Open Tibial Shaft Fractures Requiring Flap Coverage: The Impact of Orthoplastic Reconstruction on outcomes.

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Doctor of Philosophy (PhD) by Publication

Edinburgh Napier University

July 2023

A thesis submitted in partial fulfilment of the requirements of Edinburgh Napier University, for the award of Doctor of Philosophy

Word count: 17,200

Abstract

Introduction

Open tibial shaft fractures requiring soft tissue coverage (Gustilo-Anderson type IIIB) have been associated with unacceptably high deep infection rates. There remains considerable variation in orthoplastic management. The aim of this thesis was to evaluate the effect of a standardised two-stage orthoplastic protocol in the management of type IIIB open tibial fractures requiring flap coverage, with a primary outcome of deep infection rate.

Methods

This thesis consists of nine peer-reviewed research articles. The two-stage orthoplastic protocol was analysed. For studies from the study unit, retrospective analysis was undertaken from a main database for clinical/functional outcomes between May 2014 and January 2018. For studies where established literature was present, a systematic review and meta-analysis was undertaken for the variable studied.

Results

Deep infection rate ranged from 7.1%-8.9% in all studies. In those who did and did not experience an infection, there was no difference when devitalised bone was retained, or if temporary plate was retained. On meta-analysis, debridement earlier than 12 hours and use of definitive intramedullary nail was associated with lower complication rates. Time from definitive fixation to definitive flap cover of upto 2 days was associated with a lower infection rate compared to delay greater than 2 days.

Conclusion

The novel two-stage orthoplastic was not associated with inferior clinical or functional outcomes. It also appears as though a time to debridement of less than 12 hours and definitive intramedullary nailing is associated with a lower deep infection rate. Additionally, a single-stage “fix and flap” approach is associated with a lower deep infection rate, however a delay of up to 2 days between definite fixation and soft tissue cover appears safe. These results should be considered within the strict context of an orthoplastic approach.

Declaration

I, Khalid Ghassan Al-Hourani, declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research. Where I have consulted the published work of others, this is always clearly attributed and where I have quoted the work of others, the source is always referenced. With the exception of such references, full contribution has been made for every publication included in this thesis. The material contained in this thesis has not been submitted in whole or any part for any other degree or qualification at this university or any other.

Khalid Ghassan Al-Hourani

July 2023

Acknowledgements

I would like to give thanks to:

My supervisors Professor Elizabeth Anne McKay and Dr David Hamilton for their invaluable direction, particularly in the writing of the thesis. Mr Michael Kelly for his lateral thinking and support throughout this research journey.

I would like to thank my mother Zaida, my father Ghassan, my brother Ammar and my sister Dania for their continued love and support throughout my life, without which I would not succeed.

Last but not least, I am grateful to my loving wife Maria for her kindness and belief. And our daughter Arabella, who is the joy in our lives.

“وَأَن لَّيْسَ لِلإِنسَانِ إِلاَّ مَا سَعَى”

“One can have only that for which they make the effort”

LIST OF PUBLISHED WORKS

1. **Al-Hourani K**, Fowler T, Whitehouse MR, Khan U, Kelly M. Two-stage combined ortho-plastic management of type IIIB open diaphyseal tibial fractures requiring flap coverage: Is the timing of debridement and coverage associated with outcomes?. Journal of orthopaedic trauma. 2019 Dec 1;33(12):591-7.
2. Foote CJ, Tornetta III P, Reito A, **Al-Hourani K,** Schenker M, Bosse M, Bozzo A, Furey A, Leighton R, GOLIATH Investigators. A Reevaluation of the Risk of Infection Based on Time to Debridement in Open Fractures: Results of the GOLIATH Meta-Analysis of Observational Studies and Limited Trial Data. JBJSAm. 2021 Feb 3;103(3):265-73.
3. **Al-Hourani K,** Pearce O, Bott A, Riddick A, Trompeter A, Kelly MB. Three-vessel view debridement of the open tibial fracture: a surgical technique. European Journal of Orthopaedic Surgery & Traumatology. 2021 Sep 10:1-7.
4. **Al-Hourani K,** Stoddart M, Pearce O, Riddick A, Khan U, Kelly MB. Acute Compartment Syndrome in Type IIIB Open Tibial Shaft Fractures Using a 2-Stage Orthoplastic Approach. Journal of Orthopaedic Trauma. 2021 Dec 1;35(12):643-9.
5. Stoddart M, **Al-Hourani K,** Fowler T, Khan U, Kelly MB. Plate-Assisted Intramedullary Nailing of Gustilo Type IIIBOpen Tibial Diaphyseal Fractures: Does Adjunctive Plate Retention Affect Complication Rate? Journal of Orthopaedic Trauma. 2020 July 34(7):363-9.
6. **Al-Hourani K,** Donovan R, Stoddart MT, Foote CJ, Kelly MB, Tornetta P. Definitive fixation outcomes of open tibial shaft fractures: systematic review and network meta-analysis. Journal of Orthopaedic Trauma. 2021 Nov 1;35(11):561-9.
7. **Al-Hourani K,** Stoddart M, Khan U, Riddick A, Kelly M. Orthoplastic reconstruction of type IIIB open tibial fractures retaining debrided devitalized cortical segments: the Bristol experience 2014 to 2018. The Bone & Joint Journal. 2019 Aug;101(8):1002-8.
8. **Al-Hourani K**, Pearce O, Stoddart M, Riddick A, Khan U, Kelly MB. Orthoplastic Reconstruction of Type IIIB Open Tibial Shaft Fractures Using Debrided, Devitalized Cortical Segments: Health-Related Quality-of-Life Outcomes. Journal of Orthopaedic Trauma. 2022 Jul 1;36(7):332-8.
9. **Al-Hourani K,** Foote CJ, Duckworth AD, White TO, Kelly MB, Tornetta III P, SPARTA Investigators. What is the safe window from definitive fixation to flap coverage in type 3B open tibia fractures? Supporting Plastics and Orthopaedics Alliance in Reducing Trauma Adverse Events (SPARTA). Journal of orthopaedic trauma. 2023 Mar 1;37(3):103-8.

LIST OF PUBLISHED WORKS (Extended Summary)

Publication 1.
Journal of Orthopaedic Trauma
Impact factor 2.512
Cited by 26

Al-Hourani K, Fowler T, Whitehouse MR, Khan U, Kelly M. Two-stage combined ortho-plastic management of type IIIB open diaphyseal tibial fractures requiring flap coverage: Is the timing of debridement and coverage associated with outcomes?. Journal of orthopaedic trauma. 2019 Dec 1;33(12):591-7.

Retrospective comparative cohort studies analysing type IIIB open tibial shaft fractures requiring flap coverage. The aim was to evaluate time to debridement utilising the two-stage orthoplastic protocol to these injuries. In 45 patients, there was a mean time to initial debridement of 19 hours. Longer time to both initial debridement and definitive reconstruction was not found to be associated with deep infection, infected flap failure, or nonunion.

Publication 2.
JBJSAm.
Impact factor 4.578
Research design: International Collaborative: Systematic review and meta-analysis
Cited by 11

Foote CJ, Tornetta III P, Reito A, **Al-Hourani K,** Schenker M, Bosse M, Bozzo A, Furey A, Leighton R, GOLIATH Investigators. A Reevaluation of the Risk of Infection Based on Time to Debridement in Open Fractures: Results of the GOLIATH Meta-Analysis of Observational Studies and Limited Trial Data. JBJSAm. 2021 Feb 3;103(3):265-73.

International collaborative project; GOLIATH *(Global Open Fracture CoLlaborative to Investigate Available Evidence in THe Literature)*. This is the largest systematic review and meta-analysis of the field, encompassing 84 studies, analysing 18,239 patients that sustained an open lower limb injury with subgroup analysis of type IIIB open lower limb injuries requiring flap coverage. This study demonstrated that in low-grade open injuries of the lower limb (grades 1 and 2), which are amenable to primary closure, a threshold time of 24-hours to debridement is recommended before a rise in deep infection rate. However, in high-grade open injuries (grade 3 and above), a threshold of less than 12-hours is recommended. An increased risk of infection is predicted with increased delays above these thresholds. This publication was unable to account for the varied orthoplastic set-ups in the studies analysed, which is believed to reduce the threshold for time to debridement before an increase in deep infection rate.

Publication 3.
European Journal of Orthopaedic Surgery and Traumatology
Impact factor 1.79
Research design: Retrospective comparative cohort
Cited by 2

Al-Hourani K, Pearce O, Bott A, Riddick A, Trompeter A, Kelly MB. Three-vessel view debridement of the open tibial fracture: a surgical technique. European Journal of Orthopaedic Surgery & Traumatology. 2021 Sep 10:1-7.

Surgical technique paper reporting on the first stage management of the two-stage protocol. This encompasses patient set-up, debridement technique and post operative rehabilitation. The debridement technique has been given the sobriquet name “three-vessel view” owed to the exposure of all three neuromuscular bundles in the leg, and this allows easy access to all compartments of the leg for debridement. This paper presents the detailed debridement protocol used in the studies presented by the orthoplastic unit in question, aiding consistency in technique and contributing to the positive outcomes seen.

Publication 4.
Journal of Orthopaedic Trauma
Impact factor 2.512
Research design: Retrospective comparative cohort
Cited by 3

Al-Hourani K, Stoddart M, Pearce O, Riddick A, Khan U, Kelly MB. Acute Compartment Syndrome in Type IIIB Open Tibial Shaft Fractures Using a 2-Stage Orthoplastic Approach. Journal of Orthopaedic Trauma. 2021 Dec 1;35(12):643-9.

Retrospective study involving 93 patients who all sustained a type IIIB open tibial shaft fracture requiring flap coverage. The study evaluates the complication of acute compartment syndrome - one of the most devastating complications of any long bone injury. Expected rates of compartment syndrome are 6% for open injuries. All patients in this cohort underwent a standardised “3-vessel view” debridement, colloid resuscitation and two-stage orthoplastic protocol for initial and definitive management of these injuries. No patients required management of acute compartment syndrome via fasciotomy, and no patient sustained clinical sequelae of a missed compartment syndrome at latest follow up. At latest follow up, this study presents the notion that the devastating complication of compartment syndrome is negligible within the orthoplastic two-stage protocol for this specific injury.

Publication 5.
Journal of Orthopaedic Trauma
Impact factor 2.512
Research design: Retrospective comparative cohort
Cited by 13

Stoddart M, **Al-Hourani K**, Fowler T, Khan U, Kelly MB. Plate-Assisted Intramedullary Nailing of Gustilo Type IIIBOpen Tibial Diaphyseal Fractures: Does Adjunctive Plate Retention Affect Complication Rate? Journal of Orthopaedic Trauma. 2020 July 34(7):363-9.

Retrospective study assessing 98 patients with the primary independent variable being method of definitive fixation, namely that being the plate assisted nailing technique. Subsequent retention of adjunctive plate (RAP) was compared to those in whom the plate was not retained (non-RAP). Plates were retained in 67 (67/98, 68.4%) patients in this study. For the primary outcome of deep infection, 8 patients (8/92, 8.2%) experienced this. More patients experienced a deep infection in the RAP group compared to non-RAP, however this was not significant (RAP 6/67, 9.0% vs non-RAP 2/31, 6.5%, p-0.674). There was also no significant difference in non-union, isolated flap failure or overall complication rate between the two groups.

Publication 6.
Journal of Orthopaedic Trauma
Impact factor 2.512
Research design: Level 1 systematic review and network meta-analysis
Cited by 2

Al-Hourani K, Donovan R, Stoddart MT, Foote CJ, Kelly MB, Tornetta P. Definitive fixation outcomes of open tibial shaft fractures: systematic review and network meta-analysis. Journal of Orthopaedic Trauma. 2021 Nov 1;35(11):561-9.

Systematic review and meta-analysis of randomised controlled trials. This study assessed difference in definitive fixation strategies in the management of open tibial shaft fractures. Eighteen studies were eligible for inclusion following a PRISMA guided review process. Intramedullary nailing was associated with a lower all-cause unplanned reoperation rate compared to definitive external fixation for this injury (RR 0.91, 95% CI 0.58–1.4, P = 0.68). UN had a lower reoperation risk compared with reamed intramedullary nailing (RR 0.91, 95% CI 0.58–1.4, P = 0.68); however, this was not significant and did not demonstrate a clear advantage.

Publication 7.
Bone & Joint Journal.
Impact factor 4.306
Research design: Retrospective comparative cohort
Cited by 22

Al-Hourani K, Stoddart M, Khan U, Riddick A, Kelly M. Orthoplastic reconstruction of type IIIB open tibial fractures retaining debrided devitalized cortical segments: the Bristol experience 2014 to 2018. The Bone & Joint Journal. 2019 Aug;101(8):1002-8.

Retrospective comparative cohort analysing 113 patients with a type IIIB tibial shaft fracture incorporating a new technique named “ORDB” (orthoplastic reconstruction using mechanically relevant devitalized bone). This technique was incorporated primarily due to the unsatisfactory alternative surgical options in current practice. Alternative options continue to have a relatively high complication rate and often require multiple operative episodes to reconstruct the bony defect as a result of discarding devitalised mechanical segments. This study is somewhat controversial due to the retention of devitalised “dead” bone as part of the acute reconstruction of bone loss due to the assumed higher deep infection rate. Forty-four patients underwent ORDB with the remaining 69 not requiring this. ORDB was not associated with an increased rate of deep infection in the context of a two-stage orthoplastic protocol for the management of this injury. One limitation of this study however, was the lack of functional outcomes.

Publication 8.
Journal of Orthopaedic Trauma
Impact factor 2.512
Research design: Retrospective comparative cohort
Cited by 1

Al-Hourani K, Pearce O, Stoddart M, Riddick A, Khan U, Kelly MB. Orthoplastic Reconstruction of Type IIIB Open Tibial Shaft Fractures Using Debrided, Devitalized Cortical Segments: Health-Related Quality-of-Life Outcomes. Journal of Orthopaedic Trauma. 2022 Jul 1;36(7):332-8.

Retrospective comparative cohort analysing 74 patients with a type IIIB tibial shaft fracture incorporating a new technique named “ORDB” (orthoplastic reconstruction using mechanically relevant devitalized bone). This study addressed the limitations of the previous study analysing the ORDB technique. This was a new data outcome set looking at health related quality of life, including functional outcomes and return to sport/work. ORDB was shown to be non-inferior in the ORDB group compared to the non-ORDB group, with no clear difference in return to work and sport rates. However, half of patients were unable to return to their previous level of work and 75% unable to return to their pre-morbid level of sport. Despite this, in comparison to the known surgical alternatives in the literature, this study further informs the literature as to the safety of the ORDB technique, which provides particular advantages in the form of significantly reduced surgical episodes when reconstructing any defect.

Publication 9.
Journal of Orthopaedic Trauma
Impact factor 2.512
Research design: Retrospective comparative cohort

Al-Hourani K, Foote CJ, Duckworth AD, White TO, Kelly MB, Tornetta III P, SPARTA Investigators. What is the safe window from definitive fixation to flap coverage in type 3B open tibia fractures? Supporting Plastics and Orthopaedics Alliance in Reducing Trauma Adverse Events (SPARTA). Journal of orthopaedic trauma. 2023 Mar 1;37(3):103-8.

International multi-centre comparative cohort study which aimed to delineate whether a “safe” window exists for timing from definitive fixation to definitive soft tissue coverage in the treatment of open tibial diaphyseal fractures requiring flap coverage. This has not previously been defined in the literature. A total of 373 patients with a type 3b open tibial shaft fracture were analysed and in comparison to time base 0 (those who underwent single stage fix and flap), definitive fixation to flap coverage time of up to 2 days was not associated with an increased risk of infection, (RR 1.12, 95% CI 0.92 to 1.37, p=0.26). There was an increased risk of deep infection for more than 2 days (RR=1.59) and >5 days (RR=1.64). This is a unique study in the literature which required multi-centre involvement in order to be able to study variations in timing from fixation to flap coverage.

CONFERENCE PRESENTATIONS

1. **Orthopaedic Trauma Association**. Definitive flap coverage within 48 hours of definitive fixation reduces deep infection rate in open tibial shaft fractures requiring flap coverage. **Texas. USA. Podium.** October 2021
2. **American Academy of Orthopaedic Surgeons (AAOS) Annual Conference.** Fixation to flap coverage within a 48 hour safe window reduces deep infection rate in open tibial shaft fractures requiring flap coverage. **San Francisco, USA. Podium.** September 2021.
3. **Orthopaedic Trauma Association**. Two-Stage Orthoplastic Debridement of Type IIIB Open Tibial Shaft Fractures Is Protective of Acute Compartment Syndrome. V**irtual podium. USA.** September 2020.
4. **British Orthopaedic Association.** Plate assisted intramedullary nailing of Gustilo type IIIB open tibial diaphyseal fractures. **Virtual. UK. Podium.** September 2020.
5. **British Orthopaedic Trainees Association.** Orthoplastic reconstruction of grade IIIB open tibial fractures using devitalized cortical segments. The Bristol experience 2014-2018. **Edinburgh, UK. Podium.** December 2019.
6. **Orthopaedic Trauma Association.** Orthoplastic reconstruction of type IIIB open tibial shaft fractures using devitalised cortical segments. The Bristol experience 2014-2018. **Denver, USA**. **Podium.** September 2019.
7. **Orthopaedic Trauma Association.** Plate assisted intramedullary nailing of Gustilo type IIIB open tibial diaphyseal fractures: Does adjunctive plate retention affect complication rate? **Denver, USA. Podium.** September 2019.
8. **British Orthopaedic Association.** Orthoplastic reconstruction of grade IIIB open tibial fractures using devitalized cortical segments. The Bristol experience 2014-2018. **Liverpool, UK. Podium.** September 2019.
9. **EFORT**. Two-Stage Management Of Open Diaphyseal Tibial Fractures: Is The Timing Of Debridement And Coverage Associated With Outcomes? **Lisbon, Portugal. Poster.** June 2019.

INTERNATIONAL AWARD

Orthopaedic Trauma Association Bovill Award for Best Research Paper, 2021.
Presentation titled: "**Definite flap coverage within 48 hours of definitive fixation educes deep infection rate in open tibial shaft fractures requiring flap coverage.**"

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1. INTRODUCTION

The incidence of open fractures is rising world-wide, particularly in low and middle income countries (O'Neill et al., 2016). The incidence is also rising in the United Kingdom, and it is thought to be 6.94per 100,000 person years for all open injuries, and 1.87 per 100,000 person years in the tibia (Shah et al., 2022). As a result of their impact on health and country economics, these injuries were recognised by the Lancet Commission on Global Surgery as a “bellwether procedure”, denoting this injury as one of three top surgical priorities world-wide (O'Neill et al., 2016). These injuries place a large economic burden on some countries, costing as much as 8% of gross domestic product in the treatment of approximately 1.2 million potentially preventable complications, which could be reduced with better access to important treatment factors. In the context of open fractures, this includes access to pre-hospital antibiotics, early surgical debridement, and early stabilisation and soft tissue coverage (Meara et al., 2015, 2016).

1.0 Definition and epidemiology of open tibial fractures

A fracture is defined as primarily a soft tissue injury with discontinuity of underlying bone (Casagrande, 1961). An open fracture is one in which a fracture communicates with the external environment via a break in an epithelial barrier i.e. skin (Godina, 1986c). This is in contrast to a closed fracture, whereby despite trauma to the soft tissue envelope, it remains intact, providing coverage to the fracture site. The tibia (colloquially known as the shinbone) is one of two bones, along with the fibula, which forms the skeletal structure of the lower leg. This bone is at particular risk of open injury owing to the fact that there is a paucity of soft tissue cover (skin, muscle, fascia) overlying. In particular, the tibial shaft (also known as the diaphysis), is an area which is particularly at risk given its relatively subcutaneous position compared to the proximal and distal metaphyseal sections (spongy vascular bone either end of the shaft). These injuries represent a spectrum of injuries ranging from non-ischaemic injuries (arterial perfusion to the limb remains intact) to ischaemic injuries which require primary/secondary amputation owing to the massive soft tissue loss and lack of blood supply to the limb.

Open long bone fracture incidence stands at around 11.5 per 100,000 person-years in the western world (Court-Brown et al., 2012). This incidence is unknown in low and middle income countries (LMIC). The open tibia forms the most common open long bone injury within this subset of injuries, with an incidence of around 3.4 per 100,000 person years (Tampe et al., 2014). This particular injury therefore forms a significant proportion of open injuries and is a significant source of morbidity if management is not optimised (Giannoudis et al., 2006).

In the available data, the open tibial shaft fracture tends to be in a male population of working age (Court-Brown et al., 2012; Court-Brown & Caesar, 2006; Singh et al., 2018) The mean age is 37.7 years with 76% male (Schade et al., 2021). The aetiology for these injuries is primarily high-energy trauma, with over 50% thought to be as a result of road traffic accidents, with other modes of injury consisting of sports-related, falls and direct blows (Court-Brown et al., 2012).

Economically, this translates to a per patient direct cost of up to £126,000, rising to over £400,000 per patient if amputation is required, and societal costs as a result of loss of vocation of over £50,000 per patient (Schade et al., 2021).

1.1 Classification

Classification of open fractures is important as it allows communication of injury characteristics and has prognostic implications for the patient through a graded severity. In some injuries, this can also have implications on the type of treatment required.

Gustilo-Anderson

Gustilo et al, in his seminal article, analysed 1025 open lower limb fractures between 1976. A spectrum of injuries were identified with, with three subtypes classified in order of worsening prognosis. The three subtypes included; 1) contaminated wounds; 2) massive soft tissue loss and 3) compromised vascularity. Wound sepsis in those with soft tissue loss was over 50%, with a 16% amputation rate noted (Gustilo & Anderson, 1976). This is commonly known as the Gustilo-Anderson classification.

In an effort to further recognise the importance of the soft tissue envelope in these injuries, Gustilo and colleagues modified their original classification of massive soft tissue loss into three further subtypes following their review of a further 87 open tibial fractures, now known as types A, B and C. Type A injuries encompass those high energy injuries with significant periosteal stripping but, crucially, adequate skin cover regardless of open wound length following debridement, type B injuries where due to massive soft tissue loss, free soft tissue cover (skin/muscle/fascia with or without a vascular pedicle) is required from a donor site, and type C injuries which includes vascular compromise requiring vascular intervention with arterial repair.(Gustilo et al., 1984) These are now more commonly known as Types IIIA, IIIB and IIIC (Figure 1).

This thesis concerns management of only type IIIB injuries that represent the most severe non-ischaemic injury of the tibial shaft. Type IIIC open tibial shaft fractures are not considered in this thesis as ischaemic injuries represent a different type of injury with significantly worse outcomes in the literature owing to the ischaemic nature and noted high secondary amputation rates (Lin et al., 1997; Rajasekaran et al., 2006; Rajasekaran et al., 2015).

[redacted]

Figure 1. Type III open fracture subtypes. Adapted from <u>www.aofoundation.org</u>

It is important to note that despite its widespread use, this classification system has several limitations owing to retrospective methodology on which the data was collected, its use of a single outcome as a measure of prognosis (deep infection) and due to the lack of definition of subjective terms such as energy of injury. Additionally, it has been shown to have a “moderate” inter-observer agreement at most (Ghoshal et al., 2018), which results in limitations in clinical interpretation.

Orthopaedic Trauma Association-Open Fracture Classification (OTA-OFC)

To address the limitations outlined above for the Gustilo-Anderson classification, and its specificity to open tibial fractures, the American Orthopaedic Trauma Association (OTA) sought to create a new classification encompassing all open fractures of the body including those in paediatric patients. Their secondary aim was to determine treatment and for future research.

Through expert panel discussion, 34 factors were identified as being important, with five key categories shown to be applicable to all open fractures. These were injury to skin, muscle, vascular injury, degree of contamination and degree of bone loss (Figure 2). This classification system is not yet well adopted into mainstream orthopaedic practice and is currently primarily utilised for specific journal publication. The lack of specificity to open tibial fractures is considered a limitation (Ghoshal et al., 2018; Orthopaedic Trauma Association: Open Fracture Study, 2010), further validation may be required to displace the Gustilo-Anderson classification in clinical usage.

The Orthopaedic Trauma Society Classification of Open Fractures

More recently, the United Kingdom Orthopaedic Trauma Society have devised the latest proposed classification system. This was devised as a result of the continued concern regarding subjectivity of current classification systems using wording such as “contamination” and “periosteal stripping”, with continued concern regarding misclassification. Furthermore, it is thought that this new classification addresses patient reported outcomes and does not necessarily focus on clinical outcomes, such as deep infection, alone (Trompeter et al., 2020).

Skin	1. Laceration with edges that approximate. 2. Laceration with edges that do not approximate. 3. Laceration associated with extensive degloving.
Muscle	1. No appreciable muscle necrosis, some muscle injury with intact muscle function. 2. Loss of muscle but the muscle remains functional, some localized necrosis in the zone of injury that requires excision, intact muscle-tendon unit. 3. Dead muscle, loss of muscle function, partial or complete compartment excision, complete disruption of a muscle-tendon unit, muscle defect does not reapproximate.
Arterial	1. No major vessel disruption. 2. Vessel injury without distal ischemia. 3. Vessel injury with distal ischemia.
Contamination	1. None or minimal contamination. 2. Surface contamination (not ground in). 3. Contaminant embedded in bone or deep soft tissues or high-risk environmental conditions (eg, barnyard, fecal, dirty water).
Bone loss	1. None. 2. Bone missing or devascularized bone fragments, but still some contact between proximal and distal fragments. 3. Segmental bone loss.

Figure 2. OTA-OFC Classification. Adapted from the Journal of Orthopaedic Trauma.

A nested cohort of adult patients sustaining open lower limb fractures were identified from two major United Kingdom clinical trials, namely WHIST (Wound Healing in Surgical Trauma) and WOLLF (Wound Management of Open Lower limb Fractures).

The Classification divides patients into a simple and complex group, with subdivisions of the complex types into type A (requiring a bone deforming procedure), type B (requiring free soft tissue cover) or type C (requiring vascular arterial repair) (Figure 3). The simple group correlated directly with higher functional outcomes as opposed to the complex group. However, the more complex group was not found to be associated with a higher deep infection rate, which goes against traditional orthopaedic literature (MacKenzie et al., 2002; MacKenzie et al., 2005). This brings into question the prognostic capablility of such a classification, which is traditionally thought of as an essential component of any classification system. Additionally, the utility of the OTS score remains uncertain in common practice, it is a relatively new classification which was not available at the time of inception of the studies in this thesis. Therefore this was not utilised as a measure of injury severity.

[redacted]

Figure 3. OTS Classification. Adapted from Trompeter, 2021

The Ganga Hospital Score

Rajasekaran et al, as a result of their hospital experience of these injuries in Ganga Hospital (India), also developed a scoring system in order to decipher the need for salvage or amputation during the index procedure. It was developed in 2006 and is specifically designed to score type IIIb open tibial injuries, recognising this unique injury (Rajasekaran et al., 2006). There are three components to this score; 1) the skin, 2) the bone, 3) the functional muscle unit and neurovascular structures involved. Additional weight is given the general condition of the patient including comorbodities. The final score is calculated by addition of the score of each component, with a score <14 correlating with a prediction for imp salvage, score of 15/16 being a grey zone, and score of 17 or more correlating with a prediction of amputation. In a more recent study, it was found that this hospital score correlated well with hospital readmission, length of stay, number of operations, functional score and time to union (Parikh et al., 2020).

However, the studies have all remained reliant on the Gustilo-Anderson score to classify these injuries. The score is yet to be validated in other institutions and given the relatively low number of patients in each Gustilo-Anderson type, wide confidence intervals resulted in uncertainty with regards to statistical significance. Additionally, there remained uncertainty with regards to the model itself, given the decision making made was assumed to be correct in all cases, lacking real objectivity. In addition to the limitations mentioned above, in addition to the fact it does not provide a classification of open tibial injuries in themselves, that this score was not utilised in the studies mentioned in the thesis.

1.2 Rationale for focussing on Type IIIB Open Tibial Shaft Fractures

The type IIIB open tibial shaft fracture is a high energy open tibial injury, with significant periosteal stripping, and with a critical degree of skin/muscle loss necessitating soft tissue reconstruction. The periosteal layer of bone provides both blood supply to bone as well as healing potential for bony union. However, whilst vascular injury may be present, this does not lead to an ischaemic limb and therefore vascular arterial repair is not required (Stranix et al., 2017). As a result of periosteal stripping as well as significant skin/muscle loss, any bony healing is not possible as an open wound remains, which is likely to progress to nonunion, deep infection and possibly subsequent osteomyelitis (deep infection of bone involving the bone marrow) (Khatod et al., 2003).

Massive skin/muscle loss can lead to the inability to primarily close the wound overlying the bone, and therefore skin/muscle/fascia from a donor site is needed. It is this need for tissue transplant that makes type IIIB open tibial shaft fracture particularly challenging to treat. This also leads to two distinct timing variables that are crucial to clinical outcomes, namely the time from initial injury to initial debridement of the open fracture on one end of the timing spectrum, with time from injury to definitive fixation of the bone and definitive free soft tissue cover at the other end of the spectrum.

In between these two treatment variables, there are various significant variables which should be optimised in order to achieve favourable outcomes. These include standardisation of debridement, management of devitalised bone, management of any subsequent bony defects and type of definitive fixation used. Optimising management of this injury therefore requires careful planning and a solid evidence base on which devise protocols.

Suboptimal management of this injury can yield potentially avoidable complications such as deep infection and amputation which can be devastating for the patient (Saddawi-Konefka et al., 2008). Additionally it has been shown that deep infection has a significant impact on patient quality of life despite a salvaged limb (a limb which has been saved without the requirement for amputation) (Parker et al., 2018). With regards to the healthcare system, deep infection can lead to a six-fold increase in hospital length of stay and a five-fold increase in healthcare costs. This can lead to a significant burden on healthcare systems world-wide and negatively impact resources for future healthcare service planning (Hoekstra et al., 2017). With this in mind, and given type IIIB open tibial shaft fractures are the most severe non-ischaemic long bone injury, optimisation of treatment strategies and outcomes can form the basis for management of all open long bone injuries. This provides the overall rationale for the focus of this thesis on this specific injury subtype.

1.3 Outcomes in type IIIB open tibial shaft fractures

1.3.1 Surgical outcomes utilised

The primary aims of treatment of these injuries are to salvage (save) the limb, optimise limb function, and the avoidance of potentially devastating negative outcomes such as deep infection, nonunion, and amputation, which can be costly for both the patient as well as healthcare system (Khatod et al., 2003; Papakostidis et al., 2011). Other surgical outcomes which are considered significant in open tibial fracture care include; flap failure rate, unplanned operation rate and acute compartment syndrome.

The diagnosis of deep infection is derived from the criteria for ‘deep incision surgical site infection’, as outlined by the Centers for Disease Control and Prevention (Horan et al., 1992). Deep infection is defined as infection requiring surgical debridement and/or prolonged antibiotic therapy following definitive soft-tissue reconstruction. Notably the definition is not reliant on positive cultures (Fowler et al., 2019; Mathews et al., 2015).

For nonunion, the United States Food and Drug Administration definition was used: a fracture that is over nine months old with no radiological signs of progression towards healing for three months (Bishop J et al., 2012). This definition was used strictly for cases in which it was felt the nonunion was not as a result of infection, however it is recognised that waiting nine months before diagnosing a non-union is not mainstream practice. In the absence of a more recognised definition however, it is vital that a benchmark for diagnosis is used for objectivity.

Flap failure can be defined as total or partial necrosis of the transferred tissue. Flap failure occurring one month or more after coverage is considered failure secondary to deep infection (Boriani et al., 2017).

Acute compartment syndrome is defined as a condition in which there is increased pressure within the limited myofascial compartments of the leg, leading to compromised circulation and neurological function within the tissues of that compartment (Mubarak et al., 1978). There is no consensus in the literature on how best to diagnose compartment syndrome (Schmidt A et al., 2019; Schmidt et al., 2017), however in the study unit the practice is to diagnose acute compartment syndrome based on clinical grounds only without formal compartment pressure measurement. This relies on the degree of pain (and pain medication utilised), clinical assessment of the affected compartments and degree of pain on passive stretch of the compartments.

Unplanned reoperation is defined as any of the following:

1. Unplanned repeat debridement, removal/exchange of hardware for deep infection
2. Unplanned intervention for established nonunion, malunion or malalignment
3. Unplanned intervention for implant removal/exchange due to compromised construct stability

The primary outcome of deep infection has been extensively used in the literature as the marker of positive/negative clinical outcome and as such will be the main clinical outcome utilised in this thesis (Court-Brown et al., 1990; Gopal et al., 2000; Gustilo et al., 1984; Khatod et al., 2003; Lack et al., 2015; Mathews et al., 2015; Naique et al., 2006; Pollak et al., 2010; Rajasekaran et al., 2006; Singh et al., 2018; Tornetta et al., 1994; Tropet et al., 1999; Wordsworth et al., 2016).

1.3.2 Functional outcomes utilised

More recently, there has been a drive towards patient reported outcome measures for these injuries (Costa et al., 2018; Trompeter et al., 2020). This is due to the requirement to focus on subjective patient assessment as part of any developed treatment pathway. In particular, global health outcomes such as the Euro-Qol 5 Dimension (EQ-5D) and Short-Form-36 (SF-36) questionnaires have been utilised as they encompass assessment of various constructs, including; activities of daily living , both physical and mental health, as well as pain scoring.

The EQ-5D is a particularly widely used index that enables assessment of function according to 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) providing a 5-level response, of which calculated index values can be compared against population norms (Brooks, 1996; Group, 1990). The index lies on a scale of full health (value equal to 1) and a status as bad as death (value equal to 0). A higher index represents a greater health related quality of life (HRQoL) outcome.

The SF-36 is a generalised assessment of patient health with 8 scaled scores with each value converted to an index of 0– 100. It assesses physical, emotional, functional, and social well-being. Responses are weighted and aggregated to physical component and mental component summary scores (McHorney et al., 1993; Stewart et al., 1989). A higher score indicates less disability.

Further secondary outcomes which are indicators of success include return to work and return to sport, particularly given the primarily working age demographic of this injury group.

It is recognised that functional outcomes remain an issue in trauma. These remain clinical measures as opposed to patient driven outcome measures. For example, measurement of return to work/sport relies on the assumption that these are important outcomes for the patient, when this may not be the case, in view of the fact the majority of patients in the study cohort play sport socially and may not be concerned about the impact this has on their future participation in sport. Additionally, it may not be the case that patients wish to return to the same level of work following an injury of this nature, however when measuring this outcome, it is assumed that returning to their pre-morbid level of work is a positive outcome. Additionally, it is recognised that functional scoring systems have both floor and ceiling effects, whereby a considerable number of patients may score in each domain at either the lowest or highest score, thereby being unable to discriminate between subjects at either extremes for certain functional domains.

1.4 Traditional Management of open tibial fractures

1.4.1 Major Trauma Care

The advent of major trauma system care in the United Kingdom has furthered our understanding around the optimal site of care of these injuries. In 2010, twenty-two major trauma centres (MTC) were founded within national major trauma networks which meant that all patients identified with major trauma, such as in open tibial fractures, were transferred to the nearest MTC as opposed to the nearest hospital (McCullough et al., 2014).

In 2016, Wordsworth et al published their seminal article analysing outcomes in open tibial care pre and post advent of their local major trauma centre. The treatment and outcomes of 65 type IIIB open tibial fractures were analysed, noting a maintained limb salvage rate of 94% and a lower deep infection rate of 1.6% compared to 8%. It is proposed that the aspects of care which led to this positive shift in outcomes included earlier transfer to a definitive centre of care, earlier pre-hospital antimicrobial administration at time of injury, as well as availability of senior consultant orthopaedic and plastic surgeons for all stages of operative care (Wordsworth et al., 2016). Additionally, a major trauma set up has also recently shown that early transfer to a single all encompassing orthoplastic (joint orthopaedic and plastic surgical) point of care is more likely to lead to better compliance with national treatment guidelines for these injuries (Shepherd KL et al., 2017).

1.4.2 Orthoplastic care

Orthoplastic care is defined as orthopaedic and plastic surgeons working in tandem in providing care for acute trauma patients.(Khan et al., 2011) This is a concept which dates back almost 50 years, when it was acknowledged by Godina in his seminal thesis discussing management of open lower limb injuries. Godina proposed that there was a significant lack of understanding of the modern management of these open injuries amongst orthopaedic/plastic surgeons, and that involvement of experienced plastic surgeons was paramount when looking to achieve favourable outcomes (Godina, 1976).

The “Godina method”, utilised the principles of early aggressive debridement and early definitive soft tissue coverage. In his thesis, emphasis on microvascular repair was considered a key factor in reducing deep infection rates, through maintaining a patent blood supply to the distal limb, even if only single vessel (Godina, 1986a, 1986b). Godina encouraged the use of a side-to-end vascular anatomisis in free flap reconstructions to mitigate the risk of vascular insufficiency to both the flap and distal limb. Furthermore, Godina emphasised the need for vascular anastomoses to occur proximal to the zone of injury and arterial autografts to be used within the zone of injury. Godina also postulated that flap anastomoses proximal to the zone of injury potentially allowed antibiotic bathed flaps to provide a route of local antibiotic delivery directly to the open wound (Godina, 1979).

There has been significant development based on the “Godina method” since this work. Gustilo built on many of these principles, incorporating the importance of massive soft tissue loss within the widely used classification described in section 1.1. Other advances include the array free soft tissue flaps available to the treating surgeon as a result of microsurgical advances. Traditionally, some zones of injury were considered too distal or too large to enable pedicled flap reconstruction (skin/fascia/muscle rotated around a vessel attached at the original site of injury) alone. With the emergence of microvascular repair, free muscle transfers and myocutaneous free flaps have not only become available, but now the emerging gold standard, both due to their utility and their devolvement from the original zone of injury (Anthony et al., 1991; Arnez & Hanel, 1991; Brumberg et al., 2021).

1.4.3 Early antibiotics

Early antibiotic administration had been noted in animal models in the past (Penn-Barwell et al., 2012), however several clinical studies have also noted delay in antibiotic administration over 24 hours as being detrimental to deep infection outcomes. In 1989, Patzakis and Wilkins analysed 1104 open lower limb fractures, noting a higher deep infection rate in those delayed over 3 hours (Patzakis & Wilkins, 1989). Al-Arabi et al conducted a similar study, noting a longer range of 24 hour delay before increased infection rate (Al-Arabi et al., 2007). However, Lack et al in their landmark study assessed 137 type III open lower limb fractures, and found a delay of over 66 minutes as being significant (Lack et al., 2015). However, this was an observational retrospective study, with a relatively low number of patients not specific to type IIIb open tibial shaft fractures. Additionally, the outcome of deep infection was only measured to 90 days, when many of these infection may present later an upto one year. Therefore whilst this study remains the most relevant with regards to administration of antibiotics in clinical open fractures, there remains a lack of strong evidence with regards to this facet of open fracture care. This has however, led to the standard of care being administration of intravenous antibiotics within 1 hour of injury. As such, time to antibiotics is not considered within the work presented here given it is standard practice in the study for all patients to receive broad spectrum intravenous antibiotic cover within 1 hour of injury.

1.4.4 Surgical Debridement

Surgical debridement is defined as the enlargement of a wound to remove devitalised tissue. The issue of a thorough surgical debridement has become especially important in open tibial fracture care as this has been shown to have a significant impact on the prognosis for these injuries. Without a systematic and thorough debridement, unfavourable outcomes such as deep infection are more likely to occur (Melvin et al., 2010; Namdari et al., 2011).

The principle tenet of a thorough surgical debridement is the full exposure of the entire zone of injury, with extension of the wound along the length of the limb. It is paramount that this occurs as the superficial wound frequently does not reflect the true severity of deep tissue contamination/devitalisation. This is particularly the case in higher energy injuries such as type IIIB open tibial fractures (Melvin et al., 2010; Namdari et al., 2011).

Despite this being an essential stage of surgical care, surgical debridement remains inadequately defined and non-standardised, with great variability between and within institutions (Marecek et al., 2018). This forms an essential component of this thesis.

1.4.5 Time from injury to debridement

In 1995, Kindsfater et al. noted early debridement within six hours of injury as being key for deep infection rates (7% compared to 38%) (Kindsfater & Jonassen, 1995). This became known as the "six hour rule" and has been traditionally accepted as a definitive cut-off. This has been disproven in more recent literature though and is now not considered to be evidence based. Furthermore, many studies have not noted an association between time to debridement and deep infection rates (Harley et al., 2002; Pollak et al., 2010; Weber et al., 2014). There is currently no consensus on optimal timing from injury to debridement, with significant confounding in the literature as a result due to unstandardised protocols, lack of orthoplastic care and lack of accurate recording of timing. This has led to significant debate and confusion in the orthopaedic community (Kortram et al., 2017; Prodromidis & Charalambous, 2016; Schenker et al., 2012; Wood et al., 2012).

There is a clear need for clarification on this timing window in the literature and this consideration forms a novel aspect of this thesis.

1.4.6 Definitive fixation strategy

Identifying the definitive fixation strategy as part of the management of open fractures is an essential aspect of care. Any device utilised to obtain fixation of the long bone should aim to stabilise the whole long bone and allow immediate range of motion for the joint above (knee) and below (ankle) the tibia in order to allow immediate weight bearing in order to optimise recovery.

There are a range of fixation options available to meet these aims, however these should be considered within the context of a large open soft tissue defect which will require coverage. These range from internal fixation options (implants covered by the soft tissues) versus external fixation implants (metalwork within the long bone attached to a stabilising structure out-with the soft tissues).

Traditional examples of internal fixation include an intramedullary nail (metal rod within the long bone, inserted either with or without reaming) or plate and screw fixation. Reaming is the insertion of a drill to expand the inner diameter of the long bone and thereby allow the ability to insert a larger diameter intramedullary nail. The idea behind this being a larger diameter nail allows a “tighter” fit around the fracture, creating increased construct rigidity and has been shown to reduce time to fracture healing (Bhandari et al., 2008). The use of unreamed nails however, allows preservation of the endosteal internal vasculature of bone, and therefore theoretically should improve fracture healing and infection rates (Utvag et al., 1998). In essence the trade-off is stability for biological integrity with each type of intramedullary nail used. There is a choice of intramedullary nailing, namely reamed (where a channel is created within the bone and sequentially increased in diameter), and unreamed (where a nail the intramedullary diameter is not increased). This has been a source of debate in the past as it was thought that unreamed nails preserve the endostial bloody supply which could have a positive effect on healing and infection rate, compared to reamed nailing which allow the used of larger diameter intramedullary nails offering greater stability but at the expense of bloody supply. A previous meta-analysis of randomised trials by Foote et al demonstrated no significant difference in re-operation rate or secondary outcomes between reamed and unreamed nailing (Foote et al., 2015). Common practice in the United Kingdom remains for reamed intramedullary nailing largely as a result of offering greater stability to the construct and the ability to immediately weight bear these injuries.

Plate fixation is a metallic device which is fastened to bone with screws. This is designed to provide stability to the long bone, and traditionally required larger incisions. However newer plates off minimally invasive percutaneous techniques for insertion without stripping the bone of its soft tissue envelope. Additionally, newer implants are scalloped at the plate bone interface to allow less contact between the plate and bone. This is thought to preserve the periosteal supply under the plate for fracture healing (Ahmad et al., 2007).

External fixation entails the use of percutaneously placed pins and/or wires secured to external scaffolding to provide stability to the bone.

1.4.7 Management of bone defects

Open tibial shaft fractures can be complicated by the presence of defects in the tibia, resulting in loss of mechanical integrity of the bone (Keating et al., 2005). Bone loss can occur as a result of the high energy impact at the time of injury, and owing to the relatively subcutaneous nature of this bone, fragments are extruded into the environment. Furthermore, some fractures can be discarded at the time of injury either due to the highly multi fragmentary nature of the fracture, or due to fragment devitalisation (devoid of any soft tissue and bloody supply) (Mauffrey et al., 2012). The general consensus in the orthopaedic literature is that for all tissue, including bone, to be assessed for contamination and devitalisation, and if deemed devitalised, the bone should be discarded. This is designed to reduce the risk of infection and to leave a "clean" wound based for further reconstructive surgery or for healing to occur (Mauffrey et al., 2012).

The issue with discarding bone however, is that a bone defect occurs, which affects bone stability, limb alignment and limb length (Trompeter et al., 2020). All of these lead to a negative outcome on patients and in the main necessitate further surgery to correct (Blick et al., 1989; Edwards et al., 1979).

Several options exist when bone is discarded. These include distraction osteogenesis, whereby following initial shortening of the tibia to negate the defect, an internal or external fixation device (or both) is used to gradually distract at the fracture site in order to lay new bone to restore limb length and correct any deformity. This is usually utilised for bone defect measuring greater than 5cm.

Another method is terms the "Masquelet technique" via an induced membrane (Masquelet & Begue, 2010). The idea behind this technique being that polymethyl methacrylate cement (bone cement), is implanted into the defect and the bone stabilised via an external fixator. The bone cement acts as a spacer in effect, and over 6-8 weeks a vascular membrane forms around the cement and bone ends. At the stage of membrane maturation, this is incised and morcellised cancellous bone graft is substituted into the defect in place of the cement. The cancellous bone consolidated over time into a stable unit to allow weight bearing. This technique is typically reserved for defects measuring 5-25cm (Masquelet et al., 2000).

A final method which has been popularised includes segmental structural bone grafts, particularly a fibular graft to act as a strut to maintain stability of the long bone. This could either be vascularised (attached to a vascular pedicle), or non-vascularised. The fibula is often used due to its proximity to the tibia, its mechanical strength, and its predictable vascular pedicle. The advantage of including a vascular supply to the fibular graft, is that this forms a more predictable mode of bone healing, either primary or secondary depending on the construct rigidity, whereas in non-vascularised grafts this is likely to occur by creeping substitution, which is a more prolonged and less predictable mode of healing. Additionally, vascularised grafts leads to reduced graft resorption, maintenance of graft integrity throughout healing, and reducing risk of stress fracture, loss of contract integrity and with that deep infection rate (Bumbasirevic et al., 2014).

Whilst these techniques have shown promise with regards to their clinical, they remain debatable due to several issues. Deep infection rates have remained high (masquelet 18% and bone transport 38%), (Chan et al., 1984; Morelli et al., 2016) while multiple operations and prolonged fixation (and healing time) is required for both bone transport and masquelet techniques without clear functional outcomes or bone regenerate superiority (Giannoudis et al., 2011; Rigal et al., 2012).

To date, retention of devitalised fragments has not been explored. To do so is thought to be controversial as these fragments are considered contaminated and act as a possible nidus of infection. However, if these fragments could be retained without inferior clinical/functional outcomes, then this could be of significant benefit, mitigating the need for the complex procedures described above, multiple procedures and/or prolonged treatment times.

1.4.8 Time from injury to definitive fixation and soft tissue coverage

Godina et al. noted the importance of early definitive stabilisation (fixation) of the tibia and early definitive soft tissue coverage. In his retrospective series analysing 532 injuries, it was observed that those definitively covered within 72 hours had a lower deep infection rate of 1.5% compared to those over 72 hours (17.5%) (Godina, 1986c). This paper set the standard of care, with Godina being heralded as the forefather of the early soft tissue coverage approach. So much so that this has now been implemented within United Kingdom national treatment guidelines for open fractures (BOA & BAPRAS, 2017). Godina's work formed the basis of a radical approach called the "fix and flap" approach, whereby definitive skeletal fixation and definitive free soft tissue coverage is achieved at the same operative sitting as opposed to stages on different days. Gopal et al. noted a significantly lower infection rate of 10% using this technique (when undertaken within 72hours) compared to traditional literature that reports deep infection rates as high as 52% (Gopal et al., 2000; Singh et al., 2018). More recently Mathews et al. reported an infection rate of only 4.2% compared to 34.6% when patients underwent a single stage "fix and flap" in contrast to a staged fixation and definitive soft tissue cover process (Mathews et al., 2015).

1.5 Novel aspects to this thesis

To the author's knowledge, there is no single body of work which analyses the important independent variables of management of type IIIB open tibial shaft fractures requiring flap coverage. Furthermore, it is vital that a standardised treatment protocol is devised in order to provide the orthopaedic community with an objective and reproducible model of care, provided that the outcomes of said model are positive.

Additionally, in order to ascertain the safety of such a protocol, it is clear that the various components should be clearly analysed, including clinical and functional outcomes to prove its efficacy. Consequently, this should include the stages of timing from injury to debridement, assessment of the "fix and flap" approach, novel technical aspects of the surgical protocol, clinical outcomes and functional outcomes. This thesis addresses each of these aspects.

1.6 Aims

There remains several deficiencies in the literature with regards to open tibial fracture care. The themes of controversy have been described in section 1.4. This thesis aims to address these deficiencies. The aim of this thesis is:

1. To evaluate a standardised protocol for the management of type IIIB open tibial fractures requiring flap coverage through the evaluation of the following variables:

- Timing from injury to debridement
- Surgical debridement
- Type of surgical fixation utilised
- Addressing bone defects
- Time from injury to definitive fixation and flap coverage
- Time from definitive fixation to definitive flap coverage

The primary clinical outcome in this these is deep infection rate. The secondary outcomes, as appropriate, include rate of acute compartment syndrome (ACS), flap failure rate, rate of nonunion, unplanned re-operation rate and functional outcomes as described in section 1.3.

2. ORTHOPLASTIC PROTOCOL

As a result of variation both between and within institutions with regards to the various management factors discussed in section 1.4, a novel two-stage orthoplastic approach to the management of open tibial shaft fractures was designed by orthopaedic and plastic surgeons within the study unit, namely Southmead Hospital in Bristol. This was designed to address all aspects of care to fall in line with the existing national guidelines. These national guidelines are otherwise known as the British Orthopaedic Association Standards for Trauma (https://www.boa.ac.uk/resources/boast-4-pdf.html) (BOA & BAPRAS, 2017). This document represents a national standard agreed upon by orthopaedic and plastic surgical colleagues. It includes early transfer of care to the treating orthoplastic unit, early (within 1 hour) intravenous antibiotic administration and once in hospital, standardised resuscitation protocols and emergent management of the open tibia in order to stabilise the limb.

Surgical debridement should occur immediately for gross contamination, within 12 hours for high energy injuries, or within 24 hours for low energy mechanisms. As explored in section 1.4, this is not evidence based. Definitive soft tissue coverage should occur in the same setting as definitive fixation, and ideally within 72 hours of injury.

This two-stage surgical protocol was analysed in six of the nine publications submitted within this thesis and should be considered novel (Al-Hourani, Fowler, et al., 2019; Al-Hourani K, 2021; Al-Hourani K; Al-Hourani, Stoddart, et al., 2019). The study unit aims to undertake a two-stage protocol for all patients presenting with an open tibial shaft fracture (Figure 4).

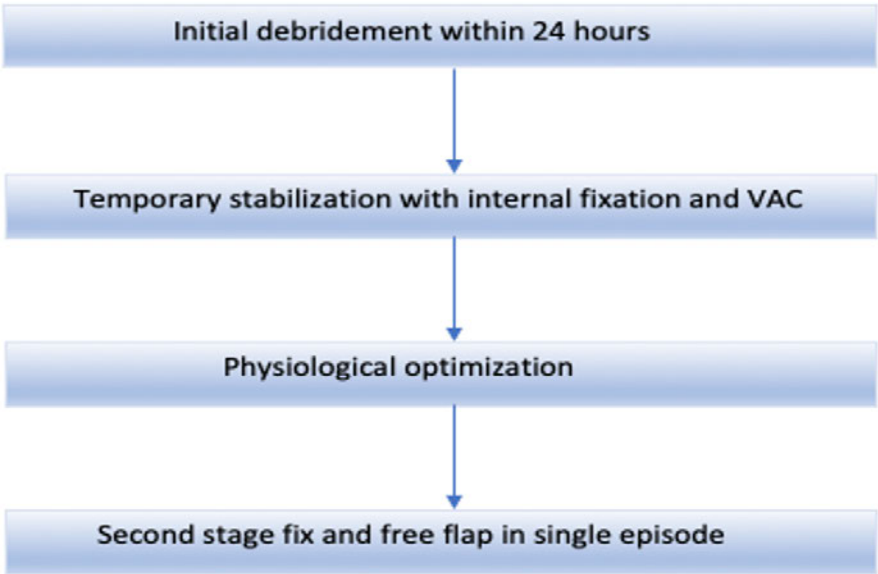

Figure 4. Two-stage surgical protocol

All patients within the included studies are transferred to the treating orthoplastic unit. All patients are administered intravenous antibiotics within 1 hour of injury by the paramedical team “in the field”. Stage one consists of initial wound debridement which consists of a “three-vessel view” debridement as per standard protocol in the study unit (Al-Hourani et al., 2021). This will be explored later in this chapter. Following this initial debridement, temporising internal fixation is applied to the bone to stabilise the tibia. This consists of a 3.5mm low contact dynamic compression plate. The study unit has ceased to use external fixation as a temporising measure since May 2015, switching to temporising internal fixation (In-fix), owing to the unnecessary risk of pin site infection close to the zone of injury, which can be as high as 28% (Blick et al., 1989; Edwards et al., 1979). The use of an “in-fix” mitigates against this risk and can be used in bridging mode (to span the fracture area at a fixed point either side of the fracture) to bridge large zones of multifragmentary fractures and to stabilise devitalised bone fragments.

The use of an “in-fix” also encourages the adequate exposure of the zone of injury which is a vital component of an adequate debridement. The use of the infix has been analysed by the study unit previously and has not been shown to be associated with any increased risk of infection, nonunion or flap failure in comparison to the traditional external fixation (Fowler et al., 2019). The wound is then dressed with negative pressure wound therapy (vac therapy) which is not removed until the second stage of the protocol.

Following stage one, the patient is physiologically stabilised until definitive fixation and definitive soft tissue coverage is undertaken in the same sitting on a dedicated orthoplastic operating list.

At stage two, the temporary in-fix is removed, a further wound inspection occurs, with debridement of any further tissue that is considered devitalised. A fresh 3.5mm in-fix is applied, with screws in the anterior transcortical position in order to facilitate plate-assisted intra-medullary nailing of the tibia. A fresh “in-fix” is applied in every case at stage two. Definitive soft tissue coverage is achieved, often utilising a fascial anterolateral thigh free flap at the same operative sitting. Intravenous antibiotics are continued until stage two has been completed.

2.1 Time from injury to debridement

This section pertains to the following publications as part of this thesis:

1. ***Al-Hourani K***, Fowler T, Whitehouse MR, Khan U, Kelly M. Two-stage combined ortho-plastic management of type IIIB open diaphyseal tibial fractures requiring flap coverage: is the timing of debridement and coverage associated with outcomes?. Journal of Orthopaedic Trauma. 2019 Dec 1;33(12):591-7.
2. Foote CJ, Tornetta III P, Reito A, ***Al-Hourani K,*** Schenker M, Bosse M, Coles CP, Bozzo A, Furey A, Leighton R, GOLIATH Investigators. A reevaluation of the risk of infection based on time to debridement in open fractures: results of the GOLIATH meta-analysis of observational studies and limited trial data. JBJS. 2021 Feb 3;103(3):265-73.

As part of this novel two-stage protocol, it is vital that all significant components of care are analysed separately in order to assess the protocol. Timing from injury to debridement is a vital variable owed to the controversy in the literature surrounding the optimal timing. It has traditionally been strongly attributed as a factor in the development of deep infection.

2.1.1 Publication 1 (Al-Hourani, JOT, 2019)

This study aimed to delineate whether timing from injury to initial debridement had any effect on the primary outcome of deep infection. Secondary outcomes included flap failure and nonunion.

This was a retrospective study over a defined two-year period (May 2014-May 2016). Patients were identified from the Southmead Hospital internal unit orthoplastic database which is collected prospectively, and this was cross-referenced against the national Trauma Audit and Research Network (TARN) database. TARN is a national initiative which measures and monitors processes of care and outcomes of major trauma (including open fractures), providing local, regional and national information on trauma patient outcomes.

A total of 145 patients were identified who sustained open lower limb injuries requiring soft tissue coverage in this time window. The inclusion criteria for this analysis were adult patients (>18 years old), who sustained open tibial shaft fracture patients requiring soft tissue coverage (type IIIB injuries) and who underwent the two-stage protocol. Those excluded include those who are unfit for two anaesthetic procedures, died prior to reconstruction, underwent primary amputation due to massive soft tissue loss or had primary fixation due to a prosthetic knee replacement above the fracture. Following exclusions, a total of 45 patients were therefore eligible for final study inclusion. As anticipated the main demographic were young males.

In addition to accurate assessment of timing intervals, other independant variables collected included type of temporising measure used, type of flap, anaesthetic grade (ASA), fracture severity and smoking/diabetic status. Mean follow up was 2.0 years (SD 0.42).

A total of four patients (4/45, 8.9%) developed a deep infection. There was no difference in mean time to debridement in the infected and non-infected groups (18.9hours (SD 7.68), vs 18.9hours (SD 12.8), p=0.990). There was no difference in time to initial debridement for those who developed infection associated flap failure (n=3), p=0.724. No patients experienced nonunion. The independant variables noted above were also not found to be predictive of the primary or secondary outcome on multi-variate regression.

This study analysed whether time to debridement in patients who sustained a type IIIB open tibial shaft fracture, had any influence on the primary outcome of deep infection. The deep infection rate utilising this two-stage protocol was 8.9%. There was no evidence to suggest that time to debridement correlated with deep infection rate.

To the author's best knowledge, this is the first article to assess this novel protocol in the management of type IIIB open tibial shaft fractures. The lack of association between time to initial debridement and deep infection rate is contentious in the literature. Kindsfater et al popularised the "6 hour rule" whereby it was thought that debridement within 6 hours of an open tibial fracture reduced deep infection rate. This was based on a retrospective series of 47 fractures, with 1 of 15 (7%) fractures debrided under 6 hours sustaining a deep infection, with 12 of 32 (38%) fractures debrided after 6 hours sustaining a deep infection. Whilst this study had merit in highlighting the importance of expedient debridement, several drawbacks existed including the lack of standardisation of time to antibiotics, lack of assessment of the quality of debridement as well as the lack of applicability to the most severe non-ischaemic open tibial fractures (type IIIB) given all were closed primarily in Kindsfater's study (Kindsfater & Jonassen, 1995). Pollak et al, in a multi-centre retrospective study, analysed 315 open lower limb injuries including the ankle as part of the Lower Extremity Assessment Project (LEAP) study group. Allowing for adjustment for time to "aggressive" debridement, antibiotic administration and time to soft tissue coverage, 84 (27%) of patients had developed a deep infection within 3 months. Timing intervals to both debridement and soft tissue coverage were not found to be predictive of deep infection as an outcome, however, late transfer to a definitive treatment centre was found to be an independant predictor of increased deep infection rate (Pollak et al., 2010). Weber et al, in perhaps the largest study to date, prospectively analysed 736 patients to include both upper and lower limb injuries. A total of 46 injuries (6%), experienced deep infection, with no clear difference found in timing to debridement between those who did and did not experience infection (mean time to debridement difference of 2 hours 35mins between groups). The severity of open fracture was found to be the most significant predictor of deep infection rate with type IIIB and IIIC injuries forming 17/46 (37%) of these infections. This paper supported modern timing to debridement evidence, however did highlight that the more severe type IIIB open tibial injuries are a specific subset which required specific analysis (Weber et al., 2014). Hull et al supported the notion that type IIIB/C injuries required a subset analysis, with their study which included 459 open upper and lower limb injuries in a United Kingdom major trauma centre. It was found that with every 1 hour delay in debridement, there was a 3.3% increased in deep infection rate, with a greater effect seen in the more severe injuries (Hull et al., 2014).

The key strengths to publication 1 of this thesis is that this is the first study in the literature to highlight that timing to debridement specifically in type IIIB open tibial shaft fractures should not be compared to other open long bone injuries. This is particularly the case given that these require free soft tissue coverage as opposed to primary closure of the wound at time of initial surgery. Additionally, the study introduced the two-stage orthoplastic protocol for the standardised management algorithm of these injuries. The deep infection rate of 8.9% is much lower than that in the literature which can be significantly higher (Blick et al., 1989; Edwards et al., 1979; Tornetta et al., 1994; Tu et al., 1995). The study proposes the notion that when other vital variables are optimised, time to initial debridement becomes less important. In particular, the early rates of soft tissue coverage in the same sitting as definitive fixation is a key component which has been proven to be the more significant timing variable in this patient population which will be discussed later in the thesis (Kuripla et al., 2021).

There are limitations however, with the retrospective nature of this study offering an inferior level of evidence given the usual biases associated with such a study. However, mitigating this, recollection bias was reduced as the study unit maintains an in-house prospective database against which all notes were cross-referenced. Additionally, whilst timing to debridement was not associated with deep infection, causation of time to debridement cannot be definitively attributed to the outcome of deep infection. This study did however, form the precursor to a wider collaborative systematic review as part of the “GOLIATH (Growing Open Fracture Evidence with Large In-Progress Cohort Studies) study group.

[redacted]

2.1.2 Publication 2 (Foote et al, JBJSAm, 2020)

Given the low incidence of open tibial shaft fractures (Court-Brown et al., 2012), prospective trials on an injury of this nature is difficult to perform. As such, and consequent to the timing discussion above, the international "GOLIATH (Growing Open Fracture Evidence with Large In-Progress Cohort Studies) study group was formed to provide the highest quality estimates from all published and unpublished data in the literature (Foote et al., 2021). Specifically, the thesis author was a founding member of the GOLIATH study group, with contribution of data, formation of study methodology which focus on type IIIB tibial shaft fractures, analysis of data as well as manuscript draft formation.

This study is the largest systematic review and meta-analysis of all published data in the literature pertaining to time to debridement in open lower limb injuries. The aim was to evaluate the impact of delay to debridement on deep infection rate in adult open lower limb injuries with a subset analysis for type IIIB open tibial fractures. Of the 26,857 initial potential references yielded, and following exclusions, 84 studies including 18,239 patients were analysed.

To obtain an initial broad understanding of delay to debridement, the terms "early" (e.g., <6, <12, or <24 hours) and "delayed" (e.g., >6, >12, or >24 hours) were used according to the cut-points in the individual publications. Additionally these results were not stratified according to Gustilo type or site of fracture to maintain this broad understanding.

The results noted a significant impact of delay to debridement on infection risk (OR = 1.29, 95% CI = 1.11 to 1.49, p <0.001, 84 studies, n =18,239). Specifically for type IIIB open tibial fractures, delayed debridement later than 12 hours compared with earlier than 12 hours was associated with a substantial increase in deep infection (OR = 1.46, 95% CI = 1.13 to 1.89, p = 0.004, 12 studies, n = 1,255). Those treated later than 24 hours had a significant twofold higher infection rate than those treated earlier than 24 hours (OR = 2.17, 95% CI = 1.73 to 2.72, p < 0.001,29 studies, n = 5,214).

However, several limitations existed in the literature. Secondary delays as a result of delay of transfer to the definitive treatment centre was not reported in all studies. Additionally, it was not clear in all papers when the timing origin had initiated, which clearly highlighted a deficiency in reporting of the literature. This could therefore be a significant bias which requires to be accounted for in future studies. Furthermore, many of the studies included were either observational or retrospective in nature, leading to the standard biases associated with such studies such as recall bias and data entry bias.

However, this study is the largest known in the literature to analyse timing in this nature, with a focus on reduction of confounding. For each paper methodological quality, statistics used and author interpretation of results were scrutinised, in order to glean the conclusion noted. The pooling of data as a result of the meta-analysis however does provide the most comprehensive assessment of timing to debridement in the literature. This is particularly important due to the nature of this injury, which does not lend itself readily to prospective randomised studies.

Publication 2 (Foote et al), JBJSAm, 2020), highlighted that early debridement in type IIIB open tibial fractures is likely to reduce the risk of deep infection occurring, and this supports the message of publication 1 (Al-Hourani, JOT, 2019). However, there is a discrepancy in terms of the exact timing windows, whereby publication 1 (Al-Hourani, JOT, 2019) does not define 12 hours as a threshold for debridement in type IIIB injuries. This therefore raised the question for further work to be conducted on this specific subgroup as to why this may be the case. It is likely that the various elements which come into play as outlined in section 1.4, undergo an interplay which should all be analysed specifically in order to further understand the question of timing in this specific injury subgroup.

2.2 Surgical Debridement

This section pertains to the following publications as part of this thesis:

3. ***<u>Al-Hourani K</u>***, Pearce O, Bott A, Riddick A, Trompeter A, Kelly MB. Three-vessel view debridement of the open tibial fracture: a surgical technique. European Journal of Orthopaedic Surgery & Traumatology. 2021 Sep 10:1-7.
4. ***<u>Al-Hourani K</u>***, Stoddart M, Pearce O, Riddick, Khan U, Kelly M. Acute Compartment Syndrome in Type IIIB Open Tibial Shaft Fractures Using a 2-Stage Orthoplastic Approach, Journal of Orthopaedic Trauma. 2021 Dec, 35(12):643-9

2.2.1 Publication 3 (Al-Hourani, EJOST, 2021)

As a result of a lack of a standardised debridement technique that is accepted in clinical practice and supported by the literature, there was a clear need for a standardised debridement technique to be proposed to the orthopaedic community. The purpose of this paper was to define a clear debridement technique as part of the two-stage orthoplastic protocol for the management of type IIIB open tibial shaft fractures. Whilst no data is presented with this debridement technique, it does provide a methodical and novel way to safely debride these injuries fully. Furthermore, the proposed debridement technique was used in all publications form the Southmead study unit presented in this thesis and this should be considered as part of the assessment of the publications in question (publications 1 and 3-9).

The debridement technique, termed the “three-vessel view”, essentially looks to either directly access, or make easily accessible, the three arteries surrounding the tibial shaft. namely the anterior tibial (accessing anterior compartment), posterior tibial artery (accessing the superficial posterior and medial aspect of deep posterior compartment) and the peroneal artery (accessing lateral and lateral aspect deep posterior compartments) (Figure 5).

The first component of the debridement is patient set-up. It is vital that these patients are debrided on a dedicated orthoplastic list with the appropriate senior expertise present. The patient is set up supine, with no tourniquet on the relevant limb in order to be able to identify and repair/ligate any active bleeding.

[redacted]

Figure 5. A) Showing access to via the relevant musculature. B) Showing access to the relevant compartments. Adapted from Al-Hourani et al, 2021.

The second aspect is adequate wound extension. The traumatic wound should be extended along fasciotomy lines in order to be able to expose the relevant compartments.

The third aspect is the debridement technique itself whereby the wound is inspected and debrided from superficial to deep. The skin is inspected for its viability via the presence of underlying venous thrombosis. Any gross degloving (planar injury between the skin and underlying deep soft tissues eg fascia) must then be assessed as it is highly likely the relevant degloved skin is unviable. Attention is then turned to the deeper zones of injury and it is from the author's experience that the deep tissues furthest away from the initial traumatic skin wound that retain the nidus for continued infection. The tibial fracture itself is placed into the "shotgun" position in order to visualise both the extra-medullary and intra-medullary regions for curettage (Figure 6).

Additionally it allows clearance of the surgical field in order to identify the three vessels (anterior tibial artery, posterior tibial artery and peroneal arteries) within the compartments around the leg. Identification of the vessels and their related coursing nerves (deep peroneal nerve, tibial nerve and superficial peroneal nerve) provides the surgeon with a "lit runway" to circumferentially access the compartments of the leg as well as safe corridors of debridement without risking the neuromuscular bundles in the process.

Figure 6. “Shotgunning” the tibia to access all compartments.
Adapted from Al-Hourani, 2021.

Following soft tissue debridement, thorough lavage is undertaken with warmed saline in order to dilute the microbial presence.

To the author’s best knowledge, an algorithm for debridement such as this has not previously been described in the literature. Standardization is important as it provides consistency in the way these injuries are initially debrided. Additionally, any variability in outcomes can be attributed to other variables as part of the granular analysis of this injury.

2.2.2 Publication 4 (Al-Hourani, JOT, 2021)

The aim of this study was to analyse the clinical outcomes of type IIIB open tibial shaft fractures utilising the two-stage protocol, with specific reference to the first stage "three-vessel view" debridement described in publication 3. A total of 83 patients who experienced this injury and underwent this surgical debridement were analysed. The primary outcome measure was rate of acute compartment syndrome (ACS), given this is the first debridement technique which accesses all compartments as part of standard debridement. Deep infection rate was a secondary outcome measure. The two-stage orthoplastic protocol was utilised for all patients included in final analysis for the study.

The diagnosis of acute compartment syndrome was made clinically in accordance with common practice. This was on the basis of pain, examination of the leg compartments and pain on stretching of the compartments (Marchand et al., 2020; Saiz et al., 2020). The diagnosis was not reliant on compartmental monitoring. Monitoring of acute compartment syndrome occurred during the inpatient stay as part of the flap monitoring protocol for patients upto day 5. Patients were also clinically followed up until clinical and radiological healing had occurred and therefore this allowed for monitoring of signs of missed compartment syndrome. The independent variables considered were age, gender, diabetes, smoking, injury severity score, time to initial and definitive debridement, primary or secondary transfer, type of flap, location of wound (axial and coronal planes), vessel injury, vessel run-off, the involved compartment and AO fracture morphology. Independant variables were forced into one regression model, and in a separate step-wise fashion to find the most accurate predictive model based on the number of outcomes.

A total of 83 patients were analysed, median age 45.4 years (interquartile range, IQR, 35) and majority males (51/83, 61.4%). Median follow up was 1.6 years (IQR 0.8). No patients experience acute compartment syndrome or early/late sequelae at latest follow up. Additionally, the deep infection rate remained low (6/83, 7.2%), with only diabetes being associated with deep infection.

The value of this study lies in its analysis of outcomes, adjusting for independent variables, based on the two-stage orthoplastic protocol utilising a standardised three-vessel view technique. This study provides a novel message, that in those who undergo a standardised two-stage protocol with a three-vessel view debridement, the devastating complication of acute compartment syndrome is negligible. Additionally, utilising deep infection rate as a surrogate for a thorough debridement, the “three-vessel view” technique provides an adequate debridement.

The concept of debridement is extremely important as it is thought that this step is a vital step in infection prevention (Bhandari et al., 2003; Edwards et al., 1988; Namdari et al., 2011). There is only one study in the literature which has been shown to analyse debridement technique as a variable. Marecek et al, in their prospective cohort study at a level 1 trauma centre, analysed 68 open tibial fractures. Forty-eight patients had direct extension of the open wound as per the study in this thesis, as opposed to 21 patients who underwent a defined surgical approach through an anterolateral window. Whilst rate of ACS was not analysed, those in whom a direct wound extension was not utilised had a lower infection rate (9.5% vs 11%), lower flap requirement (0% vs 19%), and lower mean re-operation rate (1.29 vs 1.96 mean operations). The result for free flap requirement and mean operation rate were significant (Marecek et al., 2018). The rationale for utilising a separate soft tissue window (eg anterolateral incision away from site of injury medially), is the ability to close the wounds primarily. There are several limitations to this study however. No clear algorithm for debridement was given on which patients this may be suitable for. Additionally, the surgical algorithm, including vital variables such as time to debridement, time to antibiotics, type and duration of antibiotics and time to flap coverage could not be controlled and this has a significant affect on the interpretation of the results in relation to the debridement technique. Finally, the overall deep infection rate of 12% is higher than that noted compared to the publications mentioned in this thesis (7% vs 12%). The infection rate difference of 5% is significant clinically, and whilst cannot be attributed to debridement technique alone, it is a vital variable which should be considered.

The strengths of publications 3 and 4 lies in the prescriptive debridement method which is separately analysed within the context of clinical outcomes. This is unique as the adequacy of debridement has historically been difficult to analyse between and within institutions (O'Toole et al., 2009). Additionally, the finding of a negligible rate of ACS in open fractures is an important finding, which historically has been as high as 6% (McQueen et al., 1990). It was thought that compartment syndrome in open injuries could still occur owing to the lack of adequate decompression of a compartment even in the presence of an open wound. The “three-vessel view”, which exposes all compartments, in effect decompresses said compartments in the process of adequate exposure. Additionally, given the initial debridement is directly correlated to deep infection rate, it is likely that the low deep infection rate observed in this study highlights the “three-vessel view” as an adequate debridement technique.

Several limitations however remain. This remains a retrospective series in which retrospective data collection bias occurs. The appearance of skin/muscle/bone was not strictly recorded for all patients. Additionally, these patients sustained injuries as a result of blunt force trauma and it is difficult to extrapolate these findings to heavily contaminated or farmyard injuries.

2.3 Type of surgical fixation utilised

This section pertains to the following publications as part of this thesis:

5. *Stoddart M*, ***Al-Hourani K***, Fowler T, Khan U, Kelly MB. Plate-Assisted Intramedullary Nailing of Gustilo Type IIIBOpen Tibial Diaphyseal Fractures: Does Adjunctive Plate Retention Affect Complication Rate? Journal of Orthopaedic Trauma. 2020 July 34(7):363-9.
6. ***Al-Hourani K***, Donovan R, Stoddart M, Foote C, Kelly MB, Tornetta P. Definitve Fixation Outcome of Open Tibial Shaft Fractures: Systematic Review and Network Meta-Analysis. Journal of Orthopaedic Trauma. 2021 Nov, 35(11):561-69

2.3.1 Publication 5 (Stoddart et al, JOT, 2020)

Continuing the evaluation of the two-stage protocol, choice of definitive fixation utilised as part of this injury required assessment as a separate variable in order to isolate the role of the implant as part of the overall treatment algorithm. The choice of definitive fixation remains equivocal, with a lack of clarity in the literature with regards to whether internal or external fixation is the superior method (Foote et al., 2015). In the context of open tibial shaft fractures, plate assisted nailing is often performed in order to reduce and realign the fracture prior to definitive intramedullary nailing. The purpose of the plate is to bridge the fracture and stabilise this, thereby “assisting” the nailing procedure. The adjunctive plate may then be retained (retained adjunctive plate, RAP), or discarded. This is often left to surgeon discretion within the context of the fracture pattern.

Publication 5 analysed the primary outcome of deep infection rate in a cohort of patients , all of whom underwent intramedullary nailing with the use of an adjunctive plate (plate-assisted nailing). It compared those in whom there was retention of the adjunctive plate (RAP) versus those in whom the plate was not retained (non-RAP). This was a retrospective study of 137 consecutive patients, all of whom sustained a type IIIB open tibial shaft fracture. Following exclusions, 98 were eligible for analysis. Median age 44years (IQR 37) with a median follow up of 1.9 years (IQR 0.7). All 98 patients underwent plate-assisted nailing, however plates were retained in 67 (67/98, 68.4%) of these. There was a higher proportion of multi fragmentary fractures in the RAP compared to non-RAP group (14.5% vs 6.5%, p=0.239).

For the primary outcome of deep infection, 8 patients (8/92, 8.2%) experienced this. More patients experienced a deep infection in the RAP group compared to non-RAP, however this was not significant (RAP 6/67, 9.0% vs non-RAP 2/31, 6.5%, p=0.674). There was also no significant difference in non-union, isolated flap failure or overall complication rate between the two groups.

Maintaining fracture reduction during intramedullary nailing of the tibia is paramount in order to avoid pain, instability, deformity and loss of functional outcome during the healing phase (Foote et al., 2015; Giannoudis et al., 2006). Plate assisted nailing is an accepted technique in the management of severe open long bone injury. Some authors advocate removing the adjunctive plate as this may increase the risk of deep infection (Dunbar et al., 2005), however others propose retaining them in order to maintain reduction and avoid later deformity (Archdeacon & Wyrick, 2006). The proposed risk of deep infection arises from the notion that further devitalisation and periosteal stripping may be required (Schlegel & Perren, 2006) as well as the additional surface area for potential colonisation and biofilm formation (Metsemakers et al., 2018; Schmidt & Swiontkowski, 2000).

Dunbar et al were perhaps the first to describe the technique using a provisional plate in open tibial fracture following debridement of the fracture. Despite all provisional plates being removed, the deep infection rate remained at 13.3% (Dunbar et al., 2005). Revak et al conducted a similar study involving both open and closed tibial shaft fractures having undergone plate assisted nailing. Of the 91 patients undergoing plate assisted nailing, with 39 having the plate retained, no difference was found in deep infection rate, union rate or time to union (Revak et al., 2021). Ludwig et al analysed 104 patients who had provisional plate fixation as part of their open tibial fracture fixation. There was a deep infection rate of 11.1%. Plate removal was not associated with a significantly decreased odds of deep infection rate in their study (Ludwig et al., 2016).

Publication 5 adds to the body of literature surrounding this modern fixation technique. Whilst there is a paucity of literature surrounding this topic, it does seem to support the results of the publication. Adjunctive plate retention does not seem to be associated with a higher deep infection rate. The strengths of this work, highlights that in the most severe non-ischaemic long bone injuries, additional plate fixation is not associated with deep infection rate, without attributing causation. Furthermore, a main strength of this work is the standardised algorithm which was undertaken for each patient, which was the two-stage protocol for management of a type IIIB open tibial shaft fracture. The deep infection rate of 8.2% is lower than that of similar studies in the literature. It is proposed that this is likely due to early single stage fix and flap approach, which is largely controlled for in the study.

It is clear however that publication 5 has certain limitations. Retrospective studies of this nature introduce bias which may be difficult to account for. This includes biases such as data recall bias, follow up bias and data entry bias. The decision to retain a plate was at surgeon discretion and this was assessed based on fracture pattern and stability. This could therefore introduce selection bias into the cohort. These were mitigated against with the involvement of two authors for data collection and entry. Additionally, it is difficult to extrapolate the findings of this study to other trauma centres given the unique availability of an orthoplastic service in the study unit.

[redacted]

2.3.2 Publication 6 (Al-Hourani et al, JOT, 2021)

Given type IIIB open tibial shaft fractures remain relatively uncommon, it is readily apparent that publication 5, with the use of intramedullary nailing for all patients, was not sufficient to analyse the effect of the definitive implant choice as a variable for this injury. Publication 6, via way of systematic review and network meta-analysis, aimed to assess the effect of the definitive fixation choice in open tibial shaft fracture management.

Only randomised or quasi-randomised studies were included in the review, for adult patients with any definitive fixation type. Studies were excluded if they were not randomized, if non-operative management was undertaken, or if the fracture was pathological. Two methods of quality assessment for bias were undertaken including the Cochrane Risk of Bias tool and the Grading of Recommendation Assessment, Development and Evaluation (GRADE). The primary outcome was unplanned reoperation rate and deep infection rate.

Of the 1556 studies eligible for potential inclusion, 18 studies were analysed. Direct evidence comparing unreamed versus definitive uniplanar external fixation demonstrated a lower risk estimate of unplanned re-operation with nailing (RR 0.67, 95% CI 0.43 – 1.05, p-0.08, moderate confidence). This estimate was down-graded to low quality for imprecision (i.e. a nonsignificant p-value). The network estimate demonstrated a lower risk of reoperation with primary unreamed nailing compared with uniplanar external fixation (RR 0.63, 95% CI 0.38 – 0.91, p=0.01, moderate confidence). The network generated a risk difference (i.e. event rate improvement) of 7% (95% CI 2 – 13%, p=0.02), which means fewer adverse events with nailing with a number needed to treat of 14 patients to prevent a surgical complication. This risk difference may be as high as 46% for Gustilo type IIIB fractures (95% CI 0.09 – 0.85, p=0.02). Unreamed nailing did not show a statistically significant lower reoperation rate than reamed nailing. The direct estimate (RR 0.88, 95% CI 0.68 – 1.15, p = 0.36, low confidence) and network estimate (RR 0.90, 95% CI 0.58 – 1.40, p=0.68, very low confidence).

For deep infection rate, there was a non-significant relative risk reduction associated with unreamed nailing when it was directly compared to uniplanar external fixation (RR 0.59, 95% CI 0.30 – 1.17, p = 0.13, moderate confidence). Comparable risk of deep infection was seen with unreamed nailing versus reamed nailing (RR 1.01, 95% CI 0.62 – 1.66, p = 0.96, low confidence of a RR difference). In summary, there was no significant difference seen in wound infection risk when comparing either unreamed or reamed nailing to uniplanar external fixation.

This was the most comprehensive level one study in the literature comparing definitive fixation types for open tibial fractures. Overall, definitive intramedullary nailing demonstrated a lower unplanned reoperation rate (either reamed or unreamed), compared to monoplanar external fixation. However, there was no significant difference between fixation types for deep infection rate.

Only one previous meta-analysis of this nature has been conducted to compare definitive fixation types in open tibial shaft fractures. That study by Bhandari et al concluded that unreamed nailing was less likely to lead to an unplanned reoperation compared to external fixation. No clear difference was found between reamed and unreamed. However the survival time of the meta-analysis had been exhausted with the volume of literature being published on open tibial shaft fractures. Additionally, no specific analysis for type IIIB injuries was included (Foote et al., 2015). An additional 4 randomised studies had since been published which were included in publication 6. A specific analysis of type IIIB open tibial shaft fractures was included which highlighted the importance of type of definitive fixation in these injuries. It was noted that intramedullary nailing for this injury was the superior method in terms of unplanned reoperation rate, with the risk difference being as high as 46%.

A significant proportion of patients were included from the SPRINT trial, which is a multi-centre randomised controlled trial including 392 open injuries, and comparing reamed and unreamed nailing, no clear difference was shown. Whilst this did not highlight a need for change in practice, the overall literature has been shown to be deficient with regards to reporting of confounders which affect study bias (eg timing intervals pertinent to type IIIB fractures), lack of reporting on standardisation of care outwith fixation strategy, and ill defined outcomes such as that of unplanned reoperation and deep infection.

2.4 Addressing bone defects

This section pertains to the following publications as part of this thesis:

7. **Al-Hourani K**, Stoddart M, Khan U, Riddick A, Kelly M. Orthoplastic reconstruction of type IIIB open tibial fractures retaining debrided devitalized cortical segments: the Bristol experience 2014 to 2018. The Bone & Joint Journal. 2019 Aug;101(8):1002-8.
8. **Al-Hourani K**, Pearce O, Stoddart M, Riddick A, Khan U, Kelly MB. Orthoplastic Reconstruction of Type IIIB Open Tibial Shaft Fractures Utilising Debrided Devitalised Cortical Segments: Health-Related Quality of Life Outcomes. Journal of Orthopaedic Trauma. 2022 Feb;36(7)332-8.

2.4.1 Publications 7 and 8 (Al-Hourani, BJJ, 2019 & Al-Hourani, JOT, 2022)

Bone loss as part of this injury pattern can occur either at the time of injury (fragment extrusion), or during the initial debridement. The traditional management of such fragments are to excise and discard if they are devoid of any soft tissue attachments (Edwards et al., 1979). However, such a move would leave a large bony defect which would require further surgery to address, given the mechanical integrity of the tibia is compromised. Retention of said fragments from the initial injury, is considered controversial in the literature and has not previously been described. This is due to the notion that devitalised fragments form a focussed nidus of infection, and it is assumed that said fragments would lead to a significantly higher deep infection rate.

In the study unit for publication 7, practice has been to retain mechanically relevant fragments following debridement in type IIIB open tibial shaft fractures. The has been labelled as orthoplastic retention of devitalised bone (ORDB). Publication 7 aimed to analyse whether there was a difference in deep infection rate between patients who required ORDB and those in whom it was not required.

This was a consecutive cohort utilising prospectively collected data between May 2014 and January 2018. Following exclusions, 113 patients were identified as being eligible for inclusion, 44 of whom required ORDB and the remaining 69 did not. Median follow up was

1.7 years (IQR1.2 - 2.1). A binary logistic regression model to account for the multiple variables computed odds ratios (95% confidence intervals). Overall, a total of 8/113 (7.1%) experienced a deep infection with 1/44 (2.3%) patients experiencing a deep infection in the ORDB group with 7/69 (10.1%) in the non-ORDB group. The odds ratio of deep infection in the ORDB compared to non-ORDB was 0.21 (95% CI 0.02 to 1.74). This was not significant, p=0.119. The median number of operations was 2.0, with only 16 unplanned operations being undertaken for the entire patient cohort.

Publication 8 utilised a new dataset to assess health-related quality of life outcomes in ORDB versus non-ORDB patients. Functional outcomes comprised of Euro-Qol 5D (EQ-5D) and the Short-Form 36 (SF-36) scores. The new dataset was acquired for the 74 patients who were eligible for inclusion. This comprised of 3 rounds of patient data acquisition (2 postal questionnaires and a telephone questionnaire if did not respond by post). Median follow up was 3.8 years (IQR 1.5).

The EQ-5D index scores for ORDB cohort were 0.743 (IQR 0.195) and 0.748 (IQR 0.285) for non-ORDB cohort, with no significant difference between the 2 cohorts (P = 0.71). Furthermore, no significant differences were observed with corresponding visual analog scores for health [ORDB cohort, median 85 (IQR 28.0) versus non-ORDB cohort, median 80 (IQR 41.0); P = 0.46] and pain (ORDB cohort, median 17 (IQR 38) versus non-ORDB cohort, median 10 (IQR 46.75); P = 0.66). The overall median SF-36 physical component score was 80 (IQR 50), the median SF-36 physical component score for ORDB cohort was 80 (IQR 34.5), and the median SF-36 physical component score for non-ORDB cohort was 77.5 (IQR 58.75), with no significant difference, P = 0.72. The overall median mental component SF-36 score was 80 (IQR 28), the median mental component SF-36 score for ORDB cohort was 80 (IQR 21), and the median mental component SF-36 score for the non-ORDB cohort was 80 (IQR 36), with no significant difference, P = 0.29.

Publications 7 and 8 were the first in the literature to introduce the novel technique of ORDB. This is a simple technique whereby following the initial debridement, any mechanically relevant bone fragment(s) are assessed, debrided and then re-incorporated with anatomical reduction if possible and compression utilising the plate assisted nailing technique. This is the first study to show that this technique appears safe when utilising an orthoplastic approach with regards to the primary outcome of deep infection. Additionally, when utilising the two-stage orthoplastic approach, ORDB did not demonstrate inferior health-related quality of life scores compared to non-ORDB.

No previous studies in the literature have reported on retaining discarded devitalised fragments as part of the reconstruction for this injury type. However, despite it being common practice to discard bony fragments, there remains a paucity of evidence with regards to this. Additionally, there is clear strategy to address the bony defect primarily which has been shown to have either improved clinical or functional outcomes compared to retention of the bony fragment.

The alternatives to retention of devitalised bone vary in complexity and depend on the location and type/size of the defect in question. This includes bone graft and bone graft substitutes. For defect sizes <5cm this remains the preferred alternative however this has been historically associated with a high complication rate of over 19% and persistent pain from the donor site (Dimitriou et al., 2011). A further strategy for larger defects, named the "masquelet technique". This consists of a staged procedure with stage one involving filling the defect with bone cement to create an overlying vascular membrane, with stage two consisting of incising the membrane, removing the bone cement and substituting this with morcellised cancellous bone graft. The results in the literature also vary for this, ranging from 85%-92% success rate (Apard et al., 2010; Karger et al., 2012; McCall et al., 2010). The final common method of addressing larger bone defects is distraction osteogenesis, which involves transporting a segment of bone using external/internal fixation or a combination of both. Distracting the bone allows new bone formation to occur to fill the segmental defect. However the main drawbacks of this technique is the length of time required for treatment, with multiple operations and a complication rate of 20% recorded in the literature (Chaddha et al., 2010).

The argument against retention of devitalised bone stems from past studies. Edwards et al analysed 202 open tibial injuries comparing two surgical management protocols. In their second treatment protocol, with external fixation used as the stabilising fixation, a lower infection rate of 9% compared to 15% from stage ones directly attributed to discarding devitalised bone. The caveat is that in those with the lower infection rate, these patient required multiple operative episodes to reconstruct the bony defect (Edwards et al., 1979). Blick et al conducted a similar study assessing 53 open tibial fractures, discarding devitalised bone in all patients and bone grafting in order to assess time to union. Whilst there was an eventual 96% healing rate, 34% healed with complications as part of their surgical journey, requiring unplanned operations to address this (Blick et al., 1989). Chan et al in also performed a similar study to that of Blick and found a much higher deep infection rate of 38% (Chan et al., 1984).

With regards to functional outcomes, publication 8 has demonstrated that those in whom ORDB was required, functional outcomes are not inferior to those in whom no segmental or partial defect was present. To date, only one study has reported on functional outcomes in bony defects. Gopal et al studied 34 type IIIB/C open tibial fractures reporting a mean EQ-5D of 0.68 and a mean physical and mental component score of 49 and 62 respectively. Those who had a bony defect of 2.5cm and greater showed even lower physical and mental component SF-36 scores of 37 and 40 respectively, including multiple operations required to reconstruct the defect (Gopal et al., 2004). Publication 8 reported vastly improved functional outcomes than the study by Gopal et al with SF-36 physical and mental component scores of a median 80, and a higher median EQ-5D of 0.74. It is postulated that the improved outcomes are as a result of negating any segmental defect via the ORDB technique as this maintains the patient's leg length and provides an accurate cortical read for accurate leg alignment. Additionally, the median operation number for each patient was 2.0 operations, thereby not falling into diminishing returns with additional surgeries, which has been shown to produce unreliable outcomes (Kadhim et al., 2017).

There are limitations to publications 7 and 8. Whilst data was prospectively collected, and a new data set sought for publication 8, there remained a loss to functional follow up of 25%. This was despite multiple rounds of data collection. However this was not unexpected given the study unit covers a population catchment area of 2.5million where there is a mobile patient group with an expected rate of out of area movement. Additionally, given the retrospective nature, whilst the authors were able to demonstrate no association between ORDB and negative outcomes, causation could not be inferred. Furthermore, it is important that this technique is not taken out of context. This has not been assessed for ballistic type injuries or the frail/elderly populations who it may not be suitable for. The majority of patients were middle aged males having experienced blunt force trauma. Additionally, ORDB centres around the concept of retention of a mechanically relevant fragment. This is yet to be definitively agreed upon in the literature (Tetsworth et al., 2021). For the purposes of the studies in this thesis, this was defined as any segment deemed large enough to cause a partial/segmental defect and compromise the mechanical integrity of the construct. This included any defect leading to loss of bone-on-bone contact thereby overstraining the intramedullary nail or defects that would lead to loss of limb length and require reconstructive measures to restore. Finally, the ORDB technique should be considered only within the strict context of the orthoplastic set up described in the unit. It should not be left to inexperienced units without plastic surgical input, or those who do not optimise the variables described in all publications above, as this could lead to mismanagement and a higher deep infection rate.

2.5 Time from injury to definitive fixation and flap coverage

This section pertains to the following publications as part of this thesis:

1. ***Al-Hourani K***, Fowler T, Whitehouse MR, Khan U, Kelly M. Two-stage combined ortho-plastic management of type IIIB open diaphyseal tibial fractures requiring flap coverage: is the timing of debridement and coverage associated with outcomes?. Journal of Orthopaedic Trauma. 2019 Dec 1;33(12):591-7.

2.5.1 Publication 1 (Al-Hourani, JOT, 2019)

Publication 1 analysed both time from injury to debridement as well as time from injury to definitive fixation and flap coverage. All publications in this thesis pertaining to the study unit, employed a two-stage protocol whereby definitive fixation and flap coverage is performed at the same sitting. This therefore mitigates the timing window of definitive fixation to definitive flap coverage as a variable. This study aimed to delineate whether timing from injury to definitive fixation and flap coverage had any effect on the primary outcome of deep infection. Secondary outcomes included flap failure and nonunion.

This was a retrospective study over a defined two-year period (May 2014-May 2016). Patients were identified from the internal unit orthoplastic database which is collected prospectively, and this was cross-referenced against the national Trauma Audit and Research Network (TARN) database. A total of 145 patients were identified who sustained open lower limb injuries requiring soft tissue coverage. The inclusion criteria were adult patients (>18 years old), who sustained open tibial shaft fracture patients requiring soft tissue coverage (type IIIB injuries) and must have undergone the two-stage protocol. Following exclusions, a total of 45 patients were therefore eligible for final study inclusion. As anticipated the main demographic were young males. Time from injury to definitive fixation and flap coverage was recorded to the nearest hour based on pre-hospital ambulance sheets, in addition to electronic operation note records which were timed to the minute.

In addition to accurate assessment of timing intervals, other independant variables collected included type of temporising measure used, type of flap, anaesthetic grade, fracture severity and smoking/diabetic status. Mean follow up was 2.0 years (SD 0.42).

A total of four patients (4/45, 8.9%) developed a deep infection. There was no difference in mean time to fixation and flap coverage in the infected and non-infected groups (66.0hours (SD 20.4), vs 67.9hours (SD 62.7), p=0.952). There was no difference in time to initial debridement for those who developed infection associated flap failure (n=3), p=0.873. No patients experienced nonunion. The independant variables noted above were also not found to be predictive of the primary or secondary outcome on multi-variate regression.

This study analysed difference in time to definitive fixation and flap coverage in patients who sustained a type IIIB open tibial shaft fracture, with the primary outcome of deep infection. The deep infection rate utilising this two-stage protocol was 8.9%. There was no evidence to suggest that time to definitive fixation and flap coverage correlated with deep infection rate.

Godina et al popularised the timing window of 72 hours for definitive fixation and flap coverage for open fracture care. In his landmark retrospective series analysing 532 injuries, it was observed that those definitively covered within 72 hours had a lower deep infection rate of 1.5% compared to those over 72 hours (17.5%) (Godina, 1986c). This paper set the standard of care, with Godina being heralded as the forefather of the early soft tissue coverage approach. So much so that this has now been implemented within United Kingdom national treatment guidelines for open fractures (BOA & BAPRAS, 2017). Several United Kingdom studies have remained true to this concept by introducing the “fix and flap” approach as the standard of treatment over the last 20 years. Gopal et al analysed 84 severe open tibial fractures, with only 30 of those achieving fix and flap within 72 hours. This was associated with ah higher deep infection rate compared to those within 72 hours (Gopal et al., 2000). Mathews et al also analysed this timing window in 48 type IIIB open tibial shaft fractures. however in that study the findings of Gopal and Godina were not supported, with chigger deep infection rate (20%) in those definitely managed within 72 hours compared to 12.2% later than 72 hours (Mathews et al., 2015). Pincus et al, in a study encompassing 140 North American centres and 672 patients with open lower limb injuries, also looked at this timing window. A total of 412 pattens (61.3%) had delayed coverage beyond 7 days, and this was associated with a significantly increased complication rate compared to those definitively managed within 7 days (16.2% versus 6.2%, p<0.001).

The findings by these main studies should be considered within the context of the key variables discussed above in this thesis. This timing window should not be analysed in isolation and it is important that all other variables are standardised and optimised in order to analyse the true effect of time from injury to definitive fixation and flap cover. This is the main strength of publication 1, which standardises all other variables in order to be able to isolate the timing variable in question. Mean time to definitive management for this small cohort was under 72 hours, and given the impact of a single stage fix and flap approach, it is likely that this negates the effect of delay on deep infection rate. This is also strengthened by the standardised two-stage approach for all patients including a standardised thorough debridement. The limitations to this study have been covered previously in section 2.1.1.

[redacted]

2.6 Time from definitive fixation to definitive flap coverage

This section pertains to the following publication as part of this thesis:

9. ***Al-Hourani K,*** Foot CJ, Duckworth AD, White TO, Kelly MB, Tornetta P III. What is the Safe Window From Definitive Fixation to Flap Coverage in Type 3B Open Tibia Fractures? Supporting Plastics & Orthopaedics Alliance in Reducing Trauma Adverse Events (SPARTA). Journal of Orthopaedic Trauma. Accepted September 2022

2.6.1 Publication 9 (Al-Hourani, JOT, 2022)

It is recognised that definitive fixation and definitive flap coverage in the same operative sitting is the gold standard (Gopal et al., 2000; Mathews et al., 2015; Naique et al., 2006). A recent study by Tornetta et al highlighted the importance of the timing window between definitive fixation and flap coverage as the most significant in the management of open tibial shaft fractures requiring flap coverage (Kuripla et al., 2021). However, no previous study has analysed whether a "safe" window exists prior to an increased odds of deep infection in these injuries. The thesis author co-founded a further collaborative study group named SPARTA (Supporting Plastics and Orthopaedics Alliance in Reducing Trauma Adverse Events) in order to address this question. Publication 9 aimed to address whether a "safe" window exists between definitive fixation and definitive flap coverage prior to the onset of an increased deep infection rate.

Fifteen level 1 trauma centres across the United States and the United Kingdom contributed data for type IIIB open tibial shaft fractures. Data was retrospectively analysed through this anonymised database. The primary outcome measure was deep infection rate. A total of 417 patients were included, all of whom were skeletally mature and had a type IIIB open tibial shaft fracture. Patients who were skeletally immature and were definitively treated with external fixation were excluded. A total of 373 were eligible for final analysis.

Due to the varying practice and orthoplastic set-ups between units, there were varying definitive fixation to definitive flap intervals. Patients were placed into timing groups based on cut-points determined for deep infection rate via receiver operating characteristic curves. Time base 0 was used as the baseline to compare against, and these were the patients who underwent same sitting “fix and flap”. Univariate analysis to identify significant independant variables were undertaken, and these were then imputed into a multivariate model generating estimates of the relative risk between groups.

The overall demographic was consistent with previous studies in this thesis with 72% males with a median age of 42.4 years (SD 18.2). Mean follow up was 1.9 years (SD 1.28). Cut-points from the ROC analysis identified increased infection rate inflections at days 2 and 5. Therefore patients were divided into baseline group day 0 (same day definitive fixation and flap coverage patients, n=183), group <2days (n=51), group 2-5 days (n=49) and >5 days (n=90). On univariate analysis, the variables of time from injury to debridement, time to antibiotics and time from definitive fixation to definitive flap coverage were found to be significant. However on multivariate analysis, only time from definitive fixation to definitive flap coverage was significant. There was no difference in the relative risk of infection in baseline group 0 and group <2 days. However, there was a significantly increased deep infection risk ratio at day 2-5 compared to baseline group 0, RR 1.59 (p=0.04) and this was even more pronounced and >5 days compared to baseline group 0, RR 1.64 (p<0.001).

This multi-centre study identified a “safe” window of upto 2 days prior to onset of deep infection between definitive fixation and definitive flap coverage. There was a 59% relative risk increase, which was significant, if the interval between these stages was over 2 days.

In recent times, there has been a paradigm shift towards the “fix and flap” approach being the gold standard, whereby the definitive fixation and definitive flap coverage occurs in the same operative sitting (Gopal et al., 2000; Mathews et al., 2015; Naique et al., 2006). This seems to lead to the lowest deep infection rates in these injuries, with the notion that it reduces the time the implant remains exposed. Gopal et al introduced the concept of definitive soft tissue cover in the same sitting, with those covered within 24 hours of injury having a lower deep infection rate than those covered within 72hours (3% versus 10% respectively) (Gopal et al., 2000). Mathews et al noted that a coordinated orthoplastic “fix and flap” approach had a reduced deep infection rate of 4.2% compared to those that had a staggered definitive fixation and flap coverage, albeit within 72 hours (deep infection rate 34.6%) (Mathews et al., 2015). In effect, it was relatively clear in the literature that early and coordinated flap coverage was more beneficial. However, the literature had failed to establish timing cut-offs to provide precise optimisation on flap optimization.

More recently, in a multi-centre observational study conducted by Tornetta et al, it was noted that the definitive fixation to flap interval was the most predictive modifiable variable for the outcome of deep infection. A total of 297 patients across 14 centres were analysed for modifiable and non-modifiable risk factors. On univariate analysis only flap failure and time from fix to flap were noted to be predictive, with time from fix to flap found to be most predictive (odds ratio 1.04, 95% confidence interval 1.01 to 1.08, n = 260, P = 0.02) (Kuripla et al., 2021). The work in publication 9 provides an original and simple message to the orthopaedic community and is the first to establish a cut-off for flap optimisation. Namely, that definitive flap coverage can occur upto a period of 2 days following definitive fixation, prior to an expected significant rise in deep infection rate. This message is key as it provides the basis on which to form national guidelines for a basic standard for the definitive management of open tibial shaft fractures. Additionally, it is the first work which can be cited which allows for the planning of orthoplastic system redesign, particularly in healthcare systems who have not optimised their orthoplastic set up to date. This is particularly relevant in the developed countries such as the United States of America, where the coordination between orthopaedic and plastic surgeons is not readily apparent throughout the healthcare system.

It is important however to be aware of the limitations of such a study. It is key that all modifiable risk factors are optimised in order to achieve positive outcomes in this injury type. This includes time to antibiotic administration, safe timing from injury to initial debridement and adequacy of the initial debridement to name a few. This study involved units across multiple states and countries, and therefore it is very difficult to ensure that standardised treatment upto the definitive fixation timepoints was optimal. Furthermore, there are non-modifiable risk factors which were not clearly recorded in all cases such as include such as the injury severity, minor non-ischaemic vessel damage, muscle unit damage, degree of contamination and whether this injury was a part of polytrauma. However, the limitations noted above may have the added advantage of increasing generalisability of these results.

3. CONCLUSION

3.1 Summary

This thesis aimed to assess the two-stage orthoplastic approach in managing type IIIB open tibial shaft fractures. Where the literature consisted of inadequate data with regards to certain variables, a systematic review and meta-analysis of the literature was undertaken to complement the publications from the main study unit. The primary type of studies utilised consisted of retrospective reviews of prospectively collected data. The primary outcome utilised in all studies was primarily deep infection rate.

Based on the publications in this thesis, when utilising the two-stage orthoplastic approach for type IIIB open tibial shaft fractures, deep infection rate at minimum median 1 year follow up is significantly lower in comparison with the mainstream literature for this specific injury. This is achieved through optimisation of several vital variables in the management of these patients. This includes early intravenous antibiotics in all patients (within 1 hour in the pre-hospital setting), orthoplastic three-vessel view debridement within 24 hours of injury, stable fixation and negating bony defects through retention of devitalised bone if required, and early definitive fixation and flap coverage within the same sitting. The results within this thesis should be considered strictly within the dedicated orthoplastic approach utilised and should not be considered generalisable to units without this expertise. Additionally, these results may not apply to heavily contaminated (farmyard/marine type) injuries, ballistic injuries, or those in the frail elderly population who may not be suitable for a two-stage approach.

Finally, this thesis has provided a body of work which comprehensively analyses the two-stage orthoplastic approach, and where deficiencies occurred in the retrospective analysis, further comprehensive work was conducted either through systematic review or via a multi-centre approach. Several significant novel messages have been observed which should inform the orthopaedic literature. This includes the comprehensive analysis of the two-stage orthoplastic approach and its effect on deep infection rate which is the lowest known in the literature, the proposal of two novel techniques such as the three-vessel view debridement and the orthoplastic retention of mechanically relevant devitalised bone

(ORDB), and finally the establishment of a “safe” window for the definitive fixation to flap coverage utilising data from the study unit. Furthermore, the two most comprehensive systematic reviews in areas of controversy have been conducted, to analyse time from injury to debridement for lower limb open injuries, as well as an updated level 1 systematic review analysing the definitive fixation method for these injuries.

3.2 Implications for practice

This thesis offers a comprehensive evidence-based approach to the management of open tibial shaft fractures requiring flap coverage. With the input of a coordinated orthoplastic service, it is possible to reduce deep infection rate in these injuries to much lower rates than historically quoted in the literature. The fundamental tenet in the management of these injuries is a coordinated and methodical orthoplastic approach and hospital set-up in order to manage these injuries in a safe and standardised manner. Based on the results shown in this thesis, it is clear that this remains the gold standard approach to managing these injuries and it is hoped that this will provide the impetus both nationally and internationally to reformat trauma services in order to incorporate a clear orthoplastic service.

Additionally, with the concept of orthoplastic retention of mechanically relevant devitalised bone, this has added a new alternative to the reconstructive options available in open tibial shaft fractures with devitalised fragments. Traditionally, these have been excised, leading to multiple future operative episodes in order to reconstruct any segmental defect which results. However, in the presence of a coherent orthoplastic setup, with adequate pre-hospital management, debridement, and subsequent adequate definitive fixation and flap coverage, any segmental defect can potentially be negated with the use of mechanically relevant devitalised fragment. Prior to the publication of the studies 7 and 8 in this thesis (Al-Hourani, 2019 and 2022), this had not been though of as a viable option. However, in appropriately selected patients, under the appropriate orthoplastic set-up, this is now thought to be a safe alternative to traditional methods of treating devitalised bone fragments.

With particular reference to publication 9 (Al-Hourani, 2022), the orthopaedic community now have a reference timing window on which to base any orthoplastic planning. It is recognised that single sitting definitive fixation and flap coverage is not a viable option for many healthcare systems. However, with a safe timing window of 48 hours shown in this thesis, this has the potential to influence service planning without compromising patient safety, provided that other facets of open fracture care are also standardised.

It is important to note however that the results of this thesis should take into account that the majority of studies presents are as a result of retrospective work. Retrospective studies are designed to analyse pre-existing data and therefore are open to bias. This provides an inherent lower level of evidence in comparison to prospective work, whereby causation cannot be attributed, and only an association measured. One such reason is as a result of recall or misclassification bias due to the nature of data collection, whereby patients are either missed entirely, or misclassified as a result of poor record keeping. One such way to mitigate against this was to cross reference multiple sources of data, including a prospectively collected departmental database, in addition to the Trauma Audit and Research Network (TARN), as well as the electronic patient records uploaded onto the hospital system. As a result of the retrospective nature, data collection is also prone to confounding whereby risk factors which were present were not measured, including a detailed smoking history, diabetes or a clear mechanism of injury. All of these factors, whilst measured as accurately as possible, remained present as the data collected is limited by the quality of record keeping. When record keeping is not intended for research at the time of entry, it is possible that certain risk factors were not included, having a knock-on effect on later data collection. Finally, the outcome of deep infection remained a fairly low occurrence in the study groups, this leads to low study power primarily due to low sample size. This further leads to type II error, whereby no differences are seen between groups, when in fact there would be a difference had the sample size been larger. This marks one of the true difficulties in conducting prospective work in this specific injury pattern as it remains a fairly low common injury subgroup.

There are also specific limitations with regards to the functional outcomes measured including return to work and sport. To date, publication 8 is the only source of literature to analyse this outcome in type 3b open tibial shaft fractures. This is a positive step towards moving towards functional outcomes for this injury, however, return to work/sport remain clinical measures as opposed to patient driven outcome measures. Measurement of return to work/sport relies on the assumption that these are important outcomes for the patient, when this may not be the case, in view of the fact the majority of patients in the study cohort play sport socially and may not be concerned about the impact this has on their future participation in sport. Additionally, it may not be the case that patients wish to return to the same level of work following an injury of this nature, however when measuring this outcome, it is assumed that returning to their pre-morbid level of work is a positive outcome. A future switch to patient drive outcome measures may be an answer to achieving equitable future outcomes. To date, no such outcome measure exists for trauma, however a drive towards this (involving the patient and related stakeholders), will lead to more focussed care aimed at delivering patient centred goals. Additionally, it will help the patient regain ownership of their own care, and mitigate against development of treatments that do not further patients' progress.

3.3 Future research

The current thesis has highlighted several areas for future direction. Type IIIB open tibial shaft fractures remain less common in comparison to closed injuries of long bones. As such the literature is primarily limited to retrospective series, underpowered prospective studies or nested cohorts within a wider open fracture study.

Publication 6 has highlighted deficiencies in the literature with regards to independant variable and outcome reporting in these injuries. There is a distinct lack of standardisation of important variables in past literature which includes timing variables at all stages, timing of antibiotics, type of fixation and fix to flap interval. This also includes outcome reporting such as that for deep infection, union and in particular functional outcomes. Specifically highlighted limitations in the literature include:

1) a high proportion of studies at high risk of bias mainly related to lack of blinding after randomization
2) lack of reporting on plausible confounders such as time to debridement, timing and type of antibiotics administered, irrigation solution/volume use, and approach/timing of wound coverage
3) lack of reporting on standardisation of care outside the fixation strategy used

4) an overall lack of standardisation of debridement methods between units, and little mention of an orthoplastic set up that are powerful factors in a successful operative outcome
5) lack of reporting on method of temporary fixation in multiple included studies

This renders the ability to undertake accurate meta-analysis difficult due to heterogeneity between studies and as a result, bias in pooled estimates. One method to try to address this would include a scoping review of the literature for all studies addressing type IIIB open tibial shaft fractures, to define the variability in variables and outcomes reported. A consensus statement should then be conducted via a large scale delphi study would then be required in order to obtain agreement for the future publications in major orthopaedic trauma journals.

The adequacy of debridement is a particular area of concern in the literature. A surrogate for adequacy of debridement is usually the event rate of deep infection as a ratio to the number of operations undertaken. Publication 3 (Al-Hourani, 2021) in particular aims to address this concern with a specific technique utilised in all studies conducted in the study unit. This thesis would therefore propose that debridement technique is adequately described in published studies addressing this injury.

Furthermore, whilst the gold standard for definitive fixation and soft tissue coverage is to occur in the same sitting, it is still not known what the “safe” time-window interval between definitive fixation and flap coverage is prior to a significant increase in deep infection rate. This is particularly relevant to trauma units outwith the United Kingdom, where a coherent orthoplastic set up is not available. This would allow service planning in order to optimise treatment strategies, reduce overall deep infection rates and allow for cost-saving as a result. Publication 9 (Al-Hourani, 2022) aimed to address this issue with a comprehensive multi-centre database which was assembled looking at this very question and concluding that a window of 48 hours between definitive fixation and definitive soft tissue coverage may be a safe interval. This does however require continued and dynamic assessment in order to maintain the findings of such a study. One way which is gaining traction in the orthopaedic literature, is the use of artificial intelligence, and in particular machine learning algorithms which dynamically assess a prospectively collected mega-database of variables and outcomes for such an injury. This would not only inform the orthopaedic literature of the veracity of previous study findings, but would also allow individualised risk prediction for patients who present with this injury, leading to greater prognostic information for patients. This could also lead to prediction of which patients would be clinically and functionally better off with primary amputations even in a non-ischaemic injury of this nature. Additionally, the use of artificial intelligence can lead to “smarter” database management. This includes data categorisation whereby multiple sources of data can be input including photos, handwritten notes and electronic notes into a program, followed by automated data reading and entry. Data cataloging and analysis becomes easier as specified codes can lead to almost instantaneous result output contiguous with the desired question requiring answered. Finally, data security is improved as the data can then only be used in accordance with data protection laws, and any requests out-with this can be denied avoiding any litigation, particularly in view of any multi-national database.

There are further variables as part of this injury which require specific assessment. It is not definitively clear or standardised which form of anti-microbial therapy is useful for the management of this injury, or how long this should be administered for. It seems that early intravenous antibiotic therapy likely leads to a longer window before initial debridement is required. However this has not been shown to be the case in humans, and is based on animal model studies. Additionally, it is not known for how long antibiotic therapy should continue and whether prolonged antibiotic therapy even after definitive soft tissue protection is useful. The additional of local antibiotic delivery is again not definitive and does not seem evidence based. Recent evidence seems to suggest in closed high energy injuries, locally administered vancomycin may lead to reduction in deep infection rate. However this has not been translated into open tibial shaft fractures to date. Another variable is that of the level of wound contamination and the effect this has on deep infection rates. Clearly a farmyard or marine type injury differs from that of a blunt force mechanism, however this again has not been confirmed and is rather based on logic.This thesis does not address level of contamination but this should form the basis for future study. Furthermore, many of these patients attend as part of a polytrauma (or multiply injured). It is not known to what extent the physiological insult from other injuries has on the outcomes of an open tibial shaft fracture. Part of this analysis would include the resuscitative response by the treating emergency team as this could have consequences on the delayed development of devitalised tissue. This has been touched upon in publication 4 (Al-Hourani, 2021), where colloid resuscitation was used in the patient cohort and this is thought to have a delayed protective effect against secondary muscular hypovolaeima. To this effect, it can be proposed that to answer these questions, a prospective evaluation of such variables is required. For this to occur to a study powered to the primary outcome variable of deep infection, a multi-centre and perhaps a multi-national effort is required from developed orthoplastic units in order to increase the homogeneity of both the pre-operative, operative and post-operative management of such an injury. It may not be required for this to be either a time consuming or cost inefficient process, as this can be achieved through the use of novel analytic methods through adaptive designs in clinical trials. Adaptive designs are a novel way of bypassing classic clinical trial inflexibility, by allowing for options for change during the study period. Scheduled interim reviews of any trial can be undertaken and pre-specified changes to the course of the trial can be made based on interim data accumulation without damaging the integrity of the trial. Specifically to open tibial shaft fractures, this could include refining to a smaller sample size based on the outcome of deep infection if an obvious association is made between the variables mentioned above and the primary outcome, changing allocation of patients to a trial arm if randomisation is likely to prolong the trial longer than necessary, or prematurely concluding the trial with lower sample size if an obvious conclusion can be made at any interim review stage.

Finally, it is recognised that open fractures represent a significant global burden. This has led to them being recognised as a “Bellwether Procedure” by the Lancet Global Commission (O'Neill et al., 2016). This is a particular issue for low and middle income countries where the economic burden for both patients and healthcare systems can be overwhelming. It is important to find strategies to optimise variables which can be cost efficient and applicable to resource-scarce health systems. One example on how this may occur is through the administration of intravenous antibiotics in the field, in order to expand timing windows prior to debridement. This thesis does not aim to definitively address the open fracture burden in low and middle income countries, particularly as the facilities available to the study unit are out of financial reach of these health economies. However, it does provide a basis on which to build future collaborative work with these nations in order to address the most cost-effective options first.

3.4 Highlights from the thesis

The development of a cohesive orthoplastic service within the study unit for the work undertaken in this thesis, has as previously mentioned, led to an approach that may be considered overly aggressive. The main advantage of an aggressive approach being that this does not "under-call" the severity of the soft tissue injury, and leads to a thorough debridement thereby reducing deep infection rates to world leading levels. However, it is also noted that this type of service is not available to all units, particularly out-with the United Kingdom, as a result of service set-up constraints, system culture, or resource limitations.

This thesis however does highlight key areas which could lead to a rapid improvement in outcomes (based on evidence) for this injury pattern if implemented efficiently. The first is administration of intravenous antibiotics in the field, at the time of injury. The second is primary transfer to the definitively treating orthoplastic unit if available, and if not available, transfer to the definitively treating unit. The third is a thorough enough debridement in accordance with principles of debridement published in this thesis, which requires a thorough knowledge of anatomy by the treating surgeon. Once soft-tissue coverage has been decided, the technical aspects of treatment can be decided by the surgeon within the confines of the resources available to the treating surgeon, however the literature on type of implant and timing of initial and definitive surgery is now fairly established. It is important to note that positive outcomes result from all variables of care being undertaken correctly at each stage, as opposed to the isolation of one particular variable. This requires a nationwide drive to develop a system capable of doing this otherwise results for this injury could be erratic, which could be devastating for the patient.

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