related outcome score. These data suggest that BACH will be able to have a role in the predication of patient reported outcome measures with the less complex cases correlating with an improved reported outcome.

4.8 Strengths and limitations of Retrospective analysis

This retrospective analysis of 96 patients treated at the BIU has demonstrated some of the strengths and limitations of the BACH classification system. In addition, it has highlighted the limitations of performing a retrospective analysis. The BACH classification was successfully applied to a cohort of patients regardless of age, gender, infected bone and aetiology. On the basis of this evaluation, modifications will be performed to optimise the classification system.

4.8.1 Non-long bone cases

The cases of non-long bone osteomyelitis included a sacro-iliac joint (deemed as a B3) and 3 calcaneal cases (all deemed as B1). These patients were more difficult to classify due to deciding whether a joint had truly been involved and because of the differences in long-bone infection compared to non-long bone infection. For example, in the pelvic case, the sacro-iliac joint was deemed to be involved and would have been scored as a B3 despite not needing a joint reconstruction. In reality, these cases should be excluded from the classification system because it is designed for long-bone osteomyelitis only. Despite the small sample size and on the basis of this, the classification system should remain for long-bone osteomyelitis only.

4.8.2 Strengths of this retrospective analysis

The benefit of this retrospective analysis has demonstrated the need for modification or optimisation of the classification system. It has demonstrated:

- The need for the optimisation of each of the BACH variables.

- The need for an inter-user assessment for the BACH classification system.
- The success of removing the aetiology and time course variables from the classification of osteomyelitis.
- The primary aim of the classification system is to direct management of osteomyelitis to a relevant centre with appropriate expertise. Although, this preliminary data has demonstrated that BACH has scope to predict prognosis in terms of clinical outcomes and health reported outcome measures.

4.8.3 Limitations of this retrospective analysis

Although this retrospective analysis has contained a number of strengths, there are limitations.

All of the cases in this analysis have been taken from a cohort within a tertiary referral centre. This encompasses some patients who have been operated on previously at other centres. Previous operations may influence each of the variables used for classification. For example, a patient who has had previous bone resection that has failed, may need a more extensive resection upon further operation, thus moving them from a B1 to a B2 or B3. This can apply to any of the categories, especially the anti-microbial options where this may select for the resistant bacteria and place patients into the A2 or A3 categories. Even in this situation, only one patient was classified as A3 which, may make this category underused. However, with increasing bacterial resistance patterns, the number of XDR and PDR bacteria may increase over time.

The main aim for the classification system is to decide the optimum place to manage the patient. Therefore, this classification system would ideally be validated in a centre that does not specialise in bone infection. This may give better information on prognosis and subsequent management, especially as to when to refer to other centres.

There are limitations when using the EQ-5D-3L. Firstly, there are only 3 levels of score per individual domain of the EQ-5D-3L. Although this allows the patient

to score between 'no impairment', 'some impairment' and 'complete impairment', it makes assessment of the individual domains difficult. However, the index score was used to compile the scores from these domains. Using this score, it is impossible to attribute any individual domain to cases that are scoring poorly. Furthermore, due to small numbers in the subgroups in this analysis, statistical testing was not performed.

4.9 Summary

This chapter has demonstrated that version 1 of the BACH classification is able to be applied to a patient cohort retrospectively. By modifying this classification system accordingly, version 2 will be presented, chapter 5. This will be used in the inter-user assessment presented in chapter 6.

5

Retrospective limitations and BACH version 2

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5.1 Introduction

In chapter 4, the BACH classification system was retrospectively applied to 96 cases of long bone osteomyelitis. This retrospective assessment identified a number of limitations. The objective of this chapter is to discuss and address these, which will lead on to the proposal of BACH version 2. The problems that were encountered when performing the retrospective assessment can be summarised according to each of the BACH variables, table 5.1.

Variable	Problems identified through the retrospective analysis (chapter 4)
Bone involvement	The terminology used was unclear defining whether it was the extent of infection that was being described or the nature of the defect left after surgical debridement.
Anti-microbial options	ESCMID gives descriptions for MDR, PDR and XDR of only *S. aureus*, *Enterococcus* spp., *Enterobacteriacae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp..This resulted in difficulty in the classification of 14.6% of the patients and 20.2% of isolates. The ESCMID criteria for MDR is complex for non-specialist clinicians to apply due to defining individual antibiotics and antibiotic classes for specific bacterial isolates.
Coverage of the soft tissues	There are no criteria for making the distinction between C1 and C2 making the variable subjective.
Host status	The term 'optimisation' was subjective and is not specific to osteomyelitis. The H1 category was too strict (the majority of the retrospective cohort, 72.5%, were deemed H2)

Table 5.1: Summary of the limitations encountered during the retrospective analysis. Limitations are categorised by the variable to which they are related: Bone involvement, anti-microbial options, coverage of the soft tissues and host status.

5.2 Bone Involvement

The application of the bone involvement variable ('B') was limited by the interpretation of the terminology used to describe the three categories. In the retrospective analysis, it was unclear whether the pre-operative pattern of bone involvement or the nature of the surgical debridement (the 'bone defect') was being classified. Both the bone involvement and the surgical debridement can be described as cavitary, segmental or involving the joint. There were four cases in the retrospective analysis where this

	B1	B2	B3
Clinical findings:			
Stable fracture	✓	x	-
Pain on movement of the joint	-	-	✓
Radiological findings:			
Evidence of fracture healing (x-ray)	✓	x	-
Involvement of partial width of the bone (CT/MRI)	✓	x	-
Involvement of the whole width of the bone (CT/MRI)	x	✓	-
Intra-articular fracture with clinical features of osteomyelitis (x-ray)	x	x	✓

Table 5.2: Clinical and radiological features that are used to classify the 'B' variable prior to debridement surgery. A ✓indicates that the variable has the clinical or radiological finding present, an 'x' indicates that it is not present and a '-' indicates that it may be present.

distinction was important. These included cases where a segmental debridement was performed for a cavitary involvement in the case of an amputation stump and in the case of intra-lesional debridement of a segmental infection. A combination of clinical and radiological findings can be used to make the classification of the 'B' variable, table 5.2. This classification may be confirmed at the time of operation by the surgeon where the bone involvement is observed. However, the bone defect made following surgery may vary amongst surgeons and by classifying this, it would be classification of the management option rather than the osteomyelitis. Therefore, the pre-operative 'bone involvement' is a more reliable and consistent measure compared to the term 'bone defect'.

To improve the 'B' variable, the definition in the user key and the classification system will specify that it is the 'bone involvement' that is being classified. The 'B' variable will remain as three categories, denoted as B1, B2 and B3.

5.3 Anti-microbial options

The anti-microbial options variable relies on the 2012 ESCMID criteria for defining MDR, PDR and XDR bacteria (Magiorakos et al., 2012). By using these criteria, 20.2% of isolates were unable to be classified. One reason for this is because the ESCMID criteria apply to 5 groups of bacteria only. Furthermore, due to a limited number of antibiotic susceptibility tests performed, the application of XDR and

PDR was based on the assumption of resistance to susceptibility tests that were not presented. The British Society for Antimicrobial Chemotherapy (BSAC), have not released criteria for the definition of multi-drug resistant bacteria. The present chapter assesses a method of simplifying ESCMID, relevant to susceptibility panels performed in UK laboratories under the guidance of BSAC and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

The ESCMID definitions of MDR, XDR and PDR are based on the number of resistant susceptibility tests that an isolate possesses to specific antibiotics. Therefore, it was hypothesised that the total number of resistant tests would correlate with MDR status.

To address this hypothesis a three parts analysis was performed:

1. Define how well the number of resistant tests and MDR status correlate using the area under a Receiver Operating Characteristic (ROC) curve and subsequently define the optimum cut off point for defining MDR according to number of anti-biotics an isolate has resistance against.

2. Validate this on a different cohort of patients.

3. Apply this rule to non-ESCMID classifiable microbial isolates.

The following analysis is a method of using microbial resistance to susceptibility tests to define whether an isolate is 'high resistance' (equivalent to MDR, XDR or PDR) or 'low resistance' (not fulfilling the criteria for MDR defined by ESCMID). A similar analysis, in 3 parts, is presented in appendix D that focuses on the percentage of sensitive susceptibility tests as a measure of high or low resistance isolates.

5.3.1 Patient selection

All cases of long bone osteomyelitis that received surgical debridement in the BIU in Oxford between 2013 and 2017 were included for analysis (n=253). For validation purposes, a second cohort (presented in part (ii)) from the same centre who received debridement surgery between 2001 and 2004 (n=176) were also used.

Inclusion criteria were similar to those used in chapter 4. A diagnosis of osteomyelitis could be made if symptoms were present for >6 months or radiological appearances were suggestive of osteomyelitis in addition to one of the following intra-operative findings: (i) histology suggestive of infection, (ii) sinus, abscess or pus present at the time of surgery and (iii) greater than two deep bone specimens (taken under sterile conditions) with indistinguishable microbial isolates (Sheehy et al., 2010). Patients who did not meet the criteria were excluded from the analysis.

5.3.2 Assessment of resistant isolates

Resistant bacterial isolates was assessed using the criteria that was set out by ESCMID in 2012 for *S. aureus*, *Enterobacteriacae*, *Enterococcus* spp., *Pseudomonas aeruginosa* and *Acinetobacter* spp. (Magiorakos et al., 2012). Two individual reviewers, AJH (DPhil candidate) and MD (ST4 Academic Clinical Fellow in Infectious Diseases) classified each isolate to minimise human classification error.

5.3.3 Patient Demographics and Infection information

In the 2013-2017 cohort, there were 222 patients who met the inclusion criteria, figure 5.1. The 96 cases that comprised the retrospective analysis in chapter 4 were included as part of this cohort. A total of 166 males and 56 females were included with an average age of 51.3 years (range 17.8 – 88.6 years, SD 16.0 years). Of these included patients, 72 (32.4%) had culture negative osteomyelitis which is in line with other studies (Kremers et al., 2015). Of the remaining patients (n=150), there were a total of 247 bacterial isolates with 181 (73.3%) being ESCMID classifiable and 66 (26.7%) being non-ESCMID classifiable. The most common sites of osteomyelitis were the tibia (99/222; 44.6%), femur (54/222; 24.3%) and the humerus (27/222; 12.2%), table 5.3.

The 181 isolates that were ESCMID-classifiable were comprised of *S. aureus* (94/181, 51.9%), *Enterobacteriacae* (57/181, 31.5%) *Pseudomonas aeruginosa* (15/181, 8.3%) and *Enterococcus* spp. (15/181, 8.3%), figure 5.2. No *Acinetobacter* spp. were isolated. For these isolates, the mean number of susceptibility tests was

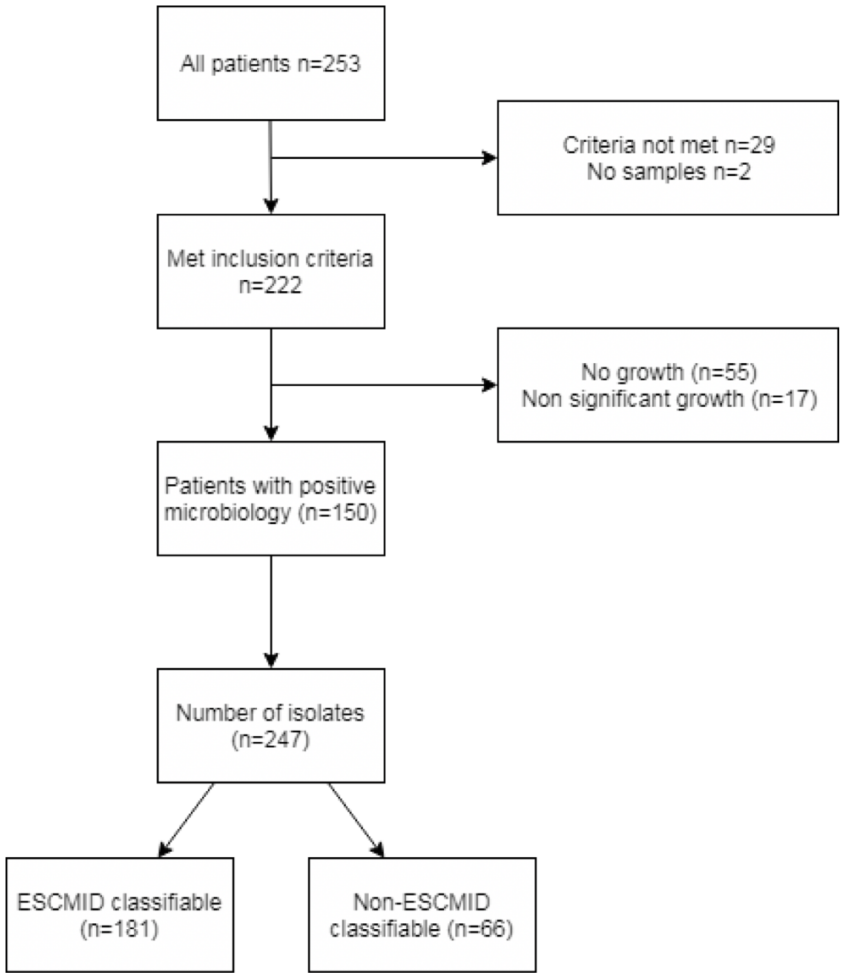


Figure 5.1: Flow diagram of patients that were included in the 2013 - 2017 cohort.

Site	**n (%)**
Tibia	99 (44.6%)
Femur	54 (24.3%)
Humerus	27 (12.2%)
Forearm	16 (7.2%)
Calcaneum	8 (3.6%)
Pelvis	7 (3.2%)
Ankle	7 (3.2%)
Fibula	4 (1.8%)
Knee	2 (0.9%)
Clavicle	2 (0.9%)

Table 5.3: The sites of infection from the 2013 - 2017 cohort. The commonest site of infection was in the lower limb, from the tibia and femur.

16.2 (range 0-28, SD 4.8), although this varied between species, figure 5.3. The overall percentage of resistant susceptibility tests was 18.3% and this conformed to a normal distribution (95% CI 15.8 - 20.7%, p<0.01 Shapiro-Wilk test for normality).

In the 2001-2004 cohort, there were 157 patients who met the inclusion criteria. The mean age for this group was 45.0 years (range 12.0 – 90.0 years, SD 16.6 years) and there were 116 males (73.9%) and 41 females (26.1%). Of these patients, 47 had culture negative osteomyelitis. Of the remaining patients (n=110), a total of 166 bacteria were isolated with 94 (56.6%) being ESCMID classifiable and 72 (43.4%) being non-ESCMID classifiable. Of the 94 isolates that were ESCMID classifiable, there were 51 (54.3%) *S. aureus*, 26 (27.7%) *Enterobacteriacae*, 9 (9.6%) *Pseudomonas aeruginosa* and 8 (8.5%) *Enterococcus* spp., figure 5.2. As with the 2013 - 2017 cohort, no *Acinetobacter* spp. were isolated.

5.3.4 Part (i): Defining the correlation between resistance tests and MDR

The total number of isolates deemed to be MDR when using the ESCMID guidelines was 40 (40/181, 22.1%). In this group, there was a mean of 16.7 sensitivities tested per isolate and an overall resistance rate of 42.7% (95% CI: 37.0% - 48.5%). The non-MDR group had a similar number of antibiotic sensitivity tests performed per isolate (MDR: 16.7 tests, non-MDR: 16.1 tests, p=0.5, *t-test*), figure 5.4. Susceptibility testing was guided by the panel specified by BSAC which is closely aligned with various other European microbiology societies and the European Committee on Anti-microbial Susceptibility Testing (EUCAST) (Andrews, 2007).

The bacterial isolates that were defined by ESCMID as MDR had a significantly higher number of resistant susceptibility test results (MDR: 42.7%, non-MDR:11.4%, p<0.05, χ^2 *test*). The mean absolute number of resistant susceptibility test results were also significantly higher in the isolates deemed MDR (MDR: 6.5 vs non-MDR 1.7, p<0.01, *t-test*).

To ascertain whether there was a correlation between MDR and non-MDR isolates based on the number of resistant anti-microbial tests, a ROC curve was

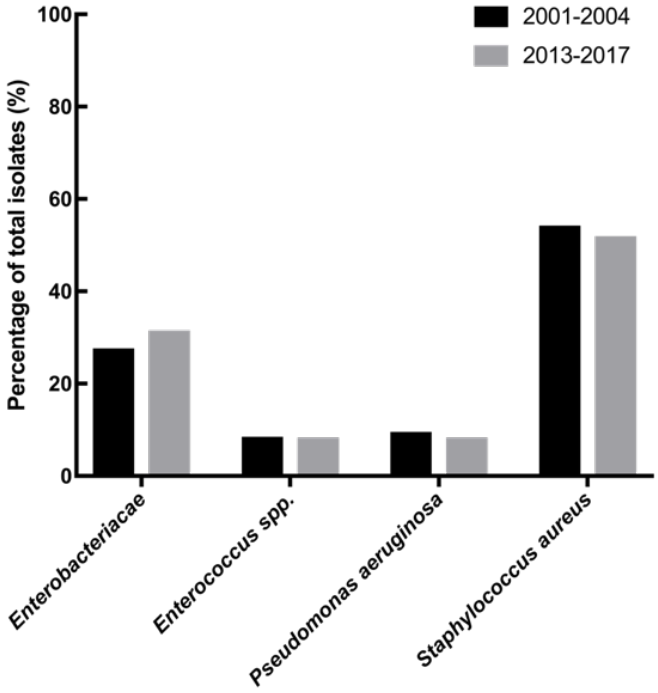


Figure 5.2: Histogram of the proportions of isolates in the two cohorts 2001 – 2004 cohort = black bins; 2013 – 2017 = grey bins.

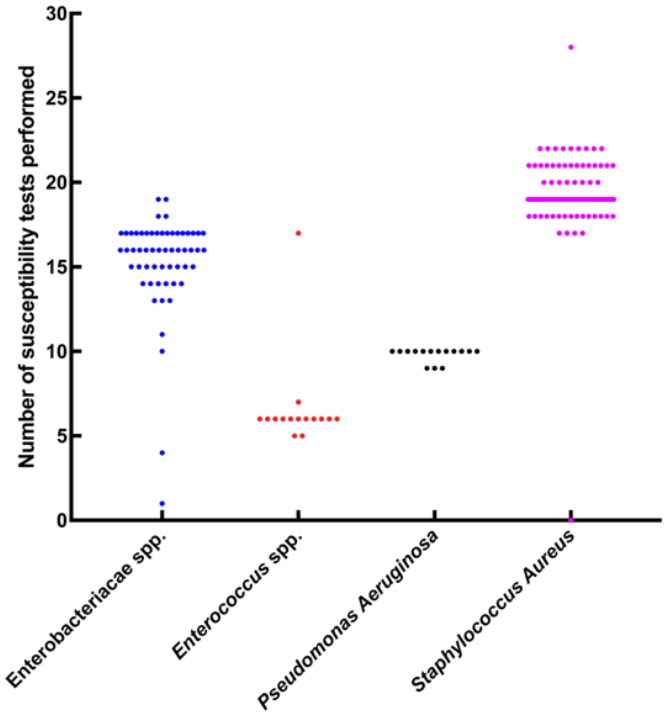


Figure 5.3: Dot plot of the number of sensitivities for each of the ESCMID groups for 2013 - 2017 Blue = *Enterobacteriacae*; Red = *Enterococcus*; Black = *Pseudomonas aeruginosa*; Pink = *S. aureus*

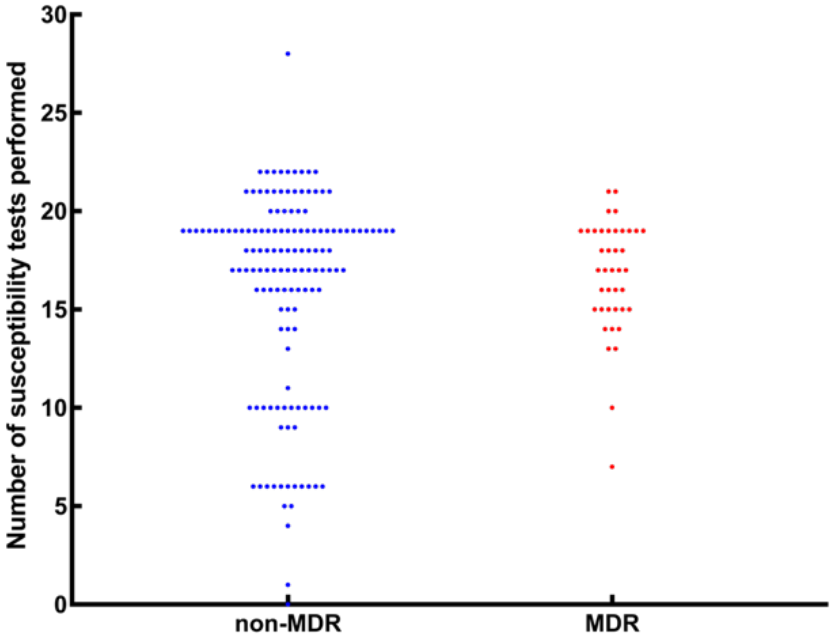


Figure 5.4: Dot plot of total antibiotic tests of MDR versus total antibiotic tests of non-MDR isolates. There are similar number of susceptibility tests performed between the two cohorts (p=*0.5*). Blue = non-MDR isolates; red = MDR isolates.

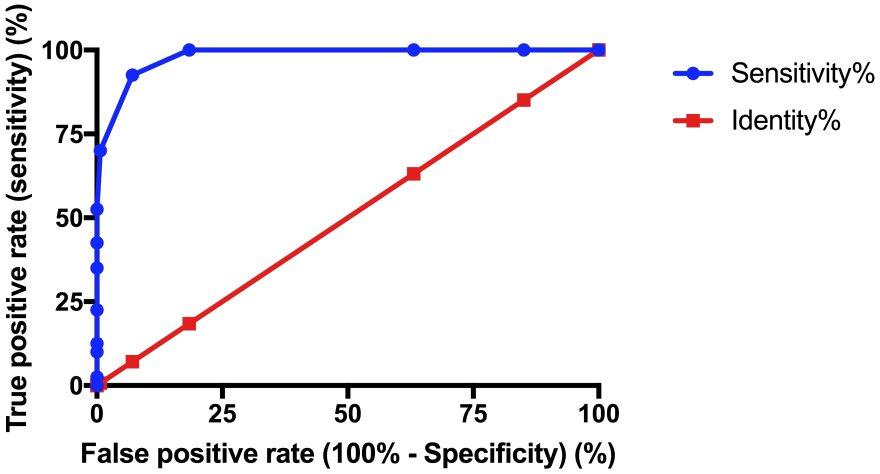


Figure 5.5: ROC curve generated from the number of resistant anti-biotic susceptibility tests for bacteria defined by ESCMID as MDR and those defined by ESCMID as non-MDR. From the 2013 - 2017 cohort. The AUC of 98.1% confirms that the number of resistant anti-biotic susceptibility tests has a high predictive value as a measure for prediction of whether a bacterial isolate is 'ESCMID MDR'.

plotted, figure 5.5. This gave an area under the curve (AUC) of 98.1 (95% CI 96.6% – 99.6%) demonstrating an excellent correlation between number of resistant susceptibility tests and MDR status.

5. Retrospective limitations and BACH version 2

To quantify the optimum transition point for defining MDR and non-MDR isolates using this method, the specificity and sensitivity at each threshold was calculated, figure 5.6. Specificity and sensitivity were calculated using the equations 5.1 and 5.2. The optimum threshold can then be calculated by using the Youden index [YI], denoted in equation 5.3 (Youden, 1950). This demonstrated that the optimal cut-off point was ≥4 resistant susceptibility tests (YI = 0.85). This was confirmed by plotting the percentage of resistant susceptibility tests against the total number of tests for both MDR and non-MDR isolates, figure 5.7. This demonstrated that 92.5% of MDR isolates were placed above the ≥4 resistant susceptibility test line.

$$\text{Sensitivity} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}} \tag{5.1}$$

$$\text{Specificity} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}} \tag{5.2}$$

$$\text{Youden Index} = (\text{sensitivity} + \text{specificity}) - 1 \tag{5.3}$$

Using the criteria of resistance to ≥4 anti-biotic tests to denote MDR-equivalence gave a sensitivity of 92.5% (95% CI 79.6 – 98.4%) and specificity of 92.9% (95% CI 87.3 – 96.6%). Whilst using ≥3 resistant antibiotic susceptibilities as an equivalence of MDR gives a sensitivity of 100.0% (95% CI 91.2% - 100.0%), the sensitivity was 81.6% (95% CI 74.2 – 87.6%). This equates to a false positive rate 18.4%, which, for many medical conditions would be deemed too high to use in clinical practice. There were 47 isolates (26.0%) that had resistance to ≥4 of the antibiotics that were tested. This compared to 40 (22.1%) that were classified as MDR when using the ESCMID criteria.

The number of sensitivities tested in the ESCMID classifiable bacteria was similar in both those that were deemed MDR and those deemed non-MDR. In this cohort, using the number of resistant tests as an estimate of MDR had a

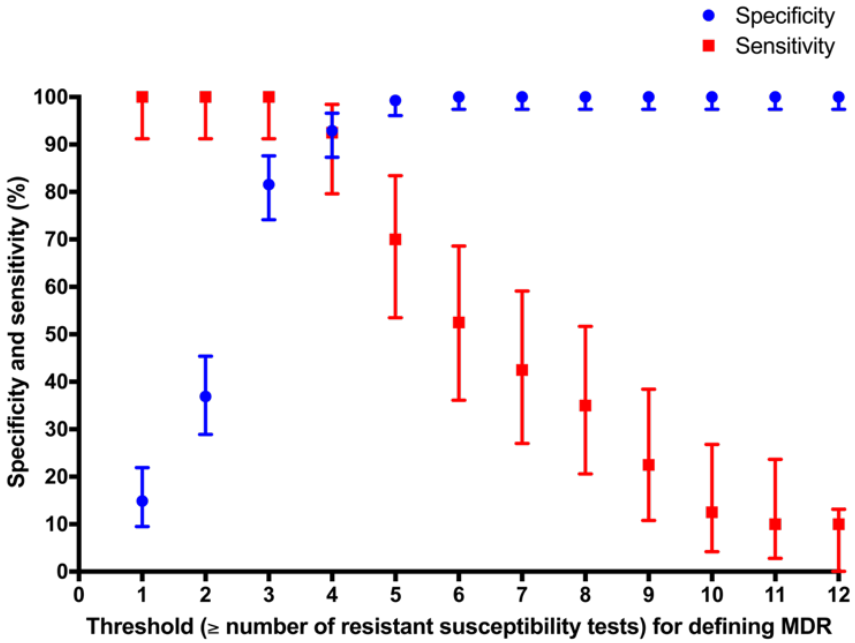


Figure 5.6: Plot of sensitivity and specificity of using the ≥ number of resistant susceptibility tests to as a measure of MDR as defined by ESCMID. Error bars are 95% confidence intervals. Red=sensitivity; Blue=specificity.

predictive value of 98.1%. It is likely that using the susceptibility panels, isolates exhibiting resistance to ≥4 anti-biotics are likely to be deemed as MDR. To validate this method of classification, this will be applied to a similar cohort from the same centre from 2001 – 2004.

5.3.5 Part (ii): Validation of defining MDR using number of resistant susceptibility tests

The individual proportion of *Enterococcus* spp., *Pseudomonas aeruginosa* and *Enterobacteriacae* remained similar between the study periods, figure 5.4. The proportion of MDR isolates were also similar in both cohorts (2001-2004: 17.2% vs. 2013-2017: 15.2%, p=0.44, χ^2 *test*). However, there was a decrease in the proportion of MRSA isolated in the later cohort by 37.0% (2001-2004: 30.8% vs 2013-2017: 11.4%, $p<0.05$, χ^2 *test*).

The mean number of susceptibility tests performed in the 2001 – 2004 cohort was 12.4, which was statistically fewer than in the 2013 – 2017 cohort (p<0.001, *unpaired t-test*). However, a similar proportion of isolates were deemed MDR

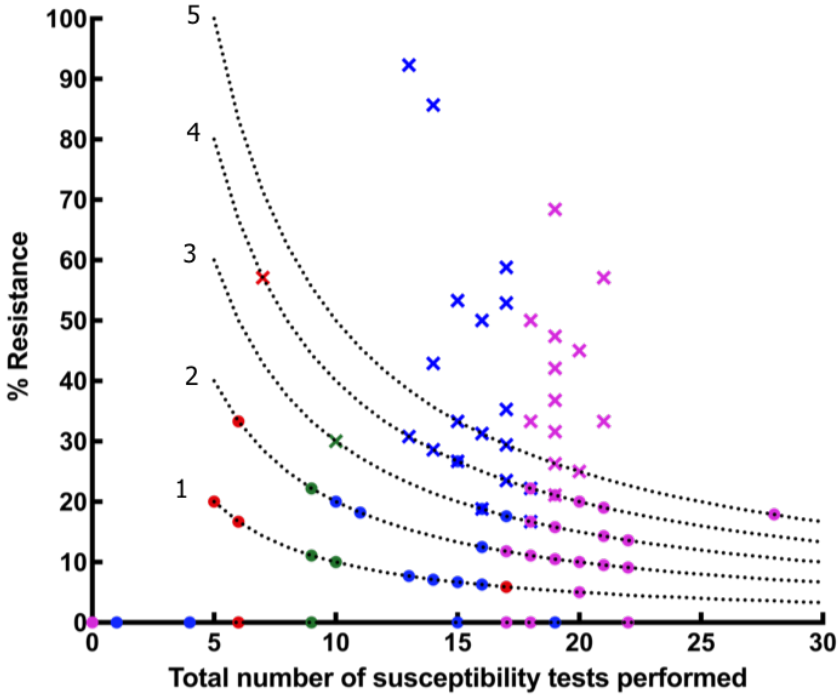


Figure 5.7: Scatter plot of number of anti-microbial tests versus percentage resistant tests for each of the individual ESCMD classifiable isolates in the 2013 – 2017 cohort. Blue = *Enterobacteriacae*, pink = *S. aureus*, green = *Pseudomonas aeruginosa*, red = *Enterococcus* spp. Dots = ESCMID non-MDR, crosses = ESCMID MDR. The black dotted lines represent a number of different thresholds, varying from 1 – 5 resistant susceptibility tests as indicated on the graph. Isolates below each dotted line are deemed 'low resistance' and those above the dotted line are deemed 'high resistance'.

according to the ESCMID criteria (32/94, 33.0% vs. 40/181, 22.1%, p=0.06, χ^2 *test*). One explanation for this could be because of changes to the antibiotic break points used to define isolate resistance in the time period between the two cohorts. The ROC curve demonstrated that anti-microbial resistance to susceptibility tests gave a 91.0% (95% CI 85.2% - 96.8%) predictive value of ESCMID MDR status in the 2001 – 2004 cohort, figure 5.8.

Using the criteria of ≥4 antibiotics would give a good estimation of MDR and therefore antimicrobial options; the total number of susceptibility tests performed were plotted against the percentage resistance of each isolate, figure 5.9. The 2001 – 2004 cohort gave a specificity of 85.5% (95% CI 74.2 – 93.1) and sensitivity of 87.5% (95% CI 71.0 – 96.5%). As in the 2013-2017 cohort, using ≥4 antibiotics was the optimal threshold, giving a Youden index of 0.74. This was confirmed by

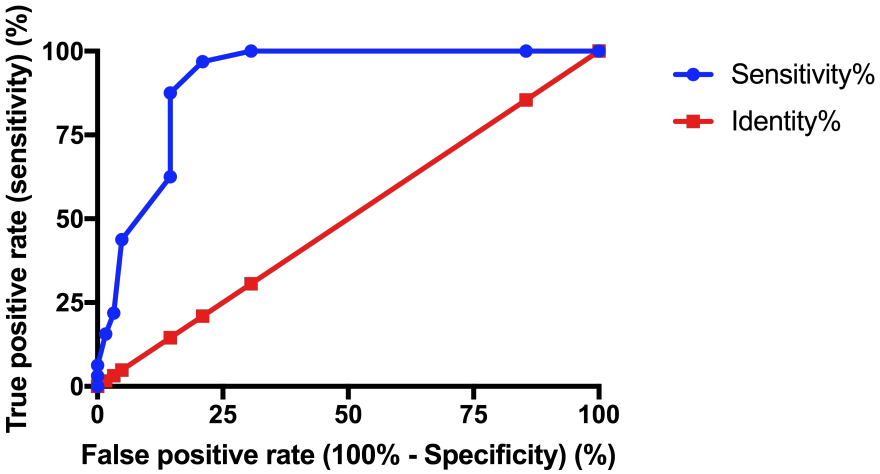


Figure 5.8: ROC of the 2001-2004 cohort demonstrating the correlation between using number of antibiotic tests and whether n isolate is deemed MDR. AUC = 91.0% (95% CI 85.2% - 96.8%).

the sensitivity and specificity intersecting at this point, figure 5.10.

In the 2001-2004 cohort, the false positive rate for using ≥4 resistant susceptibility test results to define whether an isolate should be deemed MDR was 9.6% (9/94). Of these 9 isolates, *Pseudomonas aeruginosa* was the commonest (7/9, 77.8%), and was increased from zero false positives in the 2013-2017 cohort. To explain this increase the anti-biotics sensitivities tested were analysed. One difference was that 100.0% of the antibiotics tested in the 2013-2017 cohort for Pseudomonas aeruginosa were part of the ESCMID criteria which compares to 57.9% of the antibiotic sensitivities tested from the 2001-2004 cohort. As previously discussed, this may be explained by a number of changes to guidelines on susceptibility testing and anti-biotic breakpoints during the 13 year period that separates the two cohorts (Andrews, 2007). Furthermore, of the tests that were not part of the ESCMID criteria, 75.6% were resistant, increasing the chance of a false positive result.

The remaining two isolates that were deemed false positives, comprised an *Enterobacteriacae* spp. and an *Enterococcus* spp.. The false positive *Enterobacteriacae* was a *Proteus mirabilis* and had a total of 20 antibiotic susceptibility tests measured. This was the highest number of susceptibility tests performed in the *Enterobacteriacae* group (average of 11.9 tests performed per isolate, range 9 – 20, SD 1.9). In

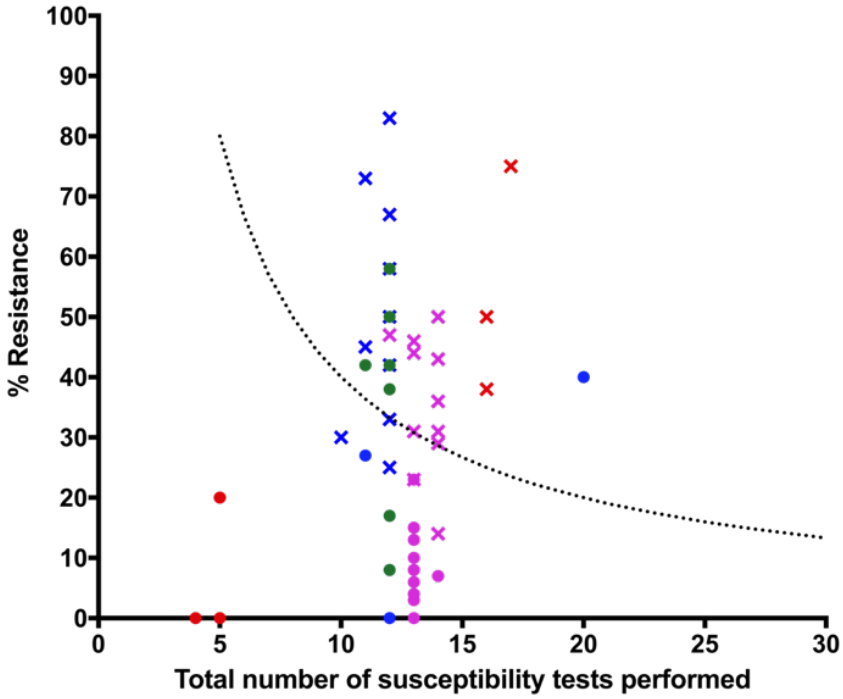


Figure 5.9: Scatter plot of number of anti-microbial tests versus percentage resistant tests for each of the individual ESCMD classifiable isolates in the 2001 − 2004 cohort. Blue = *Enterobacteriacae*, pink = *S. aureus*, green = *Pseudomonas aeruginosa*, red = *Enterococcus* spp. Dots = ESCMID non-MDR, crosses = ESCMID MDR. Isolates below each dotted line are deemed 'low resistance' and those above the dotted line are deemed 'high resistance'.

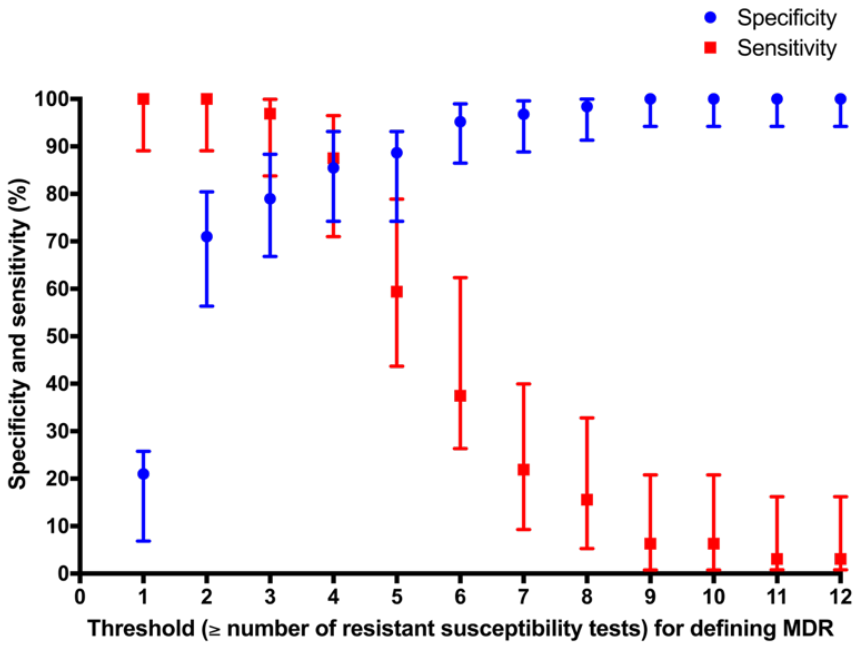


Figure 5.10: Plot of sensitivity and specificity of using the ≥ number of resistant susceptibility tests as a measure of MDR as defined by ESCMID.

contrast to *Pseudomonas aeruginosa*, 97.8% of susceptibility tests performed for the *Enterobacteriacae* group were part of the ESCMID criteria. However, the false positive *Proteus mirabilis* accounted for 6 out of 7 non-ESCMID criteria sensitivities tested with all 6 being resistant. Of these, *Proteus mirabilis* possesses intrinsic resistance to 5 of 6 anti-biotics tested and therefore resistance would have been expected (erythromycin, penicillin, vancomycin, linezolid and fusidic acid) (Livermore et al., 2001). In the 16 years following this cohort, guidelines have been introduced to ensure efficiency and economy of antibiotics susceptibility testing (EUCAST). These serve to eliminate performing susceptibility testing for antibiotics to which micro-organisms are intrinsically resistant.

For *Enterococcus* spp., a mean of 9.1 tests were performed on each isolate (range 4 – 17, SD 5.8). Of the three isolates that had $\geq$4 antibiotic resistant tests, two were deemed MDR according to ESCMID. Interestingly, all three of these isolates were tested against 16 (n=2) or 17 (n=1) antibiotics, whereas the remainder of this group only had four (n=1) or five (n=4) susceptibility tests performed. This discrepancy between the total number of antibiotic tests between isolates could account for the false positive *Enterococcus* spp.. Similar to *Pseudomonas aeruginosa*, susceptibility tests to antibiotics from the ESCMID criteria comprised only 43.8% of all tests within the *Enterococcus* spp. group.

Using this criteria to define 'resistance status' a total of 37 (37/94, 39.4%) isolates were classified into the higher resistant group. This compared to the ESCMID criteria where 32 (32/94, 34.0%) were classified in the higher resistance (MDR) group. Overall, for the 2001-2004 cohort, there was an agreement of 86.2% between the ESCMID MDR and the 'resistance status' methods of classification. The false positive rate can be explained by a variance in the number and type of anti-biotic sensitivities that are reported, which has been streamlined over this 16 year study period.

5.3.6 Part (iii): Application to non-ESCMID classifiable isolates

In the 2013 – 2017 cohort, there were a total of 66 (26.7%) isolates that could not be classified according to the ESCMID criteria. By applying the method of defining isolates with increased resistance using ≥4 resistant susceptibility test results, all isolates were then able to be classified, figure 5.11.

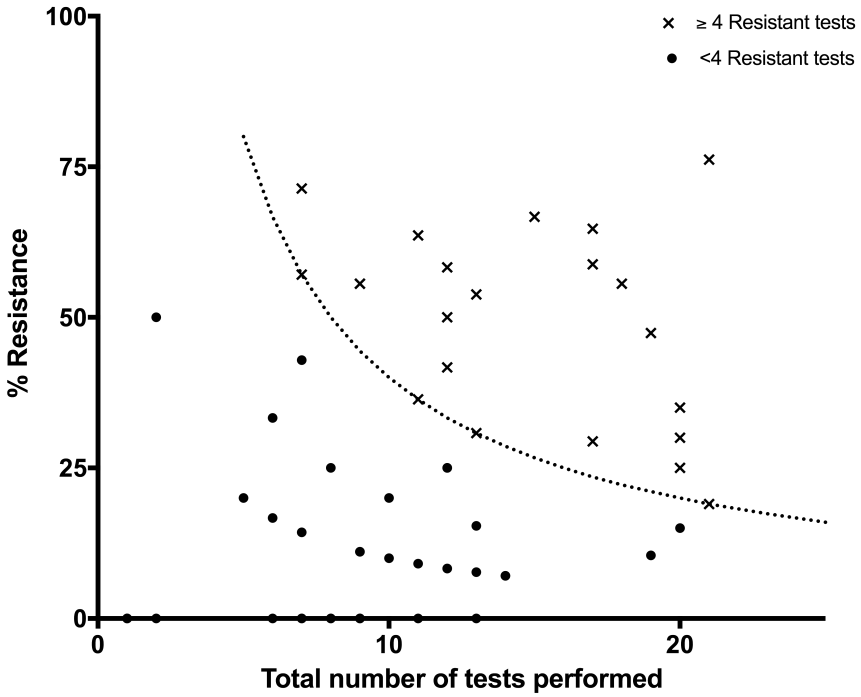


Figure 5.11: Scatter plot of percentage resistance against the total number of sensitivity tests performed on each of the ESCMID non-classifiable isolates. Crosses denoted those that had ≥4 resistant susceptibility tests and circles denote those that had <4 resistant tests.

Of the 66 isolates, 44 (44/66, 66.7%) were defined as having 'low resistance' with a mean of 0.86 resistant susceptibility test results (SD 1.0) and received an average of 5.7 susceptibility tests performed per isolate (range 0 – 20). In comparison to the group with 'high resistant' isolates, a similar number of tests were performed per isolate (14.6 tests per isolate, SD 4.6, p=0.54, *t-test*) but more of these were resistant at an average of 6.9 per isolate (SD 3.0, p<0.001, *t-test*).

5.3.7 Discussion

The number of resistant susceptibility test results had a 98.1% correlation with the MDR status according to ESCMID. Despite this, there are some pragmatic problems when using this system in clinical practice.

Firstly, using the number of resistant susceptibility tests as a measure of bacterial resistance relies on the treating clinician having access to the full antibiotic susceptibility panel that has been tested by the laboratory. This rarely occurs in clinical practice due to prescribing restrictions placed on antibiotics for non-specialist clinicians. Alternatively, a full susceptibility panel may not be given because it allows more room for error within interpretation, preventing inappropriate antibiotic prescribing. An alternative method of defining whether an isolate is high or low resistance using the percentage of sensitive tests is presented in appendix D.

Secondly, the panel of susceptible tests performed varies throughout different institutions. As previously mentioned, guidelines for susceptibility testing used throughout the UK are produced by BSAC and EUCAST. However, these are guidelines and there may be certain local policies that are used in some centres. As demonstrated, the individual susceptibility test results varied between the two cohorts, possibly due to the introduction of these guidelines. However, especially in the earlier cohort (2001 – 2004), certain isolates received susceptibility tests for antibiotics for which they possess intrinsic resistance. In these cases, the number of resistant susceptibility test results is pushed towards the threshold that would deem that isolate 'high resistance'. This is one of the shortfalls of simplifying the ESCMID definitions of MDR, XDR and PDR, which take into account resistance to specifically relevant antibiotics and antibiotic classes.

Finally, it is not known how MDR isolates affect treatment outcomes and management in osteomyelitis. It follows, as the number of resistant susceptibility tests increase and the options become fewer, the choice of antibiotic becomes more difficult. However, 77.5% of isolates that met the ESCMID criteria for MDR had sensitivities to >50% of the susceptibilities tested. Currently, it is not clear how these isolates contribute to poor outcomes in osteomyelitis, but it is

evident that as the number of treatments options become fewer, antimicrobial management becomes more complex.

5.3.8 Summary

In summary, this in depth analysis has demonstrated the complexities of classifying the antimicrobial options. It has demonstrated that even when an isolate is deemed MDR according to ESCMID, there may still be various 'anti-microbial options' available. However, the analysis has demonstrated an equivalent method of applying MDR to non-ESCMID classifiable isolates. It is not clear at this point exactly how to use this for defining the 'anti-microbial options category' in the B.A.C.H. classification for osteomyelitis. Feedback from the inter-observer assessment will be combined with this analysis to optimise this part of the classification system, in chapter 7.

On the basis of the limitations from the retrospective cohort, the anti-microbial options category will be altered to: A1 or Ax: treatment options available; A2: limited treatment options available (MDR according to ESCMID) OR resistance to anti-biofilm antibiotics in the presence of an implant OR isolates that are not part of the ESCMID guidelines with resistance to appropriate antibiotics and A3: Few or no medical treatment options available (XDR or PDR according to ESCMID).

5.4 Coverage of the soft tissues

The retrospective analysis demonstrated that the coverage of the soft tissue variable was able to be applied to a cohort in which surgery has already been performed. It is important to note that 82.6% of the cases that required plastic surgical expertise, the site of infection was the tibia. This information will be important in highlighting which cases are more likely to require plastic surgical expertise when disseminating how to use the classification system. A more complete assessment of the coverage of the soft tissues will be made in the inter-user analysis, where the classification will be applied prior to debridement surgery.

5.5 Host status

In the retrospective assessment, 79.2% of patients were deemed to be H2 hosts and had multiple comorbidities that required optimisation prior to surgery. The purpose of the BACH classification system is to stratify patients into 'low risk' and 'high risk' groups that can guide both prognosis and management. The high proportion of patients who are deemed H2 means that this distinction is too broad to stratify patients in this manner. To define an H2 host, the classification system should include specific co-morbidities that are unable to be optimised that compound the treatment of osteomyelitis. This will be discussed in the following sections.

5.5.1 Optimisation

Version 1 of the B.A.C.H. classification system defined H1 as patients who do not require optimisation and H2 as patients who required specialist intervention prior to definitive surgery. In the retrospective analysis, it was possible to classify patients on the basis of co-morbidity that necessitated optimisation. However, this was limited by three factors. Firstly, as previously discussed, the definition of the term "optimisation" is subjective and will hold a different meaning to different clinicians in different patients. Secondly, using medical notes instead of real time clinical assessment to define whether a patient required optimisation relies on the quality of the documentation. This may show considerable variability because optimisation addresses numerous medical conditions and patients are referred to the surgical service. Finally, it was difficult to assess whether the patients had received 'optimisation' and whether this 'optimisation' had been successful prior to surgical intervention. It was unclear whether following optimisation the patient would stay in the H2 group or, once optimised return to the H1 group.

As discussed in chapter 3, optimisation implies that specific medical co-morbidities are modifiable or reversible. However, it does not specify the severity of the condition. All patients should be assessed for 'optimisation' need prior to elective surgery in a pre-operative assessment clinic (Podmore et al., 2018). This serves to ensure the best possible outcomes following surgery. However, the terminology used in

version 1 of the classification system needs to be refined to ensure that patients are stratified appropriately and that health care workers understand the term correctly.

5.5.2 Host status in osteomyelitis

The host status should be used to stratify co-morbidity that are present despite specialist intervention or optimisation. If co-morbidities are able to be successfully optimised the patient will be designated as an H1. The H2 category should address specific co-morbidities that will compound the treatment of osteomyelitis that are still present regardless of whether the patient undergoes optimisation. These co-morbidities may be systemic, such as immunosuppression, or local, such as vascular insufficiency to the site of infection. Vascular insufficiency may be secondary to a variety of pathology such as atherosclerosis in peripheral vascular disease or diabetes mellitus. Finally, due to changes in the local anatomy, osteomyelitis that has reoccurred at the same site with previous appropriate surgical intervention should be stratified into the H2 group.

In summary, there will be three groups used for the host status variable. These are:

- H1: Fit and well with optimisation if required
- H2 Definitive surgery possible but with continued host compromise (micro / macrovascular disrpution to affected limb of irreversible immunocompromise) after optimisation *or* recurrent osteomyelitis after previous debridement.
- H3 unfit for definitive surgery despite specialist intervention *or* patient declines an operation.

5.6 B.A.C.H. version 2

Accounting for these changes, the B.A.C.H. classification system will be modified as shown in figure 5.12. This classification system will be used in the inter-observer analysis, chapter 6.

	Bone involvement (B):	**Antimicrobial options (A):**	**Coverage by soft tissue (C):**	**Host status (H):**
Uncomplicated	B_1: Cavitary infection without joint involvement	A_1: treatment options available or (A_X): unknown / no anti-microbial growth	C_1: Direct closure possible	H_1: fit for definitive surgery with optimisation if required
Complex: Specialist intervention needed	B_2: Segmental infection without joint involvement	A_2: limited treatment options available (MDR according to the ESCMID guidelines) **or** Resistance to anti-biofilm antibiotics in presence of an implant **or** Bacteria that is not part of the ESCMID guidelines with resistance to appropriate anti-microbial agent	C_2: Direct closure not possible; plastic surgery expertise required	H_2: definitive surgery possible but with continued host compromise (micro / macrovascular disruption to affected limb or irreversible immunocompromise) after optimisation **or** Recurrent osteomyelitis after previous debridement
	B_3: Any osteomyelitis with associated joint involvement			
Limited treatment options available		A_3: No medical treatment options available (XDR or PDR according to the ESCMID guidelines)		H_3: unfit for definitive surgery despite specialist intervention / patient refusal for surgery

Figure 5.12: Version 2 of the BACH classification system for long bone osteomyelitis. Version 2 has altered the terminology of the Bone involvement variable, the anti-microbial options variable and the host status variable.

6 Inter-user Assessment

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6.1 Introduction

A second version of the BACH classification system was proposed in chapter 5. It addressed a number of key issues encountered during the retrospective

analysis (chapter 4). To assess the application of BACH version 2, an inter-observer assessment was performed. This will serve three key functions. Firstly, it will allow the development of a 'key' that will be used to disseminate the classification system to clinicians and guide how it is used. Secondly, it will give a measure of the reproducibility of the classification amongst a range of users who have a variety of clinical experience. Finally, it will demonstrate specific areas of the classification system that need to be addressed to make a BACH version 3 that will be presented in chapter 7.

To achieve these aims, the inter-user assessment consisted of two parts. These were:

(i) **Pilot assessment** – Four users received oral and written instructions regarding how to use the classification system. After reading the briefing instructions, the users classified 20 cases of long bone osteomyelitis. After completion of these cases, feedback was sought from the users and then utilised to optimise the case presentations and the user 'key' for use in the full assessment.

(ii) **Full assessment** – The full assessment included 30 users with the aim of assessing the reproducibility of the BACH classification system. Each user received the optimised user key and was asked to classify the same 20 cases. The 30 users represented a number of specialities from a range of centres throughout Europe and North America. Feedback was sought from users and detailed case analysis was then performed in order to improve the classification system.

6.2 Case selection

Twenty patients were chosen from two centres (Addenbrooke's Hospital, Cambridge and the Bone Infection Unit, Oxford). The cases were selected from a pool of patients who attended the two centres between 2015 – 2017. This was to capture a diverse range of case presentation and ensure that cases would be unfamiliar to all users. Cases were classified by the DPhil student (AJH) and 20 cases with a variety of classification scores were chosen, table 6.1. Information was extracted from the medical notes relating to each of the variables, table 6.1. The

cases were presented using an encrypted password protected online form. Patient information was handled according to Caldicott principles and all patient identifiable information was removed.

Variable	% of cohort (n)	Information provided
Bone involvement		
B1	65.0% (13)	Imaging (including CT, MRI, x-ray and PET-CT)
B2	10.0% (2)	Site of infection
B3	25.0% (5)	Previous surgeries
		Age at presentation
Anti-microbial options		
Ax	35.0% (7)	Isolates
A1	45.0% (9)	Full antibiotic susceptibility panels
A2	10.0% (2)	Truncated susceptibility panels
A3	10.0% (2)	
Coverage of the Soft tissues		
C1	35.0% (7)	Photographs of the limb
C2	65.0% (13)	
Host status		
H1	60.0% (12)	List of co-morbidity with the result of recent investigations
H2	40.0% (8)	Regular medications
H3	0.0%	Surgical history
		Allergy status

Table 6.1: Summary of the cases for the inter-user assessment. The number of each cases is presented for each variable with the corresponding clinical information that was provided on the online form.

6.3 Part (i): Pilot study

6.3.1 Users and Methods

The aim of the pilot study was to assess and optimise the user key. The pilot study included four observers. These observers were chosen because they represented both surgical and medical specialities and were willing to provide feedback of both the patient cases and the classification key.

The observers were divided into two groups of two. The first group received an electronic copy of the user key only. The second group were provided with the user key but also had the DPhil student present whilst and after they had read the key. During this time, the observers in this group were able to ask and discuss aspects of the key that they did not understand. This was to ascertain components of the key that may have required further explanation. The DPhil student did

not provide any support during their classification of the 20 cases. By comparing the classifications made by the two groups, the DPhil student was able to observe whether challenges in the application of the classification system were attributable to the user key or to the classification system itself.

The key was supplied to all users as a PDF (Portable Document Format) document and was divided into three parts. Part 1 explained the purpose of the study, part 2 explained each variable in turn and part 3 gave a table of examples. Version 1 of the key is shown in appendix B.

Following the briefing, the users completed the cases without a time limit. Feedback was obtained after the users completed all of the cases either as part of the online form, or verbally at the end of the assessment. Feedback was obtained with regard to format of the case presentation, content of the case presentation and ease of using the key.

6.3.2 Results of pilot study

Results were analysed according to the reference classification made by the DPhil student and accuracy of application were presented as a percentage. For the pilot study, the mean score was 86.9% (SD 9.3%, range 73.8% - 95.0%) when compared to the reference answers. The highest scoring variable was the coverage of the soft tissues at 92.5% and the lowest scoring variable was the bone involvement (B) at 73.8%, figure 6.1. The mean score for the group who received both written and oral instruction was 93.1% and the group who received written instruction only was 80.6%.

The most notable difference between the two methods of dissemination was in the 'B' category, figure 6.1. Both users who were given written instructions alone scored 55.0%, which was significantly lower than the users who were given written and oral instruction (mean 92.5%, $P<0.05$, *unpaired t-test*). The 'B' variable gave a higher co-efficient of variation compared to the other variables (B: 0.29; A: 0.082; C: 0.13; H: 0.080). The lowest score in each of the 'A', 'C' and 'H' variable was in a user who received written instructions alone.

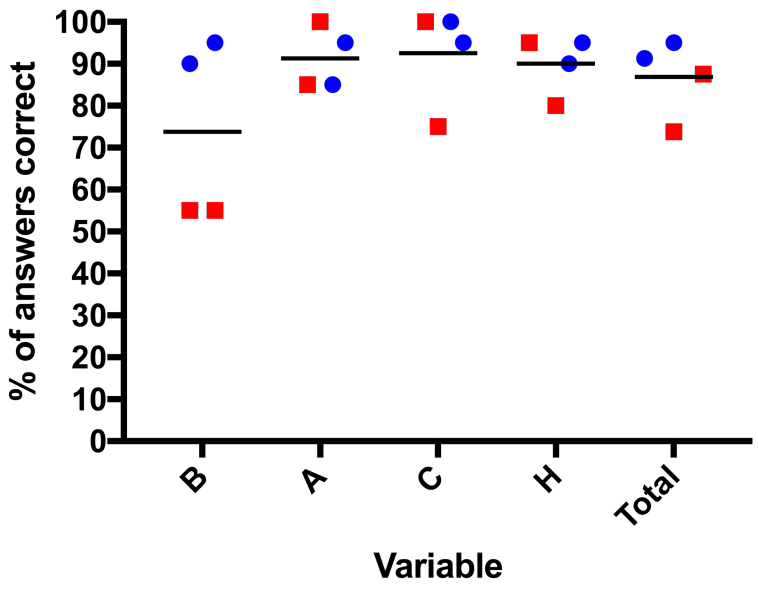


Figure 6.1: Dot plot of the results from the pilot study for the inter-user assessment. Blue dots are users who received both written and oral discussion, red dots are those who received written instructions alone. Black line is the overall average score for each variable.

6.3.3 Feedback: Key development

The aim of the pilot study was to optimise the user 'key' and the case presentations that would be used for the full inter-user assessment. The development of the user 'key' will be discussed first.

Firstly, further guidance was required by users to better understand the application of the bone involvement variable. The original version of the user key included a custom diagram as an anterior to posterior view of the tibia, figure 6.2a. This was intended as a method of depicting cavitary versus segmental bone involvement. However, an axial view through the width of the bone functioned as a superior method to make this classification.

To address this issue, the diagram that depicted the 'B' variable was modified to include axial images in order to further illustrate the concept of a cavitary versus segmental involvement, figure 6.2b. It also attempted to highlight that an image in the longitudinal plane may misrepresent a cavitary for segmental involvement. In addition, it was specified that infected non-union should be classified as a B2

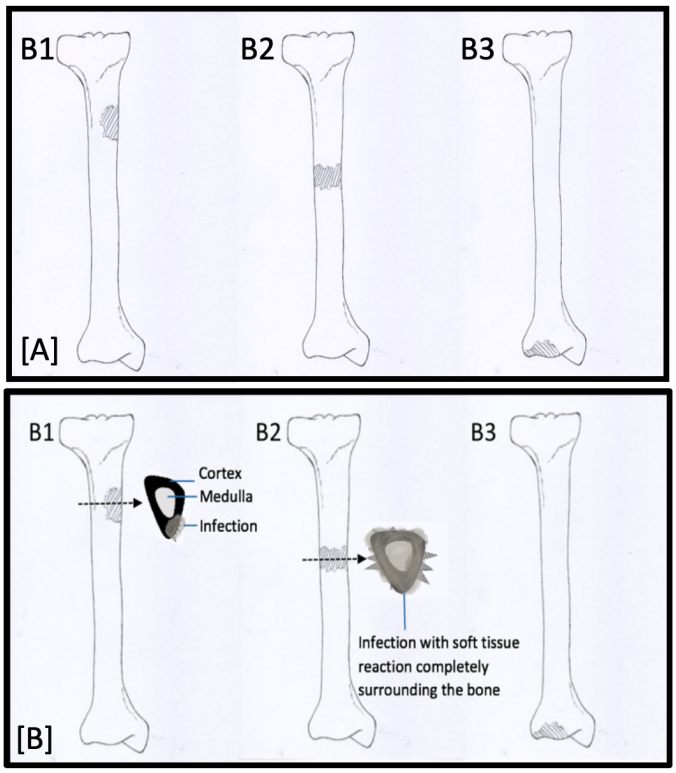


Figure 6.2: (A) Diagram of the bone involvement variable from version 1 of the inter-user key. (B) Diagram of the bone invovlement variable from version 2 of the inter-user key. The updated diagram used in version 2 of the inter-user key helped to explain the bone involvement variable by using cross sectional axial images.

unless the infection extended into the joint, where it would be classified as a B3.

For the anti-microbial options variable, feedback demonstrated that none of the users were familiar with the ESCMID criteria that guided the classification of antimicrobial resistance. However, the two users in the group who received both written and oral instruction were sign-posted to the ESCMID criteria (Magiorakos et al., 2012). This group scored higher than the group who received the written instruction alone. To address this issue, the link for the ESCMID criteria was added to the homepage of the online form to ensure that users could reference this if needed.

The coverage of the soft tissues variable, returned the highest score from all users at 92.5%. None of the users in the pilot study were specialist plastic surgeons. Feedback demonstrated that users had challenges in making the decision regarding the involvement of a plastic surgeon. The cases varied in difficulty

with some cases presenting completely healthy soft tissues, some presenting soft tissues that were severely compromised and others that were less polarised. Those cases where the soft tissues were clearly healthy or clearly severely compromised were scored correctly, however, the cases that were less definitive gave rise to discrepancies between the users.

The host status scored highly, at 90.0%, and there was a low co-efficient of variation (0.081) between users in the pilot assessment. However, feedback suggested that it was difficult to define the level of co-morbidity that would classify a patient as an H2. To address this, the user key was modified to include illustrative examples aimed to assist users in making the classification.

Finally, to ensure that the key was accessed and utilised by the user in the full inter-user assessment, part ii of this chapter, the password required to gain access to the online form was added at the end of the inter-user key. The full version 2 of the user key is presented in appendix E.

6.3.4 Feedback: Case development

When designing the case presentation for use in the online form, it was important to include relevant information only. Originally, the cases were presented as a vignette using the chronological order of a classical medical history (history of presenting complaint, past medical history, examination findings, results of investigations including imaging and microbiology). However, feedback demonstrated that this became laborious for the users as they were required to classify 20 cases in this manner. To improve the accessibility of the online form and vignettes for the classification system, the clinical information was presented in four sections that corresponded to each classification variable, table 6.2.

Feedback demonstrated that users experienced difficulty in the interpretation of clinical imaging. To address this, the radiology reports were appended to as many cases as possible to assist in making the classification, noting that these are commonly available in clinical practice. In addition, where the medical history included one of fracture, information on fracture healing and timescale was provided

	'B'	'A'	'C'	'H'
Osteomyelitis history	✓			✓
Past medical history				✓
Examination findings and photographs			✓	
Imaging	✓			
Results from deep bone biopsy		✓		

Table 6.2: The information used to classify each variable for the inter-user assessment.



Figure 6.3: MRI slice demonstrating a B3 osteomyelitis with joint involvement. Arrow at (a) denotes the extension of osteomyelitis into the joint.

so that the user would reasonably be able to make a decision regarding whether the case was an infected non-union or not. One specific case was highlighted due to ambiguous imaging as to whether there was joint involvement on the MRI, figure 6.3. Based on the image provided, users reported difficulty in definitively classifying this as a B1 or B3. In view of this, and in the absence of an available report for the MRI, information stating that the patient did not have pain when moving the ankle was appended to this case to imply that clinically, the joint was not

involved and that the correct answer was a B1.

Feedback relating to the anti-microbial options variable was predominantly regarding the limited panels that were supplied to make the diagnosis of MDR, XDR or PDR. This was intentional, as it represents the real-life situation commonly encountered in clinical practice where not all susceptibility tests are released to the clinician. In addition, it underlines the need for inter-disciplinary collaboration, in particular when pathogens that exhibit anti-microbial resistance are isolated.

6.3.5 Summary of pilot study

In summary, the pilot study has addressed specific issues with the user key and the case presentations. Issues concerning the user key related predominantly to the description of the different variables. The key was adapted accordingly and can be found in appendix B. To improve the case presentations, the radiology reports were added to imaging (where possible) and the presentation format of the cases were refined. The pilot study demonstrated that the cases selected for the inter-observer assessment were appropriate to be used in the full assessment.

6.4 Part (ii): Full assessment

6.4.1 Users

Thirty users were recruited to perform the complete study. Recruitment was performed through clinical contacts of the DPhil student and supervisors. Users were required to be practising as either (i) a trauma and orthopaedic surgeon, (ii) a plastic surgeon or (iii) a physician (either infectious diseases, microbiologist or anaesthetist). Observers were required to have completed either membership examination or fellowship examination or equivalent in their speciality to be included.

The experience of users in treating osteomyelitis was assessed by how many cases of osteomyelitis they treat on average per month. Experience varied from those who treated <1 case per month (n=10) to those who treated ≥ 1 case per week (n=9). Users were predominantly consultants (15/30, 50%), but a variety of training grades were included. Clinicians from seven different countries were

recruited to perform the analysis, table 6.3. Throughout the UK, clinicians from a total of 8 different centres were recruited, which included district general hospitals and specialist bone infection units, table 6.4. All countries that were outside of the UK were University teaching hospitals. Of the 7 users who were from outside the UK, 6 were consultants and 1 was a senior clinical fellow.

6.4.2 Data and statistical analysis

Two principle methods of assessment for the full inter-observer assessment are presented. Firstly, to measure how well each of the questions were answered, the responses were marked according to the reference answers. This produced an 'accuracy score' for each user and each variable. The reference answer was derived by the DPhil student and supervisors following their completion of the inter-observer assessment. To analyse these scores, heatmaps were produced using MATLAB R2018a (MathWork, UK). The different attributes of each of the users (speciality, grade, centre type, centre location and regularity of osteomyelitis clinical exposure) were assessed using a multivariate linear regression to assess for correlation between scores and clinical attribute. This was performed using R in RStudio (RStudio Inc, Boston, MA).

$$F\kappa = \frac{\rho - \rho_e}{1 - \rho_e} \tag{6.1}$$

$\rho - \rho_e$ = case by case agreement accounting for the agreement by chance
$1 - \rho_e$ = total possible agreement accounting for agreement by chance
$F\kappa$ = Fliess' kappa value

To assess the degree of agreement between users, the Fleiss' kappa ($F\kappa$) was calculated. The $F\kappa$ is calculated on a case by case level of agreement ρ accounting for the agreement that may occur by chance $1 - \rho_e$, equation 6.1. This will give an $F\kappa$ value that lies between -1.0 and +1.0. An $F\kappa$ of +1.0 demonstrates a perfect agreement between raters and an $F\kappa$ of -1.0 demonstrates a perfectly negative agreement between raters. The $F\kappa$ will be interpreted according to Landis

and Koch, table 6.5 (Landis and Koch, 1977). The $F\kappa$ will be calculated using MATLAB R2018a (MathWork, UK).

Each variable was analysed using a heatmap which represents the proportion of correct scores in each category (for example figure 6.7a). Each variable was then analysed in turn using 2 graphs. The first graph (for example 6.7b) is a bar chart of each of the cases grouped by variable against the accuracy score. The mean score is plotted using a dotted line. This graph highlights the worst performing cases and allows comparison of these to the mean score for that variable. The second graph (for example figure 6.7c) demonstrates how each case was answered individually and allows the visualisation of the user assessed classification against the reference classification.

6.4.3 Overall results

The mean accuracy across all variables was 86.2% (95% CI 83.9% - 88.6%, SD 6.2%), with the 'C' variable scoring the highest at 92.5% (95% CI 88.5% - 95.6%, SD 8.2%) and the 'B' variable scoring the lowest at 77.0% (95% CI 71.2% - 82.8%, SD 15.5%), figure 6.4. The variable that had the highest agreement between users was the anti-microbial options variable with an $F\kappa$ of 0.815 (95% CI 0.811 – 0.819) which correlated to an 'almost perfect agreement'. The most variability was seen in the bone involvement variable with an $F\kappa$ of 0.479 (95% CI 0.475 – 0.483) which correlated to a 'fair agreement'. The $F\kappa$ for all the variables with corresponding interpretation are given in table 6.6. Multiple linear regression demonstrated that there was no correlation between any of the measured user clinical attributes (speciality, type of centre working in, grade, and monthly exposure to treatment of osteomyelitis) and ability to make the classification. However, UK users were more likely to classify the soft tissues according to the reference classification, (p=0.025), appendix C. Each variable will now be discussed in turn, highlighting the cases that appeared to be challenging to classify.

	Total (n)	Orthopaedic surgeon (n)	Plastic surgeon (n)	Physician (n)
Country:				
United Kingdom	23	10	3	10
Switzerland	2	1	0	1
Sweden	1	1	0	0
The Netherlands	1	0	0	1
Germany	1	1	0	0
Spain	1	0	0	1
United States of America	1	1	0	0

Table 6.3: A summary of the country and speciality of each of the users included in the assessment. The speciality is divided into surgical (orthopaedic and plastic surgeons) and physician (infectious disease physician, microbiologist or anaesthetist).

Centre	Type of centre	Number of users
Oxford University Hospitals	Bone Infection Unit	5
Cambridge University Hospitals	Bone Infection Team	4
Oxford University Hospitals	University teaching hospital	4
Cambridge University Hospitals	University teaching hospital	4
Mid-Essex Hospital	District general hospital	1
Broomfield Hospital	District general hospital	1
Stoke Mandeville Hospital	District general hospital	1
Harlow Hospital	District general hospital	1
Royal Berkshire Hospital, Reading	District general hospital	1
Salisbury Hospital	District general hospital	1

Table 6.4: A summary of the UK hospitals where users were practising. The type of centre and corresponding number of users are shown.

$F\kappa$	Degree of agreement
<0.01	Poor agreement
0.01 - 0.20	Slight agreement
0.21 - 0.40	Moderate agreement
0.41 - 0.60	Fair agreement
0.61 - 0.80	Substantial agreement
0.81 - 1.00	Almost perfect agreement

Table 6.5: The interpretation of the Fk according to Landis and Koh (Landis and Koch, 1977).

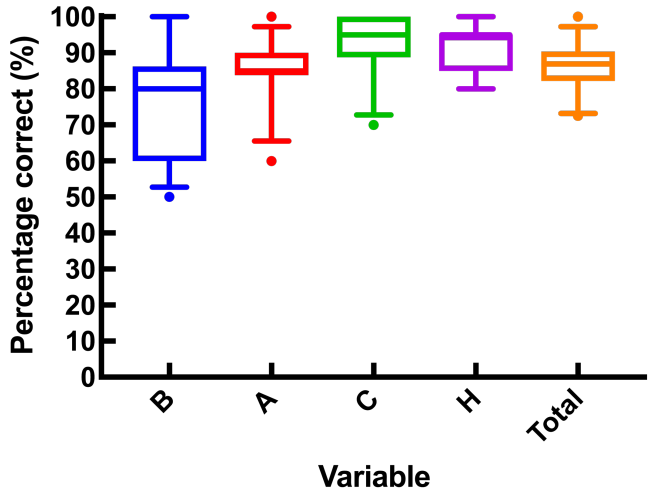


Figure 6.4: Box and whisker plot of each of the overall accuracy of inter-user classification of each of the individual variables of the BACH classification. Boxes are the inter-quartile range and the whiskers represent the 5%-95% range. Points outside this range are denoted by dots.

Variable	**Fk (95% CI)**	**Agreement**(Landis and Koch, 1977)
Bone involvement	0.479 (0.475 – 0.483)	Fair agreement
Antimicrobial options	0.815 (0.811 – 0.819)	Almost perfect agreement
Coverage of the soft tissues	0.729 (0.723 – 0.734)	Moderate agreement
Host status	0.719 (0.714 – 0.725)	Moderate agreement

Table 6.6: The $F\kappa$ for each of the BACH variables. The 95% confidence intervals are shown alongside the interpretation of the $F\kappa$ according to Landis and Koh.

6.4.4 Bone Involvement

6.4.4.1 Results

The bone involvement variable had both the lowest average score (77.0%, range 40.0% - 100.0%) and also the lowest $F\kappa$ agreement between users (0.479; 95% CI 0.475 – 0.483). The B1 cases were classified correctly 72.3% of the time which was the lowest of the B variables, figure 6.5a. B1 cases were incorrectly classified as B2 in 20.8% and B3 in 6.9%. Two of the 20 cases were B2 and these were answered correctly 95.0% of the time. B3 cases were classified correctly 82.0% of the time. B3 cases were incorrectly classified as B1 three times as frequently as they were classified as B2 (13.3% vs 4.7%), figure 6.5b. Figure 6.5c highlights the individual scores per case according to the 'B' variable.

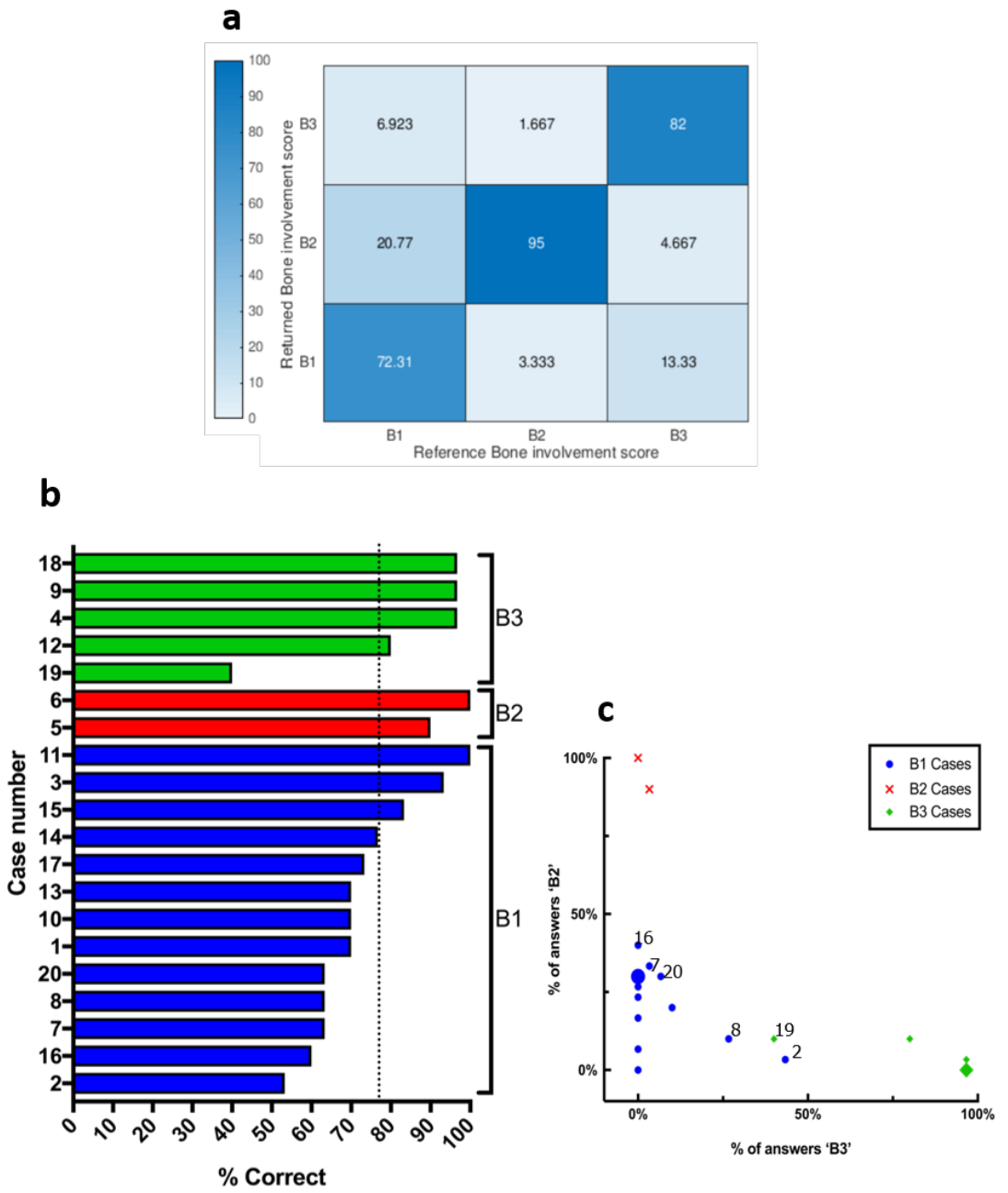


Figure 6.5: Summary of the results of the Bone involvement variable from the inter-user analysis.(a) Heatmap of the results for each of the B variables. Dark blue represents a high accuracy for the variables. (b) The case number organised by reference 'B' value and in order of accuracy. Green = B3, Red = B2 and Blue = B1. (c) Scatter density plot of the individual responses to the 20 cases. The six cases highlighted (16, 7, 20, 8, 19 and 2) are the cases that scored in the lowest quartile. Reference colours for each case are shown: Blue = B1, Red = B2 and Green = B3.

Case	Correct answer	% accuracy	Unclear radiology report	Distorted anatomy	Insufficient imaging	Insufficient clinical information
19	B3	40.0%	n/a		✓	✓
8	B1	63.3%	✓		✓	
2	B1	53.3%	n/a		✓	
16	B1	60.0%	n/a		✓	
20	B1	63.3%	n/a	✓	✓	✓
7	B1	63.3%	n/a		✓	

Table 6.7: Summary of the cases which were in the lowest quartile for accuracy for the 'B' variable. Reasons for why these cases did not have a high accuracy are included.

6.4.4.2 Discussion

The cases in the lowest quartile were reviewed in detail and a summary of potential reasons are given in table 6.7. The potential reasons included (i) insufficient imaging and clinical information to make the classification, (ii) radiology reports that were unclear and (iii) cases where a patient had distorted anatomy. These will be discussed below individually, using cases to illustrate each point.

(i) Insufficient imaging

All of the cases that scored in the lowest quartile had insufficient imaging to make the classification. Insufficient imaging was either due to a single slice of an MRI or CT or cases that did not provide MRI or CT images.

Single slices of CT or MRI were insufficient due to only allowing a 2-dimensional (2-D) visualisation of the pattern of infection. To classify the pattern of osteomyelitis as either cavitary, segmental or involving a joint, a 3-D assessment is required. This is a notable limitation of the online form specifically in the cases where only one MRI or CT slice was provided. In clinical practice, web-based images systems such as the Picture Archiving and Communication System (PACS) are used that show the whole length of the bone allowing the clinician to make a 3-D assessment of the pattern of infection. This issue is specifically highlighted by two cases. Firstly, case 19 where the involvement in a joint is difficult to be seen on the single MRI slice, figure 6.3. Secondly, case 16, where the coronal image is easily mistaken

for a segmental pattern of involvement, figure 6.6. In this case, 40.0% of users scored it as a B2 and the remaining 60.0% scored it correctly as a B1. These cases demonstrate that even when images are provided in perpendicular planes, a single slice provides inadequate information to make the classification.

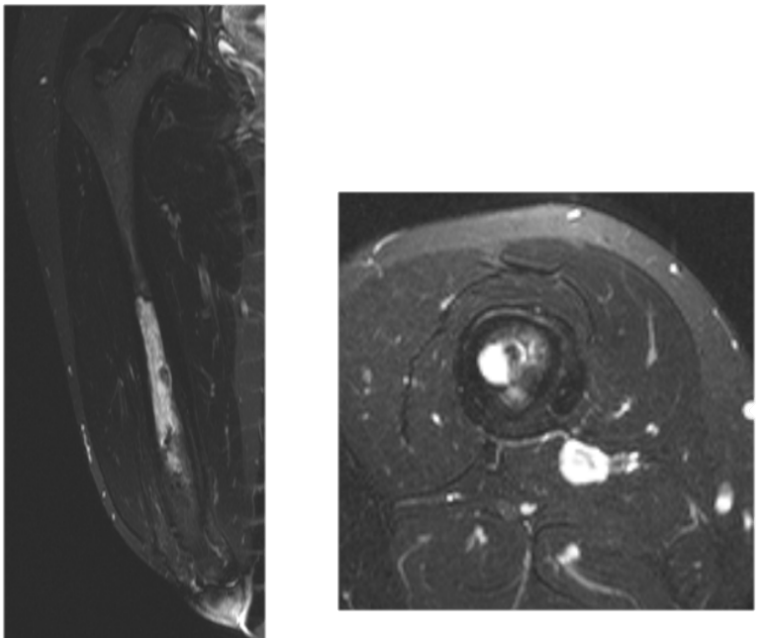


Figure 6.6: MRI slice of a B1 type infection, case 16. However, on the lateral, it appears as a segmental pattern of involvement. The axial image is required to make the diagnosis of a cavitary image.

The second manner in which insufficient imaging may have caused the users to answer incorrectly was in the imaging modality presented. There were two cases that did not present CT or MRI images and required the combination of clinical information and x-rays to make the classification. Both of these cases (cases 2 and 7) were post-traumatic and had metal work in situ which meant that CT or MRI would give limited information. In these cases, it was impossible to classify the infection based on the x-ray images alone. Despite this, the x-ray indicated that the bone had healed, thereby excluding a B2 infection. However, the metalwork in both cases was situated in close proximity to a joint, making it difficult for users to discern whether the joint was involved or not. Clinical information stated that the patients were pain free on movement of the nearby joint, implying that the joint was not involved. This demonstrates that the classification of the 'B' variable

can be made based on clinical information and plain x-rays. However, the user key suggests that the B classification should be made on radiology alone. This will be modified so that clinical information may be combined with radiology to adequately make the correct classification.

(ii) Unclear radiology reports

The feedback from the pilot study suggested that addition of radiology reports may help assist with the classification, especially if the imaging is unclear. However, the one case that scored in the lowest quartile of the 'B' variable had a radiology report that did not help some users make the classification. In this case, the radiology report specified *"degenerative changes within the joint but no evidence of osteomyelitis"*. Despite this, eight users (26.7%) incorrectly classified this case as a B3 indicating that these users may have incorrectly attached meaning to this report. Similarly, as with the above cases (2 and 7), this mistake may have been due to users interpreting the imaging only and not the alternative information provided to help make the classification. Again, this demonstrates the importance of highlighting that the classification should be made using a combination of clinical and radiological findings.

(iii) Distorted anatomy

The final problem when classifying bone involvement arose in those cases which involved distorted anatomy. This was demonstrated by case 20 in which there was only a small region of active infection on the PET-CT representing a cavitary infection, figure 6.7. However, there was also significant tibial deformity owing to previous debridement operations. The severe tibial deformity appeared to lead to 30.0% of users classifying this case as a B2. The users were also provided with an x-ray image that demonstrated the presence of a metal rod that extended into the knee joint. This, may have been the underlying reason for 6.3% of users classifying this infection as a B3. This case is complex in that users were required to classify the active infection only for the bone involvement variable but also to take into account the surrounding anatomy when making the host status classification (i.e. this patient had received multiple debridement options in the past making them an H2).

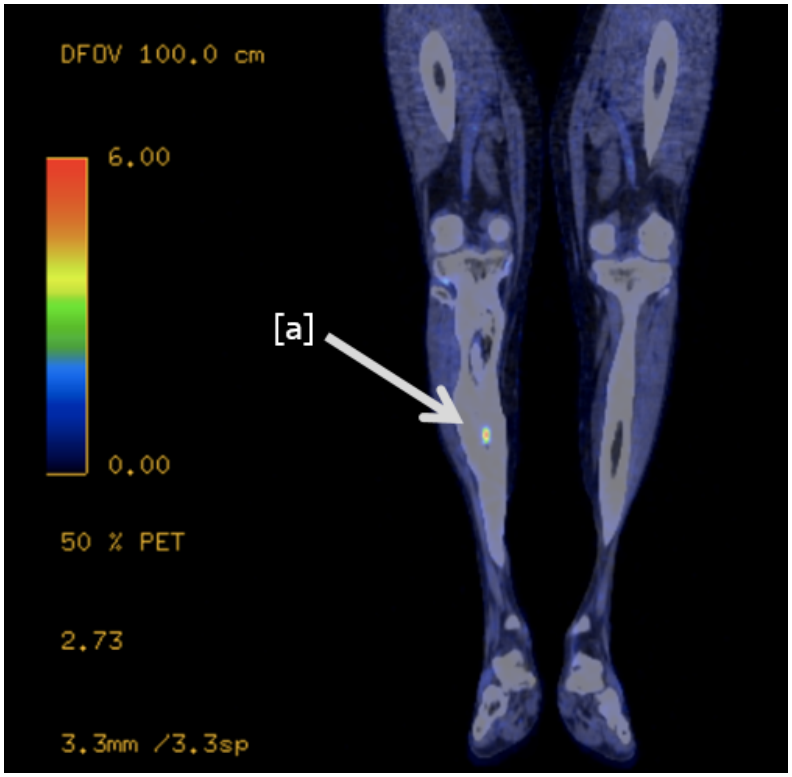


Figure 6.7: PET scan of case 20 demonstrating the area of active infection. Despite the deformity present in this limb and the metal work present in the right knee joint, this is a B1 cavitary type of bone infection. This is due to the area of 'active' infection (the hotspot on the PET-CT).

6.4.4.3 Summary

In summary, the reasons underlying the more frequent instance of incorrect classification of bone involvement related to the imaging provided to users and the case presentation. It has highlighted a number of points that should be addressed in the user key. Version 2 of the user key suggested that the bone involvement variable should be diagnosed using imaging information alone. However, this has been shown not to be the case and should be amended prior to dissemination of the classification system. Furthermore, this inter-user assessment of the bone involvement variable has demonstrated the limits in the methodology of using an online form. This was a pragmatic decision, to allow the assessment to be performed in multiple centres. However, it only allows 2-D visualisation of the bone and could have been responsible for the resultant score and $F\kappa$ demonstrated in this group. To investigate this further, additional analysis of the bone involvement variable

will be performed in chapter 7 to ascertain whether 3-D imaging will improve the percentage correct and the $F\kappa$ value of users.

6.4.5 Anti-microbial options

6.4.5.1 Results

The anti-microbial options variable had the highest agreement between users with a $F\kappa$ of 0.815, indicating an 'almost perfect agreement'. This is confirmed by the heatmap shown in figure 6.8a which demonstrates that 3 out of 4 categories had a $\geq$90.0% agreement between users. Despite an almost perfect agreement between users, the more highly resistant cases (i.e. the A2 and A3 cases) did not offer a good correlation with the reference value. This demonstrates that these cases were consistently classified incorrectly. This reduced the mean score for this variable to 92.2% with a wide range of scores for individual cases (range 6.7% - 100.0%). The Ax and the A1 category demonstrated a 100.0% and 94.4% successful classification rate respectively. Sub group analysis demonstrated that physicians answered 100.0% of the A1 and Ax cases correctly and surgeons made up the 5.6% of incorrect answers in the A1 group, appendix C. As the resistance of the isolates increased, the percentage of correct answers reduced regardless of speciality. In both the A2 and A3 groups, more than 50.0% of patients were incorrectly classified into the less severe category (i.e. the classification of A2 patients as A1 and A3 patients as A2), figure 6.8b. Only 10.0% (6/60) of responses for the A3 cases were correct with the remainder of users classifying these cases as A2. The four cases that returned the most incorrect responses were either A2 or A3, figure 6.8c.

6.4.5.2 Discussion

The potential problems encountered when classifying the anti-microbial options can be summarised by (i) the complexity of the ESCMID criteria, (ii) the classification of non-ESCMID isolates and (iii) the presentation of truncated susceptibility panels. The four cases which were the most frequently classified incorrectly are summarised in table 6.8 with corresponding reasons for poor performance.

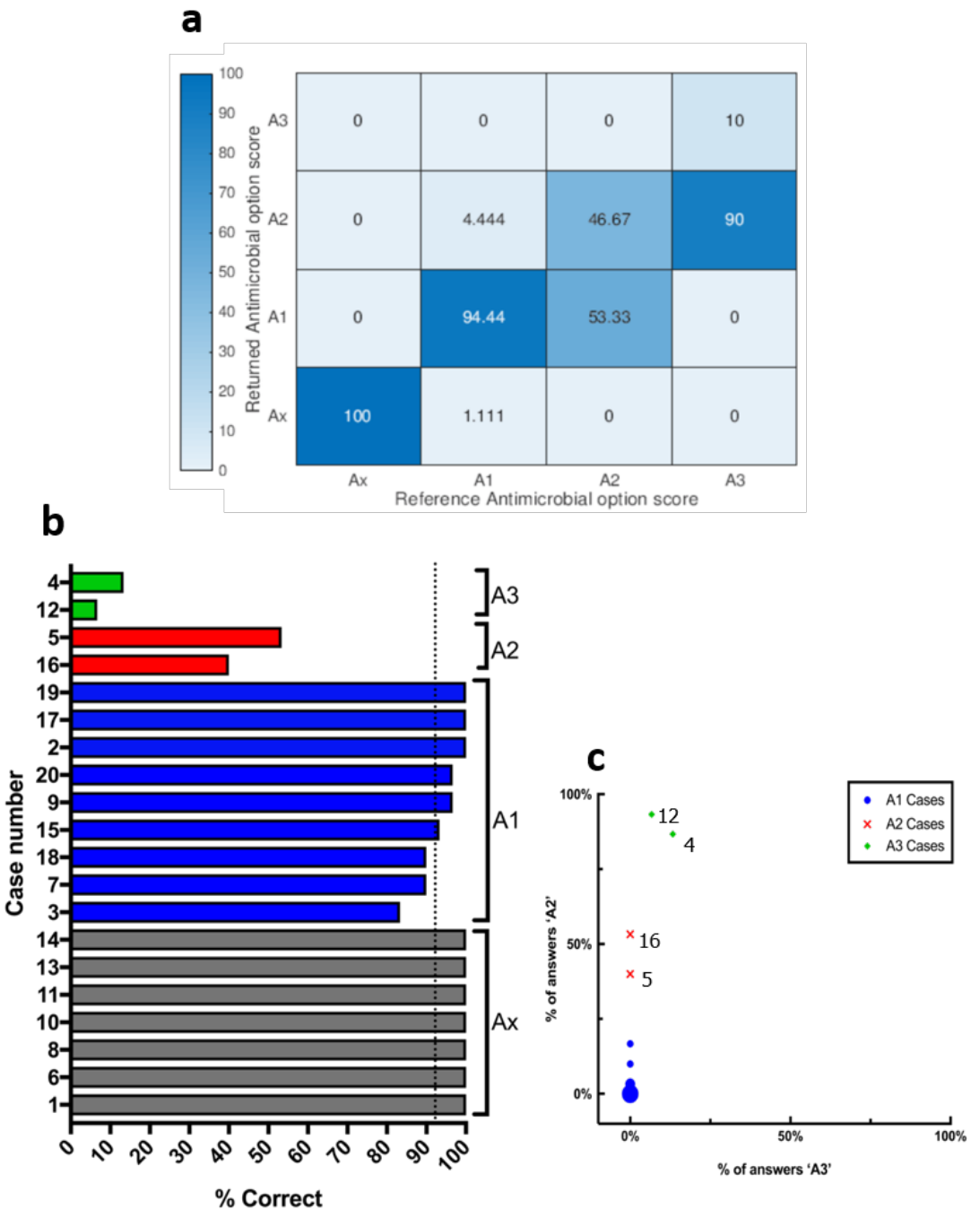


Figure 6.8: Summary of the results of the Anti-microbial options variable from the inter-user analysis.(a) Heatmap of the results for each of the 'A' variables. Dark blue represents a high accuracy for the variables. (b) The case number organised by reference 'A' value and in order of accuracy. Grey = Ax, Blue = A1, Red = A2 and Green = A3. (c) Scatter density plot of the individual responses to the 20 cases. The four cases highlighted (12, 4, 16 and 5) are the cases that scored in the lowest quartile. Reference colours for each case are shown: Blue = A1, Red = A2 and Green = A3.

(i) Complexity of the ESCMID criteria

There was difficulty in using the ESCMID criteria when making the classification of both XDR and MDR isolates. This was demonstrated in both cases 12 (XDR isolate) and 16 (MDR isolate), table 6.8.

Case No.	% Accuracy	Isolate	Total number of susceptibility tests performed	Number of resistant susceptibility tests	ESCMID class	'A' Class	Reason for poor performance
12	6.7%	*Morganella morgagni*	13	12	XDR	A3	Complexity of ESCMID criteria
16	40.0%	*Serratia marcescens*	14	8	MDR	A2	Complexity of ESCMID criteria
4	13.3%	*Pseudomonas aeruginoa*	3	2	XDR	A3	Truncated susceptibility panels
		Enterococcus faecium	5	4	XDR	A3	
5	53.3%	*Staphylococcus hominis*	4	2	Non-ESCMID	A2	Truncated susceptibility panel Non-ESCMID

Table 6.8: Summary of the complex anti-microbial options cases. The isolate, total number of susceptibility tests, resultant ESCMID class and the reason for the problems are presented.

For XDR isolates, even when only one option was available, users were reluctant to make the classification of A3. Case 12 had resistance to 12 out 13 anti-biotic susceptibility tests and only 6.7% of users correctly classified it as an A3. However, all users appeared to recognise that this isolate would be challenging to treat, with the remaining users (93.0%) classifying it as A2. One explanation for this could be that 9 of the 15 classes of anti-biotics used in the ESCMID criteria to define resistant *Enterobacteriacae* were not reported and therefore the decision to classify the isolate as XDR was limited. Alternatively, it could have been because there was one 'option' available which would steer the user away from making a 'no options available' A3 classification. These are both issues that could be addressed by altering the terminology used in the BACH classification system and renaming the 'no options available' category.

A second case where there was a similar reluctance to make the classification of A2 was in the case of an MDR *Serratia marcescens*. For this isolate, resistant

susceptibility tests included amoxicillin, colistin, ceftriaxone, gentamicin, piperacillin-tazobactam and co-amoxiclav which are all part of the ESCMID criteria for diagnosing MDR in *Enterobacteriacae*. However, it was incorrectly classified as an A1 by >50.0% of users. ESCMID define MDR as resistance to ≥1 anti-microbial agent in ≥3 of the specified anti-microbial categories. Therefore, this isolate was a definite case of MDR having resistance to ≥1 agent in 6 anti-microbial categories. However, the isolate also had 6 available anti-microbial options including commonly prescribed antibiotics such as ciprofloxacin, ceftazidime and meropenem. Although this was classified an ESCMID MDR, it was incorrectly placed in the A1 category by more than 50.0% of users, likely due to the multiple options available. These cases demonstrate the issues with the complexity of the ESCMID criteria at both the MDR and XDR level of resistance.

(ii) Truncated susceptibility panels

Another reason for the cases shown in table 6.8 being incorrectly classified may have been due to the presentation of limited susceptibility panels. Case 4 presented two ESCMID classifiable isolates with only one option available. If resistance is assumed to the susceptibility tests that are not presented, then these isolates are classified as XDR and therefore A3. However, it is difficult to make this classification on the basis of <5 antibiotic susceptibility tests because the user must assume resistance to multiple tests that are not present. This demonstrates the limitations of the ESCMID classifiable isolates in truncated susceptibility panels.

(iii) Non-ESCMID isolates

There were also limitations in non-ESCMID classifiable isolates. Case 5 presented a limited susceptibility test panel to *Staphylococcus hominis*, a non-ESCMID classifiable isolate. In this case, the results of four susceptibility tests were presented, two of which were resistant and two were sensitive. As specified in version 2 of the classification system, 'bacteria that were not in the ESCMID guidelines with resistance to appropriate anti-microbial agents' should be classified as A2. On the basis of only two available options and without the aid of the ESCMID criteria,

this isolate should have been deemed an A2. Just over half (53.3%) of the users agreed with this. However, the remainder classified this incorrectly as A1. As discussed in chapter 5, clinicians are usually given a limited range of the total number of susceptibility tests that are performed. Both cases 4 and 5 use susceptibility panels that were presented in clinical practice. Applying these limited tests in both ESCMID classifiable and non-ESCMID classifiable isolates caused significant challenge to users in classifying the anti-microbial options.

6.4.5.3 Summary

The anti-microbial options variable was answered reproducibly and in 16/20 cases (80.0%), the returned answers had a >80.0% correlation with the reference answer. The $F\kappa$ was deemed as an 'almost perfect agreement' despite disagreements with the reference answer. Cases that were clear cut A1 or Ax were both classified reproducibly. However, when presenting a limited number of available susceptibility tests, the classification system was applied less successfully. The three main problems that were highlighted by this analysis were making the classification of XDR and MDR with multiple available susceptibility tests, applying the ESCMID criteria to a truncated susceptibility panel and applying the classification system reproducibly to non-ESCMID classifiable isolates.

6.4.6 Coverage of the Soft Tissues

6.4.6.1 Results

The coverage of the soft tissues had the highest overall classification score at 92.5% correct (range 63.3% - 100.0%). The $F\kappa$ was 0.729 (95% CI 0.723 – 0.734) which demonstrates a 'moderate agreement' between raters. Individually, the C1 and C2 variables had over 90.0% of cases correctly classified. The cases defined as C2 in the reference classification had more than twice as many incorrect responses than those defined as C1 (9.5% versus 3.8%), figure 6.9a. Figure 6.9b and 6.9c shows how individual cases were answered and highlights the cases that had the lowest individual scores.

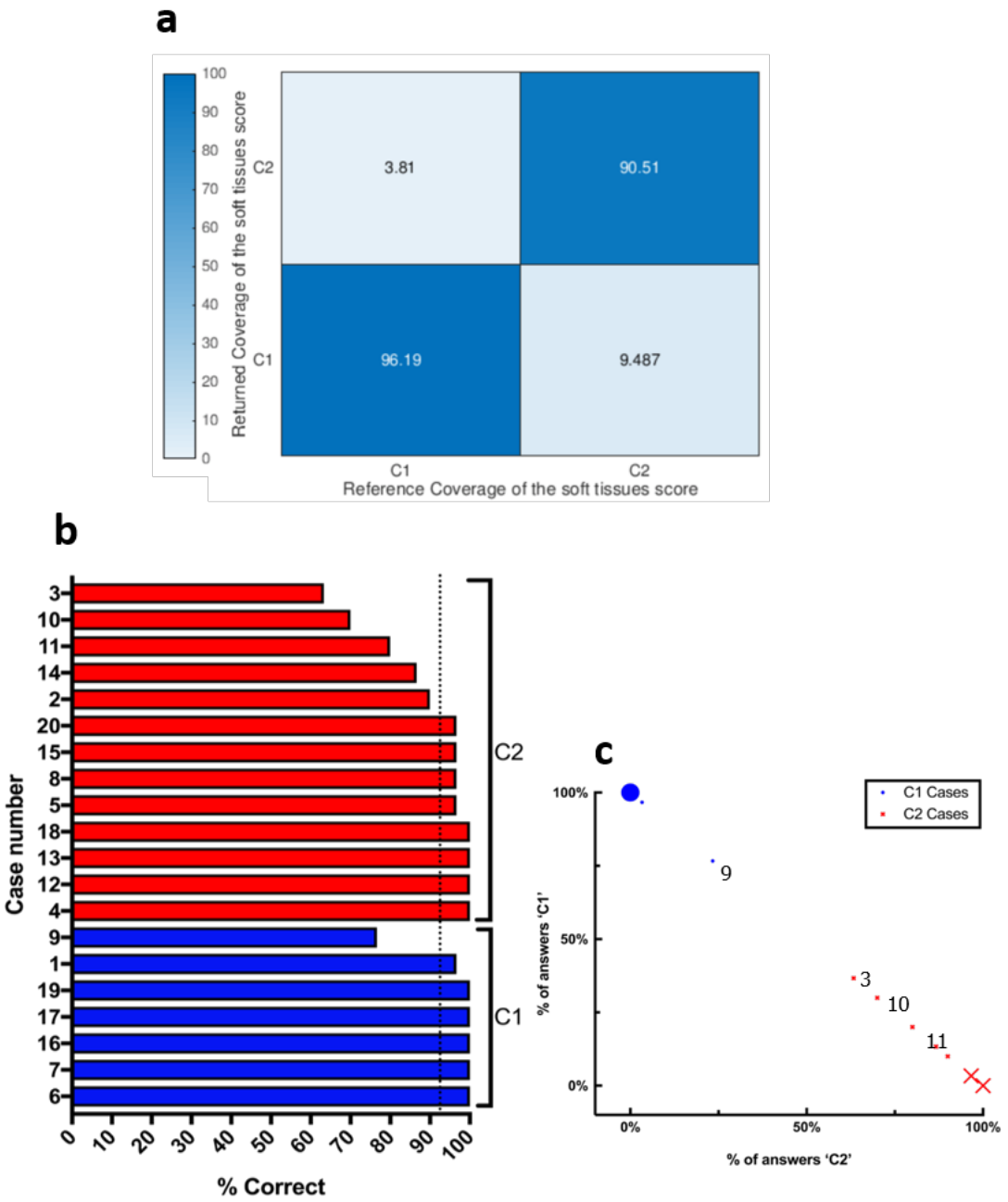


Figure 6.9: Summary of the results of the Coverage of the soft tissues variable from the inter-user analysis.(a) Heatmap of the results for each of the 'C' variables. Dark blue represents a high accuracy for the variables. (b) The case number organised by reference 'C' value and in order of accuracy. Blue = C1 and Red = C2. (c) Scatter density plot of the individual responses to the 20 cases. The four cases highlighted (9, 3, 10 and 11) are the cases that scored in the lowest quartile. Reference colours for each case are shown: Blue = C1 and Red = C2.

6.4.6.2 Discussion

Classification of the coverage of the soft tissues in the retrospective analysis presented in chapter 4 was uncomplicated because soft tissue transfer procedures had definitively been performed. The inter-observer assessment is based on a different form of information; users were asked to make the decision whether each case would need specialist plastic surgical input based on clinical photographs. There were 3 C2 cases that were frequently classified incorrectly (cases 3, 10 and 11). Common to all of these cases was the presence of a small (2-3cm) anterior tibia lesion, figure 6.10. In all of these cases, soft tissue management required plastic surgical expertise. However, this system may be beneficial and account for the individual expertise of the surgeon.



Figure 6.10: The images used in the inter-user analysis for classification of cases 3, 10, 11 and 9. For cases 3, 10 and 11, the soft tissue defect is present on the anterior tibia. For case 9 (magnified image in red dashed box), the soft tissue defect is present on the distal femur.

6.4.7 Host status

6.4.7.1 Results

The host status had an accuracy of 91.5% (range 60.0% - 100.0%). It had a 'moderate' agreement between users according to the $F\kappa$ which had a value of 0.719 (95% CI 0.714 – 725). The H1 cases were classified correctly more frequently than the H2 cases with 93.9% correct answers. This could have been due to seven cases being 'fit and well', which is the most unequivocal classification to make. The rate of incorrect responses in the H2 cases was almost double that of the H1 cases (H1: 6.1% versus H2: 12.5%), figure 6.11a.

Co-morbidities that consistently scored as an H2, included immune diseases (such as auto-immune neutropaenia), chronic kidney disease, vascular pathology (for example stroke or TIA), smoking and diabetes mellitus (either type 1 or type 2), figure 6.11b. The corrected co-morbidity score was calculated to give a measure of the influence of each individual co-morbidity on the H2 classification. Correcting for cases which presented as one of multiple co-morbidities, diabetes mellitus and smoking were less likely to impact the decision for users to score a case H2. Low corrected co-morbidity scores were demonstrated in conditions such as hypertension, asthma, hay fever, hypertension and childhood hepatitis, figure 6.11b.

6.4.7.2 Discussion

One reason that specific cases were frequently classified incorrectly was due to a lack of recognition amongst users that a history of previous debridement surgery should be classified as an H2. This is highlighted by cases 7 and 18, both of which were in the lowest quartile for correct classifications, figure 6.11c and 6.11d. Both cases were of neurological disease, one with well controlled epilepsy (no seizure for >2 years) and one with early stage Parkinson's disease. Neither of these well controlled conditions would necessarily complicate the treatment of osteomyelitis or preclude the patient from undergoing an anaesthetic. However, the difference was that one had received a previous debridement for osteomyelitis. This patient should have been deemed an H2 and the patient who had not received previous surgery deemed an H1.

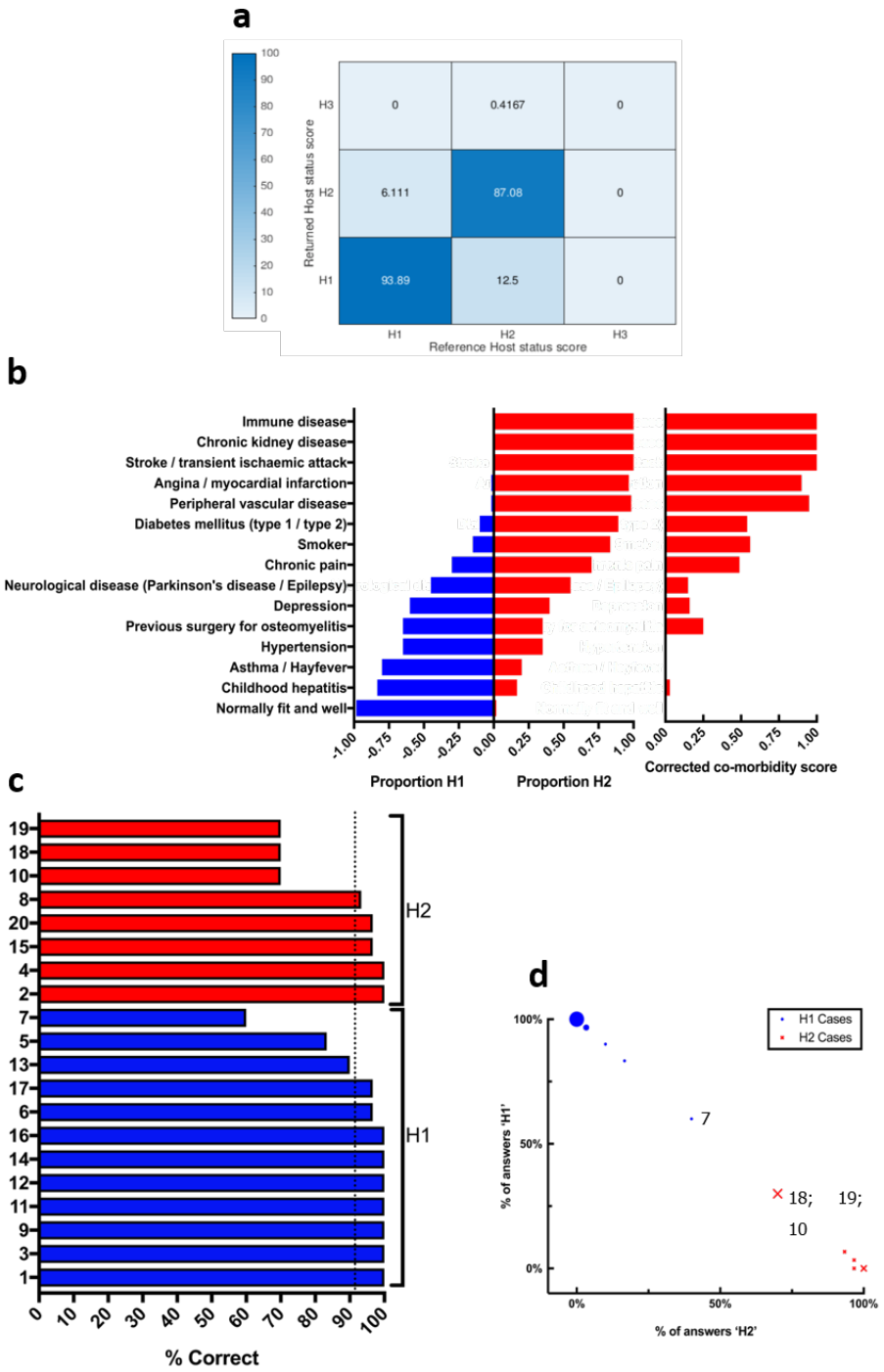


Figure 6.11: Summary of the results of the Host status variable from the inter-user analysis.(a) Heatmap of the results for each of the 'H' variables. Dark blue represents a high accuracy for the variables. (b) The proportion of cases that were deemed H1 and H2 for all of the co-morbidities presented in the inter-observer analysis with the corrected co-morbidity score accounting for cases with multiple co-morbidity. (c) The case number organised by reference 'H' value in order of accuracy. Dashed line is the mean score at 91.7%. Blue = H1 and Red = H2. (d) Scatter density plot of the individual cases to highlight cases that performed poorly (cases 7, 18, 19 and 10). Reference colours for each case are shown: Blue = C1 and Red = C2.

Despite this, previous surgery for osteomyelitis had a poor predictive value (0.25) for being deemed an H2 despite it being specified as such in the user key. Therefore, this needs further clarification in both the classification system and the user key.

The second issue appeared to arise from user uncertainty in the classification of conditions that were 'well controlled'. As shown in figure 6.11b, 89.0% of patients who had diabetes mellitus were classified as H2. The cases presented had varying levels of glycaemic control reported. However, this should not influence the classification. The presented cases of diabetes mellitus commonly had associated co-morbidity such as peripheral vascular disease or previous myocardial infarction which were correctly classified as H2. Case 19 presented a case of well controlled diabetes (HbA1c of 6.5%) with associated well controlled hypertension. As the corrected co-morbidity score for hypertension demonstrates, users did not regard it as a co-morbidity that should be classified as H2. However, the correct classification for this case would have been H2, owing to their underlying diabetes, for which they were on third line treatment to achieve an acceptable HbA1c. This reason arises from the likelihood of secondary associated microvascular disease that may compound the treatment of osteomyelitis. This was recognised by 70.0% of users who correctly classified this case as H2. This case demonstrates the difficulties in classifying patients who appear to have well controlled disease but due to the underlying pathophysiology should be classified as H2.

6.4.7.3 Summary

In summary, the host status was classified with a high percentage accuracy and inter-user agreement. The inter-user assessment has highlighted themes in the users' perceptions of individual comorbidities. This has highlighted areas for development in the Host status section of the user key, which will focus on refining and clarifying instructions for classifying comorbid chronic disease. It supports the removal of placing any significance on whether a chronic condition is 'optimised', as this appears to have caused confusion amongst users.

6.5 Limitations

Limitations of this analysis have been discussed for each variable. These are predominantly associated with the online form used to present the cases and collect the user responses. The most marked of these was the inability to provide 3-D assessment of the 'B' variable using single slices of MRI and CT scans. This will be explored further in chapter 7.

A multi-variate analysis of user subgroups based on clinical attribute was conducted. Using a multivariate linear regression model, statistical significance was only achieved in non-UK clinicians making the coverage of the soft tissue classification. This could be attributable to a different threshold for making a plastic surgical referral outside the UK. However, the sample size was not powered to detect a difference between groups as this was not the primary aim of the inter-user assessment. At 80% power, 278 users would be required to demonstrate significance with an effect size of 0.2 (i.e. 20% between groups). A cohort of 30 users is approximately 10% of that which would be required, making this assessment underpowered.

6.6 Summary

The inter-observer assessment demonstrated limitations in the usability of the key and the classification system. Interpretation of the $F\kappa$ demonstrated that there was a minimum of a 'fair' agreement between users in all variables. Both the pilot assessment and the full inter-observer assessment has demonstrated issues with specific categories that are able to be addressed in chapter 7. Through feedback from the pilot study, the user key has been developed and optimised. The full inter-observer assessment has demonstrated that the classification system can successfully be applied regardless of osteomyelitis experience, type of centre and speciality. It has highlighted issues that need to be addressed in each category. One such issue is the 2-D versus 3-D classification of the bone involvement variable. These will be explored in chapter 7 where version 3 of the BACH classification system will be presented.

7

Limitations and BACH version 3

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7.1 Introduction

The assessment of usability of the BACH classification system has been performed by retrospective and inter-user analysis. To develop the classification system and

the user-key further, these limitations will be addressed and BACH version 3 will be presented. This version of BACH and the accompanying user key will be used in the prospective validation of the classification system, presented in chapter 8.

Chapter 7 will be divided into three parts:

(i) Part 1 presents a further assessment of the bone involvement 'B' variable exploring whether the results of the inter-observer analysis were secondary to the classification system itself or the nature of the case presentation. This involved a further inter-user assessment with 9 users who will classify 10 cases of osteomyelitis using the imaging software typically used in clinical practice.

(ii) Part 2 summarises the findings of the investigations performed from chapter 4 onwards. The findings of these assessments will be used to optimise the BACH classification system and also to provide information for the user key.

(iii) Part 3 presents BACH version 3 and discusses how it may influence the management and prognosis of osteomyelitis.

7.2 Part (i): 3-D assessment of the 'B' Variable

7.2.1 Introduction

Chapter 6 demonstrated that the bone involvement had the lowest agreement between users ($F\kappa$ 0.479) and the lowest percentage accuracy of responses (77.0%) amongst the four variables. Although more than three-quarters of the responses for this variable correlated with the reference answer, it was hypothesised that the nature of the online form was a major limiting factor in the accuracy of the classification. The cases that scored the lowest accuracy in the inter-observer assessment had either a single MRI / CT slice available or relied on the combination of clinical information and x-ray findings to make the classification. To ascertain whether the low scores experienced within this variable were due to the classification system, the user-key or the nature of the online case presentations, a second assessment was performed. This assessment used the web-based imaging system that is used in clinical practice

Number of cases:	10 (B1 = 4; B2 = 3; B3 = 3)
Information provided:	Patient medical record number
	Patient year of birth
	Site of infection
	Relevant imaging date
Type of Imaging:	MRI and CT scan with radiologist report available

Table 7.1: Information given to classification users as part of the 3-D assessment of the 'B' variable.

(PACS) instead of relying on screenshots from x-ray, CT, MRI and/or PET image series. The PACS system allowed access to the complete image series including radiologist report, allowing users to scroll through the images in their own time.

7.2.2 Case selection

Ten patients were selected from the 96 cases used in the retrospective analysis performed in chapter 4. None of these cases were used in inter-observer analysis presented in chapter 6. These cases were grouped into their corresponding 'B' variable and blindly selected to ensure that each category was represented, table 7.1. All cases included had either CT or MRI images performed.

7.2.3 Methods

Nine users who had volunteered for the inter-user assessment and had access to the Oxford University Hospitals PACS computer system were invited to complete the 3-D assessment of the' B' variable. The users had a variety of clinical backgrounds, table 7.2. The user key was unchanged from version 2, appendix B, and was re-sent to the users if required. Details of the cases were sent using an encrypted online form (*online-surveys.ac.uk*; approved for use by the University of Oxford). The user was then required to search for and identify the patient on the PACS database. Users were encouraged to view only the scan that was presented on the online form. Results were collected from the online form and entered onto an electronic spreadsheet for analysis (Microsoft Excel 2016).

Clinical attribute	Number of users
Speciality:	
Surgeon	4
Physician	5
Predominant Centre:	
Bone infection unit	3
University Hospital	6
Number of cases of osteomyelitis seen per month:	
<1 per month	3
1-3 per month	3
1 per week	3
Grade:	
Consultant	3
Speciality registrar	6

Table 7.2: The clinical attributes and experience of the users that were included in the 3-D assessment of the 'B' variable.

7.2.4 Data and statistical analysis

The accuracy score for the 3-D assessment was calculated by comparing the returned answers against the reference answer. The reference answers were compiled by the DPhil student and one supervisor (MM).

For simplicity, the assessments performed in chapter 6 will be termed '2-D' and the assessment using the PACS imaging system will be termed '3-D'. The difference between these groups was that the users completing the 3-D assessment were able to scroll through the images in their own time and assimilate a 3-D image of the bone infection. The 2-D assessment performed in chapter 6 contained several imaging modalities such as x-ray, CT, MRI and PET. However, in this instance, the images were static single slices which were hypothesised to limit the classification that could be performed using the online form.

The agreement between users was then calculated using Fleiss' kappa ($F\kappa$) as described in chapter 6 (MATLAB 2018a, Mathworks, UK). The users who completed the 3-D assessment were tested to ensure that they represented the total population who completed the 2-D assessment using the Kolmogrov-Smirnov test

(R in RStudio). One-way analysis of variance (ANOVA) was performed to assess for a difference between the 3-D and 2-D assessment results. In the presence of significance, Dunnett's post-hoc test allowed comparison of sample populations to a reference population (R in RStudio). The reference group was the total population who completed the 2-D assessment performed in chapter 6.

7.2.5 Results

The mean accuracy score achieved by users in the 3-D bone assessment was 95.7% (95% CI 90.8% - 100.0%). The accuracy of making the classification was significantly higher in the group who underwent the 3-D assessment when compared directly to the same users completing the 2-D assessment ($p<0.05$, *paired t-test*) and with the total population who completed the 2-D assessment ($p<0.01$, *ANOVA with Dunnett's post-hoc test*), figures 7.1 and 7.2. This result was substantiated by an improvement in the $F\kappa$ which improved from 0.479 in the 2-D analysis to 0.899 (95% CI 0.869 – 0.929) in the 3-D analysis. Interpretation of this value using the criteria set out by Landis and Koh (Landis and Koch, 1977) demonstrates an 'almost perfect' agreement between users. Compared to the full inter-user assessment, this assessment of the 'B' variable gave the highest score and $F\kappa$ amongst variables. The sample population were deemed to be representative of the total population who undertook the 2-D inter-user assessment performed in chapter 6 ($p=0.98$, *Kolmogrov-Smirnov test*).

7.2.6 Discussion

The use of complete CT and MRI series significantly improved user accuracy and agreement of bone involvement classification. This supports the hypothesis that the performance in the 'B' variable in chapter 6 was limited by the use of an online form presenting a single sliced screen shot of the PACS image. The 3-D assessment presented in part (i) demonstrates that the 'B' variable of the classification system can be applied accurately and reproducibly amongst users, when they have access to clinical information as they would in the real world.

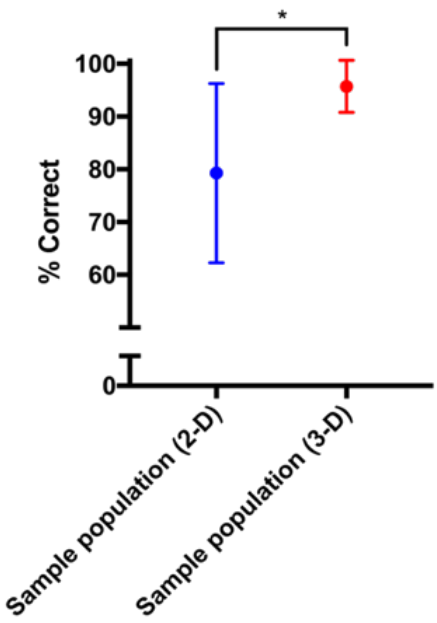


Figure 7.1: Comparison of scores from the 2-D[1] and 3-D[2] sample population. *p<0.05, *paired t-test.* [1]*2-D corresponds to assessment made using print screens from x-ray, CT, MRI and PET images on the online form.* [2]*3-D corresponds to assessment made using a combination of CT and MRI series.*

In the 2-D assessment presented in chapter 6, there was a total of 600 'B' questions answered across all users and all cases. This compares to a total of 90 'B' questions that were asked as part of the 3-D assessment, 15.0% of the total number presented in the full inter-user assessment. This smaller number may have resulted in a lower error detection rate. However, significance was achieved when comparing the sample user's 2-D scores with their 3-D scores (*paired t-test*) and when comparing the overall mean of the 3-D scores with the total user population in the 2-D assessment (*ANOVA with Dunnett's post-hoc* testing).

The 'B' variable is a less clear ordinal variable compared to other variables in the classification. Due to this, a low accuracy will likely be associated with a low agreement between users. In the cases where users did not respond correctly (in comparison to the reference answer), the result was more likely to return as random, thus reducing the inter-user agreement. Therefore, an improvement in the inter-user agreement in this variable combined with an improvement in accuracy is likely to represent an overall improvement of the user to apply the classification system.

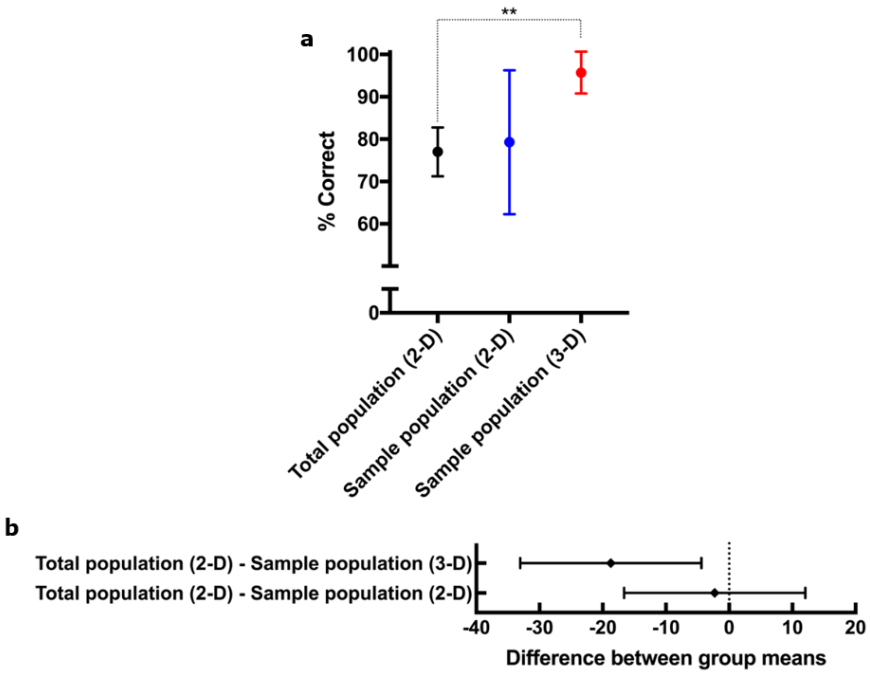


Figure 7.2: Compaison of sample population in both 2-D and 3-D analysis with the total population from the inter-user analysis. [**a**] Mean scores from the total population (2-D[1]), sample population (2-D[1]) and sample population (3-D[2])). **p<0.01 *ANOVA with post-hoc Dunnett's test.* [**b**] Results from Dunnett's post-hoc test demonstrating that the mean for the total population (2-D) was significantly reduced compared to the mean of the sample population (3-D). The mean for the total population (2-D) was similar to the mean of the sample population (2-D) which confirms that this population is representative of the total population.

The observed improvement in score may be attributable to a number of factors. Firstly, the users included have already classified 20 cases and the natural learning process may result in a higher score at the second assessment. However, users did not receive feedback regarding individual cases or variables for the 2-D assessment and therefore it would have been possible to make similar mistakes. Secondly, the users that completed the assessment were all part of the same centre. This was necessary for access to the PACS online system used in the assessment. Thirdly, the centre used included specialist clinicians who predominantly worked in a Bone Infection Unit but also clinicians who were less sub-specialised. To ensure a range of experience, the assessment contained different training grades (speciality registrar and consultant) to ensure that users were comparable to the original 2-D assessment. Finally, the improvement in performance may have been secondary to the number

of cases and variables that were asked to be classified. In the full assessment, applying a new classification system to 20 cases may have resulted in an overload of information. By using fewer cases and only one variable, the user was less likely to fatigue by the end of the assessment resulting in an improved score.

7.2.7 Summary

The bone involvement variable was investigated further using a '3-D' assessment which allowed visualisation of the complete pattern of the infection. This resulted in a significantly improved outcome compared to the results presented in the 2-D inter-user assessment, chapter 6. Based on these results, the 'B' variable should remain unchanged. However, in the user-key, it should be specified that a combination of clinical and radiological information (from x-rays, CT scans, MRI scans and the radiology report) must be used to make the classification.

7.3 Part (ii): Summary of Assessments Performed

7.3.1 Introduction

A series of investigations have been performed for each of the four BACH variables, to assess usability and reproducibility of the classification system. The findings from these investigations have been used to modify the classification system and highlight further information to be incorporated into the user key. Based on this discussion, version 3 of the classification system will be presented in part 3 of this chapter.

7.3.2 Bone involvement 'B'

The bone involvement variable was first presented as three options, B1, B2 and B3. The main change to the classification was an update of the term 'bone defect' to 'bone involvement' from version 1 to version 2.

Specific information is required in the user-key to ensure the classification system is applied accurately and with good agreement amongst users. Firstly, the classification of the 'B' variable can be performed prior to surgery based on a combination of clinical information, plain radiographs and 3-D images (such as

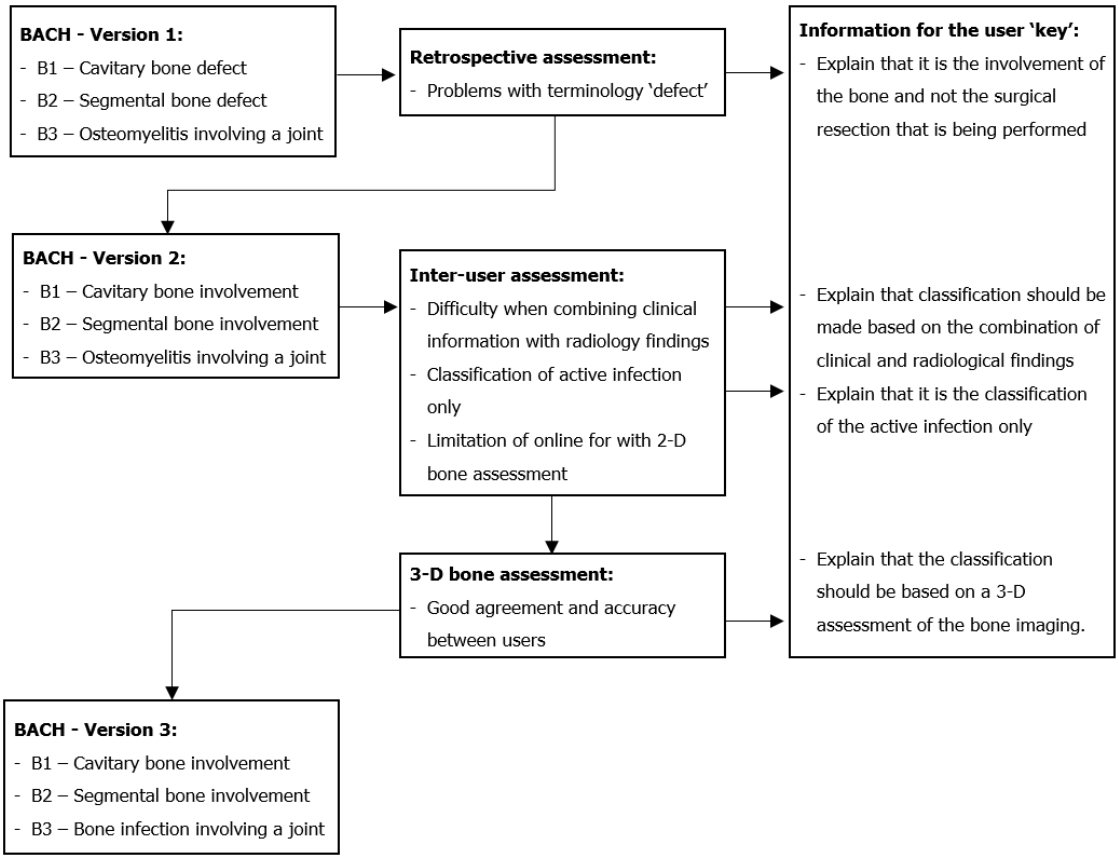


Figure 7.3: A summary of the different versions of the 'B' variable along with how each of the assessments has influenced the user key. The left column shows the three versions of the BACH classification system. The middle column highlights the findings of the individual assessments performed within this thesis and the right column shows the information that will be used in the user key.

CT or MRI) with a clinical imaging system. Secondly, the user key should also denote that it is the 'active' area of infection that is to be classified and not the anatomical disturbance that may be caused by surgical debridement.

Following the assessments performed in the previous chapters, the bone involvement variable should be used as in version 2. However, the user-key should highlight specific features of the classification system which will support accuracy and agreement amongst users. The modifications recommended following each assessment are shown in figure 7.3. This includes describing that the classification may be made based on the combination of clinical and radiological findings but best practice would be 3-D assessment of the bone imaging using a clinical imaging system (such as PACS).

7.3.3 Anti-microbial options 'A'

Version 1 of the BACH classification system designated 4 categories for anti-microbial options. Version 2 reduced this to 3 categories where A1 and Ax are both denoted as 'good options available', A2 as 'limited options available' and A3 'no options available'. A summary of assessments performed is shown in figure 7.4.

The ESCMID criteria for defining MDR, XDR and PDR have been used to define the level of anti-microbial availability. These guidelines offer a pre-determined method of stratifying bacterial isolates that will be updated as resistance patterns change over time. However, 20.2% of isolates in the retrospective cohort were unable to be classified without the assistance of a specialist infectious disease clinician, chapter 5. The inter-user assessment demonstrated that as the resistance of the isolate increased, the accuracy of the classification decreased (i.e. the accuracy of the classification of A3 cases was 10.0%). Further assessment of anti-microbial resistance patterns in a complete cohort of osteomyelitis demonstrated that isolates with "resistance to $\geq$4 susceptibility tests" had a 98.1% (95% CI 97.6-100.0%) correlation with ESCMID MDR. This was not incorporated into version 2 of the classification system to assess whether the ESCMID criteria alone would be adequate to make the classification. The inter-user assessment demonstrated that the presentation of truncated susceptibility panels caused difficulty when using the ESCMID criteria for classification. In view of this, similar methods were used on the cohort presented in chapter 5 (part 2) to assess whether the number of sensitive susceptibility tests correlated with ESCMID MDR. This demonstrated that isolates with <80% sensitive results of all susceptibility tests performed had a 98.8% (95% CI 98.0-100.0%) correlation with ESCMID MDR status. This assessment is presented in appendix D. In view of this, these statements will be additionally included in the classification of this variable. They will be explained in the user key. Figure 7.5 demonstrates how this will be applied to the 'A' category of the classification system.

The ESCMID criteria can be used to make the classification if the user is familiar. Adding "resistance $\geq$4 susceptibility tests" and "<80% sensitive results of all susceptibility tests performed" improves usability. This will allow the A2 category

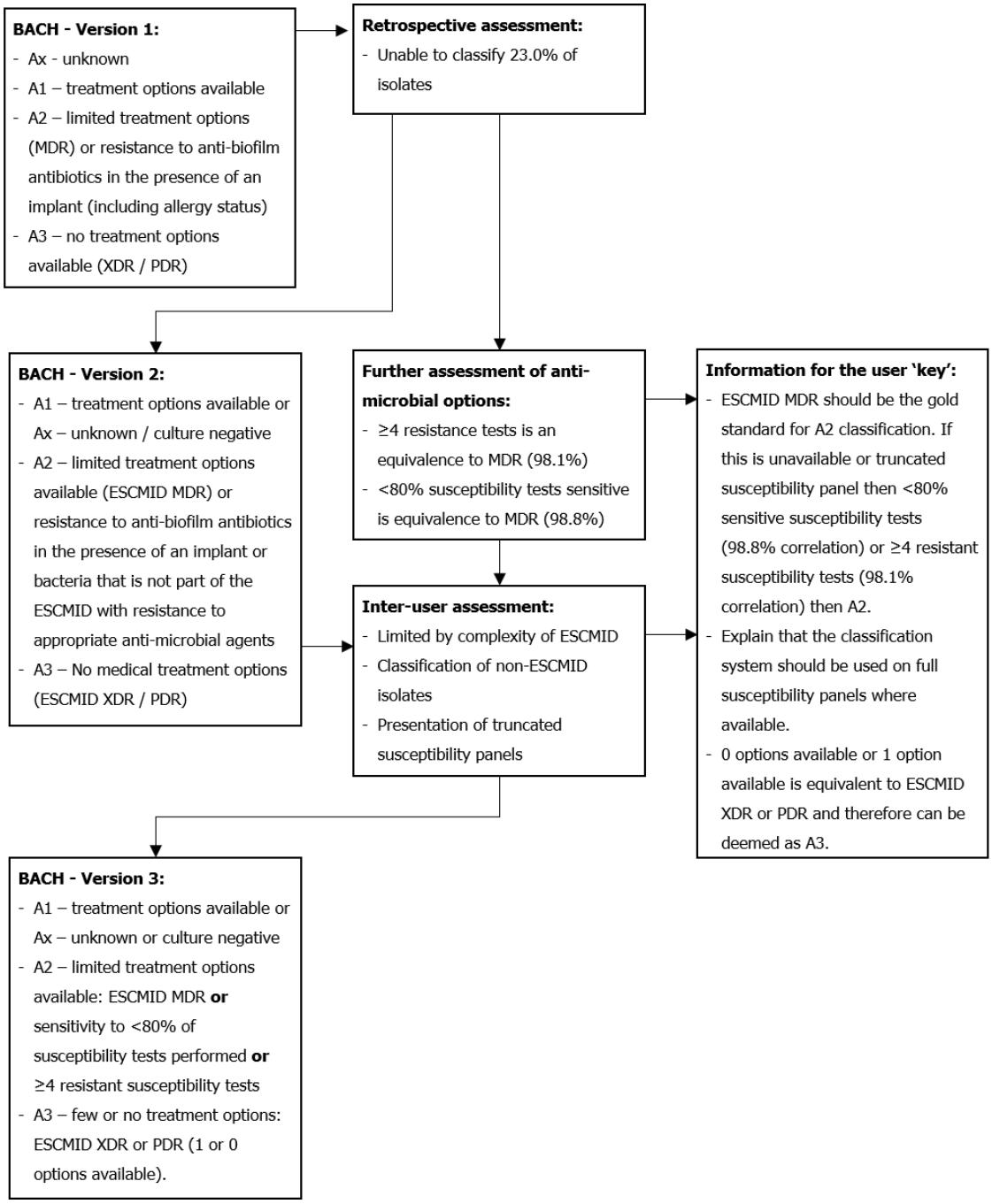


Figure 7.4: A summary of the different versions of the 'A' variable along with how each of the assessments have influenced the user key. The left column shows the three versions of the BACH classification system. The middle column highlights the findings of the individual assessments performed within this thesis and the right column shows the information that will be used in the user key.

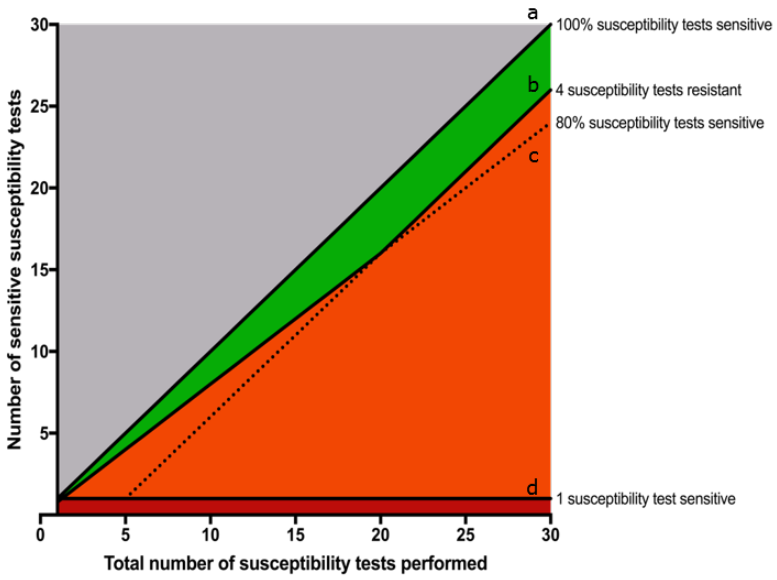


Figure 7.5: The number of sensitive susceptibility tests versus the total number of susceptibility tests performed for an isolate. Line (a) 100% of susceptibility tests are sensitive; (b) 4 susceptibility tests resistant; (c) 80% of susceptibility tests are sensitive and (d) 1 susceptibility tests sensitive. This gives areas under the graph as either A1 (green), A2 (orange) or A3 (red). The grey shading represents an unachievable area of the graph where the number of sensitive susceptibility tests > total tests performed.

to be easily applied to all isolates. Secondly, it will allow clinicians who are unfamiliar with the ESCMID criteria for MDR to apply the classification system reproducibly. Thirdly, it will allow this to be applied to isolates with truncated susceptibility panels in a reproducible manner. It is important to denote in the user key that the clinicians who are not infectious disease specialists or microbiologists must request for advice when they feel uncomfortable with the classification of the 'A' variable.

For the A3 group, PDR is defined as resistance to all susceptibility tests performed. Therefore, any isolate with 0 options available will be deemed PDR and A3. XDR is defined by ESCMID as resistance to $\leq$2 of the anti-microbial categories tested. To define limited available options, A3 will now be defined as 'one or zero options available' where an isolate is sensitive to 0 or 1 susceptibility test, regardless of the extent of the susceptibility panel presented.

7.3.4 Coverage of the Soft Tissues (C)

The coverage of the soft tissues variable has been classified into two groups based on whether specialist expertise is required to close the wound following debridement surgery.

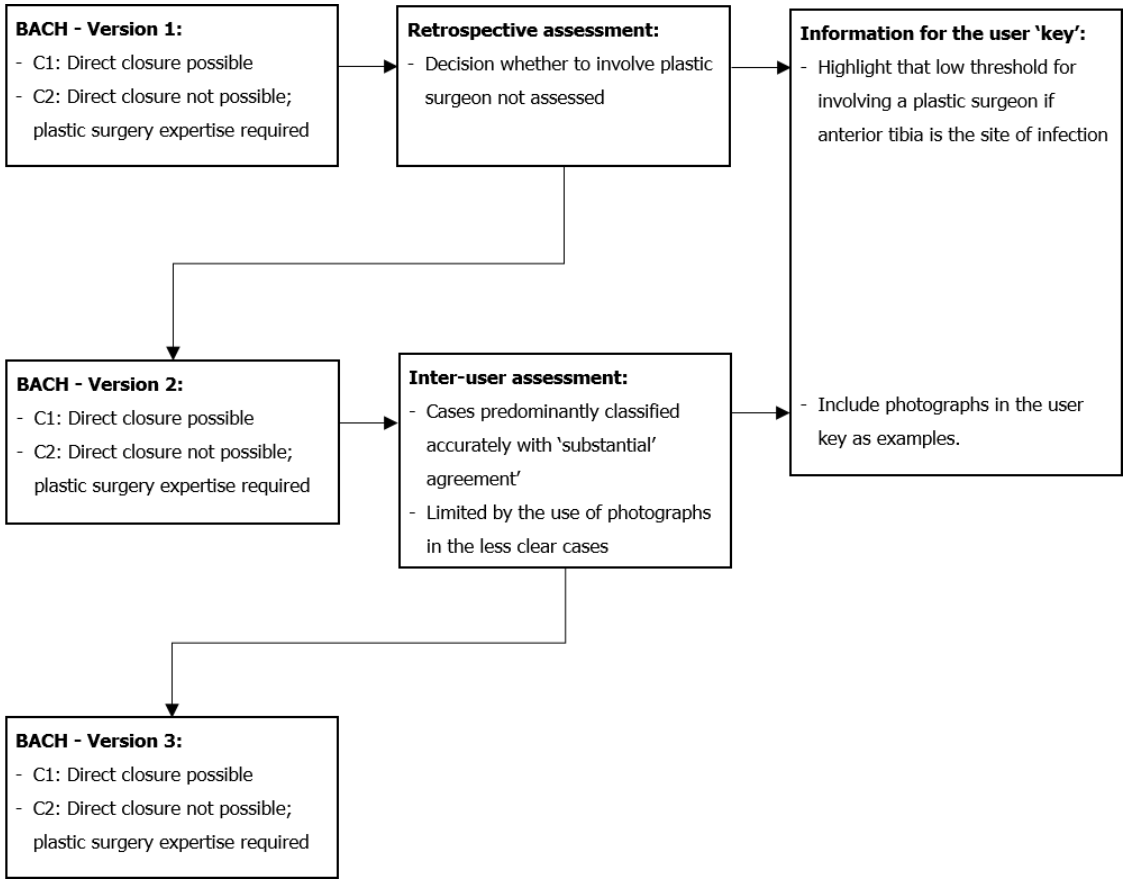


Figure 7.6: A summary of the different versions of the 'C' variable along with how each of the assessments have influenced the user key. The left column shows the three versions of the BACH classification system. The middle column highlights the findings of the individual assessments performed within this thesis and the right column shows the information that will be used in the user key.

Chapters 4 and 6 demonstrated that limited guidance regarding whether to involve the plastic surgical team was the main limitation of the coverage of the soft tissue variable, figure 7.6. However, the orthopaedic surgeons who will predominantly be making the classification of the 'C' variable will be able to use their own personal expertise to decide whether a surgical wound can be closed directly or requires plastic surgical expertise. The inter-user assessment demonstrated that the majority of

cases were classified accurately and with good agreement. However, this assessment was limited by the use of photographs on the online form to make the classification. To aid this decision, examples will be presented in the user key, that assist less experienced users to make the decision to involve the plastic surgical team.

7.3.5 Host Status (H)

The host status was classified into 3 groups from H1 to H3. This attempts to stratify patients according to the severity of their associated co-morbidity. The H1 category represents patients who do not have co-morbidity that compounds the treatment of osteomyelitis. The H2 category represents patients who are fit to undergo curative surgery, but who have co-morbidities. H3 patients are classified based on either being too unwell for curative surgery or decline of surgery. The main challenge in the application of the Host classification is the distinction between H1 and H2, figure 7.7.

BACH version 1 attempted to define whether 'specialist intervention' was required to optimise the patient prior to debridement surgery. However, in practice, patients with severe disease that is well controlled may not necessitate 'specialist intervention' because they are already being treated by a specialist. Furthermore, user definitions of 'optimisation' are subjective and may be inconsistent, affecting accuracy of classification. To address this, version 2 defined specific 'irreversible' co-morbidity that may complicate the treatment of osteomyelitis. These included micro- or macrovascular disruption to the site of the infection or osteomyelitis recurrence following previous debridement surgery. Despite this, the inter-user assessment demonstrated that well controlled conditions were commonly mis-classified. It highlighted how co-morbidities can present with a range of 'disease severity' and 'disease control'.

To define the 'disease control', established guidelines can be used to classify diseases that are either controlled or uncontrolled. This distinction between these groups can be based on pre-specified clinical measurement thresholds (as defined by NICE). For example, in type 2 diabetes mellitus, the HbA1c is commonly used to

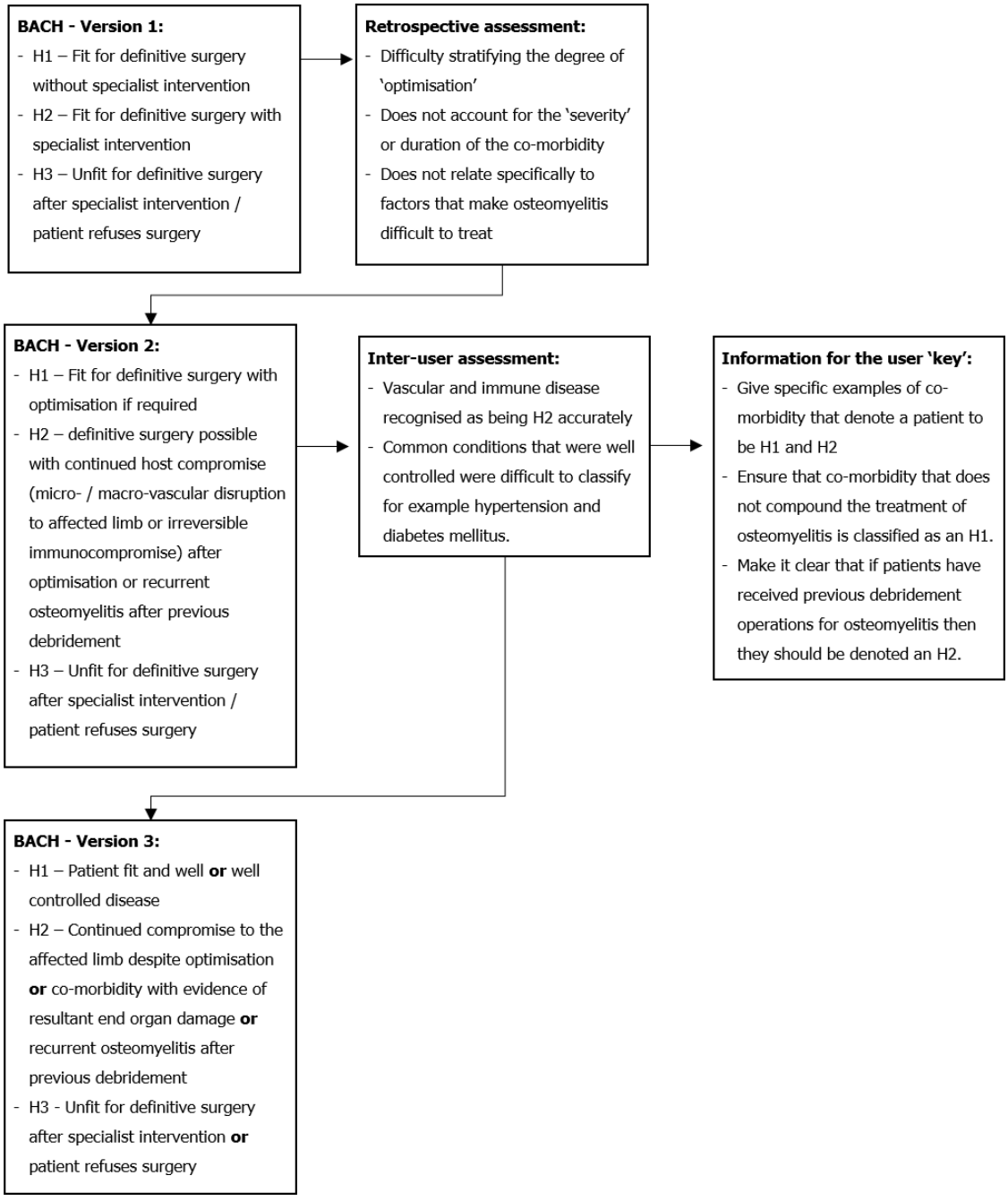


Figure 7.7: A summary of the different versions of the 'H' variable along with how each of the assessments have influenced the user key. The left column shows the three versions of the BACH classification system. The middle column highlights the findings of the individual assessments performed within this thesis and the right column shows the information that will be used in the user key.

	No end organ damage	End organ damage
Controlled	HbA1c 7.0% (53mmol)	≥1 of: Gastroparesis, diabetic neuropathy, autonomic neuropathy, diabetic foot complications, diabetic kidney disease, erectile dysfunction, diabetic retinopathy, peripheral vascular disease (including stroke, MI and hypertension)
Uncontrolled	HbA1c 7.0% (53mmol)	

Table 7.3: A summary of how type 1 or type 2 diabetes mellitus can be classified by both the presence of secondary complications (end organ damage) and disease control. Co-morbidity that is well controlled and not severe would be classified as H1. Poor control or severe co-morbidity would be classified as H2.

distinguish between well controlled and uncontrolled disease with a threshold of 7.0%, table (National Institute for Health and Care Excellence (NICE), 2009).

To define 'disease severity', the presence of end-organ damage can be used. This indicates that there is poor disease control that has led to secondary disease. For example, in diabetes mellitus, end-organ damage can be defined as the presence of co-morbidity such as chronic kidney disease, diabetic retinopathy or peripheral vascular disease, table 7.3.

To apply this to the BACH classification system, patients who have co-morbidities with end-organ damage and / or those that are not well controlled (according to NICE guidelines) will be classified as H2. Examples of these will be included in the user key. However, given the variety of possible diseases in medicine, the terms 'controlled' and 'uncontrolled' will continue to have a varying degree of subjectivity.

7.4 Part (iii): BACH version 3

7.4.1 BACH version 3

Based on the findings from the assessments presented within this thesis, BACH version 3 is proposed, figure 7.8. This table illustrates each of the variables within a 'traffic light' system which indicates uncomplicated, complex osteomyelitis (both with good or fair treatment options) or osteomyelitis with limited treatment options.

	Bone involvement (B):	Antimicrobial options (A):	Coverage by soft tissue (C):	Host status (H):
Uncomplicated	B_1 Cavitary infection without joint involvement	A_1 treatment options available **or** A_X unknown / culture negative osteomyeliits	C_1: Direct closure possible: Plastic surgery expertise not required	H_1: Well controlled disease **or** Patient fit and well
Complex: Specialist intervention needed	B_2: Segmental infection without joint involvement B_3 Any bone infection with associated joint involvement	A_2 limited treatment options available: ESCMID MDR **or** Sensitivity to <80% of all susceptibility tests performed **or** ≥4 resistant susceptibility tests **or** in the presence of a foreign body – gram positive cocci resistance to rifampicin or fluoroquinolone resistance to gram negative bacilli	C_2 Direct closure not possible: Plastic surgery expertise required	H_2: Continued compromise to the affected limb despite optimisation **or** Severe co-morbidity (with evidence of end organ damage) **or** Recurrent osteomyelitis after previous debridement
Limited treatment options available		A_3: Few or no medical treatment options (ESCMID XDR / PDR): sensitive to 0 or 1 susceptibility test		H_3: unfit for definitive surgery despite specialist intervention **or** patient declines for surgery

Figure 7.8: Version 3 of the BACH classification system for long bone osteomyelitis. The green row corresponds to 'uncomplicated', the orange 'complex' and the red 'no or few options available'.

7.4.2 BACH version 3 in management

The influence of BACH version 1 on the patient management of osteomyelitis was discussed in chapter 3. The present section will discuss how BACH version 3 will influence how osteomyelitis is managed compared to version 1. It should help to identify so called 'complex' cases. Although this term is not uniformly defined, it denotes cases that require referral to a specialist bone infection centre due to the complexity of disease. These cases are those that have increased risk of complications associated with the surgical intervention. It may also help to identify

patients with no or only limited treatment options.

The first time point where the classification system can be applied is at the first consultation. Here, the patient will have undergone imaging studies and the 'B' variable can be classified using appropriate software (for example PACS). Clinical assessment can be made at this consultation to classify the 'C' and 'H' variable. If this is performed in a hospital without plastic surgical expertise, the 'C' variable should be classified based on the expertise of the treating orthopaedic surgeon. Any co-morbidities should be optimised prior to surgery. Patients with 'well controlled' or absence of co-morbidity will be deemed an H1. Patients who are deemed H3 should have an anaesthetic assessment and, if H3 confirmed, a discussion should be held with the patient to explain that reconstructive surgery would not be appropriate. Due to the continuum of going from H2 to H3, it is possible that anaesthetic assessment may be necessary for certain H2 cases. As with version 1, at the first consultation, the anti-microbial options variable will be deemed an 'Ax' as potential causative organisms will be unknown. Ultrasound or CT-guided tissue sampling may be an option in certain cases. The 'A' variable may be available in those who have undergone unsuccessful previous debridement with deep sampling. Referral to a specialist centre will be based on the B, C and H variables in most cases. The classification system has not yet been validated for the necessity to refer. However, it is reasonable to refer a patient to a specialist centre that has the appropriate expertise when they score $\geq$2 in any category.

Following CT guided bone biopsy or surgery, the 'A' variable can be classified. Patients scoring either A2 or A3 should have their cases discussed with a specialist musculoskeletal infectious disease physician. The final classification of all variables should be confirmed when surgery has been performed and microbial culture results have been finalised. BACH aims to ensure the best possible prognosis for complex cases of osteomyelitis through early referral to a specialist centre, where all elements of the condition can be addressed.

7.4.3 BACH version 3 in prognosis

The role of BACH in prognosis was previously discussed in chapters 3 and 4. Here, it was hypothesised that the higher the BACH score, the poorer a patient's prognosis. Defining prognosis is multifactorial and it includes the presence of clinical outcomes (for example, functional outcome of the extremity, cure of infection) and patient quality of life.

The retrospective assessment demonstrated that an increased score in a particular variable was associated with a risk of relevant complications. For example, higher severity in the bone involvement variable correlated with increased risk of bone related complications such as recurrence or non-union. The analysis presented in Chapter 4, was based on small sample size and was limited by the retrospective nature of the cohort. The correlation between prognosis and the score in each of the BACH variables will be assessed using the prospective analysis, chapter 8. It is hypothesised that each variable will correlate with relevant clinical complications.

A further measurable outcome related to prognosis is quality of life. This has been assessed extensively with regard to lower limb trauma (Gopal et al., 2004; Giannoudis et al., 2009; Dickson et al., 2015). However, there are limited published data regarding quality of life following treatment for osteomyelitis. Quality of life questionnaires, such as the EQ-5D-5L, have been validated for use in chronic disease generally. The EuroQol EQ-5D has been validated as a health related quality of life questionnaire (Brazier et al., 1993). These domains are graded a score (1-5) by patients, where 1 represents no problems and 5 represents severe problems (Rabin and de Charro, 2001). The retrospective assessment of BACH demonstrated an observational association with classification score and quality of life assessment score. The prospective study will include this measurement as one aspect for the assessment of prognosis, detailed in chapter 8.

8

Prospective Pilot and Prospective Protocol

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8.1 Introduction

Following retrospective and inter-user analysis of BACH, a prospective assessment of the classification will be made. This chapter will detail the protocol that will be used for this assessment and will be divided into 2 parts. In part (i), the logistics and feasibility of performing a multi-centred prospective study will be assessed by a pilot including 40 cases. These cases will be used to optimise a protocol for performing a full prospective assessment of BACH, presented in part (ii).

8.2 Part (i): Prospective pilot collection

8.2.1 Aims

The aim of the pilot study is to assess the feasibility of performing a prospective assessment in a cohort of patients who have been diagnosed with long bone osteomyelitis. Specifically, the aims of the pilot study are:

1. Assess the application of the H3 variable.
2. Assess the number of H3 patients who attend clinic for use in sample size calculation and duration.
3. Draw up relevant and appropriate data collection templates to be used in the full prospective study.

8.2.2 Methods

To assess the application of BACH in a prospective cohort, an assessment of 40 newly referred cases of osteomyelitis was undertaken. Consecutive cases of long bone osteomyelitis referred to two specialist bone infection centres (Nuffield Orthopaedic Centre, Oxford and Addenbrooke's Hospital, Cambridge) between March – July 2018 were included. Cases were eligible to be included if they met the inclusion criteria defined previously, chapter 4.

Cases were assessed in the outpatient clinic by the treating clinician. Here, the clinician applied the BACH criteria and demographic information regarding the

patient. This included date of birth, gender, site of infection, previous operation and co-morbidity. The EQ-5D-5L will not be assessed at this point due to lack of approval from the EuroQol at the time of commencement of the pilot.

8.2.3 Results

All 40 patients were able to be classified using BACH. The mean age of the patient at the time of clinic assessment was 52.6 years (SD 16.75, range 17.0 – 79.8 years). Half of the patients included were referrals from within the trust (designated as 'new patients') and half were referred from an orthopaedic clinic outside the two study centres (these were designated as 'new referrals').

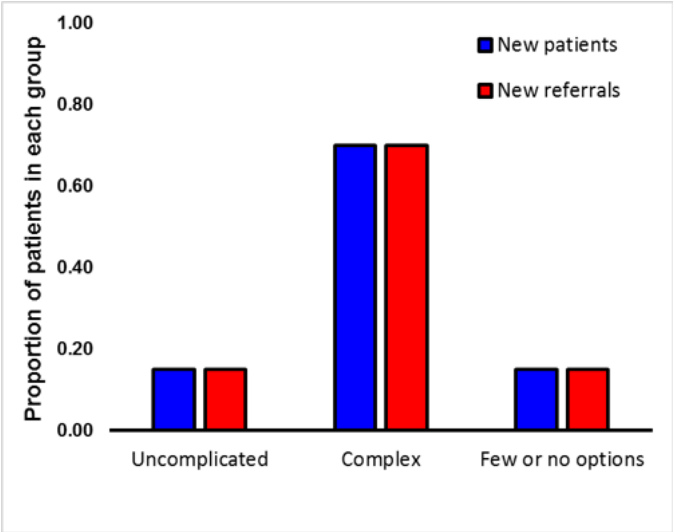


Figure 8.1: The Proportion of patients who were either new patients or referrals in the prospective pilot assessment. Patients were classified as either uncomplicated, complex or as having few or no treatment options. New patients (i.e. patients from within the trust) are shown in blue and new patients (i.e. patients referred from a non-specialist centre) are shown in red.

Overall, 6 patients were classified as 'uncomplicated' (15.0%), 28 patients as 'complex' (70.0%) and 6 as 'few or no options available' (15.0%), figure 8.1. The proportion of patients classified as 'uncomplicated', 'complex' and 'limited / few options' were identical in those that were new referrals and those that were from within the trust (new patients). Of the 20 referrals from other centres, 3 (15.0%) were deemed 'uncomplicated'. The remainder were classified as either 'complex'

or 'limited / few options available' reflecting appropriate referral to a centre with access to specialist clinicians with expertise in bone infection.

The majority of patients were classified as B1 (25/40, 62.5%) with the remainder being classified as either B2 (6/40, 15.0%) or B3 (9/40, 22.5%).

As hypothesised, a high proportion of patients (30/40, 75.0%) had not received previous deep tissue sampling and therefore were classified as Ax. In the remaining 10 cases, previous debridement or biopsy had been taken which made classification of the 'A' variable possible. Of these 10 cases, 7 were classified as A1 (70.0%), 2 as A2 (20.0%) and 1 as A3 (10.0%).

When classified according to the coverage of soft tissues, 19/40, (47.5%) were classified as requiring plastic surgical input and 21/40 (52.5%) classified as being suitable for primary wound closure. These proportions differ from the retrospective cohort where the majority of surgical wounds (76.0%) could be closed primarily without the aid of a plastic surgeon.

For the host status, 12.5% (5/40) of cases were classified as H3 due to patients either declining surgery (predominantly due to a quiescent infection) or being unfit for an operation. The remaining patients were either classified as H1 (40.0%) or H2 (47.5%). Six patients classified as H2 (6/40, 15.0%) had recurrent osteomyelitis that had undergone previous debridement surgery. Patients who were deemed H3 still received the classification of the other BACH variables despite being recommended for expectant management.

8.2.4 Discussion

This pilot study has demonstrated that BACH version 3 is applicable during clinical practice. It has also demonstrated the requirements for data collection templates that can be used in the prospective study. This preliminary data has demonstrated that 15.0% of referrals are 'uncomplicated' and may be managed in a non-specialist centre. However, it is unable to determine how many cases classified as 'complex' were not referred for specialist management.

In comparison to the retrospective cohort, chapter 4, only the 'B' variable was of similar distribution amongst classification variables. Feedback from surgeons have demonstrated that the optimum time point for the assessment of the bone involvement is at the time of surgery. In the prospective assessment, the intra-operative assessment of the bone involvement will therefore be compared to the 'B' classification variable.

The proportion of Ax patients in the prospective pilot was higher than in the retrospective cohort (70.0% vs. 34.4%) due to fewer patients having undergone surgical tissue sampling. The cases who had undergone tissue sampling were all 'new referrals' from other centres within the UK where previous osteomyelitis debridement had been performed. Of the 10 bacteria that were isolated, 30.0% were deemed high resistance which is more than double that of the retrospective cohort (12.5% were either A2 or A3). This preliminary data suggests that patients who have previously undergone debridement surgery with higher resistant isolates are more likely to require referral following treatment in a non-specialist centre. However, the sample size is limited and may be further limited by the sampling technique. This will be assessed further in the prospective cohort.

The coverage of the soft tissues were approximately divided equally into those classified as C1 and those classified as C2. These proportions differ from the retrospective cohort where the majority of surgical wounds (76.0%) could be closed primarily without the aid of a plastic surgeon. It may be that, following plastic surgical review, some of the cases classified as C2 will be reclassified as C1 thereby reducing the proportion of osteomyelitis that requires specialist management of the soft tissues. This will be assessed by the prospective cohort.

This pilot has suggested that 15.0% of referrals are H3. In the full prospective study, these patients would then enter the follow-up section of the prospective pathway, figure 8.2. However, it is possible for patients who have declined curative surgery to be reclassified as either an H1 or H2 if appropriate. To assess prognosis, it is important to record which patients are classified as H3 due to declining surgery or those who are unfit for surgery.

In terms of data collection, the data collection templates will allocate the reasons why patients have been classified as each value. For example, patients can be classified as Ax either because they have 'unknown growth' (because sampling has not occured) or culture negative osteomyelitis. Furthermore, the follow up time points have been defined as the usual time in which patients attend clinic after surgery. These will be 6 weeks, 3 months, 6 months, 1 year and 2 years. Using these follow up time points, the estimated duration of the study (based on sample size calculation) can be made. The data collection templates are presented in appendix F.

8.3 Part (ii): BACH ORGAN study protocol

8.3.1 Synopsis

The synopsis for the BACH ORGAN study is shown in table 8.1.

Study title	The BACH classification of long bone osteomyelitis: Outcomes Related to a Graded Assessment of osteomyelitis using a New classification system.
Internal reference number (or short title)	BACH ORGAN
Study design	Prospective, multi-centre observational cohort study
Study participants	Adult patients (aged 18 and over) attending with a new or recurrent presentation of long bone osteomyelitis
Planned sample size	281 patients (20% loss to follow up, 10% not meeting criteria)
Summary	The aim of this study is to examine endpoints after stratification of patients with long-bone osteomyelitis on the basis of a new classification system. This study will provide a prospective validation of the multidisciplinary BACH classification system of long bone osteomyelitis. The principle aim of BACH is to triage patients into groups where specialist management is required (complex) and where specialist management is not required (uncomplicated). This will allow an easy method of defining the requirement of specialist referral in osteomyelitis and allow patients to understand the complexity of their disease.
Planned study period / follow-up duration	From attendance in the outpatient clinic to 2 years following debridement surgery. The end point of the study is 2 years following the final patient is seen in the outpatient clinic. Patients will be enrolled over a 3-year period.

Table 8.1: Synopsis of the BACH ORGAN study protocol. Details of the BACH ORGAN study are presented with a summary and planned sample size. Follow-up time is specified.

8.3.2 Background and rationale

8.3.2.1 Research question

Can the application of the BACH classification system in adult patients with long bone osteomyelitis be applied accurately and appropriately stratify disease complexity in terms of referral and prognosis?

8.3.2.2 Definition of long bone osteomyelitis

Osteomyelitis is defined as the infection and inflammation of bone. It can be diagnosed based on a combination of clinical, radiographic, microbiological and histological criteria. Accepted definitions include the presence of symptoms and radiological evidence for >6 months in addition to either (i) pus surrounding a bone focus or osteo-cutaneous sinus tract (ii) 2 or more indistinguishable microbiological samples and (iii) histology suggestive of active infection (Sheehy et al., 2010). A long bone is defined by the presence of two physes. This study will include osteomyelitis that is present in the clavicle, humerus, radius, ulna, femur, tibia and fibula. It will not include the acral bones, axial skeleton or bones of the head and neck.

8.3.2.3 Definition of the BACH classification

The BACH classification system is a new classification system for long bone osteomyelitis that is based on the multi-disciplinary approach of successful treatment. BACH stands for Bone involvement, Anti-microbial options, Coverage of the soft tissues and Host status. These four variables are informed by a systematic review of the published classification systems in the literature (Hotchen et al., 2017). To define how these variables are classified, it has been developed using retrospective and inter-observer assessment. These assessments have resulted in version 3 of BACH and it is this version that will be used for the present study, (chapter 7, figure 7.8). Accompanying the version 3 of the classification system is a 'user key' that details how it should be applied in clinical practice, appendix E. It is hypothesised that application of the classification system will guide referral, therapeutic management and predict the prognosis of osteomyelitis.

8.3.2.4 Need for research

Osteomyelitis is a feared complication of trauma, surgical procedures and soft tissue infection (Gustilo and Anderson, 1976; Harris et al., 2009; Pollak et al., 2010) in addition to arising haematogenously (Waldvogel et al., 1970a; Lazzarini et al., 2004; McNally and Nagarajah, 2010). At present, patients commonly receive multiple operations which are a major burden on both the patient and the health care service. Over the last 40 years, multiple classification systems for bone and joint infection have been presented within the literature. However, these are not commonly used either due to complexity or because they are outdated with the application of current management strategies (Hotchen et al., 2017). Furthermore, patients are commonly unaware of the significance of infection as a complication of surgery (Kuiper et al., 2018; Lachman et al., 2018).

The BACH classification system reflects the modern day multi-disciplinary approach used in the management of osteomyelitis. Preliminary investigations have correlated higher BACH scores with an increased risk of clinical complications and worse health reported outcome measures (EQ-5D-5L), chapter 4. BACH has several distinct aims, listed below.

1. To act as a triage tool that allows the early referral of complex cases to a specialist centre. This will ensure that appropriate specialist care can be provided for the most complex cases.

2. The stratification of the complexity of osteomyelitis treatment will allow an evidence based prognosis to be offered to the patient at an early stage in the disease process.

3. The BACH classification system will allow the comparison of different osteomyelitis series. This will prove invaluable for the evaluation of multiple variables at scale, including differing treatment approaches, anatomical disease location, microbiology and geographical centres.

8.3.3 Objectives and study end points

For the BACH ORGAN study, primary, secondary and tertiary end points have been defined, table 8.2. The primary end point is to assess the application of BACH. The secondary end points are to assess the individual variables of the classification system against gold standards or alternative methods of measuring the classification system. The tertiary end points are to investigate for correlation between clinical outcome (for example the success of curative treatment and any complications) and health reported outcome scores to the returned classification scores.

8.3.4 Study design

The proposed study is a prospective, multi-centred observational cohort study that will assess the real-time application of the BACH classification system for use in clinical practice. It will assess the ability for BACH to guide referrals compared to a multi-disciplinary team and assess how the BACH classification correlates with patient reported and clinical outcomes. This study will not influence the treatment or clinical decisions that are offered to patients who are included.

8.3.5 Participant identification

8.3.5.1 Study participants

Consecutive patients in the included centres who are diagnosed with long bone osteomyelitis on the basis of clinical criteria will be entered into the study. Eligible patients should meet all of the inclusion and have none of the exclusion criteria listed below.

8.3.5.2 Inclusion criteria

- Age $\geq$18 years old
- Diagnosis of new or recurrent osteomyelitis
- Able to comply fully with the study protocol
- Patient consent for inclusion

	Objectives	Outcome measures
Primary end points	Assess the ability of BACH to guide referrals of long bone osteomyelitis. This will be in terms of:	
	(i) The outcome of MDT assessment	(i) Calculate the agreement between outcome of MDT discussion and BACH classification. Outcome can be: [a] treatment to be provided at a non-specialist unit [b] treatment to be provided at specialist unit [c] suppressive / non-reconstructive treatment [d] more information required
	(ii) The completeness of the BACH assessment compared to the MDT assessment	(ii) Assess the completeness of classification using BACH. Analyse cases where there is a discrepancy between the outcome of BACH and the outcome of the MDT. Record the reason the case was recommended for specialist referral.
	(iii) The accuracy of recommendation at 1 year follow-up	(iii) Compare the outcome of BACH classification with patient outcome at 1 year. Outcomes can be described as one of [a-d] above.
Secondary end points	Assess the application of the individual variables of the BACH application	
	(i) Bone involvement: correlate the pre-operative and intra-operative bone involvement score.	(i) Report the percentage accuracy of the bone involvement measured my clinical information and imaging (pre-operative) and intra-operative findings. Use this to calculate and report the $C\kappa$.
	(ii) Antimicrobial options: correlate the final anti-microbial options score and the ESCMID classification of multi-, extensive and pan drug resistant isolates (MDR, XDR and PDR).	(ii) Percentage accuracy of the 'A' score to the classification using the ESCMID criteria.
	(iii) Coverage of the soft tissues: correlate the pre-operative assessment for plastic surgical expertise and intra-operative requirement for plastic surgical expertise.	(iii) Report the percentage accuracy of the pre-operative 'C' classification with the inter-operative 'C' classification. Calculate the $C\kappa$ of 'C' classification pre-operatively and inter-operative assessment of the soft tissues.
	(iv) Host status classification: compare the assessment of host status in the pre-operative clinic to the assessment of host status at the time of surgery.	(iv) Report the agreement between host status defined in clinic (pre-operatively) and in hospital.
	(v) Assessment of the inter-user variability of the classification system	(v) Repeat classification at 1-year follow-up in a retrospective manner for each of the variables using a combination of imaging, susceptibility panels, operation details and clinical history. The classifier will be blinded to the results of previous classification. Compare the inter-observer $C\kappa$ value and accuracy.
Tertiary end points	Assess the ability of BACH to correlate clinical outcomes.	
	(i) Investigate whether clinical outcomes are predicted by the BACH classification score. Report on clinical outcomes of osteomyelitis including, but not limited to: Surgical complications: - Recurrence - Non / mal union - Fracture - Flap failure - Soft tissue abscess Medical complications: - DVT / PE - Drug reaction - Myocardial infarction / stroke - Kidney failure	(i) Patients will be followed for 2 years and clinical outcomes will be reported on an incidence per year basis. Complications will be assessed at routine clinic follow-up (6 weeks, 3 months, 6 months, 1 year and 2 years). Comparison using a binomial multivariate regression model to compare individual outcomes (per complication) to assess whether the recommendation for treatment with and without BACH was able to accurately stratify patients accurately. Variables to be included in the multivariate analysis: Bone involvement score, anti-microbial options score, coverage of the soft tissues score, host status score, age, gender, aetiology, treatment centre and site of infection.
	(ii) Assessment of the patient reported outcome measures and correlate this with the individual scores of the BACH classification system.	(ii) Compare EQ-5D score at the pre-operative clinic, 3-months, 6-months, 1-year and 2-years post debridement surgery. Correlate scores with individual BACH variables.

Table 8.2: Summary of the end points of the prospective assessment of BACH. The primary, secondary and tertiary end points are detailed with the individual objectives and the outcome measures that will be assessed throughout the study. $C\kappa$ = Cohen's kappa.

8.3.5.3 Exclusion criteria

- <18 years of age
- Unable to consent to participation in the study
- Patients who have already received debridement surgery for long bone osteomyelitis and have not been diagnosed with recurrence
- Not fulfilling the diagnosis of osteomyelitis (as described in 8.3.2).
- Unable to sign a patient consent form and without next of kin available to sign on the patient's behalf.
- Diagnosis of cognitive impairment.

8.3.6 Study procedures

8.3.6.1 Recruitment

Patients will be approached on the basis of suspected bone and joint infection. Patients who have a clinical diagnosis of lone bone osteomyelitis (either persistent symptoms or radiological changes for >6 months) will be approached at the outpatient clinic. Prior to debridement surgery, patients will be recruited using clinical criteria or radiological criteria for long bone osteomyelitis as described above (Sheehy et al., 2010).

After receipt of the full patient information leaflet and verbal explanation of the study, screening, consent and baseline data collection may take place at the initial conversation with the patient.

8.3.6.2 Informed consent

All researchers involved in consenting patients will be required to undergo Good Clinical Practice (GCP) training and this will be offered via the National Institute for Health Research (NIHR) Clinical Research Network. Individuals who meet the eligibility criteria will be provided with the participation information leaflet and consent form prior to any study procedures being performed. Participants

will be required to fully complete all consent procedures as detailed below before any study specific procedures are performed.

The participant will be allowed to consider the information, and will have the opportunity to question the investigator, study team or recruiting healthcare professional in order to decide whether they would like to participate in the study.

Written and verbal versions of the Participant Information Leaflet and Informed Consent will be presented to participants, appendix H. It will be clearly stated on the Participant Information Leaflet that the participant is free to withdraw from the study at any time for any reason without affecting their care or legal rights and with no obligation to give the reason for withdrawal.

There will be three copies of the informed consent. These will be the (i) patient copy (ii) copy for medical notes and (iii) copy for the study coordinator.

Patients will be consented for collection of information including NHS number and telephone number. These will be used for obtaining relevant information from the patient's notes and contacting the patient to organise follow-up. Patients will be consented to be contacted regarding the health quality of life questionnaire (EQ-5D-5L) at 6-8 weeks, 3 months, 6 months, 1 year and 2 years either following surgery or, in the case of non-reconstructive management, after the classification of H3 has been made.

8.3.6.3 Screening and eligibility assessment

A medically qualified individual or appropriately qualified nurse will assess the participant's eligibility against the criteria. The patients will be informed that they will be excluded from the study, if the diagnostic criteria for osteomyelitis are not met.

8.3.6.4 Study database

Identifiable data will be stored separately and according to local data protection guidance and NHS policy. Patients will be allocated a study number upon signing the consent form. This study number will be linked to patient NHS number and stored on the central University servers for 5 years from the commencement of the

study, as per GCP and University guidelines. Study data will be entered into the Research Electronic Data Capture (REDCap) database by a designated research nurse. No patient identifiable data will be stored on REDCap, only study number.

Data will be stored as encrypted comma separated value (.CSV) or portable document format (.PDF) files. At each centre, patients will be assigned a unique study identifier. The study identifier will comprise of 3 parts. The first part will denote the name of the study: ORG. The second will denote the centre where that the patient is recruited: Ox (i.e. Oxford). The final number will be allocated in ascending numerical order for each patient: 01 (i.e. the first patient recruited). An example study number would therefore be: ORG_Ox_01. The principle investigator will be responsible for overall data management in each centre.

8.3.7 Assessments

8.3.7.1 Baseline assessments

For patients who are eligible, baseline data will be collected at the initial consultation. This includes demographic data (specifically: date of birth, sex, occupation, allergy status and medications), contact details (specifically: home address and telephone number) and referral information (specifically: new patient or from another centre). Specific co-morbidities will be recorded along with their control, listed in table 8.3. Details of the infection will be recorded which includes aetiology (post-traumatic, secondary to a soft tissue infection, haematogenous or secondary to an orthopaedic procedure), site (upper limb: radius, ulna, humerus, clavicle and lower limb: femur, tibia and fibula), recurrence and details of previous procedures performed. Previous microbiology results will be recorded including susceptibility testing. Relevant laboratory tests to infection and control of co-morbidity will be recorded (specifically: c-reactive protein (CRP), haemoglobin (Hb) erythrocyte sedimentation rate (ESR), HbA1c, urea, creatinine, height, weight and leukocyte count). These data are routinely collected for assessment and management of long bone osteomyelitis. Additional parameters will not be collected as part of this study.

System	Co-morbidity
Cardiovascular	Myocardial infarction (<6 months / >6months) Angina (unstable / CABG / PTCA / no treatment) Congestive heart failure (please give exercise tolerance) Arrhythmia (supraventricular / atrial fibrillation / ventricular arrhythmia) Anaemia (Hb <11.5g/dL for women; Hb<12.5g/dL for men) Hypertension Peripheral venous disease (i.e. pulmonary embolus, deep vein thrombosis) Peripheral arterial disease (i.e. gangrene or aneurysm or intermittent claudication)
Respiratory	Chronic obstructive pulmonary disease Smoking (please provide details) Restrictive lung disease (please provide details)
Gastrointestinal	Acute or chronic pancreatitis Hepatic failure
Renal	Acute kidney injury (please provide creatinine and urea measurements) Chronic kidney injury (please provide creatinine and urea measurements) Dialysis therapy
Neurological	Stroke (significant neurological deficit / no residual deficit) TIA (<6 months / >6 months) Dementia (mild / moderate / severe) Paralysis (paraplegia / hemiplegia) Other intra-cerebral pathology (e.g. Parkinson's disease) Other peripheral neurological pathology (e.g. multiple sclerosis, myasthenia gravis)
Endocrine	Type 1 diabetes mellitus Type 2 diabetes mellitus (HbA1C ≥8.0% / HbA1C <8.0%)
Immunological	Long term corticosteroid use (>20mg per day for >4 weeks) Haematological malignancy Other acquired immunodeficiency (please specify)
Body weight	Malnutrition (albumin <30g/L) Obesity (BMI ≥38kg/m^2)
Malignancy	Remission (please specify primary) Currently under treatment with curative intent Previous radiation therapy Palliation Presence of pathological fracture
Other	Condition not listed (i.e. inflammatory arthritis)

Table 8.3: Summary of the specific medical co-morbidity that will be collected as part of the BACH ORGAN study. Co-morbidity are grouped into sub-categories. CABG = coronary artery bypass graft, PTCA = percutaneous coronary angiography.

Assessment of quality of life will be performed at the first consultation. Patients will be assessed for their level of perceived health using the EQ-5D-5L questionnaire, appendix G. This requires the patient to rate 5 domains of daily activity (mobility, self-care, ability to perform usual activities, pain and anxiety) (Rabin and de Charro, 2001). A visual analogue score will be used to allow the patients to rate their overall health at the precise moment in time on a scale of 0 – 100. Permission has been granted by the EuroQol Research Foundation to use the EQ-5D-5L for this study for up to 450 patients (reference number 27103). EQ-5D-5L has

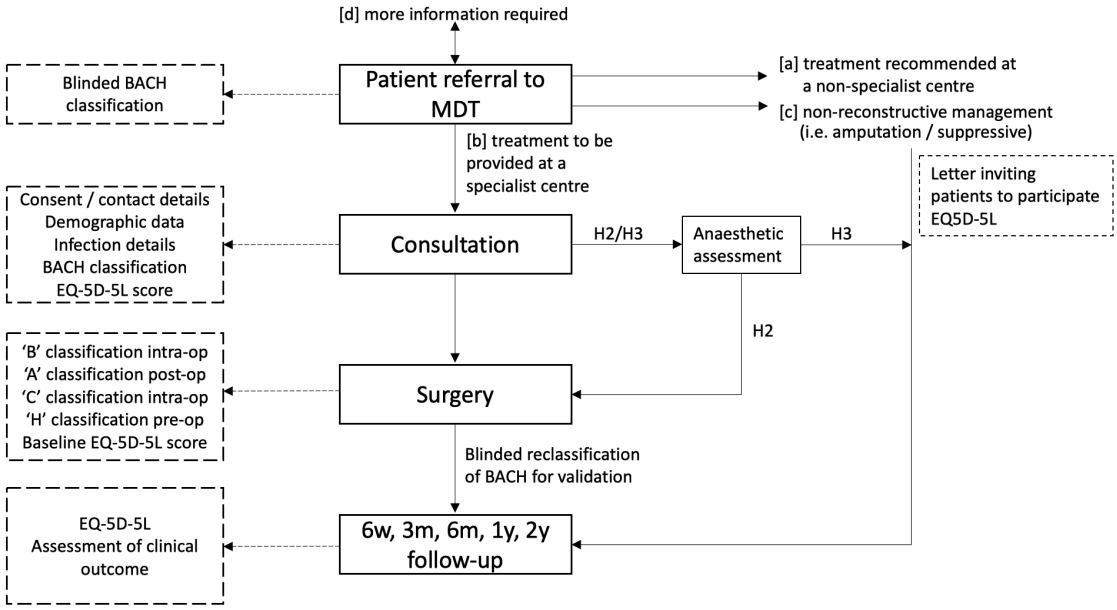


Figure 8.2: Flow diagram of the BACH ORGAN study protocol, detailing the assessments that will be performed at each time point. The boxes bounded by a dashed line are the assessments that will be made as part of the BACH ORGAN study. The four options that can arise from the MDT are detailed in the primary end point of the study. If a patient is classified as either H2 or H3, they should undergo an anaesthetic assessment. If H3 is confirmed, then the patient should enter the follow-up part of the study. Data collection templates are shown in appendix F.

demonstrated superiority in terms of measurement properties when compared to EQ-5D-3L (Buchholz et al., 2018).

Other clinical attributes will be recorded including the requirement for an anaesthetic assessment and whether the patient consents to debridement surgery. These will be used to classify the host status. At this point, patients who are classified as H3 will enter the 'follow-up' phase of the study. This process is summarised in figure 8.2.

8.3.7.2 In hospital assessment

All patients who are deemed H1 and H2 will be admitted to the ward for osteomyelitis treatment, figure 8.2. At this point, the co-morbidity will be reassessed as detailed in table 8.3 and the final host status will be made by the assessor. Further hospital attendance between the pre-operative clinic and admission for debridement surgery will be recorded. Attendance at an anaesthetic pre-operative appointment will

be recorded prior to surgery.

Intra-operatively, the surgeon performing the debridement will be asked to assess the bone involvement. The requirement for plastic surgical expertise to close the wound will also be recorded. This will finalise the bone and coverage of the soft tissues classification. Any stabilisation (either internal or external fixation, including circular frame) will be recorded at the time of surgery.

Post-operatively, confirmation of eligibility through intra-operative, microbiological and histological findings will be assessed. Any patient who is excluded at this point will be informed of the outcome, why they have been excluded and thanked for their willingness to participate. Following 7 days of microbial culture, the 'A' classification will be finalised.

8.3.7.3 Follow-up phase of the study

The follow-up phase of the study will commence from discharge after the debridement surgery or following the classification of a patient as an H3, figure 8.2. The follow-up is outlined below.

Clinic follow-up at 6 weeks, 3 months, 6 months and 24 months

Standard follow-up will be performed in clinic to assess medical and surgical complications including EQ-5D-5L assessment. If a patient does not attend any of the above outpatient clinic appointments, patients will be contacted and invited to attend clinic. If the patient still does not attend, then they will be asked relevant questions over the telephone (regarding complications and the 5 domains of the EQ-5D) and asked to complete a VAS by text message.

Clinic or telephone follow-up at 12 months

Standard clinic follow-up will be performed at 12 months to assess the EQ-5D-5L score and the assessment of clinical outcome. This will include assessing the outcomes of patients who were managed at [a] a non-specialist centre or at [c] for suppressive / non-reconstructive management. These outcomes will be compared to the outcome defined by the BACH classified at the entry point of the study.

8.3.8 Discontinuation of participants from the study

Individuals who agree to participate in the study have a right to withdraw at any time. In addition, investigators may discontinue a patient from the study at any point if they consider this necessary including:

- Absence of intra-operative evidence of osteomyelitis
- Significant protocol deviation or significant non-compliance
- Loss to follow-up
- Withdrawal of follow-up for data collection
- If the patient does not meet the eligibility criteria

8.3.9 Definition of end of study

The maximal end point of this study is the final clinic appointment at 2 years. If this time point is not met (i.e. secondary to patient mortality or lost to follow-up), then last point of patient contact that is recorded in the database will be the end of study for that patient. The end of the study will be the date of the last medical notes review of the final study participant. Patients will be continued to be followed up if they have recurrence or any other surgery during the entire study period. The pilot collection has suggested that the required number of patients will be recruited over a 3-year period. Patient recruitment will be stopped if the required number is reached before the end of this time period.

8.3.10 Data analysis

8.3.10.1 Statistical analysis

Data analysis will follow the general principles of the CONSORT 2010 statement. Quantitative data will be presented as mean or median values (as appropriate) with 95% confidence intervals or standard deviations. Baseline statistics will be correlated with scores of individual groups using a multi-variate analysis and presented with odds ratios. Individual details are discussed below.

The primary end points will assess the ability of the BACH classification of long bone osteomyelitis to guide referrals during clinical practice. This will be performed

by comparing the outcome of assessment by specialist clinicians (at a specialist Bone Infection MDT meeting) with the outcome of assessment using the BACH classification system. Both BACH and the MDT meeting has four possible outcomes. These are [a] treatment to occur in a non-specialist centre, [b] treatment to occur in a specialist centre, [c] suppressive or non-reconstructive management and [d] more information required. The ability of BACH to predict these outcomes will be assessed and presented as the percentage of cases where management was successfully stratified. A qualitative assessment will highlight areas used for the guidance of treatment from the MDT that are not included in the classification system.

The secondary end points assess how the classification of each variable may change over the treatment course. All four variables will be assessed at different time points during the clinical course. The bone involvement will be assessed at the first consultation and intra-operatively, the antimicrobial options will be compared to the ESCMID classification and the coverage of the soft tissue classification (as defined pre-operatively) will be correlated to the requirement for soft tissue transfer by a plastic surgeon. The agreement for each of these variables will be reported as a percentage accuracy and assessed using Cohen's kappa ($C\kappa$) (presented with 95% confidence intervals). The inter-observer reliability will be assessed using a blinded retrospective classification of each case following debridement surgery at 1 year based on (i) pre-operative imaging, (ii) full anti-microbial susceptibility panels, (iii) the requirement of a flap and (iv) the co-morbidity of the patient. This will be compared using a $C\kappa$ to the classification made during the hospital admission for surgery.

The tertiary end points will assess how the BACH score can be used in prognosis. Clinical complications (either surgical or medical) will be assessed and compared to the individual variables of BACH using a multi-variate binomial analysis. This will account for any confounding based on patient attributes such as age, sex, aetiology of infection, treatment centre and site of infection. Patient reported outcome measures will also be recorded. The VAS will be compared to the previously reported average scores for the UK population (Williams, 1995). The EQ-5D-5L index score will be calculated using the weighting prescribed to the UK population

(Devlin et al., 2018). These measures will be used to assess the ability for BACH to predict patient reported outcome measures.

8.3.10.2 Number of participants / sample size

Power calculation has demonstrated that to achieve a significant improvement in the accuracy of classification at 80%, alpha of 0.05 with a superiority margin of 0.07, then 212 patients with osteomyelitis will need to be included. Based on previous studies, it is hypothesised that 20% of patients will be lost to follow-up. It is expected that a further 10% of patients will be excluded owing to a lack of intra- and post-operative evidence of osteomyelitis when the participant undergoes debridement. This results in a total of 281 patients required to be recruited for this study to report outcomes appropriately.

8.3.11 Data management

Electronic case report forms (CRFs) will be used to collect patient data that is specified in the study protocol. CRFs will contain the unique study identifier only and will not include any identifiable data. Data collected in the CRFs will be tailored to each follow-up time point to include (but not limited to) the following where relevant: information regarding the infection (site, previous debridement surgery, aetiology, details regarding co-morbidity), BACH classification scores at baseline, pre-operatively, inter-operatively and post-operatively, retrospective 'reference' classification scores, relevant laboratory results (CRP, WBC, ESR and HbA1c), records of medical complications and records of health-related outcome measures. The data collection templates are shown in appendix F.

8.3.11.1 Access to data

Direct access will be granted to authorised representatives from the host institution and the regulatory authorities to permit study related monitoring, audits and inspections. Anonymised data will be stored on the REDCap server and will only be accessible by named individuals on the study team.

All patient information presented as part of a publication, oral or podium presentation will be anonymised. Requests for data sharing will be assessed on an individual basis. These will be decided by the chief investigator and only be granted following demonstration of (i) strict adherence to encryption of data with anonymisation as required, (ii) strict adherence to data analysis that the patient will have given informed consent and (iii) data is disposed of following the intended timeframe of use. Any users that request data will be required to adhere to the safeguards that are detailed within the Data Protection Act 1998.

8.3.11.2 Quality assurance procedures

This study will be monitored and audited to the standards that are set out on the currently approved protocol, GCP and standard operating procedures. Data will be assessed for the compliance with protocol.

8.3.12 Ethical and regulatory considerations

8.3.12.1 Declaration of Helsinki

The chief investigator will ensure that this study is performed in accordance with the Declaration of Helsinki (present version, 2013).

8.3.12.2 Good clinical practice

The chief investigator will be responsible in ensuring that this study is conducted in accordance with GCP guidance.

8.3.12.3 Approvals

Protocols and consent forms will be submitted for approval by local research ethics committees of the centres that are involved in the study including the host institutions. It will be the responsibility of the chief investigator to ensure that this is performed prior to the commencement of the study.

8.3.12.4 Reporting

The principle investigators shall submit an annual report to the local research and ethics committee and host institution. In addition to this, a final summary of the data collected will be submitted to the relevant research and ethics committees.

8.3.12.5 Participant confidentiality

Confidentiality will be maintained at all times by all involved within the study. Only staff who are part of the study will have access to the data collected. The CRFs will be identifiable only by the individual study identification number. CRFs will hold the relevant clinic and patient outcome data. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is feasible to do so.

8.3.12.6 Publication policy

The investigators will be involved in the compiling of manuscripts, posters, podium presentations and other significant output from this work. Work from this study will be presented in peer reviewed journals and at scientific meetings and conferences. The authors will acknowledge any funding bodies that have supported this research.

9

General Discussion, Concluding Remarks and Summary

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9.1 General discussion

9.1.1 Thesis aims

The aims of this thesis were posed in chapter 1. To address these, a number of investigations and analysis have been performed. Firstly, a systematic review of the literature revealed that 13 previous classification systems for long bone osteomyelitis were available. By analysing these with current management strategies, four variables were concluded to be the most important for classification. These were

the bone involvement (B), the anti-microbial options (A), the coverage of the soft tissues (C) and the host status (H). Using parallels from other classification systems (TMN classification of cancer and diabetic foot classification) and learning from different scoring systems of the 'host', each of the four variables was stratified in terms of severity. Eventually, the BACH classification system aimed to focus on the guidance of management and offering prognosis to patients who have long bone osteomyelitis. The individual assessments within this thesis have aimed to optimise the utility and application of the classification system.

Throughout retrospective analysis, inter-user analysis and subsequent detailed investigation into the variables included, the classification system has been revised to continually optimise its reproducibility and usability. This version of the classification system will be applied to a prospective cohort to assess (i) the application, (ii) assistance with management and (iii) the prediction of prognosis for osteomyelitis. Following a pilot assessment, this study will be commenced on a larger scale for the validation of BACH. The protocol for this study, named the BACH ORGAN study, was presented in chapter 8.

9.1.2 Application of BACH

The inter-user assessment performed in chapter 6 assessed the application of the BACH classification system amongst a number of users who had a variety of clinical backgrounds. Although osteomyelitis is optimally treated by a multi-disciplinary approach (Ziran et al., 2003; Salvana et al., 2005), patients are commonly referred to an orthopaedic surgeon when osteomyelitis is suspected or diagnosed. In non-specialist centres, we propose that an orthopaedic surgeon, who may be inexperienced with the treatment of osteomyelitis, should apply the classification system. The inter-user assessment suggested application of the classification system is possible regardless of clinical speciality and clinician experience. However, it is possible that users who do not commonly use the classification system may find it complex. For these clinicians, the infrequent application of BACH may result in an inaccurate classification. One method of addressing this problem is to provide a tool (for

example an interactive key or form) to assist with the classification. This tool should be easy to access via a website. Schmidt (Schmidt et al., 2014a) published a diagnostic scoring system for osteomyelitis which was accompanied by a website to aid with its application (Schmidt et al., 2014b).

9.1.3 Scoring of the individual variables

One issue that adds to the complexity of the classification system is that the numerical weighting or scoring of each variable is inconsistent. This is illustrated by the presence of a B3 category which is not equivalent to the H3 category. In terms of scoring the bone involvement, it is clinically important to distinguish osteomyelitis as part of an infective non-union (B2) and osteomyelitis that involves a joint (B3) for both management and prognosis (Ferguson et al., 2014; Bose et al., 2015). This has been substantiated by the preliminary results from chapter 4. B2 and B3 osteomyelitis had poorer clinical and reported outcomes. It is therefore appropriate to include B2 and B3 osteomyelitis in the 'complex' group.

Preliminary data has suggested that clinical outcomes were not well stratified by the antimicrobial options variable, chapter 4. One explanation for this may be that all cases presented were treated by specialist ID physicians. Furthermore, there was a small proportion of A3 and A2 cases in comparison to A1 and Ax cases which did not allow a statistically robust conclusions to be drawn. Despite this, it appears logical that as the grading of a variable increases, so do the severity of disease and the complexity of management. It is therefore unclear whether the A3 category should be part of the 'complex' or 'few or no options available' tier of the classification system. The classification of the anti-microbial options is made after either CT- or ultrasound guided biopsy or sampling from debridement surgery. The classification of this variable is made based on antibiotic susceptibility testing. However, debridement surgery may involve the application of local antibiotics that can achieve concentrations that are significantly higher than peripherally administered antibiotics. This may result in a more effective treatment for patients where isolates are resistant to the concentrations of peripherally administered

antibiotics but susceptible to the concentrations of locally applied antibiotics. The prospective study will assess whether this group have a poorer prognosis compared to the Ax, A1 and A2 groups. Based on these results, the scoring for each of the variables will be finalised.

Throughout the retrospective (chapter 4) and inter-user assessment (chapter 6), none of the included patients were deemed H3. In the prospective pilot study, chapter 8, 12.5% of patients were deemed H3. This included two sub-groups of patients who are not directly comparable. Firstly, the H3 classification consists of patients who are medically unfit to receive an anaesthetic. These patients are systemically unwell and they will have a poor prognosis following debridement surgery. The second sub-classification of the H3 variable are patients who have 'declined' surgery. As the description suggests, a patient may enter this group because they do not wish to undergo an operation. However, in patients where the osteomyelitis is quiescent, the patient may still 'decline' surgery because it may not be beneficial to undergo debridement at that stage in the disease process. These two patient groups clearly differ significantly and have different management options and prognoses. To assess this, the reason why patients are classified as H3 will be recorded in the prospective assessment. These patients will be followed up over two years with outcomes recorded. A further group, H0 or Hx, may need to be introduced to denote patients who do not require an operation because it is not problematic at that specific time point.

9.1.4 Versions of the classification system

The BACH classification system has evolved as a consequence of the investigations performed as part of this thesis. Due to this progression, the retrospective analysis and the inter-user analysis does not necessarily represent validation of the final version of the classification system. The prospective assessment will use version 3 of BACH and validate it for use in clinical practice.

9.1.5 Evolution of the classification system over time

Previous classification systems for osteomyelitis have become outdated with the advancement of medical therapies and treatment options. In comparison to the Ceirny Mader classification system (Cierny and Mader, 1984), BACH has incorporated two additional variables that represent essential treatment teams of the multi-disciplinary approach (Ziran et al., 2003; Salvana et al., 2005). These are the plastic surgeons (the soft tissues) and the infectious disease physicians (the anti-microbial options). Of the four BACH variables, the anti-microbial options is the one that is most likely to vary over time along with changing bacterial resistance patterns (Kremers et al., 2015). In osteomyelitis, the microbiology has only been classified once previously (Romanò et al., 2011). BACH has taken an alternative approach and adapted the ESCMID criteria for use in bone and joint infections (Magiorakos et al., 2012). The ESCMID criteria are pre-defined which mean that as resistance patterns change, the definitions for each group of isolate will be updated over time. However, it is unknown how the multi-drug resistant bacteria as classified by ESCMID influence outcome in osteomyelitis. It follows that as the number of 'options' that are available for treatment decrease, the more complex an isolate is to treat. Therefore, using an 'equivalence' method to measure the degree of isolate complexity is a reasonable alternative to these guidelines. How these equivalence methods will work in alternative centres will be investigated using the prospective assessment.

9.1.6 Use in paediatric osteomyelitis

The BACH classification system has been designed for use in adult patients with long bone osteomyelitis. During the analyses performed as part of this thesis, the application of BACH to paediatric patients has not been tested. This was due to the cohorts available and to minimise the complexity of the target group. Thus, it is unknown whether BACH is feasible in a paediatric population, since the hosts, the need of soft tissue cover and most likely the epidemiology of the micro-organisms differ in comparison to an adult osteomyelitis population.

9.2 Concluding remarks

The development of the BACH classification has involved combining the current approaches, comprehensive systematic review and world leading expert opinion in osteomyelitis. Despite this, distilling a complex condition into a simple and usable classification system is difficult. As stated in chapter 3, classification systems need to be simple to remember and easy to use. However, the creation of BACH has demonstrated achieving a balance between simplicity and an appropriate level of clinical relevance is difficult to achieve.

Looking forward, large scale testing needs to be undertaken with longitudinal follow-up to define the boundaries of how the classification system is used. To develop a useful classification system, it requires a clinical application that improves the care that can be offered to patients. In the case of BACH this is to assist clinicians in making early referral of complex cases and to offer prognosis to patients.

The final part of validation is the prospective assessment that will be completed in multiple centres. BACH will be used to measure the prognosis and compare clinical outcome between these cohorts.

9.3 Summary

This thesis has introduced a simple, non-invasive intervention that can be used to improve the clinical care that is offered to patients with long bone osteomyelitis. By applying the results from systematic review, published literature and detailed statistical analysis, a triage tool and a classification system for long bone osteomyelitis has been developed. This classification system has undergone retrospective and inter-user assessment, allowing modifications to be made so that it can be improved. The work performed as part of this thesis has led to a prospective assessment that will be used to apply BACH to clinical practice in an effort to optimise the treatment that patients with long bone osteomyelitis receive.

Appendices

A

Systematic review search terms and PRISMA flow diagram

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A.1 Systematic Review Search Terms

1. Medline – "Bone Infection"[title/abstract] → 697
2. Medline – Osteomyelitis MESH [title/abstract] → 18,956
3. Medline – Classification[title] → 52884
4. Medline – Scoring[title/abstract] → 55107
5. Medline – Staging[title/abstract] → 58203
6. Medline - (1 OR 2) AND 3 → 42
7. Medline – (1 OR 2) AND 4 → 38
8. Medline – (1 OR 2) AND 5 → 68

9. Ovid / EMBASE – "Bone Infection"[Abstract/Title] →1724
10. Ovid / EMBASE – Osteomyelitis[Abstract/Title] → 44712
11. Ovid / EMBASE – Classification[Title] → 129291
12. Ovid / EMBASE – Scoring[Title/abstract] → 153249
13. Ovid / EMBASE – Staging[title/abstract] → 160527
14. Ovid / EMBASE – (9 OR 10) AND 11 → 93
15. Ovid / EMBASE – (9 OR 10) AND 12 → 104
16. Ovid / EMBASE – (9 OR 10) AND 13 → 172
17. Ovid / EMBASE – removal of duplicates from 14 OR 15 OR 16 → 188

A.2 PRISMA flow diagram

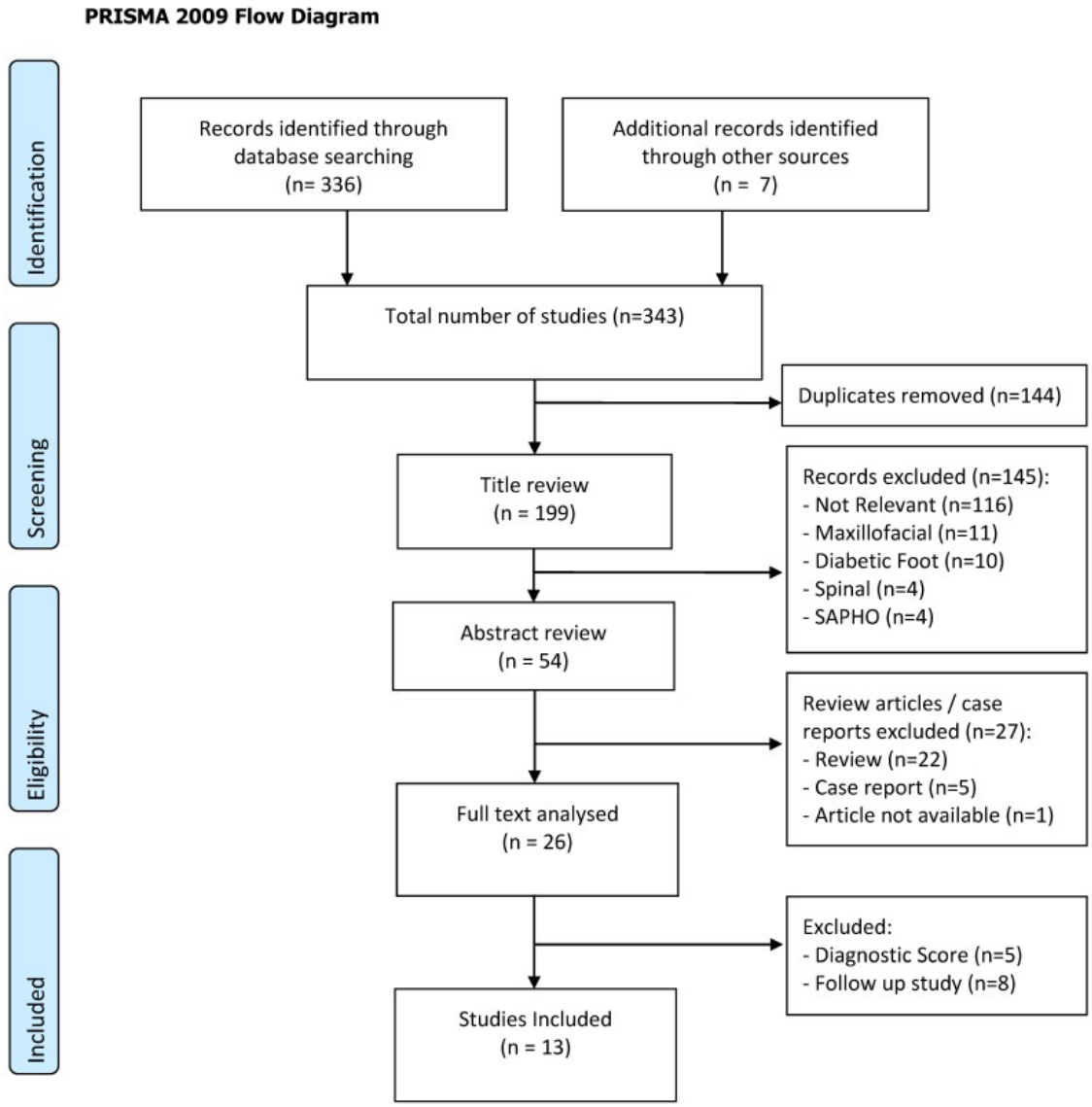


Figure A.1: PRISMA flow diagram. Flow diagram of the articles returned from the search strategy and how each were included or excluded from review.

B

Development of the inter-user key

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B.1 Version 1 of the inter-user key

Version 1 of the inter-user key is presented on the following pages. This version of the key was used in the inter-user pilot assessment presented in chapter 6, part 1.

Introduction:

We have designed a new classification system for long-bone osteomyelitis which uses four elements of the multi-disciplinary team to stratify patients into groups that deem the osteomyelitis as uncomplicated, complex or palliative. These elements are the **B**one involvement, **A**ntimicrobial options, **C**overage of the soft tissues and the **H**ost status. Ultimately, these groups determine where the patient should be treated, either in a specialist centre or a non-specialist centre.

Aim:

The aim of this intra-observer analysis is to assess the new classification system for reproducibility.

Key:

Bone involvement

Bone involvement is divided into three categories:

- B1 that has a cavitary pattern of bone involvement (figure 1a),
- B2 that has a segmental pattern of bone involvement (figure 1b)
- B3 that has either cavitary or segmental osteomyelitis with the involvement of a joint (figure 1c).

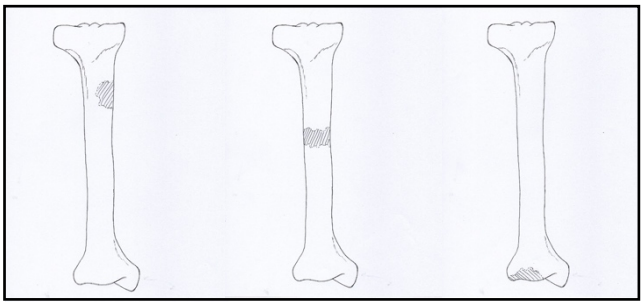


Figure 1a: cavitary bone involvement (denoted by hatched area); 1b segmental bone involvement; 1c osteomyelitis with joint involvement.

Antimicrobial treatment options

The antimicrobial options can be divided into groups:

- Ax which denotes, no microbial growth or not known,

If the microbiology has been defined by deep sampling, then:

- A1 or Ax: good treatment options,
- A2: limited treatment options (MDR according to ESCMID)
- A3: that denotes no treatment options – pan drug resistant (XDR or PDR according to ESCMID)

Coverage of the soft tissues

The soft tissue coverage can be divided into two categories.

- C1 are patients who do not need plastic surgical intervention to close the wound.
- C2 are patients who necessitate complex tissue management for wound closure

Host status

The host status can be divided into three categories. H1 denotes that the patient is:

- Free from irreversible immunocompromise

- Free from either micro or macrovascular disruption to the affected limb
- Without previous osteomyelitis debridement (for infection at the same site)

Any person who does not meet the requirements are deemed H2 or H3. Those who are not fit and can not be made fit for an anaesthetic are deemed H3 and the remainder are deemed H2.

The classification can be summarised by the following table with an example for each category.

Category	Score	Definition	Example
Bone	B1	Cavitary pattern of osteomyelitis involvement	
	B2	Segmental pattern of osteomyelitis involvement	
	B3	Osteomyelitis that extends into a joint	
Anti-microbial options	Ax	No microbial growth or unknown	-
	A1	Good antimicrobial options	Staphylococcus aureus – susceptible to everything except penicillin
	A2	Limited antimicrobial options	Staphylococcus aureus – resistant to flucloxacillin (MRSA) Staph aureus sensitive to fluclox but resistance to rifampicin in the presence of metal work Patient anaphylactic to penicillin,
	A3	No antimicrobial options	VRE resistant to everything
Soft tissue	C1	Plastic surgical expertise not required	Haematogenous femoral osteomyelitis with intact soft tissues. Skin easily closable after excision.
	C2	Plastic surgical expertise required	Middle third tibial infected non-union with ulceration requiring free muscle transfer.

Host status	H1	Host has no impairment with osteomyelitis healing (free from antibiotic allergy, free from irreversible immunosuppresion, free from macro or micro vascular compromise of the infected limb, free from previous osteomyelitis surgery).	19 year old motor cyclist who is normally fit and well. Non-smoker and infected tibial fracture.
	H2	Antibiotic allergy, irreversible immunosuppression, macrovascular / macrovascular compromise to affected limb or previous osteomyelitis surgery	Patient with long term steroids for rheumatoid arthritis, patient with peripheral vascular disease or evidence of end stage organ damage with diabetes mellitus, previous failed surgery for osteomyelitis
	H3	Patient not fit for surgery despite optimisation or refuses surgery	Patient with previous respiratory failure following anaesthetic.

B.2 Version 2 of the inter-user key

Version 2 of the inter-user key is presented on the following pages. This version was optimised based on the results and feedback obtained following the pilot inter-user assessment presented in chapter 6, part 2.

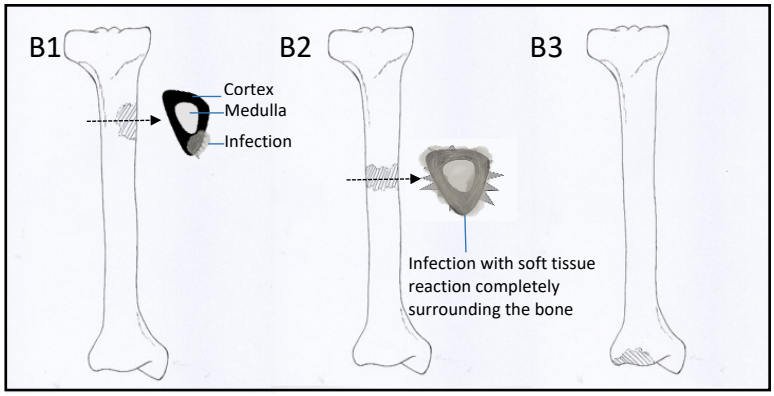
Introduction: We have designed a new classification system for long-bone osteomyelitis. The classification system uses the multi-disciplinary approach to osteomyelitis. The aim is to stratify patients so they can be treated in a centre that has appropriate services.

The categories that are used are the **B**one involvement, **A**ntimicrobial options, **C**overage of the soft tissues and the **H**ost status (**BACH**).

Aim / Task: We have compiled a selection of 20 long bone osteomyelitis patients that we would like you to classify. Regardless of your speciality, we would like you to classify each category of BACH. The classification of each category is explained below.

Bone involvement: The bone involvement is divided into three groups:

- B1: Cavitary pattern of bone infection (best diagnosed on transverse MRI / CT imaging).
- B2: Segmental pattern of bone involvement. This includes infected non-union (best diagnosed on transverse MRI / CT imaging).
- B3: Osteomyelitis that extends into a joint.



Antimicrobial treatment options: The antimicrobial options can be divided into the following groups:

- Good treatment options – A1: patients are able to take anti-biotics that are active against the bacteria isolated or Ax no microbial growth or sensitivities unknown.
- Limited treatment options – A2: antibiotic options are limited by either resistant bacteria (e.g. MDR according to ECSMID or resistance to anti-biofilm antibiotics in the presence of metalwork) or patient factors (allergy / limited absorption syndromes)
- No treatment options – A3: that denotes no treatment options: pan or extensively drug resistant

Coverage of the soft tissues: The coverage of the soft tissues can be divided into two groups:

- C1: patients who do not need plastic surgical intervention to close the wound.
- C2: patients who necessitate plastic surgical expertise for wound closure

Host status: The host status is divided into three categories.

- H1: denotes that the patient is free from conditions that affect wound healing and is optimised for surgery. An H1 patient is:
  - (i) Free from **irreversible immuno-compromise**
  - (ii) Free from either **micro-** (e.g. diabetes mellitus) or **macro-vascular** (e.g. angina, stroke, peripheral vascular disease) disruption to the affected limb
  - (iii) No history of **debridement surgery for the same osteomyelitis** infection
- H2: Any person who does not meet these requirements but is fit for surgery

- H3: Any person who does not meet these requirements but is not fit for surgery OR does not wish to have an operation.

Below is a table summarising the BACH classification system:

<table>
<tr><th></th><th>Bone involvement (B):</th><th>Antimicrobial options (A):</th><th>Coverage by soft tissue (C):</th><th>Host status (H):</th></tr>
<tr><td>Uncomplicated</td><td>B_1: Cavitary infection without joint involvement</td><td>A_1: treatment options available or (A_x): unknown / no anti-microbial growth</td><td>C_1: Direct closure possible</td><td>H_1: fit for definitive surgery with optimisation if required</td></tr>
<tr><td rowspan="2">Complex: Specialist intervention needed</td><td>B_2: Segmental infection without joint involvement</td><td rowspan="2">A_2: limited treatment options available (MDR according to the ESCMID guidelines)
or
Resistance to anti-biofilm antibiotics in presence of an implant
or
Bacteria that is not part of the ESCMID guidelines with resistance to appropriate anti-microbial agent</td><td rowspan="2">C_2: Direct closure not possible; plastic surgery expertise required</td><td rowspan="2">H_2: definitive surgery possible but with continued host compromise (micro / macrovascular disruption to affected limb or irreversible immunocompromise) after optimisation
or
Recurrent osteomyelitis after previous debridement</td></tr>
<tr><td>B_3: Any osteomyelitis with associated joint involvement</td></tr>
<tr><td>Limited treatment options available</td><td></td><td>A_3: No medical treatment options available (XDR or PDR according to the ESCMID guidelines)</td><td></td><td>H_3: unfit for definitive surgery despite specialist intervention / patient refusal for surgery</td></tr>
</table>

Examples of the classification system are given in the table below.

		Definition	Criteria
Bone	B1	Cavitary infection without joint involvement	CT / MRI: • Coronal: partial thickness lesion • *Sagittal: unable to diagnose* X-ray: • Superficial infection • Presence of united fracture or mal-union PET CT: • Only the area of active infection Clinical: • Able to weight bear with / without internal / external stabilisation
	B2	Segmental pattern of osteomyelitis involvement Non healed fracture	CT / MRI: • Coronal: complete thickness lesion, involving the surrounding muscle • *Sagittal: unable to diagnose* X-ray: • Infected non-union PET CT: • Only the area of active infection Clinical: • Need for internal / external fixation to have stability
	B3	Osteomyelitis that extends into a joint	CT / MRI: • Coronal: visualisation of high intensity signal into the joint • Sagittal: visualisation of high intensity signal into the joint X-ray: • Fracture extending into the joint PET CT: • Only the area of active infection Clinical: • Pain on movement of the joint
Anti-microbial options	Ax	No microbial growth or unknown	
	A1	Good antimicrobial options	Microbiology grows a Staphylococcus aureus that has full sensitivity to all antibiotics tested apart from amoxicillin and penicillin Micobiology grows Enterobacter cloacae that is sensitive to ciprofloxacin, gentamicin, meropenem, ceftriaxone but is resistant to amoxicillin, co-amoxiclav and cephalexin.
	A2	Limited antimicrobial options	Microbiology grows a multi-drug resistant Staphylococcus aureus that is resistant to flucloxacillin, amoxicillin, ciprofloxacin, tetracycline and gentamicin (MRSA). Microbiology grows a Staphylococcus aureus that is sensitive to flucloxacillin, ciprofloxacin and gentamicin but resistant to rifampicin in the presence of an implant or metalwork. Microbiology grows Staphylococcus aureus that is sensitive to flucloxacillin, ciprofloxacin and gentamicin but patient is anaphylactic allergic to penicillin.
	A3	No antimicrobial options	Microbiology grows a vancomycin resistant Enterococcus that is resistant to all antibiotics tested

Soft tissue	C1	Plastic surgical expertise not required	Haematogenous femoral osteomyelitis with intact soft tissues. Skin easily closable after excision. Easily excisable sinus. Post-traumatic tibial osteomyelitis will good, healthy soft tissues. Skin easily closable after excision. No evidence of sinus.
	C2	Plastic surgical expertise required	Middle third tibial infected non-union with ulceration requiring free muscle transfer.
Host status	H1	Host has no impairment with osteomyelitis healing (free from antibiotic allergy, free from irreversible immunosuppresion, free from macro or micro vascular compromise of the infected limb, free from previous osteomyelitis surgery).	19 year old motor cyclist who is normally fit and well. Non-smoker and infected tibial fracture.
	H2	Antibiotic allergy, irreversible immunosuppression, macrovascular / macrovascular compromise to affected limb or previous osteomyelitis surgery	Patient with long term steroids for rheumatoid arthritis, patient with peripheral vascular disease or evidence of end stage organ damage with diabetes mellitus, previous failed surgery for osteomyelitis
	H3	Patient not fit for surgery despite optimisation or refuses surgery	Patient with previous respiratory failure following anaesthetic.

Password for 20 cases: Blue105

C

Detailed Results of the Inter-User Assessment

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C.1 Introduction

The following appendix details the individual results of the inter-user assessment by the attributes of each of the users that were included. These attributes are speciality, type of hospital, number of cases seen per month and grade of the user. As stated in chapter 6, (with the exception of UK practice in the classification of the coverage of the soft tissues) significance was not achieved using a multivariate regression model to assess the accuracy of classification (dependent variable) against speciality, experience, type of centre or grade of clinician (independent variable). However, clinicians who have increasing experience with osteomyelitis are more likely to practice in a specialist centre or be a higher grade (i.e. consultant),

introducing co-linearity into the model.

C.2 Bone Involvement

The bone invovlement variable had the lowest overall Fleiss' kappa ($F\kappa$) value and percentage accuracy score. Surgeons tended to have a higher score compared to physicians over all of the 20 cases (Figure C.1a). Clinicians who had overall less experience treating bone infection (<1 case per month) returned the lowest scores on the most complex cases (Figure C.1c).

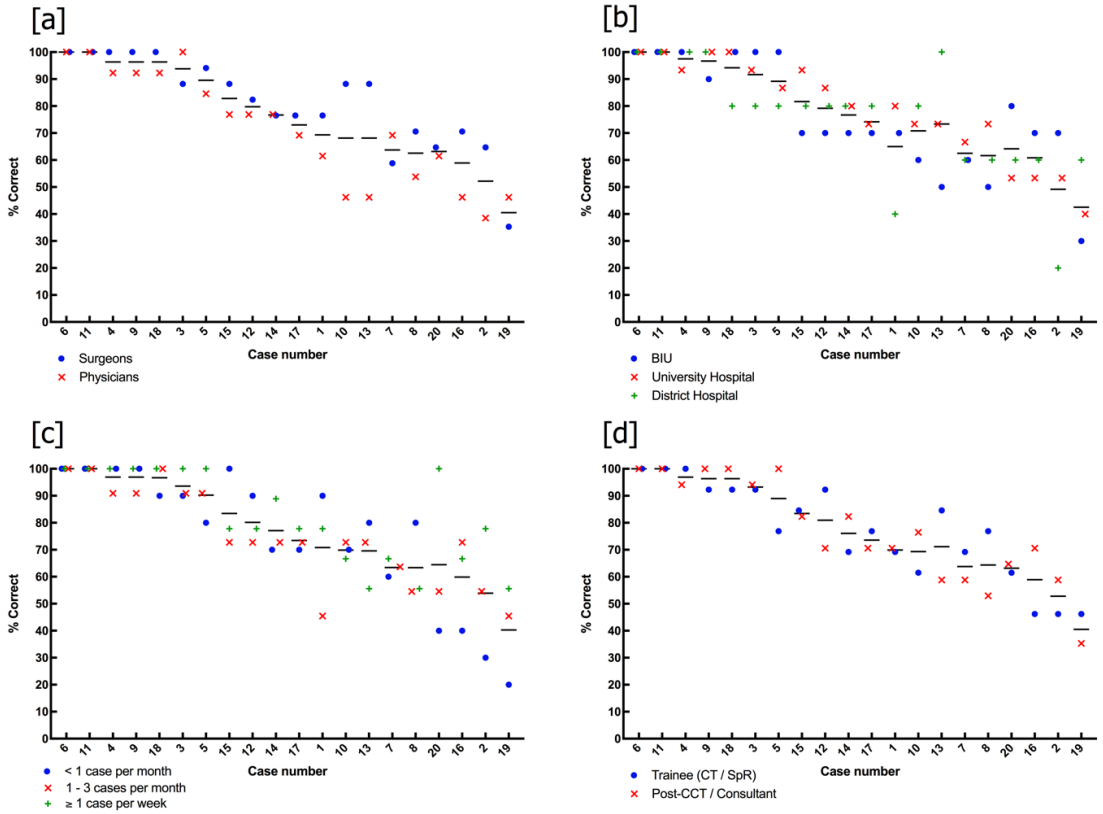


Figure C.1: The percentage accuracy for the Bone involvement variable across users by speciality. Attributes are classified by [a] speciality [b] experience [c] centre the clinician practices in [d] training grade.

C.3 Anti-microbial Options

The antimicrobial options were classified accurately with 16 of the 20 cases scoring >80%, figure C.2. However, as the complexity of the cases increased, with the isolates

having an increased number of resistant susceptibility tests, the responses became less accurate. Interestingly, all physicians correctly classified 100% of the Ax and A1 cases, figure C.2a. In general, surgeons were less accurate when applying either the A1, A2 or A3 classification, figure C.2a. Centre of practice, experience or training grade did not influence how the antimicrobial options were classified, figures C.2b-d.

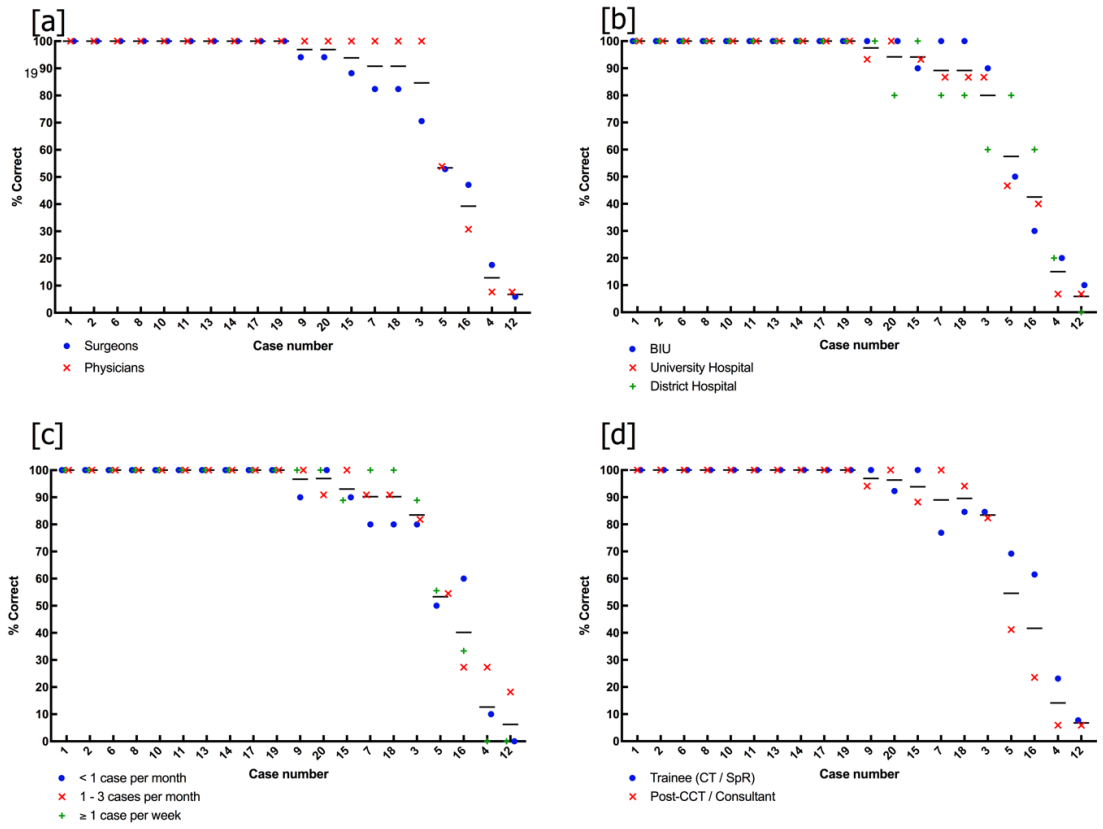


Figure C.2: The percentage accuracy for the Anti-microbial options variable across users by clinical attribute. Attributes are classified by [a] speciality [b] experience [c] type of centre where the clinician practices [d] training grade / grade of clinician.

C.4 Coverage of the Soft Tissues

The coverage of the soft tissues was classified accurately throughout. Generalised linear regression demonstrated that centres within the UK were more likely to classify the soft tissues accurately, figureC.4 (p=*0.03*). However, other attributes did not achieve statistical significance using this model, C.3. This may be explained

by the different thresholds in countries outside the U.K. that necessitate referral to a plastic surgeon.

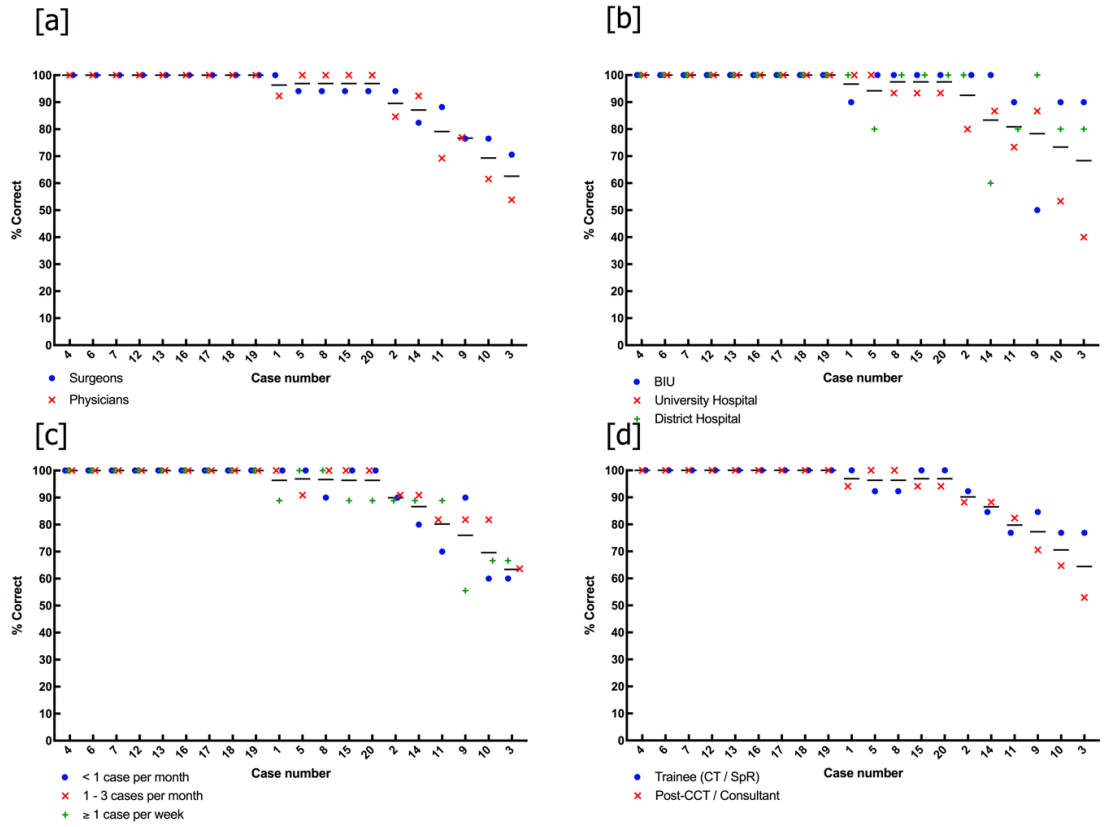


Figure C.3: The percentage accuracy for the Coverage of the soft tissues variable across users by clinical attribute. Attributes are classified by [a] speciality [b] experience [c] centre where the clinician practices [d] training grade / grade of clinician.

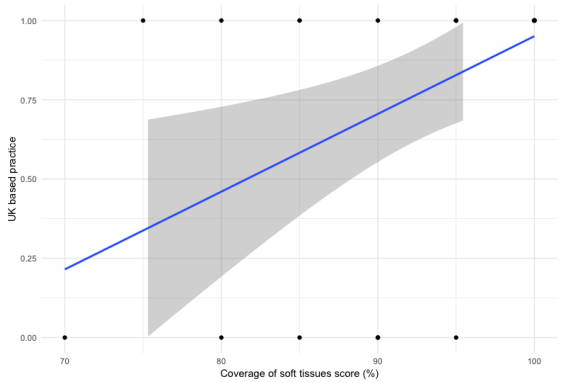


Figure C.4: Generalised linear regression model of the Coverage of the soft tissue score with UK based practice. Place of clinician practice was either UK (y=1) or non-UK (y=0) which achieved significance accounting for other attributes using a generalised linear regression model *p=0.03*.

C.5 Host status

The host status was classified with 100% accuracy in 9 of the 20 cases. These cases were definitive H1 or H2 cases with patients presenting with severe disease (H2) or were described as otherwise fit and well (H1). The remaining cases were classified with less certainty as they were open to a subjective interpretation and based on whether there was well-controlled systemic disease. There was no correlation between clinician speciality, centre of practice, experience or training grade with the host status C.5.

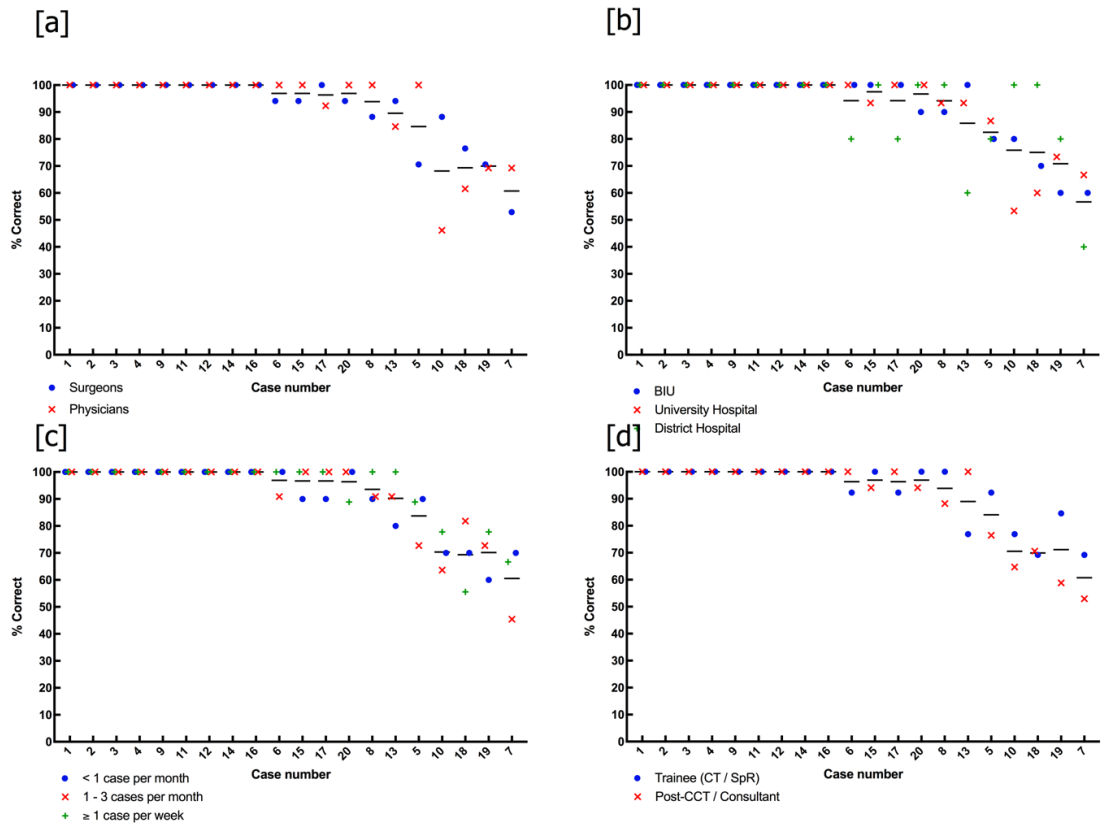


Figure C.5: The percentage accuracy for the Host status variable across users by clinical attribute. Attributes are classified by [a] speciality [b] experience [c] primary centre of practice [d] grade of clinician.

D

Further Assessment of Isolate Sensitivities

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D.1 Patients, Demographics and classification of isolates

Patients were used as in chapter 5.3.1. In brief, 253 consecutive patients who underwent debridement surgery between the period 2013 and 2017 in the Bone Infection Unit, Oxford were included for analysis. 31 (12.3%) patients were excluded because they did not meet the eligibility criteria. This resulted in 222 eligible patients for analysis. There were 247 distinguishable isolates grown on microbiological culture. Of these, 181 were classifiable using the ESCMID criteria as MDR (or XDR and PDR) as described in chapter 5.3.2, (Magiorakos et al., 2012). The remaining 66 were unable to be classified using the ESCMID criteria. Demographics of this cohort are presented in chapter 5.3.3. A second cohort was used for validation of

this method that was taken from the same centre in the period 2001 and 2004 as described in 5.3.3. This cohort had 157 patients and included 166 isolates. Of these isolates, 56.6% were ESCMID classifiable and 43.4% were not.

D.2 Defining the correlation between percentage number of sensitive tests and MDR

A receiver operating characteristic (ROC) curve was plotted of the correlation between percentage sensitive susceptibility tests and correlation between ESCMID MDR. This gave an area under the curve (AUC) of 98.8% (95% confidence interval [CI] 98.1 – 100%), figure D.1. This suggested that using the percentage of sensitive susceptibility tests had a 98.8% equivalence to ESCMID MDR status.

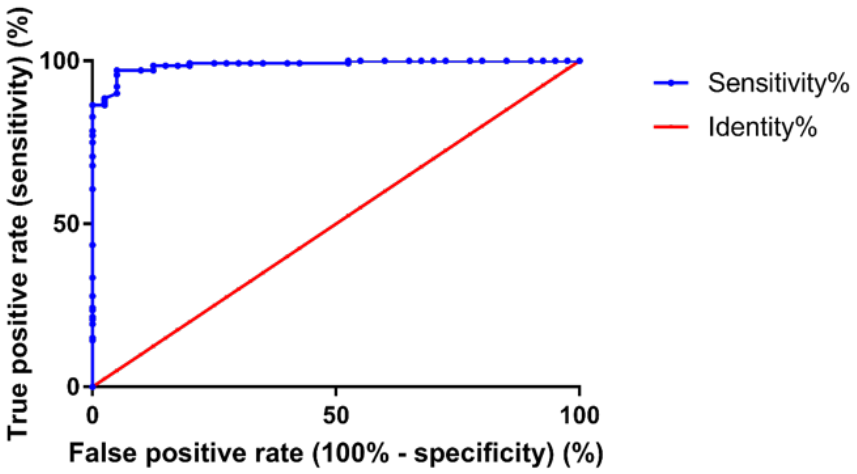


Figure D.1: ROC analysis for percentage sensitive susceptibility tests and correlation with ESCMID MDR status for the 2013 - 2017 cohort. AUC = 98.8% (95% CI 98.1-100.0%).

To ascertain the optimal cut off point, calculation of the Youden index was performed as described in chapter 5.3.4 (equation 5.3). This demonstrated that the optimum cut off point (the point at which sensitivity and specificity is at its maximum) was at 0.961 (sensitivity = 97.1%, specificity = 95.0%), figure D.2. This equates to isolates that had <78.5% sensitive susceptible tests having a 98.8% (95% CI 97.6-100.0%) chance of being deemed ESCMID MDR.

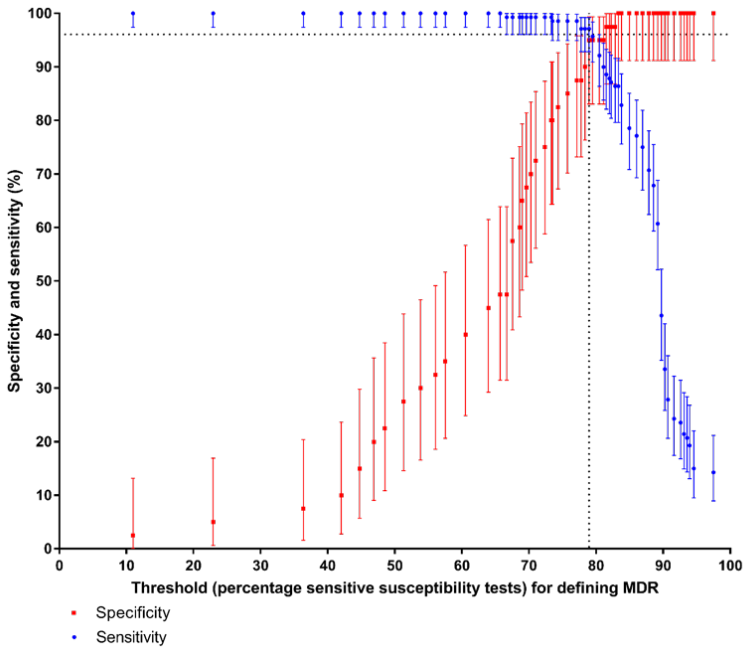


Figure D.2: Specificity (red) and sensitivity (blue) the percentage of susceptibility tests equating to whether an isolate is MDR or not in the 2013-2017 cohort. Dashed line is the maximal Youden index representing the optimum threshold (x=78.5%) between sensitivity and specificity.

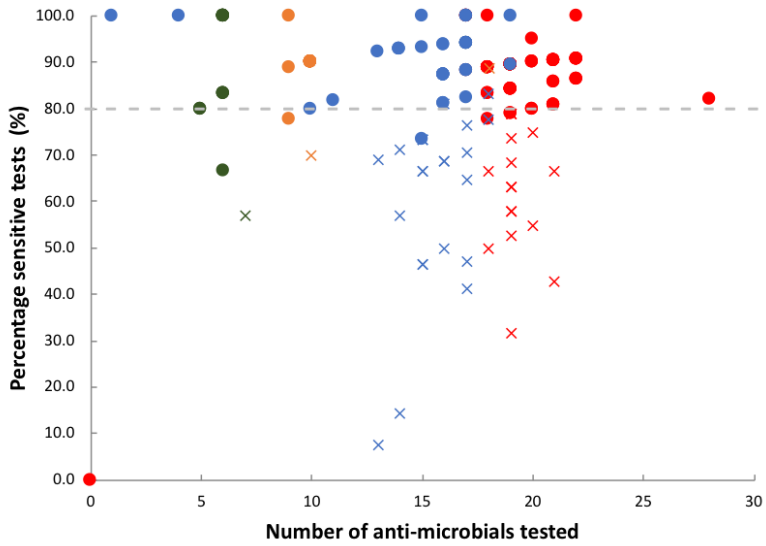


Figure D.3: Scatter plot of the percentage of sensitive tests for each of the individual ESCMID classifiable isolates against the total number of susceptibility tests performed. Isolates plotted as either MDR (crosses) or non-MDR (circles). Different colours represented the different groups of bacteria as defined by ESCMID (Blue = *Enterobacteriacae*, orange =*Pseudomonas aeruginosa*, green = *Enterococcus* spp., red = *S. aureus*). Dotted line = sensitive to 80% of susceptibility tests.

Applying this rule to the MDR isolates in the 2013 to 2017 cohort, it can be demonstrated that using a cut off of <80% is appropriate for defining whether an isolate is deemed high resistance, figure D.3.

D.3 Application to an older cohort

Applying this rule to a separate cohort demonstrates that there is a similar correlation between ESCMID MDR and the percentage of sensitive susceptibility tests performed. Analysis using a ROC curve demonstrates that the AUC is 91.2% (95% CI 85.4% – 96.9%), figure D.4. In this cohort, the Youden index was 0.779 (sensitivity = 84.1%, specificity = 93.8%), which is of a similar value to that of the original cohort, figure D.5.

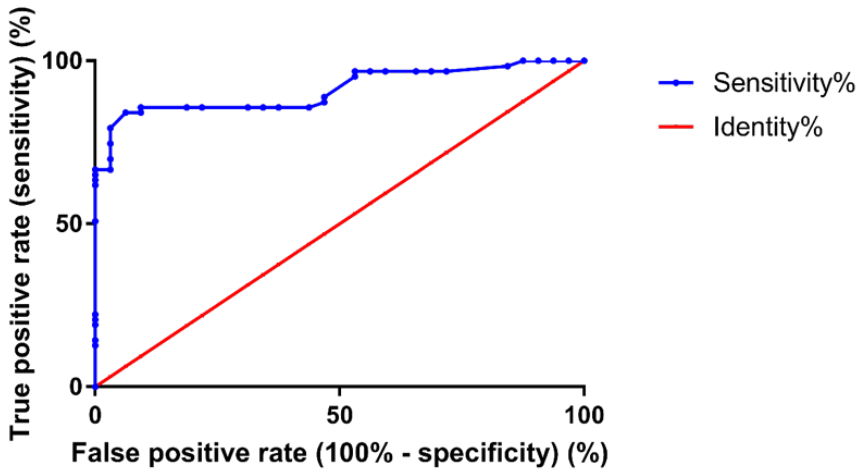


Figure D.4: ROC analysis for percentage sensitive susceptibility tests and correlation with ESCMID MDR status for the 2013 – 2017 cohort. AUC = 98.8% (95% CI 98.1-100.0%).

This method of classifying high resistant isolates was applied to the 66 non-ESCMID classifiable isolates from the 2013 - 2017 cohort. Of these, 71.2% (47/66, 95% CI 59.4% - 80.7%) of isolates were classified as 'low resistance' and 28.7% (19/66, 95% CI 19.2%-40.6%) of isolates were in the high resistant group, figure D.6. This is similar to the proportion of isolates classifiable by ESCMID where 22.1% (40/181, 95% CI 16.7% - 28.8%) were deemed MDR, XDR or PDR.

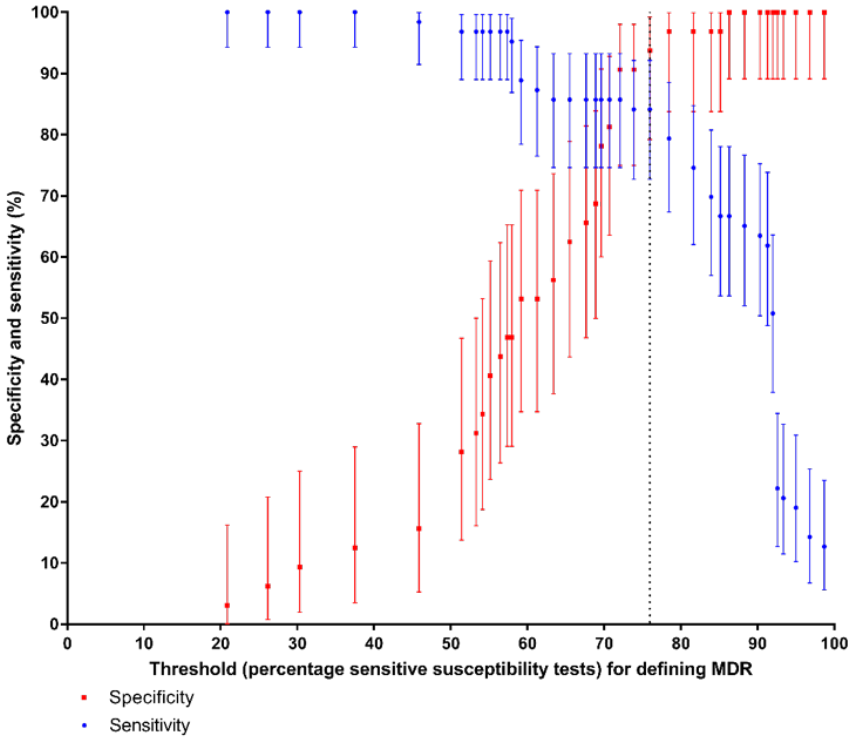


Figure D.5: Specificity (red) and sensitivity (blue) of the percentage of susceptibility tests equating to whether an isolate is MDR or not for the 2001 – 2004 cohort.

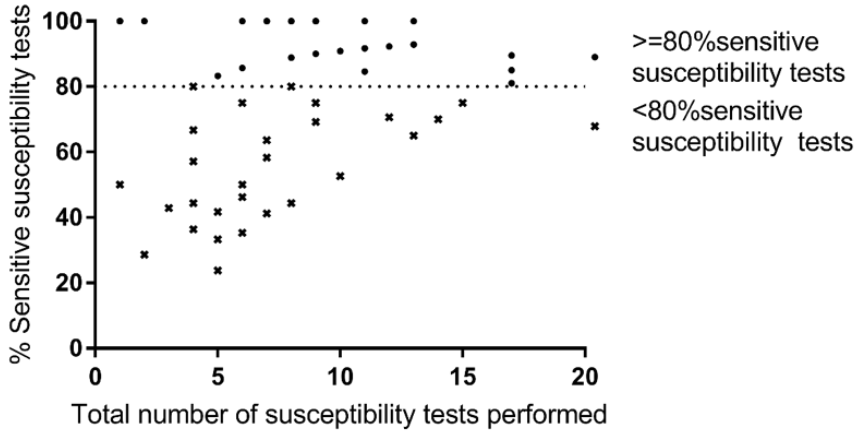


Figure D.6: Scatter plot of the non-ESCMID classifiable isolates from the 2013 – 2017 cohort with the total number of susceptibility tests performed and the percentage sensitive susceptibility tests performed. Dotted line represents the 80% threshold for defining high and low resistance isolates.

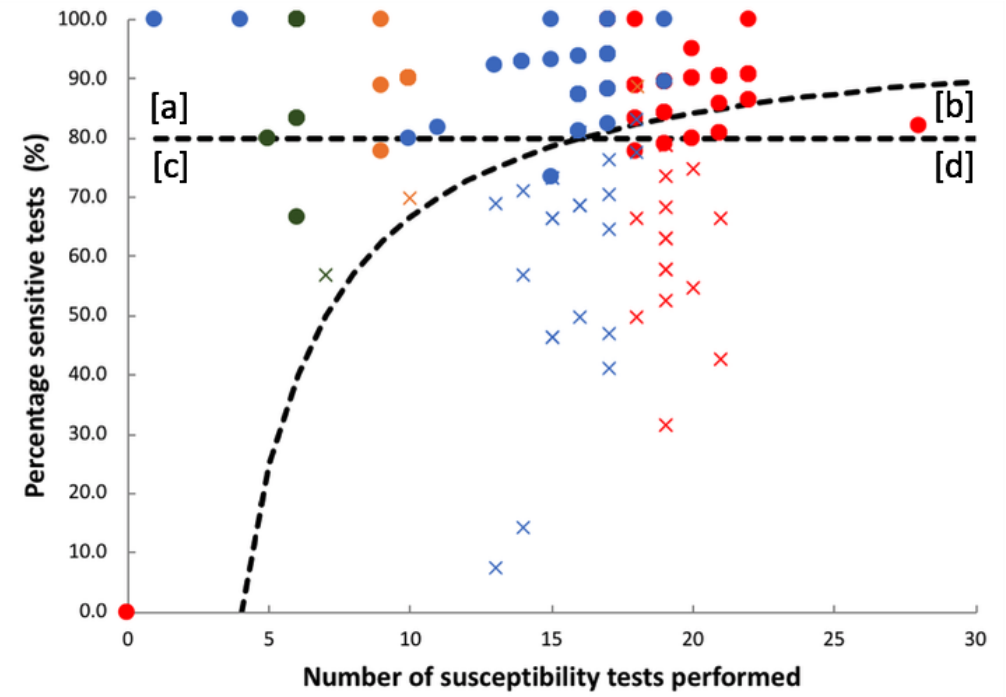
D.4 Combining two methods of equivalence to ESCMID MDR

Two methods of equivalence to ESCMID MDR status have been demonstrated in this thesis, the first by defining the absolute number of resistant tests and the second by defining the proportion of tests that are sensitive. Both have demonstrated a good correlation with defining ESCMID MDR. Both will be applied to the BACH classification system to define the complexity of microbiology treatment.

When applying both of these equivalence methods, there is significant overlap due to the range of susceptibility tests performed. However, it is possible that isolates may meet the criteria for one method and not the other. Using the isolates from the 2013 – 2017 cohort, a 92.5% overlap between the two methods of MDR equivalence was demonstrated. Furthermore, there was only 1 isolate that met the criteria for one method and not the other. The method that used $\geq$4 resistant susceptibility tests did not detect any additional 'high resistant' isolates compared to using <80% sensitive susceptibility tests, figure D.7. Using both methods, there was a false negative rate of 5.0% where isolates deemed MDR by ESCMID did not meet either criteria.

Analysing the isolates that are ESCMID non-MDR (i.e. low resistant) from the 2013 – 2017 cohort, both methods of MDR-equivalence correctly classified 90.8% of 'low resistant' isolates. However, this gave a false positive rate of 9.2%. Using the percentage of sensitive susceptibility tests methods gave a lower false positive rate compared to using the absolute number of resistant susceptibility tests (2.1% versus 4.3%).

This analysis has demonstrated that using both of these methods can assist in applying the ESCMID criteria. Both the true positive rate and the true negative rate is greater than 90% when using both methods. Using both methods allows a system that is easily applicable. However, it is hypothesised that calculating the percentage of sensitive susceptibility tests may not be straight forward at the bedside and therefore both methods should be included in the classification system.



ESCMID MDR / XDR / PDR	≥80% sensitive susceptibility tests	<80% sensitive susceptibility tests
<4 resistant susceptibility tests	[a] 2 (5.0%)	[c] 1 (2.5%)
≥4 resistant susceptibility tests	[b] 0 (0.0%)	**[d] 37 (92.5%)**

ESCMID non-MDR	≥80% sensitive susceptibility tests	<80% sensitive susceptibility tests
<4 resistant susceptibility tests	**[a] 128 (90.8%)**	[c] 3 (2.1%)
≥4 resistant susceptibility tests	[b] 6 (44.3%)	[d] 4 (2.8%)

Figure D.7: Scatter plot presenting the ESCMID classifiable isolates from 2013-2017 cohort with percentage susceptibilities sensitive and the total number of susceptibility tests performed. MDR = circles, non-MDR = crosses. (Blue = *Enterobacteriacae*, orange =*Pseudomonas aeruginosa*, green = *Enterococcus* spp., red = *S. aureus*). Dotted lines represent the thresholds for the equivalence methods for ESCMID MDR. Area [a] ≥80% sensitive and <4 resistant tests; [b] ≥80% sensitive and ≥4 resistant tests; [c] <80% sensitive and <4 resistant tests; [d] <80% sensitive and ≥4 resistant tests. Tables represent the proportions ESCMID classifiable isolate that fall into each of the areas [a-d] of the graph. For ESCMID MDR / XDR / PDR table, [d] (bold) is the true positives and for ESCMID non-MDR, [a] are the true negatives.

D. Further Assessment of Isolate Sensitivities

To ensure that the classification system is easy to use, both tests will be applied to the BACH classification in version 3. The A2 category will have a hierarchy which will be as follows: (i) ESCMID MDR, (ii) if unfamiliar with ESCMID guidelines or unable to classify using ESCMID guidelines then: <80% sensitive susceptibility tests, (iii) if unable to calculate the percentage of sensitive susceptibility tests then: ≥4 resistant susceptibility tests or (iv) if still unsure, then seek advice from microbiologist or infectious disease specialist.

E
User Key

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E.1 Introduction

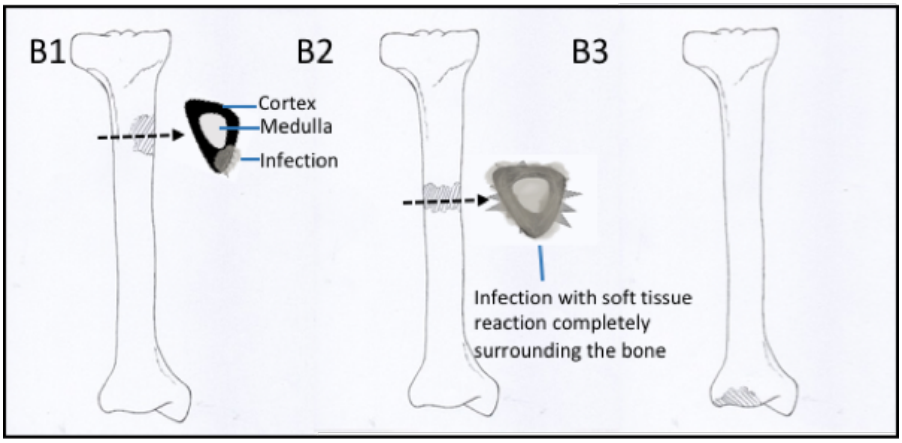
BACH is a new classification system for long-bone osteomyelitis that uses the multi-disciplinary approach to easily stratify patients so they can be treated in a centre that has appropriate services. The variables that are measured are: **B**one involvement, **A**ntimicrobial options, **C**overage of the soft tissues and the **H**ost status (BACH) which will be now individually explained.

E.2 Variables

B: Bone involvement: The bone involvement variable can be made based on a combination of clinical information, examination findings and radiological imaging. The optimum method (95.7% [95% CI 90.8% - 100.0%]) to make this

classification pre-operatively is using clinical imaging software that allows the 3-D visualisation of infection (for example PACS). However, the bone involvement variable can be based on clinical information and plain radiographs which can assess whether fractures have healed (presence of non-union). Where possible, it should be confirmed using 3-D imaging.

B1 Cavitary involvement
B2 Segmental involvement
B3 Any bone infection involving a joint



A: Anti-microbial treatment options: The antimicrobial options should be classified on the basis of the results of susceptibility testing on deep tissue samples or biopsy. Before deep tissue samples or biopsy are retrieved or in culture negative osteomyelitis, patients will be deemed Ax. The gold standard for application of the anti-microbial options classification is using the ESCMID criteria (Magiorakos et al., 2012). These define multi-, extensive and pan-drug resistant isolates for Staphylococcus aureus, Enterococcus spp., Enterobacteriacae, Pseudomonas aeruginosa and Acinetobacter spp.. For simplicity and the purposes of inclusion, MDR can be defined either as an isolate that is sensitive to <80% (98.8% [95%CI 98.1 – 100.0%]) or resistant to ≥4 (98.1% [95% CI 96.6-99.1%]) susceptibility tests. XDR and PDR can be defined as sensitivity to ≤1 antibiotic susceptibility test. In addition, A2, limited options, should be include isolates that have resistance to

appropriate anti-biofilm antibiotics in the presence of an implant (gram positive resistance to rifampicin and gram-negative resistance to fluoroquinolones).

Ax Unknown or culture negative
A1 Isolate sensitive to ≥80% of susceptibility tests
and
resistant to <4 susceptibility tests
A2 Isolates meet the ESCMID criteria for MDR
or
sensitive to <80% of susceptibility tests
or
resistant to ≥4 susceptibility tests
or
resistance to anti-biofilm antibiotics in the presence of an implant
A3 Isolates meet the ESCMID criteria for PDR or XDR
or
isolates are sensitive to ≤1 susceptibility test

C: Coverage of the soft tissues The coverage of the soft tissues should be classified based on clinical assessment. It can be classified by the orthopaedic surgeon or, if available, the plastic surgeon. It is important to realise that cases that involve the anterior and medial tibia, knee and elbow should have a low threshold for designating as a C2 and necessitating plastic surgery referral. Other cases that should have low threshold for referral should include those where previous free or local tissue transfer procedures have been performed.

C1 Plastic surgical expertise not required to provide adequate soft tissue coverage
C2 Plastic surgical expertise required to provide adequate soft tissue coverage

H: Host status The host status should be classified based on the clinical assessment of the treating surgeon or physician. Those that are deemed H3 due to anaesthetic concerns should undergo a formal anaesthetic assessment and, if H3 is confirmed, offered options to suppress the infection. H1 patients are fit and well (no previous co-morbidity) or have co-morbidity that is well controlled. H2 patients have co-morbidity that is either poorly controlled (according to the NICE guidelines)

or have co-morbidity that has resulted in secondary end-organ damage. Patients who have had previous osteomyelitis debridement surgery should be deemed an H2.

H1 Patient fit and well
or
Patient has well controlled co-morbidity

H2 Patient with poorly controlled co-morbidity
or
Evidence of any end organ damage
or
Recurrent osteomyelitis after previous debridement

H3 Patient who is unfit for surgery
or
Declines an operation

E.3 The BACH Classification System

	Bone involvement (B):	**Antimicrobial options (A):**	**Coverage by soft tissue (C):**	**Host status (H):**
Good treatment options 'uncomplicated'	B_1: Cavitary infection without joint involvement	A_1: treatment options available **or** A_X: unknown / no anti-microbial growth	C_1: Direct closure possible	H_1: Fit and well **or** Well controlled co-morbidity
Limited treatment options 'complex': requires specialist management'	B_2: Segmental infection without joint involvement	A_2: ESCMID MDR **or** sensitive to <80% of susceptibility tests **or** resistant to ≥4 susceptibility tests **or** Resistance to anti-biofilm antibiotics in presence of an implant	C_2: Direct closure not possible; plastic surgery expertise required	H_2: Poorly controlled co-morbidity (despite optimisation) **or** Presence of end-organ damage due to co-morbidity **or** Recurrent osteomyelitis after previous debridement
	B_3: Any osteomyelitis with associated joint involvement			
Few or no options available		A_3: ESCMID XDR or PDR **or** 0 or 1 sensitive susceptibility test		H_3: unfit for definitive surgery despite specialist intervention **or** Patient declines surgery

F

Data collection templates for prospective study

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F.1 Timepoint 1: MDT Meeting

F.1.1 Study identification number

NHS number:

Study identification number*: ORG_

**Researcher to complete*

F.1.2 Inclusion criteria

Does the patient meet the following criteria? (*please tick*)

☐ Aged ≥18 years old

☐ Diagnosis of new or recurrent osteomyelitis

☐ Radiological evidence *or* clinical symptoms of osteomyelitis for >6 months

☐ None of the above criteria

F.1.3 Patient details

☐ New patient / ☐ New referral from another centre (*please specify*):

Demographic information:

Gender:

Date of birth:

Initials:

Site of infection:

F.1.4 Outcome of MDT

What was the outcome of the MDT?

☐ [a] Treatment in a non-specialist centre

☐ [b] Treatment in a specialist centre

☐ [c] Suppressive or non-reconstructive treatment

☐ [d] More information required

F.1.5 BACH Classification

For researcher to complete

Bone:

☐**B1** Cavitary involvement

☐**B2** Segmental involvement – e.g. infected non-union

☐**B3** Bone infection with the involvement of a joint

☐Other / unsure

Antimicrobial options:

☐**Ax** – unknown

- ☐ No growth
- ☐ Unknown

☐**A1** - Good treatment options

- ☐ ≥80% of susceptibility tests sensitive
- ☐ <4 resistant susceptibility tests

☐**A2** - Limited treatment options

- ☐ ESCMID MDR
- ☐ <80% of susceptibility tests sensitive
- ☐ ≥4 resistant susceptibility tests
- ☐ Resistance to anti-biofilm antibiotics in the presence of an implant

☐**A3** - Few or no treatment options

- ☐ ESCMID XDR or PDR
- ☐ ≤1 sensitive susceptibility test

☐ Other / unsure

Coverage of the soft tissues:

☐**C1** Direct closure possible

☐**C2** Direct closure not possible; requiring plastic surgery

☐ Other / unsure

Host status:

☐**H1**

- ☐ Fit and well

☐ Well controlled disease

☐**H2**

☐ Severe disease (presence of end organ damage)

☐ Uncontrolled disease (as defined by NICE)

☐ Recurrent osteomyelitis after previous debridement surgery

☐**H3**

☐ Patient refuses surgery

☐ Not fit for an anaesthetic

☐ Other / unsure

Outcome of BACH classification:

☐ Uncomplicated osteomyelitis

☐ Complex osteomyelitis

☐ Suppressive or non-reconstructive management

F.2 Timepoint 2: Consultation

F.2.1 Study identification number

NHS number:

Study identification number*: ORG_

**Researcher to complete*

F.2.2 Inclusion criteria

Does the patient meet the following criteria? (*please tick*)

☐ Aged ≥18 years old

☐ Diagnosis of new or recurrent osteomyelitis

☐ Radiological evidence *or* clinical symptoms of osteomyelitis for >6 months

☐ None of the above criteria

F.2.3 Patient details

☐ New patient / ☐ New referral from another centre (*please specify*):

Demographic information:

Gender:

Date of birth:

Initials:

Site of infection:

F.2.4 BACH classification

Bone:

☐**B1** Cavitary involvement

☐**B2** Segmental involvement – e.g. infected non-union

☐**B3** Bone infection with the involvement of a joint

☐Other / unsure

Antimicrobial options:

☐**Ax** – unknown

- ☐ No growth
- ☐ Unknown

☐**A1** - Good treatment options

- ☐ ≥80% of susceptibility tests sensitive
- ☐ <4 resistant susceptibility tests

☐**A2** - Limited treatment options

- ☐ ESCMID MDR
- ☐ <80% of susceptibility tests sensitive
- ☐ ≥4 resistant susceptibility tests
- ☐ Resistance to anti-biofilm antibiotics in the presence of an implant

☐**A3** - Few or no treatment options

- ☐ ESCMID XDR or PDR
- ☐ ≤1 sensitive susceptibility test

☐ Other / unsure

Coverage of the soft tissues:

☐**C1** Direct closure possible

☐**C2** Direct closure not possible; requiring plastic surgery

☐ Other / unsure

Host status:

☐**H1**

☐ Fit and well

☐ Well controlled disease

☐**H2**

☐ Severe disease (presence of end organ damage)

☐ Uncontrolled disease (as defined by NICE)

☐ Recurrent osteomyelitis after previous debridement surgery

☐**H3**

☐ Patient refuses surgery

☐ Not fit for an anaesthetic

☐ Other / unsure

F.2.5 Patient medical history:

Cardiovascular system

☐ Myocardial infarction ☐ <6 months ago; >6 months ago

☐ Angina ☐ unstable ☐ previous CABG ☐ previous PTCA

☐ Congestive heart failure (please give exercise tolerance:)

☐ Arrhythmia ☐ Atrial fibrillation ☐SVT ☐ Ventricular tachycardia

☐ Hypertension

☐ Peripheral venous disease ☐ previous DVT ☐ previous PE

☐ Peripheral arterial disease

Respiratory system

☐ Chronic obstructive pulmonary disease

☐ Restrictive lung disease (please give details)

☐ Smoker (please give details)

F. Data collection templates for prospective study

Gastrointestinal system

☐ Pancreatitis ☐ Acute ☐ Chronic

☐ Hepatic failure

Renal system

☐ Acute kidney injury (Creatinine: Urea:)

☐ Chronic kidney injury (Creatinine: Urea:)

☐ Patient on dialysis

Neurological system

☐ Stroke: ☐ Significant neurological deficit ☐ no residual deficit

☐ TIA: ☐ <6 months ago ☐ >6 months ago

☐ Dementia ☐ mild ☐ moderate ☐ severe

☐ Paralysis ☐ Hemiplegia ☐ Paraplegia

☐ Other intra-cerebral pathology: *please give details: e.g. Parkinson's disease*

☐ Other peripheral neurological pathology *please give details: e.g. MS*

Endocrine system

☐ Type 1 diabetes mellitus

☐ Type 2 diabetes mellitus: ☐ HbA1c $\geq$ 8.0% / ☐<8.0

Immune system

☐ Long term corticosteroid use (>20mg per day for >4 weeks)

☐ Haematological malignancy

☐ Other acquired immunodeficiency (*please specify*)

Body weight

☐ Malnutrition (☐ albumin <30 g/L)

☐ Obesity (☐ BMI $\geq$38kg/m^2)

Malignancy

☐ Remission (*please specify primary*)

☐ Currently under treatment with curative intent

☐ Previous radiation therapy

☐ Palliation

☐ Presence of pathological fracture

Other

☐ Condition no listed (for example inflammatory arthritis, *please specify:*)

F.2.6 EuroQol-EQ-5D score

See appendix G for complete EuroQol EQ-5d-5L questionnaire.

- Pain / discomfort (score 1-5)
- Ability to perform usual activities (score 1-5)
- Anxiety / depression (score 1-5)
- Mobility (score 1-5)
- Self-care (score 1-5)
- Visual analogue score (0-100)

F.3 Timepoint 3: In hospital assessment

F.3.1 Study identification number

NHS number:

Study identification number*: ORG_

**Researcher to complete*

F.3.2 Patient information

Date of surgery:

Date of assessment:

Following debridement surgery did the patient have (*please tick*):

☐ Intra-operative pus

☐ Microbiology with ≥2 indistinguishable isolates

☐ Histology suggestive of infection

F.3.3 BACH classification

Bone Involvement: ***(intraoperative assessment)***

☐**B1** Cavitary involvement

☐**B2** Segmental involvement – e.g. infected non-union

☐**B3** Bone infection with the involvement of a joint

☐Other / unsure

Antimicrobial options: ***(at 7 days post sampling)***

☐**Ax** – unknown / no growth

☐**A1** - Good treatment options

☐**A2** - Limited treatment options

☐**A3** - Few or no treatment options

☐ Other / unsure

Coverage of the soft tissues: ***(post-operatively)***

☐**C1** Direct closure possible

☐**C2** Direct closure not possible; requiring plastic surgery

☐ Other / unsure

Host status:

☐**H1**

☐**H2**

☐**H3**

☐ Other / unsure

F.3.4 Additional information:

Did the patient have an application of either internal or external fixation device? *(Please give details)*

How many surgical biopsy samples were taken?

Was a free tissue transfer performed at the time of surgery (either free or local flap)? *(Please give details)*

F.3.5 EuroQol - EQ-5D score

See appendix G for complete EuroQol EQ-5d-5L questionnaire. At this time point, the EQ-5D-5L questionnaire should be recorded between 4-7 days post-operatively.

- Pain / discomfort (score 1-5)
- Ability to perform usual activities (score 1-5)
- Anxiety / depression (score 1-5)
- Mobility (score 1-5)
- Self-care (score 1-5)
- Visual analogue score (0-100)

F.4 Timepoints 4-8: Follow-up

F.4.1 Study identification number and patient details

NHS number:

Study identification number*: ORG_

**Researcher to complete*

Date of assessment:

Date of surgery:

F.4.2 Complication following procedures

Please detail complications following debridement surgery at follow-up appointment, please give details if applicable:

☐ Recurrence

☐ Non-union

☐ Malunion

☐ Fracture

☐ Flap failure

☐ Soft tissue infection

Medical complication:

☐ DVT

☐ PE

☐ Non-surgical site infection

☐ Myocardial infarction

☐ Stroke

☐ Other not listed:

F.4.3 EQ-5D score (follow-up):

See appendix G for complete EuroQol EQ-5d-5L questionnaire.

- Pain / discomfort (score 1-5)
- Ability to perform usual activities (score 1-5)
- Anxiety / depression (score 1-5)
- Mobility (score 1-5)
- Self-care (score 1-5)
- Visual analogue score (0-100)

G

Euro-Quol EQ-5D-5L Questionnaire

Contents

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G.1 Registration and permission of EQ-5D-5L

This appendix presents the EuroQol EQ-5D-5L questionnaire and the accompanying visual analogue score assessment. Approval from the EuroQol was sought from EuroQol at the following web address:

https://euroqol.org/eq5dregistrationform/

Permission to use this study as part of the prospective assessment presented in chapter 8 was approved for a cohort of up to 450 patients (reference number 27103).

G.2 EQ-5D-5L Questionnaire

The complete EQ-5D-5L and VAS are presented over the next 3 pages as detailed by EuroQol.

EQ-5D-5L

Health Questionnaire

English version for the UK

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Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

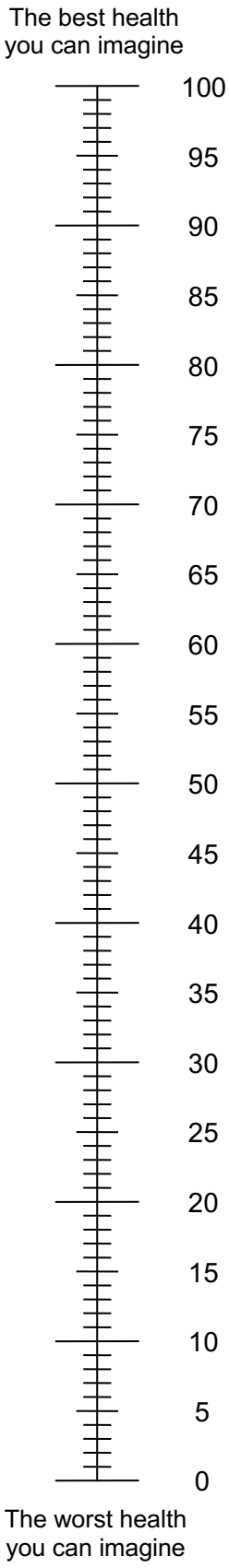
I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

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- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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H

BACH ORGAN Study Patient Information Sheet and Consent Form

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H.1 Patient Information Sheet

This appendix includes patient information sheets that will be offered when patients are eligible for inclusion in the BACH ORGAN study. Patients will be given time to read, take in, ask questions and weigh up whether they wish to be included in the study. Patients will be allowed to retain a copy of the patient information sheet and the informed consent form.

The next 3 pages include the patient information sheet. The template used is supplied by the University of Oxford Clinical Trials Research Group (CTRG) and conforms to the standard set by Oxford University.



Mr Andrew James Hotchen

PARTICIPANT INFORMATION SHEET

The BACH classification of osteomyelitis.

We would like to invite you to take part in the present study. Before you make your decision, it is important to understand why the research is being performed and how you would be involved. Please take the time to read this information carefully and discuss it with others if you wish. If there is anything that is unclear, then please ask us.

What is the purpose of the study?

This study has been designed to assess the application and use of a new classification system for bone infections, named the BACH classification system. BACH is designed to improve the patient care that is delivered for patients who have a bone infection. This works by grouping the patients according to the severity of the disease. The purpose of this trial is to explore whether there is a link between patients who have complex bone and joint infections (as determined by BACH) and outcomes (both clinical outcomes and patient reported outcomes). By making this link, patients can be treated in a centre that can offer an appropriate level of expertise.

Why have I been invited?

- You have been invited to participate in this study because you have been diagnosed clinically with a bone infection.
- We intend to include 300 patients in this study.

Do I have to take part?

- Participation is voluntary.
- If you choose to participate and change your mind, you may withdraw from the study at any time without giving a reason.
- Withdrawal does not and will not affect clinical care.

What will happen to me if I decide to take part?

- Clinical details will be taken at the bone infection clinic. This will include your age and the site (part of the body) that has the bone infection.
- At the first consultation, you will be asked to score a quality of life questionnaire that contains 5 questions. These relate to pain, anxiety/depression, mobility, usual activities and self-care. There is also a visual analogue score that asks you to rate your health on a scale of 0-100.
- If surgery is performed, we will ask you to answer a short questionnaire at different time points after surgery. These time points are: at baseline, 6 weeks post-operative, 3 months post-operative, 6 months post-operative, 1 year post-operative and 2 years post-operative.

These are all common follow-up time scales for patients who have had an operation for a bone infection.

- If surgery is not performed, we will ask you a short questionnaire regarding your daily living at different time points following the clinic appointment. These are at 6 weeks, 3 months, 6 months, 1 year and 2 years. These appointments may not be routinely offered and we may be able to perform these over the telephone.
- Inclusion in the study does not require additional blood tests, clinic appointments or hospital admission compared to those that you would routinely be offered.
- We will not make any changes to the clinical care pathway that you would have otherwise received.

What should I consider?

This study includes:

- All patients over the age of 18 years who have a diagnosis of a bone infection

What are the possible benefits of taking part?

- This study aims to improve the care that can be offered to patients who have a diagnosis of bone infection.

Will my taking part in the study be kept confidential?

- All information collected as part of this study will be anonymised to the researchers who are performing the data analysis.
- All patient identifiable information (i.e. name, date of birth, address, telephone number) will remain on encrypted servers on NHS computers. This data will remain on NHS servers and will be erased at 5 years after the completion of the study (according to University regulations).
- All patients will be given a unique study identifier. The researchers will use the unique study identifier to analyse data which will not contain patient identifiable information.
- The only time we will use the study identifier for patient identification is in the case of arranging follow-up appointments.
- If you decide to withdraw from the study, then all information recorded will be removed from the study at that specific time point (patient identifiable and study identifier).
- Responsible members of the University of Oxford [and the relevant NHS Trust(s)] may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What will happen to my data?

- The data collected as part of this study will be used primary in the described research. However, it may be possible that future researchers may request access to the data for related studies.

What will happen if I don't want to carry on with the study?

- Participation in the study is entirely voluntary and you can change your mind at any point.
- Withdrawal from the study will not affect the care that you receive from the healthcare team.
- If you choose to withdraw, at your discretion, we will remove all of the relevant patient records from the study database (see section on confidentiality).

What happens at the end of the study?

- Any material that is published from the study that enters the public domain will remain completely anonymous. In the rare event that we would publish specific patient identifiable information, we would ask for specific consent for this.
- We intend to publish the data from this research so that it can be applied in centres around the world where bone infection is treated. The data will potentially be presented at international and national meetings and conferences.
- At any point in the study, we would welcome you to contact the clinical team to enquire about the progress of the study and the information that has been disseminated.
- Some of the research will be undertaken as part of a research degree such as a doctor of philosophy (DPhil / PhD).

What if there is a problem?

- The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study.
- If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Mr Andrew Hotchen / Mr Martin McNally or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrg@admin.ox.ac.uk.
- The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study.

  If you wish to contact the PALS team please contact: http://www.ouh.nhs.uk/patient-guide/pals.aspx

Further information and contact details:

Please contact Mr Andrew Hotchen by email: andrew.hotchen@wolfson.ox.ac.uk

Thank you for reading this information.

H.2 Patient consent form

The following 2 pages give an example of a blank consent form that will be given to patients to express whether patients wish to be involved in the BACH ORGAN study. Patients will be required to initial the parts of the consent form they agree to. The name of the patient and researcher will be entered into the consent form along with signatures.

The consent form follows the standardised template issued by the University of Oxford CTRG.

Oxford University Hospitals
NHS Foundation Trust

Study Code: *Site ID Code:* *Participant identification number:*

CONSENT FORM

BACH ORGAN: A study to assess the application of a new classification of bone infection in adults that will allow better stratification to patients and giving patients a prognosis regarding their treatment.

Name of Researcher: A J Hotchen

If you agree, please initial box

1. I confirm that I have read the information sheet dated 18/11/18 ver 1.1 for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. (If appropriate) *I understand that the information collected about me may be used in an anonymous form to support other research in the future. It will not be possible for me to be identified by it.*	
5. I agree to take part in this study.	

6. I agree to be contacted about ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	

Name of Participant	*Date*	*Signature*
Name of Person taking Consent	*Date*	*Signature*

**1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes* (if participant is a patient).

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