

**Surgical Site Infection following Major  
Lower Limb Amputation: analysing the  
clinical effectiveness of antibiotic  
prophylaxis duration and skin preparation**

Mr Panayiotis Souroullas,

MBCChB, MRCS(RCEng), PGC Research Methods

A Thesis Submitted for the Degree of Doctorate of Medicine

The University of Hull and the University of York

Hull – York Medical School

September 2017

---

---

# *Abstract*

Background: Major LLA remains a common operation in the United Kingdom with ~5000 procedures performed yearly. Amputations are described as ‘clean surgery’ and SSIs in this patient cohort have been previously under-reported. The true incidence lies between 13-35% and is associated with patient mortality, morbidity and implications on health economics. Previous work done in this thesis has demonstrated lack of consensus in clinical practice regarding perioperative antibiotic prophylaxis, and lack of high quality studies to formulate and sustain a common practice across the UK.

Methods: A single centre RCT was designed to which a total of 161 patients were recruited and randomised to receive either a 5-day or a 24-hour prophylactic antibiotic course. Within the groups further allocation to skin preparation (alcoholic chlorhexidine Vs. alcoholic povidone iodine) was performed by stratification.

Results: A total of 153 patients were included in the final analysis. Groups were well matched for comorbidities and demographics. The use of a 5-day course was associated with a statistically significant lower incidence of SSI(n=9, 11.5%) when compared to the 24-hour group (n=27, 36%) (P<0.001) and lower incidence of IWH(n=20, 25.6% Vs. n=40, 53.3% respectively) (P<0.001). History of diabetes, smoking, and transmetatarsal amputations performed, were statistically significant independent factors associated with an increase in SSI incidence (P=0.018, P=0.005, and P<0.001 respectively). Choice of skin preparation between alcoholic chlorhexidine and povidone iodine had no effect on the incidence of SSI / IWH (P=0.851 and P=0.326 respectively). The presence of SSI statistically significantly increased the post-operative length of hospital stay (from median 14 to 28 days, P=0.015)

Conclusions: This is a Level 1 study which demonstrated that the use of a 5-day over a 24-hour antibiotic course can significantly reduce incidence and risk of SSI/IWH development. It has also highlighted 3 independent factors, 2 of which could be addressed during the preoperative optimisation stage to reduce the risk of developing an SSI post-operatively. The presence of SSI is associated with prolonged hospital stay, something which has significant implications on patient morbidity as well as incurring significant costs on healthcare resources.

---

## ***Published Work and Prizes from this Thesis***

### ***Peer Reviewed Publications***

1. Barnes R, **Souroullas P**, Chetter IC, A survey of perioperative management of major lower limb amputations: current UK practice. *Published Ann Vasc Surg. October 2014* (PMID 25011084)
2. Barnes R, **Souroullas P**, Lane RA, Chetter I, The Impact of Previous Surgery and Revisions on Outcome after Major Lower Limb Amputation. *Published Ann Vasc Surg December 2013* (PMID 24370498)

### **Book Chapter**

1. **Souroullas P**, Chetter IC, McCollum P. Chapter 91: Amputations. Corson JD, Williamson RCN (eds). *Surgery: Core Principles and Practice*, 2nd ed. London: Jaypee; 2017. pp. 1473-1482. ISBN 978-93-86261-12-0

### **Abstracts**

1. **Souroullas, P.**, Barnes, R., Smith, G., Chetter, I. and Carradice, D. (2016). ASSIT - The Amputation Surgical Site Infection Trial. A randomised controlled trial to determine whether a 5-day course of antibiotics is more clinically effective than a 24-hour prophylactic course for the prevention of surgical site infection following major lower limb amputation. In: *Vascular Society of Great Britain and Ireland Annual Scientific Meeting*. Glasgow: The British Journal of Surgery, John Wiley & Sons, pp.10-11
2. Barnes R, **Souroullas P**, E Mironska Chetter IC Perioperative management of major lower limb amputations. Published in Brit J Surg August 2013

### **Presentations**

1. **Souroullas P**, Barnes R, Smith G, Chetter I, and Carradice D (2016). ASSIT - The Amputation Surgical Site Infection Trial. A randomised controlled trial to determine whether a 5-day course of antibiotics is more clinically effective than a 24-hour prophylactic course for the prevention of surgical site infection following major lower limb amputation. *Vascular Society of Great Britain and Ireland Annual Scientific Meeting*
2. **Souroullas P**, Barnes R, Smith G, Chetter I (2016) Meta analysis of the use of antibiotic prophylaxis in the prevention of surgical site infection in patients undergoing major lower limb amputations. *Vascular Society of Great Britain and Ireland Annual Scientific Meeting, December*
3. **Souroullas P**, Barnes R, Chetter I. ASSIT (2013) Randomized Controlled Trial to determine whether a 5-day course of antibiotics is more clinically and cost effective than a 24-hour prophylactic course for the prevention of surgical site infection following lower limb amputation. *Yorkshire and the Humber National Inter-deanery Academic Presentation day, May 2013.*

### Prizes

1. British Journal of Surgery Prize for Best Scientific Paper of the Year 2016: ASSIT - The Amputation Surgical Site Infection Trial. A randomised controlled trial to determine whether a 5-day course of antibiotics is more clinically effective than a 24-hour prophylactic course for the prevention of surgical site infection following major lower limb amputation.
2. 2<sup>nd</sup> Place Prize Yorkshire and the Humber National Inter-deanery Academic Presentation 2013: ASSIT – A Randomized Controlled Trial to determine whether a 5-day course of antibiotics is more clinically and cost effective than a 24-hour prophylactic course for the prevention of surgical site infection following lower limb amputation.

## Table of Contents

<i>Abstract</i>	<u>1</u>
<i>Published Work and Prizes from this Thesis</i>	<u>2</u>
<i>List of Figures</i>	<u>11</u>
<i>List of Tables</i>	<u>13</u>
<i>Acknowledgements</i>	<u>16</u>
<b>Chapter 1 - INTRODUCTION</b>	<u>19</u>
<i>Section 1.1 A History of Amputation</i>	<i>20</i>
1.1.1 Etymology through time and early evolution to the 18 <sup>th</sup> Century	20
1.1.2 Eponymous Amputation Surgeons	29
<i>Section 1.2 Epidemiology of Lower Limb Amputation</i>	<i>48</i>
1.2.1 The Global and Ethnicity Picture	48
1.2.2 Epidemiology of Lower Limb Amputation in the United Kingdom	59
<i>Section 1.3 Major Lower Limb Amputations: Indications, the anatomy and procedures.</i>	<i>63</i>
1.3.1 Lower Limb Amputation Surgery	63
1.3.2 Amputations about the foot	75
1.3.3 Transtibial Amputations	83
1.3.4 Amputations about the knee	88
1.3.5 Amputations above the knee	91
<i>Section 1.4 Wound healing and Surgical Site infection</i>	<i>96</i>
1.4.1 Structure and function of skin	96
1.4.2 Wound healing	96

1.4.3	Surgical Site Infections .....	105
1.4.4	Amputation surgery and the amputation stump – A Dock for cutaneous complications and Surgical Site Infection.....	119

## **Chapter 2 - STUDY METHODOLOGY \_\_\_\_\_ 129**

<i>Section 2.1 Study 1: A Survey of perioperative management of major lower limb amputations .....</i>		<i>129</i>
<i>Section 2.2 Study 2: A Meta-analysis of the use of antibiotic prophylaxis in the prevention of surgical site infection in patients undergoing major lower limb amputations. ....</i>		<i>129</i>
2.2.1	Information sources and search strategy:.....	130
2.2.2	Study selection:.....	131
2.2.3	Data collection and items: .....	131
2.2.4	Study characteristics:.....	132
<i>Section 2.3 Study 3: The Amputation Surgical Site Infection Trial.....</i>		<i>133</i>
2.3.1	Rationale: .....	133
2.3.2	Study Approvals:.....	135
2.3.3	Ethical Conduct:.....	135
2.3.4	Quality Assurance: .....	136
2.3.5	Data handling and storage: .....	136
2.3.6	Indemnity:.....	137
2.3.7	Study Design: .....	137
2.3.8	Sample size and power calculation:.....	137

2.3.9 Identification of potential participants: .....	137
2.3.10 Patient Population:.....	138
2.3.11 Inclusion criteria: .....	138
2.3.12 Exclusion criteria: .....	139
2.3.13 Screening evaluation:.....	139
2.3.14 Randomisation: .....	140
2.3.15 Trial Treatments: .....	140
2.3.16 Outcome measures: .....	142
2.3.17 Study procedures: .....	143
2.3.18 Statistical Analysis: .....	144
2.3.19 Withdrawals and dropouts: .....	144
2.3.20 Trial Exit:.....	145
2.3.21 Overall timescale for the study: .....	145

<i>Section 2.4 - Study 4: The Impact of Previous Surgery and Revisions on outcome after Major Lower Limb Amputation.....</i>	<i>146</i>
--	------------

## **Chapter 3 - RESULTS** \_\_\_\_\_ **147**

<i>Section 3.1 Study 1 : A Survey of perioperative management of major lower limb amputations.....</i>	<i>147</i>
3.1.1 Infection Rates .....	148
3.1.2 Skin Preparation .....	148
3.1.3 Skin Closure.....	149
3.1.4 Drains .....	149
3.1.5 Antibiotics .....	149
3.1.6 Nutrition.....	150

3.1.7	Warming .....	150
3.1.8	Dressings .....	150
<i>Section 3.2 Study 2: Meta-analysis of the use of antibiotic prophylaxis in the prevention of surgical site infection in patients undergoing major lower limb amputations .....</i>		
		<i>151</i>
3.2.1	Study, population characteristics and indications for surgery. ....	151
3.2.2	Characteristics of antibiotic prophylaxis and outcomes recorded .....	161
3.2.3	Study subgroup analysis .....	165
3.2.4	Risk of bias.....	167
<i>Section 3.3 Study 3: The Amputation Surgical Site Infection Trial.....</i>		
		<i>172</i>
3.3.1	Screening and randomisation.....	172
3.3.2	Primary outcomes – Surgical Site infection and Impaired Wound Healing incidence.....	177
3.3.3	Other factors related to SSI/IWH: .....	183
3.3.4	Effects of amputation and SSI/IWH on general post-operative complications .....	188
3.3.5	Effects of SSI/IWH on complications requiring return to theatre .....	188
3.3.6	Effect of SSI/IWH on postoperative length of stay .....	191
3.3.7	Effect of SSI on Mortality at 30 days and 1 year post-operatively.....	191
<i>Section 3.4 Study 4: The Impact of Previous Surgery and Revisions on Outcome after Major Lower Limb Amputation.....</i>		
		<i>193</i>
3.4.1	Previous Revascularisation .....	194

3.4.2 Amputation Level and Revisions .....	195
--	-----

3.4.3 Mortality .....	196
-----------------------	-----

## **Chapter 4 DISCUSSION, LEARNING POINTS AND**

<b>LIMITATIONS</b> .....	<b>198</b>
--------------------------	------------

### **Section 4.1 Study 1: A Survey of perioperative management**

<i>major lower limb amputations</i> .....	<i>198</i>
---	------------

### **Section 4.2 Study 2: A Meta-analysis of the use of**

*antibiotic prophylaxis in the prevention of*

*surgical site infection in patients undergoing*

<i>major lower limb amputation</i> .....	<i>203</i>
--	------------

### **Section 4.3 Study 3: The Amputation Surgical Site**

<i>Infection Trial</i> .....	<i>211</i>
------------------------------	------------

### **Section 4.4 Study 4: The Impact of Previous Surgery and**

*Revisions on Outcome after Major Lower Limb*

<i>Amputation</i> .....	<i>218</i>
-------------------------	------------

<b>Chapter 5 - CONCLUSION</b> .....	<b>220</b>
-------------------------------------	------------

<b>References</b> .....	<b>223</b>
-------------------------	------------

<b>Appendices</b> .....	<b>243</b>
-------------------------	------------

### **Appendix 1 : Health Protection Agency- Surgical wound**

<i>healing post discharge questionnaire</i> .....	<i>244</i>
---	------------

<b>Appendix 2 Patient Information Leaflet</b> .....	<b>246</b>
---	------------

<i>Appendix 3 Patient Consent Form.....</i>	<i>252</i>
<i>Appendix 4 A survey of Perioperative Management of Major Lower Limb Amputations: Current UK Practice.....</i>	<i>254</i>
<i>Appendix 5 The Impact of Previous Surgery and Revisions on Outcome after Major Lower Limb Amputation.....</i>	<i>261</i>
<i>Appendix 6 Level of evidence <sup>(311)</sup> .....</i>	<i>267</i>
<i>Appendix 7 The PRISMA Checklist<sup>(379)</sup>.....</i>	<i>269</i>
<i>Appendix 8 Hull and East Yorkshire Hospitals Local Antibiotic guideline.....</i>	<i>271</i>
<i>List of Abbreviations/Index _____</i>	<i>272</i>

---

# List of Figures

FIGURE 1 PROPORTIONAL RATES OF AMPUTATION AND REVASCULARISATION ACROSS ENGLISH REGIONS <sup>(1)</sup> .....	61
FIGURE 2 TRANSMETATARSAL AMPUTATION (ORIGINAL SKETCH BY EMMA WRAY) .....	78
FIGURE 3 MARKINGS AND INCISION FOR A SYME'S PROCEDURE (ORIGINAL SKETCH BY EMMA WRAY) .....	79
FIGURE 4 PASSING A DRAIN FOLLOWING A SYME'S PROCEDURE (ORIGINAL SKETCH BY EMMA WRAY) .....	80
FIGURE 5 LOWER LEG MAGNETIC RESONANCE ANGIOGRAM <sup>(200)</sup> .....	84
FIGURE 6 CROSS-SECTIONAL ANATOMY OF THE LOWER LEG <sup>(5)</sup> .....	84
FIGURE 7 MARKINGS FOR LONG POSTERIOR FLAP <sup>(6)</sup> .....	85
FIGURE 8 MARKINGS FOR SKEW FLAPS <sup>(6)</sup> .....	86
FIGURE 9 LIGAMENTS ABOUT THE KNEE ( <a href="http://imggood.com/knee-joint-ligaments.html">HTTP://IMGGOOD.COM/KNEE-JOINT-LIGAMENTS.HTML</a> ) .....	88
FIGURE 10 NEUROVASCULAR BUNDLE IN THE KNEE <a href="http://clinicalgate.com/knee-arthroscopy-setup-diagnosis-portals-and-approaches/">HTTP://CLINICALGATE.COM/KNEE-ARTHROSCOPY-SETUP-DIAGNOSIS-PORTALS-AND-APPROACHES/</a> .....	88
FIGURE 11 MUSCLES OF THE THIGH <sup>(3)</sup> .....	91
FIGURE 12 ANATOMY OF THE GLUTEAL REGION <sup>(4)</sup> .....	92
FIGURE 13 MARKINGS FOR TRANSFEMORAL AMPUTATION <sup>(6)</sup> .....	93
FIGURE 14 ANATOMICAL STRUCTURE OF SKIN <sup>(8)</sup> .....	96
FIGURE 15 STAGES OF WOUND HEALING <sup>(2)</sup> .....	97
FIGURE 16 ANATOMICAL LEVELS OF SSIs <sup>(7)</sup> .....	105
FIGURE 17 RISK FACTORS FOR SSIs .....	108
FIGURE 18 INCIDENCE OF SSIs BASED ON SURGICAL SPECIALTY / DISEASE <sup>(256)</sup> .....	109
FIGURE 19 PRISMA DIAGRAM FOR SYSTEMATIC REVIEW AND META-ANALYSIS OF THE USE OF ANTIBIOTIC PROPHYLAXIS IN MAJOR LLA .....	133
FIGURE 20 THE AMPUTATION SURGICAL SITE INFECTION TRIAL (ASSIT) PATHWAY .....	142
FIGURE 21 DISTRIBUTION OF RESPONSES PER DEANERY.....	148
FIGURE 22 RISK OF TYPES OF BIAS ACROSS THE STUDIES .....	167
FIGURE 23 FOREST PLOT - COMPARISON OF THE USE OF ANTIBIOTIC VERSUS NO ANTIBIOTIC / PLACEBO TO ESTABLISH THE EFFECT ON THE RISK OF DEVELOPING AN SSI .....	168
FIGURE 24 FOREST PLOT - COMPARISON OF BETWEEN DIFFERENT ANTIBIOTICS TO ESTABLISH THE EFFECT ON THE RISK OF DEVELOPING AN SSI .....	169

FIGURE 25 FOREST PLOT - OVERALL EFFECT OF INCREASING THE DURATION OF ANTIBIOTIC PROPHYLAXIS FROM 24 TO 48 HOURS ON THE RISK OF DEVELOPING AN SSI .....	170
FIGURE 26 FOREST PLOT - THE EFFECT OF A 5-DAY VERSUS A 3-DAY COURSE OF ANTIBIOTICS ON THE RISK OF DEVELOPING AN SSI .....	171
FIGURE 27 CONSORT DIAGRAM OF PATIENTS INVOLVED IN THE RCT. (ABX – ANTIBIOTICS, CHLORHEX – CHLORHEXIDINE)....	173
FIGURE 28 CUMULATIVE SURVIVAL FOR THOSE WITH / WITHOUT A PREVIOUS REVASCULARISATION .....	196

---

# List of Tables

TABLE 1 INCIDENCE OF MAJOR LLAS IN DIABETIC PATIENTS .....	57
TABLE 2 INCIDENCE OF LLAS OVER TIME .....	58
TABLE 3 NUMBER, PREVALENCE AND PROPORTIONAL DISTRIBUTION OF RISK FACTORS OF LOWER LIMB AMPUTEES BY REGION <sup>(1)</sup> .	60
TABLE 4 ODDS RATIO OF HAVING AN AMPUTATION BY RISK FACTOR <sup>(1)</sup> .....	61
TABLE 5 PATHOGENS COMMONLY ASSOCIATED WITH DIFFERENT SURGICAL PROCEDURES <sup>(8)</sup> .....	116
TABLE 6 CLASSIFICATION OF WOUNDS .....	117
TABLE 7 THE ASEPSIS SCORING TOOL FOR SSIS .....	119
TABLE 8 COMMON POST LLA DERMATOLOGICAL CONDITIONS, AND INFECTION TYPES, CAUSATIVE STRESS AND TREATMENT OPTIONS .....	122
TABLE 9 COMMON PATHOGENS LEADING TO AND CAUSING SSIS POST-AMPUTATION.....	128
TABLE 10 THE IMPACT OF SKIN PREPARATION ON INFECTION RATES.....	148
TABLE 11 IMPACT OF SKIN CLOSURE, INTRAOPERATIVE WARMING, NUTRITIONAL ASSESSMENT, ANTIBIOTIC USAGE, AND DRAIN USAGE ON INCIDENCE OF INFECTION .....	149
TABLE 12 IMPACT OF SURGICAL DRESSINGS ON INFECTION INCIDENCE.....	150
TABLE 13 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>PATIENTS SCREENED AND RECRUITED</b> .....	153
TABLE 14 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>NUMBERS RECRUITED PER GROUP (INTERVENTION / CONTROL)</b> ....	154
TABLE 15 LIST OF STUDIES SELECTED FOR META-ANALYSIS - MALE : FEMALE RATIO AND AGE (INTERVENTION) .....	155
TABLE 16 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>MALE : FEMALE RATIO AND AGE (CONTROL GROUP AND OVERALL)</b> .....	156
TABLE 17 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>INCLUSION / EXCLUSION CRITERIA, DROP-OUTS AND REASON</b> ‡COURSE INITIATION: 1-ON SURGICAL INDUCTION, 2-WITHIN 1 HOUR BEFORE SURGERY, 3- TWO HOURS PRIOR TO SURGERY, 4-THREE HOURS PRIOR TO SURGERY, 5-FOUR OR MORE HOURS PRIOR TO SURGERY.....	158
TABLE 18 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>INDICATIONS FOR AMPUTATION, NUMBERS OF AMPUTATIONS PER LEVEL</b> .....	159
TABLE 19 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>INTRA-OPERATIVE DETAILS</b> .....	160
TABLE 20 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>DESCRIPTION OF ANTIBIOTIC PROPHYLAXIS COURSE</b> .....	162

TABLE 21 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>TYPES OF AMPUTATION PER GROUP</b> .....	163
TABLE 22 LIST OF STUDIES SELECTED FOR META-ANALYSIS - <b>RECORD OF PREVIOUS INTERVENTION, POST-OPERATIVE MORTALITY BY CAUSE AND SURVIVAL RATES</b> .....	164
TABLE 23 PAST MEDICAL HISTORY OF PATIENTS RECRUITED TO THE STUDY AND THEIR DISTRIBUTION AMONGST THE TWO MAIN TREATMENT GROUPS. THE P-VALUES ALL REMAIN ABOVE 0.05 FOR THEIR CORRESPONDING TEST STATISTIC, SUGGESTING WELL-MATCHED GROUPS.....	174
TABLE 24 PATIENT DEMOGRAPHICS (AGE AND GENDER) PER GROUP ALLOCATION. THE P-VALUES FOR THEIR CORRESPONDING TEST STATISTIC SHOW THE TWO GROUPS ARE WELL MATCHED. ....	175
TABLE 25 DRUG HISTORY CHARACTERISTICS OF THE PATIENTS RECRUITED TO THE STUDY, PER ALLOCATION GROUP. THE P-VALUES FOR THEIR CORRESPONDING TEST STATISTIC SHOW THE GROUPS ARE WELL MATCHED.....	175
TABLE 26 CHARACTERISTICS OF PREVIOUS VASCULAR INTERVENTIONS OF PATIENTS RECRUITED TO THE STUDY PER GROUP ALLOCATION. THE P-VALUES FOR THEIR CORRESPONDING TEST STATISTIC SHOW THE GROUPS ARE WELL MATCHED .....	176
TABLE 27 ANALYSIS OF SEPARATE INDEPENDENT VARIABLES AND THEIR EFFECT ON SSI INCIDENCE. HISTORY OF DIABETES, SMOKING(EX/CURRENT) AND THE LEVEL OF AMPUTATION PERFORMED ARE ALL ASSOCIATED WITH A STATISTICALLY SIGNIFICANT INCREASE IN SSI INCIDENCE.....	181
TABLE 28 ADDITIONAL SEPARATE ANALYSIS OF THE EFFECT OF PREOPERATIVE LEVELS OF HAEMOGLOBIN AND ALBUMIN, AS WELL AS PREVIOUS VASCULAR PROCEDURES ON SSI INCIDENCE. THERE IS NO OBSERVED STATISTICAL SIGNIFICANCE ASSOCIATED WITH INCREASED SSI INCIDENCE .....	182
TABLE 29 BINARY LOGISTIC REGRESSION ANALYSIS OF IDENTIFIED VARIABLES ASSOCIATED WITH A STATISTICALLY SIGNIFICANT INCREASE IN SSI INCIDENCE. FOOT AMPUTATIONS, SMOKING AND DIABETES ALL INCREASE THE RISK OF SSI .....	182
TABLE 30 ANALYSIS OF SEPARATE INDEPENDENT VARIABLES AND THEIR EFFECT ON IWH INCIDENCE. THE LEVEL OF AMPUTATION PERFORMED APPEARS TO BE THE ONLY ADDITIONAL FACTOR ASSOCIATED WITH A STATISTICALLY SIGNIFICANT INCREASE IN IWH INCIDENCE .....	183
TABLE 31 NUMBER OF CASES RETURNED TO THEATRE FOR AN ADDITIONAL PROCEDURE, IN THE PRESENCE OR ABSENCE OF SSI OR IWH. THE PRESENCE OF SSI IS ASSOCIATED WITH A <b>STATISTICALLY SIGNIFICANT INCREASE IN THE RETURN TO THEATRE FOR AN ADDITIONAL PROCEDURE (P=0.007)</b> . THE PRESENCE OF IWH IS ASSOCIATED WITH A <b>STATISTICALLY SIGNIFICANT INCREASE IN THE RETURN TO THEATRE(P&lt;0.0001)</b> .....	186
TABLE 32 THE LENGTH OF STAY IN MEDIAN NUMBER OF DAYS IN THE PRESENCE/ABSENCE OF SSI/IWH. THE PRESENCE OF AN SSI IS ASSOCIATED WITH A <b>STATISTICALLY SIGNIFICANT INCREASE IN LENGTH OF STAY TO 28 DAYS (IQR 16-40) COMPARED TO 14(IQR 9-21) (P=0.015)</b> .....	191

<i>TABLE 33 NUMBER OF MORTALITY CASES AT 30-DAY FOLLOW-UP RECORDED BY PRESENCE/ABSENCE OF SSI.</i> .....	193
<i>TABLE 34 NUMBER OF MORTALITY CASES AT 1-YEAR FOLLOW-UP RECORDED BY PRESENCE/ABSENCE OF SSI.</i> .....	193
TABLE 35 PREVIOUS IPSILATERAL PROCEDURES IN SECONDARY AMPUTATION GROUP .....	195
TABLE 36 COMPARISON OF BASELINE CHARACTERISTIC .....	195
TABLE 37 IMPACT OF PREVIOUS REVASCULARISATION ON AMPUTATION LEVEL.....	196
TABLE 38 IMPACT OF PREVIOUS REVASCULARISATION ON MORTALITY RATES .....	196
TABLE 39 TYPE OF REVASCULARIZATION AND MORTALITY .....	196

---

## *Acknowledgements*

I would firstly like to thank my supervisor; Professor Chetter, for his ongoing support, advice and training, and additionally for believing in me; trusting me with this programme of research. I am also incredibly grateful to Ms Rachel Barnes not only for all her hard work in the early days of conception of this project, but also for her endless support as well as her mentorship throughout the course of this project and for being one of the first people who believed in me. I would also like to thank Mr George Smith and Mr Dan Carradice for their experienced and supportive guidance as well as their backup in conducting this resource-demanding study.

I would like to thank the whole of the Academic Vascular Research Unit in Hull for their kind support and friendship, particularly; Emma Clarke, Anna Firth and Josie Hatfield for their support with patient ward follow-ups, Carole Tenison for her kind words and support at times of difficulties. I am also very grateful to Claire Acey for her kindness and help with administration as well as her tolerance and support, and Barbara McCloy for her help with the database construction. I would also like to thank my research fellow colleagues Clement Leung, Hashem Barakat and Christina Moody for their ongoing support and at times patient recruitment during my time in the Academic Vascular Surgical Unit.

I am indebted to the vascular clinical team for all of the great teaching, experience and support over the years: Mr Renwick, Mr Johnson and Mr Akomolafe for their clinical supervision in my early years in Vascular surgery and the invaluable skills gained on amputation surgery; Professor Chetter and Professor McCollum for their support and guidance through the world of academia. I am especially grateful to Mr Renwick, Mr Johnson and Professor Chetter for their extraordinary efforts to support my on-going surgical career, despite the different career path in Trauma and Orthopaedics I chose to follow; I can only hope that they are happy that my progress was worth their investment, even though this is in a different surgical sub-specialty altogether.

I would also like to thank my family and friends for their support and for not forgetting me during these relentless years of research. I would especially like to thank my mother and father who have invested in me both financially and mentally and my sister for believing in me; without their childhood guidance I would not have reached this far. I would also like to thank my uncle Sergios Sergiou, an old school Orthopaedic surgeon who was my inspiration and drive and the first person who put a scalpel in my hand and introduced me to the thrills

of the operating theatre! I am also eternally indebted to my uncle Chris Norman, for his words of wisdom at times of hardship and mental challenge; they provided a driving force and the fuel to continue: 'Not failure, just feedback'. Thank you for helping me keeping it real.

Last but certainly not least, I would also like to especially thank and remember those whom I have neglected in recent months especially my girlfriend and future fiancé; Emma, whom I love more than I can say. Thank you for your tolerance, for being my one-person fan club, thank you for the exceptional illustrations you have produced for me, and thank you for living this experience with me. It has been a roller-coaster. I look forward to catching-up.

## **Declaration**

**I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources.**

**I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.**

**Panos Souroullas**

**September 2017**

---

## Chapter 1 - *INTRODUCTION*

Amputations are unquestionably one of the oldest surviving surgical operations, with the indications for their performance continuously evolving as new limb salvaging options become available and procedures showing increasing longevity of post-interventional clinical outcomes<sup>(9)</sup>. Traditionally, amputation surgery has been frowned upon and as a form of surgery it has suffered in terms of lack of attention, financial support and technological advance. Amputation surgical techniques have progressed and have been refined by surgeons over the years and with the availability of advanced educational resources (cadaveric courses, simulation courses, etc.) and unfortunate recent world warfare, dissemination and practice of surgical techniques have been more notable. Whilst it is essential for the operating surgeon to be attentive and meticulous in their technique, it is equally important to adopt an optimistic and dogmatic approach to dealing with a patient in the post-surgical setting. It is of utmost important for health care providers to realise that the responsibility for the patient extends far beyond the wound healing stage, and into the rehabilitation. Unquestionably, the most difficult and demanding aspects of amputee care are frequently related to the decision making process, the physiological and psychological rehabilitation, and in particular, post-operative phantom limb pain, and post-traumatic emotional distress related to the distorted body image and reduced function.<sup>(10)</sup>

## ***Section 1.1 A History of Amputation***

### ***1.1.1 Etymology through time and early evolution to the 18<sup>th</sup> Century***

A procedure with origins stretching as far back as the Neolithic era<sup>(11)</sup>, and certainly a term that is talked down on with an intrinsic undertone of disapproval and failure, amputations remain an operation that is accepted by both patients and clinicians and is performed in a surprisingly increasing manner especially amongst individuals with peripheral vascular disease or diabetics.

The word itself is derived from the Latin noun *Amputatio*, originating from two separate words, *amb* for about and *putare*, for prune or lop, and from its little use in roman texts, it is believed to have described the aforementioned surgical procedure<sup>(12)</sup>. Despite its original etymology relating to horticulture, it is in fact rarely used in that context.

A procedure deeply implanted in lay beliefs as the epitome of barbaric and cruel surgery in the absence of anaesthesia and used in previous centuries as a disciplinary measure for criminals, amputations were also referred to in a medical context in the writings of Hippocrates (460-377 BC) where emphasis was given to its use in the extensive ablation of gangrenous tissue, although at the time, it was common practice to adopt a more conservative approach. In fact, remembering that the word ‘surgery’ itself is derived from the Greek word ‘χειρουργική’, directly translating to ‘hand-work’, makes it highly likely that such practice involving manual application of ointments, extensive dressings and bandaging to counter suppuration and mask the odour, whilst waiting for necrotic tissues to demarcate and auto-amputate was often adapted. The first ever documented amputation performed electively, and on that particular occasion as a life-saving procedure following serious trauma, can be seen in Herodotus’s inscriptions, where Hegesistratus, a Persian soldier trapped in stocks, freed himself by self-mutilation, later replacing his foot with a wooden prosthesis<sup>(13)</sup>.

Since time immemorial This elective/expectant approach was still favoured in the 2<sup>nd</sup> century AD, as seen in the writings of Galen, and even later on in 1363, Guy de Chauliac, although confessing that he himself had never performed one such procedure, he gave an extensive account of how to perform an amputation for gangrene, either through bone or even at joint level. His advice however once again, pertained to anticipation of scarification of dead skin

followed by application of arsenic to the necrotic area, after isolating healthy tissues by extensive dressing application and bandaging, in hope that the gangrenous tissues will auto-amputate.<sup>(12)</sup>

Other classical authors suggested a more surgically aggressive approach, describing the excision of the mortified limb at the level of the interface between necrotic and live tissue, recognising it not only as sometimes the only remedy to a life-threatening pathology, but also as an attempt to improve quality of life by removing malodourous tissue. Celsus, for example, in the 1<sup>st</sup> century AD described this approach, whilst recognising the risks of haemorrhage related to the process. His technique involved deep dissection down to bone at the level of the interface, preferably excluding the joint, and occasionally necessitating the removal of some healthy tissue. Although recognising the risk of haemorrhage, there is no explanation on the handling of neurovascular structures, nor the employment of haemostatic devices such as tourniquets or iron cautery. It was also concluded that any surgical dissection of healthy tissue, was confined to the level of the skin, and that was performed in order to allow for soft tissue coverage of bone. In a separate chapter on wounds and haemorrhage, Celsus mentioned vessel ligation in severe cases, and withheld cautery as a last resort to haemorrhage control.<sup>(14)</sup> Lister, as well as Wangesteen both concluded that, although Celsus described his two concepts independently, he would have applied his haemorrhage control principles when dealing with amputations.<sup>(12)</sup>

Additional evidence from Archigenes, a Greek physician of the 1<sup>st</sup>-2<sup>nd</sup> Century AD, appear to give a detailed account of a more radical amputation approach. He described the exposure and ligation of major vascular structures as one of the first stages of the surgical procedure, whilst a simultaneous “ligature” was applied to the external aspect of the limb proximal to the level of the amputation, making his writings the first to explore the concept of tourniquets as a method of haemostasis and described the use of cold water as a means to achieve vasoconstriction. Albeit fragmentary documentation to a certain extent, Archigenes not only recognised that his patients were at grave risk of intra-operative haemorrhage, but he also provided practical solutions to confront the dangers. He described what translated into ‘upward traction of the soft tissues assisted periosteal elevation and bone sawing as high as possible, above the soft tissue, after which heat cautery was employed to bleeding points’<sup>(12)</sup>. Some history commentators even accepted this as a description of amputation through healthy tissue as performed to date, although Archigenes did not precisely describe it. The concepts described by Archigenes and Celsus were marginalised for centuries to come, and it wasn’t until the Renaissance Era when surgical resection was becoming more elective in nature.

Paul of Aegineta in the 7<sup>th</sup> Century AD described an ‘assisted auto-amputation’, where he accentuated in a manner, the demarcation line between necrotic and living tissue, making extensive use of heat cautery and compression bandaging to absorb any wound discharge, stimulate suppuration and promote healing <sup>(15)</sup>.

The use of heat cautery was encountered in the 9<sup>th</sup> Century AD in the writing of various Arabic Authors, and with the exception of Haly Abbas and Albucasis, the approach to an amputation was once again largely conservative <sup>(15)</sup>. Haly Abbas advocated that dissection of less watershed tissues from areas such as the ‘front leg and outer thigh’ was preferably done as a first step, followed by bone resection, with vascular structures to remain the last structure to be ligated and divided. Although not clearly defined in his texts, such method can almost be seen as a primitive process of soft tissue flap fashioning for adequate bone coverage <sup>(15)</sup>. Albucasis, a surgeon of the same Era, mentions amputation not only as a solution for congenital polydactyly, but also as a life-saving measure following venomous bites. It is doubtful that he himself has actually performed any major amputations, as he paradoxically extensively expresses his adamant refusal at performing the operation for one of his patients. He advocated the use of extensive soft tissue bandaging in the capacity of not only haemostasis, but also as a means of providing for soft-tissue traction to aid surgical excision as well as to protect soft tissues from the saw. In addition, he too described the use of hot oil cautery as well as application of styptic powders to achieve haemostasis. <sup>(15)</sup>

The use of amputation as a treatment modality for life threatening ascending infection was also recognised by an Indian physician, earlier on in the same century, who recommended amputation for patients following infected injuries from bush thorns. <sup>(15)</sup>

Later on, in the Anglo-Saxon Leech books, Payne once again reported on the use of amputation as a ‘last-resort’ form of surgery, favouring the conservative approach. Nonetheless, one physician of the same Era, Theodoric, controversially questioned the practice of his colleagues and in the 13<sup>th</sup> century AD, he was one of the pioneers to encourage dissection through healthy tissue, recognising it as the determining step towards healthy wound healing. He was also one of the more humane practitioners, as he suggested the inhalation of a mixture of naturally occurring medications, including opium, hyoscyamus, mandragora, and hemlock, as a mode of intraoperative analgesia. Delivery of these narcotic type drugs to the patient was by means of a sponge soaked in vinegar which was applied to the nostrils, also known in the medieval times as the ‘spongia somnifera’. <sup>(12)</sup> Although a commendable attempt at achieving anaesthesia and analgesia, it was sadly highly toxic, with a significant proportion of patients failing to wake up following the procedure. <sup>(12)</sup>

The 12<sup>th</sup> and 13<sup>th</sup> Centuries AD saw the Catholic Church as a major inhibitor to advances in surgery. Through several declarations of the Church, the field was condemned, and previous contributions from official university trainees as well as priests with special interests in the field of medicine were withdrawn, leaving the practice in the hands of empirics and barbers. Consequently, the quality of surgical care deteriorated significantly and even barber-led surgical interventions were limited to venesection and minor procedures.<sup>(12)</sup> Amputation surgery was no exception to this medieval neglect and prejudice, and, as a result, surgery and the introduction of prosthetic limbs which were originally seen as far back as the writings of Herodotus and Pliny were considerably marginalised<sup>(16)</sup>.

Surgical intervention resurfaced again in the early 14<sup>th</sup> century AD, and rapidly owing to two major inventions, gunpowder and paper printing, and although they were both available centuries in advance, genuine surgical interest in gunshot wounds was not seen until the 15<sup>th</sup> century AD, when Pfolspeundt, a German surgeon, described the first gunshot wound debridement. He was succeeded by another two German wound surgeons, Brunswig, and then later Gersdor, both of Strasbourg. The latter described an operation of elective amputation through an illustration. In his report he appears to have employed the use of tourniquets or ‘constricting bands’ as he described them, above and below the amputation sites and styptics in order to minimise haemorrhage, as well as the use of warm or hot oil in order to decontaminate the wound of gun powder.<sup>(12)</sup>

The lack of initiative and fear of peer, public and religious criticism prevented surgical practitioners from recognising any form of scientific advance and so the expectant approach was seen as the mainstay of treatment even if it ultimately led to an amputation.<sup>(12)</sup>

Extensively comprehensive accounts on amputations with actual surgical approaches, epidemiological and historical facts, complications, and detailed illustrations did not make an appearance until the renaissance era. Even then, most information was based on personal experience and specific case references. On such detailed, illustrative account was that of Ryff in 1545. He described an amputation in progress, with a priest attending to the patient, along with a comprehensive account of the instruments and types of dressings applied.<sup>(12)</sup>

Franco in his 1556 *Petit Traité*, gave a step-by-step instruction of a limb amputation. The account recommended the following <sup>(12)</sup>:

1. Ingestion by the patient of a mixture of syrups and herbs for several days before and after surgery
2. Attachment of the patient when lying on a bench.

3. Application of a tight ligature applied two or three fingers-breadth above the proposed incision, to control haemorrhage and cause numbness below
4. Marking the proposed incision on the skin in ink.
5. Use of a razor with the handle tied securely to prevent buckling when cutting the flesh in one sweep down to bone
6. Pulling on the soft tissues by means of the ligature to expose the bone as high as possible
7. Section with a bow saw
8. Loosening the ligature to allow discharge of 'corrupted' blood
9. Application of hot iron cauteries
10. To the flesh and bone to stop bleeding and cleanse the tissues
11. Application of a liniment to assuage pain
12. Dressing with an emplaster
13. A firm bandage left untouched for 2-3 days

In the same account, Franco described the use of a hot sickle-shaped knife as an alternative to razor, as a means of simultaneous heat cautery at the time of the incision.

The technique of hot knife cautery was later on extensively elaborated upon by Fabry (1560-1634), but was nonetheless heavily criticised by Wiseman in his account of *Severall Chirurgicall Treatises* as an extremely traumatic procedure both towards soft tissues, as well as the patient's pain experience <sup>(17)</sup>. Fabry, who additionally made other original contributions such as performing above-knee amputations through healthy tissue, fabrication of special forceps with locking mechanisms, and an amputation kit containing replacement saw blades, also wrote against the use of traction pliers or pincers during digital and hand amputations due to the residual damage inflicted on delicate structures such as nerves and tendons, making him one of the first surgeons to recognise the importance of appropriate soft tissue handling during surgery <sup>(18)</sup>. He was the author of 20 medical books, one of which *Observationum et Curationum Chirurgicarum Centuriae* published in 1641 was characterised as the best collection of illustrated surgical cases of the century <sup>(18)</sup>.

Procedural techniques such the ones described by Franco were often brutally vulgar and crude until the early 16<sup>th</sup> century when Ambroise Paré (1510-1590), a French barber surgeon

set a new cornerstone in the principles of amputation in his *La methode de Traicter les Playes Factes par Haqcuebutes et aultres bastons à feu*.<sup>(19)</sup>

Apprenticed in Paris as a barber and later a student of Hotel-Dieu, Paré served as a Royal battlefield surgeon for a number of French Monarchs. His wound encounters at a time when little was available for battle injury damage control, provided for a rich substrate for him to popularize amongst others the use of vascular ligatures, haemostats and tourniquet use (in the form of a strangulating fillet or band), vessel transfixion and replacement of oil burn cautery with suture ligation bland pressure dressings<sup>(19)</sup>. In more detail, his technique employed healthy tissue dissection, sufficient to achieve adequate bone coverage and the formation of a stump which would also allow kneeling, even if this implied a shorter stump. The vessels were exposed using a set of ‘crow-beaked’ forceps and double ligated, and, in the case of larger arteries, transfixed using needle and thread, fed through skin in an ‘inside-outside’ ‘inside-outside’ manner and securely tied outside the skin, with a piece of linen fed underneath the knot<sup>(19)</sup>. This crucial step not only allowed for prevention of local skin necrosis, but also the rapid removal of the suture in case of a surgical site infection (SSI)<sup>(12)</sup>.

As an experienced battle surgeon of his time, Paré’s approach was truly revolutionary not only in its technical aspects, but also his practice, as one could argue he recognised what was later on described as the “two-hit hypothesis”<sup>(20)</sup>. He advocated an expectant approach to amputation by encouraging preoperative patient optimisation with emphasis on nutritional strengthening with high-protein, easily digestible food<sup>(19)</sup>.

His techniques, although not always employed, were revered by some of his peers such as Clowes (1540-1604) and Lowe in 1599 who was one of the first surgeons to describe vessel ligation in English<sup>(12)</sup>.

Crossing into the realm of physiotherapy and rehabilitation, Paré designed and developed artificial limbs with the help of a locksmith whom he nicknamed “Le Petit Lorraine”. Understandably, he became known for his aggressive rehabilitation of amputee patients. One particular example is derived from his observation on the difficulties encountered by amputees with long leg stumps. On one such occasion, he suggested a further elective amputation to help resolve the problem<sup>(12, 19)</sup>. Although considerably suppressed by superstitions of his era at a time when medical practice was moving towards the discipline and order of science, Paré’s work on not only battlefield wound treatment and gangrene, but on other ailments like bone fractures, renal calculi, obstetrics and contusions has rightfully earned him a high regard as the “Father of Modern Surgery”<sup>(16, 19)</sup>.

Paré's surgical approach to amputation and the use of bland bandaging as a haemostatic agent received even more recognition when another surgeon, Etienne Morel in 1764, became the first surgeon to document the use of a tourniquet following trauma as a means to haemostasis<sup>(21)</sup>.

Amputation surgery progressed even further in 1679 when James Yonge of Plymouth, England (1647-1721) described a new, innovative surgical technique <sup>(22)</sup>. In his *Currus Triumphalis* of 1679, Yonge described a new method which aimed to produce a healed stump in 3 weeks. With the help of his colleague and brother-in-arms Lowtham of Exeter, to whom he remained indebted and repeatedly acknowledged through his account, Yonge developed the new technique which evolved around the fashioning of a long flap and fascia, enough to provide adequate bone cover whilst accommodating for the insertion of a drain and 4-5 tensionless sutures <sup>(22)</sup>. Whilst acknowledging the high incidence of post-operative infection, and stump failure/perforation, Yonge explained that such approach would produce a healthy stump within 3 weeks as opposed to months, however, he cautioned against the approach in case of pre-existing inflammation or tumour <sup>(22)</sup>. This technique was particularly favoured in major amputations, particularly following trauma, boasting lower incident of infection and stump ulceration, better pain control, and a lower risk of haemorrhage, increasing the probability of the patient tolerating a prosthesis. In addition, the costs of medication and bandaging were slashed <sup>(22)</sup>. Interestingly, Yonge did not demonstrate these advantages through case examples, neither did he discuss shortcomings of this procedure which were potentially longer operating times and consequently more pain at the time of the surgery <sup>(22)</sup>.

Throughout times, it is quite evident that limb amputation both as a procedure as well as a concept and a word which underwent extensive evolutionary modification, brought about by a combination of factors including advances in antisepsis, anaesthesia and instrumentation, as well as social acceptance and legislative changes. Previous words used to refer to amputations include “dismembering”, derived from the old French word *desmembrer* and the original Latin *membrum*, for limb, and “extirpation”. Such words preceded the use of the word amputation by almost half a century. According to the Oxford English Dictionary, the term ‘dismemberment’ was utilised since the early 13<sup>th</sup> century to describe primarily the lopping or pruning of tree branches, but also a human limb that was either lost as a result of trauma in combat or accident, or frequently in past centuries, as a result of a punishment or legal penalty imposed on a criminal.

The word ‘amputation’ did not show up in English writings until the 17<sup>th</sup> century and one of the first authors to use it was Lowe in his book “A Discourse of the Whole Art of

Chirurgie” in a chapter titled “The manner of amputation”<sup>(12)</sup>. His long experience in France is reflected by the use of the words ‘extirpation’ and ‘dismembering’, the latter of which was extensively used in the description of steps involved in the procedure as well as the surgical equipment employed in it. Other authors/translators who have used alternative wording to allude to the procedure include translations of Brunschwig’s “Busch der Chirurgia” of 1525, Vigo’s “Practica in arte chirurgia copiosa” of 1550, Gale, Clowes etc. In 1750, Dionis of Greece suggested the word “acrotiriamos - ακρωτηριασμός”, to cut off a body extremity.<sup>(12)</sup>

Later reports by medical historians whether transcribed from other languages or written in English entirely reverted to using the word amputation to describe a limb excision but one must also note the introduction of the term “disarticulation”. This was used to describe the removal of a limb through a joint without physically transecting the bone but the joint soft tissues.

John Woodall of Warwick, UK was one of the first Britons to publish extensively on amputations in the English language. His experience was largely derived from his practice involving the management of patients with gangrene at St. Bartholomew’s Hospital in London.<sup>(23)</sup> With the luxury of hospitalisation and inpatient care, Woodall was one of the first surgeons worldwide to produce some primitive, yet useful and accurate statistics on approximately 100 amputations performed on gangrenous limbs. In 1617, and following much reluctance towards publicly embracing his self-acknowledged concept of elective amputation, Woodall published his manual titled ‘The Surgeons mate’, in which he gave a detailed, illustrative account of operative instructions pertaining to an emergency amputation and the instruments required to perform the procedure. Much like his peers, he too advocated dissection through healthy tissues as a crucial step of an amputation.<sup>(23)</sup>

In the late 1700s complete transections of limbs occurred using either an axe or a sword dividing, skin, soft tissues and bone at the same level. Such amputations later came to be known as “guillotine” amputations and they were performed long before Dr. Guillot, a French physician, invented the notorious guillotine machine used extensively for beheading during the French Revolution. In 1833 Mayor described this method of amputation as a *tachyotomie*, Greek for rapid division.<sup>(12)</sup>

By then, amputations had become common practice in the Western World, particularly in scenarios where there was an obvious threat to life as a result of major trauma<sup>(24)</sup>. William Kerr of England performed the first successful hip disarticulation ever reported in 1774.

Such radical procedures were a common occurrence especially during the Napoleonic Wars<sup>(24)</sup>.

In 1797, during a coastal raid targeting Santa Cruz, Tenerife, Admiral Lord Horatio Nelson received a musket shot injury to his right arm, leading to an above elbow amputation. He potentially owed his life to his nephew Lt. Josiah Nesbit who managed haemostasis by application of a tourniquet at the time of the injury, enabling the Admiral to survive during the time taken for him to return to the fleet.

Another famous amputee who survived major trauma was the Earl of Anglesey. He underwent an above knee amputation after sustaining an injury to his leg from a cannonball whilst standing next to Lord Wellington at the Battle of Waterloo in 1815. He miraculously made a full recovery from his injury, and was subsequently fitted with a rather elegant wooden prosthesis.<sup>(25)</sup>

Declared by Napoleon Bonaparte as ‘The Worthiest man’ he had ever met and yet another graduate of the Paris Hotel de Dieu, Dominique Larrey(1776 – 1842) was a major contributor of further expanding the principles of amputation originally formulated by Paré<sup>(22)</sup>. As the the chief Surgeon of the French Army, he was responsible for the early description of the concept of trench foot and frostbite<sup>(26)</sup>; Larrey was the designer and inventor of the legendary ‘Ambulance Volante’ or ‘Flying Ambulance’, which were horse-drawn wagons used in the transport of battlefield casualties to a point of safety and care. Even in harsh terrains, this army corps was always in very close proximity to the battlefield, and could extract the wounded within 15 minutes. Such a revolutionary idea not only increased the survival rates of wounded soldiers, but also boosted the morale of the French officers, whilst providing for an uninterrupted supply line of food and medical goods.

Larrey was the first surgeon to ever perform a successful pericardiocentesis for trauma, and to triage and treat patients directly on the battlefield, should the degree of injury warrant it, regardless of rank or distinction. For less severe trauma, patients were transferred off the battlefield, to be cared for and scheduled for surgery at a subsequent stage when they would be strong enough to survive it. Larrey also introduced the use of ice as effective analgesia, and the prescription of a high-protein, high calorific diet for soldiers recovering from injuries. From third party reported evidence, and through his published four volumes of ‘Memoires de chirurgie militaire et campagnes’, Larrey was said to have performed 200 amputations within 24 hours at the Battle of Baradino and was the first surgeon to describe ‘trench foot’, and the use of muscle to cover bone following an amputation. Interestingly, unlike Paré who advocated the concept of delay of surgery until the patient was

physiologically well enough to undergo a procedure, Larrey argued that battlefield extensive trauma warranted immediate intervention, frequently on the battlefield, ignoring the harsh conditions and infection risk. This expectedly lead to loss of life often due to sepsis, although in his memoirs, he states that over 1000 treated officers and soldiers recovered to make a return to battlefield action.<sup>(27)</sup>

Subsequently, during the campaigns in Spain, the Spanish made extensive use of land mines, as well as hand-held firearms, increasing the rate of lower limb trauma, making Larrey the most experienced amputation surgeon of his era.<sup>(28)</sup>

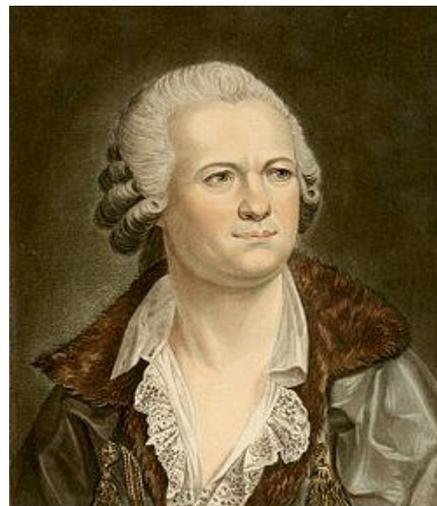
The same century saw the work of another very eminent surgeon, John Hunter (1729 – 1793) Being a distinguished physician, Hunter was a great believer in the application of scientific theories, thus making him a practitioner, different to others. Specifically, he advocated a more elective approach to amputations, and restricted to dissection / debridement of only damaged tissues. In much the same manner as Paré, he too believed that allowing time before intervention would give the patient's organism a chance to accommodate for the acute inflammatory response phase, and would allow for ample time to wash and debride the wound accordingly, and off the battlefield, thus increasing the chances of survival.

Although historians worldwide make reference to the procedure of amputation, it does not necessarily imply a widely accepted concept in elective surgery as in numerous cultures, amputation remains a form of surgery which is disregarded. This is due to a bizarre perception which declines any surgery that affects body integrity, which was ultimately associated with a distorted human image. One such community is that of the Mano Tribe in Liberia, studied by Harley in 1941, where “amputations were unheard of”<sup>(29, 30)</sup>. Much contradicting this lay belief, over the years, any limb loss sustained as a result of an accident, effectively provided for a universal portal through which society came to accept elective amputation as a form of surgery, particularly when the only alternative they were faced with, was human demise as a direct result of limb destruction.

### 1.1.2 *Eponymous Amputation Surgeons*

### 1.1.2.1 Francois Chopart (1743 - 1795)

Although undoubtedly one of the most mentioned names in the history of surgery, Francois Chopart, is a clinician who is not vividly remembered, with most of his work self-reported. Born in Paris in 1743, carrying his mother's maiden name and his father's first name, Chopart chose a classical route at the College Mazarin. Upon completion of his studies, the newly qualified



Master of Arts chose to focus on the field of surgery, and he embarked on his apprenticeship under the watchful eye of chief surgeon Maitre Moreau at the reputable Hotel Dieu hospital, home to a league of prestigious, world renowned surgeons, where he gained invaluable clinical experience through the expertise of his Mentor. Chopart, was also a keen student of Coutavoz at the Hospice de la Pitie, where he gained the majority of his surgical expertise, through exposure to trauma. <sup>(31)</sup>

As a Fellow in Hospital Bicetre, Chopart fell ill with a recurrent gastric disorder and was forced to adapt a more theoretical method of learning through the study of case reports and text books at the Academie Royale de Chirurgie. Subdued by his illness and driven by his flaming passion for the art and science of surgery, which was further fuelled by the intellectual competitions often held at the Academie, Chopart wrote extensively, and amongst others, he produced the “Essai sur les Lupes”. This not only granted him hard-earned respect and recognition, but also encouraged him to embark on further academic endeavours.<sup>(31)</sup>

His background of classical studies and knowledge of Latin, enabled him to seamlessly transform his accounts on Countercoup brain trauma in 1768, a report which he had originally presented at the Academie, into an extensive thesis. Combining this with a local exam he successfully completed, allowed him to qualify as a Maitre en Chirurgie. Contradicting the tradition of newly appointed guildsmen, Chopart, did not take any trainees under his wing, until his appointment as a Professor of Surgery at the Ecole-Pratique de Chirurgie in 1771, where he lead the teaching on anatomy and the performance of numerous surgical procedures.

His methodology was characterised by clarity and practicality. He performed his role as a chair of the Ecole-Pratique in an inspirational and didactic manner, leaving an impressionable mark, not only among a highly selected group of students but also his peers.

His self-confidence and determination were continuously reflected through the Ecole itself, which he had transformed into a leading centre of surgical training.

Chopart was a pioneer in the field of Urology, and in 1771/72, he published the two-volume *Traité des maladies des voies urinaires* putting emphasis on dealing with the urinary tract as a whole <sup>(32)</sup>. Later on 1779, he published the renowned *Traite des maladies chirurgicales et des operations qui leur conviennent*. This revolutionary 2-volume book contained lectures designed specifically for students, written by both professors, and was edited numerous times. Such was its quality that it was translated into multiple languages, including German, and it was praised by students on an international basis <sup>(32)</sup>.

Chopart's path continued to be paved with success, as he ascended through honorary positions such as Assistant Professor and Counsellor of various committees, through to Commissioner of Correspondence and Vice-Director of the Academie. It wasn't until March 1782, when he succeeded the much acclaimed Toussaint Bordenave's (1728-1782), as a Professor of Physiology at the College de Chirurgie in Paris. He shared the Chair with Antoine Louis (1723-1792), but, Chopart's performance surpassed that of his colleague, gradually placing him in the same league of fame as the two former professors. His proposal for the position of "Professeur de Pathologie Externe" of the Parisian Medical Faculty by Antoine François Fourcroy (1755-1809) was therefore no surprise. Once again, through this position, Chopart managed to project his vision and his knowledge, even at challenging times, as the educational system was undergoing vital reform and restructuring.

In 1790, after a lifetime of hard work, Chopart was appointed Director of the Hospice des Ecoles de Chirurgie founded by King Louis XVI. This was a significant professional milestone for Chopart, as, it not only marked the long-anticipated return to clinical practice but also the opportunity to prove the true value of his teachings. He successfully completed the locally set exam, demonstrating once again his solid medical knowledge and understanding of the human body<sup>(31)</sup>. The introduction of some of Chopart's new surgical techniques was marked by one particularly striking example which remains named after him to this day. This was the intertarsal disarticulation based on his precise knowledge of anatomy of the midfoot. Paradoxically, Chopart only performed this surgery once on August the 21<sup>st</sup> 1799, at the Hospice des Ecoles de Chirurgie on a 26-year old patient following the diagnosis of a local tumour, potentially a liposarcoma, and did not consider the procedure as important enough to be reported <sup>(31)</sup>. The record of the procedure exists due to one of his students at the Hospice, by the name of Lafiteau who interestingly did not consider this as Chopart's own approach. <sup>(33)</sup> The terminology such as the 'Chopart Joint', or 'Chopart

amputation' did not make an appearance in literature until the 19<sup>th</sup> century, at a time when the procedure was heavily criticised when compared to the metatarsal disarticulation described by Lisfranc in 1815.<sup>(31)</sup>

### 1.1.2.2 Jacques Lisfranc (1790-1847)

Jacques Lisfranc was born 10 months after the marriage of Pierre Lisfranc in the house of Lower Street Saint-Paul-en-Jarez. His family were no strangers to the world of medicine, as he followed a long tradition and line of ancestors.

His father, Pierre Lisfranc de St. Martin, was the descendant of three generations of Surgeons: his father John the Baptist who had served in St. Paul, his grandfather Pierre (received by the Royal College of Surgery of Lyon) and his great grandfather Pierre Cartal in Virieu.



Much contradicting the rumors that his enemies wanted the public to believe in that Lisfranc that would have ennobled himself by adopting this surname after the street name where he lived in Paris in 1815, he was known at the time as Jacques de Saint-Martin.

Lisfranc enjoyed a very privileged childhood, having lessons at home with a tutor who instilled in him a taste for arts and literature although his keenness extended into sports such as fencing, dancing and swimming. Lisfranc displayed his manual dexterity and good hand-eye coordination early through woodturning, a skill which served him later on as a surgeon.

Compelled by the surgical vocation of his ancestors and after his school years in Lyon High School in 1805, he embarked on his studies at the famous the Hôtel-Dieu de Lyon medical school. Internships at the Hôtel-Dieu de Lyon and Paris, from 1806 to 1813 were a privilege for the few, and medical studies were extremely competitive to get into, especially in this college, which served as home to many distinguished surgeons, the likes of Pare, Colles, Petit and many more.

After two years of study at the Hôtel-Dieu in Lyon, he left for Paris where he remained for just a year before returning to Lyon in April 1810, as a contestant for "student surgeon of the Hotel-Dieu" competition. The competition of the boarding of Lyon "surgeon student" was held at the Hospices Hôtel-Dieu and Charity and was chaired by senior surgeons like Rey,

Marc-Antoine Petit, Cartier and Martin. Lisfranc was called to answer questions on bone anatomy, and pathophysiology of the sarcocele before being appointed one of fifteen "Surgeon's pupils". As a new intern in Lyon, he was student to Viricel and the valedictorian Denis Mortier, future surgeon of the Hôtel-Dieu de Lyon. In addition to his medical studies, he began acquiring his operating skills under the tutelage of Claude-Antoine Bouchet, a very distinguished surgeon, and one of the first to describe and deal with iliac aneurysm repairs.

In 1811, Paris and former Lyon Intern was assigned to St. Louis to be then moved to the Hotel-Dieu, where he pursued additional apprenticeships under Dupuytren and Pelletan whom he befriended and emulated. In 1812, he was awarded his doctorate, at a time of hardship and increased tension, when France was heavily involved in the Napoleonic Wars. Lisfranc had to hastily complete his thesis, leaving for Germany almost immediately, commissioned as an Army Surgeon, only to face a demoralized army in the presence of adverse conditions. In the presence of these adversities Lisfranc perfected the art of amputations and disarticulations, salvaging many lives on the battlefield. He rose rapidly amongst army ranks and befriended some of the most distinguished military personalities, such as Dominique Larrey. Unfortunately for Lisfranc, during one of the expeditions in Metz, he contracted a mild form of typhoid.

With the end of the war, Lisfranc returned to Paris, at 159 rue Saint-Martin to establish a very successful practice. He was actively involved in the work of Dupuytren, particularly on polyps in the nasal passages, however, in 1814-15 he presented his own original work consisting of two papers on disarticulations of the shoulder and foot. In 1818 he was appointed surgeon to the Central Bureau of Hospitals. Lisfranc's operative skills soon matched if not surpassed those of Dupuytren's. Personalities clashed and it was a matter of time before animosity developed towards each other, something which soon manifested itself in the political as well as medical arenas at the time. Dupuytren's attitude changed and that decade saw leverage on his behalf trying to boycott every advance Lisfranc attempted to make in the academic world. Lisfranc demonstrated time and time again his utmost respect and gratitude towards his Master. Much to Lisfranc's righteousness, as a result of an unforeseen encounter with a magistrate, during which Lisfranc attended to him after falling off his horse, his qualities not only as a medic, but also as a gentleman were recognised and in 1819 was appointed Second Surgeon in St. Louis, and subsequently Chief Surgeon at the Pitié in 1825. Dupuytren had lost the game against Lisfranc. For the 20 years to follow he brought prestige and reputation to the institution. He had

unofficially been named ‘Professor of Surgery’, something which not only gave him an opportunity to practice surgery, but also demonstrations of dissection and anatomy in public amphitheatres.

The Eponym Lisfranc is often associated with an orthopaedic background, however the reality is that he developed the amputation skill during war time. His real love was one for anatomy and the world of gynaecology and general surgery, both of which he practiced successfully until the day he passed away, although, he wrote numerous articles on diverse subjects such as his pioneering of removal of a cancerous rectal tumour, diseases of the uterus, as well as shoulder disarticulation and diagnosis of fractures.

Amongst the countless distinctions he received, he was the founding member and ultimately the President of the French Academy of Medicine and Chevalier of the Legion of Honour. He developed an enormous practice with many students and followers, and despite his frailty both physical as well as eventually mental, he persisted with his surgery until the day he died in May 1847, at the age of 57.

### 1.1.2.3 James Syme (1799 – 1870)

Descendent of two wealthy Scottish families of significant social stature, James Syme was born in 1799 in Edinburgh to John and Barbara Syme. Contrary to the majority of other boys at his age, Syme’s education was closely attended to by his family. As a young student, aged 15, he attended the Messrs Grammar School and subsequently Edinburgh Royal High School. Syme was no ordinary teenager though. He was a somewhat singular young boy not taking much interest in other activities such as hunting and sports, but instead, he spent most of his time using his favourite science, chemistry to conduct experiments and study anatomy of small animals through dissection, and once a week he would hold experiment demonstrations at his house, for himself and the chosen few close friends he had.



In November 1815, at the age of 18, he became a student at Edinburgh University. His continued passion for sciences led to his discovery of a solvent and a process by which cloth

might be impregnated to make it waterproof. Although Symes published his discovery in 1817, he failed to follow the advice of some of his entrusted friends. Soon after that, a manufacturer from Glasgow, Charles Macintosh (1766- 1843) took out the patent for it, and manufactured caoutchouc-based waterproof coats, living his name permanently associated with the raincoat.

After two years at the University of Edinburgh studying botany and philosophy, Symes embarked on his medical studies in the anatomy class of Dr John Barclay. Robert Liston was then the principal demonstrator. In the next year, when Liston set out on his own as a teacher of anatomy, Syme joined him. Aware of the limitations of his training in anatomy due to shortage of cadaveric supplies to the School in Edinburgh, Symes, with "indomitable vigour and perseverance," overcame this obstacle and rapidly became a popular, successful demonstrator. In 1822, the year that Beaumont began his study of digestion in the exposed human stomach, Syme went to Paris to study anatomy and operative surgery under Dupuytren and Lisfranc. In Paris he met Dr Sharpey. This acquaintance developed into a lifetime of friendship, often maintained through letters, some of which have been published. In 1823, Liston went into surgery and left Syme the full responsibility of teaching anatomy. Syme's rapidly growing interest in surgery was soon becoming apparent, and he eventually became a Fellow of the Royal College of Surgery at Edinburgh which, the eighteenth and the beginning of the nineteenth century was a renowned surgical centre. To succeed in such a competitive environment surrounded by exceptional surgeons, Syme displayed commendable determination and self-discipline, and to promote opportunities. When he failed in 1829 to receive a surgical appointment to the Royal Infirmary, Syme established his own private surgical hospital at Minto House. In 1833, Syme succeeded James Russell to the premier Chair of Clinical Surgery, established by King George III, returning as a Professor leading the wards he once attended as a student. Since this professorship carried an appointment to the surgical staff at the Royal Infirmary, Syme permitted Minto House to change from a successful surgical hospital to a Maison de Sante and dispensary. Syme was extremely successful both as a surgeon and an academic. His reputation spread rapidly. When Liston accepted the chair of Clinical Surgery in the University of London, in 1835, Syme was indisputably the leading surgeon of Scotland. He introduced the practice of bringing cases, one by one, to the students in addition to their lectures. His surgical service at the Royal Infirmary became the mecca of all aspiring young surgeons. The peak of pre-Listerian surgery in Edinburgh was reached during the period when Syme was professor of Clinical Surgery. In 1837, his experimental investigation, "On the Power of the Periosteum to Form New Bone," was an important contribution to surgical pathology. In 1842, Syme

first performed the amputation at the ankle joint that bears his name, although from documentation available from the Royal College of Surgeons of Edinburgh Medical and Surgical Journal, it is evident that Syme's first ever important operation was in fact a hip disarticulation performed for the first time in Scotland in 1823. Two years later his operation of perineal section for obstinate stricture of the urethra provoked considerable discussion among the surgical community. Syme kept up with advances in surgery, readily accepting and applying them. His adoption of anaesthesia was delayed, not because he failed to identify its significance and place in surgery, but because the discovery came from the obstetrics department. In his last clinical lecture, in 1868, he spoke enthusiastically of the antiseptic system advanced by his distinguished son-in-law, Joseph Lister. Although he never earned a medical degree, Syme was awarded honorary degrees by the Universities of Dublin, Bonn, and Oxford. He received many honours, and became surgeon in ordinary to the Queen of Scotland. He was a successful teacher, a respected writer, and a great diagnostic clinician and surgeon. Of Syme it was well said by a contemporary "that he never wasted a word, nor a drop of ink, nor a drop of blood." On April 6th, 1869, Syme had a paralytic stroke. A few months later he resigned his professorship of Clinical Surgery and his position of Surgeon to the Royal Infirmary. Realizing his failing health, his many admirers and former students organized many testimonials for him, including the establishment of the Syme Surgical Fellowship at the University of Edinburgh and erection of a marble bust there. The next year, after several more strokes, Symes died on June 26, 1870.

#### 1.1.2.4 Rocco Gritti (1827-1920)

Born to Faustino and Lucia Manzoni, in December 1827 in a small suburb of Bergamasco, Gritti lost both parents in childhood. He took his first steps in education in the schools of Ficarolo, at Rovigo.

Later on as a young medical student, he studied in Verona and Bergamo, where he received his Baccalaureate of Medicine. In 1847 he enrolled at the prestigious University of Padua, home to influential pioneers the likes of Copernicus, Fabricius and many others. His studies came to an abrupt halt after a few months due to his involvement in the anti-Austrian Rising in the first War of Independence. In 1848 he enlisted as a volunteer soldier in the papal army. He



quickly rose through the ranks of the Second Battalion of the Ancona National Guard where he was promoted to Commander of the defense borders of the State of the Church. His leadership qualities as a military officer were evident through the successful completion of a number of expeditions against the Austrians across the river Po. Gritti remained in the area of operations until mid-June. Immediately after the dissolution of the Corps to which he belonged, he enlisted in the volunteers and participated in the expedition of the Tonale against the Austrians.<sup>(34)</sup>

Gritti returned to his studies following the uprising and graduated in 1853 in Pavia after completing a thesis on anaesthesia. The continuous demonstration of a rapid progress and excellence in the field of surgery granted him his appointment as a surgical apprentice at Maggiore Hospital in Milan, where he further enriched his experience and practice alongside the talented surgeon Ambrogio De Marchi Gherini.<sup>(34)</sup>

In the same year he moved to Vienna to attend at the prestigious Institution of Surgical refinement, a centre with places to accommodate only the few and privileged reserved graduates of Lombardy and Veneto. Gritti remained there from autumn 1853 to 1855 as a student in the surgical clinic of Franz Schuh, whilst attending classes at the institute of pathology of Karl Rokitanski and Karl Wedl, both recognised as internationally renowned figures in the field of histopathology<sup>(34)</sup>.

He returned to Italy with the diploma of Viennese Surgeon, holding a legacy of scientific and medical knowledge, which in 1856 earned him the appointment as a practitioner of free surgery in the Milan Hospital. His rise as a surgeon came swiftly, as Gritti became known not only for his logic and diligence but also for his academic work, as an original publication scholar of surgical problems.

One of his greatest contributions to the world of academia and surgery came in the years 1853-1856, whilst he was training alongside Professor Schuh, for whom he published an extensive report of clinical cases encountered in his clinic as well as surgical practice in the *Annals of Universal Medicine*.<sup>(35, 36)</sup>

One of the most significant technical and scientific highlights in Gritti's career, was his method of leg amputation, which involved an osteoplastic approach to the distal end of the femur, following disarticulation of the knee joint<sup>(37)</sup>.

Described by him as 'The supracondyloid amputation of the thigh', this innovative intervention consisted essentially of the formation of an anterior flap incorporating the patella, securely fixed to the posterior surface of the femoral section of the stump, making it

suitable to carry increased load. Gritti first presented this method at The Congress of Surgery in Geneva, and to this day, it remains as one of the most recognised methods of amputations about the knee. The procedure was first attempted in 1861 by Rocco Gritti, and subsequently in 1863 by his Viennese Master, Professor Schuh who went on to describe its success in a case series in 1864 <sup>(34)</sup>. The procedure was later adopted and improved upon by Sir William Stokes, whose name was associated with that of Gritti in the indication of the intervention <sup>(38)</sup>. Whilst a practicing surgeon, Gritti published another useful report in 1858 on various joint neoplasms, such as fibrochondromatosis of the scapulo-humeral joint <sup>(39)</sup>.

In May 1859, he was appointed Assistant Surgeon and was called to deal with the influx of injured soldiers during the Second War of Independence. His role was recognised not only as a military surgeon but also as a manager as he helped set up emergency services in St. Francis Hospital as well as a separate provisional military hospital in Melzi. His contributions were honored in the same year with the French Medal of Second Class Honours.

Despite his achievements, in September of the same year he failed to secure the post of chief surgeon at the hospital in Monza. In 1863 he toured several European countries in an endeavor to examine the progress made in the field of surgery. He acquired invaluable technical and scientific knowledge pertaining not only to surgical practice but also to the standard of care achieved in a variety of European Capital Hospitals such as Berlin, Brussels London and Paris. He conveyed his experience to the Council of Milan via two reports, highlighting the need for a rational and necessary adaptation of Italian Hospitals to European standards. In 1865 he was appointed Surgeon Major and despite a significant increase in his clinical commitments, he continued to contribute in academia publishing in quality journals on a variety of different specialties.

Eye disease was one of the areas that Gritti turned his attention to after close collaboration with the famous ophthalmologist Antonio Quaglino (1817-1894) in the drafting of the book 'On the internal diseases of the eye'. <sup>(34, 40)</sup>

Gritti was also interested in current affairs. He joined the Milan Committee of the Italian Association for the Medical Aid to the wounded and sick soldiers, formed in 1864 in connection with the International Committee of Geneva (that with the convention of the same year sanctioned the neutrality of the wounded and their rescuers on the battlefield forming the Red Cross).

Gritti participated in the Third War of Independence, this time as Head of Organization for medical care and transport of the wounded who arrived in Milan by train. His devotion to

humanity and the world of medicine was once again evident through a remarkable article: A statistical essay on the morbidity and mortality in soldiers managed at military hospitals at time of war. Whilst in this role, he examined matters of general interest in surgical practice, such as the value of the topical application of external sulphite dressings and the use of an unusual surgical method, with the operative field immersed in water maintained at a temperature of 25 ° C, a process already proposed by Schuh as well as other surgeons, to be followed in procedures such as thoracentesis, empyema and deep abscesses drainage, knee joint aspiration etc., as a means of antiseptics, until it was replaced by more practical approaches described by Lister<sup>(34)</sup>.

Gritti published on a variety of surgical fields including oral and maxillofacial surgery, urology, and general surgery but of note was his contribution to the field of Trauma and Orthopaedics. His military experience and medical expertise allowed him to publish extensively on the management of femoral fractures sustained from firearm injuries, as well as femoral fractures in infants and children up to the age of 16, using traction with weights in patients as young as 16 years old, thus favouring a more conservative approach.<sup>(41, 42)</sup>

As much of a surgeon and a true scholar he was, Gritti was also a man of the people. He identified the problems faced by the lower socioeconomic classes and set out to establish a more just society. Driven by his political sensibility and by capitalizing on the uncommon technical, scientific and practical challenges encountered by others, he set the cornerstone for the creation of the special medico-surgical ‘night guards’ that operated in the city of Milan between 1876 and 1881. These aimed primarily at the emergency assistance to members of the most deprived social strata. His philanthropism was continuously evident through the Masonic family, a Milanese Elite Society the members of which shared the same humanitarian ideals and practical commitment.<sup>(34)</sup>

Rocco Gritti retired from medical practice in 1892, and died on July 14, 1920 at his villa in Pallanza, on Lake Maggiore.

#### 1.1.2.5 William Stokes (1839 – 1900)

William Stokes was born on March 10th, 1839. His father William Stokes was the illustrious physician whose classical works on cardiorespiratory disease are still read by every educated physician across the Globe. Young Stokes received his early education at the Armagh Royal School, and later on in Trinity College Dublin, finishing up his undergraduate career by obtaining his Arts degree in Dublin University in 1859. Four years later he proceeded to obtain the degrees of M.B., M.D. and M.Ch. pertaining to his medical studies and in 1862 he



received the licence of the Royal College of Surgeons of Ireland. In 1864 he was appointed Surgeon to the Meath Hospital, but four years later he was transferred to the House of Industry Hospitals, where he performed most of his operating for which is rightfully remembered today. Despite the global fame of The Royal College of Surgeons of Edinburgh, there was a shortage of cadaver availability for anatomy studies. Stokes was privileged enough to be able to enrich and enhance his anatomy knowledge by extending his travels to the Continental schools of Paris, Berlin, Vienna, and Prague. These not only added to his wisdom but also marked the beginning of what proved to be a lifelong friendship with Professor Ogston, of Aberdeen. Following years of lecturing in the field surgery at the old Carmichael College, he was appointed Professor of Surgery at the Royal College of Surgeons of Ireland in 1872, and two years later was awarded the Fellowship. Stokes's love for the field was not only evident at the operating table, but also in the lecture theatre. His reputation soon superseded him and in 1886 he was elected to the Presidential Chair of the Royal College of Surgeons in Ireland, and in the same year the honour of knighthood was conferred upon him, a distinguished title which his father never came to know. In 1888, with the death of Mr. Wharton, Stokes returned to the Meath Hospital to stand in for his lost colleague, and during the years which have passed since then, he maintained the reputation which he had already won of being the finest clinical teacher in Ireland. The delightful voice, the impressive, solemn manner, the Socratic Method, and the assurance of accuracy in the knowledge which was being imparted, all combined to make him an inspiring teacher whose classes filled the wards. Stokes contributed largely to academia through surgical literature, having written at least 100 standard papers on various subjects. His earliest efforts were marked by an essay on the diagnosis and pathology of diseases of the testis, which was awarded the gold medal of the Dublin Pathological Society. His communication on Fractures

of the Neck of the Femur, made at the annual meeting of the British Medical Association in London in 1895, was attended with uncommon interest. He was the author of several papers on the treatment of urethral stricture, and amongst his most recent productions are those on Excision of the Tongue, Excision of the Jaw, Nephrectomy and Fixation of Movable Kidney, Excision of the Thyroid Gland for Exophthalmic Goitre, and A New Method of Treating Fractured Patella. Upon his resignation from the position of Surgeon to the House of Industry Hospitals, he retained his seat on the Board of Governors, of which he was an active member. He was the Governor of the Westmorland Lock Hospital, a Consulting Surgeon to the National Children's Hospital, a member of Council of the Royal College of Surgeons, and for a number of years one of the representatives of the College on the Conjoint Committee which managed the examinations conducted by that College and the sister College of Physicians. He took a genuine, rigorous interest in the Royal Academy of Medicine, and for many years occupied a seat on the Surgical Council of the Society, in addition to which for several years he has acted in the capacity of secretary for its foreign correspondence. He was one of the most regular members at the meetings of the Council and filled the position of President of the Branch with conspicuous ability. As an examiner Sir William had vast experience, and was in this respect universally popular. He formed one of the Surgical Court of Examiners in the Queen's University, in the Royal Colleges of Physicians and Surgeons, and for a number of years in the University of Oxford. Of the numerous honours that he had received, perhaps the one which he valued most highly was that of Surgeon in Ordinary to the Queen in Ireland, to which he was appointed in 1892. In addition, he was also placed in a high official position at the International Medical Congress in Berlin. Rome, and Moscow. Sir William was appointed Consulting Surgeon to the Forces in South Africa on December 29th, and took up his duties at No. 9 General Hospital at the Mooi River. His zeal and inexhaustible passion for the world of surgery gave him pleasure and never was never a subject of complaint. He was always keen to display his marvellous handicraft as if he were still on the threshold of his career. In his private communications he expressed himself well satisfied with the results of his amputations and his ligation of vessels, but he was not quite so pleased with his achievements in surgery. The South African war has been responsible for the lives of so many brilliant and eminent men and unfortunately Sir William Stokes was no exception to this fact. He had succumbed to an attack of pleurisy in the base hospital at Pietermaritzburg on August 18th 1900.

#### 1.1.2.6 Harold Buhalts Boyd (1904 – 1981)

Often remembered as an excellent conversationalist, Harold Boyd was born in 1904 in Chattanooga, Tennessee, the only child of Seventh Day Adventist missionary parents. As a child, Boyd spent a great deal of his time helping his parents with hands-on farming work and carpentry, tasks which undeniably contributed to the early development of strength and discipline, endurance, manual dexterity and precision, skills which were undoubtedly essential tools that allowed him to pursue his later career aspirations.<sup>(43)</sup>



After attending Emmanuel Missionary College in Berrien Springs, Michigan, he acquired a place to study Medicine in the College of Medical Evangelists, now known as Loma Linda University, from which he graduated in 1932, marking the start of an extremely distinguished career in the world of medicine and surgery.<sup>(43)</sup>

He started his internship in the same year at Los Angeles County Hospital and subsequently successfully completed his Surgical Residency in Kern County Hospital in 1934. His qualities as a scholar were evident early on and earned him a place as an Orthopaedic Resident at the very prestigious Campbell Clinic, Memphis Tennessee, which he completed in 1936<sup>(43)</sup>.

Boyd's clinical acumen and self-discipline led to his early professional rise, allowing him to start his orthopaedic career at the age of just 28 years old at the White Memorial Hospital in Los Angeles, California, where he remained for 2 years before being appointed at Campbell Clinic in 1938, when many centres were only just beginning to gain experience with the use of the Smith-Petersen nail for femoral neck fractures<sup>(43, 44)</sup>. It was simply anticipated that such shrewdness in the clinical and practical field would be accompanied by an equal academic ability. His early studies with Campbell and Speed were amongst the first to report on the high incidence of non-union and avascular necrosis of the femoral head, associated with this particular procedure. Boyd also pioneered work on the use isotope scanning of the femoral head in the determination of the vascular status of the femoral head at the time of the injury, which subsequently helped form the basis of understanding of the pathology of avascular necrosis. In addition, he has also published a classification system for femoral trochanteric fractures which to this day, remains useful in clinical practice<sup>(43)</sup>.

Boyd evidently had a keen interest in research and was a firm believer in the fusion of laboratory as well as clinical research. One particular area which always attracted his

attention was congenital pseudarthrosis of the tibia, although some of his original contributions involved other areas such as the concept of dual-onlay bone grafting for non-union, trochanteric fractures, and fractures and dislocations of the shoulder.

During his medical school years, he had spent a year in sanatoriums due to pulmonary tuberculosis and was ineligible for military service during World War II. It is potentially during this time that he had managed to develop not only his lifelong reading habits, but also extensive experience in dealing with trauma, and in particular, elbow injuries in the paediatric patient. Furthermore, his manipulation and reduction techniques as well as surgical skills in supracondylar humeral fractures in children were revered and often emulated. Dr Boyd was a strong advocate of open reduction, internal fixation for such injuries, to achieve better clinical outcomes.

Recurrent shoulder dislocation is another condition that Boyd always found intriguing. He had strong preference for du Toit South-African technique of stapling the labrum as well as the capsule, as this method allowed for early mobilisation without restrictions. Boyd optimised the technique by employing the use of barbed as opposed to smooth staples in order to avoid staple migration. He was also the first surgeon to describe a novel procedure in the translocation of the biceps muscle proximal tendon origin around the humerus, under the deltoid and to the back of the shoulder, for recurrent posterior dislocations. In addition, he also described a new anatomical approach used to expose the radial head and neck, along with the proximal end of the ulna<sup>(43, 44)</sup>.

As is true for most Master Surgeons, Boyd was an outstanding anatomist with a mode of thinking that was cross-sectional as opposed to two-dimensional, and this was not only reflected in his practice, but also in his mind-set. This is best reflected by the numerous timeless examples of his unique approach, one being the Boyd hip disarticulation<sup>(45)</sup>. In developing his technique, Boyd attempted to improve previous approaches by minimizing blood loss by transecting muscles at either their origin or insertion, these areas being relatively avascular. The resultant stump was well padded and provided, making it an excellent weight-bearing surface for prosthetic use. The technique still has a place in today's clinical practice particularly in the field of orthopaedic oncology<sup>(46)</sup>.

Another procedure which has put Boyd's name in history, was the Boyd foot amputation. This particular form of amputation usually involved diabetic patients or patients with peripheral vascular disease. Although rare, and less accepted than a Syme's amputation due to its dependence on the osseous calcaneotibial union<sup>(47)</sup>, Boyd's procedure has been shown to be superior to Syme's for numerous reasons. The preservation of the plantar aspect of the

calcaneus with an intact heel pad makes the procedure a biomechanically more correct construct as the heel pad is naturally designed to bear the full body weight. It also rendered the use of an artificial limb unnecessary<sup>(48)</sup>. Boyd's amputation has also been shown to be superior to Syme's when dealing with longitudinal deficiencies of the tibia, a better choice of amputation when dealing with a completely insensate foot<sup>(48)</sup>. Additional studies have also showed that a Boyd amputation is far superior from other similar approaches in the paediatric population, as it allows for a more stable weight-bearing surface and a better proprioception of the prosthesis<sup>(49, 50)</sup>.

His thirst for innovation and progress was reflected by his ability to evaluate and select clinical applications such as compression plates for the fixation of forearm fractures, total hip replacements and the electrical stimulation of bone for non-union.

Boyd contributed in an excess of 60 articles and six editions of Campbell's Operative Orthopaedics, with his academic interests extending well into his retirement. He was a proud contributor to the American Academic of Orthopaedic Surgeons. One of the many contributions to both the Clinic as well as the Academy came in 1938, during a meeting in Memphis, Tennessee. Dr Smith-Petersen had presented a series on cup arthroplasties of the hip. Willis Campbell, was inspired by this idea which he later on extrapolated through asking Harold Boyd to fashion an implant suitable for the knee, making him, according to Dr Lee Riley, the very first Orthopaedic Surgeon to perform a total knee arthroplasty.

As a surgeon, Boyd had no peer. As a physician he was outstanding. His knowledge of medicine and anatomy, coupled with his innate ability to evaluate people objectively, his passion for travel and photography have not only earned him both national and international respect and a vast practice, but also a chair as Head Professor of Orthopaedics at the University of Tennessee. He was truly a surgeon's surgeon, an excellent conversationalist and a sought-after lecturer.

Dr Harold Boyd died in retirement in Oceanside, California, on May 29, 1981.

#### 1.1.2.7 Ernest M. Burgess (1911 – 2000)

Ernest M. Burgess was born in Roosevelt, Utah on October 29, 1911. Throughout his childhood, he was captivated by the medicine practiced by his aunt, whose work as a rural doctor had a major impact on his future in medicine.



After attending Duchesne County High School in Utah, Ernest Burgess attended the University of Utah and received his BA degree in 1932. In 1937, he earned his MD from Columbia University College of Physicians and Surgeons in New York City and completed his internship at the Swedish Hospital and the Children's Orthopaedic Hospital in Seattle, Washington in 1938. His residency was completed in 1941 at the Hospital for Special Surgery at Cornell University in New York <sup>(51, 52)</sup>.

Dr Burgess' tour of duty with the Army as an orthopaedic surgeon during World War II was the stepping-stone that led to his first complex and ultimately long involvement with amputee care. As the Chief of Surgery at the Tripler Hospital in Honolulu in 1944, Dr Burgess came across an inferior quality of amputation surgery, often characterised by impaired wound healing, ill-fitting prostheses, and limited post-operative patient mobility <sup>(52)</sup>. These observations inspired Burgess' development of improved surgical techniques, better-fitting prostheses and other mobility aids, and computer-aided implementation, still used worldwide today. Upon completion of his Army tour of duty in 1946, Burgess began consulting for the Veterans Association (VA), also acting as a civilian consultant to the Army. In 1948, Burgess began a private orthopaedic surgery practice in Seattle, Washington <sup>(52)</sup>.

During the following 30 years, he pioneered total hip replacement surgery, and with contributions from his Assistant Investigator Robert L. Romano, they introduced the long posterior flap amputation technique. This procedure markedly enhanced circulation in the residuum, greatly improving prosthetic fitting. As a result of limb muscle stabilization during the operation, amputees enjoyed a level of activity they didn't imagine possible after the injury <sup>(52)</sup>.

In 1964, Burgess attended an international conference on prosthetics medicine in Copenhagen. Robert Stewart, VA's Chief of Prosthetics and Sensory Aids, inspired by a new management system of surgical amputations discussed at the conference, encouraged the

establishment of Prosthetics Research Study (PRS), a multidisciplinary research team. It was at the request of the VA, and in collaboration with the Rehabilitation Research and Development Service that Burgess founded PRS in 1964. VA- funded PRS is one of the most outstanding post-operative care centres in the world. Burgess's efforts were well known for their tenacity in the development of post-surgical amputee management and consequently had a dramatic impact in the rehabilitation of amputees. His leadership as Director and Principal Investigator at PRS pioneered various innovative surgical techniques and devices, and made artificial limbs more functional, effective, comfortable, life-like and affordable for everyone <sup>(52)</sup>.

The Immediate Post-Operative Prosthetic (IPOP) technique developed at PRS radically changed the prospect any patient facing amputation. IPOP, in which the amputee was fitted with a prosthesis immediately after surgery, encouraged improved and fast wound healing and tissue repair, and diminished postsurgical pain. The completion of the IPOP method facilitated rehabilitation in less time, allowing the amputee to have an earlier return to ambulation.

In 1984, PRS, once again under the leadership and innovative ideas of Burgess, produced the world famous Seattle Foot <sup>(53)</sup>. This life-like prosthesis is constructed of lightweight and pliable materials, giving amputees the ability to participate in a full physical life, not hindered by bulky wheelchairs, residual limb discomfort, or limited mobility <sup>(54)</sup>. PRS also developed The VA/Seattle Ankle, which remains in use to this day by over 150,000 amputees across the globe <sup>(54, 55)</sup>.

Relating to Dr Burgess' meticulous development of this prosthesis, the psychological aspects of a patient's self-motivation in adjusting to a new form of mobility had a direct impact on the overall success of the VA/Seattle Limb System. Peripheral vascular disease and diabetes account for at least 75% - 85% of all major amputations performed in the United States Burgess conducted diabetic footwear studies at PRS <sup>(56)</sup>. Diabetic foot ulcers, which sometimes go unnoticed due to foot insensitivity, are a significant risk factor for amputation. PRS conducts further research to determine the long-term effectiveness of unique footwear and custom insoles to prevent foot ulcers in the population at highest risk for diabetic reulceration and amputation.

Dr Burgess' application of the Computer Aided Design and Manufacture (CAD-CAM), one of the first systems created for prosthetics, resulted in the Automated Fabrication of Mobility Aids(AFMA). This was developed in alliance with the New York VAMC and Northwestern

University/Lakeside VAMC. This system Enables the production of high quality, low cost, and lightweight limbs in less than 4 hours. AFMA systems have improved accuracy, efficacy, and consistency in prosthesis design and production. This system is also responsible for the VA/DAV/PRS Knee development.

Seattle ShapeMaker, shape-sensing software, was developed to implement computers to support AFMA, and is used in over 150 centres worldwide. Training courses were developed and initiated for the technology transfer of AFMA, as well as training for the VA clinical staff in new PRS techniques. This has been the direct result of the continuous efforts of Burgess who transformed prosthetics medicine and revamped the prosthetic care services in 37 VA Medical Center sites in the United States.

In 1983, he proved yet again his humanitarian nature, through founding the Prosthetics Outreach Foundation (POF), a non-profit medical service which to this day provides high quality prostheses to amputees around the world. POF supports communities by establishing clinics to produce and fit amputees with prostheses manufactured with locally produced materials in countries such as the Philippines and Nicaragua.

In 1988, following an appeal from the Vietnam veterans and survivors of the war, Burgess set up initially a demonstration clinic to help victims within the Vietnamese population who constituted 20% of the total number of the Vietnam War amputee population. His efforts were commendable and in 1991, in cooperation with the Vietnamese Government and Seattle POF, he set up a dedicated medical clinic based in Hanoi, offering services to over 10,000 patients.

With the enduring legacy of warfare across the globe, his contribution expanded to Europe helping victims in Albania and Kosovo and remained active even following his retirement as a Director of Prosthetics Research Study.

Burgess's contributions have received merits and awards from national and international organisations. He held a chair as a Clinical Professor of Orthopaedic Surgery at the University of Washington. He was an extremely active academic with contributions to classic text books, and clinical journals on prosthetic and rehabilitation medicine for over 45 years <sup>(51)</sup>.

## ***Section 1.2      Epidemiology of Lower Limb Amputation***

Despite advances in limb salvage and vascular surgery in general over the last 20 years, LLA remains a significant socio-economic and health problem. With the army having endured major expeditions abroad, the rapid emergence of amputees in the form of iconic sports figures and the recent attention diabetes has received on public television, amputation as a condition simply indicates the vast variation in terms of origin and causality.

It has become the focus of renewed interest by the medical profession, and political bodies with new initiatives such as ‘Putting Feet First’ in the UK and international meetings with a lower limb salvage focus being launched in an attempt to raise awareness and reduce the incidence of amputation.

### ***1.2.1      The Global and Ethnicity Picture***

#### **Peripheral Vascular Disease and diabetes**

Global incidence in LLA has been previously reported by Ebscov et al. to occur between 3.6 - 68.4 per 100,000 in the general population <sup>(24)</sup>. The heterogeneity and variation that characterises the populations included and the study methodologies, makes international rate comparison and establishment of a trend over time, a difficult process. One particular challenge encountered was that studies collectively report on rates without a clear distinction of the amputation level, nor indications. The indications for performing a major limb amputation are very clear and often follow either a failure to revascularise the limb, or, revascularisation not being a viable option due to extensive tissue loss or a patient being a poor surgical candidate. A minor amputation on the other hand, is frequently employed as an adjunct to limb revascularisation, in order to aid the healing process and promote limb salvage. Such studies can be of debatable value in painting the true picture of the condition and therefore serve little towards guiding clinical practice.

Therefore, in order to gain a true understanding of the impact this disease has on the population, and its true incidence and prevalence, it is important to consider it in different contexts; the presence or absence of diabetes and then the level of amputation. Once these clear distinctions have been made, other adjustments and standardisation can follow on the remaining risk factors, prior to establishing the true trends.

With an age of nearly 20 years being the most significant limitation, the GLEA study<sup>(57)</sup> remains the largest well-designed global retrospective study which uses age and gender adjusted data to present the trends in LLAs from 10 centres across 6 different countries; USA, UK, Spain, Italy, Taiwan and Japan. Lower extremity amputations were divided into major and minor amputations, with major amputations defined as any surgery from the transmetatarsal joints and any procedure occurring through and proximal to the joint.

When looking at major LLAs, the most striking result from the study was the massive variation across regions worldwide with differences reported at almost a tenfold from one another. Spain and Japan reporting the lowest incidences at 2.8 and 3.8 per 100,000 men and 0.5 and 1.2 per 100,000 women respectively. The reduced incidence of LLAs in Spain was also demonstrated in a separate population-based study by Calle-Pascual et al. in September 2001 <sup>(58)</sup>. The highest amputation rates are reported in the USA with incidences of 58.7 per 100,000 men and 32.2 per 100,000 women respectively <sup>(57)</sup> with a staggering 1.7 million people living with a limb loss <sup>(59)</sup> across the country. Similar trends with USA leading in terms of amputation rates have been reported by other studies <sup>(59-61)</sup>.

Despite the variation that exists amongst nations, there are distinct patterns the amputation rates tend to display. The Danish Amputation Register, established since 1972, is one such example that can be used to demonstrate these patterns.

Epidemiological studies published from data from this register indicated a steady rise in the incidence of LLAs until the mid-1980s, when rates began to plateau <sup>(62, 63)</sup>. Studies from Sweden, Finland, UK and Netherlands published suggested a similar picture <sup>(64-68)</sup>. This can be explained not only by the increasing age in populations, but also, the resultant increased incidence of peripheral vascular disease within the population. Data from the GLEA Group, as well as from Moxey et al. suggest that peripheral vascular disease has been the leading cause of major LLAs in up to 93% of the cases, with diabetes and soft tissue infection leading to ulceration in up to 90% and 88% respectively <sup>(61, 69)</sup>. The mean age for an intrahospital amputation was found to be 73 in the male patients and 76 in the female patients with a significant proportion of the total nosocomial amputations as a result of vascular disease, diabetes or infection performed in the 60-80 year group in over 30% of the cases <sup>(24, 70, 71)</sup>.

Although peripheral vascular disease has been shown to be the leading cause of major LLA, with diabetes and soft tissue infection often incorporated as associated comorbidities, it is important to consider diabetes as a separate entity. In USA, 82% of all vascular related major LLAs are associated with diabetes, and patients with the condition, have a 30 times lifetime greater risk of having an amputation compared to those who don't <sup>(72)</sup>. In a recent study by Jorgensen et al., Type I diabetes has been shown to be the leading cause of major LLAs in younger age groups, more specifically around the age of 60. The study also demonstrated that the longer the condition was present, the higher was the amputation incidence, the amputation rates doubling when the condition was present for 15 years or more <sup>(73)</sup>. Other diabetes related risk factors included poor glycaemic control, treatment incorporating insulin and a higher systolic blood pressure <sup>(73, 74)</sup>. Of significant note is the fact that in all the major amputation patterns noted, the rates were significantly higher in men as opposed to women, with reported amputation risks increasing by almost a two-fold <sup>(24)</sup>.

With the Danish pioneering the introduction of amputation registers, vascular surgery reaching maturity in the availability and performance of revascularisation procedures, and the increasing public education on risk factor modification, major amputation rates began to show a significant reduction in rates in the mid-1980s with multiple studies reporting significant decline across the globe in the mid-1990s, despite the increasing population age and rise in the diabetic population. Disparity was once again noted amongst countries. Vamos et al. reported a reduction 1.3 per 100,000 in 1996 to 0.7 per 100,000 in 2004 in Type

I Diabetic patients <sup>(75)</sup> although variation existed in the rates reported across the UK, depending on the Strategic Health Authorities <sup>(76)</sup>. Fosse et al. published the first national estimate of all LLAs in France with rates of 13 per 100,000 in non-diabetic patients to 158 per 100,000 in diabetics <sup>(77)</sup>. Some European countries suggested no changes in amputation rates at all, whilst others reported a rise in minor amputations, probably related to the increased availability of podiatry services, and the use of the procedure as an adjunct during or following revascularisation surgery to promote limb salvage <sup>(78, 79)</sup>. In the USA, a study reported a 5% drop in minor and major amputations per year between 1989 and 1998 diabetes related amputations remained unchanged <sup>(80)</sup>. Similar discrepancies exist across Asia and Australasia, with Australia and Japan reporting reductions similar to European populations <sup>(81, 82)</sup>. Taiwan and Eastern Asia showed worsening numbers with incidence rates reported as 18.1 and 100 per 100,000 respectively <sup>(57, 83)</sup>. Table 2 summarises studies which looked at change in the incidence rates of amputations over time.

The possibility exists that lifestyle risk factor modification such as smoking cessation, weight loss and change in dietary and exercise habits for better management of diabetes, hypertension and hyperlipidaemia might have favourably affected the epidemiology of peripheral vascular disease and diabetes, and thus, amputations in general, there is no evidence to substantiate such claims.

With the emergence of the St' Vincent declaration in October 1989<sup>(84)</sup>, an initiative which came about in response to Type II Diabetes reaching pandemic status, WHO and IDF collaborated to initiate and elaborate comprehensive programmes for detection and control of diabetes and of its complications with self-care and community support as major components<sup>(84)</sup>.

This international initiative aimed at raising awareness in the population and among health care professionals of the present opportunities and the future needs for prevention of the complications of diabetes and of diabetes itself. They set 5-year targets which involved the organisation, training and teaching in diabetes management and care for people of all ages with diabetes for their families, friends and working associates and for the health care team<sup>(84)</sup>.

They also reinforced existing centres of excellence in diabetes care, education and research, created new centres where the need and potential existed, and removed hindrances to the fullest possible integration of the diabetic citizen into society.

They promoted management of diabetic patients in the multidisciplinary setting, and saw to the implementation of effective measures for the prevention of costly complications such as:

- Reduce new blindness due to diabetes by one third or more.
- Reduce numbers of people entering end-stage diabetic renal failure by at least one third.
- Reduce by one half the rate of limb amputations for diabetic gangrene.
- Cut morbidity and mortality from coronary heart disease in the diabetic by vigorous programmes of risk factor reduction.
- Achieve pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman.

Almost all studies summarised in table 1 on pg.57, attribute the decline in the numbers of LLAs to the contribution of the diabetic foot teams, their readily available accessibility and multidisciplinary nature. The positive impact of such services has been reported in recent studies; however, although these services have been in place for several decades, the impact on amputation rates was not proportionately lower. <sup>(73, 75, 85-88)</sup>.

The impact of previous attempts at lower limb revascularisation is disputed <sup>(89)</sup>. There is no doubt that the numbers of revascularisation procedures performed for critical limb ischaemia have exponentially increased over the last years, and one might have expected for this to be linked to a reduction in the need for LLAs <sup>(67)</sup>. This has indeed been reported in several series published over the last few years. There is however a strong possibility for these studies to be subject to selection bias as the case mix, referral pathways, populations and hypotheses would be of variable nature. It wasn't until the 1980s that population studies began to support the hypothesis that increased rates of revascularisation attempts, were associated with lower amputation rates <sup>(63, 67, 89, 90)</sup>. The delay between the increased rates of revascularisation in conjunction with the reduction in amputation rates may reflect a time lag phenomenon associated with arterial reconstruction in patients with earlier stages of peripheral vascular disease. Progression of the disease may be prevented or postponed by intervention at an earlier stage, thus inevitably reducing the requirement for amputation at that point in time. Infrapopliteal surgical reconstructions in patients with diffuse disease, particularly diabetics previously considered only for primary amputations, specifically seem to be associated with significant reductions in the rates of major LLAs, although, minor amputations might have been used as procedural adjuncts <sup>(63)</sup>.

Another reason for the global and sometimes national variation which exists in the incidence of LLAs is ethnicity linked to geographical and socio-economic factors. In Leicestershire for example, amputation incidence in Asians was noted to be significantly lower when

compared to White Caucasians, both in the diabetic as well as the non-diabetic population subsets (3.4 vs 14.2 per 100,000 and 0.4 vs 1.5 per 100,000 respectively) <sup>(91)</sup>. This was noted despite the higher rate of other vascular-related complications such as coronary artery and renal disease <sup>(91)</sup>. When considering the Afro-Caribbean minority in the UK, in the diabetic subset, the incidence in LLA has also been noted to be significantly lower when compared to the European population ( 147 vs 219 per 100,000) <sup>(92)</sup>. Interestingly, African-Americans continue to lead in rates of LLAs compared to White Americans, but not White British, again demonstrating the complex perplexing effects ethnicity can exert in these rates.

There are several American studies which demonstrate that LLAs are more likely to occur in African-Americans than in Caucasians (45 vs. 20%) <sup>(93, 94)</sup>, whilst Afro-Caribbean and Hispanic ethnicities constitute independent risk factors when considering patients with peripheral vascular disease <sup>(95)</sup>. Collins et al. also reported that although diabetes and hypertension are higher in incidence amongst these ethnic minorities, their impact on these subsets does not account for the increased rates of LLAs, meaning that ethnicity itself is indeed an independent risk factor <sup>(95)</sup>. Strongly linked to ethnicity, are social, economic and geographical factors which in turn contribute to the variation that exists. Such factors may prevent members of a population in accessing healthcare resources such as the diabetes multidisciplinary services, as well as vascular surgery centres, consequently not having access to potential limb-salvaging revascularisation interventions <sup>(96)</sup>. Lower education status, smoking, low income, non-White ethnic background and lack of commercial insurance, have all been shown to be predictive risk factors for LLA.

It has been suggested that indeed some of these factors are more prevalent in specific areas in the world such as the USA, where access to appropriate services is significantly affected by ethnic and social group status, low income and as a result, lack of medical insurance cover <sup>(97)</sup>. Black patients for example, were more likely to suffer an above knee amputation compared with White patients (60% vs. 53%,  $P < 0.001$ ), whilst Afro-Caribbeans undergoing revascularisation were less likely to benefit from endovascular interventions (46 vs. 51%,  $P < 0.001$ ) <sup>(93)</sup>.

Hindrance in access to healthcare alone however cannot be solely attributed to such differences. One such example is that of Native and African Americans, suffering with diabetes in Veterans' Health Hospitals, where all patients had similar access to various healthcare services. They were in fact found to have a higher relative risk (RR) of LLAs when compared to the Caucasian subset (RR 1.74 vs. 1.41 respectively), whilst Asian Americans appeared to be relatively protected (RR 0.31) <sup>(98)</sup>. To add to this, Regenbogen et

al. suggested that whilst Afro-Caribbeans were more likely to have a LLA in a low-volume hospital, performed by non-specialists, the odds of having an amputation in the first place remained 1.7 times higher than in Whites, after having adjusted for hospital type, surgeon performance, and other comorbidities <sup>(93)</sup>. Looking at the same study, tertiary referral vascular centres still reported higher LLA rates in the Afro-Caribbean compared to the general White population (7% vs. 4%,  $P < 0.001$ ), implying that factors other than socio-economic deprivation and geographical access contribute to LLA rates <sup>(93)</sup>.

### **Traumatic and Other amputation causes**

Amputations secondary to other causes such as trauma, neoplasia, congenital deformities and upper limb amputations are not as prevalent as amputations occurring due to divascularity, diabetes and soft tissue infections.

In the period 1980-90, the incidence of traumatic amputations in Denmark was reported at 1.4 per 100,000 per year. The significant difference, apart from incidence rates, lies in the age bracket to which the majority of such amputations occur <sup>(24)</sup>. The mean age was found to be 49.4 years, dropping in males at 44.8 years and 58.8 years in females <sup>(24)</sup>. In the same population, the ratio of male to female patients was found to be 2:1.

In the UK, traumatic amputations, were mainly the case in the younger patients with 71% occurring in those < 55 years of age and only 8% in those over 75 years <sup>(99, 100)</sup>. Trauma in general has been previously reported to account for 5% of LLAs performed over a year basis, although, with the last 10 years at war, this proportion may not only have increased, but also the mean age might have reduced <sup>(101)</sup>. In a small sample of military-related amputees, the average age at the time of the injury was 25.9 years <sup>(102)</sup>, and this has remained more or less unchanged with a recent study reporting on a group of patients of mean age 29 years <sup>(103, 104)</sup>. From 2003 – 2014, 265 casualties sustained 415 amputations, of which the commonest type was transfemoral amputation accounting for 36.8% of the casualties (153 cases), with the proportion dropping to 34.4% (143 cases) for transtibial amputations <sup>(103)</sup>. These values were slightly different from the data produced by the UK Ministry of defence for the time period 1997-98, where transtibial amputations were the commonest (50.6%) followed by transfemoral which only accounted 8.8%. These patterns were also apparent in USA, with transfemoral amputations accounting for 34.5% of the amputations and transtibial for 41.8% of the total amputations performed on military personnel. Although only a small proportion in general, amputations in a younger age group are associated with significant socioeconomic and psychological repercussions <sup>(103, 104)</sup>. Upper limb amputations are a

considerably rarer event and in a review of the UK Amputee database in 2003/04, trauma accounted for 54% of the causes, with mechanical trauma being the most common, occurring mostly in the 16-54 age group <sup>(100)</sup>. Trauma in general as a cause of amputation seems to be more common in developing countries <sup>(67)</sup>.

In the UK, Neoplasia constituted 14% of all referrals and was the main referral reason in the older age groups. Amputations in children fortunately only accounted for <1% and the commonest cause was Amelia. Denmark exhibited a similar picture, with 30% of such amputations occurring in the 70-79 year old group.

### **Short and Long Term Mortality**

Lower extremity amputations are performed commonly as a consequence of advanced, irretrievable peripheral vascular disease. It is an undisputed fact that patients belonging to this hospital population subgroup often have other significant co morbidities such as hypertension, tobacco use, ischaemic heart disease and diabetes, all of which constitute independent surgical risk factors for perioperative mortality <sup>(105)</sup>.

In the United Kingdom, in-hospital mortality rates have been reported at 9-17% <sup>(105)</sup> and in the USA at 10% <sup>(106)</sup>. Looking at other western populations, perioperative mortality was interestingly enough higher, and reported at 19.1-25.4%, with values more recently rising up to 30% in the first 30 days following surgery <sup>(107)</sup>.

A recent study by Scott et al. aimed at identifying patient and procedural risk factors associated with increasing mortality in patients undergoing amputation. The overall 30-day mortality following a major LLA was found to be 12.% <sup>(105)</sup>, which was consistent with what has been previously published <sup>(76)</sup>. Worse 30-day mortality was associated with worse physical status (ASA grade  $\geq$  4) and older age (age > 74 years). One year mortality was further associated with increasing age, change in ASA grade, severe renal disease and surgery performed out of hours. These findings were unsurprising and are thought to be related to the severity of the co-existing diabetes. Tseng et al. as well as Ebskov, have both identified the diabetic patient cohort to be at significantly higher risk than other amputees, and this risk increased further in those who continued to smoke <sup>(108)</sup>.

Another concept which has been previously described as a potential cause of increased mortality in patients undergoing LLAs is surgery performed outside of normal working hours. Scott et al. reported a median survival of 39 months following surgery in patients undergoing an LLA within working hours (08:00-16:00) as defined for their institution, with

the value dropping to 11 months for those being operated on outside normal working hours. There are numerous reasons why this might be the case. These merely reflect the severity of the condition at the time of presentation, as well as the urgency of the surgery, the involvement of less experienced staff (surgeons and anaesthetists) or even, a greater number of comorbidities <sup>(105)</sup> . It may be argued that out-of-hours surgery increases the chances of the patient being looked after by less experienced staff. Surgeon and anaesthetist seniority has been the subject of debate when dealing with other patients' major vascular surgery such as those undergoing aneurysm repairs and was found to be a significant risk factor for mortality <sup>(109)</sup>, however, it has been disputed by Scott et al. <sup>(105)</sup>.

Despite the fact that clear guidance has been set out by NCEPOD in cooperation with VSGBI describing in detail the steps that should ideally be follow in the pre-, peri- and postoperative management of such patients, one must appreciate that the urgency and severity with which such patients commonly present, may carry significant clinical implications, typically ones that limit chances for a preoperative assessment of the extent outlined in the guidelines. The assessment of these patients by an expert anaesthetist and surgeon remains nonetheless of paramount importance in determining the true ASA grade and optimising the modifiable risk factors thus increasing survival.

Reference	Incidence per 100,000	Year of Study	Type of Amputation	Population	Country of Study
Moxey <sup>(76)</sup>	5.1	2003–2008	Major	Total population	England, UK
Eskelinen <sup>(110)</sup>	7.3	1999–2002	Major	At risk in total population	Helsinki
Eskelinen <sup>(110)</sup>	5.3	1999–2002	Major	No diabetes	Helsinki
Remes <sup>(111)</sup>	24.1	1998–2002	Major	Elderly total population	Turku, Finland
Johannesson <sup>(112)</sup>	195	1997–2006	Major	At risk	Sweden
Johannesson <sup>(112)</sup>	23	1997–2006	Major	No diabetes	Sweden
Rayman <sup>(113)</sup>	162	1997–2000	Major	At risk	Ipswich, UK
Rayman <sup>(113)</sup>	4.5	1997–2000	Major	Total population	Ipswich, UK
Calle-Pascual <sup>(58)</sup>	5.6	1997–1999	Major	Women at risk	Madrid, Spain
	12	1997–1999	Major	Men at risk	
Wrobel <sup>(97)</sup>	383	1996–1997	Major	At risk	Medicare, USA
Wrobel <sup>(97)</sup>	38	1996–1997	Major	No diabetes	Medicare, USA
GLEAS Group <sup>(57, 69)</sup>	58.7(men) 32.0(women)	1995–1997	Major	Total population	Navajo Indians, USA
	3.8(men) 1.2(women)	1995–1997	Major	Total population	Tochigi, Japan
	19.9(men) 10.2(women)	1995–1997	Major	Total population	Leeds, UK
	7.2(men) 4.3(women)	1995–1997	Major	Total population	Leicester, UK
	27.8(men) 8.4(women)	1995–1997	Major	Total population	Middlesbrough, UK
	20.2(men) 8.8(women)	1995–1997	Major	Total population	Newcastle, UK
	3.7(men) 0.5(women)	1995–1997	Major	Total population	Madrid, Spain
	34.9(men) 17.0(women)	1995–1997	Major	Total population	Montgomery, USA
	11.3(men) 8.3(women)	1995–1997	Major	Total population	Ilan, Taiwan
	9.6(men) 7.0(women)	1995–1997	Major	Total population	Vicenza, Italy
Witso <sup>(114)</sup>	4.4	1994–1997	Major	Total population	Trondheim, Norway
Rith-Najarian <sup>(115)</sup>	600	1994–1996	Major	At risk	Chippewa Indians
Morris <sup>(116)</sup>	248	1993–1994	Major	At risk	Scotland, UK
Morris <sup>(116)</sup>	14	1993–1994	Major	No diabetes	Scotland, UK
Huber <sup>(117)</sup>	50(African American), 25(white American)	1992–1995	Major		USA
Carmona <sup>(118)</sup>	34.7	1990–1999	Major	Female total population	Switzerland
Carmona <sup>(118)</sup>	68.4	1990–1999	Major	Male total population	Switzerland
Trautner <sup>(79)</sup>	230	1990–1991	Major	At risk	Germany
Trautner <sup>(79)</sup>	4.7	1990–1991	Major	Total population	Germany
Deerochanawong <sup>(119)</sup>	5.7	1989–1991	Major	Total population	Newcastle, UK
Lindholt <sup>(67)</sup>	30.9	1989–1990	Major	Total population	Denmark
	40.9	1986–1987	Major	Total population	Denmark
Gutteridge <sup>(120)</sup>	11.6	1983–87	Major	Total population	UK
Larsson <sup>(121)</sup>	3.6	1982–1993	Major	At risk in total population	Sweden
Larsson <sup>(121)</sup>	9.4	1982–1993	Major	At risk in total population	Sweden
Larsson <sup>(121)</sup>	3.6	1982–1993	Major	Total population	Sweden
Ebskov <sup>(71)</sup>	4.5	1982–1993	Major	Female total population	Denmark
Ebskov <sup>(71)</sup>	4.7	1982–1993	Major	Male total population	Denmark
Humphrey <sup>(122)</sup>	375	1945–1979	Major		Rochester, USA
Aragon-Sanchez <sup>(88)</sup>	176	2009	Major	At risk	Gran Canaria, Spain
Aragon-Sanchez <sup>(88)</sup>	11	2009	Major	No diabetes	Gran Canaria, Spain
Renzi <sup>(123)</sup>	15	2006	Major,	Total population	USA
Renzi <sup>(123)</sup>	23	2006	Major, male	Total population	USA
Vamos <sup>(75)</sup>	0.7	2005	Major	At risk in total population	England
Vamos <sup>(75)</sup>	2.7	2005	Major	At risk in total population	England
Vamos <sup>(75)</sup>	4.9	2005	Major	No diabetes	England, UK
Winell <sup>(124)</sup>	387	2002	Major	At risk	Finland
Canavan <sup>(125)</sup>	75	2000	Major	At risk in total population	Middlesbrough, UK
Canavan <sup>(125)</sup>	15.3	2000	Major	No diabetes	Middlesbrough, UK
Chen <sup>(83)</sup>	8.8	1997	Major	Total population	Taiwan
Vaccaro <sup>(126)</sup>	3.5	1996	Major	At risk in total population	Campania, Italy
Feinglass <sup>(90)</sup>	25	1996	Major		USA
Holstein <sup>(127)</sup>	2.1	1995	Major	At risk in total population	Copenhagen, Denmark
Holstein <sup>(127)</sup>	4.1	1995	Major	At risk in total population	Copenhagen, Denmark
Holstein <sup>(127)</sup>	6.9	1995	Major	Total population	Copenhagen, Denmark
Pohjolainen <sup>(68)</sup>	28	1995	Major		Finland
Pernot <sup>(128)</sup>	17.1	1994	Major	Total population	Limberg, Netherlands
	25	1990			
	32	1989			
Ebskov <sup>(63)</sup>	32	1983	Major		Denmark
Tunis <sup>(129)</sup>	28	1979	Major		USA

Table 1 Incidence of Major LLAs in Diabetic Patients

Reference	Baseline Incidence per 100,000	End Incidence per 100,000	Years	Type of amputation and population
Canavan <sup>(125)</sup>	310	75	1996–2000	Major, Middlesbrough, UK
	253	100	1996–2000	Minor, Middlesbrough, UK
Krishnan <sup>(130)</sup>	414	67	1995–2005	Major, Ipswich, UK
	118	93	1995–2005	Minor, Ipswich, UK
Larsson <sup>(131)</sup>	16	6.8	1982–2001	Major, Sweden
	4.7	6.5	1982–2001	Minor, Sweden
Calle-Pascual <sup>(58)</sup>	70.6	12.4	1989–1999	Major, Madrid, Spain
	15.3	5.6	1989–1999	Major, Madrid, Spain
	58.9	33.1	1989–1999	Minor, Madrid, Spain
	11.9	11.3	1989–1999	Minor, Madrid, Spain
van Houtum <sup>(132)</sup>	550	360	1991–2000	All LEA, Netherlands
Trautner <sup>(133)</sup>	549	428	1990–2005	All LEA, Germany
Vamos <sup>(75)</sup>	1.5	1.2	1996–2005	Minor, England, UK
	2.4	4.1	1996–2005	Minor, England, UK
	1.3	0.7	1996–2005	Major, England, UK
	2	2.7	1996–2005	Major, England, UK
Stiegler <sup>(78)</sup>	610	660	1990–1995	All LEA, Germany
Rayman <sup>(113)</sup>	228	108	1998–2000	Major, Ipswich, UK
Winell <sup>(124)</sup>	924	387	1988–2002	All LEA, Finland
Patout <sup>(134)</sup>	9600	2200	1990s	All LEA, Louisiana, USA
Birke <sup>(135)</sup>	1003	720	1998–1999	All LEA, Louisiana, USA
Ebskov <sup>(63)</sup>	4.5	2.7	1982–1993	Major, Denmark

*Table 2 Incidence of LLAs over time*

### 1.2.2 *Epidemiology of Lower Limb Amputation in the United Kingdom*

According to Limbless Association statistics 2006/07 and 2010/11, 5500-6000 LLAs are performed on a yearly basis in the UK alone <sup>(99, 100)</sup>. This has been confirmed by numerous studies published in the last decade <sup>(61, 76, 86)</sup>, and examining the most recent statistics, the number remains consistent according to a study by Ahmad et al produced in 2014 <sup>(1)</sup>.

Ischaemia constitutes the commonest prerequisite in all age groups, with over 90% of them being performed as a direct consequence of peripheral vascular disease. This implies that patients typically present with intermittent claudication of varying severity, with associated skin manifestations of ischaemia. The ratio of symptomatic to asymptomatic disease is up to one in three, with as many as 50% of the patients not seeking medical advice <sup>(136)</sup>. Within this group of dysvascular patients, 39% of vascular disease is caused by diabetes <sup>(99, 100)</sup>. There is a tendency for the number of amputations related to vascular disease to increase with age with 13% quoted incidence in patients less than 55 years of age jumping to a staggering 38% in those above the age of 75 <sup>(99)</sup>.

There have been two major studies over the last 5 years, both of which examined the LLA rates in the United Kingdom within similar time periods <sup>(1, 76)</sup>. With written permission from the authors, Table 3 and Table 4 on pages 60 and 61 with patient characteristics, type of amputation and numbers has been reproduced.

From examining the tables in the study by Ahmad et al (see Table 3, pg.60), one can appreciate that the yearly number of LLAs has remained fairly consistent over the last 12 years, and coincides with the increasing age of the population in England. With 68.5% of the amputee population being males with peak age around 70 years old, men have twice the risk when compared to women, in having not only a LLA but also a revascularisation procedure <sup>(1)</sup>. Consistency with other global trends is evident when looking at the remainder disease factors, with diabetes being the commonest (44%), with hypertension and coronary artery disease following at 39% and 23% respectively.

Risk factor	England	North	Midlands	South
Amputations (n)	25,312	8981	4969	11,358
Prevalence rate/100,000 (95% confidence interval)	26.3 (26.0–26.6)	31.7 (31.0–32.3)	26.0 (25.3–26.7)	23.1 (22.6–23.5)
Revascularisations (n)	136,215	51,784	23,163	61,268
Prevalence rate/100,000 (95% confidence interval)	141.6 (140.8–142.3)	182.1 (180.5–183.7)	121.3 (119.8–122.9)	124.9 (123.9–125.8)
Mean age (years)	70.6	70.4	70.4	70.8
Male %	68.5	69.9	69.4	67.1
Most deprived	28.6	42.2	30.8	17.6
Second most deprived	22.7	22.7	22.2	23.9
Third most deprived	19.7	15.6	19.4	23.2
Fourth most deprived	16.3	12.0	16.4	19.3
Least deprived	12.8	7.5	11.2	16.0
Diabetes (%)	43.7	40.8	44.0	45.8
Hypertension (%)	39.1	39.9	36.1	40.2
High cholesterol (%)	8.6	9.1	6.3	9.5
History of CHD (%)	22.9	26.8	20.0	21.0
History of stroke (%)	3.3	3.2	3.6	3.3
Smoker (%)	8.9	12.2	5.0	8.2

*Table 3 Number, Prevalence and proportional distribution of risk factors of lower limb amputees by region <sup>(1)</sup>*

Regionally, differences were also present, with rates of amputation and revascularisation

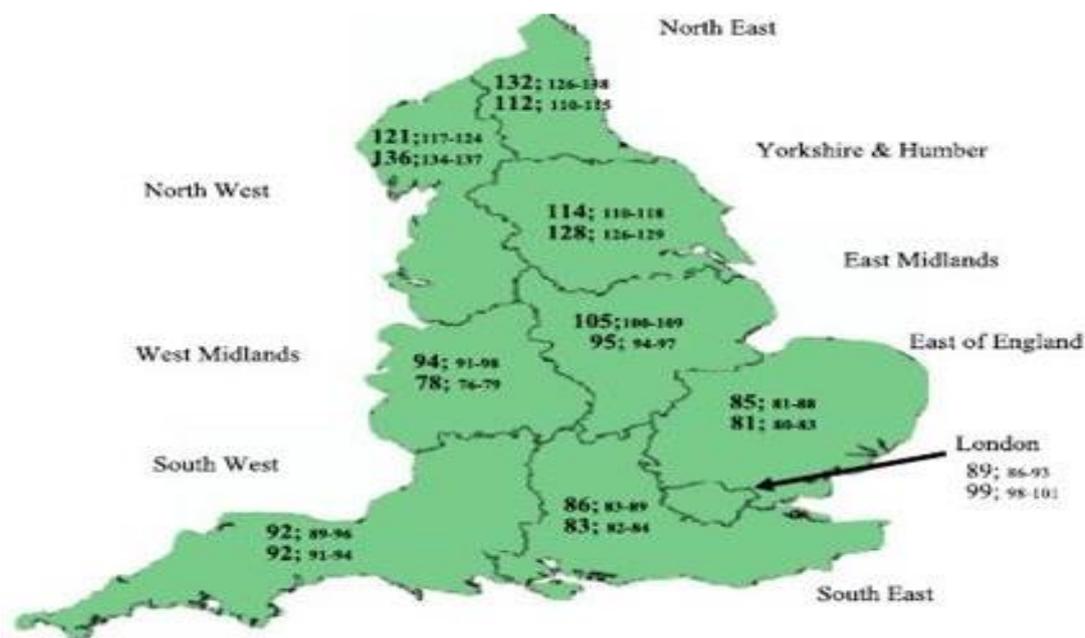


Figure 1 Proportional rates of amputation and revascularisation across English Regions <sup>(1)</sup>

		Amputation alone (n = 17 765)	Amputation with revascularisation (n = 7 543)	
		OR (95% CI)	OR (95% CI)	Sig.
Age group (years)	50–54 (standard)			
	55–59	0.79 (0.67–0.92)	1.27 (1.09–1.49)	<0.001
	60–64	0.67 (0.58–0.78)	1.49 (1.29–1.73)	<0.001
	65–69	0.66 (0.57–0.76)	1.52 (1.32–1.76)	<0.001
	70–74	0.65 (0.56–0.74)	1.55 (1.34–1.79)	<0.001
	75–79	0.71 (0.62–0.81)	1.42 (1.23–1.64)	<0.005
	80–84	0.81 (0.70–0.94)	1.24 (1.07–1.43)	<0.001
Gender	Male sex	0.94 (0.88–1.00)	1.07 (1.00–1.14)	0.051
Deprivation	Most deprived (standard)			
	Second most deprived	1.02 (0.95–1.11)	0.98 (0.90–1.06)	0.562
	Third most deprived	1.05 (0.97–1.14)	0.95 (0.87–1.04)	0.245
	Fourth most deprived	1.07 (0.97–1.16)	0.94 (0.86–1.03)	0.171
	Least deprived	0.93 (0.85–1.03)	1.07 (0.97–1.18)	0.153
Risk factors	Diabetes	1.34 (1.26–1.42)	0.75 (0.70–0.79)	<0.001
	Hypertension	0.68 (0.64–0.72)	1.48 (1.39–1.57)	<0.001
	High cholesterol	0.50 (0.46–0.52)	1.98 (1.81–2.17)	<0.001
	Coronary heart disease	0.70 (0.66–0.75)	1.43 (1.34–1.52)	<0.001
	Stroke	0.93 (0.80–1.08)	1.08 (0.93–1.25)	0.340
	Smoker	0.49 (0.49–0.53)	2.05 (1.88–2.23)	<0.001

Table 4 Odds ratio of having an amputation by risk factor<sup>(1)</sup>

being highest in the North and North-West regions of the country. The exact proportions as identified by Ahmad et al. can be seen in Figure 1<sup>(1)</sup>. Another interesting concept was the association between a previous revascularisation procedure and the prevalence of LLAs.

Table 4<sup>(1)</sup> demonstrates a pattern emerging, suggesting that the probability of having an LLA following a revascularisation procedure increases with increasing age, male gender and all other risk factors, apart from diabetes. As expected, when considering diabetics as a population subset, they were more likely to have an amputation without revascularisation and at a lower age than the rest of the population.

Contrary to previous studies which suggested that socio-economic status is associated with increased risk of amputation in other countries, Ahmad et al. suggest that social deprivation was not associated with an increased risk of amputation, whether revascularisation was attempted previously or not. Despite these results, it seems to be the case where when considering demographics (age, gender and social class) and the greater number of revascularisations in the North of England, one cannot explain the higher amputation rates in the North of England compared to the South, although disease factors themselves seem to reduce the incidence by more than 50%. It may however suggest a higher prevalence of independent disease risk factors either due to increasing age, failure of the population to comply with advice on lifestyle modification, etc. ultimately leading more major LLAs, although these possibilities have not been examined in this paper<sup>(1)</sup>.

## ***Section 1.3 Major Lower Limb Amputations: Indications, the anatomy and procedures.***

### ***1.3.1 Lower Limb Amputation Surgery***

#### **1.3.1.1 General Principles of Amputation Surgery**

Amputations have nowadays been widely accepted as an elective procedure, however, our main responsibility as surgeons is to explore, evaluate and rule out all possible alternatives prior to planning for the procedure itself. In planning the procedure itself, it is also important to always consider that the more proximal the loss, the greater is the negative impact on patient mobilisation and function.<sup>(24)</sup>

Amputation has been described by Murdoch as ‘a mutilation attended by not only physical and functional loss, but often severe psychological trauma with a body image altered and distorted’<sup>(24)</sup>. The essence of this statement implies that the role of the attending surgeon, is not limited to the performance of the operation and observation of wound healing during the postoperative stage, but also in the maintenance of a reasonably optimistic and assertive attitude during the pre-amputation assessment and the psychophysical rehabilitation of the patient under his or her care.

To this end, Murdoch has recommended a ‘team approach’ to amputation that encompasses integration of the amputation surgeon, physician, nurses, physical therapists, occupational therapists and prosthetists in the management of such patients.

Whilst the multidisciplinary approach to dealing with amputations has been popularised in the recent years, perhaps an aspect that has not been addressed to a similar extent, is one of psychological needs of the amputee. Amputations can occur due to a variety of reasons, primarily peripheral vascular disease and diabetes, but also, bone infections, soft tissue ulceration, tumours, and with the recent 12 years of world warfare, due to trauma. Although the psychological impact is undoubtedly immense in all of these patients, comprising primarily that of a disturbed body image. Regardless of the original cause, all patients seem to be affected by either depression or anxiety for up to 2 years following their surgery<sup>(137)</sup>. From multiple studies, one can see that whether the amputation was a result of a chronic condition such as diabetes or vascular disease, or a result of a significant battle injury, acceptance depends entirely on the individual’s resilience, internal and external locus of control, social support, socioeconomic status, educational level, societal attitudes towards

other disabled people and of course medical care. It is therefore of utmost importance that these needs are addressed in a manner tailored and optimised to each patient's needs.

Preoperative preparation of a patient for amputation has both physical and psychological considerations and in many areas, these may overlap. Frequently patients, requiring amputation suffer with multiple medical conditions which may include ischaemic heart disease, cerebrovascular disease, diabetes, hypertension, hypercholesterolaemia, chronic obstructive pulmonary disease, and frequently malnutrition<sup>(138)</sup>. It is essential that any such conditions are appropriately treated and stabilised prior to amputation and the involvement of an interested physician is often beneficial. Dietary assessment and, if required, supplementation by a nutritionist or dietician is also often advantageous if time permits it<sup>(139)</sup>. Malnutrition has been previously shown to be associated with poor wound healing. Amputee patients already have multiple comorbidities and adhere to lifestyles which place them at grave risk of developing SSIs which could delay healing significantly, therefore, dietitian involvement as early as possible is desirable.

Preoperative pain control is essential not only for the patients' physical and psychological wellbeing but also may help reduce post-operative flexion contractures and phantom pain.

The anaesthetist who will be responsible for the anaesthetic for amputation or the specialist hospital pain team generally best performs assessment and treatment of preoperative pain. Probably the most effective means of pre-operative pain control is by epidural infusion, which can then be supplemented as necessary by oral medication<sup>(140)</sup>. Preoperative involvement of the physiotherapist and occupational therapist responsible for postoperative rehabilitation is also advantageous to prepare the patient physically and psychologically for amputation<sup>(141)</sup>. A preoperative visit from a well rehabilitated amputee or a member of an amputee support group often helps allay patients' fear and reduce anxiety.

The exact choice of anaesthetic for the amputation surgery will vary according to the condition of the patient, available local skills and the preferences of the anaesthetist.

In general terms, however, it is probably preferable to do major amputations under spinal anaesthesia, which ideally should be sited 24–48 hours preoperatively<sup>(140)</sup>. Prophylactic antibiotics should be given immediately prior to surgery and continued post operatively according to unit protocol. Once the patient is ready for surgery, the planned skin incisions should be marked with an appropriate pen. In patients undergoing amputation for peripheral vascular disease, historically, a tourniquet should virtually never be used but may be useful in amputations performed for trauma or tumour, although this has recently been disputed<sup>(142)</sup>;

tourniquet use has been found to be beneficial in reducing haemorrhage and thus the need for subsequent transfusions.

Gentle tissue handling is by far the most important technical principal of successful amputation surgery. Minimal manipulation of the tissues with instruments is recommended and where possible the use of only fingers to manoeuvre skin flaps is encouraged. It is essential to understand that the blood supply to the skin of the lower leg is dependent upon the integrity of the vascular plexus immediately superficial to the deep fascia. This fascia, therefore, must be protected and treated as one with the skin, especially in trans-tibial amputations.

Mass ligation of neurovascular bundles should be avoided and the artery and veins should be ligated separately to avoid potential arteriovenous shunts<sup>(143)</sup>. Nerves should be dissected from the bundle, drawn down under tension, and transected. Terminal neuromas form at the end of every cut nerve, thus it is important to try to keep the ends of transected nerves away from areas of weight bearing or sites of compression or scar formation. Specific attention is important when dealing with the divided bone. Periosteal elevation should only be minimally performed and restricted to a few millimetres in distance above the level of transection to avoid damage to nutrient vessels. If possible, a cuff of periosteum can be dissected off below the intended level of amputation and used to cover the bony stump before coverage with soft tissues.

### 1.3.1.2 Indications for Amputation Surgery

#### **Amputation in Peripheral Vascular Disease**

Primary amputation, is defined as amputation of an ischaemic limb without attempted antecedent revascularisation, and is indicated in cases of advanced distal ischaemia with uncontrollable pain or infection in the specific settings of:

- ◇ unreconstructable occlusive arterial disease
- ◇ necrosis of significant areas of weight bearing portion of the foot
- ◇ fixed, unremediable flexion contracture of the leg
- ◇ very limited life expectancy due to comorbid condition.

Secondary amputation, or amputation following attempted revascularisation, is indicated when revascularisation has failed and further revascularisation options are no longer available. This is commonly due to disease progression of atherosclerosis.

Less commonly, secondary amputation may also be indicated when there is unremitting deterioration of a limb (e.g. due to progressive sepsis) despite a patent reconstruction. The effect of previous reconstructive surgery on amputation level remains to this date a topic of debate. It has been stipulated that secondary amputations are performed at a higher level than primary, whilst other authors state no difference in the eventual level between the two main classes <sup>(144, 145)</sup>. From a series in our own institution, we concluded that patients who had undergone a previous revascularisation procedure, were at higher risk of requiring revision surgery of a type, either at the same or more proximal level <sup>(146)</sup>.

Generally, the indications for amputation are relatively clear. On occasion, however, the suitability of amputation is unclear, and in particular, two principal areas of difficult decision making are frequently encountered. Firstly, the choice between amputation or reconstruction. If the patient is sufficiently fit to survive revascularisation and a previously useful limb is salvageable, then every effort should be made to revascularise the limb. Purist surgeons would argue that no limb should be amputated without the patient being offered angiography and the chance of reconstruction, and following angiography amputation should only be performed if two vascular specialists agree reconstruction is not possible.

The increasing life expectancy of the population however has become the cause of major dilemma for the vascular surgeon, who is nowadays often faced with an elderly, medically unfit patient with a borderline arterial tree. In such cases, personal audit and performance is essential. The surgeons own experience and record of success in this time consuming and technically demanding area are crucial in this decision making process. If a surgeon thinks reconstruction is advisable and possible but beyond his own technical ability, referral to a specialist unit is recommended.

A second area of difficulty that commonly arises, is when a very elderly or debilitated patient, in whom arterial reconstruction is impossible or inappropriate, presents with a critically ischaemic leg. In such scenarios, amputation or conservative, symptomatic treatment are the choices in management. Pain control can usually be achieved by appropriate analgesics and the involvement of the specialist pain team, thus amputation should very seldom be necessary.

The ultimate decision to consent for amputation, after receiving medical advice lays with the patient. This medical advice may be flavoured by the patient's medical, psychiatric and

social history and current quality of life, the details of which may require discussion with the patient's family, friends, carers and primary care team.

### **Amputation in Trauma**

In situations of trauma, the decision-making process differs significantly compared to the thought process involved in amputation following peripheral vascular disease and diabetes. This is due to the differences that exist in patient age groups and therefore commonly comorbidities. In trauma, there is seldom the luxury of time and the decision to amputate a limb needs to balance the impact of reconstruction and salvage against that of limb removal. The scientific approach, turned to when there are indecisions in treatment, is unhelpful; a randomized controlled trial is unlikely to get balanced recruitment simply because most patients will not opt to be randomly allocated to amputation if there is a reasonable chance that limb salvage might produce a functional limb.

Contemporary surgical techniques and modern vehicle design improvements have made it possible for more traffic collision victims to survive, albeit with more severe injuries. These factors, combined with the recent experience in warfare as well as civilian trauma, mean a surgeon may encounter severe limb trauma that poses the dilemma: should limb salvage be undertaken? Futile attempts to preserve a limb which should be amputated disrupt a patient's life both physically and psychologically. Early amputation can avoid this possibility but is not without its own problems <sup>(147)</sup>.

Even in the presence of limb-threatening injuries, a systematic approach is required in approaching the polytrauma patient. Advanced Trauma Life Support (ATLS) ® principles appropriately highlight the primary survey as the starting point. Life-threatening problems are identified and treated in a logical, hierarchical sequence. Assessment of limb-threatening trauma is a key part of the primary survey in 'C' for circulation and 'D' for disability. A prompt assessment of perfusion, soft tissue injury, fracture pattern and, wherever possible, sensation and motor function is crucial. Complex multi-level injuries may pose a significant challenge in that if there is a vascular or neurological deficit, identifying the level of arterial or nerve injury may not be possible from clinical examination alone. Multiple limb trauma can also pose problems.

The decision process for amputation against limb salvage is a multi-faceted process consisting of combinations of injury-, patient-, surgeon- and even family-determined variables.

Decisions to perform amputations are usually taken at two points in time <sup>(148)</sup>:

1. Immediately, as part of primary treatment, or
2. When either features of the injury or patient recovery declare themselves fully and render any further attempts to save the limb unwise. In the latter group are those cases where initial attempts at salvage fail whilst the patient remains in hospital, as well as those where the family and patient wishes are reflected on.

Immediate amputation is indicated in several open tibial fracture scenarios. These include:

1. Incomplete amputations, where the injury has almost completely severed the limb and the distal portion is itself subject to significant trauma
2. Extensive crush injury, particularly to the foot and distal tibia
3. An avascular limb with a warm ischaemia time in excess of 4 hours <sup>(149, 150)</sup>.

Unfortunately, situations like polytrauma often constitute scenarios which are less certain and can be very unpredictable creating many 'grey areas':

1. An ischaemic limb with clinical evidence of nerve dysfunction, particularly absent plantar sensation.
2. Segmental muscle loss across more than two compartments, especially if the posterior compartment is involved.
3. Segmental bone loss greater than one-third of the length of the tibia.
4. Severe open foot injury associated with the tibial fracture.

As with vascular disease, consideration of the anatomical and functional deficits (which imply the extent of reconstruction or repair needed as well as the likely outcome), is not adequate in formulating a suitable management plan. There is need for an early holistic approach, taking into account the patient's reserve - physiological, psychological, social and economic.

When confronted with a 'grey area' scenario, evidence of haemodynamic instability may shift the decision towards amputation. A patient with a substance abuse history, including alcohol, may struggle to cope with the rigours of prolonged limb salvage.

Similarly, an individual who is self-employed and a bread-winner needs a predictable and assured period of recovery and this might be better served with an amputation. To compound

matters, the acceptance of limb loss varies greatly between societies of North America and Western Europe, in contrast to the Middle and Far East.

Attempts have been made to produce clinically useful scoring systems to assist in making decisions on limb salvage in these difficult circumstances. However, none has proven useful<sup>(151)</sup>. Data from the North American Lower Extremity Assessment Project (LEAP) have yielded differences in the priority of limb-threatening variables to amputation, even amongst experienced trauma surgeons and general trauma surgeons<sup>(151-153)</sup>.

A systematic review of the literature showed similar outcomes when comparing amputation and salvage for grade IIIB and IIIC fractures<sup>(154)</sup>.

Some form of indication of time scale, surgical stages and likely outcome of reconstruction may assist in decision-making. A step back can be taken in order to gain more information – from the patient and family, or to allow a more complete assessment of the extent of limb injury.

A well-known threshold for amputation is the duration of ‘warm’ limb ischaemia as are the extent and levels of concomitant non-vascular injury in the open fracture. The longer the ischaemic time-interval, the greater the amount and significance of muscle loss secondary to necrosis, no-reflow and reperfusion injury<sup>(155)</sup>. Revascularisation and salvage of an ischaemic limb in association with an open tibial injury has to be achieved within 4–6 hours if it is to be successful. This threshold is reduced further if the patient is hypotensive throughout most of this time<sup>(156)</sup>. Temporary intravascular shunts can be extremely effective in temporarily overcoming the ischaemia, until definitive treatment is suitable. They allow for prompt fracture stabilization to proceed before definitive arterial repair<sup>(157)</sup>. Major deep venous injuries proximal to the trifurcation should also be repaired<sup>(158, 159)</sup>.

In the event of the warm ischaemia threshold being approached and the limb is unlikely to be treated with temporary shunting, consideration should be given to amputation as delayed revascularization does not only incur greater local damage but may also induce systemic toxicity through the circulation of anaerobic metabolites and breakdown products of reperfused necrotic muscle.

Absent plantar sensation is not an uncommon clinical finding to coexist with evidence of vascular disruption as both structures course the lower limb together. This type of sensory deficit at initial presentation is not however an absolute indication for amputation. Recovery of normal plantar sensation is possible in over 50% the patients and may suggest the initial

loss is due to neuropraxia and cannot be assumed to arise from nerve disruption. If structural disruption of the nerve is confirmed during wound assessment, the outcome is less predictable, even if the continuity of the nerve is restored by microsurgical repair. There is currently no evidence on long-term outcomes for patients with permanent absent plantar sensation, although analogies have been made with other non-traumatic conditions which also produce neuropathic feet, e.g. diabetes and spinal cord pathology. A significant difference between the insensate traumatic and non-traumatic groups may be the extent of muscle loss and scarring which in the former may affect pain and functional levels; these two groups are not exactly comparable. Altered plantar sensation warrants exploration of the tibial nerve at the time of debridement in open tibial fractures. Structural integrity of the nerve should prompt an expectant approach and not weigh towards a decision for amputation.

Early amputation should only be considered if the nerve is found to be divided in association with extensive muscle loss across two or more compartments (particularly if the posterior compartment is involved) and a warm ischaemia time greater than 4–6 h. A neuropathic sole with a dysfunctional foot and ankle are potential poor outcomes if limb salvage is contemplated in this scenario.

The extent and level of muscle loss directly affect the functional potential in the limb. Muscle damage may be a direct consequence of trauma or be inflicted through effects of ischaemia and reperfusion injury. Absence of dorsiflexion from anterior compartment loss can be offset by transferring tibialis posterior through the interosseous membrane. Similarly, loss of peroneal muscle action can be offset by transferring tibialis posterior to the peroneal tendons posterior to the tibia. When muscle loss spans several compartments, the probability of reliance on orthotics to support the foot and ankle is higher. Whilst this alone does not constitute an absolute indication for amputation, other variables often present with the severe soft tissue damage and warrant consideration. For example, the presence of extensive muscle damage in the posterior compartment usually is associated with segmental bone loss and disruption of posterior tibial vessels and nerve. Such a combination is seen most frequently after a crush injury and may be an indication for amputation.

Several strategies have been formulated in dealing with significant bone loss. These include:

1. autogenous bone grafts (usually of iliac crest origin)

2. bone substitutes
3. free vascularized bone
4. composite tissue transfer and bone regeneration through distraction osteogenesis

A threshold for amputation set by the amount of bone loss is difficult to quantify.

Cuneiform patterns of bone loss (typically from extrusion of butterfly fragments), even when large, are easily treated with simple autogenous grafts in comparison to segmental patterns of bone loss. Therefore, variations exist, not only in the size and type of bone defect, but also in host tissue conditions and the patient's comorbidities. Some guidance can be obtained through comparison of the scale and time needed for recovery following salvage against recovery from amputation. In the adult tibia, autogenous bone grafting of segmental defects less than 2 cm in length will heal in approximately 5 months, depending on the vascularity of the recipient site, and patient smoking cessation. Larger defects, if approached using distraction osteogenesis, usually heal at approximately 45 days per centimetre of tibia replaced. Therefore, a 5 cm defect can be successfully reconstructed using this method in about 7–8 months. One can therefore see how limb reconstruction using distraction osteogenesis is time consuming and may require multiple surgical procedures in the period. When segmental bone defects approach 10–15 cm, reconstruction by bone transport will take in excess of 12 months. It is fair to say that only well-motivated, compliant patients with appropriate domestic and financial support will be suitable to undertake this magnitude of limb salvage. Free vascularized transfer of bone into the defect (usually the fibula) may shorten the reconstruction time and prove a better alternative, but protection of the transferred bone until suitable hypertrophy occurs is necessary in the postoperative rehabilitation period <sup>(160, 161)</sup>.

In contrast to the demanding nature of reconstruction, a transtibial amputee will take approximately 5–6 months to rehabilitate to independent walking if there are no other injuries. Generally, bone loss in excess of one-third the length of the tibia will take more than 12 months to reconstruct using distraction osteogenesis. In this situation, amputation should be considered as a viable alternative solution, particularly if the patient circumstances negate early return to independent ambulation and work.

Open foot injuries (in association with open tibial fracture) require special consideration. Hind-foot injuries are usually complex, and vary from open calcaneal injuries to talar body and neck fractures. Severe cases negate extrusion of part of the talus. Whilst the

principles of management of both levels of injury are similar, some projection of the likely functional outcome after salvage is needed. Severe hind-foot injuries lead to early joint stiffness. Loss of plantar skin is extremely challenging to reconstruct, even with reinnervated flaps. In addition, salvage of early post-traumatic joint degeneration will almost certainly incur arthrodesis. This sequence of reconstruction and further salvage procedures, could potentially leave the patient with the functional equivalent if not inferior to that of a below-knee prosthesis. In this event, an early recommendation for a transtibial amputation could provide a functionally equivalent outcome with a shorter rehabilitation period.

In extreme cases of serious polytrauma, amputation may serve as the only means for haemorrhage control and resuscitation. Another life-threatening scenario is a limb that has been crushed for several hours (exceeding the warm ischaemic threshold) where reperfusion may induce severe systemic complications through circulating breakdown metabolites of muscle. When the patient's condition demands a damage control strategy, prolonged surgery for limb salvage is futile and harmful. Damage control orthopaedics in the unstable patient guided by regular clinical and physiological assessments is the approach of choice<sup>(162)</sup>.

A decision has to be made either to amputate the limb against damage control surgery, with a view to return later for more definitive surgery.

The level of temporizing can vary; intravascular shunts can be inserted for ischaemic limbs and the fracture spanned by external fixation<sup>(155)</sup>. Wound debridement is performed strictly on the basis of removal of gross contamination, aiming at avoiding extensive exposure and dissection in the coagulopathic patient. The shunts can be left *in situ* whilst the patient is under optimisation in the intensive care unit. Shunts with a 'dwell' time averaging 23.5 h have been reported, with a thrombosis rate of 5%<sup>(157)</sup>. A return for definitive arterial or venous repair and a more definitive debridement, should the patient's general condition improve, has to be undertaken at the earliest opportunity or a decision made to amputate. The timing of a return to surgery must be decided upon jointly by the intensive care specialists, vascular, plastic and orthopaedic surgical teams.

The level of amputation is a clinical decision which carries significant implications for future mobility and employment prospects<sup>(163-165)</sup>. The physical effort of walking is lower and the quality of life superior with a transtibial (below knee) as compared to a transfemoral (above knee) amputation. Energy expenditure for a transtibial amputee is 10–30%<sup>(166-168)</sup> greater as compared to a 40–67%<sup>(167)</sup> increase in transfemoral cases. Bilateral transtibial amputees

incur an extra energy cost of over 40%, whereas those with bilateral amputations where one level is transfemoral may have to double their energy costs simply to ambulate <sup>(168)</sup>. The effect of this increased energy cost will vary between patients; in younger, more able individuals the penalty may not translate into functional significance, but in others both ambulation speed and walking capacity are limited <sup>(167)</sup>. Similarly, amputees resulting from trauma have lower energy costs compared to those resulting from peripheral vascular disease <sup>(167)</sup>. Even so, function with modern transtibial prostheses can be excellent with a significant proportion of young patients returning to work and sports activities.

Amputations through the ankle or knee are not an ideal surgical option for adults. The theoretical advantage of a longer lever arm is not supported by clinical outcomes. Furthermore, patients dislike the pronounced knee level asymmetry (especially when seated) with through-knee amputations. The functional outcome of a through-knee amputation is also poorer to an above-knee equivalent <sup>(147)</sup>.

Every effort must be made to preserve the knee joint, including vascular repair or flap coverage, even if the distal limb is hopelessly injured and negates amputation. Very short below-knee amputation stumps can be avoided if, in the presence of a reasonable foot remnant, a pedicled flap of plantar skin and attached os calcis is transferred and fixed to the end of the divided tibia <sup>(169)</sup>. Such ‘partial salvage’ can make an enormous difference to ultimate function.

### 1.3.1.3 When to amputate

The vast majority of LLAs can be performed on elective operating lists. This allows ample time for preoperative optimisation of the patient medically and psychologically. Pre operative assessment and support from physicians, anaesthetists, physiotherapists, occupational therapists, pain specialists, and other amputees are often helpful. Emergency amputation should be reserved for gangrene resulting in septicaemia or irreversible acute ischaemia involving large muscle masses <sup>(170)</sup>.

### 1.3.1.4 Level Selection

Improved postoperative rehabilitation and mobility following amputation is associated with preservation of the knee joint. These advantages, however, are lost in the presence of poor stump healing and revisional surgery <sup>(170)</sup>.

Transtibial to transfemoral amputation ratios average at 0.6 in England and Wales, however, specialists with an interest in amputations achieve a higher ratio, generally greater than one. Simple clinical assessment of the patient and the limb is essential, as in 50% of transfemoral

amputations, co-existent medical problems (e.g. stroke and flexion contractures) are more influential than concerns regarding wound healing <sup>(171)</sup>. In all cases of amputation, the implicit goal is to obtain primary healing, and in those with a potentially useful limb this should be at the most distal level possible. Numerous methods have been employed in an attempt to accurately identify this site.

Clinical examination of the leg, with assessment of warmth, skin integrity and capillary refill time have been proven to be of little value <sup>(172)</sup>. The presence of a palpable pulse in the major artery immediately above the proposed level of amputation is a reliable predictor of primary healing, however this does not imply that absence of a pulse in this artery does would exclude primary healing <sup>(64)</sup>.

The ideal test for selecting amputation levels should be sensitive and specific, quick, non-invasive, inexpensive and acceptable to both patients and staff, sadly though, such a test does not exist. However in a review of investigations aimed at predicting primary healing, arterial pressures and indices measured using a hand held Doppler probe, proved to be the most accurate <sup>(173)</sup>. In a study by Larsson in 1993, diabetic patient were found to have no healing of foot amputations with an ankle pressure less than 50 mmHg and no healing of toe amputations with toe pressures less than 15 mmHg <sup>(174)</sup>. In a similar study on diabetic patients by Eneroth primary healing of forefoot and toe amputations was associated with ankle pressures greater than 80 mmHg and toe pressures greater than 45 mmHg respectively<sup>(175)</sup>. Healing was observed in 93% of 236 transtibial amputation in whom popliteal occlusion pressure exceeded 50 mmHg. Healing was by primary intention in 64% and by secondary intention or following local wedge resection in 29% of cases <sup>(175)</sup>.

Other investigations have been described including: skin blood flow measurement using iodo-antipyrine <sup>(176)</sup> and <sup>133</sup>Xenon <sup>(177)</sup>; skin perfusion pressure using radioactive tracers <sup>(178)</sup> and photoplethysmography <sup>(179)</sup>; laser Doppler flowmetry <sup>(180)</sup>; fluorescein uptake <sup>(172, 181)</sup>; transcutaneous oxygen pressure <sup>(182)</sup>; thermography <sup>(183)</sup> and capillary microscopy <sup>(184)</sup> have all been used to predict primary healing with variable results. They have not, however, been widely used, mainly because of technical complexities, cost and result variability, and although theoretically they have been proved to have a value in aiding the prediction or anticipation of wound healing, their practical use and extrapolation in a clinical setting remains to be established.

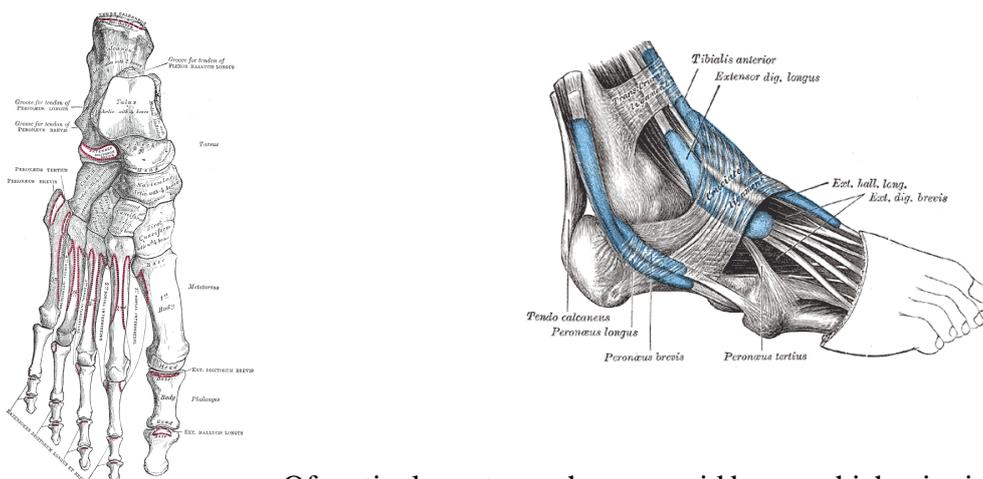
### 1.3.1.5 Who Should perform the surgery

Amputation has been traditionally perceived as surgical failure and considered an uninteresting and unrewarding procedure, often delegated to the most junior and inexperienced member of the surgical team, which unfortunately may sometimes be to the patient's disadvantage <sup>(185)</sup>. Amputation surgery in conjunction with a good prosthesis is a life changing process. It is therefore imperative that the surgery itself should be approached as a reconstructive surgical procedure, probably best performed or at least supervised by an interested and experienced surgeon, who is prepared to take the time and trouble to get it right, and who has some accountability for the patients post-operative rehabilitation, although nowadays, there is to the patient's advantage, a heavy multi-disciplinary drive to the process <sup>(170)</sup>.

### 1.3.2 *Amputations about the foot*

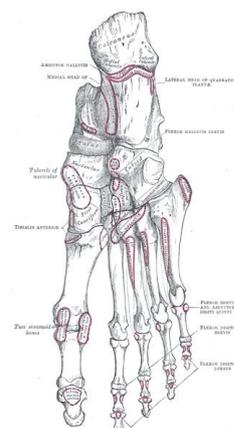
#### 1.3.2.1 Regional anatomy

The main bones of the foot are illustrated in figure 1. From a surgical perspective, the anatomy of the digits and forefoot is not complex. As seen from the dorsal aspect, in the figure 2, the majority of structures the surgeon may encounter are bony and tendinous in nature and include the long and short flexor and extensor tendons. In the case of minor amputation such as digital or ray amputation such structures can be transected with relative impunity. There are no major vessels that require specific attention.



Of particular note are the sesamoid bones which arise in the long flexor tendons to the great toe, these should be removed in the course of amputations involving this digit and 1st metatarsal.

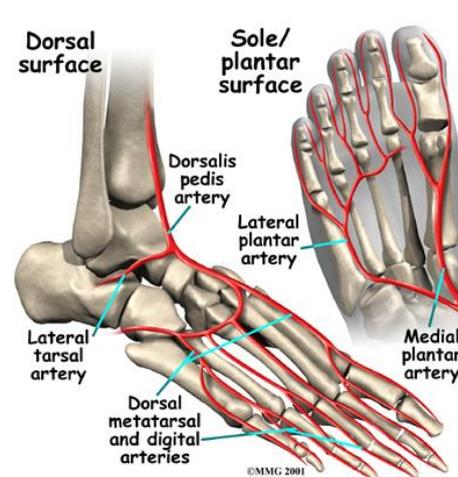
As the level of amputation becomes more proximal the surgeon may encounter bleeding from the metatarsal and digital arteries which are continuations of the dorsalis pedis artery and medial and lateral plantar arteries which arise from the posterior tibial artery (Figure 3).



Bleeding may also occur from perforating branches to the thick muscles that contribute to the sole of the foot at this point. The main muscles are illustrated in figure 4 but also include the intrinsic (Lumbricals, 2nd layer and interossei 4th layer) muscles of the foot

During midfoot amputations (e.g. Chopart or Lisfranc), care must be taken to preserve if possible the medial or lateral plantar which may be critical for skin flap viability.

The anatomy also explains the altered biomechanics, frequent deformity and thus poor functional results associated with mid foot amputations. Disruption of the peroneus brevis tendon from the base of the 5th metatarsal frequently results in an equinovarus deformity.



### 1.3.2.2 Digital Amputations

The level of infection/infarction act as determinants for the level of toe amputations. Clinical scenario permitting, amputations should ideally be performed through the proximal phalanx thus preserving normal foot architecture; this is important for reasonably normal function. This may be performed using equal dorsal and plantar flaps or a long plantar flap. With the latter technique a bulbous appearance of the residual toe is avoided by keeping the long plantar flap relatively narrow and ensuring the short dorsal flap has a wide base approximately 3 fifths of the toe circumference <sup>(186)</sup>.

In certain cases of more severe extent of disease, disarticulation at the metatarso-phalangeal (MTP) joint may be necessary using a “racquet” incision. This incision must clear the webs sufficiently to allow the lateral flaps appose naturally. The “handle of the racquet” is placed along the axis of the metatarsal shaft on the dorsum of the foot for the 2nd, 3rd and 4th toes but on the 1st & 5th toes is skewed slightly, such that the suture line lies close to the adjacent

toe. This allows for the wound to encounter less pressure from footwear. The skin flaps are taken down to bone and dissected off the phalanx, maintaining the deep transverse intermetatarsal ligament. The extensor tendons are divided, and the toe is subsequently placed under traction to divide the collateral ligaments and the flexor tendons. The vessels are suture or diathermy ligated and the nerves are divided under tension and shortened by 5-10mm.

Following haemostasis, the wound may be closed using interrupted monofilament nonabsorbable sutures to maintain a low SSI risk, or left open to heal by secondary intention, especially in cases of marginal viability / ongoing infection.

If disarticulation through the MTP joint is possible the articular cartilage should be shaved off to allow granulation tissue to evolve from the bone. Some authors would advocate resection of the metatarsal head to remove this articular cartilage <sup>(186)</sup>. Resection of the metatarsal heads of the 2nd , 3rd or 4th digits results in a lack of support of adjacent digits leading to inward displacement, reduced stability and often more discomfort <sup>(186)</sup>.

Digital amputations will only heal in the presence of reasonable blood supply and are thus frequently performed in conjunction with limb revascularization. Diabetics however may occasionally present with isolated small vessel disease and a black toe that may be suitable for amputation without the need for improvement in regional blood supply. The requirement for digital amputations can be considerably reduced by the introduction of a dedicated MDT foot clinic involving podiatrists, prosthetist / shoe fitters, nurses and physicians. Even the lesser toes cannot be removed without consequences. Amputation of the 2nd toe commonly leads to the development of a hallux valgus deformity, despite efforts to fill the gap with a toe spacer <sup>(187)</sup>. Removal of the fifth toe leaves the head of the fifth metatarsal exposed to pressure from the lateral side of the foot, sometimes with the formation of a tender bursa. Amputation of a lesser toe through or just proximal to the proximal interphalangeal joint detaches both long flexor tendons, creates a muscular imbalance. This often results in elevation of the remaining proximal phalanx. The ensuing pressure problems against the toe box of the shoe can cause pain and even ulceration. The great toe may be amputated at any level without risk of muscle imbalance because of the way the tendons are inserted. However, its loss tends to overload the neighbouring metatarsal heads significantly<sup>(188)</sup>.

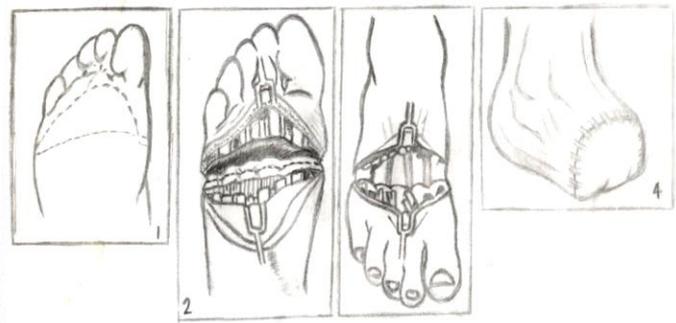
### 1.3.2.3 Ray Amputations

Sometimes, as a result of gangrene or bony infection, it is necessary to remove part or all of the metatarsal as well as the digit. This constitutes a ray resection. It should not be considered unless the blood supply to the region has been largely restored. It is invariably followed by a maldistribution of pressure under the sole of the foot and this could lead to ulceration if there is impairment of sensibility as so often is the case in diabetes.

### 1.3.2.4 Transmetatarsal Amputations

Healing of a transmetatarsal amputation generally requires palpable pedal pulses thus is valuable in very distal peripheral vascular disease or following revascularization, in extensive forefoot trauma or following frostbite when ample time should be allowed for clear demarcation to occur. The proposed level of bone section is marked on the dorsum of the foot in a gentle curve inside that of the natural metatarsal heads, the level depending on the extent of the pathology. Two points are then marked on the medial and lateral sides of the foot at the level at which the first and fifth metatarsal bones are to be resected. They are located nearer to the plantar side of the foot, roughly corresponding to the inferior borders of the two bones. A short dorsal flap, some 2cm long at its midpoint, is marked and a long plantar flap which needs to be longer towards the medial side than the lateral to provide cover for the greater thickness of the bone and soft tissues on this side. The plantar incision is carried down to bone and the flap is raised back to the level of bone section. The dorsal incision is also taken down to bone and a small dorsal flap is raised. The bones are divided with either a Gigli saw or a well-cooled oscillating saw, and the fifth metatarsal bone is bevelled laterally. The metatarsal bones should ideally be divided at the level of cancellous bone and this is either at the head or base of the metatarsal <sup>(186)</sup>.

Amputations through cortical bone diaphysis inevitably result in increased bone resorption, and ultimately sharp stumps which can lead to chronic pain, bursitis, and ulceration of the stump in an “inside-outside” manner.



*Figure 2 Transmetatarsal amputation (original sketch by Emma Wray)*

The tendons are then grasped, pulled down and cut high. The remaining soft tissues are trimmed to allow the flaps to fall comfortably together. The metatarsal arteries and other vessels are ligated.

In cases of plantar ulceration secondary to neuropathy, it is possible to preserve the toes and resect only the distal 2 thirds of the metatarsals. Ultimately though, the functional outcome is the same but preserving the toes allows for avoidance of phantom limb pain, and may even permit the return of some function in the foot, once there is bony union 1-2 years later <sup>(186)</sup>.

### 1.3.2.5 Syme's Amputation

This type of ankle disarticulation is indicated for major foot trauma, diabetes <sup>(189,190)</sup>, residual gangrene following a vascular reconstruction, foot deformities that are not amenable to correction, fibular and tibial hemimelia <sup>(191)</sup> and gross leg length discrepancy. It is contraindicated where the heel pad is not well perfused or not intact. For cosmetic reasons it may not be suitable for female patients. Peripheral neuropathy is not a contraindication, and a patient with a totally anaesthetic stump can function successfully with prosthesis for many years. The operation is performed with the patient supine and a pneumatic tourniquet is applied to the thigh,

provided the patient doesn't have significant history of peripheral

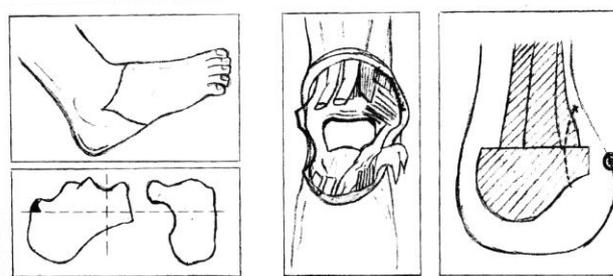


Figure 3 Markings and incision for a Syme's procedure (Original sketch by Emma Wray)

vascular disease. The lower part of the leg is supported on a receiver to allow the ankle to be moved freely and the surgeon seats himself at the end of the table.

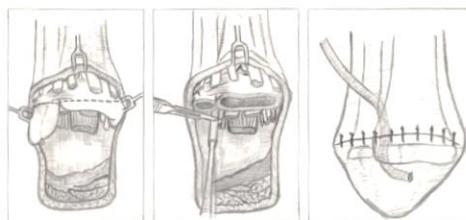
The tips of the malleoli are palpated and marked; they form the two cusps of the incision. The edge of the anterior flap takes the shortest distance across the front of the ankle, passing directly over the joint line <sup>(192)</sup>. The plantar part of the incision is formed by two lines dropping perpendicularly to the sole, which are then joined together by a slightly oblique line traversing the sole of the foot. The plantar incision is taken down to bone using a slightly raked cut. Anteriorly the incision passes through the skin and subcutaneous fat and the extensor retinaculum is divided transversely.

The extensor tendons are drawn downwards and divided as high as possible. The distal tendon stumps are divided under tension such that they are excluded from the continued

dissection. The ankle joint is entered by dividing the capsule transversely and the medial and lateral ligaments are incised. At this point attention is diverted to the posterior flap. A subperiosteal dissection of the calcaneum is commenced and continued posteriorly as far as possible<sup>(192, 193)</sup>. Returning to the dorsal incision, the posterior ankle joint capsule is divided, exposing the dorsal surface of the calcaneum. A large, sharp bone hook is then driven into the dome of the talus allowing forceful forward traction on it. The dissection then proceeds further posteriorly until the dorsal, medial and lateral sides of the calcaneum are cleared of soft tissue. When the retrocalcaneal bursa is entered, the bone hook is transferred into the back of the calcaneum and, once again, traction is applied. Working down the back of the calcaneum the Achilles is detached at its insertion. It should be borne in mind that the skin of the back of the heel is only millimeters away. At this point, it may be necessary to return to the plantar part of the incision before the calcaneum is finally released. During this whole process it is important to stay close to bone to preserve the integrity of the fatty lobules that are important in cushioning the bone and providing comfortable walking later.

After removing the foot, the flaps are detached from the periosteum up to the level of the tibial plafond. The cut ends of the peroneal, flexor hallucis and tibialis posterior digitorum longus are grasped and used to retract the soft tissues proximally, exposing the malleoli and distal tibia. A single cut with a tendon saw is used to detach the malleoli together with a sliver of the interconnecting bone. The plane and level of this cut are very important. It must be perpendicular to the long axis of the tibia as viewed in both the coronal and saggital planes. The specimen should appear translucent when it is held up to the light. That indicates that the cut is through the maximum cross-sectional area of the tibia<sup>(192)</sup>.

The medial and lateral plantar neurovascular bundles are usually encountered towards the medial side of the posterior flap. The arteries are ligated and the nerves divided under slight tension in order to avoid formation of a neuroma. The anterior tibial neurovascular bundle is treated in the



*Figure 4 Passing a drain following a Syme's procedure (Original sketch by Emma Wray)*

same way. The cut edges of the bone are smoothed with a rasp. The flexor and peroneal tendons are pulled down and cut as high as possible and loose pedicles of fibrous tissue are trimmed. The remains of the extensor digitorum brevis muscle are preserved in order to help fill some of the dead space in the heel pad.

A suction drain is passed up behind the inferior tibiofibular joint and brought out on the lateral aspect of the leg. The tourniquet is released and haemostasis is secured. The plantar fascia is sutured to the extensor retinaculum, making sure that the heel pad is located centrally under the cut surface of the bone. The wound edges are stapled. This must be done accurately, despite the difference in thickness of the skin of the two flaps.

The wound is dressed with gauze & wool and a rigid plaster of Paris is applied and moulded to hold the heel pad squarely under the cut end of the tibia. The cast extends to just below the knee. The drain is removed after 48 hours and the cast is changed at 5 days to allow inspection of the wound. It is changed again during the 3rd postoperative week and at this stage progressive weight-bearing can be commenced <sup>(192-194)</sup>. The definitive prosthesis consists of a soft inner liner which is split to allow it to be pulled over the bulbous end of the stump. Its outer surface forms part of an inverted cone, which allows it to be pushed down into the rigid socket which is bolted to an artificial foot. This has to have a low profile to avoid making the prosthetic limb too long, which would necessitate a heel raise on the normal side.

#### 1.3.2.6 Boyd's Amputation

This type of amputation is similar to Syme's but preserves the plantar part of the calcaneum with its intact heel pad, a part of the body that is naturally designed to carry full body weight. It is therefore very robust. It has been shown to be superior to Syme's amputation when dealing with longitudinal deficiency of the fibula and is the better choice for the completely anaesthetic foot. It depends on the success of a major arthrodesis, so it should not be used in the presence of heavy contamination <sup>(49, 195)</sup>. It produces a longer stump than the Syme and therefore is best used where there is already shortening to avoid the need for a raise on the contralateral shoe. Although it is necessary to fashion the flaps longer than those for the Syme, the first part of the dissection proceeds similarly with an opening up of the ankle and a dissection of the soft tissues off the talus and the upper part of the calcaneum. A disarticulation freeing most of the foot is performed through the subtalar and calcaneocuboid joints and then the upper part of the calcaneum is removed together with a 2cm slice from the front of the bone. The distal tibia and fibula are prepared, just as in the Syme, and the lower part of the calcaneum is fixed to the tibia with a wire mattress suture, a screw or, if the bone is very soft, an external fixator. The postoperative treatment is also similar to that for the Syme.

### 1.3.2.7 Midfoot Amputations

Generally produce unbalanced biomechanics resulting in deformity and thus poor functional results. Complex tendon surgery is required to prevent these complications and rarely is this practicable in the circumstances in which the amputations are performed (diabetic complications and trauma), thus these mid foot amputations are generally best avoided, however, they are described in this thesis for academic and informative reasons.

#### **Lisfranc's Amputation**

Using equal transverse dorsal and plantar skin incisions, the tarso-metatarsal joints are disarticulated, and the cartilage shaved away, or excised with a saw cut through the distal tarsal bones (Hey's modification) <sup>(196)</sup>. Another option is the disarticulation of the medial tarso-metatarsal joints combined with transection through the bases of the lateral metatarsals, disregarding the anatomy of the articulations but preserving uniform foot length. Care must be taken to preserve the plantar arteries that lie very close to the second and third cuneiform bone. Lisfranc's amputation produces a relatively unstable foot, as it is difficult to ensure the line of bone section obtains uniform contact with the ground which is inevitable because of the uneven length of the remaining articular surfaces<sup>(186)</sup>. There is a tendency to develop an equinus deformity due to the unopposed actions of peroneus longus, brevis and tertius.

#### **Chopart's Amputation**

Some authors advocate that this type of amputation should be seen as first choice because it preserves the full length of the lower limb and the ankle joint, even if it's range of motion remains limited <sup>(186)</sup>. This however has been disputed as Chopart procedures frequently lead to severe stump contractures with equinus and supination type deformities which require further corrective surgery such as subtalar joint fusions and tendo-achilles lengthening, both of which result in a prolonged rehabilitation period and a significant difficulty in prosthetic fitting <sup>(186, 197, 198)</sup>.

Chopart amputation is very similar to Lisfranc's amputation, however, it is performed at a slightly more proximal level. The incision aims at the formation of equal transverse dorsal and plantar flaps. The tarso-tarsal joints are disarticulated and the articular surfaces of the talus and calcaneous bones are rounded off to obtain a well-rounded stump. Stump contractures in equinus and supination may be prevented by external ankle fixation, or treated by lengthening of the Achilles tendon, transfer of the tibialis anterior tendon to the lateral border of the stump, or wedge osteotomy and fusion of the subtalar joint. That which pertains to Lisfranc's amputation applies to a greater degree to Chopart's trans-tarsal

amputation. As mentioned, it is probably best avoided, as the majority of tendinous attachments around the ankle have been lost and thus it is an unstable amputation.

### 1.3.3 *Transtibial Amputations*

The advantages of a transtibial amputation are summarised:

- The knee joint is retained
- Less energy consumption during walking
- Gait is less abnormal
- Easier to don prosthesis
- Cosmetically more acceptable
- Greater chance of returning to work / independence

The indications for a transtibial amputation have been reported on earlier in the text of this thesis.

Transtibial amputation is now widely accepted as the most ideal level of amputation for patients with peripheral vascular disease and diabetes <sup>(199)</sup>.

#### 1.3.3.1 Regional Anatomy

The lower leg consists of 3 compartments anterior, lateral and posterior, the latter being further sub-divided into deep and superficial compartments. Each compartment is supplied by an artery (Figure 5), vein and nerve. The distal popliteal artery bifurcates usually at the level of the superior border of the interosseous membrane into the anterior tibial artery, which passes anteriorly over the interosseous membrane into the anterior compartment, and the tibio-peroneal trunk. It then continues distally in the posterior compartment before dividing into posterior tibial and peroneal arteries.

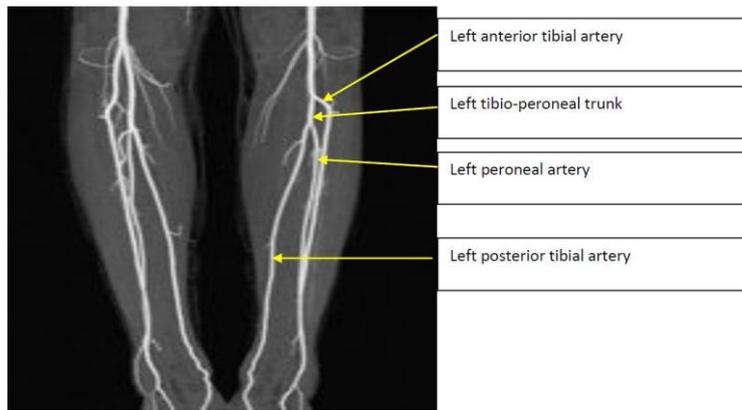


Figure 5 Lower leg Magnetic Resonance Angiogram<sup>(200)</sup>

Figure 5 demonstrates the normal anatomy on the left, and a common anatomical anomaly (proximal anterior tibial artery origin) on the right.

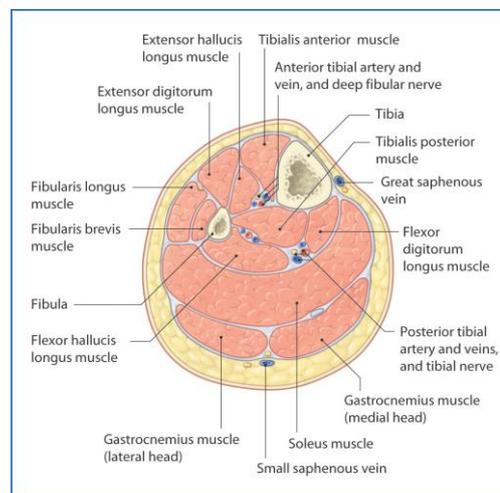


Figure 6 Cross-sectional anatomy of the lower leg<sup>(5)</sup>

Figure 6 illustrates the main neurovascular structures in each of the major compartments. The posterior tibial artery & vein, and the tibial nerve lie between the deep and superficial components of the posterior compartment, on the anterior surface of the soleus muscle. The anterior tibial artery and deep peroneal nerve lie on the anterior surface of the inter-osseous membrane. The peroneal artery lies in the deep posterior compartment just medial

to the fibula, it supplies the nutrient artery to the fibula and perforating branches to the lateral compartment, but does not run within the lateral compartment of the leg.

The most important lower leg compartment during transtibial amputation is the posterior compartment. In both the skew flap and long posterior flap burges techniques, the gastrocnemius muscle is used to cover the exposed tibia. The soleus muscle must be freed from its attachments to gastrocnemius and divided at the same level as the other muscles in the posterior compartment, to ensure that all that remains prior to stump closure, is the gastrocnemius muscle and skin, which receive their blood supply from the genicular anastomosis around the knee. It is worth noting that the surgeon will encounter the long and short saphenous veins (if present) during a below knee amputation. These vessels can bleed considerably and need to be identified and secured during the operation.

### 1.3.3.2 Long Posterior Flap

Flap amputations did not make an appearance until the late 17<sup>th</sup> century following a significant technical advance first reported by Yonge in 1679 in his treatise on the use of turpentine as a wound dressing<sup>(22)</sup>, and although he was confident of the potential benefits of his described method, he did not provide any evidence. The method remained dormant until a quarter of a century later when Verduin published more on this method in a 1696 in Latin, translated by Vergniol, a French refugee surgeon working in Amsterdam in 1697<sup>(201)</sup>. One of the procedural refinements of the awarded to Verduin was a novel method at the time of formation of calf flaps by transfixion, using a curved blade.

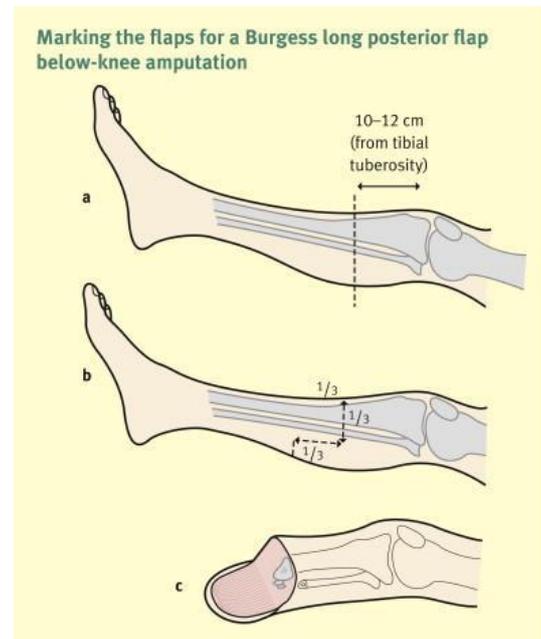


Figure 7 Markings for long posterior flap<sup>(6)</sup>

The “long posterior flap” trans-tibial amputation was first described by Heister in 1739, and later on in 1803 by Hey who went on to describe a method of determining the exact location of incision placement. For transtibial amputations in particular, he recommended marking the limb with ink following precise measurements of the limb circumference as opposed to limb diameter using ribbon, ultimately leading to the first appearance of what is known today as ‘the rule of thirds’<sup>(202)</sup>. Despite its obvious practicalities, this method failed to gain popularity until its refinement by Burgess and Romano in 1967<sup>(203)</sup>. The rationale behind the “long posterior flap” technique, is that the best blood supply to the posterior skin of the calf is from the sural artery which may be supplemented by perforating arteries from the gastrocnemius / soleus muscle mass. The anterior skin incision is made 10 - 12cm distal to the tibial tuberosity and encompasses two thirds of the circumference of the calf at this level<sup>(204)</sup>. The length of the posterior flap should be approximately one third the circumference of the calf at the level of the anterior skin incision (picture). The skin incision is deepened to include the subcutaneous fat and deep fascia.

### 1.3.3.3 Skew Flaps

The “equal skew flap” trans-tibial amputation involves the fashioning of 2 equal fasciocutaneous flaps, with the antero-medial flap based on the saphenous artery and the postero-lateral flap based on the sural artery<sup>(205)</sup>, therefore in essence, it is designed to make best use of the available blood supply below the knee level. In addition, this method aimed at forming a stump which is shaped for fitting with a patellar tendon bearing prosthesis with a scar that avoids the

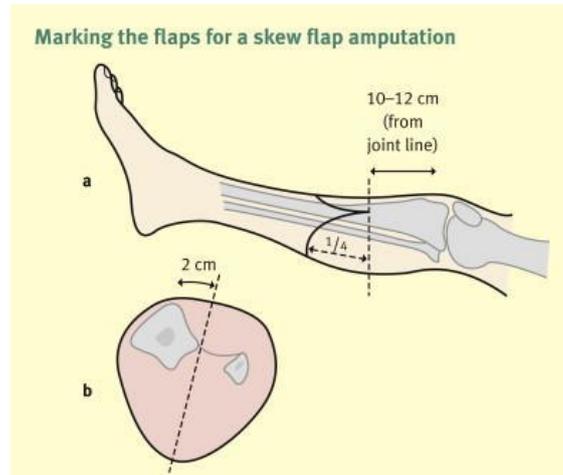


Figure 8 Markings for skew flaps<sup>(6)</sup>

bone ends whilst incorporating a form of myoplasty that ensures retention of the flexor function of the gastrocnemius remnant<sup>(206)</sup>. The advantageous impact this method carries over wound healing has been previously described<sup>(175, 207, 208)</sup>.

The formation of skin flaps occurs approximately at a level 10 – 12 cm below the knee joint. At this level, 2 - 2.5cm lateral to the subcutaneous crest of the tibia, the anterior intersection of the 2 flaps is marked. The posterior intersection of the 2 flaps is then marked at a distance of half the circumference of the calf at this level<sup>(209)</sup>. The midpoint of the base of the two flaps is marked at a quarter of the circumference from each intersection. The same quarter circumference is then used to mark the length of each flap. The skin, subcutaneous fat and deep fascia are incised along these marked lines<sup>(209)</sup>.

Whichever method of fasciocutaneous flap fashioning is used, the procedure from this point is essentially the same. The long and short saphenous veins are identified and ligated. The saphenous and sural nerves are separated, pulled down and divided under tension. The sural nerve artery and saphenous nerve artery may require ligation.

The muscles in the anterior tibial compartment are divided, and the anterior tibial artery and vein ligated. The tibia is isolated 10 cm distal to the tuberosity and, following stripping of the periosteum, the bone is divided with either a hand or pneumatic saw. The distal end of the tibia is bevelled by using a saw to cut obliquely across the anterior tip and the edges are smoothed with a file. The fibula is likewise exposed and divided 2cm proximal to the level of the tibial transection.

Following this, the myocutaneous flap consisting of skin, subcutaneous fat, deep fascia and gastrocnemius is developed, with excision of the other muscles. The peroneal and posterior

tibial arteries and veins are ligated and divided. The posterior tibial nerve is distracted downwards, transected and allowed to retract again. The myocutaneous flap is then sculpted to fit over the stump end without tension. Following this the deep fascia of the posterior flap is approximated over a suction drain to either the bone or the anterior deep fascia and periosteum. The skin edges are then approximated with simple interrupted sutures (picture) . The stump is then ideally encased in a layered dressing and plaster of Paris cast incorporating the knee joint. This rigid dressing protects the stump, prevents flexion contracture, promotes healing and early mobilisation. It may be split and temporarily removed for physiotherapy. Severe stump pain or evidence of infection should prompt the removal of the plaster cast to inspect the stump.

The trans-tibial amputation, when correctly performed provides a pain free and infection free stump, which maximises the chances of patient mobility whilst preserving limb length and most importantly knee proprioception. In addition, trans-tibial amputees have considerably less energy expenditure than trans-femoral amputees <sup>(210)</sup>. Oxygen consumption during mobilisation increases by about 9% in unilateral trans-tibial amputees compared to about 50% in trans-femoral amputees. These facts combine to mean that patients with a trans-tibial amputation are very much more likely to rehabilitate well compared with trans-femoral amputees. They also tend to live longer and have an improved quality of life, although some of these differences may be due to natural case selection with trans-femoral amputees having more severe arterial disease.

The trans-tibial to trans-femoral ratio is realistically achievable with appropriate patient selection should be at least 1:1 but in some units has been documented to approach 3:1. In large surveys, only 60% of below knee amputations for ischaemia heal by primary intention, and the prognosis in these patients is relatively poor <sup>(211)</sup>.

## 1.3.4 Amputations about the knee

### 1.3.4.1 Regional anatomy

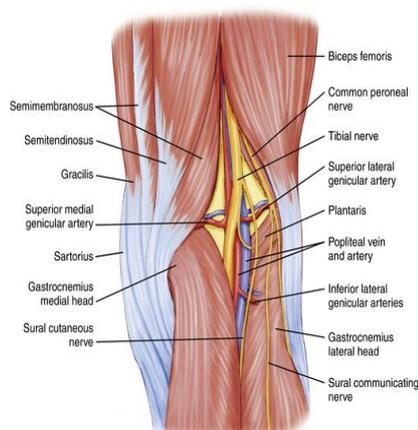


Figure 10 Neurovascular bundle in the knee  
<http://clinicalgate.com/knee-arthroscopy-setup-diagnosis-portals-and-approaches/>

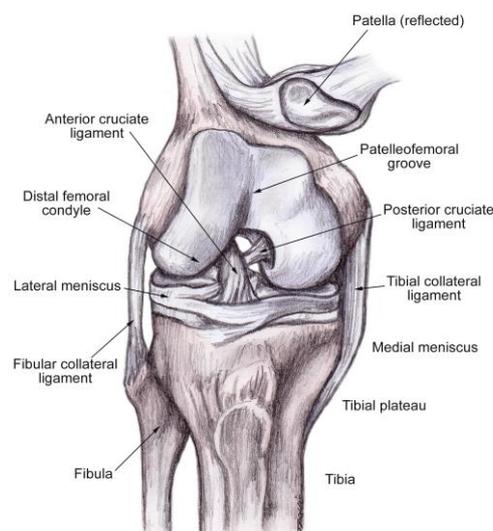


Figure 9 Ligaments about the knee  
(<http://imggood.com/knee-joint-ligaments.html>)

Important bony landmarks include the tibial tuberosity, medial and lateral tibial condyles and head of the fibula. These areas are important because they are sites of tendon insertions, which where possible should be preserved and can be fixed to the distal femur to help preserve stump function in a through knee amputation. A posterior view of the popliteal fossa provides a helpful window on this regional anatomy. It is important to appreciate how close the major neurovascular structures are to the posterior joint capsule. Inadvertent use of the scalpel or oscillating saw can easily damage these structures resulting in severe bleeding. Equally importantly, knowledge of the anatomical location of the neurovascular bundle is essential in ligating the vessels separate to the nerve, as well as to be able to catheterise the nerve post-operatively for provision of adequate analgesia.

### 1.3.4.2 Knee Disarticulation

Indications for through knee amputations include, sufficient proximal progression of the disease process (e.g. gangrene) to preclude below knee amputation, or involvement of the knee joint in the disease process rendering it unsalvageable. A through knee amputation provides a durable, stump capable of end weight bearing. Through knee amputations are associated with better rehabilitation rates than trans-femoral amputation, which reflects better stump stability and prosthetic suspension. In those patients unable to mobilise following amputation a through knee amputation results in a long, powerful muscle stabilised lever and therefore a mechanical advantage compared to a trans-femoral

amputation. Hence, through knee amputations should be performed, where possible, in preference to trans-femoral amputations in most circumstances.

There are four commonly used skin incisions performed during knee disarticulation, depending on the availability of suitable skin: the classical long anterior flap; equal anterior and posterior flaps; equal sagittal flaps; or the “no flap” technique utilising a circumferential incision made 1cm below the tibial tuberosity. These various skin flaps have been employed to minimise delayed wound healing, the major complication encountered with knee disarticulation.

The equal sagittal flap technique is perhaps the most commonly employed. Equal (4cm) semi-circular medial and lateral fasciocutaneous flaps are fashioned starting from the lower edge of the tibial tuberosity and extending to the mid-point of the knee crease posteriorly. These flaps will produce a linear posterior scar that will be sited away from any pressure points. After the fasciocutaneous flaps are fashioned, the dissection continues anteriorly with the detachment of the patellar tendon from its insertion. The hamstrings medially and the biceps femoris and iliotibial band laterally are dissected, divided and allowed to retract. The knee joint is entered anteriorly and, with the knee in flexion, the tibial insertions of the cruciate ligaments are detached. The posterior capsule of the joint is then carefully opened from the front, the popliteal artery and vein are individually dissected, clamped and suture ligated. The tibial and peroneal nerves are pulled down under tension, divided and allowed to retract into the proximal muscle mass. The patellar tendon, semitendinosus and biceps tendons are sutured to the cruciate ligaments improving muscle stability. The superficial fascia is approximated over a suction drain and the skin closed with monofilament vertical mattress sutures. Alternatively skin staples may be used. A dressing is applied with mild compression to reduce post-operative haematoma and oedema. Suction drainage for at least 72 hours is required to drain the synovial fluid.

#### 1.3.4.3 Gritti-Stokes Amputation

This amputation, described by Gritti in 1857 and subsequently modified by William Stokes, has become an increasingly popular amputation in the management of lower limb ischaemia. The femur is transected 1.5 cm above the knee joint using a saw, with an angle such that the sawn surface of the of the femur slopes upwards and backwards from the anterior aspect. This is mechanically more stable than if the femur is cut at a right angle and ensures that the patella does not slip forwards. The patella is then held firmly by encircling it with a swab and its articular surface removed using a saw. The patella is secured to the posterior end of

the femur with absorbable sutures passed through the joint capsule and the soft tissue behind the femur. Several different methods of anchoring the patella to the femur have been described including periosteal sutures, sutures or wires passing through drill holes in the cortex of the distal femur and patella and transfixion screws. Whichever method is used it is essential that the patella is firmly fixed and does not become dislodged. The myoplasty, fascia and skin closure are then performed as for a disarticulation.

#### 1.3.4.4 Supracondylar Amputation

This procedure was first described by Mazet and Hennessy in 1966 and was introduced in vascular patients in 1969 by Weale. It is performed in a similar fashion to the above using the long anterior skin flap technique. The patella, however, is enucleated from its periosteum, and the residual defect in the patellar tendon sutured. The femoral condyles are then transected transversely 1.5 cm above the knee joint using a saw, and the sharp bony edges filed smooth. The myoplasty, fascia and skin closure are then performed as for a disarticulation.

## 1.3.5 Amputations above the knee

### 1.3.5.1 Regional anatomy

The thigh has 3 muscular compartments, the anterior, posterior and medial or adductor

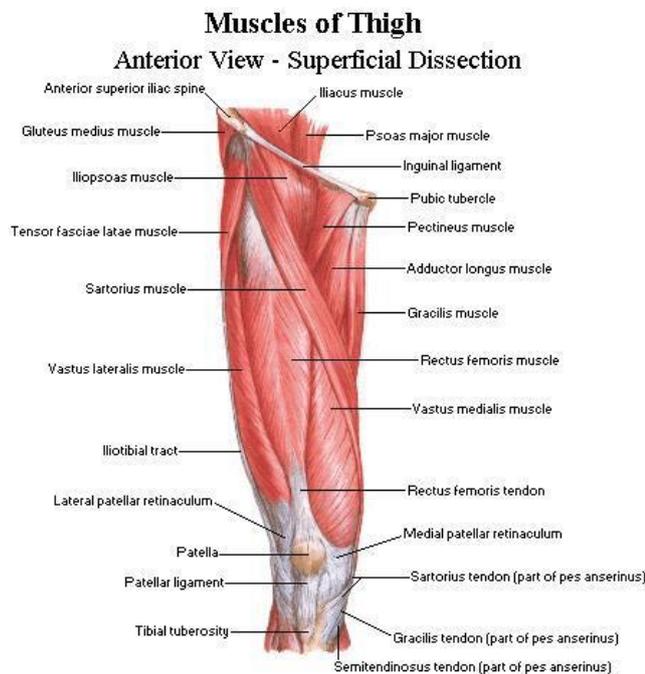


Figure 11 Muscles of the thigh<sup>(3)</sup>

compartment. The anterior compartment of the thigh contains the quadriceps and the major blood supply to the lower limb. The main blood vessel in this compartment is the superficial femoral artery which arises from the common femoral artery in the groin. It passes distally and medially in the subsartorial canal and finally posteriorly at the level of the adductor hiatus to become the popliteal artery. At the level that the superficial femoral artery arises from the common femoral artery, the profunda femoris artery takes origin and supplies the femur & the muscles of the posterior compartment. Under ischaemic conditions, this artery can become the dominant artery of the thigh and collateralise with the geniculate branches around the knee. In this instance it can make the difference between an above or below knee amputation. Finally the adductor compartment is supplied by the obturator artery, which arises from the internal iliac artery and passes through the obturator foramen to reach the medial compartment. In 20% of individuals this artery arises from the inferior epigastric and may pass through the femoral canal.

The posterior compartment of the thigh contains the hamstrings and the major nerve to the lower limb, the sciatic nerve. During a transfemoral amputation, this nerve is usually encountered after the surgeon transects the femur as it lies close to it, behind the medial portion of adductor magnus.

The most proximal anterior portion of the lower limb is the groin and femoral triangle. This is a particularly important area as it carries the femoral artery and associated structures. It is particularly relevant if the surgeon is required to perform a hip disarticulation or hindquarter amputation. In this instance it will be one of the first structures dissected. The surgeon will

also need to be familiar with this region as the origin of both the adductors and Sartorius which may need to be divided and can be found originating from the pubic bones and anterior superior iliac spine respectively.

The gluteal region, proximal femur and their overlying muscular and ligamentous structures form the working hip joint. The bony anatomy is shown below. At the most basic level the femur and acetabulum are held in apposition by the joint capsule, three sturdy ligaments (pubo-femoral, ischiofemoral & iliofemoral) and the overlying musculature.

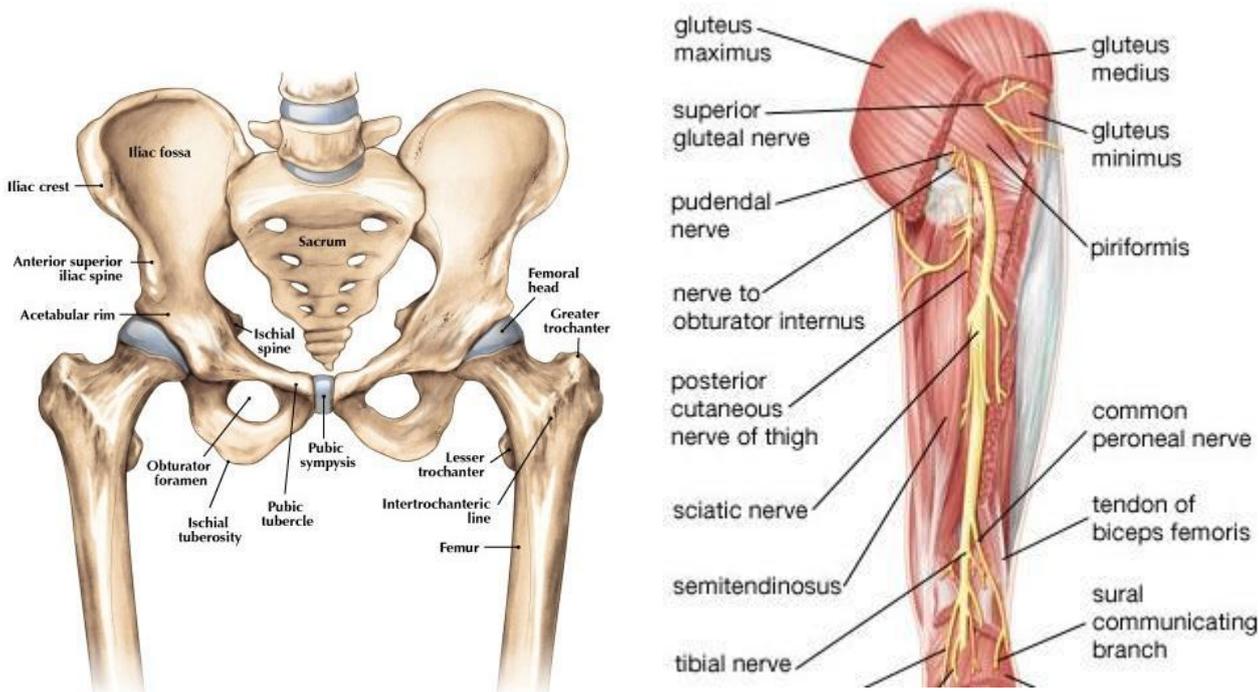


Figure 12 Anatomy of the gluteal region <sup>(4)</sup>

Anteriorly, once the femoral triangle is exposed and the major vessels retracted, the origin of the thigh adductors can be seen from the pubic tubercle, crest, rami, and ischial tuberosity. Transection of sartorius exposes the insertion of iliopsoas and pectineus on the femur. Division of these muscles reveals the anterior joint capsule. Posteriorly, of relevance to the surgeon performing an amputation at this level are the sciatic nerve, piriformis, tensor fascia lata muscle, short hip rotators, and gluteal muscles, which often form the posterior myocutaneous flap required in this radical surgery. Access to this area is obtained by dividing the tensor fascia lata from the gluteus maximus muscle, this is then retracted and the insertion of the extensor muscles and hip rotators can be visualised as they insert on the greater trochanter of the femur. Further medial retraction on the gluteus maximus will expose the sacroiliac joint and sacrospinous ligaments which would be divided in a hind quarter amputation.

### 1.3.5.2 Transfemoral amputations

Equal semi-circular anterior and posterior myo-cutaneous flaps are ideal for this amputation. However, the length and orientation of the flaps could be modified if needed in cases of trauma and in patients with previous surgical scars.

The circumference of the thigh at the site of intended femoral transection should be measured. The apex of the semicircular myocutaneous flap should be sited a minimum of 10 cm above the knee joint, and the base of the flap  $\frac{1}{4}$  of the circumference

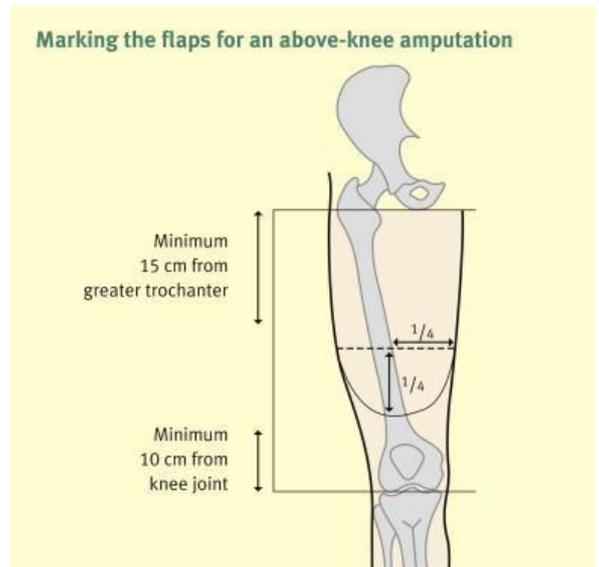


Figure 13 Markings for transfemoral amputation<sup>(6)</sup>

proximal to the apex. Ideally the femur is divided 22-28 cm from the tip of the greater trochanter, with 15 cm the absolute minimum. The skin flaps should be based slightly distal to level of intended the femur division depending on the muscle bulk of the thigh. Starting with the anterior flap first the skin and subcutaneous fat are incised down to the muscle fascia using a scalpel. The muscles of the anterior compartment (quadriceps femoris and sartorius) are divided at the same level as the skin down to the femur.

The posterior myo-cutaneous flap is then produced, using the same technique. The greater saphenous vein is encountered medially and will need to be ligated using absorbable sutures. The medial and the posterior muscle groups (adductors and biceps femoris) are divided at the same level as the skin flap. Care is taken to dissect the superficial and deep femoral neuro-vascular bundles and the arteries and veins are ligated separately. All nerves should be divided as high as possible and allowed to retract upwards. The femoral periosteum is elevated using a periosteal elevator to the level of the proposed femur division, generally 5 cm above the base of the skin flap. The femur is divided using a saw while protecting the myocutaneous flaps. The bone edges are refined using a file and the use of bone wax should be avoided. Meticulous hemostasis is mandatory to avoid haematoma formation and suction drains may be used especially in traumatic amputations.

Since the entire thigh muscles are divided distally, myodesis (myopexy) is necessary to achieve stump stability and restore function. Using a 2mm drill, an anterior cortex drill hole is created into the medullary canal, 1 cm proximal to the femur's divided end. Myodesis is performed by lifting the muscular posterior flap (mainly adductors) upwards and stitching it

with several non-absorbable sutures to the femur. Myodesis of the posterior flap and double-breasting the anterior flap on top gives extra protection to the femur end reducing the risk of it penetrating the anterior flap especially in ischaemic patients with significant muscle wasting. If double-breasting technique is used, the anterior fascio-cutaneous flap needs to be dissected for few centimetres to allow skin closure without any tension. The fascia is closed with interrupted absorbable sutures. Skin can be closed with continuous sub-cuticular, interrupted sutures or skin clips according to surgeons preference. A stump dressing is applied with mild compression to reduce post-operative haematoma and oedema. The stump is best nursed elevated for the same purpose.

### 1.3.5.3 Hip disarticulation

Fortunately, amputation at this level is seldom required, as it generally reflects massive ischaemia associated with an aortic or iliac thrombosis, falling cardiac output and approaching demise. A hasty operation at this stage may simply accelerate this outcome and thus careful judgement is required. The indications for this procedure are therefore, severe ischaemia extending above the level of an above knee amputation in a patient who is expected to survive surgery.

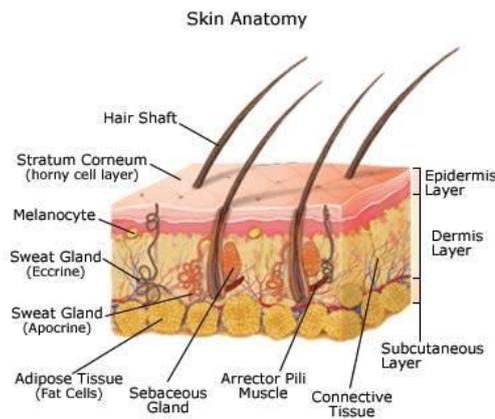
With the patient supine on the operating table, a sandbag is placed under the ipsilateral sacroiliac joint, the hip is flexed, and the skin incisions are marked. The wide posterior flap begins 3cm below the pubic tubercle and passes around the buttock to the anterior superior iliac spine. The anterior incision is made 2cm below and parallel to the inguinal ligament. Once the skin and fascia have been incised, the femoral vessels are dissected, clamped, divided and suture ligated. The femoral nerve is transected under tension and allowed to retract. Sartorius is detached from the anterior superior iliac spine and the anterior hip joint capsule exposed. With the hip in abduction, the adductors are divided, the obturator vessels suture ligated, and the obturator nerve transected under tension. Hip flexion, adduction and internal rotation facilitate development of the posterior flap. Gluteus maximus is divided, the hamstrings are cut close to the ischial tuberosity, and the sciatic nerve is transected under tension and allowed to retract into the sciatic notch. The gluteus medius and minimus muscles are divided and the superior and inferior gluteal vessels suture ligated. With the limb laid flat the anterior hip joint capsule is incised, the femoral head dislocated, the round ligament divided and the posterior capsule incised.

Division of the obturator tendons and piriformis allows removal of the limb. Following careful ligature haemostasis, and with a suction drain in the acetabulum, the posterior flap is

sutured to the inguinal ligament and anterior aspect of the pelvis. The skin is then opposed with interrupted non-absorbable monofilament sutures and a crepe bandage applied as a hip spica to eliminate potential dead space.

## **Section 1.4 Wound healing and Surgical Site infection**

### **1.4.1 Structure and function of skin**



*Figure 14 Anatomical Structure of skin* <sup>(8)</sup>

The skin is the largest organ in the body and comprises of three layers: the epidermis, the dermis and the subcutaneous layer. The epidermis is continually regenerating and is made up of keratinocytes, comeocytes which are dead keratinocytes and provide a protective layer from mechanical impacts and pressure, chemicals and micro-organisms and melanocytes which produce

melanin which protects against UV radiation. <sup>(212)</sup>

The dermis contains sweat glands which contribute to temperature regulation, hair follicles which also have a role in temperature regulation and sebaceous glands which produce sebum to keep hairs clean. The subcutaneous layer is made up of fat and connective tissue<sup>(212)</sup>.

It is therefore clear to see that the skin is able to carry out its functions of protection and regulation. The skin is also a sensory organ containing a vast network of neurones which can detect changes in the environment. Neuropathy is damage to the nerve cells resulting in a loss of sensation to the affected area and as such removes protective mechanisms increasing the risk of wounding or worsening of existing wounds.

### **1.4.2 Wound healing**

#### **1.4.2.1 Definition and pathway**

A wound is generally defined as damage to the tissue resulting in the disruption of the original tissue architecture and homeostasis<sup>(213)</sup>. Healing comprises a series of extracellular and intracellular events which serve to restore tissue integrity and physiological equilibrium<sup>(213)</sup>.

Wound healing is a dynamic, complex biological process which results in the restoration of tissue integrity. Physiologically, it can be divided into four distinct phases of haemostasis,

inflammation, proliferation and tissue remodelling. It happens at the cellular basis but can be governed by other extracellular signalling processes <sup>(214)</sup>.

Disruption in skin integrity, mucosal surfaces or organ tissue leads to the formation of a wound. Wounds can occur as part of a disease process. They may have an accidental or intentional aetiology<sup>(215)</sup>. At the time of insult, multiple cellular and extracellular pathways are activated, in a tightly regulated and coordinated fashion, with the aim of restoring tissue integrity.

Given the elaborate nature of the healing cascade, it is astonishing how this occurs commonly without complications<sup>(214)</sup>(Figure 15).

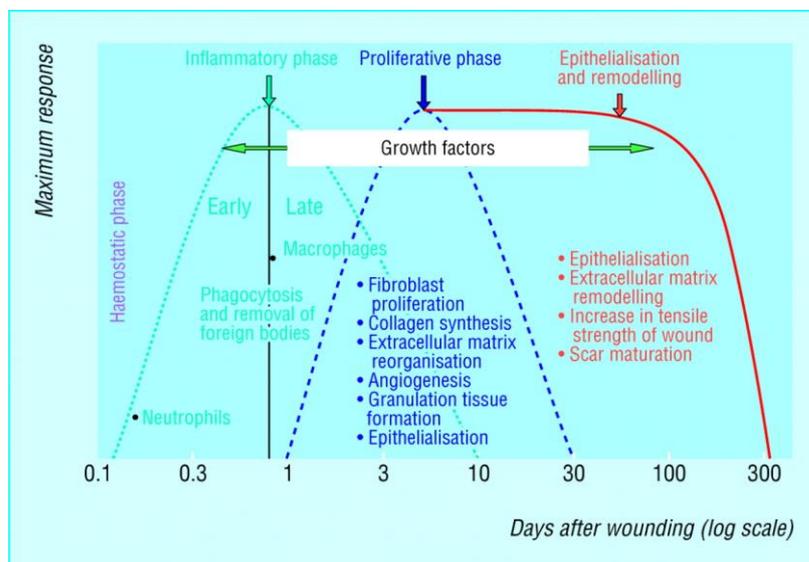


Figure 15 Stages of wound Healing <sup>(2)</sup>

This process can in day to day practice be negatively affected by numerous factors, resulting in delayed wound healing, increased patient morbidity and mortality and poor cosmetic results. The health economic effects of chronic wounds and the psychological impact they have on patients are often understated due to challenges posed in quantifying them completely.

The annual expenditure on wound related problems in the USA alone is estimated to exceed one billion dollars<sup>(216)</sup>. The inflammatory phase happens immediately following an injury, the blood vessels in the wound bed contract and the coagulation cascade results in the formation of a blood clot and hence haemostasis. Subsequent vasodilatation ensures that the cells essential for healing reach the wound, namely white blood cells, growth factors, enzymes, antibodies and nutrients. This results in wound exudate <sup>(214)</sup>. Wounds will frequently adapt a characteristic nature consisting of the classical calor, rubor, dolor and tumour(oedema). Neutrophils and macrophages mount a host response which helps autolyse necrotic and sloughy tissue.

The proliferation stage refers to the development of granulation tissue made up of collagen and extracellular matrix. Angiogenesis then ensues, leading to the development of a new

immature network of blood vessels which are vital in providing for sufficient oxygen and nutrient delivery to the fibroblasts. The colour of the granulation tissue can be an indicator of the health of the wound with pink and red tissue suggesting good perfusion and lack of infection. Following this, epithelialisation can occur to resurface the wound.

Maturation is the final phase and occurs following epithelialisation. This stage involves the remodelling of collagen from type III to type I. Cellular activity reduces and the number of blood vessels in the wounded area regress and decrease.

#### 1.4.2.2 Stages of healing

##### **Haemostasis**

Upon placing an incision, vascular injury occurs on a macro- or microvascular scale. The immediate response of the body is to prevent exsanguination and promote haemostasis. Damaged arterial vessels rapidly constrict through smooth muscle contraction in the circular layer of the vessel wall, mediated by increasing cytoplasmic calcium levels<sup>(217)</sup>. Vessels up to a diameter of 5 mm can be sealed through contraction, although this can only occur if the injury is in a transverse plane. Reduced blood flow mediated by arteriole constriction leads to tissue hypoxia and acidosis within minutes. Production of nitric oxide, adenosine and other vasoactive metabolites follows and causes a reflex vasodilatation and relaxation of the arterial vessels. A simultaneous histamine release from mast cells also acts to increase vasodilatation and increase vascular permeability, facilitating the entry of inflammatory cells into the extra-cellular space around the wound. This explains the characteristic warm, red, swollen appearance of early wounds<sup>(214)</sup>.

Further haemorrhage at this stage is also prevented through the formation of a clot. This becomes possible through three crucial mechanisms<sup>(218)</sup>:

1. The Intrinsic pathway of the clotting cascade (contact activation pathway). Damage as a result of tissue injury exposes the sub-endothelial tissues to blood which results in the activation of factor XII (Hageman factor). This initiates the proteolytic cleavage cascade which results in the activation of factor X. This triggers prothrombin to thrombin conversion resulting in the change of fibrinogen to fibrin and the formation of a fibrin plug<sup>(218)</sup>.
2. The Extrinsic pathway of the clotting cascade (tissue factor pathway) during which endothelial damage results in exposure of tissue factor (which is present in most

cells) to circulating blood. This results in activation of factor VII and the rest of the extrinsic pathway of the clotting cascade which eventually results in thrombin activation .

3. Platelet activation following activation by thrombin, thromboxane or adenosine diphosphate (ADP), platelets undergo a morphological change and secrete the contents of their alpha and dense granules. Activated platelets adhere and clump at sites of exposed collagen to form a platelet plug and temporarily arrest bleeding. This plug is strengthened by fibrin and von Willebrand factor as well as the actin and myosin filaments within the platelets<sup>(219)</sup>.

Platelets have a crucial role in wound healing process. Not only they are essential for clot formation, but also produce multiple growth factors and cytokines which continue to regulate the healing cascade. Over 300 signalling molecules have been isolated from activated platelets, which influence and modulate the function of other platelets, leukocytes and endothelial cells<sup>(220)</sup>. In addition to these factors, in response to the injured cell membranes caused by the wounding stimulus, arachidonic acid is broken down into a host of potent signalling molecules such as the prostaglandins, leukotrienes and thromboxanes, all of which have roles in stimulating an inflammatory response.

### **Inflammation**

This is a key defence process within the wound healing mechanism against infection. Regardless of the aetiology of the wound, skin, the mechanical barrier which was once the frontline against invading microorganisms is no longer intact. Neutrophils, which act as the ‘first responders’, are highly motile cells which occupy the wound within an hour of the insult and migrate in sustained levels for the first 48 hours. This is mediated through various chemical signalling mechanisms, including the complement cascade, interleukin activation and transforming growth factor- $\beta$  (TGF- $\beta$ ) signalling, which leads to neutrophils passing down a chemical gradient towards the wound, a process termed as chemotaxis<sup>(221)</sup>. Neutrophils have three main mechanisms for destroying debris and bacteria. Firstly they are phagocytic towards foreign particles. Secondly, neutrophils can degranulate and release a variety of toxic substances (lactoferrin, proteases, neutrophil elastase and cathepsin) which will destroy bacteria as well as dead host tissue. Recent evidence has shown that neutrophils can also produce chromatin and protease ‘traps’ which capture and kill bacteria in the extracellular space<sup>(222)</sup>. Oxygen free radicals generated as a byproduct of neutrophil activity, are known to have bacteriocidal properties but can also combine with chlorine to sterilize

the wound. When the neutrophils have completed their task, they either undergo apoptosis, are sloughed from the wound surface or are phagocytosed by macrophages<sup>(221)</sup>.

Macrophages are much larger phagocytic cells which reach peak concentration within 48-72 hours following injury. They are attracted to the wound by the chemotactic agents released by platelets and damaged cells and are able to survive in the more acidic wound environment present at this stage<sup>(215)</sup>. Macrophages harbour a large reservoir of growth factors, such as TGF- $\beta$  and epidermal growth factor (EGF), which are important in regulating the inflammatory response, stimulating angiogenesis and enhancing the formation of granulation tissue. Lymphocytes appear in the wound after 72 hours. They have a role in regulating wound healing, through the production of an extracellular matrix scaffold and collagen remodelling. Experimental studies have shown that inhibition of T-lymphocytes results in decreased wound strength and impaired collagen deposition<sup>(223)</sup>.

The inflammatory phase of wound healing will persist as long as there is a need for it, ensuring that all excessive bacteria and debris from the wound is cleared. Protracted inflammation can lead, however, to extensive tissue damage, delayed proliferation and result in the formation of a chronic wound. Multiple factors, including lipoxins and the products of arachidonic acid metabolism, are thought to have anti-inflammatory properties which dampen the immune response and allow the next phase of wound healing to arise<sup>(224)</sup>.

### **Proliferation**

Once the injuring stimulus is withdrawn, haemostasis has been achieved, the inflammatory response reaches a balanced phase and the wound is debris free. The proliferative stage of the healing cascade ensues, which is the first stage of repair. This complex process incorporates angiogenesis, the formation of granulation tissue, collagen deposition, epithelialisation and wound retraction all of which occur simultaneously.

### **Angiogenesis**

Angiogenesis is triggered from the moment the haemostatic plug has formed as platelets release TGF- $\beta$ , platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). In response to hypoxia, vascular endothelial growth factor (VEGF) is released which, in combination with the other cytokines, induce endothelial cells to trigger neovascularization and the repair of damaged blood vessels<sup>(214)</sup>. At first, the wound centre is relatively avascular thus relying entirely on diffusion from the undamaged capillaries at the wound edge. With progress, a rich vascular network of capillaries is formed throughout the wound from offshoots of healthy vessels. Initially the capillaries are fragile and permeable which

contributes further to tissue oedema and the appearance of ‘scarlet red’ healing granulation tissue <sup>(214)</sup>.

### **Fibroblast migration**

Following the wound insult, fibroblasts are stimulated to multiply by growth factors released from the haemostatic plug and migrate to the wound (predominantly by TGF- $\beta$  and PDGF). By the third day, the wound becomes rich in fibroblasts which lay down extra-cellular matrix proteins (hyaluronan, fibronectins and proteoglycans) and subsequently produce collagen and fibronectin. The resulting pink, vascular, fibrous tissue which replaces the clot at the site of a wound is termed as granulation tissue. This comprises a diverse range of collagens (a higher proportion of type 3 collagen) different to that seen in unwounded tissue. Once sufficient matrix has been laid down, fibroblasts change to a myofibroblast phenotype and develop pseudopodia. This enables linkage to the surrounding proteins fibronectin and collagen and assist in wound contraction <sup>(214)</sup>. Collagens synthesized by fibroblasts are the key component in providing structure and strength to tissues. In wounds closed by primary intention, collagen deposition is maximal by day 5 and this can often be palpated beneath the skin as a ‘wound ridge’. When a wound ridge is not palpable, this is an indication that the wound is at risk of dehiscence. Like with any healing / scarring process, overproduction of collagen can lead to the development of a hypertrophic scar. Hypertrophic scars remain raised and erythematous but remain within the confines of the original wound. Risks for their development include wound infections and those where there is excessive tension <sup>(214)</sup>.

### **Epithelialization**

Soon after the initial insult, epithelial cells migrate from the edges of the wound until a complete sheet of cells shelters the wound and attaches to the matrix below. An embryological process, termed epithelial-mesenchymal transition (EMT), allows epithelial cells to mobilise and travel across the wound surface <sup>(225)</sup>. In wounds that are primarily closed, this cycle completes within 24 hours. Changes in cytokine concentration allow epithelial cells to switch from a motile to a proliferative phenotype in order to repopulate epithelial cell levels and complete wound repair <sup>(226)</sup>. In wounds that heal by secondary intention, the area lacking epithelial cells can be large and the wound must contract significantly before epithelialization can be completed. In some cases this may never occur and skin grafting can be used to cover the defect <sup>(214)</sup>.

## **Wound retraction**

Wound contraction starts by day 7 post-insult, and is mediated mainly by myofibroblasts. Acto-myosin interaction pulls the cell bodies closer together decreasing the area of tissue needing to heal. Contraction can occur at a rate of 0.75 mm/day leading to shortened scars. This is influenced by numerous factors including wound shape, with linear wounds contracting fastest and circular wounds the slowest. Disorders of this phase of healing can lead to deformity and the formation of contractures <sup>(227)</sup>.

## **Remodelling**

This is the final stage of wound healing and can take up to 2 years. It results in the development of normal epithelium and maturation of the scar tissue. This phase involves a balance between synthesis and degradation, as collagen and other proteins deposited in the wound become increasingly well organised. Eventually they restructure with architecture similar to that seen in unwounded tissue (replacing type 1 collagen with type 3 collagen). Despite this, wounds never achieve the same level of tissue strength. Instead they average 50% of the original tensile strength by 3 months and only 80% long-term. As the scar matures, the level of vascularity decreases and the scar changes from red to pink to grey with time.

### 1.4.2.3 Important factors in wound healing

#### **Nutrition**

It is well established that nutritional status can influence wound healing. In the 15th century, the Portuguese explorer Vasco da Gama noted that sailors with scurvy had multiple, non-healing skin lesions. It was not until 1747 that James Lind, a Scottish surgeon, demonstrated that citrus fruit could successfully treat scurvy and enhance wound repair. Malnutrition adversely affects healing by prolonging inflammation, inhibiting fibroblast function and reducing angiogenesis and collagen deposition. There are many essential nutrients which are important for wound healing, including vitamin A (involved in epidermal growth), carbohydrates (for collagen synthesis) and omega-3 fatty acids (modulate arachidonic acid pathway). In recent years, extensive research in the field of clinical nutrition has shown clear benefit for the use of nutritional support techniques to enhance wound healing. This topic has been the subject of a number of recent review articles <sup>(228)</sup>.

## **Hypoxia**

All wounds are hypoxic to some extent as local vascular supply is disrupted. Whilst a degree of hypoxia is required to facilitate re-epithelialization, sufficient oxygen is an essential requirement for wounds to heal. It is clear in surgical practice that elderly patients and those with peripheral vascular disease have poor healing and in contrast hyperbaric oxygen improves wound healing <sup>(229)</sup>. Although hypoxia is one of the chemoattractants for neutrophils and macrophages, oxygen is the fuel in driving phagocytosis and optimal cellular function. A randomized controlled trial demonstrated that supplemental oxygen given during the perioperative period reduced the risk of wound infections <sup>(230)</sup>. Oxygen is also essential in collagen deposition as it acts as a substrate in the hydroxylation of proline and lysine residues. Smoking affects oxygen partial pressures and causes more wound complications, although it is likely that smoking may also affect immune function and collagen deposition <sup>(214)</sup>.

## **Infection**

Antibiotic prophylaxis prior to making a surgical incision was proven to reduce risk of wound infections firstly in guinea pigs in 1958 and subsequently in humans in 1960. Delayed primary closure, or closing by tertiary intention, should be considered when suturing heavily contaminated wounds as this has been shown to decrease wound infection rates <sup>(214)</sup>.

## **Immunosuppression**

Patients with human immunodeficiency virus (HIV), cancer and malnutrition all have a degree of immunosuppression which can lead to delayed wound healing. In addition, any drugs which impair the inflammatory response can impede the healing cascade. Oral steroids, such as prednisolone, have been shown to decrease cytokine concentrations during wound repair, leading to reduced collagen deposition.

## **Chronic disease**

Any chronic disease which affects the cardiorespiratory system may adversely affect the supply of oxygen and other nutrients required for wound healing. Diabetic patients have significantly impaired wound healing as they are relatively immunocompromised and higher blood glucose levels affect leukocyte function. In addition diabetes causes the long-term microvascular damage which affects both tissue oxygen levels and the supply of nutrients.

## **Wound management**

A healthy wound environment is a prerequisite for successful wound healing. There are more than 250 different types of wound dressing which act to protect the wound, allow it to remain moist and absorb excessive exudates to aid the healing process.

### **Age**

Elderly patients have a thinner epidermal layer and have slower inflammatory, migratory and proliferation responses. They are also more likely to have chronic disease, which combine to make these patients have slower wound healing and so be at higher risk of wound complications such as dehiscence.

### **Genetics**

Keloid scars occur when there is an overgrowth of scar tissue which extends beyond the wound boundaries. They can be painful and pruritic and have a high recurrence rate but can respond to steroids, cryotherapy or radiation therapy. Commonest sites of occurrence include the shoulders, arms or upper chest and rarely below the waist. There is a strong genetic component to keloid development, being significantly more commonly in patients of African, Hispanic or Asian race. Incisional herniae have also been shown to have a genetic component which is thought to be due to defects in collagen deposition, with higher levels of type 3 collagen associated with hernia development <sup>(231)</sup>.

### **Surgical technique**

Surgical technique is clearly vital in optimizing wound healing. Careful tissue handling, strict aseptic techniques, avoidance of tension across the wound and choice of suture will all contribute to minimizing wound complications. Intraoperative hypothermia should be avoided and supplemental oxygen should be give postoperatively to reduce infective complications.

### 1.4.3 *Surgical Site Infections*

#### 1.4.3.1 Definition and Epidemiology

The Centre for Disease Control defines a SSI as an infection within 30 days of an operation or up to one year if an implant is left in place and the infection is related to an operative procedure<sup>(8)</sup>. This definition has recently been revisited by Berrios-Torres et al. and operations involving the use of implants, remain under surveillance for 90 days in the post-operative setting as opposed to a year<sup>(232)</sup>. Major LLA remains in the 30-day surveillance group of procedures<sup>(232)</sup>. Figures from the SSI Surveillance reported that the highest rate of SSI was reported in association with LLA, 13.1%<sup>(233)</sup>. In clinical practice it is clear that is an under-representation and the infection rate within our institution is approximately 25%<sup>(234)</sup> which reflects the infection rate reported in a recent trial by Sadat et al (22.5%)<sup>(235)</sup>. This high rate of infection is likely to be related to underlying risk factors which affect wound healing and susceptibility to infections, namely poor perfusion and diabetes.

Despite the reported incidence of SSIs for clean surgery of <2% the incidence in practice varies significantly. Open varicose vein surgery has an incidence of SSIs reported in the literature which varies from 1.5% to 16%<sup>(236, 237)</sup> whilst figures from the SSI Surveillance

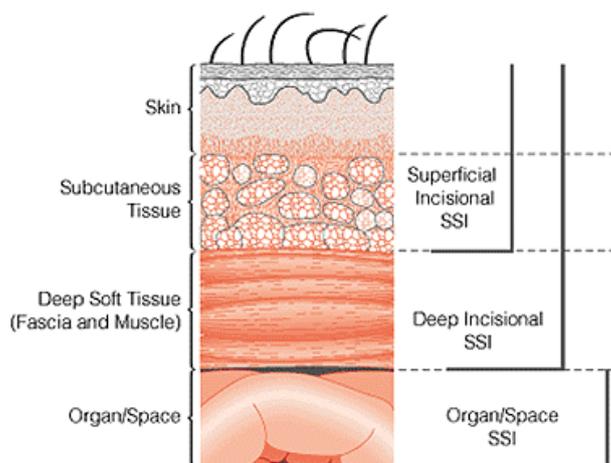


Figure 16 Anatomical levels of SSIs<sup>(7)</sup>

demonstrated a high rate of SSIs in patients undergoing LLA (13.1%)<sup>(238)</sup>.

SSIs can also be subdivided into three different anatomical levels of infection: superficial incisional SSI, deep incisional SSI and organ/space SSI<sup>(239)</sup>

SSIs have always been a major postoperative complication and it is said that until the 1860's the outcomes were so poor that surgeons elected to not operate. Introduced by Sir James Simpson the term 'Hospitalism' described SSIs. Shock, streptococcal infections or staphylococcal infections or hospital gangrene were the most common cause of post-operative mortality<sup>(240)</sup>. Indeed the head surgeon of London's University College hospital in 1874 reported a mortality rate of 36% following major LLAs which reflected the statistics of 30-50% from most of the 'civilised' operative centres of the time<sup>(241)</sup>.

Great advances have been made since this time with the understanding of micro-organisms and the development of antibiotics. However SSIs still account for 14-16% of all infections in hospitalized patients. Among surgical patients, SSIs are the most frequent healthcare

associated infections, accounting for 38 per cent of the total. Overall 5-10% of all patients who undergo a procedure will develop a SSI. These not only have a significant impact on patient morbidity, but in one study, 77% of the deaths of surgical patients were related to surgical wound infection <sup>(8)</sup>. Kirkland et al calculated a relative risk of death of 2.2 attributable to SSIs, in comparison with matched surgical patients without infection <sup>(242)</sup>.

SSIs also have substantial time and cost implications and it has been estimated that hospital stays are increased by 7-10 days and a 20% increase in costs <sup>(243-245)</sup>. On occasions further wound debridement and increased frequency of dressings is necessary to allow healing by secondary intention.

A survey by Smyth et al. undertaken in 2006 suggested that approximately 8% of patients in hospital in the UK have a healthcare associated infection. SSIs accounted for 14% of these infections and nearly 5% of patients who had undergone a surgical procedure were found to have developed an SSI <sup>(246)</sup>. Prevalence studies tend to underestimate SSIs as many of these infections occur following hospital discharge. SSIs are associated with considerable morbidity and it has been reported that over one-third of postoperative deaths are related, at least in part, to SSI <sup>(247)</sup>. However, it is important to recognise that SSIs can range from a relatively trivial wound discharge with no other complications to a life-threatening condition. Other clinical outcomes of SSIs include poor, cosmetically unacceptable surgical scars such as those that are spreading, hypertrophic or keloid, persistent pain and pruritus, contractures resulting in loss of mobility particularly when over joints, and a significant impact on emotional wellbeing <sup>(248)</sup>.

SSI can double the length of patient hospital stay and thereby increase the costs of health care. Additional costs attributable to SSI of between £814 and £6626 have been reported depending on the type of surgery and the severity of the infection <sup>(249, 250)</sup>. The main additional costs are related to re-operation, extra nursing care and interventions, and drug treatment costs. The indirect costs, due to loss of productivity, patient dissatisfaction and litigation, and reduced quality of life, have been studied less extensively.

#### 1.4.3.2 Factors affecting incidence of Surgical Site Infection

SSIs are the second commonest type of adverse event occurring in hospitalized patients following surgery and are one of the most common surgical complications <sup>(251-253)</sup>. SSI surveillance is integral to hospital infection control and quality improvement programs, with feedback of SSI rates being an important component of SSI reduction strategies <sup>(254)</sup>. The

incidence of SSI differs widely from hospital to hospital and from one geographic location to another. A number of risk factors have been shown in univariate or multivariate analyses to influence the risk of SSIs and are summarised in Figure 17.

Potential patient-related factors that have been flagged up, include older age, pre-existing infection, colonisation with *Staphylococcus aureus* and other potential pathogens, diabetes and smoking <sup>(8)</sup>. Procedure-related factors include amongst others poor surgical technique, the duration of the operation, the quality of preoperative skin preparation and inadequate sterilisation of surgical instruments <sup>(8)</sup>. Imperatori et al. have reported in a recent analysis that age and low serum albumin concentrations are the most important patient-related factors <sup>(255)</sup>, and the quality of surgical technique as an important procedure-related factor; this study has further concluded that most SSIs are attributable to patient-related factors rather than procedure-related factors <sup>(255)</sup> as leading causes of morbidity and mortality among patients undergoing major surgery.

A very extensive systematic review by Korol et al. in 2013 has summarised data on SSIs from 57 studies. Some of the key findings highlighted included stratification of SSIs by surgical specialty/pathology. From Figure 18 adopted from Korol et al. <sup>(256)</sup> it can be seen that surgery involving immunocompromised patients (Cancer, Transplant) carries the highest incidence of SSI amongst all specialties.

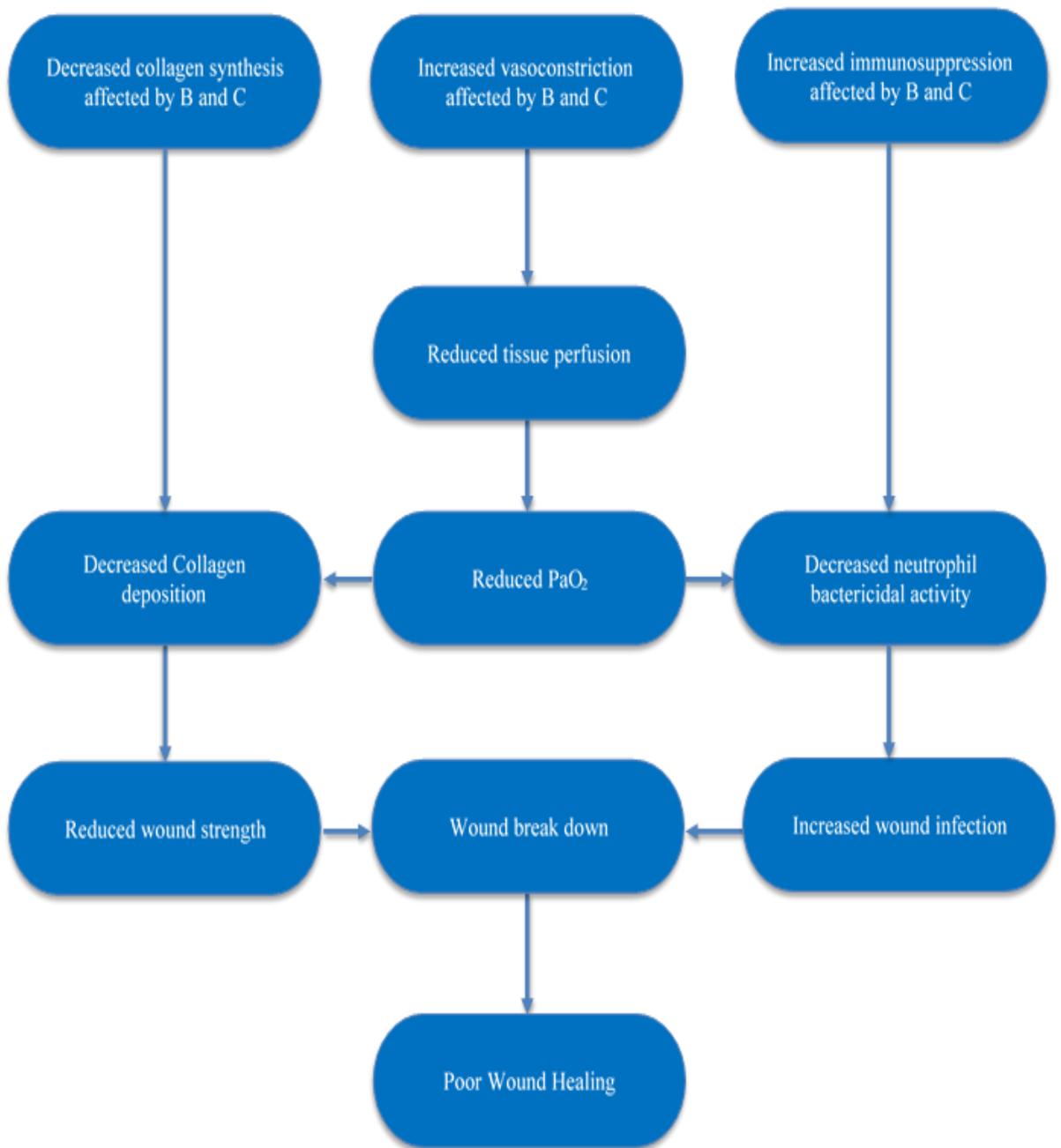
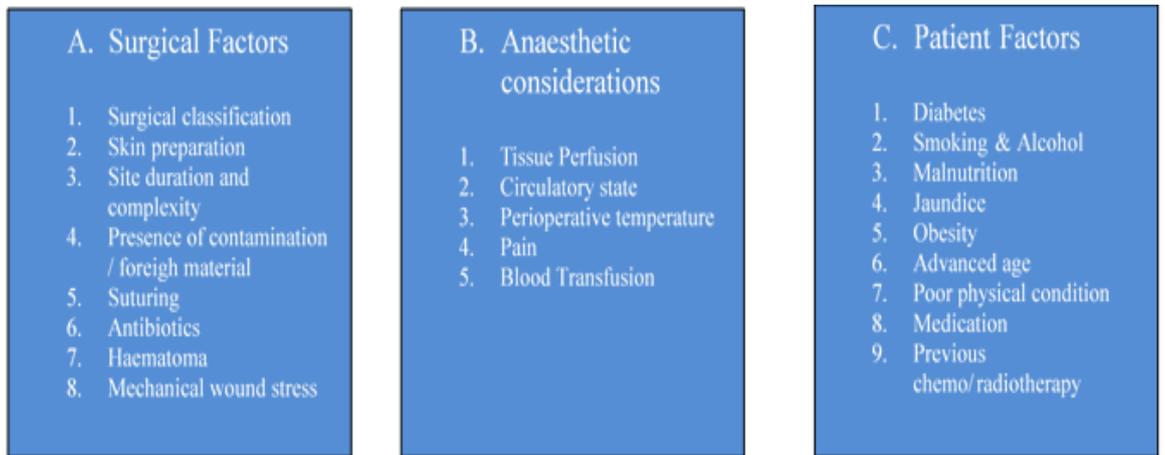


Figure 17 Risk Factors for SSIs



least one co-morbidity was associated with an estimated odds ratio for SSI of 6.1 (95% CI: 1.3-28.9) in all major surgeries<sup>(256)</sup>.

Additional studies within the systematic review considered risk factors describing patient dependence and frailty, which were characterized in a variety of ways, including independence and activities of daily living, incontinence, and admission from a long-term health-care facility <sup>(256)</sup>. The majority of these factors were only considered in unadjusted analyses; adjusted estimates include an odds ratio for SSI of 4.35 (95% CI: 1.64-11.11) associated with admission from a long-term health facility, and an odds ratio for SSI of 2.75 (95% CI: 1.16-6.46) associated with requiring assistance with three or more activities of daily living<sup>(256)</sup>.

Perioperative variables describing the complexity and/or duration of surgery as well as duration of pre-operative length of stay were also found to be associated with risk of SSI. It was reported that an increased duration of surgery was consistently found to be associated with increased risk of SSI <sup>(256)</sup>.

### 1.4.3.3 Recommendations for reducing SSIs

Prevention of SSIs is of paramount importance to patients, healthcare providers and policy-makers, as they impact on morbidity and mortality and have significant time and cost implications. For patients undergoing amputations development of an SSI can result in delayed wound healing/ wound breakdown and as such increased inpatient stay, cost of treatment (debridement/ vac/ antibiotics/ revision surgery) and delays in rehabilitation.

The National Institute for Health and Care Excellence (NICE) has extensively looked into the incidence and risks related to the development of SSI and has produced a series of recommendations in order to minimise this risk and improve outcomes following surgery.  
<sup>(257)</sup>

These have been classified into three stages/phases:

1. Preoperative phase
2. Intraoperative phase
3. Post-operative phase.

### **Preoperative phase<sup>(257)</sup>**

1. Preoperative showering: Patients are advised to shower or have a bath (or help patients to shower, bath or bed bath) using soap, either the day before, or on the day of, surgery.
2. Hair removal: This is to be avoided in order to reduce the risk of SSI. If hair must be removed, use electric clippers with a single-use head on the day of surgery.
3. Patient theatre wear: Patients are given specific theatre wear that is appropriate for the procedure and clinical setting and that provides easy access to the operative site and areas for placing devices. Patient comfort and dignity are also considered.
4. All staff should wear specific non-sterile theatre wear in all areas where operations are undertaken. Staff leaving the operating area and staff wearing non-sterile theatre wear should keep their movements in and out of the operating area to a minimum.
5. Nasal decontamination: Routine nasal decontamination with topical antimicrobial agents aimed at eliminating *Staphylococcus aureus* should be avoided to reduce the risk of SSI. This is however not the case for all surgical specialties.
6. Mechanical bowel preparation: mechanical bowel preparation should not be routinely used to reduce the risk.
7. Hand jewellery, artificial nails and nail polish: The operating team should remove hand jewellery, artificial nail and nail polish before operations.
8. Antibiotic prophylaxis: Prophylaxis is recommended in patients undergoing clean surgery where a prosthesis will be used. Antibiotics are NOT recommended for patients undergoing non-prosthetic, clean uncomplicated surgery. Prophylaxis is further indicated for clean-contaminated and contaminated procedures. Use of the local antibiotic formulary and consideration of potential adverse effects when choosing specific antibiotics for prophylaxis is also recommended. A single dose of antibiotic prophylaxis intravenously on starting anaesthesia is advised, which should be administered earlier in cases where surgery involves the use of a tourniquet. Timing and pharmacokinetics (for example, the serum half-life) and necessary infusion time of the antibiotic are also of the essence. A repeat dose of antibiotic prophylaxis may become necessary when the operation is longer than the half-life of the antibiotic given.

### **Intraoperative phase<sup>(257)</sup>**

1. Hand decontamination: The operating team should wash their hands prior to the first operation on the list using an aqueous antiseptic surgical solution, with a single-use brush or pick for the nails, and ensure that hands and nails are visibly clean. Before subsequent operations, hands should be washed using either an alcoholic hand rub or an antiseptic surgical solution. If hands are soiled then they should be washed again with an antiseptic surgical solution. The recommended duration of a hand scrub is 3 minutes <sup>(258)</sup>. Alcohol-based gel or hand rub is also recommended with exposure of 1.5 minutes <sup>(258)</sup>.
2. Incise drapes: The use of non-iodophor-impregnated incise drapes routinely for surgery is not recommended as they may increase the risk of SSI. If an incise drape is required, use an iodophor-impregnated drape unless the patient has a documented iodine allergy.
3. Use of sterile gowns: The operating team should wear sterile gowns in the operating theatre during the operation.
4. Gloves: Consider double gloving when there is a high risk of glove perforation and the consequences of contamination may be serious.
5. Antiseptic skin preparation: The skin is prepared at the surgical site immediately before incision using an antiseptic (aqueous or alcohol-based) preparation: povidone-iodine or chlorhexidine are most suitable. These should be allowed to dry so that the minimum exposure time is at least reached. If diathermy is to be used, ensure that antiseptic skin preparations are dried by evaporation and pooling of alcohol-based preparations is avoided.
6. Diathermy: Do not use diathermy for surgical incision to reduce the risk of SSI.
7. Maintaining patient homeostasis: Maintain patient temperature in line with ‘Inadvertent perioperative hypothermia’ <sup>(257)</sup>. Maintain optimal oxygenation during surgery. In particular, give patients sufficient oxygen during major surgery and in the recovery period to ensure that a haemoglobin saturation of more than 5% is maintained. Maintain adequate perfusion during surgery <sup>(259)</sup>.
8. Insulin: Insulin is not recommended to be routinely administered to patients who do not have diabetes to optimise blood glucose postoperatively as a means of reducing the risk of SSI.
9. Wound irrigation and intracavity lavage: Wound irrigation or intra-cavity lavage in reducing the risk of SSI is not recommended.

10. Antiseptic and antimicrobial agents before wound closure: Intraoperative skin re-disinfection or topical cefotaxime in abdominal surgery to reduce the risk of SSI is not recommended
11. Wound dressings: Surgical incisions are to be covered with an appropriate interactive dressing at the end of the operation.

### **Postoperative phase**

1. Changing dressings: Post-operative wounds are to be handled using an aseptic non-touch technique for changing or removing surgical wound dressings.
2. Postoperative cleansing: Sterile saline is recommended for wound cleansing up to 48 hours after surgery. Patients are to be advised that they may shower safely 48 hours after surgery. Tap water may be used for wound cleansing after 48 hours if the surgical wound has separated or has been surgically opened to drain pus.
3. Topical antimicrobial agents for wound healing by primary intention: These are not recommended in the post-surgical setting.
4. Dressings for wound healing by secondary intention: Eusol and gauze, or moist cotton gauze or mercuric antiseptic solutions are not suitable for the management of surgical wounds that are healing by secondary intention. Instead, appropriate interactive dressings are to be used in the management of surgical wounds that are healing by secondary intention. If further input is necessary, then the involvement of a tissue viability nurse and occasionally, a Plastic and Reconstructive surgeon may be considered
5. Antibiotic treatment of SSI and treatment failure: When an SSI is suspected (i.e. cellulitis), either de novo or because of treatment failure, the patient is to be administered an antibiotic that covers the likely causative organisms. Consideration of local resistance patterns, the results of microbiological tests and even the involvement of a Microbiology/Infectious Diseases Consultant may become necessary in choosing an antibiotic.
6. Debridement: This may become necessary in the postoperative setting, as occasionally the infection may be too overwhelming to eradicate by antibiotics and dressing care. If there is extensive wound debris and necrotic infected material, this may require excision in theatre in order to prevent sepsis and to facilitate wound healing.

All surgical wounds are contaminated by microbes however host defences are usually efficient enough to eliminate them. The risk of developing a wound infection is influenced not only by the degree of wound contamination but also by the interplay of host, microbial and surgical factors. Important host factors include: diabetes mellitus (particularly if glycaemic control is less than optimal), hypoxaemia, hypothermia, leucopenia, smoking, long term use of steroids or immunosuppressive agents, malnutrition, poor skin hygiene.

Perioperative / environmental factors are operative site shaving, breaks in operative sterile technique, early or delayed initiation of antimicrobial prophylaxis, inadequate intraoperative dosing of antimicrobial prophylaxis, infected or colonized surgical personnel, prolonged hypotension, poor operative room air quality, contaminated operating room instruments or environment and poor wound care postoperatively<sup>(239)</sup>.

#### 1.4.3.4 Microbiology

Microorganisms contain or distribute poisonous substances that increase their capacity to colonise and attack a host, and sometimes exhibit parasitic nature. Numerous gram-negative microscopic organisms deliver endotoxin, which animates cytokine formation. Thus, cytokines can trigger a systemic inflammatory response (SIRS) which has the potential to lead to multi-organ failure.

In most SSIs, the responsible pathogens originate from the patient's endogenous flora, and are mainly skin commensals. The most commonly isolated organisms are *S. aureus*, coagulase-negative staphylococci, *Enterococcus* spp. and *Escherichia coli*; however, the pathogens isolated depend on the procedure. An increasing number of SSIs are attributable to antibiotic-resistant pathogens such as methicillin-resistant *S. aureus* (MRSA) or *Candida albicans* <sup>(8)</sup>. This development may reflect the increasing number of severely ill or immunocompromised surgical patients, and the widespread use of broad-spectrum antibiotics <sup>(8)</sup>. Pathogens may also originate from preoperative infections at sites remote from the operative site, particularly in patients undergoing insertion of a prosthesis or other implant. In addition to the patient's endogenous flora, SSI pathogens may originate from exogenous sources such as members of the surgical team, the operating theatre environment, and instruments and materials brought within the sterile field during the procedure. Such pathogens are predominantly aerobes, particularly Gram-positive organisms such as staphylococci and streptococci. The risk of an SSI developing after microbial contamination of the surgical site will depend on the dose and virulence of the pathogen and the patient's level of resistance, according to the following equation:

$$\text{Risk of SSI} = \frac{\text{Dose of bacterial contamination} \times \text{virulence}}{\text{Resistance of patient}}$$

The risk of SSI is considered high when the level of contamination exceeds  $10^5$  organisms per gram of tissue, although lower doses may be required if foreign material such as sutures are present<sup>(260)</sup>. The virulence of the organism relates to its ability to produce toxins or other factors that increase its ability to invade or damage tissue. Mortality rates in patients infected with highly virulent pathogens such as MRSA may be as high as 74%<sup>(261)</sup>.

Skin commensals are usually gram-positive cocci, most commonly Staphylococci but gram-negative aerobes and anaerobes can be found contaminating the skin of the groin and perineum. MRSA has increased the morbidity and mortality rate from wound infections. Other gram positive organisms such as enterococci, coagulase negative staphylococci, and Streptococcus species, are less frequently involved. Operations involving hollow viscera like appendectomy, gastroduodenal, colorectal, biliary tract and urologic operations, all expose the surrounding tissues to gram negative bacilli including Escherichia coli, Enterobacter, Klebsiella, Proteus species whereas a gram-positive organism such as Enterococcus, and anaerobes<sup>(262)</sup>. Table 5 on page 116 derived from Mangram et al. <sup>(8)</sup> gives a summary of common pathogens and the type of surgery with which they are commonly associated.

Gram-positive organisms, particularly staphylococci and streptococci, are the most frequent causative organisms for SSI's and arise from not only the patient but also healthcare providers, surgical instruments and the surgical environment. The emergence of resistant strains of bacteria such as MRSA, has considerably increased the burden of morbidity and mortality associated with wound infections.

Type of surgery	Common pathogens <sup>a</sup>
Placement of graft, prosthesis or implant	<i>Staphylococcus aureus</i> ; CoNS
Cardiac	<i>S. aureus</i> ; CoNS
Neurosurgery	<i>S. aureus</i> ; CoNS
Breast	<i>S. aureus</i> ; CoNS
Ophthalmic	<i>S. aureus</i> ; CoNS; streptococci; Gram-negative bacilli
Orthopaedic	<i>S. aureus</i> ; CoNS; Gram-negative bacilli
Non-cardiothoracic	<i>S. aureus</i> ; CoNS; <i>Streptococcus pneumoniae</i> ; Gram-negative bacilli
Vascular	<i>S. aureus</i> ; CoNS
Appendectomy	Gram-negative bacilli; anaerobes
Biliary tract	Gram-negative bacilli; anaerobes
Colorectal	Gram-negative bacilli; anaerobes
Gastroduodenal	Gram-negative bacilli; streptococci; oropharyngeal anaerobes (e.g. peptostreptococci)
Head and neck	<i>S. aureus</i> ; streptococci; oropharyngeal anaerobes (e.g. peptostreptococci)
Obstetric and gynaecological	Gram-negative bacilli; enterococci; Group B streptococci; anaerobes
Urological	Gram-negative bacilli

<sup>a</sup> CoNS, coagulase-negative staphylococci.

Table 5 Pathogens commonly associated with different surgical procedures<sup>(8)</sup>

#### 1.4.3.5 Sepsis and SIRS

Systemic inflammatory response syndrome (SIRS) can be defined as, presence of any two of: hyperthermia (>38°C) or hypothermia (<36° C), tachycardia (>90 min<sup>-1</sup>, no β-blockers) or tachypnoea (>20 min<sup>-1</sup>) and white cell count >12× 10<sup>9</sup> l<sup>-1</sup> or <4 ×10<sup>9</sup> l<sup>-1</sup> <sup>(263)</sup>. Sepsis is defined as the systemic manifestation of SIRS, with a documented infection. Multiple organ dysfunction syndrome (MODS) is the effect that the infection produces systemically. Multiple system organ failure (MSOF) is the endstage of uncontrolled MODS <sup>(263)</sup>.

#### 1.4.3.6 The Use of antibiotics in SSI

In the 1960's research was reported which determined that for antibiotics to be effective they had to have been in the system at the time of the surgical incision in order to be effective <sup>(264, 265)</sup>. The antibiotics given should be effective against the most likely causative organisms, demonstrate good tissue penetration and cause minimal harm (i.e. low risk of causing disorders such as C difficile)<sup>(265)</sup>. Surgeries are classified by type in relation to the potential for SSI that is: clean; clean-contaminated; contaminated and dirty (see Table 6, pg.117).

Wound classification	Description	Infective risk (%)
Clean	Uninfected operative wound	<2

	No acute inflammation No entry to internal organs No break in aseptic technique Typically elective E.g. hernia repair	
Clean-contaminated	Opening to internal organ but minimal or no spillage of contents No evidence of infection or major break in aseptic technique E.g. appendicectomy	<10
Contaminated	Opening to internal organs with inflammation or spillage of contents Major break in aseptic technique Presence of acute non-purulent inflammation E.g. colectomy for obstruction	15-20
Dirty	Purulent inflammation present Presence of devitalised tissue Intraoperative abscess formation or visceral perforation	40

*Table 6 Classification of Wounds*

Nice Guidance 74 on SSIs clearly states that for procedures which are classified as clean surgery antibiotic prophylaxis is not required <sup>(257)</sup> however for some procedures, due to higher reported infection rates, such as in amputations and procedures involving groin incision, antibiotics are given, usually at the surgeons discretion.

Short courses of antimicrobial prophylaxis are recommended in order to reduce SSI risk. The aim of this approach is not to sterilise tissue, but to reduce intraoperative contamination to levels to avoid overwhelming the patient's defences <sup>(8)</sup>. Antimicrobial prophylaxis is primarily indicated in elective procedures in which skin incisions are closed in the operating theatre. The choice of agent should be based on a host of reasons including the pathogens most commonly associated with the procedure being performed (see Table 5 pg.116). In practice, broad-spectrum beta-lactam agents (particularly cephalosporins) are most widely used, with an agent such as metronidazole being added if necessary to provide cover against anaerobes; vancomycin is not recommended for routine prophylaxis. The first dose should be timed to ensure that bactericidal concentrations are achieved in serum and tissue at the

time of the incision, and these concentrations should then be maintained for up to a few hours after wound closure in the operating theatre.

#### 1.4.3.7 Skin preparations

A recent Cochrane review that considers the use of skin cleansers in clean surgery: ‘Preoperative skin antiseptics for preventing surgical wound infections after clean surgery’<sup>(266)</sup> includes data from one trial comparing chlorhexidine and iodine in clean surgery: “One study compared iodine and chlorhexidine. Berry 1982<sup>(267)</sup> compared povidone iodine (PI) 10% in alcohol with chlorhexidine 0.5% in spirit (Hibitane) in 371 patients undergoing clean surgery. Significantly more patients (28/176; 15.9%) in the PI group developed an infection compared with the patients cleansed with chlorhexidine (8/195; 4.1%)(OR 4.42, 95%CI 1.96 to 9.99).”

The study did however have limited follow up. As such the review concluded that “there is insufficient research examining the effects of preoperative skin antiseptics to allow conclusions to be drawn regarding their effects on post-operative surgical wound infections”.

Whilst no clear benefit from preoperative bathing / showering with chlorhexidine has been demonstrated<sup>(268)</sup>, a systematic review and cost analysis comparing chlorhexidine and povidone iodine for preoperative surgical skin antiseptics in clean-contaminated surgery reported that that “Chlorhexidine reduced postoperative surgical-site infection compared with povidone-iodine (pooled odds ratio 0.68, 95 per cent confidence interval 0.50 to 0.94;  $P = 0.019$ )”, concluding that “Chlorhexidine should be used preferentially for preoperative antiseptics in clean-contaminated surgery”<sup>(269)</sup>. A subsequent randomised controlled trial(RCT) of 849 patients undergoing clean – contaminated surgery has also demonstrated that cleansing with chlorhexidine-alcohol is superior to povidone-iodine, for preventing SSI<sup>(270)</sup>.

Multiple articles have been published regarding the risk of ignition of alcohol based skin preparation when utilising diathermy<sup>(271)</sup> <sup>(272, 273)</sup>. Whilst a rare occurrence the impact on patient morbidity and mortality is high. The NHS National Reporting and Learning System (NRES) reports 23 incidents from inception to October 2011 where the involvement of skin prep was clearly documented and a further 10 incidents where it was likely that there was a link. Four of the incidents resulted in either death or severe harm to the patient<sup>(274)</sup>. Guidelines exist regarding its usage recommend avoiding pooling of the prep and drying the site prior to commencing the surgery.

Despite these aforementioned studies and reports examining the relative merits of the different commercially available skin preparations no consensus exists. A recent survey of consultant members of the Vascular Society performed by the Chief Investigator established that in amputation surgery 44.6% of respondents utilise aqueous betadine, 29.0% alcoholic chlorhexidine, 21.4% alcoholic betadine and only 4.8% aqueous chlorhexidine. Indeed the NICE SSI guidelines for antiseptic skin preparation (intra-operative) states: “*Prepare the skin at the surgical site immediately before incision using an antiseptic (aqueous or alcohol-based) preparation: povidone-iodine or chlorhexidine are most suitable*”<sup>(257)</sup>.

### 1.4.3.8 ASEPSIS Score

ASEPSIS is a quantitative scoring method (Table 7) that provides a numerical score related to the severity of wound infection using objective criteria based on wound appearance and the clinical consequences of the infection<sup>(275, 276)</sup>. The ASEPSIS tool has been reported to be repeatable and related to outcome<sup>(277, 278)</sup>

Wound characteristic	Score
Serous exudates	3
Erythema	3
Purulent exudates	6
Separation of wound edges	6
<b>Additional treatment</b>	
Postoperative Antibiotics	10
Abscess drainage	5
Wound debridement	10
Isolation of bacteria	10
Prolonged stay/admission to hospital	5

*Table 7 The ASEPSIS Scoring tool for SSIs*

An ASEPSIS score of  $\geq 21$  is taken as indicating the presence of infection, whilst a score of  $\leq 10$  is taken to represent satisfactory healing.

## 1.4.4 *Amputation surgery and the amputation stump – A Dock for cutaneous complications and Surgical Site Infection*

### 1.4.4.1 Cutaneous complications and chronic recurrent infection

Stump skin is a transformed cutaneous landscape. The disruption of blood vessels, nerves, and lymphatics by amputation permanently halts the migration and flow of immunocompetent cells through the lymphatic system and hinders neuromediator signalling. In addition, the common previous comorbidities of PVD, diabetes, or malignancy all predispose to poor circulation or neuropathy, even before amputation. The trauma of the surgery itself also leaves scars, invaginations of the skin, and bony protrusions, making the skin more fragile and prone to problems.

Skin alterations are not something that the organ itself is physiologically adapted to, especially when considering the load and physical demand of a prosthesis; yet, the stump is placed in the enclosed prosthetic environment of the socket and made to endure high compressive and shear forces, increased temperature, and high humidity <sup>(279-281)</sup>. The combination of these factors may lead to skin breakdown, especially in situations of poor personal hygiene as well as a poorly fitted prosthesis.

The trauma of amputation, a medical history of an immunocompromised state, and stump skin breakdown from the use of a prosthesis can ultimately create a ‘district’ of immune compromise. This site is readily prone to opportunistic infections, tumours, and malignancies <sup>(282)</sup>. The term immunocompromised district provides a framework to understand the vulnerability of stump sites to skin disease after such trauma.

Healing of the surgical wound after amputation may be prolonged and complicated, especially if the amputation was secondary to PVD, diabetes, or cancer. Under such circumstances the amputee is already in an immunocompromised state, and therefore susceptible to infections and vascular insufficiency. These complications can increase the time from surgery to rehabilitation and sometimes lead to additional surgical procedures. As such, morbidity and mortality following major LLA is high and the impact on patients and national health economy is significant.

In Section 1.4.2, pg.96 of this thesis, we have seen that as part of the wound healing following surgery, a certain amount of oedema is expected. Once it begins to subside with wound healing and maturation of the scar, a reduction is expected in the overall size of the stump. To maximize shrinkage in a balanced manner and to minimize invaginations, the stump site is often wrapped postoperatively with an elastic compression bandage also known as the ‘shrinker’. This moulding process promotes the formation of a conically shaped stump site that will best fit into a prosthetic device, to reduce skin breakdown <sup>(281, 283, 284)</sup>.

In general, skin disease on stump skin can be divided into inflammatory and noninflammatory causes. Noninflammatory causes are often due to poorly fitting prostheses,

leading to increased friction, shearing and uneven forces across the stump site. Inflammatory causes may be secondary to retention of perspiration in the socket, resulting in poor hygiene and subsequent bacterial and fungal infections. A prosthesis that does not fit well compounds both inflammatory and noninflammatory dermatologic diseases at the stump sites, which underscores the importance of proper prosthesis fit.

Many dermatologic disorders are seen on stump sites as a result of skin breakdown, inflammation, infection, or malignancy (see Table 8, pg.122). Trapping of perspiration in the liners near the skin can lead to maceration and skin breakdown. Irritation caused by many components of the liners, socks, or socket can lead to dermatitis. An infected hair follicle can turn into an ulcer if not treated promptly. Such cutaneous problems can lead to prosthesis abandonment, which negatively impacts an amputee's quality of life and can lead to social isolation. Amputees who are young and active tend to have conditions related to skin breakdown, whereas diabetics and those with PVD tend to suffer from ulcers and conditions related to vascular insufficiency. It has been reported that between 34% and 75% of lower-extremity amputees suffer skin disease, and more significantly, have 65% more dermatologically related complaints than the general population <sup>(279-281)</sup>.

When amputees first wear their prosthesis, deposits of hemosiderin may be noted on the skin of the distal end of the stump. This condition is called hyperaemia and it is due to the vascular and lymphatic insufficiency of stump skin, leading to oedema and haemorrhage.

<b>Common dermatologic Complaints</b>	<b>Common Cause</b>	<b>Treatment</b>
<i>Inflammatory conditions</i>		
Acroangiokeratosis	Circulatory problem caused poor socket fit	Adjust prosthetics
Bacterial folliculitis	Rubbing of hair with socket or sock	Laser hair removal
Contact dermatitis	Allergy to components of socket or sock	Topical steroids, patch testing and barrier cream
Eczema Furunculosis	Infected hair follicle usually caused by staphylococcus aureus	Topical / oral antibiotics and laser hair removal

Hidradenitis	Trapped perspiration	Increased hygiene and botox injection
Psoriasis	Immune activation	Topical / oral steroids
Pyoderma	Bacterial infection	Topical / oral antibiotics
Ulceration	Bacterial infection	Antibiotics and prosthesis adjustment
<i>Non-inflammatory Conditions</i>		
Callus	Tissue proliferation from friction	Adjust prosthesis
Epidermoid cysts	Shearing forces	Antibiotics and prosthesis adjustment
Skin malignancies	Immunosuppression	Surgical excision and chemoradiotherapies
Tinea infection	Increased humidity and sweat retention	Antifungals
Yeast Infection	Increased humidity and sweat retention	Nystatin
Verrucous hyperplasia	Vascular disorder caused by poor fit prosthesis	Adjust prosthesis

*Table 8 Common Post LLA dermatological conditions, and infection types, causative stress and treatment options*

It is typically a transient event that occurs during the initial stages of a prosthesis use, and it may be prevented by the conscientious use of a compression bandage postoperatively. The condition also worsens if the prosthesis fit is too snug, which can occur if the patient's weight or the residual limb size has increased. The patient will present with a tender, well-circumscribed area of erythema that correlates with the area of negative pressure in the socket. The prosthesis should be adjusted for a better fit to more evenly distribute the forces over the stump to treat hyperaemia.

Acroangiodermatitis can be caused by poor circulation, usually due to an ill-fitting suction prosthesis, and subsequent stump-site oedema, hypoxia, and proliferation of fibroblasts and capillaries <sup>(281, 285, 286)</sup>. Patients usually present with painful erythematous papules, plaques, or nodules. In the majority of cases they improve with simple adjustments to or replacement of the prosthesis, but some cases require use of medications such as dapsone, ablative therapy, or even surgery if arteriovenous malformations are associated with the neovascularization <sup>(281, 285, 286)</sup>.

Folliculitis, a condition where the hair follicles can become inflamed from a combination of friction, infection by bacteria, and excessive humidity in the socket may also result in this patient cohort and can lead to erythematous, pruritic, and painful pustules <sup>(281, 287)</sup>. The condition can be exacerbated by hot weather due to greater perspiration, skin maceration, and increased friction <sup>(287, 288)</sup>. Simple hygiene and, in some cases, laser hair removal on affected areas are sufficient to provide treatment. Köbner's phenomenon, better known as isomorphic response is a well-documented phenomenon which is characterised by occurrence of new skin lesions or, recurrence of a pre-existing skin disease on immunocompromised skin sites following trauma or in the case of amputees, the operated site. It has been reported in patients with a history of folliculitis elsewhere who experienced development of the condition on their stump skin following LLA <sup>(287, 288)</sup>.

Eczema is another example of the immunocompromised district lending itself to an exaggerated immune response. Patients report scaly, erythematous, and often pruritic plaques on the stump skin. If eczema appears on the stump skin on the background of previous eczema history even affecting other body areas, this constitutes another example of Köbner's phenomenon<sup>(289)</sup>. Eczema may be related to poor fit of the prosthesis or changes in climate, diet, or medication <sup>(287)</sup>. Treatment is normally topical corticosteroids and efforts to improve the fit of the prosthesis. Psoriasis, like eczema, is an activation of the immune response and may behave in exactly the same manner <sup>(289)</sup>.

The encased, sealed environment of a socket or liner may also lead to the development of intertrigo from the friction of skin rubbing on skin in a humid environment. This mostly occurs around the inguinal area and in sockets applied close to skin invaginations or grafts. Topical steroids and prosthesis adjustment remain the mainstay of treatment <sup>(287)</sup>.

Dudek et al. have previously reported that ulceration was in fact the primary complaint of 528 individuals who underwent major LLA, most of which were transtibial <sup>(280)</sup>. Creased stump socks and liners or a poorly fitting prosthesis all potentially lead to the formation of ulcers in the younger amputee population cohort. In the UK, the overwhelming majority of amputation candidates are frail, elderly patients with multiple comorbidities who typically suffer with vascular insufficiency; they tend to have a higher rate of chronic ulcers <sup>(280, 287)</sup>. Ulceration is particularly damaging to these patients as it predisposes to SSIs in the early post-operative stages, as well as chronic infection, skin alterations and ultimately significant delay if not failure to walk on a prosthetic leg <sup>(204, 280, 287)</sup>. Prosthesis alteration, as well as topical, oral, or, in severe cases, intravenous antibiotics are essential in preventing skin

breakdown and treating infection. In cases of prolonged healing, surgical revision and debridement may be necessary<sup>(289)</sup>.

Diabetic patients, particularly those with PVD are in addition more prone to complications of chronic folliculitis, such as hidradenitis, furuncles and pyoderma<sup>(281, 287, 290)</sup>.

Another type of infection commonly encountered in the immunocompromised is one caused by fungal organisms. These are increasingly seen in stump sites due to excessive perspiration and lack of adequate ventilation. Tinea and yeast are the usual culprits. Tinea causes erythematous lesions with scale, whereas yeast infections appear intensely erythematous, wet, and macerated. Such infections are usually encountered at the stump site but may also occur in the groin in transfemoral amputees whose prosthesis extends to this area<sup>(287)</sup>. A culture or potassium hydroxide preparation of skin scrapings is usually diagnostic, and treatment consists of topical fungistatic creams and powders or oral antimycotic medication such as fluconazole for yeast and terbinafine or itraconazole for dermatophyte infections<sup>(287, 291)</sup>.

A poorly fitting prosthesis can lead to numerous dermatologic conditions, and one of the most frequently diagnosed ones is an epidermoid or inclusion cyst, caused by the invagination of keratin into the dermis<sup>(281)</sup>. The cysts tend to develop along the edge of a poorly fitting prosthesis because of shearing forces at sites of moist, hair-bearing skin<sup>(204, 280)</sup>. Untreated cases can result in cyst rupture and break down, leading to ulceration, secondary infection, and the formation of sinus tracts. Treatment consists usually of excision and drainage, oral or intravenous antibiotics, and adjustments to the prosthesis<sup>(204, 280, 287)</sup>.

Squamous and basal cell carcinomas and lymphangiosarcoma also have been reported on amputee stumps. Levy et al. reported on a case of amputation secondary to lymphangioma. The patient later presented with fatal lymphangiosarcoma of the residual limb<sup>(204, 280, 287)</sup>. Such cases are a reminder of the vulnerability of an amputee's stump site to malignancies. Pathology on the amputee's stump site, therefore, should be accurately diagnosed and treated expeditiously to avoid metastasis and other potentially life-threatening conditions<sup>(289)</sup>.

#### 1.4.4.2 The concept of 'immunocompromised district' and its impact on stump skin

In 2011, Ruocco et al. described the novel idea of an immunocompromised district<sup>(282, 292)</sup>. This description is aimed at providing an overarching term for regional immune defects of the skin due to congenital or acquired reasons<sup>(289)</sup>. Immunocompromised districts are known

to develop following infection, malignancies, immune disorders, burns, radiation, vaccinations, or trauma <sup>(293)</sup>. In the case of amputations, often pre-existing vascular disease as well as the operative trauma cause a disruption in blood and lymphatic flow and dysregulation of neuroimmune regulators <sup>(293)</sup>. Following insult, the skin of an immunocompromised district may appear normal, but the immune response is in fact forever altered.

Reports of rare dermatologic conditions on stump skin highlight the change in immune response and support the concept of an ‘immunocompromised district’. The stump skin may have been immunocompromised before the amputation, as may be the case in the patient with diabetes and history of a chronic ulcer. The amputation may have created the immunocompromised district or perhaps the medications mentioned could have created a region of immune dysfunction <sup>(289)</sup>.

Diabetes, PVD, and malignancies are also immunocompromised states that not only lead to amputations, but also could directly contribute to the formation of an immunocompromised district. Patients whose amputations were due to malignancies are also generally immunocompromised, especially during or around chemotherapy courses. These patients are predisposed to malignancies after amputation. Whether a malignancy on the stump is due to the patient’s immuno-compromised state in general or due to a newly formed immunocompromised district after amputation is not clear and therefore a high index of suspicion should always be maintained by health professionals presented with skin lesions<sup>(289)</sup>.

#### 1.4.4.3 Infection following major lower limb amputation

Patients who undergo major limb amputation represent a high-risk group for surgical intervention, with decreased capacity to tolerate complications due to significant comorbidities <sup>(294)</sup>. They often have many patient-related risk factors for developing SSI, including diabetes mellitus, old age, smoking and bacterial colonisation <sup>(294)</sup>. These patients are frequent hospital inpatient attenders and can therefore be exposed to the health care environment extensively, thus becoming colonised with pathogenic bacteria. Table 9 on page 128 summarises the findings of 9 studies in terms of bacterial microorganisms that most commonly colonise and are therefore associated with increased risks of SSI development. Where the organism was investigated for and reported, the commonest pathogen responsible

for wound infection was *Staphylococcus aureus*, which accounted for between 10% and 75% of infections (Table 9 pg. 128) <sup>(295-302)</sup>. Another study cited this organism to be the cause for the majority of infections without giving exact numerical data <sup>(301)</sup>. *Clostridium perfringens* was identified as an occasional infecting organism in five studies and was responsible for up to 2% of the SSIs although one study reported simple colonisation with no SSI<sup>(302)</sup>. Gram negative bacteria caused between 8% (1/13) and 50% (2/4) of wound infections in some studies<sup>(296, 299, 301-303)</sup>. Two studies have stipulated higher incidence of *Proteus* spp. as well as *Pseudomonas* as the commonest microorganisms to cause infection <sup>(295, 297, 298, 303)</sup>.

Studies by Rubinovich et al. and Salgado et al. have shown that patients who are exposed to a health care environment are twice as likely to be colonised with methicillin resistant *Staphylococcus aureus* (MRSA) <sup>(304, 305)</sup>. It is not infrequent for patients to be admitted from residential care facilities where MRSA colonisation is thriving. As previously mentioned, the presence of skin ulceration, necrosis and gangrene, which are often the indication for limb amputation, are all well-recognised as risk factors for developing MRSA-related complications in colonised patients <sup>(306, 307)</sup>.

MRSA currently poses a serious problem for vascular surgery, particularly in the United Kingdom. It is not unusual for patients to require major amputation who have either colonisation, or frank infection due to MRSA<sup>(308)</sup>. Surprisingly, to date there are no RCTs looking at antibiotic eradication of this organism.

Richards et al. in 2005 conducted a non-randomised cohort study which examined the efficacy of teicoplanin prophylaxis in 29 patients that had either colonisation or wound infection prior to major LLA <sup>(308)</sup>. Primary healing was evident following 22 procedures (76%); surprisingly, no patient with MRSA colonisation developed an MRSA wound infection postoperatively. Seven patients developed post-operative amputation stump infection, five of which were secondary to MRSA, three of whom had active MRSA infection at the time of amputation. The study concluded that pre-operative MRSA infection significantly increased the rate of post-operative MRSA-related stump infection ( $P = 0.007$ ), and the risk of re-amputation ( $P = 0.009$ ), as well as increasing the length of post-operative hospital stay ( $P = 0.0074$ ). Findings were also in line with what Scriven et al. reported previously in 2003 <sup>(309)</sup>. In this study, patients with MRSA (colonisation or infection) were found to have spent longer in hospital before amputation ( $P = 0.0038$ ). Furthermore, the authors concluded that patients with MRSA colonisation should be considered separately from those with active infection preoperatively, and that their management should be different. Teicoplanin prophylaxis alone was stipulated as being potentially adequate in

patients colonised with MRSA at the time of surgery, but in those with active MRSA infection, it should be treated before major limb amputation, if possible, as it was associated with a higher risk of complications. The inversely proportional relationship between post-operative MRSA stump with outcome was also emphasised in another study where it led to a significant reduction in the rate of primary healing ( $P < 0.05$ ) and a significantly increased mortality rate compared to those who did not receive post-operative MRSA infection ( $P < 0.001$ )<sup>(310)</sup>.

The consequences of infection following major limb amputation may include the need for wound revision or re-amputation at a higher level. This increases hospital stay, and also potentially increases the rate of secondary post-operative complications, which may include acute myocardial infarction, pneumonia and even death, or late complications such as poor long-term mobility and independence. Minimising the risk of stump infection after major amputation therefore reduces both hospital stay and secondary morbidity.

Study Authors	Year	Country	Infecting micro-organism(s) reported
Akinyoola et al. <sup>(295)</sup>	2008	Nigeria	Investigated 30 isolates from 58 amputations. 12/30(40%) infections caused by Pseudomonas Aureginosa, 5/30(17%) by Proteus Mirabilis, 4/30(13%) by Klebsiella Pneumoniae, 3/30(10%) by each of Staphylococcus aureus, Escherichia Coli and Coliforms.
Norlin et al. <sup>(300)</sup>	1990	Sweden	2/4 (50%) Staphylococcus aureus, 2/4 (50%) Gram negative organisms.
Thomsen et al. <sup>(302)</sup>	1990	Denmark	18/25 (72%) Staphylococcus aureus, 3/25 (12%) Gram negative organisms, 4/25 (16%) undefined (1 positive swab for Clostridium perfringens without clinical evidence of infection).
Berridge et al. <sup>(303)</sup>	1988	United Kingdom	Reported on a total of 74 isolates from 40 patients. 23/74(31%) infections were caused by Staph aureus, 13/74(18%) by Klebsiella spp., 9/74(12%) by pseudomonas aureginosa, 7/74(9%) by Enterococci, 6/74(8%) by Escherichia Coli, 4/74(5%) by Anaerobic Streptococci, 2/74(3%) by Haemolytic Streptococci, 2/74(3%) by Proteus spp. and 1/74(1%) by Clostridium Perfringens.
Friis <sup>(296)</sup>	1987	Denmark	10/47 (21%) Staphylococcus aureus, 1/47 (2%) Clostridium perfringens.
Huizinga et al. <sup>(297)</sup>	1986	South Africa	Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Streptococcus faecalis, Acinetobacter calcoaceticus anitratum, Bacteroides fragilis, Bacteroides melaninogenicus.No numerical data given

Moller and Krebs <sup>(299)</sup>	1985	Denmark	6/8 (75%) Staphylococcus aureus, 2/8 (25%) Streptococcus faecalis, 1/8 (13%) Clostridium perfringens, Escherichia coli, Pseudomonas and Enterobacter.
Sonne-Holm et al. <sup>(301)</sup>	1985	Denmark	Authors state that Staphylococcus aureus and Clostridium perfringens caused most infections, but no numerical data given.
Huizinga et al. <sup>(298)</sup>	1983	South Africa	1/13 (8%) Proteus mirabilis, other infecting organisms undefined.

*Table 9 Common pathogens leading to and causing SSIs post-amputation*

---

## Chapter 2 - *STUDY METHODOLOGY*

### *Section 2.1 Study 1: A Survey of perioperative management of major lower limb amputations*

An anonymized questionnaire was designed in order to cover multiple aspects of perioperative management. This included skin preparation, antibiotic prophylaxis, use of surgical drains, method of skin closure, dressings used, intraoperative warming, and nutrition.

It was authenticated by 10 vascular surgeons to establish whether the questions were comprehensive and obtain input as to which questions would benefit from clarification or rephrasing. The same surgeons subsequently completed the questionnaire for a second time 1 month later to ensure reliability. For 5 surgeons, the validity in relation to perioperative management was also verified.

Postal contact details for full members of the Vascular Society were sought and received from the Chief Executive of the society and the questionnaire was sent out with a stamped address envelope for its return. It was impossible to establish from the contact information obtained from the Vascular Society the seniority of the participants and therefore, the questionnaire was additionally sent to several trainees and vascular practitioners. It was decided, before receipt of the responses, not to include responses of non-consultant grade participants as their practice characteristically represents that of their consultant trainer.

The responses were analysed using the chi-squared test in SPSS version 19 (IBM Corp, Armonk, NY) to determine the impact of individual variables on the reported incidence of SSI and a regression analysis was performed. For the purposes of statistical analysis, the incidence of SSI was analysed by subdivision into two groups: those infection rates reported as 10% or >10%. SSI was defined as infection occurring within 30 days of the original surgery, requiring antibiotics  $\pm$  surgical debridement or revision.

### *Section 2.2 Study 2: A Meta-analysis of the use of antibiotic prophylaxis in the prevention of surgical site*

## *infection in patients undergoing major lower limb amputations.*

### **2.2.1 Information sources and search strategy:**

Two independent researchers performed a thorough online search into Ovid, incorporating Medline, Embase and Embase Classic, and Philosopher's index. Google Scholar, PubMed and The Cochrane Collaboration library were also examined independently. All databases were examined from 1947 to date.

All databases were searched in the following manner:

1. A simple broad-base search using MeSH terms 'antibiotic', 'antibiotic prophylaxis' and 'lower limb amputation', with the limits 'humans' and 'english language' was initially performed

A more detailed search was run in the following step-wise fashion:

1. The MeSH terms lower limb amputation, leg amputation, forefoot amputation, transtibial amputation, below knee amputation, through-the-knee amputation, Gritti-Stokes amputation, above knee amputation, transfemoral amputation and hindquarter amputation were combined into a single search using OR Boolean Operator.
2. The search procedure using the same Boolean operator was repeated in two more independent search runs, firstly using the MeSH terms surgical site infection, wound infection and stump infection and secondly for antibiotics, antibiotic prophylaxis, and antibacterial agents. The independent searches were then combined using the 'AND' Boolean operator.

The Cochrane Library was independently searched using different combinations of the aforementioned MeSH terms, yielding no results. Individual papers were also identified by manual inspection. Once the search was complete, the resultant records from all databases were inspected for duplicates and irrelevant titles, all of which were excluded. The resultant records were further examined to identify the highest level of evidence papers.

### 2.2.2 *Study selection:*

Studies intended to be selected included previous systematic as well as Critical reviews. We also aimed at selecting level 1 – 2 evidence studies. The definitions regarding levels of evidence were adopted from the Oxford Centre for Evidence-Based Medicine <sup>(311)</sup> (see Appendix 6 267).

A total of 3,508 records were identified through database search and manual inspection, of which 3,489 were excluded due to lack of relevance to the question. A total of 19 relevant articles were then further screened for inclusion eligibility using the PRISMA checklist (see Appendix 7 and the following specific criteria :

1. Any study / article deemed as Level 1 – 2 evidence as defined by The Oxford Centre for Evidence-Based Medicine. Following a review of the available studies which were deemed suitable for inclusion, we decided to include lower quality papers as they were the only available source of evidence.
2. Studies were considered only if the population consisted entirely of patients undergoing major LLA. Major LLA was defined as any procedure involving hindquarter amputation moving distally up to and including forefoot amputation. The indications for surgery included peripheral vascular disease leading to wet/dry gangrene and/or incontrollable pain, failed revascularisation intervention, osteomyelitis, persistent worsening ulceration.
3. Clearly defined end points, of which, SSI was the primary end-point under investigation. SSI was defined as any infection that occurred after surgery in the part of the body where the surgery took place. SSIs can sometimes be superficial infections involving the skin only. Other SSIs are more serious and can occur within tissues under the skin and organs within 30 days of the surgery, or, in the case of implanted material, up to 1 year after surgery. Cellulitis, stump necrosis, wound dehiscence +/- frank pus were considered as clinical signs and symptoms of SSI (CDC PDF document).
4. Course of intravenous / oral /combination of antibiotics used as the treatment modality. Duration of follow up was also noted.

### 2.2.3 *Data collection and items:*

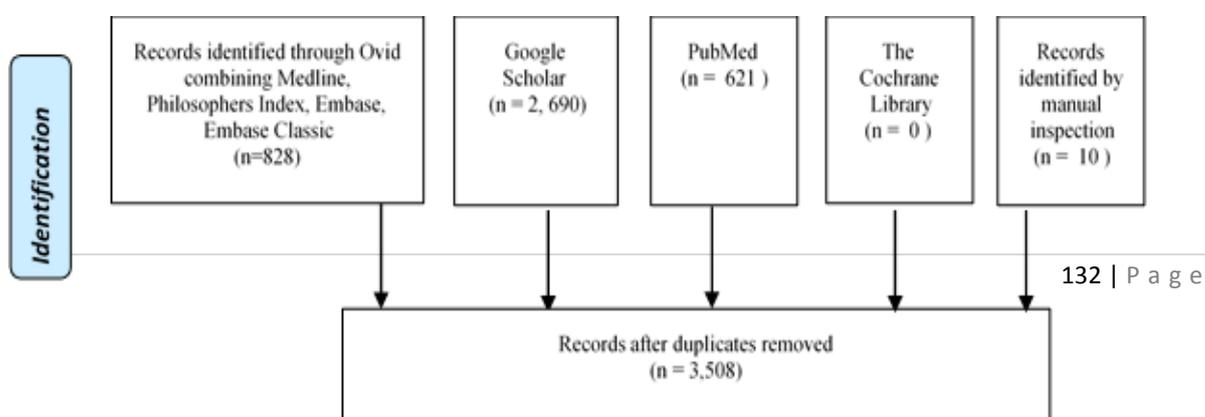
Each study was systematically assessed. We specifically looked for information on study design, patient population demographics, patient numbers, pre-existing wound

characteristics, antibiotic treatment protocols, outcome measures. In addition, we collected additional study-specific information.

#### 2.2.4 Study characteristics:

Database searches have identified a total of 3,508 records following duplicate removal. Following initial screening, 3,489 articles were removed due to lack of relevance to the question. In terms of full-text publications, 19 were further assessed, of which 10 were excluded as outlined in the study PRISMA diagram (see Figure 19, pg.133). A total of 8 studies were included in the final analysis. These included 5 prospective RCTs, 1 pilot study, 1 prospective series and the most recent one, a prospective cohort study, originally based on a retrospective audit.

Prisma Diagram



*Figure 19 PRISMA Diagram for systematic review and meta-analysis of the use of antibiotic prophylaxis in major LLA*

## ***Section 2.3 Study 3: The Amputation Surgical Site Infection Trial***

### ***2.3.1 Rationale:***

Morbidity and mortality rates following LLAs remain unacceptably high. It is known that SSIs within this cohort contribute to patient morbidity and mortality as well as having significant time and cost implications.

Amputation surgery is classed as clean surgery and according to NICE guidance 74, antibiotic prophylaxis should therefore not be indicated. However, according to Hospital

Episode Statistics, a study by Colstein et al. as well as from data from our own institution, that the incidence of SSI following major LLA is in fact under-reported and the true value lies between 13.1% and 34.6%, an incidence rate which is high compared to SSI incidence following other 'clean' procedures<sup>(257)</sup>.

A previous randomised controlled study of 443 patients undergoing groin incision during clean varicose vein surgery, run by some of the applicants here, demonstrated a benefit from a single dose of prophylactic antibiotics on induction of anaesthesia, prior to skin preparation with an aqueous solution of 10% povidone iodine. The antibiotic group had a lower rate of infection (ASEPSIS score  $\geq 21$ ) of 9.9% compared to 18.2% in the non-antibiotic group. Statistically significant superiority was observed in the antibiotic group in terms of: ASEPSIS score; wound complications necessitating GP appointment; and the requirement for post-operative antibiotics<sup>(312)</sup>.

From a previous perioperative antibiotic survey we conducted (Study 1), we concluded that there was little consensus in the perioperative wound management of patients undergoing major LLA. Of significance was the great variation in practice pertaining to antibiotic prophylaxis, in which 95.8% of the respondents gave antibiotics, with 4.2% of the surgeons not justifying the lack of use of antibiotics, despite prophylaxis being supported by level 1 evidence. The survey also identified the lack of uniformity in terms of choice of antibiotic, administration mode and duration of the course, all of which appeared to be pre-determined by a host of factors including local Trust guidance as well as surgeon preference and microbiology advice, although in a review by Macintosh et al. in 2008, this did not appear to be of significance.

From the meta-analysis we have performed within this thesis (Study 2), we have established that the use of antibiotics seems to be associated with a reduction the risk of SSI in patients undergoing major LLA. The choice of antibiotic did not seem to alter the risk. Data on duration of the course seemed to be contradictory, although a longer course was associated with a reduction in the risk of SSI with the 5-day course showing superior results versus a 24-hour prophylactic course.

It was evident from studies 1 and 2 within the Thesis that there was a need for a well-designed RCT to examine the relationship between antibiotic course duration and risk of developing an SSI following major LLA.

Data from this trial would aim to facilitate evidence-based decision making regarding optimised reduction in SSIs after amputation surgery.

### 2.3.2 *Study Approvals:*

The Research and Development Department of Hull and East Yorkshire NHS Trust acted as the sponsor in the studies. Funding was provided by the Academic Department of Vascular Surgery at Hull Royal Infirmary.

The protocols, patient information leaflets, consent forms, and all other documents pertaining to these research studies were submitted via IRAS (Integrated Research Application System) to the National Research Ethics Service (NRES) approved by the National Research Ethics Committee, North-West Greater Manchester.

The study registration and approval numbers are as follows:

1. National Research Ethics Committee, North-West Greater Manchester Project  
Number: 15/NW/0058
2. Hull and East Riding Hospitals Research and Development Project Number: R1454
3. IRAS Project ID: 93801
4. EudraCT Number: 2012-003146-32

### 2.3.3 *Ethical Conduct:*

The conduct of the study, dissemination of findings and thesis completion was performed in line with the principles outlined in the Declaration of Helsinki <sup>(313)</sup>. The health and wellbeing of the research participants was the prime concern of all the researchers.

The investigator has undergone formal training in Good Clinical Practice and is appropriately qualified and experienced in performing all interventions and investigations.

All eligible patients identified were counselled regarding the opportunity to participate in the trials. If willing a written informed consent form was completed. No patient deemed to lack capacity was included in the studies.

Patients were clearly informed that the research being undertaken may not offer them any benefit but may aid in establishing whether one duration of antibiotic therapy is superior to the other in the prevention of SSIs and improvement of wound healing. They were made aware of the additional burden of the assessments involved in the study and were aware that

they were free to withdraw at any stage in the process, without any prejudice to their ongoing or future care.

The studies were prospective in nature and approval sought and obtained from independent and institutional ethics boards, before commencement of recruitment. The studies were registered on [clinicaltrials.gov](http://clinicaltrials.gov) as per recommendations

#### 2.3.4 *Quality Assurance:*

The Chief Investigator was responsible for the day-to-day monitoring and management of the studies. The study was monitored in accordance with the Department of Health Research Governance Framework for Health & Social Care <sup>(314)</sup>, and in accordance with the Sponsor's monitoring and audit policies and procedures.

The organisation, monitoring, and quality assurance of the studies was the responsibility of the Sponsor, and Principal Investigator. In order to ensure the accuracy of data, direct access to source documents by the representatives of both the Sponsor and regulatory authorities was ensured at all times. Anonymity of the subjects was maintained at all times.

The investigator permitted study-related monitoring, audits, REC review, and regulatory inspections, providing direct access to source data / documents. Patient consent to this was specifically sought in the Consent Form.

#### 2.3.5 *Data handling and storage:*

Participants were informed that their data would be held on file, and that this data may be viewed by the Sponsor and by external auditors on behalf of either the sponsor or regulatory agencies. They were similarly informed that this data and a report of the study would be submitted to the Sponsor and may also be submitted to government agencies and perhaps for publication, but that they would only be identified in such reports by their study identification number, initials and perhaps their gender and age.

The investigators undertook to hold all personal information in confidence and in compliance with the Data Protection Act 1998 <sup>(315)</sup> and Caldicott committee <sup>(316)</sup>. Data was collected and collated using a specifically designed database. This was kept on hospital central servers on a limited access hard drive. Access was via password protected log-in on

hospital servers only and was limited to members of the Academic Vascular Surgery Unit. The file itself had password protected opening.

### **2.3.6 Indemnity:**

This was an NHS sponsored research study. Indemnity was provided by the site in accordance with local policy and NHS guidance.

The Sponsor holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants were also able to claim compensation if they could prove that the hospital has been negligent. However, since this clinical study was carried out in a hospital, the hospital continued to have a duty of care to the participant of the clinical study. Hull Royal Infirmary did not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees.

### **2.3.7 Study Design:**

A single centre Open RCT. Patients were randomised to receive either a 5-day course of antibiotics (as per local microbiology policy), 24 hours intravenously followed by 4 days oral, or a 24 hour prophylactic course. If the patients are penicillin allergic then a substitution was made (as per local microbiology policy).

### **2.3.8 Sample size and power calculation:**

The study by Sadat *et al* demonstrated a reduction in infection rate from 22.5% to 5% when patients were given a 5-day course of antibiotics compared to a single dose. The current SSI rate within our patients undergoing amputation is 25%. To demonstrate a reduction in the incidence of SSIs from 25% to 7% or less at 80% power and 5% significance 74 participants were required in each group. To allow for a 10% drop out then a total of 168 participants was required.

### **2.3.9 Identification of potential participants:**

Patients were recruited from outpatient clinics and emergency admissions to the ward. All patients were assessed for eligibility and if eligible the potential for inclusion in the study was explained to the patient and the patient information leaflet was issued.

It was the responsibility of Principal Investigator or persons delegated by the Principal Investigator to obtain written consent from each subject prior to participation in the trial. This process involved provision of patient information sheet and relevant consent (see Appendix 2 , pg.246) with explanation of the aims, methods, anticipated benefits and potential hazards of the trial. Patients, where possible, were approached more than 24 hours prior to operation.

### **2.3.10 *Patient Population:***

168 patients undergoing major LLA were recruited from a single Vascular Unit, based at Hull Royal Infirmary.

Patients were clearly informed that participation in the study is voluntary and that refusal to participate would in no way disadvantage them.

The patients were provided with a full explanation of the nature, purpose and requirements of the study including Patient Information Sheet (PIS) and signed an Informed Consent Form (ICF). The patient consent form was countersigned by researchers only when satisfied that the patient had understood the patient information sheet and was willing to give informed written consent to participate in the study, and that the patient understood that it was their right to withdraw from the trial at any time without need to explain their reasons for doing so and without prejudice to their future treatment.

No patients were recruited if they lacked capacity and if it was deemed that capacity was lost during the trial period then the patient was be removed from the trial and all information relating to them was destroyed.

They were invited to participate in a screening assessment, which included the collection of information pertaining to their general health, past medical history, drug history and a physical examination. No study related procedure will be undertaken prior to the signing of the ICF.

### **2.3.11 *Inclusion criteria:***

To be eligible for inclusion in the study the participants would have needed to meet the following criteria:

1. Adults  $\geq 18$  yrs undergoing LLAs who can consent to the trial.

2. Able to understand the Patient Information Sheet and capable and willing to give informed consent and follow the protocol requirements (including attending all follow-up visits)

### 2.3.12 *Exclusion criteria:*

Patients were be included in the study if they met any of the following exclusion criteria:

1. Allergies to chlorhexidine/ alcohol/ iodophors
2. Inability to give informed consent
3. Patients who are admitted to hospital requiring emergency amputation, with severe sepsis secondary to gas gangrene requiring multiple operations and admission to Intensive Care Unit.
4. Aged under 18 years at the time of recruitment
5. Use of investigational drug/device therapy within preceding 4 weeks that may interfere with this study.
6. Toe amputations

### 2.3.13 *Screening evaluation:*

Baseline data was collected from all consenting participants prior to randomisation. Data collected included:

- Informed consent
- Evaluation of compliance with inclusion and exclusion criteria
- Participants name and address, and, if used by the participant, mobile telephone number and email address (for the receipt of follow-up questionnaires), date of birth
- Details of participant's GPs
- BMI
- Smoking history
- Co-morbidities including diabetes mellitus
- Medication history
- Details of procedure: nature of amputation
- Physical examination

### 2.3.14 *Randomisation:*

Patients were randomised using the online services <http://www.sealedenvelope.com>. Simple randomisation in blocks of 8 was utilised, initially to allocate the patients to either a 24-hour prophylactic course of antibiotic versus 5 days of antibiotics with the first 24 hours administered intravenously, followed by 4 days orally. Stratification was utilised to achieve further randomisation into skin preparation (alcoholic chlorhexidine vs alcoholic povidone). A randomisation list was produced with the aforementioned criteria by R&D who placed the code per patient in individual sealed envelopes. The sequence and contents of the envelopes in terms of antibiotic course duration and type of skin preparation were not known to the investigator, surgeon nor patient until the time of the surgical procedure.

This was hence an open randomised control trial where neither the patient, nor the investigator or surgeon were blinded to the treatment mode, as it was not feasible.

Batches of envelopes were kept in the vascular lab as well as acute theatres so that they could be readily accessible out of hours if necessary.

### 2.3.15 *Trial Treatments:*

Patients were randomised to receive either a 5-day course of antibiotics (24 hours intravenously to start on induction, followed by 4 days oral) or a 24-hour prophylactic intravenous course. The local Trust antibiotic guideline as developed by the microbiology department was followed.

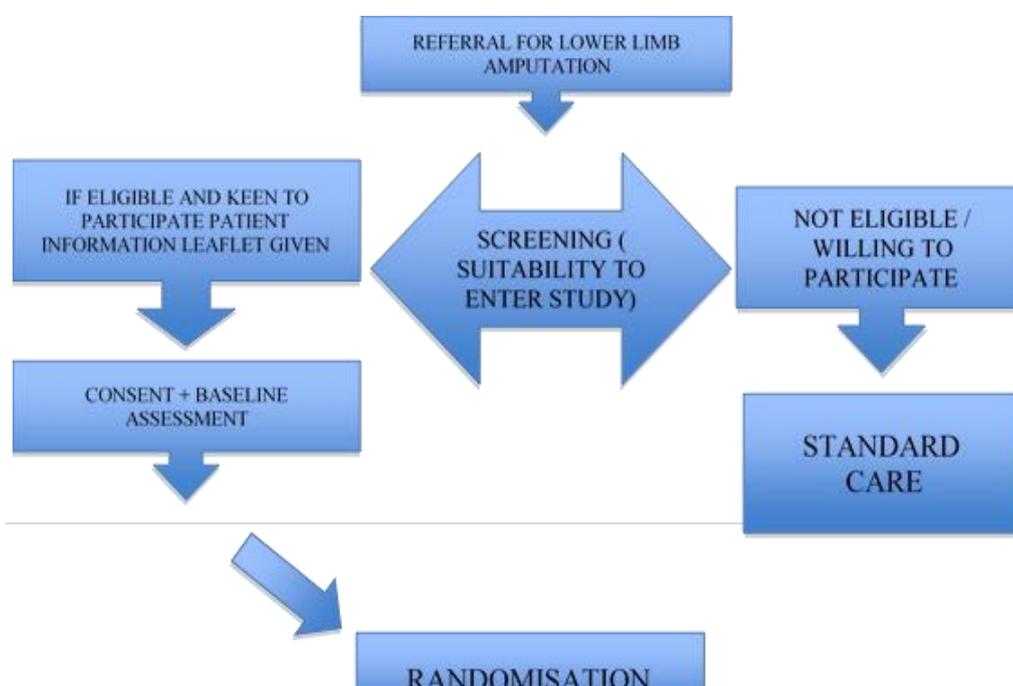
Patients were treated with Augmentin and metronidazole and, in cases of penicillin allergy, VANCOMYCIN, GENTAMICIN AND METRONIDAZOLE. In addition, if the patients who were penicillin allergic were to be treated with oral antibiotics, doxycycline and metronidazole were prescribed. The exact dosage and course length are specified in the separate Trust guidelines, which can be found in Appendix 8 on page 271. Further to this, in specific situations where a patient had long-standing history of ulceration / wound requiring long-term management including involvement of the Microbiology Department, then their antibiotic recommendation was utilised instead of the aforementioned antibiotics for an identical period of time as previously specified in the study protocol (24 hours vs 5 days post op). In addition, this was overridden where clinical need dictated so. Patients were also randomised to undergo skin preparation with alcoholic chlorhexidine and alcoholic povidone iodine.

Study medication was stored and dispensed by theatre and ward stores as there was no deviation from the local guidelines, and they were utilised in accordance with good clinical practice and good manufacturing practice.

Summary of product characteristics for trial treatments were derived from the electronic Medicines Compendium.

All antibiotics as well as Chlorhexidene and povidone skin preparations were used from routine stock and were stored in theatres according to standard NHS practice and manufacturer's guidance, and therefore were not labelled with the clinical trial label. Investigators did **not** fill in an accountability form as it was not feasible, as antibiotics and skin preparation were be dispensed from ward / theatre stock as explained above.

### *The Trial Patient Pathway*



*Figure 20 The Amputation Surgical Site Infection Trial (ASSIT) Pathway*

### 2.3.16 **Outcome measures:**

#### 2.3.16.1 Primary measures:

- SSI – total ASEPSIS score  $\geq 21$  (see Table 7 pg.119)

Participants will be asked to complete the Health Protection Agency (HPA) ‘Patient post-discharge questionnaire’ at day 7 and day 30 post-surgery\*, which is based on the ASEPSIS score (see Table 7 pg.119). On day 14 post-surgery participants will undergo clinical review by a clinician blinded to group allocation and the patient post-discharge questionnaire completed. Occurrence of a SSI will be defined as positive finding at any of the three follow-ups. The HPA post-discharge questionnaire (See Appendix 1 pg. 244) was utilised to collect

data pertaining to wound status at follow up and was used to calculate the overall ASEPSIS score.

### 2.3.16.2 Secondary measures:

All measured at baseline, 7, 14 and 30 days post-surgery:

- Satisfactory healing using ASEPSIS score
- Mortality and morbidity
- Rate of re-intervention, type and level.
- Resource use (including length of stay, number of visits to general practitioners, hospital visits, and prescription of antibiotics).

### 2.3.17 *Study procedures:*

#### 2.3.17.1 Assessments

Following the consent process participants will have their baseline assessment carried out as outlined above. Immediately pre-operatively the patients will be randomised as outlined above. The surgical procedure will be carried out as per usual protocol.

#### 2.3.17.2 Concurrent medications

No restrictions will be in place on the prescribing of the patients regular medications.

#### 2.3.17.3 Parameters for evaluation

Demography and medical history: Includes initials, date of birth, sex, BMI, ethnicity, height and weight. A full medical and surgical history will also be recorded.

#### 2.3.17.4 Physical examination

A physical examination including vital signs will be performed at screening.

#### 2.3.17.5 Assessment of Concomitant Medications

Concomitant medications taken by the patients will be monitored at screening and during the entire study period.

## 2.3.18 *Statistical Analysis:*

### 2.3.18.1 Continuous data

Prior to any analysis of continuous data histogram analysis was performed to establish the distribution. If the data appeared normally distributed the Kolmogorov statistic or Shapiro Wilk statistic was utilized to confirm this, with a P value  $> 0.05$  indicating normality.

Normally distributed data was described as mean (95% confidence interval) or mean (standard deviation). For data not normally distributed it was described as median (interquartile range).

Hypothesis testing was performed comparing groups as per distribution and whether it was paired or unpaired. N.B. paired data is that which is before and after in the same patient, whilst unpaired data is that from different patients.

The P value represents the probability of the null hypothesis being true<sup>(317)</sup> (i.e. no difference between the data). P values are quoted to 3 decimal places with values of less than 0.05 being considered significant i.e. suggesting rejection of the null hypothesis.

The comparison of baseline characteristics between the control and active groups i.e. intergroup analysis was performed using the unpaired student T test for normally distributed data and Mann Whitney U test for non-normally distributed data.

### 2.3.18.2 Categorical data

Simple categorical data is presented as percentages. The primary test utilized was Pearson's Chi squared test. If more than 20% of the expected frequencies were  $<5$  or if any were  $<1$  then the Fisher's exact test was utilized.

### 2.3.18.3 Linear Regression analysis

Secondary analysis of covariates determined to be significant predictor of device failure on univariable analysis was carried out using linear regression analysis.

## 2.3.19 *Withdrawals and dropouts:*

During the study, treatment may be discontinued for many reasons such as an adverse event that could interfere with the subject's evaluation, or simply upon the subject's request to discontinue for any reason. Concurrent medical events that do not interfere with scheduled testing, and that are judged by the Investigator to not influence the outcome measures will not disqualify a subject from continuing in the study. If a subject is withdrawn from the study because of an AE, treatment discontinuation must be explained on the CRF.

Patients will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator may withdraw a subject from the study to protect the subject's health. The Investigator may withdraw a subject from the study if it is considered that the scientific, and therefore, ethical standards of the study are compromised. Patients may also be withdrawn for not complying with study procedures. The type and timing of the withdrawal for withdrawal will be fully recorded on the CRF.

#### **2.3.20 *Trial Exit:***

Participants will exit the trial completely if:

- they have been in the trial for 30 days following randomisation and completed follow up at 3 months and 1 year.
- they request to/ are unable to continue being followed-up
- they suffer an adverse event/ reaction such that they cannot continue
- they die

#### **2.3.21 *Overall timescale for the study:***

Recruitment will begin as soon as all necessary approvals have been obtained (Ethics, MHRA and Trust R+D). Recruitment will run for approximately 12-18months or until an adequate sample size is reached. Individual participants are involved in the trial for 30 days as per the aforementioned Centre for Disease Control definition of an SSI in non-implant surgery.

***Section 2.4 - Study 4: The Impact of Previous Surgery and Revisions on outcome after Major Lower Limb Amputation.***

This study was originally created to examine the true impact of previous ipsilateral revascularization. For the purpose of this study, revascularisation procedures included: percutaneous transluminal angioplasty, thrombolysis, bypass graft reconstruction, endarterectomy, and embolectomy). The aim was examine the outcomes after major LLA of the prospectively collected data for all major LLAs performed between January 2010 and December 2011 from a single vascular tertiary referral centre. Data collected was inputted into a secure database. Variables examined included: baseline demographics, comorbidities, previous procedures, indication for surgery, and postoperative outcomes.

Data were found to be nonparametrically distributed, therefore univariate analysis was performed using SPSS (IBM SPSS v19.0, Armonk, NY). A P value of <0.05 was deemed statistically significant. Mortality was analysed by Kaplan-Meier survival curves.

---

## Chapter 3 - *RESULTS*

### *Section 3.1 Study 1 : A Survey of perioperative management of major lower limb amputations*

A total of 565 questionnaires were sent out, of which 180 were completed and returned successfully. Of these, 10 were completed by surgical trainees, 1 by a vascular senior physiotherapist, and 1 by a vascular nurse practitioner. As previously explained, these 12 questionnaires were excluded from further analysis. Sixteen questionnaires were returned unopened as the recipient no longer worked in the hospital.

At the time of the study, a total of 452 consultant members of the Vascular Society were working in the deaneries and were approached for a response. The response rate of 37.2% (168/452) was achieved and the responses were comparatively distributed throughout the UK (see Figure 21).

Approximately 51.1% of respondents worked primarily in a university teaching hospital, 48.2% in a district general hospital, and 0.6% in a private facility.

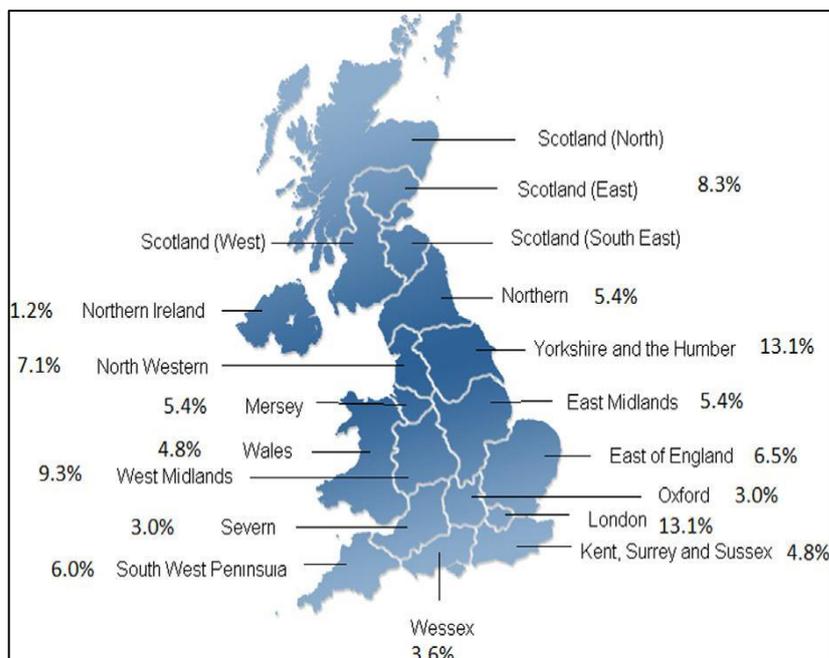


Figure 21 Distribution of responses per deanery

### 3.1.1 Infection Rates

The median-reported SSI incidence range was 6-10%. Eighty-six (51.2%) reported an SSI >10%. No data was available regarding the timing, severity, or consequences of the SSI.

### 3.1.2 Skin Preparation

The most commonly used skin preparations by order of abundance were aqueous betadine (44.6%), alcoholic chlorhexidine (28.0%), and alcoholic betadine (21.4%) with only 4.8% of respondents using aqueous chlorhexidine. Statistical analysis using chi-squared test suggested that the differences in the incidence of SSI seen with different skin preparations were not statistically significant amongst betadine versus chlorhexidine (P=0.552) and alcoholic versus aqueous (P=0.126) (see Table 10)

Skin preparation	Infection rate ≤ 10%	Infection rate >10%	P value	OR	95% CI
Betadine	54	49	0.552	0.817	0.342 - 1.950
Chlorhexidine	31	23			
Alcoholic	47	31	0.126	0.538	0.234 - 1.237
Aqueous	38	41			

Table 10 The impact of skin preparation on infection rates

### 3.1.3 *Skin Closure*

Approximately 58.3% of respondents favoured closure of the wound with continuous subcuticular sutures. The remainder surgeon choices included interrupted sutures (23.2%) or clips (16.1%) or a combination of methods (See Table 11 ).

	Infection rate 10%	Infection rate >10%	P value	OR	95% CI
<b>Closure</b>					
Interrupted	34	30	0.823	1.003	0.437-2.298
Continuous	50	41			
Sutures	71	57	0.488	0.829	0.282-2.439
Clips	13	14			
<b>Warming</b>					
Always	65	52	0.535	0.769	0.350-1.692
Never/sometimes	21	21			
<b>Nutrition assessed</b>					
Always/sometimes	81	63	0.09	1.962	0.594-6.476
Never	5	10			
<b>Antibiotics</b>					
Always	84	69	0.236	0.263	0.025-2.822
Sometimes	1	3			
<b>Drain</b>					
Always	40	29	0.394	0.798	0.396-1.607
Never	45	43			

Table 11 Impact of skin closure, intraoperative warming, nutritional assessment, antibiotic usage, and drain usage on incidence of infection

### 3.1.4 *Drains*

There were large variations in practice when considering the use of surgical drains amongst the respondents, with 44% always using drains, 39.9% sometimes using drains, and 14.9% never using drains (see Table 11).

### 3.1.5 *Antibiotics*

We found that approximately 95.8% of respondents would always give prophylactic antibiotics. About 34% of them included co-amoxiclav in their regime (28% giving co-amoxiclav alone, the most frequently prescribed prophylaxis), while 12.6% used gentamycin, 18% metronidazole, and 12.6% flucloxacillin. The duration of therapy ranged from 1 prophylactic dose to a 5-day course with most respondents opting for 24 hr. (see Table 11 pg.149)

### 3.1.6 *Nutrition*

Nutritional assessments are not routinely performed as part of standard perioperative practice within this population cohort. With only 7.7% of respondents stating that they always address this aspect of patient care. Similarly, the nutritional assessments which were undertaken varied greatly with most requesting dietician input and assessment (70%). About 41.1% of consultants used serum albumin as part of their nutritional assessment, 17.3% using BMI and only 4.8% measuring skin-fold thickness (see Table 11, pg.149).

### 3.1.7 *Warming*

About 72.6% of respondents always used intraoperative warming for their patients, whereas only 1.8% never did (see Table 11, pg.149).

### 3.1.8 *Dressings*

With regards to the type of dressing used for above-knee amputation stumps, 62.5% of respondents used stump bandages, 31.0% used a non-adhesive dressing, whilst the remaining 6% used a variety of different dressings. This was similar to the findings of below-knee stumps with 61.9% using stump bandages, 28.6% non-adhesive dressings, 4.8% stump casts, and 4.2% another form of dressing (see Table 12, pg. 150).

Dressings	Infection rate 10%	Infection rate >10%	P value	OR	95% CI
<b>AK dressings</b>					
Stump bandage	52	47	0.386	2.817	0.530-14.983
Other	30	20			
<b>BK dressings</b>					
Stump bandage/cast	58	49	0.970	0.447	0.079-2.521
Other	25	21			

*Table 12 Impact of surgical dressings on infection incidence*

## ***Section 3.2 Study 2: Meta-analysis of the use of antibiotic prophylaxis in the prevention of surgical site infection in patients undergoing major lower limb amputations***

### ***3.2.1 Study, population characteristics and indications for surgery.***

A total of 9 studies were originally identified between 1981 and the present, as relevant to this meta-analysis<sup>(235, 296, 298-302, 318)</sup>. Following the initial stages of the systematic analysis, one additional study was excluded due to poor design and inadequate description of results, making it impossible to combine with the remaining data<sup>(297)</sup>. The general characteristics of all studies can be seen in Table 13. There were a total of 2 prospective RCTs<sup>(296, 302)</sup>, 2 prospective Controlled Trials<sup>(298, 299)</sup>, 2 Randomised Trials<sup>(300, 301)</sup>, 1 pilot study<sup>(318)</sup> and 1 retrospective/prospective cohort study<sup>(235)</sup> (see Table 13, pg.153). Three of the studies were multi-centre<sup>(296, 301, 302)</sup>. In four of the studies, the amputations were performed by Trauma and Orthopaedic surgeons<sup>(296, 299, 300, 302)</sup>, in two by a Vascular surgeon<sup>(235, 318)</sup>, one by a combined Trauma and Orthopaedic and General surgical team<sup>(301)</sup> and one solely by a General surgeon<sup>(298)</sup>. With the exception of one study<sup>(235)</sup>, none of the remainder reported the total number of patients screened prior to recruitment. None of the studies described power calculations. A total of 1079 patients were recruited amongst the eight studies, and of these, 978 were included in the final analysis (see Table 13, pg.153). The number of patients recruited per group (intervention Vs. control) can be seen in Table 14. The largest study was a prospective multicentre RCT by Friis et al. in 1987 which recruited a total of 457 patients<sup>(296)</sup>.

With the exception of one study by Norlin et al. in 1990 <sup>(300)</sup>, the remaining studies gave a description of the population gender ratios(see Table 15 and Table 16, pg.155 and 156). Four studies gave the age of patients as a mean by group (intervention Vs control) <sup>(296, 298, 300, 318)</sup>, and one as a median by gender<sup>(299)</sup>. Patient age was overall comparable amongst the studies, with the exception of two studies <sup>(298, 318)</sup>. Two studies gave the overall median age of the population <sup>(235, 301)</sup> and one study failed to account for patient age altogether<sup>(302)</sup> (see Table 15 and Table 16, pg. 155 and 156).

<i>Title of study</i>	<i>Type of study</i>	Number of centres in study	Authors	Year of publication	Country	Surgical Department(*)	Number of patients screened	Number of patients recruited	Number of patients included in analysis(n)
<i>A clinical trial of a combination of amoxicillin and flucloxacillin in amputations for septic ischaemic lower limb lesions<sup>(318)</sup></i>	<i>Pilot study</i>	1	JV. Robbs, NA. Kritzinger, KA. Mogotlane, JA. Odell, WHJ. Huizinga	1981	South Africa	1	n/a	46	46
<i>Prevention of wound sepsis in amputations by peri-operative antibiotic cover with an amoxicillin-clavulanic acid combination<sup>(298)</sup></i>	<i>Prospective controlled trial</i>	1	W.K.J. Huizinga, J.V. Robbs, N.A. Kritzinger	1983	South Africa	3	n/a	46	44
<i>Prophylactic antibiotics in amputation of the Lower Extremity for Ischaemia<sup>(301)</sup></i>	<i>Randomised trial</i>	5	S. Sonne-Holm, M. Boeckstyns, H. Menck, A. Sinding, P. Leicht, O. Dichmann, J. Brorson-Prag, N. Baekgaard, P.Ostri, JK. Gotrik	1985	Denmark	2, 3	n/a	176	152
<i>Antibiotic prophylaxis in lower limb amputation<sup>(299)</sup></i>	<i>Prospective controlled trial</i>	1	B. Nue Møller, B. Krebs	1985	Denmark	2	n/a	53	50
<i>Penicillin G versus cefuroxime for prophylaxis in lower limb amputation<sup>(296)</sup></i>	<i>Prospective RCT</i>	19	H. Friis, Danish Amputation Group	1987	Denmark	2	n/a	457	401
<i>Short-term cefotaxime prophylaxis reduces failure rate in lower limb amputations<sup>(300)</sup></i>	<i>Randomised trial</i>	1	R. Norlin, A. Fryden, L. Nilsson, S. Ansehn	1990	Sweden	2	n/a	38	35
<i>Antibiotic prophylaxis in lower-extremity amputations due to ischaemia<sup>(302)</sup></i>	<i>Prospective RCT</i>	2	S. Thomsen, B.W. Jakobsen, J.O. Wethelund, J. Dalsgaard, H.N. Gregersen, U. Lucht	1990	Denmark	2	n/a	187	174
<i>Five day Antibiotic Prophylaxis for Major Lower Limb Amputation Reduces Wound Infection and the Length of Hospital Stay<sup>(235)</sup></i>	<i>retrospective/prospective cohort study</i>	1	U. Sadat, A. Chaudhuri, P.D. Hayes, M.E. Gaunt, J.R. Boyle and K. Varty	2008	UK	1	76	76	76
<i>*Surgical department: 1-Vascular surgery, 2 -Trauma and Orthopaedics, 3-General Surgery</i>									

*Table 13 List of studies selected for meta-analysis - Patients screened and recruited*

<i>Title of study</i>	<b>Authors</b>	<b>Year of publication</b>	<b>Country</b>	<b>Number of Intervention groups</b>	<b>Intervention (n)</b>	<b>Number of Control Groups</b>	<b>Control Group(n)</b>
<i>A clinical trial of a combination of amoxicillin and flucloxacillin in amputations for septic ischaemic lower limb lesions</i> <sup>(318)</sup>	JV. Robbs, NA. Kritzinger, KA. Mogotlane, JA. Odell, WHJ. Huizinga	1981	South Africa	1	24	1	22
<i>Prevention of wound sepsis in amputations by peri-operative antibiotic cover with an amoxicillin-clavulanic acid combination</i> <sup>(298)</sup>	W.K.J. Huizinga, J.V. Robbs, N.A. Kritzinger	1983	South Africa	1	33	1	13
<i>Prophylactic antibiotics in amputation of the Lower Extremity for Ischaemia</i> <sup>(301)</sup>	S. Sonne-Holm, M. Boeckstyns, H. Menck, A. Sinding, P. Leicht, O. Dichmann, J. Brorson-Prag, N. Baekgaard, P.Ostri, JK. Gotrik	1985	Denmark	1	77	1	75
<i>Antibiotic prophylaxis in lower limb amputation</i> <sup>(299)</sup>	B. Nue Møller, B. Krebs	1985	Denmark	1	27	1	23
<i>Penicillin G versus cefuroxime for prophylaxis in lower limb amputation</i> <sup>(296)</sup>	H. Friis, Danish Amputation Group	1987	Denmark	1	228	1	229
<i>Short-term cefotaxime prophylaxis reduces failure rate in lower limb amputations</i> <sup>(300)</sup>	R. Norlin, A. Fryden, L. Nilsson, S. Ansehn	1990	Sweden	1	19	1	19
<i>Antibiotic prophylaxis in lower-extremity amputations due to ischaemia</i> <sup>(302)</sup>	S. Thomsen, B.W. Jakobsen, J.O. Wethelund, J. Dalsgaard, H.N. Gregersen, U. Lucht	1990	Denmark	1	94	1	93
<i>Five day Antibiotic Prophylaxis for Major Lower Limb Amputation Reduces Wound Infection and the Length of Hospital Stay</i> <sup>(235)</sup>	U. Sadat, A. Chaudhuri, P.D. Hayes, M.E. Gaunt, J.R. Boyle and K. Varty	2008	UK	1	38	1	38

Table 14 List of studies selected for meta-analysis - Numbers recruited per group(Intervention / Control)

Authors	Year of publication	Intervention Group Mean age in years	Intervention Group Mean age in years (per group)MALE	Intervention Group Mean age in years (per group) FEMALE	Intervention Group Median age	Intervention Group Median age - Male	Intervention Group Median age - Female	Male(n)	Female(n)	M:F Ratio
JV. Robbs et al. <sup>(318)</sup>	1981	55	n/a	n/a	n/a	n/a	n/a	31	15	31:15
W.K.J. Huizinga et al. <sup>(298)</sup>	1983	55.6	n/a	n/a	n/a	n/a	n/a	37	7	37:7
S. Sonne-Holm et al. <sup>(301)</sup>	1985	n/a	n/a	n/a	n/a	n/a	n/a	95	57	5:3
B. Nue Møller, B. Krebs <sup>(299)</sup>	1985	n/a	n/a	n/a	n/a	73	75	24	26	12:13
H. Friis et al. <sup>(296)</sup>	1987	75	n/a	n/a	n/a	n/a	n/a	200	257	200:257
R. Norlin et al. <sup>(300)</sup>	1990	79	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S. Thomsen et al. <sup>(302)</sup>	1990	72	n/a	n/a	72	n/a	n/a	82	105	82:105
U. Sadat et al. <sup>(235)</sup>	2008	n/a	n/a	n/a	75	n/a	n/a	54	22	27:11

Table 15 List of studies selected for meta-analysis - Male : Female ratio and age (INTERVENTION)

Authors	Year of publication	Control Group Median age Male	Control Group Median age Female	Control Group Mean age in years (per group)	Control Group Mean age in years MALE	Control Group Mean age in years FEMALE	Overall Median Age	Overall Median age Male	Overall Median age Female	Overall Mean age	Overall Mean age Male	Overall Mean age Female	Male(n)	Female(n)	M:F Ratio
JV. Robbs et al. <sup>(318)</sup>	1981	n/a	n/a	59	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	31	15	31:15
W.K.J. Huizinga et al. <sup>(298)</sup>	1983	n/a	n/a	53.4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	37	7	37:7
S. Sonne-Holm et al. <sup>(301)</sup>	1985	n/a	n/a	n/a	n/a	n/a	74	n/a	n/a	n/a	n/a	n/a	95	57	5:3
B. Nue Møller, B. Krebs <sup>(299)</sup>	1985	70	76	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	24	26	12:13
H. Friis et al. <sup>(296)</sup>	1987	n/a	n/a	74	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	200	257	200:257
R. Norlin et al. <sup>(300)</sup>	1990	n/a	n/a	79	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S. Thomsen et al. <sup>(302)</sup>	1990	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	82	105	82:105
U. Sadat et al. <sup>(235)</sup>	2008	n/a	n/a	n/a	n/a	n/a	74.5	n/a	n/a	n/a	n/a	n/a	54	22	27:11

Table 16 List of studies selected for meta-analysis - Male : Female ratio and age (CONTROL GROUP AND OVERALL)

The inclusion criteria were clearly defined in only 3 of the studies <sup>(299, 301, 302)</sup> and the exclusion criteria in just two <sup>(301, 302)</sup> (see Table 17, pg. 158).

The reasons for drop-out were outlined in Table 17 on page 158 and of note here is that the main reason for patient drop out was mortality prior to completion of the wound assessment period. Two studies failed to outline drop-out reasons <sup>(235, 318)</sup>.

The main indication for a LLA was peripheral vascular disease resulting in changes consistent with chronic limb ischaemia including sepsis secondary to ulceration or dry/wet gangrene, intractable pain and muscle atrophy <sup>(235, 298, 299, 301, 302, 318)</sup>. Diabetes as a causative agent was only considered in two of the studies <sup>(296, 300)</sup> (see Table 18, pg.159). All studies included in this meta-analysis gave a number breakdown of all procedures into different amputation levels, apart from the study by Moller et al. which gave the total amputation number per group (intervention Vs. control) <sup>(299)</sup>.

Two studies included toe amputations <sup>(298, 318)</sup> (see Table 18, pg. 159). Surgeon grade was only specified in the study by Sadat et al. <sup>(235)</sup>. Skin preparation was specified in three studies and showed variability in preference of tincture as well as in practice, with one study involving the application 24 hours prior to the surgical procedure <sup>(298, 299, 318)</sup>. Skin closure was variable. Most surgeons used non-absorbable interrupted suture material which was left in the wound for up to 21 days post-operatively <sup>(296, 299, 301, 302)</sup>. Two studies reported on the skin being left open <sup>(298, 318)</sup>. In terms of dressing, once again, there was variability in practice. Details are outlined in Table 19, pg.160.

With regards to post-operative wound examination, two studies reported review at day 5 post-operatively unless clinically indicated otherwise <sup>(298, 318)</sup> and one study continued the review from that point onwards every 24 hours until discharge, without mentioning the total follow up period <sup>(235)</sup>. Norlin et al. did not describe this part of the process <sup>(300)</sup>. In the only two studies where the total follow up period was specified, this was set at 3 weeks post-operatively <sup>(300, 301)</sup>. A drain was left in-situ following surgery in operations performed in 4 of the 8 studies <sup>(296, 299, 300, 302)</sup>.

Authors	Course initiation (†)	Drop outs (Intervention group)	Drop outs (Control Group)	Drop outs (Total)	Patients excluded (n)	Reasons for Drop out	Inclusion Criteria clearly defined ?	Inclusion criteria	Exclusion Criteria clearly defined?	Exclusion criteria
JV. Robbs et al. <sup>(318)</sup>	1	0	0	0	0	n/a	No	n/a	No	n/a
W.K.J. Huizinga et al. <sup>(298)</sup>	3	2	0	2	2	1. Sampling errors	No	n/a	No	n/a
S. Sonne-Holm et al. <sup>(301)</sup>	1	14	10	24	24	1. Death within 3 weeks of procedure in the absence of stump necrosis or infection 2. Systemic needs for more than 24 hours of antibiotics 3. Allergic reaction to cefoxitin 4. Omitted injections due to technical reasons	Yes	All patients admitted in the relevant departments of participating hospitals, undergoing an amputation for arteriosclerosis.	Yes	1. Received antibiotic treatment within 48 hours prior to surgery 2. Had infection at the time, requiring antibiotics 3. Had temperature > 38°C 4. Had history of allergic reaction to cephalosporins 5. Refused consent to participate in the study
B. Nue Møller, B. Krebs <sup>(299)</sup>	2	n/a	n/a	3	3	1. Died before final outcome could be assessed.	Yes	Patients with ischaemic gangrene and a preoperative assessment of the skin perfusion pressure (Holstein & Lassen 1973)	No	Patients treated with antibiotics within 1 week prior to the operation
H. Friis et al. <sup>(296)</sup>	1	27	29	56	56	1. Allergic reactions to antibiotics 2. Treatment with antibiotics other than the ones intended by randomisation within 48 hours of the randomisation process 3. Withdrawn consent	No	1. All patients admitted for lower limb amputation in 19 different centres 2. Informed consent	No	1. All patients with a known allergy to penicillin or cephalosporins 2. Amputations through the knee 3. Re-amputations
R. Norlin et al. <sup>(300)</sup>	2	2	1	3	3	1. Died before final outcome could be assessed.	No	All patients undergoing a transfemoral, through-knee, and transtibial amputation were included.	No	n/a
S. Thomsen et al. <sup>(302)</sup>	1	6	7	13	13	1. Death within 3 weeks of the surgery, with no evidence of stump problems.	Yes	All patients undergoing an amputation admitted at 2 different hospitals, who are able to consent for participation	Yes	1. Those receiving antibiotics 48 hours prior to the amputation. 2. Allergy to penicillins 3. Pregnancy 4. Patients who have previously participated on the study, requiring revision amputation of the affected limb. 5. Unable / Refuse to consent. 6. Renal insufficiency
U. Sadat et al. <sup>(235)</sup>	1	0	0	0	0	n/a	No	1. Retrospective transfemoral and transtibial amputees 2. Anyone undergoing a transfemoral or transtibial amputation	No	n/a

Table 17 List of studies selected for meta-analysis - Inclusion / Exclusion Criteria, Drop-outs and reason

† Course initiation: 1-On surgical induction, 2-Within 1 hour before surgery, 3- Two hours prior to surgery, 4-Three hours prior to surgery, 5-Four or more hours prior to surgery

Authors	Indications for amputation	Toe amputation	Trans-metatarsal amputation	Trans-tibial amputation	Through-knee amputation	Trans-femoral amputation	Hindquarter amputation
JV. Robbs et al. <sup>(318)</sup>	Septic ischaemic necrosis beyond salvage	10	8	13	0	15	0
W.K.J. Huizinga et al. <sup>(298)</sup>	Dry / wet gangrene secondary to ischaemia	6	2	23	0	18	0
S. Sonne-Holm et al. <sup>(301)</sup>	Any patient admitted for an amputation secondary to peripheral vascular disease	0	0	81	16	55	0
B. Nue Møller, B. Krebs <sup>(299)</sup>	Non-healing infective ulceration with infection or impeding gangrene with severe pain	n/a	n/a	n/a	n/a	n/a	n/a
H. Friis et al. <sup>(296)</sup>	Diabetes or peripheral vascular disease	0	0	295	0	162	0
R. Norlin et al. <sup>(300)</sup>	Diabetes or peripheral vascular disease	0	0	24	6	8	0
S. Thomsen et al. <sup>(302)</sup>	Dry / wet gangrene secondary to ischaemia	0	13	92	24	58	0
U. Sadat et al. <sup>(235)</sup>	Patients with peripheral vascular disease, chronic pain and muscle atrophy.	0	0	41	0	39	0

*Table 18 List of studies selected for meta-analysis - Indications for amputation, numbers of amputations per level*

Authors	Surgeon Grade	Skin preparation	Skin Closure	Dressing used	Frequency of wound review.	Total Follow-up period	Drain-in-situ	Surgical techniques used
JV. Robbs et al. <sup>(318)</sup>	n/a	Povidone-iodine 6hr washes day prior to the operation until the time of the surgery	Skin left open(all patients)	Paraffin based gauze	Day 5 post-op unless clinically indicated otherwise	n/a	No	n/a
W.K.J. Huizinga et al. <sup>(298)</sup>	n/a	Povidone-iodine intraoperatively	Skin left open(25) vs skin closed (6) in the intervention group. Control group skin closure not specified	Paraffin based gauze	Day 5 post-op unless clinically indicated otherwise	n/a	No	n/a
S. Sonne-Holm et al. <sup>(301)</sup>	n/a	n/a	Non-absorbable interrupted sutures removed at 21 days post-operatively	Plaster of Paris / soft dressings	Day 7 post-operatively, and then weekly thereafter unless clinically indicated otherwise	Total follow up period of 3 weeks	n/a	Burgess or Persson techniques for below-knee amputation, side flaps for through-knee and myoplastic with osteoplastic techniques for above-knee.
B. Nue Møller, B. Krebs <sup>(299)</sup>	n/a	Chlorhexidene	Non-absorbable interrupted sutures removed at 21 days post-operatively	n/a	Day 3, on removal of suction drain. No clear explanation of follow up.	n/a	Yes	n/a
H. Friis et al. <sup>(296)</sup>	n/a	n/a	Non-absorbable interrupted sutures removed at 14-21 days post-operatively	Closed plaster cast, Padded plaster splint, soft bandage, or other means	Wound inspection at 21 days post operatively	n/a	Yes	Transfemoral amputations were fashioned using simple or myoplastic flaps. Transtibial amputations had either long posterior flap, sagittal flaps, fish-mouth or other fashioning.
R. Norlin et al. <sup>(300)</sup>	n/a	n/a	n/a	n/a	n/a	Total follow up period of 3 weeks	Yes	n/a
S. Thomsen et al. <sup>(302)</sup>	n/a	n/a	Non-absorbable interrupted sutures removed at 21 days post-operatively	Soft bandaging	Every 7 days unless clinically indicated otherwise	n/a	Yes	Transfemoral amputations were fashioned using myoplastic flaps and trans-tibial amputations were fashioned using the Persson technique
U. Sadat et al. <sup>(235)</sup>	Registrar and/or Consultant	n/a	n/a	n/a	Every 24 hours after day 5 until discharge	n/a	n/a	n/a

Table 19 List of studies selected for meta-analysis - Intra-operative details

### 3.2.2 *Characteristics of antibiotic prophylaxis and outcomes recorded*

The studies were allocated to four groups in order to examine the effect of antibiotic prophylaxis and the duration of the course on outcomes following LLA. The groups were as follows:

1. Antibiotic Vs Control (no antibiotic)/Placebo
2. Antibiotic Vs Antibiotic
3. 24-Hour antibiotic course Vs 48-Hour antibiotic course.
4. 24-Hour antibiotic course Vs 5-day antibiotic course

Four studies compared patient outcomes following administration of antibiotic, against no antibiotic or in the case of Sonne-Holme et al. antibiotic against a placebo drug <sup>(299-301, 318)</sup>. Three studies involved comparison of different antibiotic types. These included comparison of co-amoxiclav against benzylpenicillin, cefuroxime against penicillin, and cephalothin against methicillin <sup>(296, 298, 302)</sup>(see Table 20, pg. 162).

Duration of the antibiotic course was 24 hours in the majority of studies <sup>(296, 299-302)</sup>. Two studies administered the antibiotic course for 48 hours <sup>(298, 318)</sup>. Only one study was specifically designed to examine the effect of course duration on outcomes following LLA <sup>(235)</sup>. In order to examine the effect of course duration and establish the potential presence of a trend, data from these studies was combined into two subgroups (24-hour Vs 48-hour). Only one study was specifically designed to examine the effect of duration of antibiotic prophylaxis on SSIs (see Table 20, pg.162).

Robbs et al. in 1981 was the only study which recorded previous revascularisation surgery (angioplasty and reconstruction/bypass grafting) although the effect of this on wound complications was not analysed <sup>(318)</sup>. Wound complications were reported on by all studies. These included stump infection (cellulitis, wet necrosis, dry necrosis, dehiscence and positive cultures). Return to theatre as a form of complication with a detailed breakdown of the procedures performed was described in 3 of the studies <sup>(296, 301, 302)</sup> and as a general complication with no details in one study<sup>(299)</sup> (see Table 22, pg.164). Post-operative mortality with causality was recorded in detail in only one of the studies <sup>(296)</sup> and overall in three of the remaining <sup>(235, 301, 302)</sup>. No survival analysis was performed (see Table 22, pg. 164).

	Intervention				Control				
Authors	Antibiotics Intervention Group	Dosage (mg / interval hours)	Intervention group course duration	Route of administration	Antibiotics Control Group	Dosage (/ interval hours)	Control Group Course duration	Route of Administration	Comparison
JV. Robbs et al. <sup>(318)</sup>	Amoxycillin/flucloxacillin combination	1g/6hr	48 hours	Intravenous	No antibiotics	n/a	n/a	n/a	Antibiotic Vs. No Antibiotic
W.K.J. Huizinga et al. <sup>(298)</sup>	Amoxycillin/Clavulanic acid	750mg/8hr	48 hours	Oral	Benzylpenicillin	1000000 units 2hr prior to surgery followed by 500000 units/6hr	48 hours	Intravenous	Antibiotic types
S. Sonne-Holm et al. <sup>(301)</sup>	Cefoxitin	2g/6hr	24 hours	Intravenous	Placebo	2g/6hr	24 hours	intravenous	Antibiotic vs. Placebo
B. Nue Møller, B. Krebs <sup>(299)</sup>	Meticillin	1g/6hr	24 hours	Intravenous	No antibiotic treatment	n/a	n/a	n/a	Antibiotic Vs. No Antibiotic
H. Friis et al. <sup>(296)</sup>	Cefuroxime	1.5g/8hr	24 hours	Intravenous	Penicillin G	3g/8hr	24 hours	Intravenous	Antibiotic types
R. Norlin et al. <sup>(300)</sup>	Cefotaxime	2g/8hr	24 hours	Intravenous	No antibiotic	n/a	n/a	n/a	Antibiotic Vs. No Antibiotic
S. Thomsen et al. <sup>(302)</sup>	Cephalothin	2g/4hr	24 hours	Intravenous	Methicillin	1g/6hr	24hrs	Intravenous	Antibiotic types
U. Sadat et al. {Sadat, 2008 #180}	5-day course(flucloxacillin / vancomycin for gram +ve cover AND gentamicin or ciprofloxacin for gram -ve cover), Metronidazole for anaerobic cover	1g/6hr or 1g/12hr AND 120mg /24hr or 200mg/2hr AND 500mg/8hr	5 days	Intavenous	24 Hr course (flucloxacillin /vancomycin for gram +ve cover AND gentamicin or ciprofloxacin for gram -ve cover), Metronidazole for anaerobic cover	1g/6hr or 1g/12hr AND 120mg /24hr or 200mg/2hr AND 500mg/8hr	24 hours	Intravenous for 24 hours followed by 4 days of oral antibiotics	Course duration

Table 20 List of studies selected for meta-analysis - Description of Antibiotic prophylaxis course

Authors	Control Group							Intervention group						
	Antibiotic types	Transmetatarsal	Transtibial	Transfemoral	Through-knee	Toe	Total	Antibiotic types	Transmetatarsal	Transtibial	Transfemoral	Through-knee	Toe	Total
JV. Robbs et al. (318)	No antibiotics	4	6	6	0	6	22	Amoxycillin/flucloxacillin combination	4	7	9	0	4	24
W.K.J. Huizinga et al. (298)	Benzylpenicillin	0	8	5	0	0	13	Amoxycillin/Clavulanic acid	2	15	13	0	1	31
S. Sonne-Holm et al. (301)	placebo	0	38	27	10	0	75	Cefoxitin	0	43	28	6	0	77
B. Nue Møller, B. Krebs (299)	No antibiotic treatment	n/a	n/a	n/a	n/a	n/a	n/a	Meticillin	n/a	n/a	n/a	n/a	n/a	n/a
H. Friis et al. (296)	Penicillin G	n/a	151	77	n/a	n/a	228	Cefuroxime	n/a	144	85	n/a	n/a	229
R. Norlin et al. (300)	No antibiotic	0	11	5	3	0	19	Cefotaxime	0	13	3	3	0	19
S. Thomsen et al. (302)	Cephalothin	6	50	25	13	0	94	Methicillin	7	42	33	11	0	93
U. Sadat et al. (235)	24-hour course(flucloxacillin / vancomycin for gram +ve cover AND gentamicin or ciprofloxacin for gram -ve cover), Metronidazole for anaerobic cover	0	20	20	0	0	40	5-day course(flucloxacillin / vancomycin for gram +ve cover AND gentamicin or ciprofloxacin for gram -ve cover), Metronidazole for anaerobic cover	0	21	19	0	0	40

Table 21 List of studies selected for meta-analysis - Types of amputation per group

Authors		Previous Surgery							Wound		Return to theatre				Post - op Mortality			Survival			
		Angioplasty (Balloon / stent)	Aorto-bifemoral BG	Axillary-femoral BG	Fem-Fem Cross over	Fem-popliteal BG	Fem-crural BG	Pop-crural BG	Stump infection (cellulitis, wet necrosis, dry necrosis dehiscence, +ve cultures )	No Wound infection	Debridement / Revision	Amputation to same level	Amputation to higher level	Total re amputations	Due to wound complication	Due to other causes	Overall	30-day	1-year	Overall	
JV. Robbs et al. <sup>(318)</sup>	Control	0	2	0	0	6	0	0	16	6	Not recorded				Not recorded			Not recorded			
	Intervention	0	1	0	1	4	0	0	8	16											
W.K.J. Huizinga et al. <sup>(298)</sup>	Control (Benzylpen)	History of previous revascularisation attempt not recorded							10	3	Not recorded				Not recorded			Not recorded			
	Intervention (Co-amoxiclav)								3	28											
S. Sonne-Holm et al. <sup>(301)</sup>	control	History of previous revascularisation attempt not recorded							42	33	0	4	17	21	Not recorded		6	Not recorded			
	Intervention								21	56	0	1	6	7			9				
B. Nue Møller, B. Krebs <sup>(299)</sup>	control	History of previous revascularisation attempt not recorded							8	15	Breakdown not recorded				8	Not Recorded			Not recorded		
	Intervention								0	27					4						
H. Friis et al. <sup>(296)</sup>	Intervention (Penicillin G)	History of previous revascularisation attempt not recorded							52	122	0	0	5	5	2	20	22	Not recorded			
	Control (Cefuroxime)								65	109	0	1	7	8	5	13	18				
R. Norlin et al. <sup>(300)</sup>	Control	History of previous revascularisation attempt not recorded							3	15	Not recorded				Not recorded			Not recorded			
	Intervention								7	10											
S. Thomsen et al. <sup>(302)</sup>	Intervention (Cephalothin)	History of previous revascularisation attempt not recorded							26	62	1	1	15	16	Breakdown not recorded		6	Not recorded			
	Control (Methicillin)								24	62	3	1	10	11			7				
U. Sadat et al. <sup>(235)</sup>	control (24-hour course)	History of previous revascularisation attempt not recorded							9	31	Not recorded				Breakdown not recorded		5	Not recorded			
	Intervention (5-day course)								2	38							1				

Table 22 List of studies selected for meta-analysis - Record of previous intervention, post-operative mortality by cause and survival rates

### 3.2.3 *Study subgroup analysis*

#### Antibiotic Vs Control (No antibiotic / Placebo)

Four studies compared patient outcomes following administration of antibiotic, against no antibiotic or in the case of Sonne-Holme et al. antibiotic against a placebo drug<sup>(299-301, 318)</sup>. Figure 23 on page 168 shows a forest plot which describes the combined effect of using an antibiotic compared to no prophylaxis. Three studies specifically compared at the use of prophylactic antibiotics against none<sup>(299, 300, 318)</sup>. A total of 69 patients were allocated to the intervention group and 62 in the control group. The risk reduction ranged from 64% [95% CI 0.25-0.85] - 95% [95% CI 0.00 – 0.83] among the 3 studies with a significant combined risk reduction of 63% [95% CI 0.17-0.83] (Z=2.42, P=0.02)<sup>(299, 300, 318)</sup>. There was no significant heterogeneity amongst the three studies (I<sup>2</sup>=30%, P=0.24), therefore data were analysed using a Random effects model. Only one study compared the use of antibiotic prophylaxis against a placebo<sup>(301)</sup>. There were 77 patients allocated to the antibiotic group compared to 75 in the control group. This study showed a statistically significant risk reduction in the development of SSI by 51% [95%CI 0.32 – 0.74] (Z=3.39, P=0.0007) (see Figure 23, pg.168)<sup>(301)</sup>.

Overall analysis of this group of studies involved a total of 146 patients allocated to antibiotic administration, and 137 patients to receiving no prophylaxis or a placebo. The use of antibiotic prophylaxis was associated with a significant risk reduction in developing an SSI by 54% [95%CI 0.33-0.64] (Z=4.65, P<0.00001). There was no significant inter- or intra-study heterogeneity amongst these studies (P=0.56, I<sup>2</sup>=0% and P=0.56, I<sup>2</sup>=0% respectively) (see Figure 23, pg.168).

#### Intervention antibiotic Vs Control antibiotic

Figure 24 on page 169 shows a forest plot of the three studies which compared different antibiotic types to examine their overall effect on the risk of developing an SSI<sup>(296, 298, 302)</sup>. Friis et al. was the largest of the 3 studies with a total of 368 patients included in the final analysis, 187 in the intervention group and 181 in the control group<sup>(296)</sup>. From the forest plot, the use of Penicillin G seemed to be associated with a risk reduction in the development of an SSI by 26% [95% CI 0.96-1.64], however this did not seem to be statistically significant (P>0.05). Huizinga et al. compared the use of co-amoxiclav against benzylpenicillin in 44 patients, 31 in the intervention group and 13 in the control group<sup>(298)</sup>. This study showed that co-amoxiclav was superior to benzylpenicillin in reducing the risk of SSI, in this case by 87% [95% CI 0.04-0.38](P<0.001). Thomsen et al. was the final study

of this type, and it included a total of 176 patients in the final analysis, 88 allocated to each group<sup>(302)</sup>. This study showed that the use of methicillin was associated with a reduction in the risk of SSI by 14% [95% CI 0.59-2.20], however this was not statistically significant (P=0.3094). Overall analysis of this group of studies did not show any significant outcomes in terms of antibiotic choice (Z=0.82, P=0.41). There was however significant heterogeneity amongst the 3 studies (P=0.0004, I<sup>2</sup>=87%).

#### 24 Hours Vs 48 Hours of antibiotic course

A comparison of 24 versus 48-hour antibiotic prophylaxis is demonstrated in Figure 25 on page 170. This group included a total of 7 studies, with 869 patients included in the final analysis<sup>(296, 298-302, 318)</sup>. A total of five studies involved administration of a 24-hour antibiotic course<sup>(296, 299-302)</sup>. The use of an antibiotic for 24 hours was associated with a significant risk reduction in developing an SSI by 36% (Z=2.25, P=0.02) [95% CI 0.44-0.94]. There was significant heterogeneity among the studies (P=0.05, I<sup>2</sup>=57%), therefore the random effects model was adapted. A total of two studies involved the administration of 48 hours of antibiotics<sup>(298, 318)</sup>. In this sub-group, the administration of an antibiotic for 48 hours was associated with a significant risk reduction in SSI development by 74% (Z=2.06, P=0.04)[95%CI 0.07-0.94]. Once again, there was significant heterogeneity amongst the studies in this subgroup (P=0.04, I<sup>2</sup>=75%), therefore the random effects model was adapted. Overall analysis of all the studies in this group suggested that an increase in the duration of antibiotic prophylaxis course was associated with a 59% risk reduction in the development of SSI post LLA (Z=3.17, P=0.002) [95% CI 0.33-0.77]. There was significant inter-study heterogeneity amongst the studies (P=0.0003, I<sup>2</sup>=69%), but no significant intra-study heterogeneity amongst the population groups (P=0.19, I<sup>2</sup>=42.8%).

#### 5-day Vs. 24-hour antibiotic antibiotic prophylaxis

Figure 26 on page 171 shows a forest plot which demonstrates the effect of using a 5-day antibiotic course compared to a 24-hour course on the risk of developing an SSI.

There was only one study identified which was designed to examine the effect of duration of antibiotic prophylaxis on the risk of developing an SSI post LLA<sup>(235)</sup>. A total of 80 patients, 40 in the 5-day group and 40 in the 24-hour group were included in the final analysis. The use of a 5-day antibiotic prophylaxis course was associated with a 78% risk reduction in the risk of developing an SSI which was significant (Z=2.01, P=0.04)[95%CI, 0.05-0.96].

### 3.2.4 Risk of bias

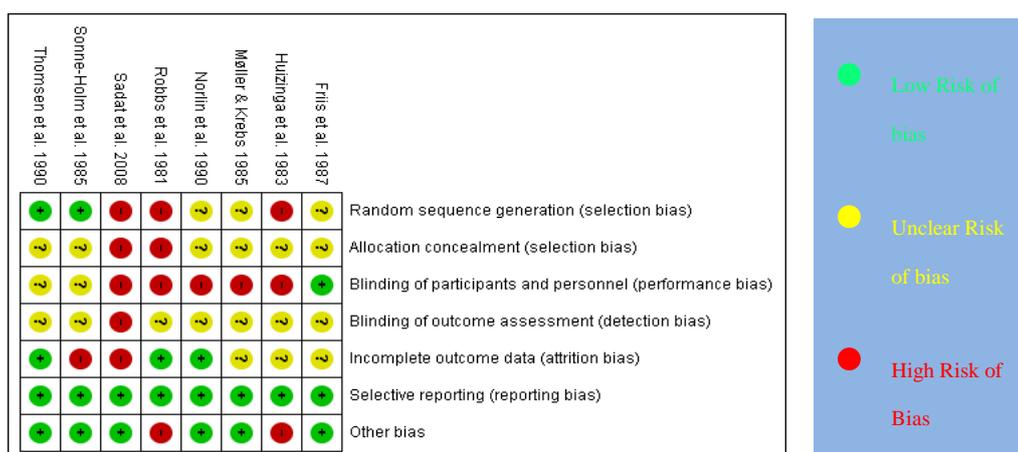


Figure 22 Risk of types of bias across the studies

Studies were assessed for different types of bias (see Figure 22, above):

1. Selection bias (allocation concealment, randomisation)
2. Performance bias (blinding of personnel / participants)
3. Detection bias (blinding of outcome assessment)
4. Attrition bias (incomplete outcomes)
5. Reporting bias (selective reporting)
6. Other types of bias

The most noticeable feature of all studies was the lack of blinding of both participants and personnel. A total of 5 studies were at high risk of performance bias due to lack of description of the blinding process of personnel/participants<sup>(235, 298-300, 318)</sup>, whilst 2 studies made reference to the blinding process, however this was not explicit<sup>(301, 302)</sup>. A similar pattern was observed with regards to detection bias, where almost all studies failed to give a clear explanation of the assessment process and blinding towards it<sup>(296, 298-302, 318)</sup>. The most recent of the studies by Sadat et al.<sup>(235)</sup> was at high risk of detection bias, as wound assessment was at times performed by the investigators.

The process of randomisation was not explained in 3 studies<sup>(296, 299, 300)</sup>, whilst in 3 others, allocation of participants to treatment modality was at the discretion of the clinician, or happened in a sequential as opposed to a random manner<sup>(235, 298, 318)</sup>.

None of the studies were at risk of reporting or other types of bias.

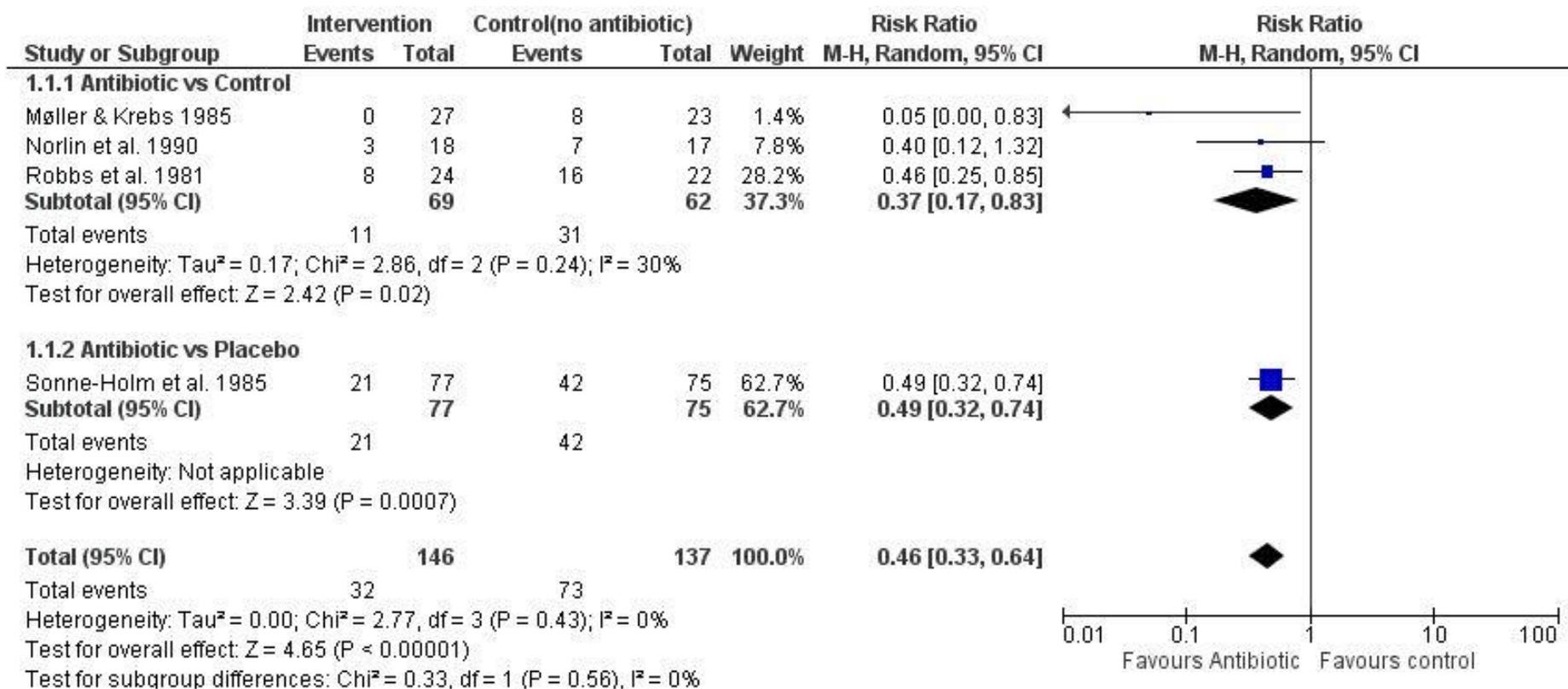
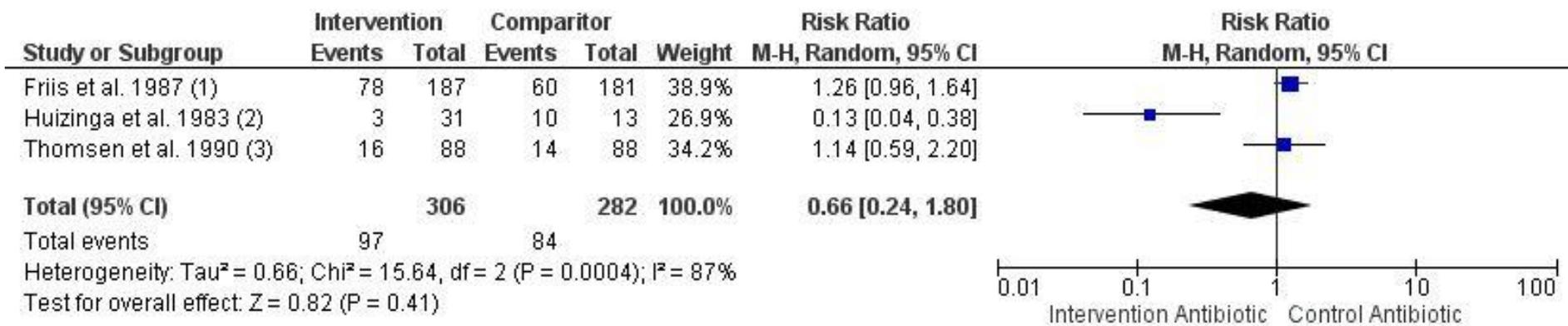


Figure 23 Forest plot - Comparison of the use of antibiotic versus no antibiotic / placebo to establish the effect on the risk of developing an SSI



**Footnotes**

- (1) Cefuroxime (Intervention) Vs Penicillin G(Control)
- (2) Amoxycillin/Clavulanic acid (Intervention) Vs Benzylpenicillin(Control)
- (3) Cephalothin (Intervention) Vs Methicillin (Control)

Figure 24 Forest plot - Comparison of between different antibiotics to establish the effect on the risk of developing an SSI

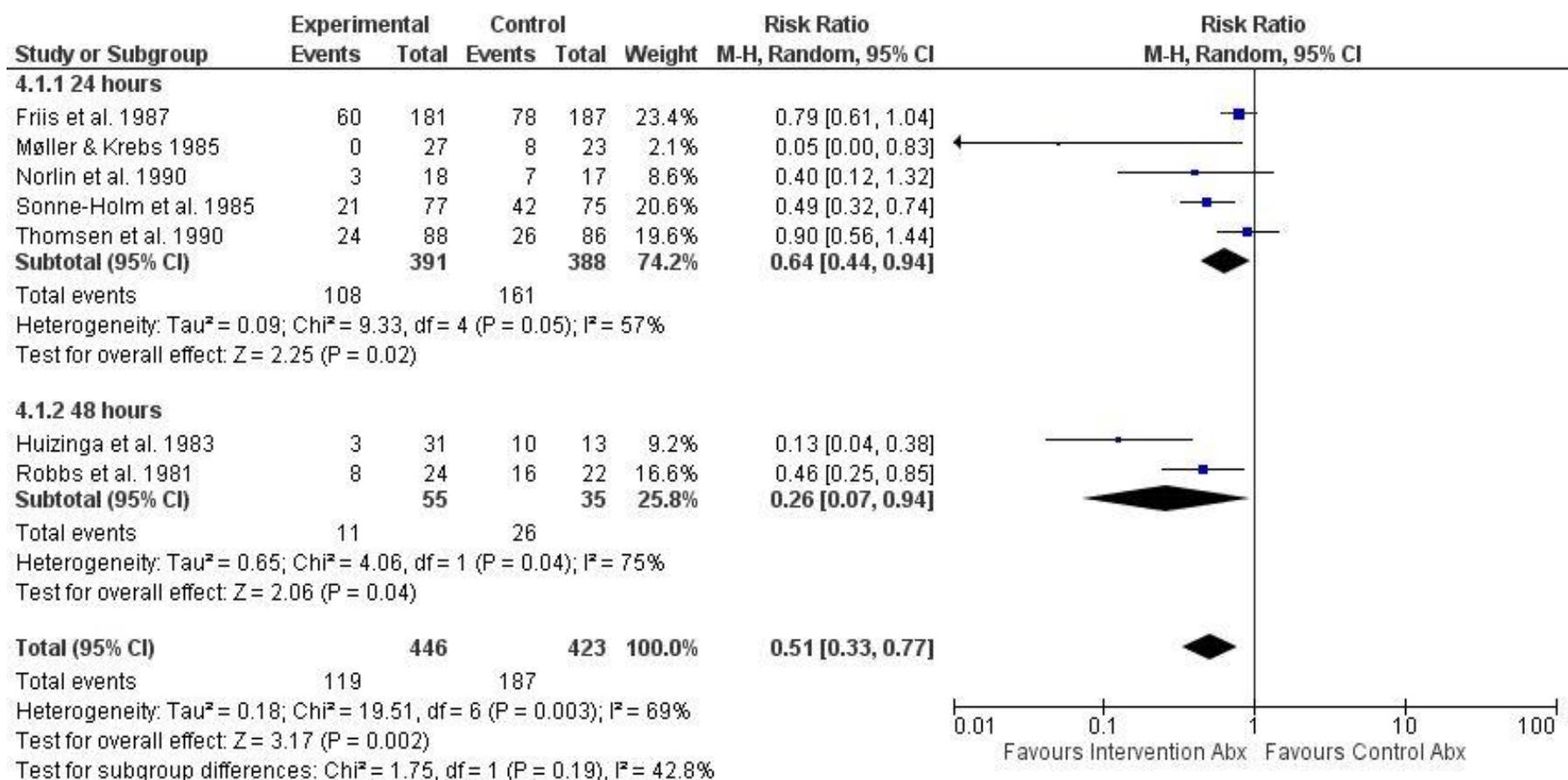


Figure 25 Forest Plot - Overall effect of increasing the duration of antibiotic prophylaxis from 24 to 48 hours on the risk of developing an SSI

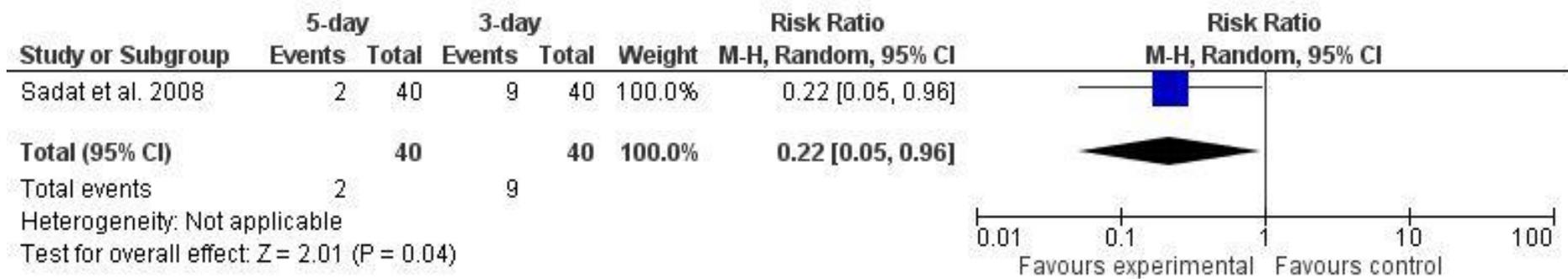


Figure 26 Forest plot - The effect of a 5-day versus a 3-day course of antibiotics on the risk of developing an SSI

## ***Section 3.3 Study 3: The Amputation Surgical Site Infection Trial***

Figure 27 on page 173 shows progression of the patients from the point of screening and selection through the RCT protocol.

### ***3.3.1 Screening and randomisation.***

Through the course of the recruitment phase, a total of 208 patients were screened for eligibility, of which 47 were excluded prior to randomisation. Of these, 8 declined to participate, 26 lacked capacity, 4 required an emergency amputation, and 9 were excluded due to other reasons (allergy to skin preparation and requirement of complex antibiotic regimes predesigned by the Microbiology Department). A total of 161 patients were recruited to the RCT, of which 40 were female. Of the 161 patients, 82 were randomised to the 5-day antibiotic course group and 79 patients to the 24-hour course group. Within the groups further stratification occurred to control for choice of alcohol based skin preparation. As such, within the 5-day course group, 48 patients were allocated to receive chlorhexidine skin preparation and 34 to povidone iodine. Within the 24-hour group, 33 patients received chlorhexidine and 46 had povidone iodine. Table 23 - Table 26 show the comparison of subject demographics, comorbidities, past medical and social history and current medication respectively amongst the two groups, indicating that the two groups were well matched in terms of patient characteristics. A total of 8 patients dropped out, all due to mortality within 30 days of the operation, 4 of which were allocated to the 5-day antibiotic group and 4 to the 24-hour group.

One hundred and fifty-three patients were included in the final analysis, of which 78 were allocated to the 5-day antibiotic group and 75 in the 24-hour group.

Once screened and recruited, patients were randomised to treatment using sealed paper envelopes. The antibiotics and skin preparation were prescribed at or before the time of the operation and were administered on induction to anaesthetic.

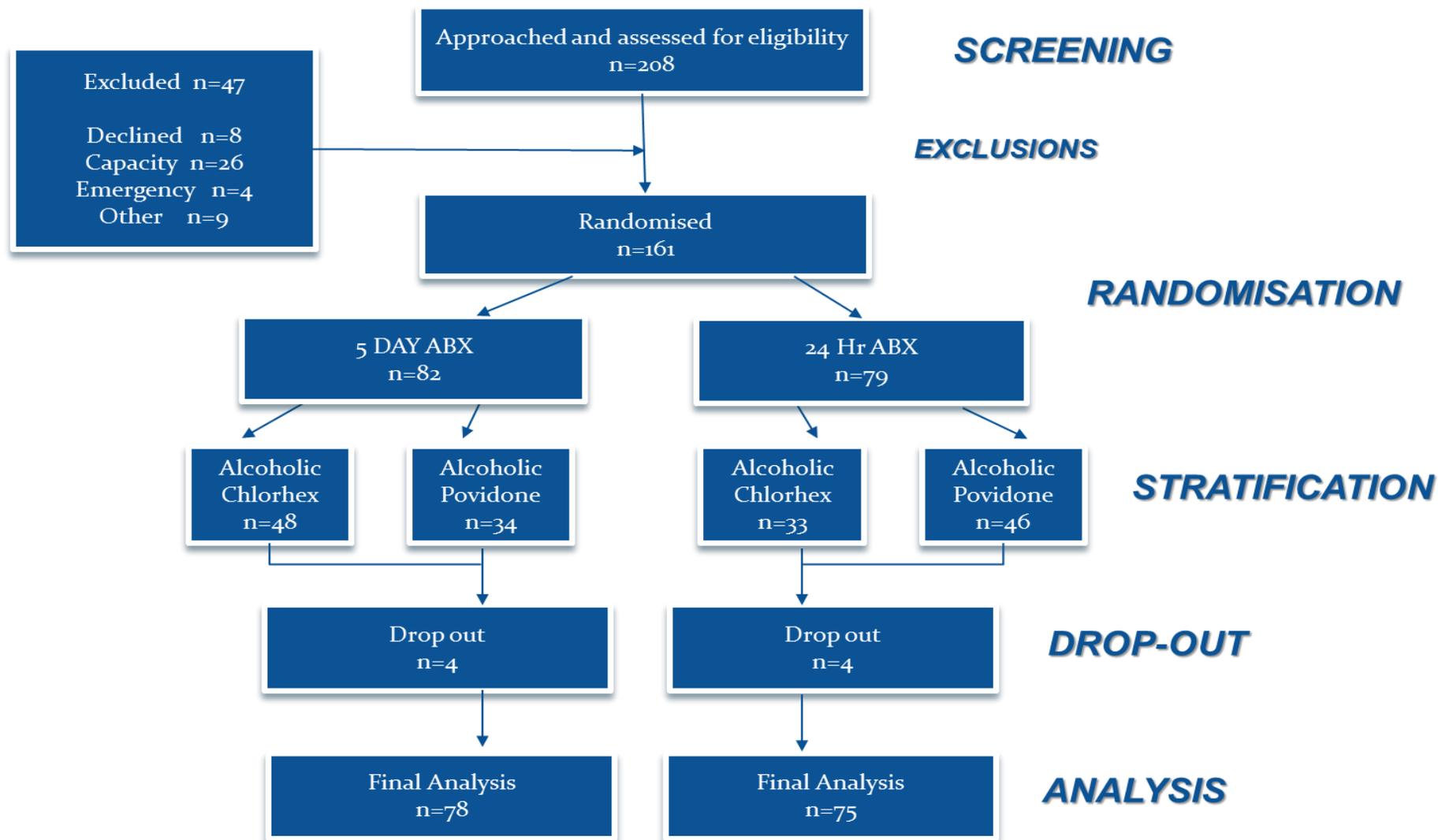


Figure 27 CONSORT diagram of patients involved in the RCT. (ABX – antibiotics, Chlorhex – chlorhexidine)

		Antibiotic Course Group		P-value
		5-day antibiotic course prophylaxis	24-hour antibiotic course prophylaxis	
		Count	Count	
Cause for amputation	Malignancy	2	2	0.560*
	Critical limb ischaemia	24	33	
	Diabetes	11	11	
	Mixed Chronic Limb Ischaemia & Diabetes	32	23	
	Osteomyelitis	2	3	
	Other Causes	11	7	
Diabetes	Insulin-controlled Diabetes	33	24	0.144*
	Tablet-controlled Diabetes	16	11	
	Diet-controlled Diabetes	0	0	
	No history of Diabetes	33	44	
Smoking	Current smoker	16	19	0.769*
	Ex-smoker	53	49	
	Non-smoker	13	11	
HTN	Uncontrolled Hypertension	0	1	0.159*
	Single agent control	20	26	
	Double agent control	24	13	
	Triple or more agent control	18	13	
	No previous history of hypertension	20	26	
Cerebrovascular disease	Disease present	12	11	1.000 <sup>‡</sup>
	Disease absent	70	68	
Cardiovascular disease	Disease present	48	43	0.636 <sup>‡</sup>
	Disease absent	34	36	
Respiratory disease	Disease present	23	30	0.240 <sup>‡</sup>
	Disease absent	59	49	
Hepatic Disease	Disease present	9	11	0.637 <sup>‡</sup>
	Disease absent	73	68	
MSK disease	Disease present	25	26	0.866 <sup>‡</sup>
	Disease absent	57	53	
Neurological disease	Disease present	17	18	0.849 <sup>‡</sup>
	Disease absent	65	61	
Renal/Urogenital disease	Disease present	35	25	0.192 <sup>‡</sup>
	Disease absent	47	54	
Dermatological disease	Disease present	13	7	0.234 <sup>‡</sup>
	Disease absent	69	72	
Hypercholesterolaemia	Disease present	12	7	0.331 <sup>‡</sup>
	Disease absent	70	72	

\*: Pearson's  $\chi^2$  test

<sup>‡</sup>: Fisher's Exact  $\chi^2$

Table 23 Past medical history of patients recruited to the study and their distribution amongst the two main treatment groups. The P-values all remain above 0.05 for their corresponding test statistic, suggesting well-matched groups

	Antibiotic Course Group								P-value
	5-day antibiotic course prophylaxis				24-hour antibiotic course prophylaxis				
	Median	Percentile 25	Percentile 75	Count	Median	Percentile 25	Percentile 75	Count	
<b>Age</b>	65.5	57.0	76.0		67.0	57.0	75.0		0.753*
<b>Gender</b> Male				60				61	0.588 <sup>‡</sup>
Female				22				18	

\*: Independent samples median test  
<sup>‡</sup>: Fisher's exact  $\chi^2$  test

Table 24 Patient demographics (age and gender) per group allocation. The P-values for their corresponding test statistic show the two groups are well matched.

		Antibiotic Course Group		P-value (Fisher's Exact $\chi^2$ )
		5-day antibiotic course prophylaxis	24-hour antibiotic course prophylaxis	
		Count	Count	
ACE inhibitors	Taking medication	31	25	0.508
	Not taking medication	51	54	
Statins	Taking medication	47	45	1.000
	Not taking medication	35	34	
Clopidogrel	Taking medication	18	15	0.699
	Not taking medication	64	64	
Aspirin	Taking medication	30	30	0.872
	Not taking medication	52	49	
Warfarin	Taking medication	12	13	0.829
	Not taking medication	70	66	
Dipyridamole	Taking medication	1	0	1.000
	Not taking medication	81	79	

Table 25 Drug history characteristics of the patients recruited to the study, per allocation group. The P-values for their corresponding test statistic show the groups are well matched

		Antibiotic Course Group		P-value
		5-day antibiotic course prophylaxis	24-hour antibiotic course prophylaxis	
		Count	Count	
Previous Angioplasty	Yes	46	40	0.529 <sup>‡</sup>
	No	36	39	
Previous endarterectomy	Yes	6	10	0.300 <sup>‡</sup>
	No	76	69	
Previous Bypass Surgery	Yes	18	17	1.000 <sup>‡</sup>
	No	64	62	
Level of Bypass	Fem-pop bypass	4	8	0.428 <sup>*</sup>
	Pop-TPT bypass	3	1	
	Axilo-fem bypass	1	0	
	Fem-fem bypass	0	1	
	Combination bypass	7	3	
	Fem-crural bypass	7	6	
	No bypass	60	60	
	Ilio-fem bypass	0	0	
*: Pearson's $\chi^2$ test ‡: Fisher's Exact $\chi^2$ test				

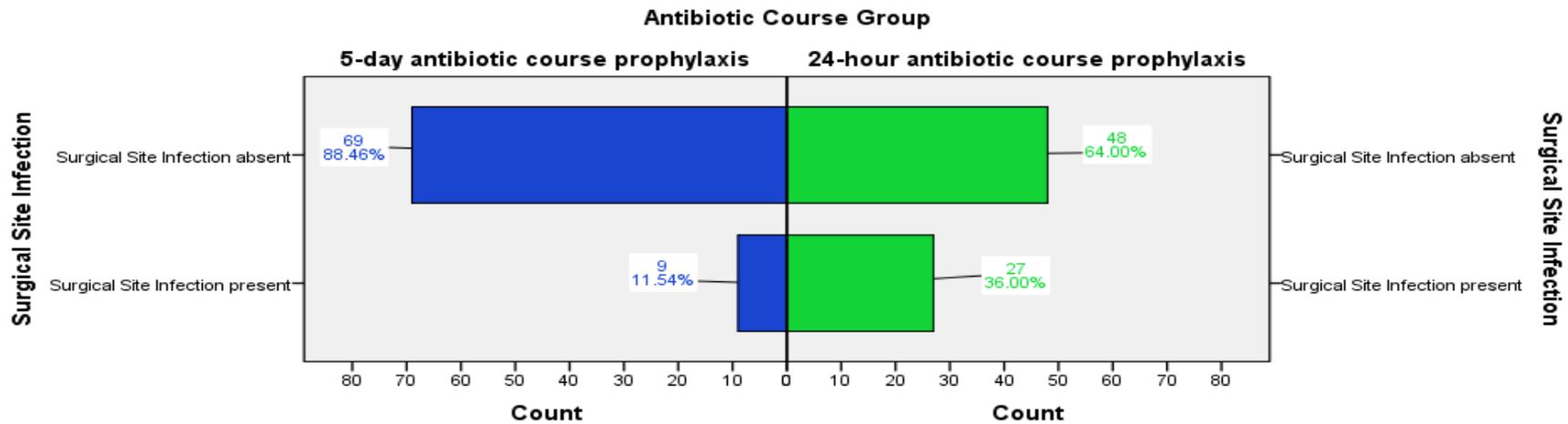
Table 26 Characteristics of previous vascular interventions of patients recruited to the study per group allocation. The P-values for their corresponding test statistic show the groups are well matched

### 3.3.2 *Primary outcomes – Surgical Site infection and Impaired Wound Healing incidence*

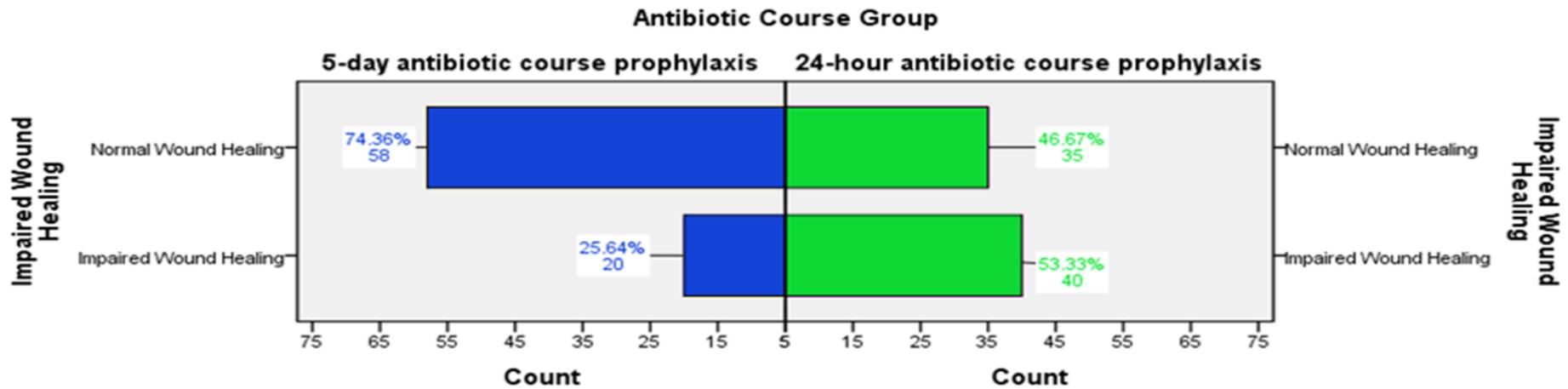
#### 3.3.2.1 Incidence of SSI / Impaired Wound Healing (IWH) per antibiotic group allocation.

Plot 1 shows a bar chart indicating the number of SSI/no SSI cases (%) per antibiotic group. Of the 78 patients in the 5-day group, only 9 patients(11.5%) **developed** an SSI compared to 27 out of 75 patients in the 24-hour group(36%). The use of a 5-day antibiotic course was found to be associated with statistically significant reduction in the incidence of SSI (**P=0.000268-Pearson's  $\chi^2$  test**).

Plot 2 shows a bar chart indicating the number of IWH/normal wound healing cases per antibiotic group. Of the 78 patients in the 5-group, 20 patients (25.6%) **experienced** IWH compared to 40 out of 75 patients in the 24-hour group(53.3%). The use of a 5-day antibiotic prophylaxis was associated with a statistically significant reduction in the incidence of IWH (**P=0.000520-Pearson's  $\chi^2$  test**).



Plot 1 Bar chart showing the number of SSI/no SSI cases (%) per antibiotic group. The use of a 5-day antibiotic course is associated with statistically significant reduction in SSIs (Pearson's 2-tail  $\chi^2$  test  $P=0.000268$ )



Plot 2 Bar chart showing the number of Impaired Wound Healing(IWH) /normal healing cases (%) per antibiotic group. The use of a 5-day antibiotic course is associated with statistically significant reduction in IWH (Pearson's  $\chi^2$  test  $P=0.000520$ )

### 3.3.2.2 Incidence of SSI / Impaired Wound Healing (IWH) per skin preparation group.

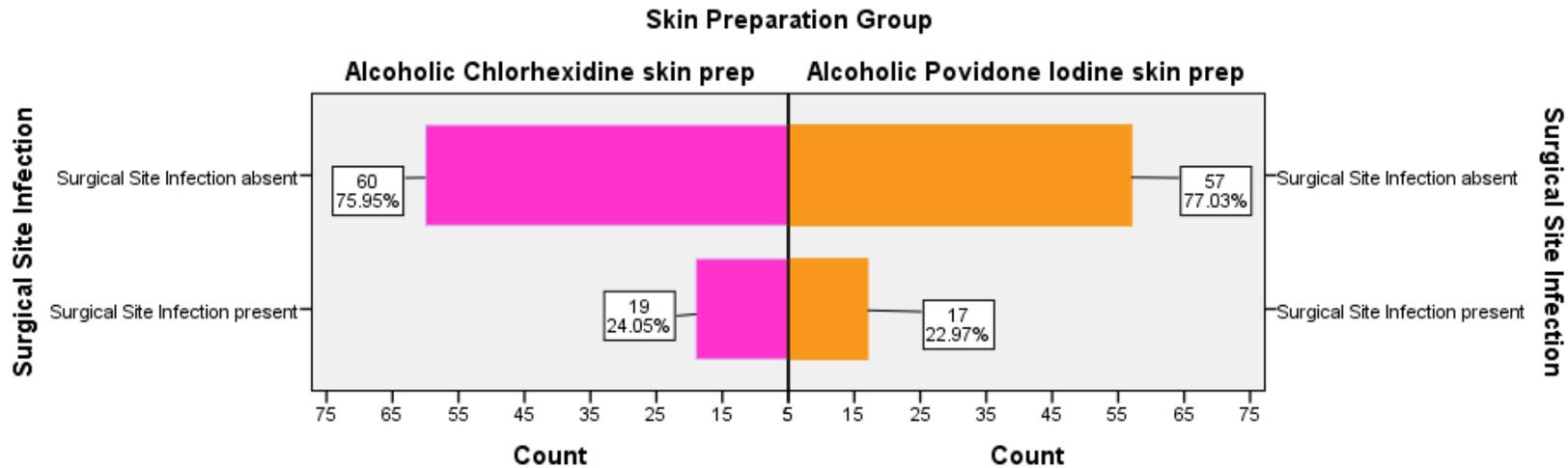
Plot 3 on page shows a bar chart indicating the number of SSI/no SSI cases (%) per skin preparation group. Of the 79 patients in the Chlorhexidine group, 19 patients(24.05%) **developed** an SSI compared to 17 out of 74 patients in the Povidone group(23%). The use of alcoholic chlorhexidine **was not** associated with a statistically significant reduction in the incidence of SSI when compared to alcoholic povidone (**P=0.851-Pearson's  $\chi^2$  test**).

Plot 4 shows a bar chart indicating the number of IWH/normal wound healing cases per skin preparation group. Of the 79 patients in the chlorhexidine group, 34 patients (43.04%) **experienced** IWH compared to 26 out of 74 patients in the povidone group(35.14%). The use of alcoholic chlorhexidine skin prep **was not** associated with a statistically significant reduction in the incidence of IWH when compared to alcoholic povidone (**P=0.326-Pearson's  $\chi^2$  test**).

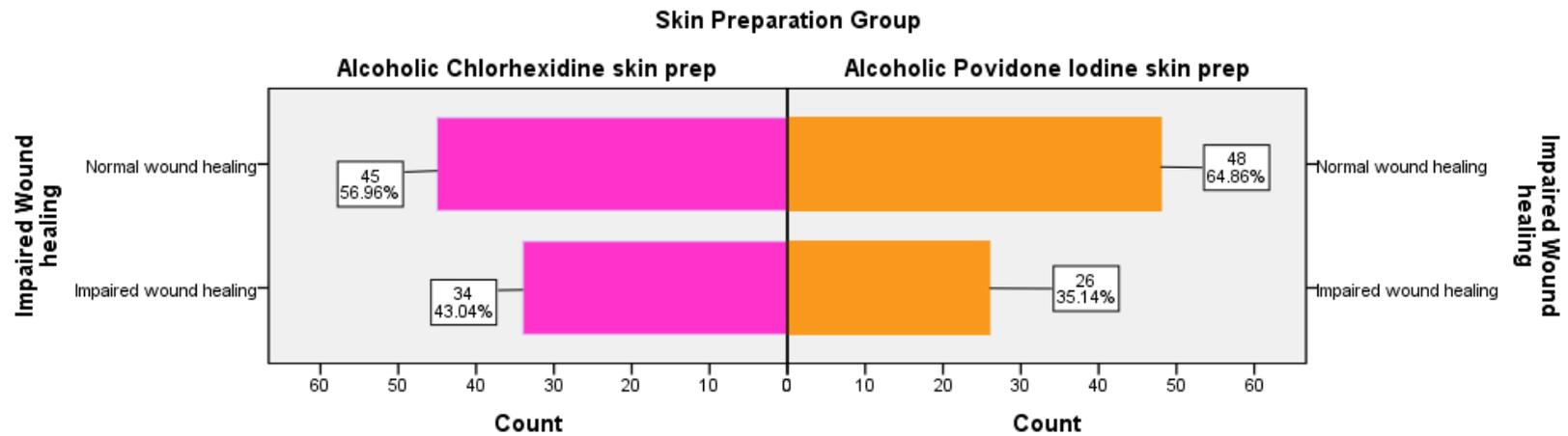
### 3.3.2.3 Overall risk of using different antibiotic course durations, and interactions with Skin preparation

Separate bivariate binary logistic regression analysis was performed to assess the risk of developing an SSI when using a 5-day antibiotic course compared to a 24-hour course. Skin preparation choice was also incorporated into the model, to account for the potential interaction between antibiotic duration and different types of skin preparation on the overall risk of developing an SSI or impaired wound healing (see Table 29, pg. 182).

The use of a 24-hour as opposed to a 5-day course **was found to significantly increase the risk** of developing an SSI by nearly a 5-fold (**OR 4.980, 95%CI(2.109-11.764)(P=0.000251)**). The choice of skin preparation between chlorhexidine and povidone **was not found to have a significant effect** on the overall risk of developing an SSI (**OR 1.536, 95%CI(0.691-2.412)(P=0.292)**) (see Table 29, pg. 182). The use of a 24-hour as opposed to a 5-day course **was found to significantly increase the risk** of developing IWH by nearly a 4-fold (**OR 3.792, 95%CI(1.860-7.733)(P=0.000246)**). Choice of skin preparation **was not found to have a significant effect** on the overall risk of developing IWH (**OR 1.852, 95%CI(0.911-3.766)(P=0.089)**) (see Table 29,pg. 182).



Plot 3 Bar chart showing the number of SSI/no SSI cases (%) per Skin preparation group. The use of alcoholic chlorhexidine compared to alcoholic povidone is *not* associated with a statistically significant reduction in SSIs ( $P=0.851$ -Pearson's  $\chi^2$  test)



Plot 4 Bar chart showing the number of IWH/normal wound healing cases (%) per Skin preparation group. The use of alcoholic chlorhexidine compared to alcoholic povidone is *not* associated with a statistically significant reduction in IWH ( $P=0.326$ -Pearson's  $\chi^2$  test)

		Surgical Site Infection					P-Value (Pearson's $\chi^2$ test)	
		Surgical Site Infection absent			Surgical Site Infection present			
		Median	Count	Row N %	Median	Count		Row N %
Age		66.0			63.0		0.741	
Gender	Male		86	75.4%		28	24.6%	0.852
	Female		30	76.9%		9	23.1%	
History of diabetes	No diabetes history		57	85.1%		10	14.9%	<b>0.018</b>
	Insulin/tablet-controlled Diabetes		59	68.6%		27	31.4%	
History of Smoking	Non-smokers		88	82.2%		19	17.8%	<b>0.005</b>
	Current/Ex Smokers		28	60.9%		18	39.1%	
Level of current amputation	About the foot		7	38.9%		11	61.1%	<b>0.000190</b>
	Below the knee		74	81.3%		17	18.7%	
	Through the knee		2	40.0%		3	60.0%	
	Above the knee		32	84.2%		6	15.8%	
Cause for amputation	Malignancy		4	100.0%		0	0.0%	0.582
	Critical Limb Ischaemia		44	78.6%		12	21.4%	
	Diabetes (neuropathy/microvascular disease)		13	61.9%		8	38.1%	
	Mixed Peripheral Vascular Disease and Diabetes		38	76.0%		12	24.0%	
	Osteomyelitis		4	80.0%		1	20.0%	
	Other causes		13	76.5%		4	23.5%	
Presence of infection at the time of admission	Yes		52	71.2%		21	28.8%	0.206
	No		64	80.0%		16	20.0%	

Table 27 Analysis of separate independent variables and their effect on SSI incidence. History of diabetes, smoking(ex/current) and the level of amputation performed are all associated with a statistically significant increase in SSI incidence

	Surgical Site Infection						P-Value (Pearson's $\chi^2$ test)	
	Surgical Site Infection absent			Surgical Site Infection present				
	Mean	Count	Row N %	Mean	Count	Row N %		
Preop Hb g/dL	108.61			107.49			0.194	
Preop albumin g/L	26.46			27.30			0.129	
Perioperative transfusion	Yes		46	73.0%		17	27%	0.399
	No		70	78.9%		19	21.1%	
Previous Endarterectomy +/- Bypass graft surgery	Yes		32	76.2%		10	23.8%	0.947
	No		84	75.7%		27	24.3%	
Previous Angioplasty	Yes		60	73.2%		22	26.8%	0.411
	No		56	78.9%		15	21.1%	

Table 28 Additional separate analysis of the effect of preoperative levels of haemoglobin and albumin, as well as previous vascular procedures on SSI incidence. There is no observed statistical significance associated with increased SSI incidence

	B	S.E.	Wald	df	Sig.	Odds Ratio	95% C.I. for Odds ratio	
							Lower	Upper
Level of amputation - About the Foot	2.098	0.697	9.055	1	<b>0.003</b>	<b>8.149</b>	2.078	31.951
Level of amputation - Below the knee	0.096	0.550	.030	1	0.862	1.100	0.375	3.231
Level of amputation - Through the knee	1.891	1.075	3.092	1	0.079	6.627	0.805	54.545
Smokers (Ex / current)	1.202	0.439	7.514	1	<b>0.006</b>	<b>3.328</b>	1.409	7.861
Diabetics (Tablet / insulin)	0.899	0.467	3.706	1	<b>0.050</b>	<b>2.456</b>	0.984	6.133

Table 29 Binary logistic regression analysis of identified variables associated with a statistically significant increase in SSI incidence. Foot amputations, smoking and diabetes all increase the risk of SSI

	Impaired Wound Healing	
	Normal Wound Healing	Impaired Wound Healing present

		Median	Count	Row N %	Mean	Median	Count	Row N %	Mean	P-Value (Pearson's $\chi^2$ test)
Age		66.0				64.5				0.541
Gender	Male		70	61.4%			44	38.6%		0.789
	Female		23	59.0%			16	41.0%		
History of diabetes	No diabetes history		45	67.2%			22	32.8%		0.154
	Insulin/tablet-controlled		48	55.8%			38	44.2%		
	Diabetes									
History of Smoking	Non-smokers		68	63.6%			39	36.4%		0.285
	Current/Ex Smokers		25	54.3%			21	45.7%		
Level of amputation	About the foot		1	5.6%			17	94.4%		<0.0001
	Below the knee		63	69.2%			28	30.8%		
	Through the knee		1	20.0%			4	80.0%		
	Above the knee		27	71.1%			11	28.9%		
Cause for amputation	Malignancy		3				1			0.431
	Critical Limb Ischaemia		37				19			
	Diabetes (neuropathy/microvascular disease)		9				12			
	Mixed Peripheral Vascular Disease and Diabetes		31				19			
	Osteomyelitis		2				3			
	Other causes		11				6			
Presence of infection at the time of admission	Yes		41				32			0.264
	No		52				28			
Preop Hb g/dL					109.27				106.86	0.457
Preop albumin g/L					26.49				26.93	0.280
Previous Angioplasty	Yes		48				34			0.541
	No		45				26			
Previous Endarterectomy +/- Bypass graft surgery	Yes		25	59.5%			17	40.5%		0.844
	No		68	61.3%			43	38.7%		

Table 30 Analysis of separate independent variables and their effect on IWH incidence. The level of amputation performed appears to be the only additional factor associated with a statistically significant increase in IWH incidence

### 3.3.3 Other factors related to SSI/IWH:

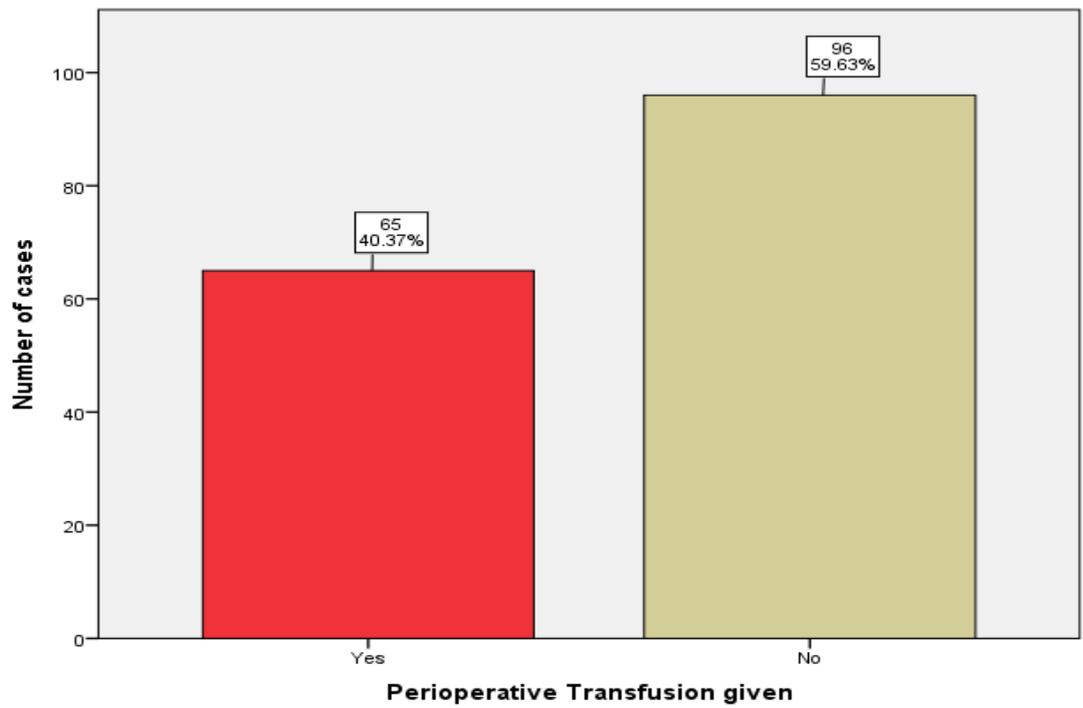
Additional analysis was performed in order to investigate the effect of other factors on the incidence of SSI and IWH. These included age, gender, history of diabetes and smoking, level and cause of the current amputation, presence of infection at the time of admission, preoperative haemoglobin and albumin levels, as well as the effect of perioperative transfusion of blood products (one week preoperatively – thirty days post-operatively) and the presence of previous vascular interventions. The effects of the aforementioned variables on the incidence of SSIs are summarised in Table 27 on page 181 and Table 28 on page 182.

History of diabetes, smoking and level of amputation were the only factors which statistically significantly increased the incidence of SSIs following major LLA. Previous history of insulin/tablet controlled diabetes was seen in 86 patients. Of these, 27 patients(31.4%) developed an SSI (**P=0.018**). A total of 46 patients were ex/current smokers. Of these, 18 patients(39.1%) developed an SSI (**P=0.005**). The level of amputation also suggested an effect on the incidence of SSI (**P=0.000190**).

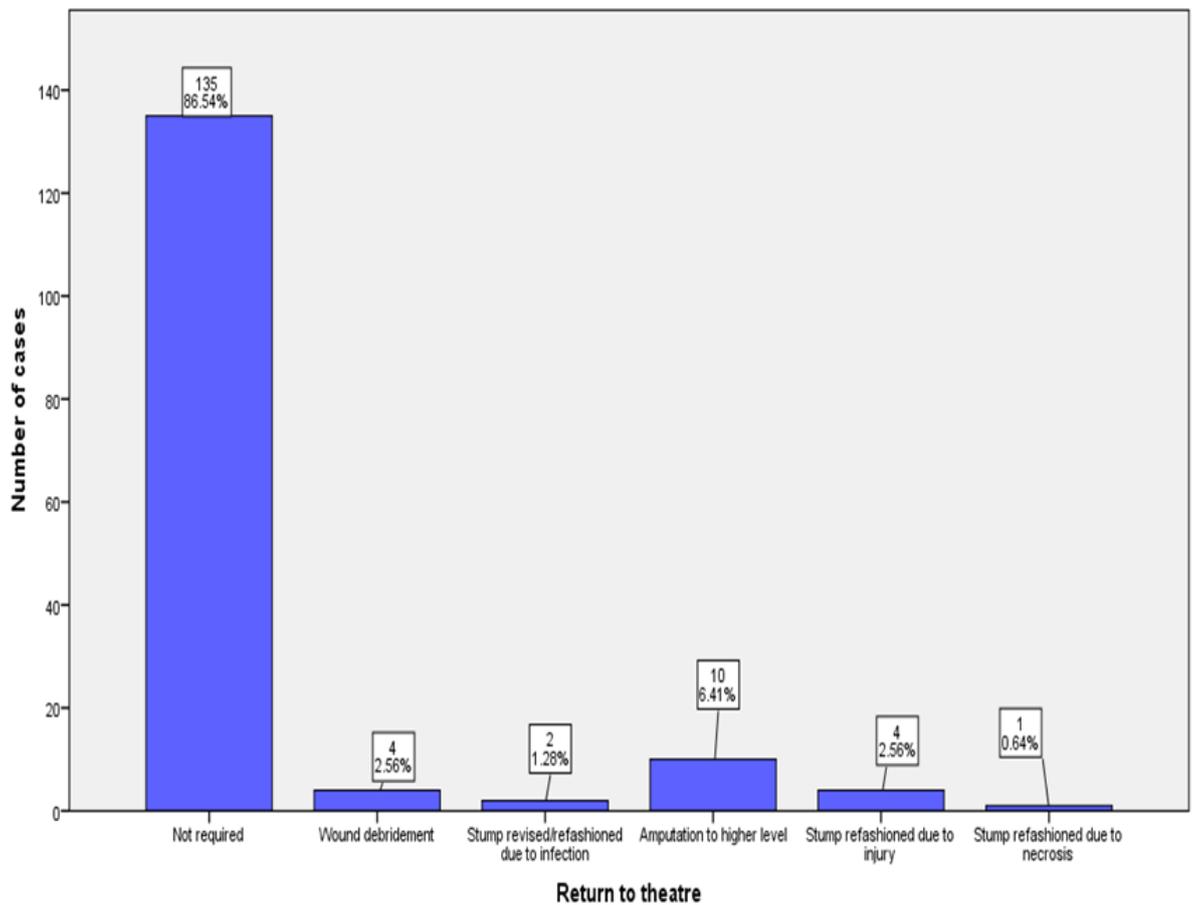
These factors were further examined within a binary logistic regression analysis model to account for potential interactions amongst them (see Table 29, pg. 182). This analysis revealed that amputation at the level of the foot was the most significant in terms of odds of SSI development, **increasing its risk by almost an 8-fold (P=0.003 OR 8.149 95%CI 2.078-31.951)**. History of smoking was also associated with **statistically significant increase in the risk of post op SSI by a 3-fold (P=0.006, OR 3.328 95%CI 1.409-7.861)** Previous/current history of diabetes nearly doubled the risk of SSI development (**P=0.050, OR 2.456 95%CI 0.984-6.133**) .

An identical statistical model was employed to examine the effect of the same set of independent factors on the incidence of IWH. The only statistically significant factor identified was the level of amputation (**P<0.0001**).

A previous vascular intervention, presence of infection/wound at the time of admission, the cause for amputation, the administration of a perioperative transfusion and preoperative levels of albumin and haemoglobin were not associated with a statistically significant rise in the incidence of SSI/IWH (See Table 27-Table 30, pg.181-183).



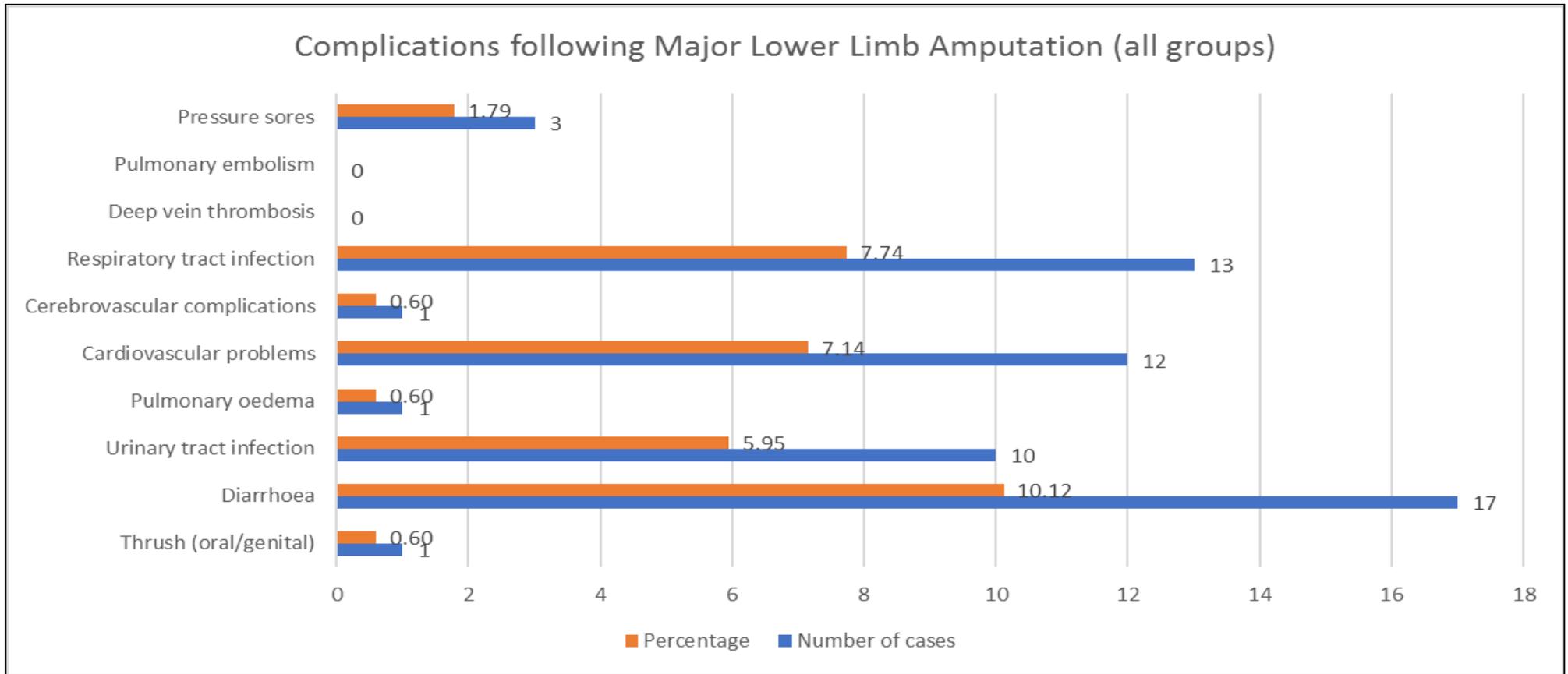
Plot 5 Number of amputation cases requiring a perioperative transfusion across both groups



Plot 6 Number of cases returned to theatre for an additional procedure as a complication following a major LLA. The incidence is across both groups

		Return to theatre												P - value (Pearson's $\chi^2$ test)
		Not required		Wound debridement		Stump revised/refashioned due to infection		Amputation to higher level		Stump refashioned due to injury		Stump refashioned due to necrosis		
		Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %	
Surgical Site Infection	Surgical Site Infection absent	104	90.4%	2	1.7%	1	0.9%	3	2.6%	4	3.5%	1	0.9%	<b>0.007</b>
	Surgical Site Infection present	27	73.0%	2	5.4%	1	2.7%	7	18.9%	0	0.0%	0	0.0%	
Impaired Wound Healing	Normal Wound Healing	87	93.5%	0	0.0%	1	1.1%	1	1.1%	4	4.3%	0	0.0%	<b>&lt;0.0001</b>
	Impaired Wound Healing present	44	74.6%	4	6.8%	1	1.7%	9	15.3%	0	0.0%	1	1.7%	

Table 31 Number of cases returned to theatre for an additional procedure, in the presence or absence of SSI or IWH. The presence of SSI is associated with a statistically significant increase in the return to theatre for an additional procedure (**P=0.007**). The presence of IWH is associated with a statistically significant increase in the return to theatre (**P<0.0001**)



Plot 7 Additional complications following a major LLA across both antibiotic groups.

### 3.3.4 *Effects of amputation and SSI/IWH on general post-operative complications*

Plot 7 shows post-operative complications recorded across both antibiotic groups following a major LLA. The commonest complication experienced by these patients was postoperative non-infective diarrhoea occurring in 17 subjects(10.12%). There was only one case of active clostridium difficile diarrhoea and this was in a patient who was previously a toxin carrier. The second commonest complication included respiratory tract infection, occurring in 13 cases(7.74%). The remainder general complications post-operatively were summarised in Plot 7 on page 187 across both groups. These were in small numbers, therefore, no statistical analysis was performed.

In terms of perioperative transfusion, 65 patients(40.37%) required blood products. For those patients who received the transfusion in the post-operative setting only, the presence of SSI/IWH did not have a statistically significant effect on the need for transfusion (P=0.442 and P=0.502 respectively).

### 3.3.5 *Effects of SSI/IWH on complications requiring return to theatre*

Of the 156 patients included in this analysis, 21(13.6%) returned to theatre in the post-operative setting in the first 30 days across both groups for one of the following additional procedures (see Plot 6, pg.185 and Table 31, pg.186):

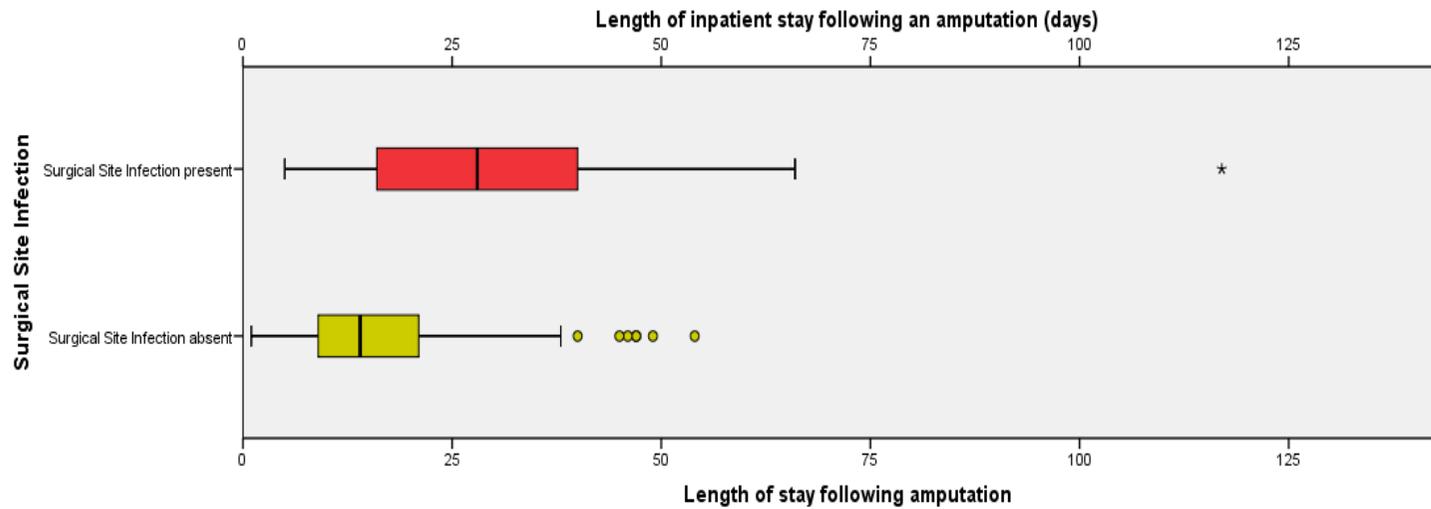
1. Simple wound debridement
2. Stump refashioning/revision
3. Amputation to higher level due to infection/necrosis
4. Stump refashioned due to injury
5. Stump refashioned due to ischaemia/necrosis

The commonest cause for a return to theatre was for amputation to a higher level due to infection/necrosis(10 cases, 6.41%). The effects of SSI and IWH were examined independently.

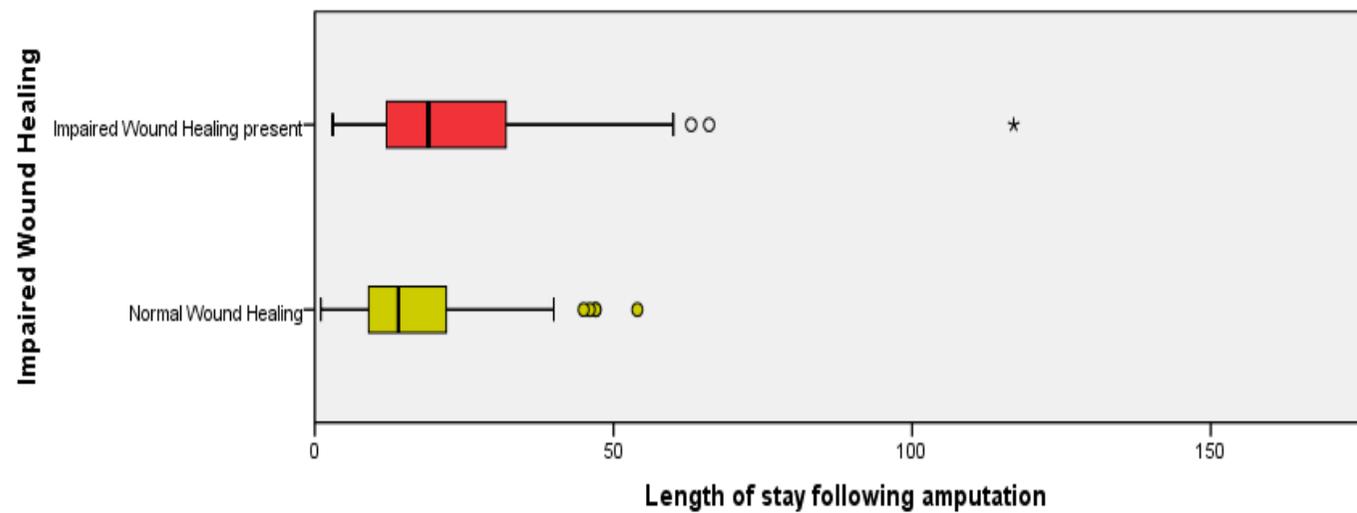
Of the 37 patients who developed an SSI in the post-operative setting, 10 required return to theatre (27%). The presence of SSI **statistically significantly increases the incidence of return to theatre (P=0.007)** (see Table 31, pg.186). **The risk of returning to theatre, in**

**the presence of post-operative SSI increases by 27.2% (P=0.008, OR0.272, 95%CI(0.105-0.710)).**

Of the 60 patients who developed IWH, 15 required return to theatre (25%). **The presence of IWH statistically significantly increases the incidence of return to theatre (P<0.0001) (see Table 31, pg.186). The risk of returning to theatre, in the presence of IWH increases by 20.2% (P=0.002, OR0.202, 95%CI(0.073-0.558)).**



Plot 8 The length of stay in median number of days in the absence of SSI is 14 (IQR 9-21) and it increases to 28 days (IQR16-40) in the presence of SSI. The rise in length of stay is **statistically significant** (***P=0.015 - Pearson's  $\chi^2$  test***)



Plot 9 The length of stay in median number of days is 14 (IQR 9-22). It increases to 19 days (IQR 12-32) in the presence of IWH. This rise is **not statistically significant** (***P=0.182 - Pearson's  $\chi^2$  test***)

		Length of stay following amputation			P - value (Pearson's $\chi^2$ test)
		Median	Percentile 25	Percentile 75	
Surgical Site Infection	Surgical Site Infection absent	14	9	21	<b>0.015</b>
	Surgical Site Infection present	28	16	40	
Impaired Wound Healing	Normal Wound Healing	14	9	22	0.182
	Impaired Wound Healing present	19	12	32	

Table 32 The length of stay in median number of days in the presence/absence of SSI/IWH. The presence of an SSI is associated with a statistically significant increase in length of stay to 28 days (IQR 16-40) compared to 14(IQR 9-21) (P=0.015)

### 3.3.6 Effect of SSI/IWH on postoperative length of stay

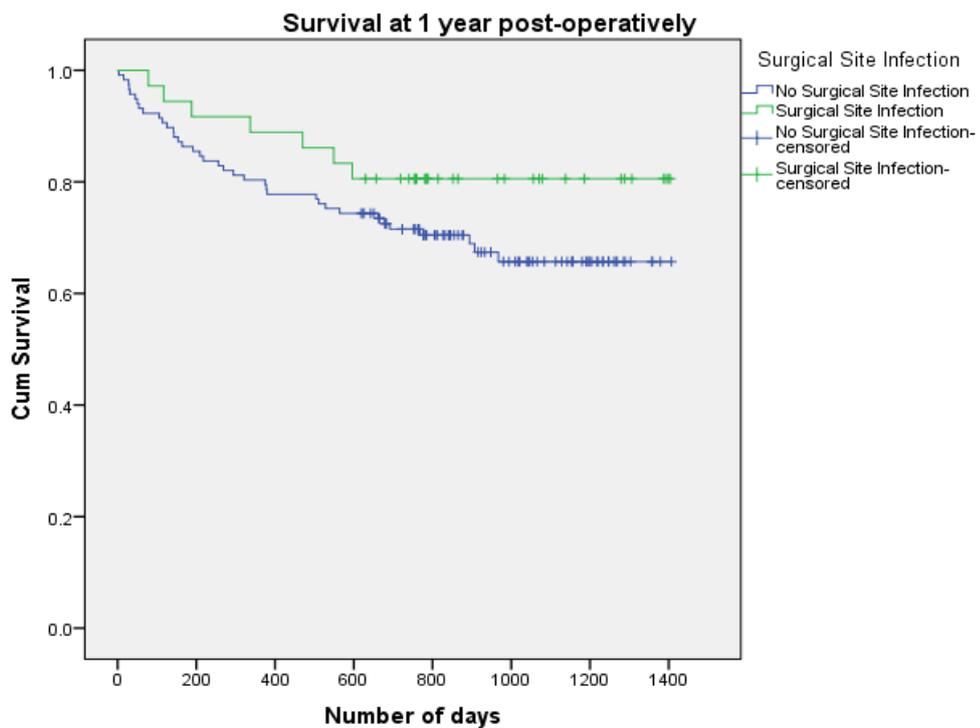
The length of stay in median number of days in the absence of SSI is 14(IQR 9-21) and it increases to 28 days (IQR16-40) in the presence of SSI. The rise in length of stay is **statistically significant (P=0.015)** (See Plot 8, pg.190 and Table 32, pg. 191)

The length of stay in median number of days is 14 (IQR 9-22). It increases to 19 days (IQR 12-32) in the presence of IWH. This rise is not statistically significant (P=0.182) (See Plot 9, pg.190 and Table 32, pg. 191).

### 3.3.7 Effect of SSI on Mortality at 30 days and 1 year post-operatively.



Plot 10 Kaplan-Meier Cumulative survival at 30 days post-operatively. The presence of SSI has no statistically significant effect on cumulative survival ( $P=0.826$ )



Plot 11 Kaplan-Meier Cumulative survival at 1 year post-operatively. The presence of SSI has no statistically significant effect on cumulative survival ( $P=0.167$ )

Number of deaths at 30 days post-operatively

Surgical Site Infection	Total Number	Number of deaths	Censored	
			N	Percent
No Surgical Site Infection	117	4	113	96.6%
Surgical Site Infection	36	1	35	97.2%

Overall	153	5	148	96.7%
---------	-----	---	-----	-------

Table 33 Number of mortality cases at 30-day follow-up recorded by presence/absence of SSI.

**Number of deaths at 1 year post-operatively**

Surgical Site Infection	Total Number	Number of Deaths	Censored	
			N	Percent
No Surgical Site Infection	117	37	80	68.4%
Surgical Site Infection	36	7	29	80.6%
Overall	153	44	109	71.2%

Table 34 Number of mortality cases at 1-year follow-up recorded by presence/absence of SSI.

The presence of SSI had no statistically significant effect on the number of cases and on the overall cumulative patient survival at 30 days nor at 1 year post-operatively (see Plot 10 Plot 11, pg. 192 and Table 33 and Table 34, pg. 193).

**Section 3.4 Study 4: The Impact of Previous Surgery and Revisions on Outcome after Major Lower Limb Amputation**

One hundred forty-eight major LLAs were undertaken over the time frame: 53 AKAs, 90 BKAs, 4 through knee, and 1 hindquarter. Limited data pertaining to 6 patients were available because the patients were referred from other units and transferred back postoperatively. The mean patient age was 68 years. Indications for surgery were acute ischemia 31.9%, non-resolving sepsis in patients with peripheral arterial disease (including osteomyelitis) 15.6%, chronic ischemia (rest pain or gangrene) 47.6%, complex regional pain syndrome 2.8%, and trauma 2.1%. For the purpose of analysis, amputations carried out for complex regional pain syndrome or trauma were excluded. Primary amputations were carried out for patients with no revascularisation options or if revascularisation was deemed inappropriate (i.e., extensive necrosis, life-threatening sepsis, or instances of a functionally useless limb).

### 3.4.1 *Previous Revascularisation*

Forty-six (32.6%) patients had undergone a previous ipsilateral revascularization procedure including embolectomy, angioplasty, and bypass procedures (see Table 35, pg.195 ). The patients were subdivided accordingly.

The groups were well matched for demographics and comorbidities, although those who had previous interventions were older ( $P=0.018$ ), had a higher incidence of hypercholesterolemia ( $P < 0.001$ ), and were less likely to have chronic renal failure ( $P=0.034$ ; see Table 36, pg.195).

Previous revascularization procedures	n
Angioplasty	14
Thrombolysis	1

Embolectomy	5
Endarterectomy	1
Bypass graft	9
Angioplasty + bypass	9
Embolectomy + bypass	1
Endarterectomy + bypass	2
Embolectomy + endarterectomy	1
Bypass + thrombolysis	1
Angioplasty + bypass +thrombolysis	1
Angioplasty + endarterectomy +bypass + thrombolysis	1

*Table 35 Previous ipsilateral procedures in secondary amputation group*

	Previous revascularization	No previous revascularization	P
n	46	88	
Age	72.2	66.5	0.018 <sup>b</sup>
Sex (F/M)	13/33	31/64	0.599 <sup>a</sup>
Emergency <sup>c</sup>	29	47	0.256 <sup>a</sup>
Diagnosed hypertension	23	39	0.366 <sup>a</sup>
Chronic renal failure	3	18	0.034 <sup>a</sup>
Hypercholesterolemia	19	12	<0.001 <sup>a</sup>
Cerebrovascular disease	9	12	0.290 <sup>a</sup>
Current smokers	9	15	0.646 <sup>a</sup>
COAD	6	12	0.934 <sup>a</sup>
Diabetes mellitus	21	45	0.650 <sup>a</sup>
Previous myocardial infarction	7	10	0.389 <sup>a</sup>
Venous thromboembolism	5	4	0.147 <sup>a</sup>

COAD, chronic obstructive airways disease.

<sup>a</sup>Chi-squared test.

<sup>b</sup>Mann-Whitney U test.

<sup>c</sup>Emergency refers to patients admitted acutely and operated on within 48 hours of admission.

*Table 36 Comparison of baseline characteristic*

### 3.4.2 Amputation Level and Revisions

The level of amputation did not appear to be affected by previous revascularization procedure history (see Table 37, pg.196). Twelve patients required a second procedure on the same admission. This included re-suturing (3 patients), debridement (2 patients), revision from BKA to AKA (6 patients), and, in one case, a contralateral AKA. Supplementary analysis to determine the impact of previous interventions necessitating revision surgery on the same admission revealed that 15.4% of patients who had a previous intervention required stump revision during the same admission compared with 4.5% who did not (P=0.025).

	Mortality, n(%)	P-value(Chi-squared)
Combined	2(18)	0.321
Surgery	5(33.3)	
Endovascular	9(45)	

Table 39 Type of revascularization and mortality

Level	Previous revascularisation	No previous revascularisation	P (Chi-squared)
Hindquarter	0	1	0.485
Above knee	16	34	0.907
Through knee	3	1	0.067
Below knee	28	59	0.887

Table 37 Impact of previous revascularisation on amputation level

Mortality	Previous Revascularisation	No previous Revascularisation	P -value(Chi-squared)
30-day mortality	6	12	0.582
6-month mortality	9	18	0.394
1-year mortality	12	22	0.446
2-year mortality	16	26	0.367

Table 38 Impact of previous revascularisation on mortality rates

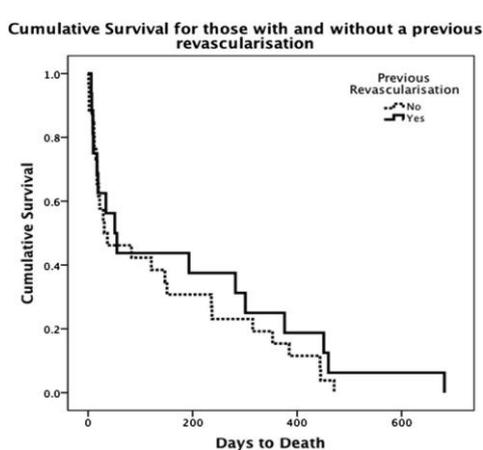


Figure 28 Cumulative survival for those with / without a previous revascularisation

### 3.4.3 Mortality

Mortality data were available for 141 patients. Analysis of the mortality rates showed 30-day, 1-year and 2-year mortality to be 8.4%, 24.1%, and 29.8%, respectively (see Table 38, pg.196 and Figure 28, pg.196). The mean number of days until death was 156.3 days. The most frequently recorded cause of death was multisystem failure.

Previous revascularisation was not found to increase the risk of mortality after amputation. Sub-group analysis did not indicate higher risk when comparing endovascular and surgical with combined procedures (see Table 39, pg.196). Previous ipsilateral amputation equally was not associated with increased mortality (P=0.609).

Undergoing >1 surgical procedure on the admission was not found to be a significant risk factor for mortality (P=0.705).

---

## Chapter 4 *DISCUSSION, LEARNING POINTS AND LIMITATIONS*

### *Section 4.1 Study 1: A Survey of perioperative management major lower limb amputations*

The aim of this study was to examine the current practice with respect to perioperative care across the UK, in patients undergoing major LLA

#### **Response Rates**

The response rate of 37.2% from vascular consultants was encouragingly higher than anticipated as we know from previous similar postal surveys that response rates have been reported to range between 12-37% <sup>(319-321)</sup>. This could be attributed to the ease of questionnaire completion and inclusion of a stamped addressed return envelope. The low number of responses from trainees could be explained by the nature of the surgical rotations which involves hospital rotations happening every 6-12 months. As a result of the anonymized nature of questionnaire, it was not possible to approach non-responders to optimize the response rate.

#### **Outcomes**

This survey has shown that the majority of surgeons underestimated the infection rates within their patient cohort with a median infection rate of 6-10%, whilst other studies specifically examining postoperative infections report rates up to 35%. This could be explained by the late development of infections, namely after discharge to rehabilitation centres or repatriation to local hospitals within the first 30 days of their operation. The majority of SSIs become evident within the first 3 weeks after the procedure with up to 84% of infections detected following hospital discharge <sup>(322)</sup>. It is also acknowledged that the many different definitions and grading scales for wound infections can lead to variations in the reported infection rates across the different institutions <sup>(275)</sup>.

This survey suggests that there is little consensus in practice regarding perioperative wound management of patients undergoing major LLA. This was likely to be due to the lack of high-level evidence demonstrating superiority of one technique over another. The different disease processes encountered may also account, in part, for the differing practices reported. This lack of evidence, was addressed through the design and conduction of the ASSIT study, as described in this Thesis (See Section 2.3, Section 3.3 and Section 4.3, pgs. 133, 172 and 211 respectively).

### **Skin preparation**

The National Institute for Health and Care Excellence (NICE) SSI guidelines for anti-septic skin preparation (intraoperative) states that “Prepare the skin at the surgical site immediately before incision using an antiseptic (aqueous or alcohol-based) preparation: povidone-iodine or chlorhexidine are most suitable. <sup>(257)</sup>” The guidelines fail to distinguish between the different skin preparations in relation to efficacy at reducing SSI. A Cochrane review has been previously carried out in order to examine the role of skin antiseptics in clean surgery <sup>(266)</sup>. It included data from one trial: “Berry 1982 compared povidone iodine (PI) 10% in alcohol with chlorhexidine 0.5% in spirit (Hibitane) in 371 patients undergoing clean surgery. Significantly more patients (28/176; 15.9%) in the PI group developed an infection compared with the patients cleansed with chlorhexidine (8/195; 4.1%) (OR 4.42, 95% CI 1.96 to 9.99).” The review notes that this study had limited follow-up but gave it an ‘adequate’ rating, however the risk of bias was not assessed <sup>(323)</sup>. The review concluded that further research is needed regarding the relative effectiveness of the different skin antiseptics.

Although our study involved only estimates of infection rates, no statistically significant differences were found in the incidence of SSIs when comparing the different skin preparations.

### **Skin closure technique.**

NICE Clinical Guideline 74 <sup>(257)</sup> “SSI” states that “further research is required on use of different suture materials and skin adhesives and their effect on the rate of surgical site infection.” The studies carried out to date do not report a statistically significant difference

in infection rates with differing closure methods <sup>(323, 324)</sup> and no recent trials have looked into closure methods for amputation stumps.

A Cochrane review published in 2010 investigated the infection and dehiscence rates of leg wounds following vein harvesting for bypass graft<sup>(325)</sup>. The review comprised 3 randomized control trials all with suboptimal methodology and at risk of bias. They reported infection rates of 10.8% with staples and 8% with sutures and dehiscence rates of 9.3% with staples and 8.8% with sutures. The review concluded that there is no significant difference between the 2 closure methods but that further trials were needed. A similar Cochrane review was carried out to investigate the role of tissue adhesives/glues. They compared adhesives with sutures and staples and found no significant difference in the incidence of SSI but did note that fewer wounds dehisced with sutures/staples and that adhesives are more time consuming <sup>(326)</sup>. The only study to examine SSI rates associated with different skin closure techniques demonstrate higher SSI rates with skin clips compared with sutures <sup>(327)</sup>.

Although our study involved only estimates of SSI rates, no statistically significant difference was found in the incidence of SSIs when comparing the different skin closure techniques.

### **Drains**

A recent study suggested that the use of suction drains postoperatively may result in a higher SSI rate <sup>(327)</sup>. This contradicts the findings of previous studies which found that the use of surgical drains had no significant impact on infection rates <sup>(328)</sup>.

### **Antibiotics.**

The great variation in practices pertaining to antibiotic prophylaxis, reported in this study, meant that it was not possible to perform any statistical analysis to establish the impact of differing regimes on reported infection rates. Consensus appears to exist regarding the need for antibiotic prophylaxis for major amputation surgery with 95.8% of respondents always giving antibiotics, this is supported by level 1 evidence <sup>(294)</sup>. No justification was given by the 4.2% of surgeons who do not routinely give antibiotics as to this practice. The actual antibiotic used varied according to local hospital policy; however, this variation is unlikely to be clinically important as a recent review determined that “the type of antibiotic had no significant effect on wound infection.”<sup>(294)</sup>. The duration of antibiotic therapy is subject to differing opinions and little evidence exists relating to this. A recent trial reported a significantly lower SSI rate with a 5-day course of antibiotics compared with a 24-hour course <sup>(235)</sup>; however, the trial comprised a retrospective and prospective review and as such

was subject to significant bias. The American “Surgical Care Improvement Program” mandates that prophylactic antibiotics should be given within an hour before the first incision and are discontinued within 24 hours of surgery, reporting lower infection rates if this is followed<sup>(329-331)</sup>. No such guidelines exist in the UK.

### **Nutrition.**

Nutritional status has long been recognized as an important determinant of surgical outcome in terms of morbidity and mortality. This has led to the development of enhanced recovery programs for patients undergoing gastrointestinal surgery<sup>(332)</sup>. Recently, the “Strong for Surgery” initiative has begun to evaluate the existing evidence pertaining to key aspects of presurgical care to optimize postoperative outcomes following the identification by the “Surgical Care and Outcomes Assessment Program” clinicians of nutrition as a key factor. Initiatives such as this should lead to more proactive management of nutritional status of those in need.

Hypoalbuminemia is a commonly used marker to indicate the nutritional status of patients and has been the subject of numerous studies. Hennessey et al.<sup>(333)</sup> determined that a serum albumin level of <30 mg/dL is an independent risk factor for the development of an SSI and that the duration of in-patient stay is negatively correlated with preoperative albumin. However, it has been established that a surgeon’s clinical judgment regarding the nutritional status of patients correlates significantly with albumin, transferrin, and cholesterol levels and weight loss<sup>(334)</sup>. Despite this, nutritional status currently remains a commonly under addressed factor in perioperative patient care.

### **Hypothermia**

Maintaining intraoperative normothermia has long been thought to reduce SSI both in elective and emergency surgery and this is supported by the results of several trials<sup>(335, 336)</sup>. In this study, no statistically significant difference was found between the SSI rates of those who received intraoperative warming.

### **Dressings**

There is a paucity of evidence regarding the use of dressings post amputation. A recent study to assess the role of stump casts failed to show any difference in the incidence of SSI<sup>(337)</sup>.

A Cochrane review, conducted to evaluate the available evidence regarding the impact of different dressings to prevent SSIs, concluded that there was insufficient evidence to determine superiority of any dressing over another. It noted that many of the reported trials were small and of poor quality <sup>(338)</sup>.

Although this study involved only estimates of infection rates, no statistically significant difference was found in the incidence of SSI when comparing the different dressings used in both above- and below-knee amputations.

In the UK, the Joint Commission published a National Patient Safety Goal focused on prevention of SSIs which outlined the evidence-based requirements to reduce the incidence of SSI. However, the guidance failed to outline direction as to how they should be implemented. As such, The Joint Commission's SSI Change Project was carried out leading to the development of the Joint Commission's Implementation Guide<sup>(339)</sup> which defines the 23 effective practices identified for SSI prevention. Despite this, it is clear that there remains a lack of consensus in the UK. However, in the United States, the "Surgical Care Improvement Project" (SCIP) has been introduced. Module 1 focuses on perioperative care practices aiming to reduce the incidence of SSIs and is very prescriptive in its nature, allowing easier implementation. Studies have shown that compliance with SCIP measures statistically significantly reduces the incidence of SSIs <sup>(340)</sup>. It is possible that more prescriptive practice guidelines in the UK may be beneficial to ensure compliance.

### **Learning points and study limitations**

This study enabled us to examine the current perioperative practice in patients undergoing major LLA. One of the main criticisms of this type of study design is the reliance on collection of questionnaires, and, although a response rate of 37.2% is considered to be well within acceptable margins compared to other studies, it remains nonetheless relatively low and this may introduce bias due to a misrepresentation of the true picture. In this particular survey potential areas of misrepresentation include :

1. Definition of SSI: This could vary amongst clinicians, and consequently amongst institutions, leading to over/underreporting of the true incidence.
2. Hospital patient discharge and access to healthcare: A number of factors affect patient hospital discharge back into the community and subsequent availability of

access to healthcare services. Drawing from the first point of variable SSI definition as well as access to services and treatment, this directly impacts not only on accurate wound assessment and detection of SSIs, but also a timely identification and treatment of these in the community.

3. Misinterpretation of the survey questions.
4. Lack of consistency in assessing and reporting SSIs amongst the participants.

These are well known survey related issues, and one way of addressing them is to assign individuals to conduct the survey and complete the questionnaires in the form of an interview, having informed the participants in advance of a set definition for SSI, and subsequently conduct the face-to-face interview in a prospective manner. This however carries a heavy financial burden and significant time consumption.

It is therefore important to consider these limitations when making inferences and performing and interpreting statistical tests on such data; a significant learning point drawn from this study is that conclusions drawn from it, should not be taken as the sole representation of true rates of SSI and current perioperative practice in patients undergoing major LLA, and as such should not be used to guide / change clinical practice. However, it does give a cross-sectional representation of the aforementioned areas, has identified a potential widespread variation in clinical practice and can be used as a guide in identifying potential areas of deficit, requiring further investigation in the form of more formal research.

#### ***Section 4.2      Study 2: A Meta-analysis of the use of antibiotic prophylaxis in the prevention of surgical site infection in patients undergoing major lower limb amputation***

This meta-analysis (MA) was designed to:

1. Group and highlight the findings of the highest quality available evidence regarding the use of antibiotic prophylaxis in the prevention of SSI in patients undergoing major LLA.
2. Qualitatively assess each of the studies.
3. Statistically assess and summarise the effects of: using antibiotic prophylaxis, the course duration and type of antibiotic choice on the risk of developing SSI.

With the exception of only one other critical review<sup>(294)</sup>, this study is the only systematic review(SR) performed since 2009 and the only MA available to date. McIntosh et al. have highlighted the scarcity of studies available and produced an exclusively qualitative analysis and summary of the available data in the due to ‘significant heterogeneity’<sup>(294)</sup>, although through specific tests this can be adjusted for.

### **Qualitative analysis:**

Our SR summarised data from 8 studies<sup>(235, 296, 298-302, 318)</sup> compared to 7 included in McIntosh et al.<sup>(294)</sup>.

All the studies included in our analysis were of similar design in terms of comparison groups (intervention versus control) (see Table 15, pg.155)<sup>(235, 296, 298-302, 318)</sup>. One study by Huizinga et al.<sup>(297)</sup> included in the previous critical review<sup>(294)</sup> involved allocation of participants to numerous antibiotic combination groups (flucloxacillin, amoxicillin, combination of both, and a group receiving amoxicillin and clavulanic acid combination). Although this study addressed the question asked in this MA, it was excluded from the analysis due to significantly poor design as well as design heterogeneity and thus inability to amalgamate results particularly in the quantitative analysis.

The studies were also comparable with regards to patient demographics, with the overwhelming majority of them reporting a gender ratio description and mean age per group, except for 2 studies<sup>(300, 302)</sup> which gave median age as their resultant measure. Inclusion criteria were only described in 3 studies<sup>(299-301)</sup> whilst exclusion criteria in only 2 of them<sup>(301, 302)</sup>. The main reason for drop-out across all studies was mortality prior to completion of the wound assessment period. Two studies failed altogether to describe drop-out reasons<sup>(235, 318)</sup>.

Another similarity in study design that this SR has highlighted, was that all studies reported on primary wound healing as well as SSI as primary outcomes/end-points, although only 3 of them have recorded postoperative return to theatre as a complication, and in those studies, only re-amputation rates were commented upon without a clear explanation of the cause<sup>(299-301)</sup>. Sonne-Holm et al. and Norlin et al. further reported the level of re-amputation<sup>(300, 301)</sup>. Two of the studies have also reported on dry necrosis as a postoperative wound complication<sup>(299, 301)</sup>. These outcome measures were in line with the review by McIntosh et al.<sup>(294)</sup>.

### **Risk of bias**

Qualitative analysis within this study has demonstrated that the studies included in this MA were prone to bias, mainly selection and performance bias due to lack of explicit explanation of the randomisation process as well as allocation concealment. This was expected as, with the exception of the study by Sadat et al.<sup>(235)</sup>, most of the studies were conducted in the mid-1980s prior to the introduction of the CONSORT statement in 1996<sup>(317)</sup>, a report which set clearer criteria for the reporting of RCTs, setting the bar for the design, and conduction of better RCTs even higher.

In our MA studies were grouped by design similarity:

1. Antibiotic Vs. No antibiotic (placebo / no antibiotic)
2. Intervention Vs. Control antibiotic
3. 24-Hour – 48-Hour antibiotic prophylaxis
4. 5-day versus 24-hour antibiotic prophylaxis

### **The use of prophylactic antibiotics against no antibiotic / placebo**

Four studies compared patient outcomes following administration of antibiotic, against no antibiotic or in the case of Sonne-Holme et al. antibiotic against a placebo drug<sup>(299-301, 318)</sup>. Three studies specifically compared the use of prophylactic antibiotics against none<sup>(299, 300, 318)</sup>. Figure 23, pg. 168 shows a forest plot which describes the combined overall effect of using an antibiotic compared to no antibiotic prophylaxis. The risk reduction ranged from 64% [95% CI 0.25-0.85] – 95% [95% CI 0.00 – 0.83] among the 3 studies with a significant combined risk reduction of 63% ( P=0.02)<sup>(299, 300, 318)</sup>.

This reduction associated with antibiotic use was expected, and reflects what was reported by all studies individually (P<0.01<sup>(299)</sup> , P<0.001<sup>(300)</sup>, P=0.005<sup>(301)</sup>). Our MA showed no significant inter- or intra-study heterogeneity amongst these studies (P=0.56, I<sup>2</sup>=0% and P=0.56, I<sup>2</sup>=0% respectively), which contradicts what was previously stated by McIntosh et al.<sup>(294)</sup>.

The overall effect of using antibiotics and the incidence of SSIs on postoperative return to theatre or indeed re-amputation rates was not possible to assess statistically in this MA, due to significant variations in reporting such postoperative complications across all the studies. Of interest, was the study by Moller et al.<sup>(299)</sup>, where the rate of re-amputation secondary to

dry necrosis was greater following the use of an antibiotic (methicillin) compared to no antibiotics (4/27, 14.8% Vs 1/23 4.3% respectively); re-amputations however did not become necessary due to infected necrosis in the antibiotic group compared to the seven performed in the control group. None of these hypotheses however were statistically proven. Sonne-Holm et al. demonstrated no difference in dry necrosis incidence between the groups, however, re-amputation rates were higher in the placebo group (21/75, 28% Vs. 7/77, 9%,  $P < 0.005$ ) and these were usually performed at higher level. These findings were similar to ones in the study by Norlin et al.<sup>(300)</sup>

Variations like these may arise purely due to the way in which data is recorded. For instance, dry necrosis doesn't always imply the presence of infection and may suggest the presence of other pathology such as diabetes or peripheral vascular disease, both of which may act as confounding factors, which are unrelated to and cannot be controlled by antibiotic prophylaxis, but due to study design issues, they have been unaccounted for when data was collected and analysed.

### **Comparison of different antibiotics**

Three studies were allocated to this group<sup>(296, 298, 302)</sup>, two of which compared broad spectrum penicillins against broad spectrum cephalosporins<sup>(296, 302)</sup>, and showed no statistically significant superiority of one antibiotic over another (See Section 3.2.3, pg. 165). One study looked at different penicillin types<sup>(298)</sup>.

One potential area of criticism of the study by Friis et al. was that some patients had received antibiotics within 48hrs of the procedure albeit for different clinical indications, and although such data was presented separately no appropriate statistical analysis was performed to examine the true effect (intention-to-treat Vs. per protocol)<sup>(296)</sup>.

Huizinga et al. in 1983 suggested that co-amoxiclav was superior to benzylpenicillin in reducing the incidence of SSIs (4/31, 12.9% Vs. 10/13, 76.9%,  $P < 0.001$ ). The high efficacy of a more broad-spectrum antibiotic such as co-amoxiclav comes to no surprise, however one may argue that the recruitment of some amputations such as toes, may significantly skew results and make populations heterogeneous<sup>(341)</sup>.

Overall analysis of this group of studies did not show any significant outcomes in terms of antibiotic choice ( $Z = 0.82$ ,  $P = 0.41$ ). There was however significant heterogeneity amongst

the 3 studies ( $P=0.0004$ ,  $I^2=87\%$ ). This verifies the results from the individual studies (296, 298, 302).

### **The effect of antibiotic course duration**

With the exception of a single study by Sadat et al. (235), there are no other studies to date which are specifically designed and powered to examine the true effect of antibiotic duration on the incidence and risk of development of SSIs.

A total of five studies involved administration of a 24-hour antibiotic course (296, 299-302). From this MA, the use of an antibiotic for 24 hours was associated with a significant risk reduction in developing an SSI by 36% ( $Z=2.25$ ,  $P=0.02$ ) [ $95\% CI 0.44-0.94$ ]. There was significant heterogeneity among the studies ( $P=0.05$ ,  $I^2=57\%$ ), therefore the random effects model was adapted.

A total of two studies involved the administration of 48 hours of antibiotics (298, 318). In this sub-group, the administration of an antibiotic for 48 hours was associated with a significant risk reduction in SSI development by 74% ( $Z=2.06$ ,  $P=0.04$ ) [ $95\% CI 0.07-0.94$ ]. Once again, there was significant heterogeneity amongst the studies in this subgroup ( $P=0.04$ ,  $I^2=75\%$ ), therefore the random effects model was adapted. Overall analysis of all the studies in this group suggested that an increase in the duration of antibiotic prophylaxis course was associated with a 59% risk reduction in the development of SSI post LLA ( $Z=3.17$ ,  $P=0.002$ ) [ $95\% CI 0.33-0.77$ ].

There was significant inter-study heterogeneity amongst the studies ( $P=0.0003$ ,  $I^2=69\%$ ), but no significant intra-study heterogeneity amongst the population groups ( $P=0.19$ ,  $I^2=42.8\%$ ).

From Sadat et al. the use of a 5-day antibiotic course was associated with significant drop in SSI rates (22.5% to 5%,  $P=0.023$ ). From our MA, the use of a 5-day antibiotic prophylaxis course was associated with a 78% risk reduction in the risk of developing an SSI which was significant ( $Z=2.01$ ,  $P=0.04$ ) [ $95\% CI, 0.05-0.96$ ].

It could be therefore deduced that increasing the duration of the antibiotic course can lead to a reduction in SSI rates as well as the overall risk of developing SSIs.

### **Learning points and study limitations**

Section 2.2 of this thesis includes a thorough methodology on search strategy, study selection and systematic assessment of each study using a PRISMA checklist. Although the

description is thorough, and the question to be answered can be derived from the methodology it is absolutely imperative that this is addressed separately.

This constitutes a study limitation. A significant learning point derived from this was the need for the use of a well-established concept such as the PICO model as described by the Centre for Evidence Based Medicine <sup>(342)</sup>. This model enables a researcher to construct a well-thought foreground question to be answered through the metanalysis. This typically encompasses 4 basic components :

1. P = Patient, Problem, Population (How would you describe a group of patients similar to you? What are the most important characteristics of the patient?)
2. I = Intervention, Prognostic Factor, Exposure (What main intervention are you considering? What do you want to do with this patient? What is the main alternative being considered?)
3. C = Comparison (Can be None or placebo.) (What is the main alternative to compare with the intervention? Are you trying to decide between two drugs, a drug and no medication or placebo, or two diagnostic tests?)
4. O= Outcome (What are you trying to accomplish, measure, improve or affect? Outcomes may be disease-oriented or patient-oriented.)

Although the search strategy was adequate and systematic, amalgamation of this into the PICO model, would have made the study selection process more robust and reliable. This will certainly be addressed prior to publication of the study.

It is a well-established fact that metanalyses have been providing a broadly used means of quantifying the effects of medical intervention for several years. To this effect, a well-designed meta-analysis has been previously described as the same high level of evidence as a well-designed RCT, and therefore of the same clinical significance and gravity <sup>(343)</sup>. Consequently, meta-analyses provide the starting point for health professionals to remain up-to-date, as well as to drive grant applications and justify further research in a medical field. As a result of this concept, we have seen an exponential rise in the number of published systematic reviews and metanalyses in the last decade <sup>(344)</sup>.

Ideally, in any meta-analysis, the inclusive studies should be ones of readily comparable design and methodology, population and of course intervention and outcome measures. The individual studies would be expected to show similar trends but have inadequate statistical power to make inferences on an individual basis. In reality however this is rarely achieved and metanalyses often combine studies which can be potentially small in size and differ in

numerous respects such as choice and duration of intervention, type of participants, duration of follow-up and outcome measures.

Study 2 in this thesis is no exception to this rule, as the studies included were characterised at least by significant statistical heterogeneity, something which has been identified in Section 3.2, on page 151. A substantial learning milestone reached, was the understanding that naturally, studies grouped together within a metanalysis, will have some degree of heterogeneity, with statistical heterogeneity being just one of 3 distinct types <sup>(344)</sup>:

1. Clinical heterogeneity: differences amongst patient population choice and intervention offered.
2. Methodological heterogeneity: differences in study design and risk of bias.

Statistical heterogeneity involves a test statistic, e.g.  $I^2$  as used in study 2, and is characterised by more significant differences in the outcomes of individual studies than one would expect to occur entirely due to chance. This statistical heterogeneity, may or may not be a result of clinical or methodological heterogeneity. Even in metaanalyses with the most stringent of study selection criteria, for no heterogeneity to exist is virtually impossible, although this can be regulated to a degree by basing the selection criteria on study design. This type of heterogeneity is usually one that occurs due to chance, and although its quantification seems to be more objective, the accuracy of the estimate is unknown <sup>(344)</sup>.

Several methods of attempting to quantify heterogeneity have been previously described, namely Cochrane's Q, and the derived percentage  $I^2$ . Q takes into account individual studies, whereas  $I^2$  reflects the degree of heterogeneity amongst the studies in the form of percentage variation, that can be attributed to study flaws as opposed to chance alone, and can be classified from low to high from 25% to 75% respectively. From the results in section 3.2.3 of this thesis, we can see that, on some occasions,  $I^2$  values are not only the 3<sup>rd</sup> percentile, but are also noted to have wide CIs. One could therefore potentially dispute the meaningfulness of the metanalysis, although, this should not be done solely on the basis of one such test.

Unfortunately, such challenges can be inevitable as the quality of existent studies is questionable. These studies are nonetheless, the only available evidence and as long as the data is collected and analysed systematically, reasonable conclusions can be drawn, not to drive clinical practice, but to aid in the identification of unclear / deficient areas in perioperative amputation management, such as the use of prophylactic antibiotics, where further research is necessary before clinical inferences can be made with confidence.



## ***Section 4.3 Study 3: The Amputation Surgical Site Infection Trial***

Amputation surgery was previously classed as clean surgery and according to NICE guidance 74, antibiotic prophylaxis should therefore not be indicated. However, according to Hospital Episode Statistics, a study by Coulston et al. as well as from data from our own institution, that the incidence of SSI following major LLA is in fact under-reported and the true value lies between 13.1% and 34.6% <sup>(99, 100, 327, 345)</sup>, an incidence rate which is high compared to SSI incidence following other ‘clean’ procedures<sup>(257)</sup>

### **Combined Incidence of SSI / IWH amongst LLA patients**

The ASSIT study (Study 3) has demonstrated a combined incidence of SSI of 23.5% (36 out of 153 subjects) across both antibiotic groups, a figure which is more in line with the true incidence of post-operative SSI in patients undergoing major LLA, and in line with incidence previously reported in the literature from national statistics as well as individual studies <sup>(99, 100, 235, 294, 327, 345)</sup>. This study has also demonstrated a combined incidence of IWH at 39.2% (60 out of 153 subjects). IWH as an outcome was previously defined in this piece of work as an ASEPSIS score of 11-20 and as the name implies, it suggests wound complications which are milder than an SSI but are nonetheless significant implications which carry other consequences on patient morbidity. One criticism of the use of ASEPSIS score in this study as a tool for wound assessment, although validated and reproducible <sup>(275, 276)</sup>, it is a tool that has been developed to assess sternal wounds, and as it has not been previously used to assess amputation stumps, it should be used with caution. However, there are very few if indeed any alternatives which could be employed as alternatives<sup>(346, 347)</sup>.

The antibiotics administered to patients during the course of this trial can be seen in Appendix 8 on page 271.

### **Effect of antibiotic duration on incidence and risk of SSI / IWH development**

In this study, the use of a 5-day antibiotic course (AC) was found to reduce the incidence of SSI from a combined 23.5% to 11.5% (9 out of 78), a reduction by over 10%. Analysis of the 24-hour AC group showed an incidence of SSI at 36% (27 out of 75), which is nearly 13% over the combined incidence of SSI in this patient population. This reduction in incidence of SSI observed when the 5-day AC is administered was statistically significant ( $P < 0.001$ ). The same AC was also responsible for reducing the incidence of IWH from a

combined incidence of 39.2% to 25.6% (20 out of 78) compared to an incidence of 53.3% observed in the 24-hour AC group (40 out of 75). This reduction in IWH incidence related to a 5-day AC administration was statistically significant ( $P<0.001$ ).

The use of a 24-hour as opposed to a 5-day AC was found to significantly increase the risk of developing an SSI by nearly a 5-fold (OR 4.980, 95%CI(2.109-11.764)( $P<0.001$ ). Similarly, the use of a 24-hour AC statistically significantly increased the risk of developing IWH by nearly a 4-fold (OR 3.792, 95%CI(1.860-7.733)( $P<0.001$ ).

Overall this study demonstrates that the administration of a 5-day broad spectrum AC significantly reduces risk of developing as well as the incidence of SSI and IWH, a finding which provides Level 1 evidence to confirm the findings of study 2 within this thesis as well as reflect reports by previous authors of historic, poorly designed trials<sup>(235, 297-302)</sup>

### **Effect of skin preparation on incidence and risk of SSI/IWH development**

Of the 79 patients in the Chlorhexidine group, 19 patients(24.05%) developed an SSI compared to 17 out of 74 patients in the Povidone group(23%). The use of alcoholic chlorhexidine was not associated with a statistically significant reduction in the incidence of SSI when compared to alcoholic povidone ( $P=0.851$ ).

Of the 79 patients in the chlorhexidine group, 34 patients (43.04%) experienced IWH compared to 26 out of 74 patients in the povidone group(35.14%). The use of alcoholic chlorhexidine skin prep was not associated with a statistically significant reduction in the incidence of IWH when compared to alcoholic povidone ( $P=0.326$ ). The choice of skin preparation between chlorhexidine and povidone was not found to have a significant effect on the overall risk of developing an SSI nor IWH (OR 1.536, 95%CI(0.691-2.412)( $P=0.292$ ) and (OR 1.852, 95%CI(0.911-3.766)( $P=0.089$ ) respectively.

From this finding, it can be stipulated that choice of skin preparation amongst alcohol based tinctures has no bearing on risk and incidence of SSI/IWH. This confirms what we know to date; there is no available evidence to suggest that one tincture is superior over another and current national guidance as well as a Cochrane review suggest that there is need for further level 1 studies to be carried out in order to address this question <sup>(257, 266)</sup> .

A limitation of note is that the ASSIT trial was not originally powered to answer the skin preparation question, therefore this further supports the notion for the need for further studies.

## **Other factors affecting outcomes following major LLA**

### ***Effect of diabetes, smoking and amputation level***

This study has demonstrated that previous history of diabetes, smoking and level of amputation were the only factors which statistically significantly increased the incidence of SSI following major LLA. Previous history of insulin/tablet controlled diabetes was seen in 86 patients. Of these, 27 patients(31.4%) developed an SSI (P=0.018). A total of 46 patients were ex/current smokers. Of these, 18 patients(39.1%) developed an SSI (P=0.005). The level of amputation also suggested an effect on the incidence of SSI (P<0.001).

Further analysis revealed that amputation at the level of the foot was the most significant in terms of odds of SSI development, increasing its risk by almost an 8-fold (P=0.003 OR 8.149 95%CI 2.078-31.951). History of smoking was also associated with statistically significant increase in the risk of post op SSI by a 3-fold (P=0.006, OR 3.328 95%CI 1.409-7.861) Previous/current history of diabetes nearly doubled the risk of SSI development (P=0.050, OR 2.456 95%CI 0.984-6.133).

These findings are partly in line with a previous study by Dunkel et al. They have analysed data from 289 major LLAs. Initial analysis revealed that median age of 74 years and previous history of diabetes increased the incidence of SSI and dehiscence (P=0.03 and P=0.01 respectively)<sup>(348)</sup>.

In our study, age was not found to be a contributory factor in the risk/incidence of SSI/IWH, which is contradictory, however, it may be explained by the fact that the overwhelming majority of patients were of similar age therefore any preventing any difference from arising.

Amputations about the foot have been previously shown to have a predisposition to wound complications<sup>(349-351)</sup>, as did previous/current history of smoking<sup>(352)</sup>, and findings from the ASSIT study further support these claims. This did not seem to be the case in the study by Dunkel et al<sup>(348)</sup>.

### ***Gender, original cause for amputation and presence of infection/wound on admission***

Gender, the original cause for amputation, as well as the presence of wound/infection at the time of admission/amputation did not have an effect on the incidence/risk of SSI/IWH (P=0.852, P=0.582 and P=206 respectively). This finding was in line with other studies<sup>(348)</sup>.

***Preoperative haemoglobin and albumin levels, history of previous vascular intervention, perioperative transfusion***

Additional independent variables were also assessed in this study for their effect on wound complications, including the following: preoperative haemoglobin (P=0.194) and preoperative albumin levels (P=0.129), history of previous revascularisation procedure (angioplasty Vs. endarterectomy/bypass surgery) (P=0.411 Vs. P=0.947), and perioperative transfusion (0.399). As indicated, none of the aforementioned variables were found to have a statistically significant effect on the incidence of SSI/IWH.

This is somewhat contradictory for some of them, as anaemia and tissue hypoxia for instance have previously been shown to be associated with poor post-operative wound healing<sup>(353)</sup>, however, in our study, anaemia was measured purely as haemoglobin levels compared to haematocrit levels, and resultant tissue pO<sub>2</sub> in the paper by Heughan et al.<sup>(353)</sup>, an outcome which we did not measure, and consequently these findings may be incomparable.

Low levels of albumin have previously been reported to be independent predictors of poor wound healing<sup>(333, 354, 355)</sup>. In an MA by Yuwen et al.<sup>(354)</sup> albumin levels <3.5g/dL (P<0.0001) were associated with nearly a 3-fold increased risk of post-operative SSI in patients undergoing orthopaedic procedures. This was in line with findings from Hennessey et al., where albumin levels <3.0g/dL were associated with increased risk of SSI (P<0.001). The mean albumin levels for patients in our study were 26.46g/dL and 27.3g/dL in both cohorts (SSI vs No SSI) however, even with albumin levels lower than those mentioned in previous studies, there was still no statistically significant effect on the incidence/risk of SSI/IWH development.

Recent studies have also stipulated a strong association between allogeneic blood transfusion and an increased risk of SSI development<sup>(356, 357)</sup>.

Kim et al. in their MA have reported on an increased risk of SSI development in patients who received a blood transfusion (OR 1.71, P=0.002). This was not the case in our study. One possible explanation is the possibility of intra and interstudy variability, as well as poorly matched patient comorbidities amongst the groups and resultant heterogeneity.

Kaneko et al. reported a statistically significant increase in the risk of SSI development by nearly a 3-fold (OR 3.05, P=0.004)<sup>(357)</sup>. This contradicts the findings in our study where transfusion had no effect on SSI/IWH incidence (P=0.399).

Kaneko et al. was a study looking at gastrointestinal cancer patients. Although patients with diabetes and PVD are patients who may have very extensive medical backgrounds and

comorbidities, a patient cohort such as the one in the study by Kaneko et al., is characterised by a gross immunocompromised state related not only to their cancer disease process but also to their extensive chemotherapy treatment regimes, therefore, their immune system capacity to sustain further compromise may be in question, hence placing them at a baseline higher risk of developing an SSI.

### *Effect of previous vascular intervention*

The impact of previous vascular intervention on the incidence and risk of SSI was found to be statistically significant (P=0.411 and P=0.947). This has been separately investigated and extensively discussed in study 4 of this thesis (See Section 3.4 and Section 4.4, pgs. 193 and 218).

### *Impact of SSI/IWH on return to theatre and post-operative length of stay.*

Of the 156 patients included in this analysis, 21(13.6%) returned to theatre in the post-operative setting. The commonest cause for a return to theatre was for amputation to a higher level due to infection/necrosis(10 cases, 6.41%). The effects of SSI and IWH were examined independently.

Of the 37 patients who developed an SSI in the post-operative setting, 10 required return to theatre (27%). The presence of SSI statistically significantly increases the incidence of return to theatre (P=0.007). The risk of returning to theatre, in the presence of post-operative SSI increases by 27.2% (P=0.008, OR0.272, 95%CI(0.105-0.710)).

Of the 60 patients who developed IWH, 15 required return to theatre (25%). The presence of IWH statistically significantly increases the incidence of return to theatre (P<0.0001) The risk of returning to theatre, in the presence of IWH increases by 20.2% (P=0.002, OR0.202, 95%CI(0.073-0.558)). These findings are consistent with previous reports <sup>(235, 348)</sup>.

The length of stay in median number of days in the absence of SSI is 14(IQR 9-21). To date, only one abstract has commented on the average length of inpatient post-operative length of stay following LLA (11.1 days).

The length of stay increases to 28 days (IQR16-40) in the presence of SSI. The rise in length of stay is **statistically significant (P=0.015)**. The length of stay is not affected by the presence / absence of IWH.

There were no other studies that reported on length of stay to date. SSI/IWH are both associated with increased incidence and risk of return to theatre, and ultimately it would be reasonable to deduce that this could result in increasing the length of hospital stay.

In the course of this study, there were only two incidences of hospital superbug encounters, therefore a statistical analysis was not deemed necessary. There was one incidence of *c.difficile* diarrhoea in a previous *c.difficile* carrier, and one incidence of post-surgical MRSA wound infection in a patient whose swab tested negative prior to surgery. Both of these were eradicated successfully.

This contradicts findings from previous studies. In the study by Sadat et al. reported post-operative *c.difficile* incidents in 7.5% of their cases (n=3) in the 5-day cohort, however no comparison was possible with the 24-hour group since that was retrospective data and was not available. It is fair to argue that although *c.difficile* colitis secondary to broad spectrum antibiotic therapy is a known issue, due to the small sample size in this study, the effect appears amplified <sup>(235)</sup>.

A study by Grimble et al. reported a rate of 21% MRSA incidence in their patient cohort. This study further reported that in patients who tested positive for MRSA in the preoperative setting, they were more likely to end-up with colonization and a resultant SSI ( $P<0.05$ ) as well as experience delayed wound healing ( $P<0.01$ ) and higher mortality rates ( $P<0.01$ )<sup>(310)</sup>. This was not the case in our study. This may be explained by the fact that in the recent years, there MRSA screening is incorporated within the preoperative preparations, and active eradication is employed upon detection, consequently, MRSA incidence may now be significantly lower than 16 years ago.

### **Mortality following SSI**

The presence of SSI had no statistically significant effect on the number of cases and on the overall cumulative patient survival at 30 days nor at 1 year post-operatively. This finding is in line with two other major studies<sup>(106, 358)</sup>

### **Learning points and study limitations**

Inclusion of patients with variable indications for amputation, although relatively small in numbers can have advantages and disadvantages.

In its own right, by definition, this potentially gives rise to selection bias, as patients with different types of indications for surgery ultimately affect the type of healing and risk of development of SSI / IWH. For example, patients with diabetes and PVD, can be expected to have poorer healing than patients undergoing an amputation due to malignancy.

One has to bear in mind however that:

1. This is a pragmatic trial, and, although it would have been ideal to examine the effect of antibiotic prophylaxis in each of these groups independently, this degree of indication variability makes the trial more applicable to the wider population group undergoing major LLA for causes other than diabetes / PVD. Furthermore, the ability to deal with patients such as these who are known to have a poor physiological reserve, could certainly enable clinicians to adapt the same approach in dealing with patients with conditions which have far less systemic impact more effectively.
2. Recruitment of patients with a wide range of indications for surgery enabled completion of the study at a reasonable pace with achievement of full power within a single recruitment centre. A future modification of this would be to conduct the study on a multi-centre basis in order to narrow down the selection criteria in patients with a single type of pathology.

As part of the PICO model, when formulating a research question, clear definitions are necessary. In the case of study 3, the choice of a standard definition as produced by CDC was necessary<sup>(7)</sup>. Such definitions such as this one or the one given by the Surgical Site Infection Surveillance Service<sup>(359)</sup> are all based on the appearance of clinical signs and symptoms previously described in various scoring systems such as the Southampton<sup>(360)</sup> or ASEPSIS score<sup>(276)</sup> used in this thesis. Whilst very reproducible and validated, these scores remain subjective and are dependent on the experience and understanding of the healthcare professional conducting the review. Although these methods are well validated, one has to anticipate a certain degree of interobserver variability which may in turn introduce reporting bias. In addition, the use of definitions such as these, fails to take into account other aspects of SSI diagnosis which may prove useful. These include additional tests such as wound swabs and blood inflammatory markers, which although in isolation, they are poor diagnostic tools, in conjunction with each other they can improve accuracy of diagnosis.

Whilst in presenting the findings of a randomised trial, the commonest form of primary analysis and presentation of the results is through a regression model analysis, in this thesis, initial variables were individually examined through a Chi<sup>2</sup> test statistic to examine the effect of each variable independently. Whilst this is useful in identifying the variables which are most likely to affect the final outcome, individual test statistics do not take into consideration potential interactions between different variables, which would reflect the true effect. It is important nonetheless to examine data in their simplest form, and, in cases where significant results were obtained, these were then combined into a regression model to identify the magnitude of the risk, taking into account interaction among variables.

Secondary outcomes were performed on a post-hoc basis and were largely exploratory in nature. A post-hoc analysis involves looking at the data after a study has been concluded, and trying to find patterns that were not primary objectives of the study. Although such analyses can introduce reporting bias, they are often useful in identifying outcome associated factors which may require further investigation.

#### ***Section 4.4 Study 4: The Impact of Previous Surgery and Revisions on Outcome after Major Lower Limb Amputation***

Vascular surgery has come of age in the last 20 years and as such the current evidence suggests recent trends in favour of more aggressive revascularization and particularly reconstructive surgery in patients with critical ischemia, with excellent results reported in terms of amputation-free survival<sup>(361)</sup>. However, the impact of previous revascularisation on the level and mortality rates of patients who eventually require amputation has been brought into question.

Local postoperative complications are relatively common in amputees. The National Surgical Quality Improvement Programme reported a 34% rate of perioperative complications for BKAs, with 15.6% of patients requiring a return to theatre<sup>(362)</sup> and half of these involving a conversion from BKA to AKA.

This reflects the published literature reporting stump revision rates between 4 and 24% <sup>(89, 362-367)</sup>.

Our study indicates comparable outcomes, reporting a 17% rate of revision on the same admission with half of these involving a conversion from BKA to AKA. Analysis of the impact of previous intervention in this study demonstrated that 36% of the patients (19 of 55) who had previous ipsilateral revascularization had an AKA compared with 37% (34 of 93) who had no previous intervention (P=0.341), that is, the level of amputation did not appear to be affected by previous intervention/ revascularization in this patient cohort. It could be that although failed revascularization attempts have been shown to increase the level of amputation <sup>(145, 368)</sup>, in other patients with partially successful revascularization, the level of amputation is lowered <sup>(369)</sup>. However, choice of amputation level is dependent on multiple factors, such as extent of dis-ease, rehabilitation potential, and presence of contractures.

Seventeen percent of the previous revascularisation group required a second surgery on the same admission compared with 4.5% in the group of patients with no previous intervention. As such, previous revascularization may indicate a group of patients at higher risk of postoperative complications requiring revision surgery. These findings reflect those of previous trials, which have concluded that wound infection and stump failure are the leading causes for return to theatre, particularly in the group of patients who have undergone previous revascularization <sup>(68, 362, 367, 370, 371)</sup>.

It is nonetheless widely accepted that arterial reconstruction prolongs the amputation-free period <sup>(372)</sup> and improves physical functional outcome and mobility and overall generic quality of life <sup>(373, 374)</sup>.

As such, despite a higher rate of revision surgery, the potential benefits of revascularization outweigh the risks <sup>(89)</sup>.

Thirty-day mortality in this study is similar to that reported in the literature and was not affected by previous revascularization attempts (P=0.782), type of revascularization (P=0.321), or multiple procedures during the same admission (P=0.717). This contradicts the findings of Jaar et al. who reported increased postamputation mortality in haemodialysis patients who had previously undergone revascularization, and this was more marked in patients who had undergone bypass versus angioplasty <sup>(375)</sup>. An increased mortality rate was also reported by Simsir et al. after failed revascularization attempts <sup>(376)</sup>. The most commonly recorded cause of death was multisystem failure (n=9, 6%); however, data pertaining to cause of death was lacking in 23 patients because of the nature of our facility as a tertiary

referral centre. This contradicts a larger study by Belmont et al. that reported postoperative sepsis (31.7%) as the leading cause of death, followed by cardiopulmonary complications (23.9%), and return to operating theatre (17.6%)<sup>(362)</sup>. The impact of previous revascularization on postamputation mortality and morbidity has been investigated previously <sup>(65, 66, 374, 377-382)</sup>.

It has also been reported by Tsang et al. that the longer the time interval between arterial reconstruction and amputation, the more likely it was for the patient to have a BKA as opposed to an AKA <sup>(65, 383)</sup>. However, Schenkler et al. examined the indication for surgery (rest pain with gangrene, intermittent claudication < or soft tissue with skin compromise), angiographic findings, and presence of diabetes and determined that they had no impact on amputation level <sup>(381)</sup>.

The impact of intraoperative, perioperative, and postoperative care (e.g., skin antiseptic and perioperative antibiotic regime, choice of wound dressings and subsequent stump management) on the final level of amputation have received little attention and merits further investigation <sup>(381)</sup>.

---

## Chapter 5 - *CONCLUSION*

Study 1 has clearly demonstrated that SSI is a complication which although recognised, it is grossly underestimated. A consequence of not only this misrepresentation but also the previous lack of high level evidence from the now historic studies, there seemed to be a general lack of consensus regarding various aspects of perioperative wound management of major LLAs in relation to SSI prevention, and more specifically when considering perioperative antibiotic usage.

The infection rates across the UK have therefore remained high and inevitably contributed to the unacceptable peri-operative mortality and morbidity figures. If improvements are to be made it is imperative that all measures to reduce SSI are employed. It is also essential that standardised reliable definitions which are available, should be used when monitoring of this post-operative complication.

Study 2 in this thesis was a SR and MA of the available studies specifically addressing perioperative antibiotic practice and its effect on SSIs. It has emphasised not only the

paucity, but also the largely historical value of the evidence that currently exists in answering the question posed in this thesis; this highlighted the lack of information available to help develop strategies to reduce SSIs and perhaps justified the significant lack of clinical practice uniformity which was demonstrated by the survey.

The findings across the various studies were very similar and demonstrated the significance of perioperative antibiotic prophylaxis in patients undergoing major LLA, although, it could be argued that these were flawed with errors due to poor design and inconsistencies.

However, following amalgamation of information from best available studies to date, it could be deduced that the use of any antibiotic prophylaxis is associated with a reduction in the risk and rates of SSIs, and increasing the duration of one such course further enhances this effect. Choice of antibiotic does not seem to affect this, although, broad spectrum penicillins appear to have a superior effect.

It has been stipulated by McIntosh et al. <sup>(294)</sup> that the undertaking of larger contemporary trials is unlikely to happen due to a ‘general’ agreement that exists amongst clinicians in that antibiotic prophylaxis is necessary in patients undergoing major LLA. This is highly contradictory since we know from our published survey <sup>(234)</sup> that at least 4.8% of the surgeons do not routinely prescribe antibiotics prior to a major LLA despite the presence of previous studies, albeit historical and of poor quality.

We therefore designed and conducted a single centre, open, RCT to examine the true effect of antibiotic course duration on the rate and risk of SSI development.

This study has demonstrated that the use of a 5-day antibiotic course is associated with statistically significant reduction in the incidence as well as the risk of SSI/IWH development. SSI, although not directly affecting patient mortality due to other significant comorbidities which tend to co-exist, has nonetheless significant effects on patient morbidity including higher incidence of return to theatre, as well as increased length of hospital inpatient stay. These in turn carry significant financial and resource implications and a burden on an already exhausted national healthcare service.

In the process of optimisation of perioperative amputation care, in addition to antibiotic administration, it has previously been suggested that previous vascular interventions may have an effect on post-operative wound complications. Evidence from studies 3 and 4 suggest that there is no statistically significant relationship between the two, although, in

cases where an amputation does become necessary, the level at which it may be performed, or revised to at a later stage is affected by the presence of previous vascular intervention.

The work produced throughout the 4 studies in this thesis is valuable in formulating, optimising and standardising clinical care for the assessment and management of patients undergoing amputation surgery. The outcomes of this thesis can lead to the conception of new projects including:

1. Other studies to look at the effect of choice of dressings (rigid Vs. soft) on SSI/IWH
2. Additional studies powered to examine the true effect of choice of skin preparation on the incidence and risk of SSI
3. Other studies to examine modes of antibiotic delivery vessel systems including comparison of IV administration against antibiotic pellet application on the incidence and risk of SSI development.

---

## *References*

1. Ahmad N, Thomas GN, Gill P, Chan C, Torella F. Lower limb amputation in England: prevalence, regional variation and relationship with revascularisation, deprivation and risk factors. A retrospective review of hospital data. *J R Soc Med.* 2014;107(12):483-9.
2. Pinsdaddy. Wound healing. Pinterest2007.
3. Chetter I. Muscles of the Thigh. In: Manual TAC, editor. London: Royal college of Surgeons of England; 2013.
4. Chetter I. Anatomy of the gluteal region. In: Manual TAc, editor. London: The Royal College of Surgeons of England; 2013.
5. chart ABS-Haba. Gastrocnemius muscle Cross sectional Anatomy. In: Anatomy GmCs, editor.: Anatomy Body System; 2017. p. Cross-sectional anatomy of the lower leg.
6. Marshall C, Stansby G. Amputation and rehabilitation: Elsevier; 2010.
7. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol.* 1992;13(10):606-8.
8. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol.* 1999;20(4):250-78; quiz 79-80.
9. Brosi P, Dick F, Do DD, Schmidli J, Baumgartner I, Diehm N. Revascularization for chronic critical lower limb ischemia in octogenarians is worthwhile. *Journal of Vascular Surgery.* 2007;46(6):1198-207.
10. Bhuvaneshwar CG, Epstein LA, Stern TA. Reactions to Amputation: Recognition and Treatment. Primary Care Companion to The Journal of Clinical Psychiatry. 2007;9(4):303-8.
11. Buquet-Marcon C, Charlier P, Anaick S. The oldest amputation on a Neolithic human skeleton in France2007.
12. Kirkup J. A History of Limb Amputation. 1 ed. London: Springer-Verlag; 2007. 184 p.
13. Herodotus, Godley AD. Herodotus. The Loeb classical library. 4. Revised and repr. ed. London: Heinemann; 1926. p. 203-5.
14. Celsus AC, Spencer WG. Celsus : De medicina. London: Heinemann; 1935.
15. Adams F. The Seven Books of Paulus Aegineta. 1846 14/07/2015. London: Sydenham Society; [59-60].

16. Garrison FH. An introduction to the history of medicine : with medical chronology, suggestions for study and bibliographic data. 4th ed, revised and enlarged ed. Philadelphia ; London: W. B. Saunders; 1929. 996p p.
17. Wiseman R, Flesher Ef, Macock J, Royston R, Tooke Bd, Bristol Library S. *Severall chirurgicall treatises* 1676.
18. Jones EW. The life and works of Guilhelmus Fabricius Hildanus (1560-1634). *Med Hist.* 1960;4:196-209.
19. Pare A. *Ten Books of Surgery With the Magazine of The Instruments Necessary for It.* 2 ed. North Carolina, USA: University of Georgia Press; 1564.
20. Rotstein OD. Modeling the two-hit hypothesis for evaluating strategies to prevent organ injury after shock/resuscitation. *J Trauma.* 2003;54(5 Suppl):S203-6.
21. C Lee KP, TJ Hodgetts. Tourniquet use in the civilian prehospital setting. *Emergency Medicine Journal.* 2007;24(8):584-7.
22. Yonge J. *Currus triumphalis, è terebinthô. Or an account of the many admirable vertues of oleum terebinthinæ... And... a new way of amputation, and a... method of curing stumps... with divers other useful matters* [Electronic Medium]. Royal Society, St' Pauls London: J. Martyn; 1679. Available from: [http://books.googleusercontent.com/books/content?req=AKW5QacZcGa2RfW6ipBSJYqBNMLG FPY GUXJHhbEFcYxpJvvcP5-SmA8oYNfnza\\_nOiLzfx7J1yHnXtUs98240N0P89eYIILtuyX5njI1fAJu6tsym9fCfhajbLHxwP9QZTBdMysKRYpLGqP1bx-pxLkGIZOXcbF18kycxZL31pfMbgujlzMdyous0aMQ0AycVGAUMnTwPDmHxuu7fhD8LzIGwi1AiOmnNIQe2lxYY-3u8HJff5uarE\\_zJctoKuCsHbpHvL68dsxg-ppiHcZMr5jHqI-pe9c1HZZaYTC6rMNHX4\\_cuJJ0U](http://books.googleusercontent.com/books/content?req=AKW5QacZcGa2RfW6ipBSJYqBNMLG FPY GUXJHhbEFcYxpJvvcP5-SmA8oYNfnza_nOiLzfx7J1yHnXtUs98240N0P89eYIILtuyX5njI1fAJu6tsym9fCfhajbLHxwP9QZTBdMysKRYpLGqP1bx-pxLkGIZOXcbF18kycxZL31pfMbgujlzMdyous0aMQ0AycVGAUMnTwPDmHxuu7fhD8LzIGwi1AiOmnNIQe2lxYY-3u8HJff5uarE_zJctoKuCsHbpHvL68dsxg-ppiHcZMr5jHqI-pe9c1HZZaYTC6rMNHX4_cuJJ0U).
23. Woodall J. *The Surgeons Mate* [Digital PDF copy]. London: Edward Griffin, Laurence Lifle; 1617. Available from: <http://www.archive.org/details/surgionsmateortrOOwood>.
24. Ebskov B, Ebskov L. Epidemiology. In: Murdoch GM, Wilson AB, editors. *Amputation : surgical practice and patient management.* London: Butterworth-Heinemann; 1996. p. 23-9.
25. Anglesey HWP, Anglesey GCHVP. *One-leg : the life and letters of Henry William Paget, first Marquess of Anglesey, 1768-1854.* London 1961. 428 p p.
26. Dominique jean larrey (1766-1842)—surgeon-in-chief of the grande armée. *JAMA.* 1963;185(5):404-5.
27. Willmott-Hall R. *Memoirs Of Military Surgery and Campaigns of the French Armies* [Electronic Medium]. Maryland, USA: Joseph Cushing; 1814. Available from: <https://ia801406.us.archive.org/15/items/memoirsmilitary01hallgoog/memoirsmilitary01hallgoog.pdf>.
28. Skandalakis PN, Lainas P, Zoras O, Skandalakis JE, Mirilas P. "To afford the wounded speedy assistance": Dominique Jean Larrey and Napoleon. *World journal of surgery.* 2006;30(8):1392-9.
29. Harley GW. *Notes on the Poro in Liberia.* Cambridge, Mass.: The Museum; 1941. v, 39 pages p.
30. Watson BA. *A treatise on amputations of the extremities and their complications* Philadelphia, USA: Philadelphia, P. Blakiston, son & co; 1885 27/11/2014]. Available from: <http://www.archive.org/details/atreatiseonampu00watsgoog>.
31. Wolf J. François Chopart (1743–1795) — Inventor of the partial foot amputation at the tarsometatarsal articulation. *Orthop Traumatol.* 2000;8(4):314-7.
32. Enersen OD. *Francois Chopart Norway 1994-2015* [cited 2015 29/07/2015]. Electronic Edition:[Digital Dictionary of Medical Eponyms]. Available from: <http://www.whonamedit.com/doctor.cfm/3269.html>.
33. Lafiteau M. *Observation sur une amputation pied par M Lafiteau élève de l'écoles de chirurgie* In: Fourcroy A-F, editor. *La médecine éclairée par les sciences physiques, ou*

Journal des découvertes relatives aux différentes parties de l'art de guérir: Volumes 3 à 4. 4. Paris: Buisson; 1792. p. 85-9.

34. Armocida G. GRITTI, Rocco Italy: TRECCANI; 2002 [Electronic Edition:[Website].
35. Gritti R. Gritti. Resoconto della Clinica chirurgica del Professor Schuh negli anni scolastici 1853-54, 1854-55. *Annali universali di medicina*. 1856;19(465):512-63.
36. Gritti R. Gritti. Resoconto della Clinica chirurgica del Professor Schuh negli anni scolastici 1853-54, 1854-55. *Annali universali di medicina*. 1856;20(466):53-87.
37. Gritti R. Gritti. Dell'amputazione del femore al terzo inferiore e della disarticolazione del ginocchio. Valore relativo di cadauna, coll'indicazione di un nuovo metodo denominato amputazione del femore ai condili con lembo patellare. *Annali universali di medicina*. 1857;25(481):5-33.
38. Stokes W. On Supra-condyloid Amputation of the Thigh. *Medico-Chirurgical Transactions*. 1870;53:175-86.1.
39. Gritti R. Gritti. Di alcuni tumori fibro-condromatosi riscontrati nell'articolazione scapulo-omerale. Osservazione. *Annali universali di medicina*. 1858;27(488):318-31.
40. Quaglino A. Sulle malattie interne dell'occhio : saggio di clinica e d'iconografia ottalmoscopica 1858.
41. Gritti R. Della Fratture del femore per arma da fuoco studiate sotto il punto di vista della chirurgia militare. Milano: Coi tipi del Pio Istituto di Patronato; 1866. 150 p.
42. Gritti R. Della cura della frattura del femore mediante l'apparecchio a trazione coi pesi applicato sopra bambini e fanciulli fino all'età di sette anni. *Annali universali di medicina e chirurgia*. 1880;253(762):478-93.
43. Anonymous. Harold Buhalts Boyd, M.D. 1904-1981. *J Bone Joint Surg Am*. 1981;63(8):1351-2.
44. Calandruccio RA. Harold Buhalts Boyd 1904-1981. *Clin Orthop*. 1982(165):4-5.
45. Listed NA. Harold Buhalts Boyd 1904-1981. In: Mostofi SB, editor. *Who's Who in Orthopedics*: Springer London; 2005. p. 33-5.
46. Grimer RJ, Chandrasekar CR, Carter SR, Abudu A, Tillman RM, Jeys L. Hindquarter amputation: is it still needed and what are the outcomes? *Bone Joint J*. 2013;95-B(1):127-31.
47. Blum CE, Kalamchi A. Boyd amputations in children. *Clin Orthop Relat Res*. 1982(165):138-43.
48. Tosun B, Buluc L, Gok U, Unal C. Boyd amputation in adults. *Foot Ankle Int*. 2011;32(11):1063-8.
49. Eilert RE, Jayakumar SS. Boyd and Syme ankle amputations in children. *J Bone Joint Surg Am*. 1976;58(8):1138-41.
50. Fulp T, Davids JR, Meyer LC, Blackhurst DW. Longitudinal deficiency of the fibula. Operative treatment. *J Bone Joint Surg Am*. 1996;78(5):674-82.
51. Malchow D. Tribute to Ernest M. Burgess, MD, PhD October 29, 1911-September 27, 2000. *J Rehabil Res Dev*. 2001;38(3):viii-ix.
52. Finklea L. Commending Ernest M. Burgess, MD, PhD with Senate Resolution 278 for his unwavering global service to prosthetics medicine. *J Rehabil Res Dev*. 2000;37(4):vii-x.
53. Burgess EM, Poggi DL, Hittenberger DA, Zettl JH, Moeller DE, Carpenter KL, et al. Development and preliminary evaluation of the VA Seattle foot. *J Rehabil Res Dev*. 1985;22(3):75-84.
54. Burgess EM. The SEATTLE foot prosthesis. *Prosthetics and orthotics international*. 1985;9(1):55-6.
55. Reswick JB. Evaluation of the Seattle Foot. *Journal of Rehabilitation Research*. 1986;23(3):77-94.
56. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. *Diabetes Care*. 1990;13(5):513-21.

57. Global Lower Extremity Amputation Study G. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. The Global Lower Extremity Amputation Study Group. *Br J Surg*. 2000;87(3):328-37.
58. Calle-Pascual AL, Garcia-Torre N, Moraga I, Diaz JA, Duran A, Monux G, et al. Epidemiology of nontraumatic lower-extremity amputation in area 7, Madrid, between 1989 and 1999: a population-based study. *Diabetes Care*. 2001;24(9):1686-9.
59. Ziegler-Graham K, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Arch Phys Med Rehabil*. 2008;89(3):422-9.
60. Jeffcoate WJ, van Houtum WH. Amputation as a marker of the quality of foot care in diabetes. *Diabetologia*. 2004;47(12):2051-8.
61. Moxey PW, Gogalniceanu P, Hinchliffe RJ, Loftus IM, Jones KJ, Thompson MM, et al. Lower extremity amputations--a review of global variability in incidence. *Diabetic medicine : a journal of the British Diabetic Association*. 2011;28(10):1144-53.
62. Ebskov B. The Danish Amputation Register 1972-1984. *Prosthet Orthot Int*. 1986;10(1):40-2.
63. Ebskov LB, Schroeder TV, Holstein PE. Epidemiology of leg amputation: the influence of vascular surgery. *Br J Surg*. 1994;81(11):1600-3.
64. Dwars BJ, van den Broek TA, Rauwerda JA, Bakker FC. Criteria for reliable selection of the lowest level of amputation in peripheral vascular disease. *J Vasc Surg*. 1992;15(3):536-42.
65. Ernst CB, Rutkow IM, Cleveland RJ, Folse JR, Johnson G, Jr., Stanley JC. Vascular surgery in the United States. Report of the Joint Society for Vascular Surgery--International Society for Cardiovascular Surgery Committee on Vascular Surgical Manpower. *J Vasc Surg*. 1987;6(6):611-21.
66. Liedberg E, Persson BM. Increased incidence of lower limb amputation for arterial occlusive disease. *Acta Orthop Scand*. 1983;54(2):230-4.
67. Lindholt JS, Bovling S, Fasting H, Henneberg EW. Vascular surgery reduces the frequency of lower limb major amputations. *Eur J Vasc Surg*. 1994;8(1):31-5.
68. Pohjolainen T, Alaranta H. Lower limb amputations in southern Finland 1984-1985. *Prosthet Orthot Int*. 1988;12(1):9-18.
69. Comparing the incidence of lower extremity amputations across the world: the Global Lower Extremity Amputation Study. *Diabetic medicine : a journal of the British Diabetic Association*. 1995;12(1):14-8.
70. Ebskov LB. Epidemiology of lower limb amputations in diabetics in Denmark (1980 to 1989). *Int Orthop*. 1991;15(4):285-8.
71. Ebskov LB. Level of lower limb amputation in relation to etiology: an epidemiological study. *Prosthet Orthot Int*. 1992;16(3):163-7.
72. Dillingham TR, Pezzin LE, MacKenzie EJ. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. *South Med J*. 2002;95(8):875-83.
73. Jorgensen ME, Almdal TP, Faerch K. Reduced incidence of lower-extremity amputations in a Danish diabetes population from 2000 to 2011. *Diabetic medicine : a journal of the British Diabetic Association*. 2014;31(4):443-7.
74. Davis WA, Norman PE, Bruce DG, Davis TM. Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia*. 2006;49(11):2634-41.
75. Vamos EP, Bottle A, Majeed A, Millett C. Trends in lower extremity amputations in people with and without diabetes in England, 1996-2005. *Diabetes Res Clin Pract*. 2010;87(2):275-82.
76. Moxey PW, Hofman D, Hinchliffe RJ, Jones K, Thompson MM, Holt PJE. Epidemiological study of lower limb amputation in England between 2003 and 2008. *British Journal of Surgery*. 2010;97(9):1348-53.

77. Fosse S, Hartemann-Heurtier A, Jacqueminet S, Ha Van G, Grimaldi A, Fagot-Campagna A. Incidence and characteristics of lower limb amputations in people with diabetes. *Diabetic medicine : a journal of the British Diabetic Association*. 2009;26(4):391-6.
78. Stiegler H, Standl E, Frank S, Mendler G. Failure of reducing lower extremity amputations in diabetic patients: results of two subsequent population based surveys 1990 and 1995 in Germany. *Vasa*. 1998;27(1):10-4.
79. Trautner C, Haastert B, Spraul M, Giani G, Berger M. Unchanged incidence of lower-limb amputations in a German City, 1990-1998. *Diabetes Care*. 2001;24(5):855-9.
80. Mayfield JA, Reiber GE, Maynard C, Czerniecki JM, Caps MT, Sangeorzan BJ. Trends in lower limb amputation in the Veterans Health Administration, 1989-1998. *J Rehabil Res Dev*. 2000;37(1):23-30.
81. Lim TS, Finlayson A, Thorpe JM, Sieunarine K, Mwipatayi BP, Brady A, et al. Outcomes of a contemporary amputation series. *ANZ J Surg*. 2006;76(5):300-5.
82. Mattes E, Norman PE, Jamrozik K. Falling incidence of amputations for peripheral occlusive arterial disease in Western Australia between 1980 and 1992. *Eur J Vasc Endovasc Surg*. 1997;13(1):14-22.
83. Chen SY, Chie WC, Lan C, Lin MC, Lai JS, Lien IN. Rates and characteristics of lower limb amputations in Taiwan, 1997. *Prosthet Orthot Int*. 2002;26(1):7-14.
84. The Saint Vincent Declaration. *Acta Ophthalmologica Scandinavica*. 1997;75(S223):63-.
85. Kennon B, Leese GP, Cochrane L, Colhoun H, Wild S, Stang D, et al. Reduced incidence of lower-extremity amputations in people with diabetes in Scotland: a nationwide study. *Diabetes Care*. 2012;35(12):2588-90.
86. Vamos EP, Bottle A, Edmonds ME, Valabhji J, Majeed A, Millett C. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. *Diabetes Care*. 2010;33(12):2592-7.
87. Hinchliffe RJ, Jeffcoate WJ. Diabetes: Diabetes mellitus: are amputation rates falling in England? *Nat Rev Endocrinol*. 2010;6(8):422-4.
88. Aragon-Sanchez J, Garcia-Rojas A, Lazaro-Martinez JL, Quintana-Marrero Y, Maynar-Moliner M, Rabellino M, et al. Epidemiology of diabetes-related lower extremity amputations in Gran Canaria, Canary Islands (Spain). *Diabetes Res Clin Pract*. 2009;86(1):e6-8.
89. Ebskov LB, Hindso K, Holstein P. Level of amputation following failed arterial reconstruction compared to primary amputation--a meta-analysis. *Eur J Vasc Endovasc Surg*. 1999;17(1):35-40.
90. Feinglass J, Brown JL, LoSasso A, Sohn MW, Manheim LM, Shah SJ, et al. Rates of lower-extremity amputation and arterial reconstruction in the United States, 1979 to 1996. *Am J Public Health*. 1999;89(8):1222-7.
91. Gujral JS, McNally PG, O'Malley BP, Burden AC. Ethnic differences in the incidence of lower extremity amputation secondary to diabetes mellitus. *Diabetic medicine : a journal of the British Diabetic Association*. 1993;10(3):271-4.
92. Leggetter S, Chaturvedi N, Fuller JH, Edmonds ME. Ethnicity and risk of diabetes-related lower extremity amputation: a population-based, case-control study of African Caribbeans and Europeans in the United kingdom. *Arch Intern Med*. 2002;162(1):73-8.
93. Regenbogen SE, Gawande AA, Lipsitz SR, Greenberg CC, Jha AK. Do differences in hospital and surgeon quality explain racial disparities in lower-extremity vascular amputations? *Annals of surgery*. 2009;250(3):424-31.
94. Resnick HE, Valsania P, Phillips CL. Diabetes mellitus and nontraumatic lower extremity amputation in black and white Americans: the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, 1971-1992. *Arch Intern Med*. 1999;159(20):2470-5.

95. Collins TC, Johnson M, Henderson W, Khuri SF, Daley J. Lower extremity nontraumatic amputation among veterans with peripheral arterial disease: is race an independent factor? *Med Care*. 2002;40(1 Suppl):I106-16.
96. Lavery LA, van Houtum WH, Armstrong DG, Harkless LB, Ashry HR, Walker SC. Mortality following lower extremity amputation in minorities with diabetes mellitus. *Diabetes Res Clin Pract*. 1997;37(1):41-7.
97. Wrobel JS, Mayfield JA, Reiber GE. Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. *Diabetes Care*. 2001;24(5):860-4.
98. Young BA, Maynard C, Reiber G, Boyko EJ. Effects of ethnicity and nephropathy on lower-extremity amputation risk among diabetic veterans. *Diabetes Care*. 2003;26(2):495-501.
99. United National Institute for Prosthetics and Orthotics Development (UNIPOD) UoS. *Limbless Statistics*. 2012 ed. Salford, Greater Manchester: United National Institute for Prosthetics and Orthotics Development (UNIPOD), University of Salford; 2006/07. p. 1-119.
100. United National Institute for Prosthetics and Orthotics Development (UNIPOD) UoS. *Limbless Statistics*. 2013 ed. Salford, Greater Manchester: United National Institute for Prosthetics and Orthotics Development (UNIPOD), University of Salford; 2010/11. p. 1-119.
101. Stewart C. *Lower Limb Amputation : Synopsis of Causation*. In: Defence Mo, editor. London: Ministry of Defence; 2008.
102. Stewart CP, Jain AS. An epidemiological study of war amputees and the cost to society. *Prosthet Orthot Int*. 1999;23(2):102-6.
103. Edwards DS, Phillip R, Bosanquet N, Bull AJ, Clasper J. What Is the Magnitude and Long-term Economic Cost of Care of the British Military Afghanistan Amputee Cohort? *Clinical Orthopaedics and Related Research®*. 2015;473(9):2848-55.
104. Ladlow P, Phillip R, Etherington J, Coppack R, Bilzon J, McGuigan MP, et al. Functional and Mental Health Status of United Kingdom Military Amputees Postrehabilitation. *Arch Phys Med Rehabil*. 2015.
105. Scott SW, Bowrey S, Clarke D, Choke E, Bown MJ, Thompson JP. Factors influencing short- and long-term mortality after lower limb amputation. *Anaesthesia*. 2014;69(3):249-58.
106. Karam J, Shepard A, Rubinfeld I. Predictors of operative mortality following major lower extremity amputations using the National Surgical Quality Improvement Program public use data. *J Vasc Surg*. 2013;58(5):1276-82.
107. Kristensen MT, Holm G, Kirketerp-Møller K, Krasheninnikoff M, Gebuhr P. Very low survival rates after non-traumatic lower limb amputation in a consecutive series: what to do? *Interactive CardioVascular and Thoracic Surgery*. 2012.
108. Tseng CH, Chong CK, Tseng CP, Cheng JC, Wong MK, Tai TY. Mortality, causes of death and associated risk factors in a cohort of diabetic patients after lower-extremity amputation: a 6.5-year follow-up study in Taiwan. *Atherosclerosis*. 2008;197(1):111-7.
109. Walsh SR, Bhutta H, Tang TY, Nunn DL, Armon MP, Clarke JM, et al. Anaesthetic specialisation leads to improved early- and medium-term survival following major vascular surgery. *Eur J Vasc Endovasc Surg*. 2010;39(6):719-25.
110. Eskelinen E, Eskelinen A, Alback A, Lepantalo M. Major amputation incidence decreases both in non-diabetic and in diabetic patients in Helsinki. *Scand J Surg*. 2006;95(3):185-9.
111. Remes L, Isoaho R, Vahlberg T, Hiekkanen H, Korhonen K, Viitanen M, et al. Major lower extremity amputation in elderly patients with peripheral arterial disease: incidence and survival rates. *Aging clinical and experimental research*. 2008;20(5):385-93.
112. Johannesson A, Larsson GU, Ramstrand N, Turkiewicz A, Wirehn AB, Atroshi I. Incidence of lower-limb amputation in the diabetic and nondiabetic general population: a

10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations. *Diabetes Care*. 2009;32(2):275-80.

113. Rayman G, Krishnan ST, Baker NR, Wareham AM, Rayman A. Are we underestimating diabetes-related lower-extremity amputation rates? Results and benefits of the first prospective study. *Diabetes Care*. 2004;27(8):1892-6.

114. Witso E, Ronningen H. Lower limb amputations: registration of all lower limb amputations performed at the University Hospital of Trondheim, Norway, 1994-1997. *Prosthet Orthot Int*. 2001;25(3):181-5.

115. Rith-Najarian S, Branchaud C, Beaulieu O, Gohdes D, Simonson G, Mazze R. Reducing lower-extremity amputations due to diabetes. Application of the staged diabetes management approach in a primary care setting. *J Fam Pract*. 1998;47(2):127-32.

116. Morris AD, McAlpine R, Steinke D, Boyle DI, Ebrahim AR, Vasudev N, et al. Diabetes and lower-limb amputations in the community. A retrospective cohort study. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit. *Diabetes Care*. 1998;21(5):738-43.

117. Huber TS, Wang JG, Wheeler KG, Cuddeback JK, Dame DA, Ozaki CK, et al. Impact of race on the treatment for peripheral arterial occlusive disease. *J Vasc Surg*. 1999;30(3):417-25.

118. Carmona GA, Hoffmeyer P, Herrmann FR, Vaucher J, Tschopp O, Lacraz A, et al. Major lower limb amputations in the elderly observed over ten years: the role of diabetes and peripheral arterial disease. *Diabetes Metab*. 2005;31(5):449-54.

119. Deerochanawong C, Home PD, Alberti KG. A survey of lower limb amputation in diabetic patients. *Diabetic medicine : a journal of the British Diabetic Association*. 1992;9(10):942-6.

120. Gutteridge B, Torrie P, Galland B. Trends in arterial reconstruction, angioplasty and amputation. *Health Trends*. 1994;26(3):88-91.

121. Larsson J, Apelqvist J, Agardh CD, Stenstrom A. Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? *Diabetic medicine : a journal of the British Diabetic Association*. 1995;12(9):770-6.

122. Humphrey LL, Palumbo PJ, Butters MA, Hallett JW, Jr., Chu CP, O'Fallon WM, et al. The contribution of non-insulin-dependent diabetes to lower-extremity amputation in the community. *Arch Intern Med*. 1994;154(8):885-92.

123. Renzi R, Unwin N, Jubelirer R, Haag L. An international comparison of lower extremity amputation rates. *Ann Vasc Surg*. 2006;20(3):346-50.

124. Winell K, Niemi M, Lepantalo M. The national hospital discharge register data on lower limb amputations. *Eur J Vasc Endovasc Surg*. 2006;32(1):66-70.

125. Canavan RJ, Unwin NC, Kelly WF, Connolly VM. Diabetes- and nondiabetes-related lower extremity amputation incidence before and after the introduction of better organized diabetes foot care: continuous longitudinal monitoring using a standard method. *Diabetes Care*. 2008;31(3):459-63.

126. Vaccaro O, Lodato S, Mariniello P, De Feo E. Diabetes-related lower extremity amputations in the community: a study based on hospital discharge diagnoses. *Nutr Metab Cardiovasc Dis*. 2002;12(6):331-6.

127. Holstein P, Ellitsgaard N, Olsen BB, Ellitsgaard V. Decreasing incidence of major amputations in people with diabetes. *Diabetologia*. 2000;43(7):844-7.

128. Pernot HF, Winnubst GM, Cluitmans JJ, De Witte LP. Amputees in Limburg: incidence, morbidity and mortality, prosthetic supply, care utilisation and functional level after one year. *Prosthet Orthot Int*. 2000;24(2):90-6.

129. Tunis SR, Bass EB, Steinberg EP. The use of angioplasty, bypass surgery, and amputation in the management of peripheral vascular disease. *N Engl J Med*. 1991;325(8):556-62.

130. Krishnan S, Nash F, Baker N, Fowler D, Rayman G. Reduction in diabetic amputations over 11 years in a defined U.K. population: benefits of multidisciplinary team work and continuous prospective audit. *Diabetes Care*. 2008;31(1):99-101.
131. Larsson J, Eneroth M, Apelqvist J, Stenstrom A. Sustained reduction in major amputations in diabetic patients: 628 amputations in 461 patients in a defined population over a 20-year period. *Acta Orthop*. 2008;79(5):665-73.
132. van Houtum WH, Rauwerda JA, Ruwaard D, Schaper NC, Bakker K. Reduction in diabetes-related lower-extremity amputations in The Netherlands: 1991-2000. *Diabetes Care*. 2004;27(5):1042-6.
133. Trautner C, Haastert B, Mauckner P, Gatcke LM, Giani G. Reduced incidence of lower-limb amputations in the diabetic population of a German city, 1990-2005: results of the Leverkusen Amputation Reduction Study (LARS). *Diabetes Care*. 2007;30(10):2633-7.
134. Patout CA, Jr., Birke JA, Horswell R, Williams D, Cerise FP. Effectiveness of a comprehensive diabetes lower-extremity amputation prevention program in a predominantly low-income African-American population. *Diabetes Care*. 2000;23(9):1339-42.
135. Birke JA, Horswell R, Patout CA, Jr., Chen SL. The impact of a staged management approach to diabetes foot care in the Louisiana public hospital system. *J La State Med Soc*. 2003;155(1):37-42.
136. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007;45 Suppl S:S5-67.
137. Ferguson AD, Richie BS, Gomez MJ. Psychological factors after traumatic amputation in landmine survivors: the bridge between physical healing and full recovery. *Disability and rehabilitation*. 2004;26(14-15):931-8.
138. Melsom H, Danjoux G. Perioperative care for lower limb amputation in vascular disease. *Continuing Education in Anaesthesia, Critical Care & Pain*. 2011;11(5):162-6.
139. Eneroth M. Factors affecting wound healing after major amputation for vascular disease: a review. *Prosthet Orthot Int*. 1999;23(3):195-208.
140. Ong BY, Arneja A, Ong EW. Effects of anesthesia on pain after lower-limb amputation. *Journal of clinical anesthesia*. 2006;18(8):600-4.
141. Rehabilitation BAoCPIA. Evidence Based Clinical Guidelines for the Physiotherapy Management of Adults with Lower Limb Protheses. CSP Clinical Guideline 03. Derby: British Association of Chartered Physiotherapists; 2012.
142. Choksy SA, Lee Chong P, Smith C, Ireland M, Beard J. A Randomised Controlled Trial of the Use of a Tourniquet to Reduce Blood Loss During Transtibial Amputation for Peripheral Arterial Disease. *European Journal of Vascular and Endovascular Surgery*. 2006;31(6):646-50.
143. Naylor A. Arteriovenous Fistula Complicating an Amputation Stump. *British Medical Journal*. 1950;2(4685):928.
144. Bloom RJ, Stevick CA. Amputation level and distal bypass salvage of the limb. *Surg Gynecol Obstet*. 1988;166(1):1-5.
145. Evans WE, Hayes JP, Vermilion BD. Effect of a failed distal reconstruction on the level of amputation. *Am J Surg*. 1990;160(2):217-20.
146. Barnes R, Souroullas P, Lane RA, Chetter I. The impact of previous surgery and revisions on outcome after major lower limb amputation. *Ann Vasc Surg*. 2014;28(5):1166-71.
147. MacKenzie EJ, Bosse MJ, Castillo RC, Smith DG, Webb LX, Kellam JF, et al. Functional outcomes following trauma-related lower-extremity amputation. *J Bone Joint Surg Am*. 2004;86-A(8):1636-45.
148. MacKenzie EJ, Bosse MJ, Kellam JF, Burgess AR, Webb LX, Swiontkowski MF, et al. Factors influencing the decision to amputate or reconstruct after high-energy lower extremity trauma. *J Trauma*. 2002;52(4):641-9.

149. Blaisdell FW. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. *Cardiovascular surgery (London, England)*. 2002;10(6):620-30.
150. Eckert P, Schnackerz K. Ischemic tolerance of human skeletal muscle. *Annals of plastic surgery*. 1991;26(1):77-84.
151. Busse JW, Jacobs CL, Swiontkowski MF, Bosse MJ, Bhandari M, Evidence-Based Orthopaedic Trauma Working G. Complex limb salvage or early amputation for severe lower-limb injury: a meta-analysis of observational studies. *J Orthop Trauma*. 2007;21(1):70-6.
152. Webb LX, Bosse MJ, Castillo RC, MacKenzie EJ, Group LS. Analysis of surgeon-controlled variables in the treatment of limb-threatening type-III open tibial diaphyseal fractures. *J Bone Joint Surg Am*. 2007;89(5):923-8.
153. Bosse MJ, McCarthy ML, Jones AL, Webb LX, Sims SH, Sanders RW, et al. The insensate foot following severe lower extremity trauma: an indication for amputation? *J Bone Joint Surg Am*. 2005;87(12):2601-8.
154. Saddawi-Konefka D, Kim HM, Chung KC. A systematic review of outcomes and complications of reconstruction and amputation for type IIIB and IIIC fractures of the tibia. *Plast Reconstr Surg*. 2008;122(6):1796-805.
155. Glass GE, Pearse MF, Nanchahal J. Improving lower limb salvage following fractures with vascular injury: a systematic review and new management algorithm. *J Plast Reconstr Aesthet Surg*. 2009;62(5):571-9.
156. Khalil IM, Livingston DH. Intravascular shunts in complex lower limb trauma. *J Vasc Surg*. 1986;4(6):582-7.
157. Subramanian A, Vercruyse G, Dente C, Wyrzykowski A, King E, Feliciano DV. A decade's experience with temporary intravascular shunts at a civilian level I trauma center. *J Trauma*. 2008;65(2):316-24; discussion 24-6.
158. Kuralay E, Demirkilic U, Ozal E, Oz BS, Cingoz F, Gunay C, et al. A quantitative approach to lower extremity vein repair. *J Vasc Surg*. 2002;36(6):1213-8.
159. Barros D'Sa AA, Harkin DW, Blair PH, Hood JM, McIlrath E. The Belfast approach to managing complex lower limb vascular injuries. *Eur J Vasc Endovasc Surg*. 2006;32(3):246-56.
160. Banic A, Hertel R. Double vascularized fibulas for reconstruction of large tibial defects. *J Reconstr Microsurg*. 1993;9(6):421-8.
161. Song HR, Kale A, Park HB, Koo KH, Chae DJ, Oh CW, et al. Comparison of internal bone transport and vascularized fibular grafting for femoral bone defects. *J Orthop Trauma*. 2003;17(3):203-11.
162. Pape HC, Giannoudis PV, Krettek C, Trentz O. Timing of fixation of major fractures in blunt polytrauma: role of conventional indicators in clinical decision making. *J Orthop Trauma*. 2005;19(8):551-62.
163. Dougherty PJ. Transtibial amputees from the Vietnam War. Twenty-eight-year follow-up. *J Bone Joint Surg Am*. 2001;83-A(3):383-9.
164. Dougherty PJ. Long-term follow-up of unilateral transfemoral amputees from the Vietnam war. *J Trauma*. 2003;54(4):718-23.
165. Dougherty PJ. Long-term follow-up study of bilateral above-the-knee amputees from the Vietnam War. *J Bone Joint Surg Am*. 1999;81(10):1384-90.
166. Mattes SJ, Martin PE, Royer TD. Walking symmetry and energy cost in persons with unilateral transtibial amputations: matching prosthetic and intact limb inertial properties. *Arch Phys Med Rehabil*. 2000;81(5):561-8.
167. Czerniecki JM. Rehabilitation in limb deficiency. 1. Gait and motion analysis. *Arch Phys Med Rehabil*. 1996;77(3 Suppl):S3-8.
168. Esquenazi A, Meier RH, 3rd. Rehabilitation in limb deficiency. 4. Limb amputation. *Arch Phys Med Rehabil*. 1996;77(3 Suppl):S18-28.

169. Ghali S, Harris PA, Khan U, Pearse M, Nanchahal J. Leg length preservation with pedicled fillet of foot flaps after traumatic amputations. *Plast Reconstr Surg.* 2005;115(2):498-505.
170. Souroullas PC, I.; McCollum, P. Amputations. In: Corson JDWRCN, editor. *Surgery, Core Principles and Practice.* 2. 2nd ed. India: JayPee Brothers; 2017.
171. McCollum PT, Spence VA, Walker WF. Amputation for peripheral vascular disease: the case for level selection. *Br J Surg.* 1988;75(12):1193-5.
172. Wagner WH, Keagy BA, Kotb MM, Burnham SJ, Johnson G, Jr. Noninvasive determination of healing of major lower extremity amputation: the continued role of clinical judgment. *J Vasc Surg.* 1988;8(6):703-10.
173. Sarin S, Shami S, Shields DA, Scurr JH, Smith PD. Selection of amputation level: a review. *Eur J Vasc Surg.* 1991;5(6):611-20.
174. Larsson J, Apelqvist J, Castenfors J, Agardh CD, Stenstrom A. Distal blood pressure as a predictor for the level of amputation in diabetic patients with foot ulcer. *Foot & ankle.* 1993;14(5):247-53.
175. Cumming JG, Spence VA, Jain AS, McCollum PT, Stewart C, Walker WF, et al. Further experience in the healing rate of lower limb amputations. *Eur J Vasc Surg.* 1988;2(6):383-5.
176. McCollum PT, Spence VA, Walker WF. Circumferential skin blood flow measurements in the ischaemic limb. *Br J Surg.* 1985;72(4):310-2.
177. Moore WS, Henry RE, Malone JM, Daly MJ, Patton D, Childers SJ. Prospective use of xenon Xe 133 clearance for amputation level selection. *Archives of surgery.* 1981;116(1):86-8.
178. Holstein P, Sager P, Lassen NA. Wound healing in below-knee amputations in relation to skin perfusion pressure. *Acta Orthop Scand.* 1979;50(1):49-58.
179. van den Broek TA, Dwars BJ, Rauwerda JA, Bakker FC. Photoplethysmographic selection of amputation level in peripheral vascular disease. *J Vasc Surg.* 1988;8(1):10-3.
180. Kram HB, Appel PL, Shoemaker WC. Prediction of below-knee amputation wound healing using noninvasive laser Doppler velocimetry. *Am J Surg.* 1989;158(1):29-31.
181. Silverman D, Wagner FW, Jr. Prediction of leg viability and amputation level by fluorescein uptake. *Prosthet Orthot Int.* 1983;7(2):69-71.
182. McCollum PT, Spence VA, Walker WF. Oxygen inhalation induced changes in the skin as measured by transcutaneous oxymetry. *Br J Surg.* 1986;73(11):882-5.
183. McCollum PT, Spence VA, Walker WF, Swanson AJ, Turner MS, Murdoch G. Experience in the healing rate of lower limb amputations. *Journal of the Royal College of Surgeons of Edinburgh.* 1984;29(6):358-62.
184. Fagrell B, Lundberg G. A simplified evaluation of vital capillary microscopy for predicting skin viability in patients with severe arterial insufficiency. *Clinical physiology.* 1984;4(5):403-11.
185. White SA, Thompson MM, Zickerman AM, Broomhead P, Critchley P, Barrie WW, et al. Lower limb amputation and grade of surgeon. *Br J Surg.* 1997;84(4):509-11.
186. Baumgartner R. The Foot. In: G. Murdoch ABWJ, editor. *Amputation Surgical Practice and Patient Management.* London: ButterWorth Heinemann; 1996. p. 93-104.
187. Seligman RS, Trepal MJ, Giorgini RJ. Hallux valgus secondary to amputation of the second toe. A case report. *J Am Podiatr Med Assoc.* 1986;76(2):89-92.
188. Poppen NK, Mann RA, O'Konski M, Buncke HJ. Amputation of the great toe. *Foot & ankle.* 1981;1(6):333-7.
189. Wagner FW, Jr. The dysvascular foot: a system for diagnosis and treatment. *Foot & ankle.* 1981;2(2):64-122.
190. Pinzur MS, Stuck RM, Sage R, Hunt N, Rabinovich Z. Syme ankle disarticulation in patients with diabetes. *J Bone Joint Surg Am.* 2003;85-A(9):1667-72.

191. Birch JG, Walsh SJ, Small JM, Morton A, Koch KD, Smith C, et al. Syme amputation for the treatment of fibular deficiency. An evaluation of long-term physical and psychological functional status. *J Bone Joint Surg Am.* 1999;81(11):1511-8.
192. Harris RI. Syme's amputation; the technical details essential for success. *J Bone Joint Surg Br.* 1956;38-B(3):614-32.
193. Harris RI. Syme's Amputation: The Technique Essential to Secure a Satisfactory End-Bearing Stump. Ii. *Can J Surg.* 1964;7:53-63.
194. Harris RI. Syme's Amputation. The Technique Essential to Secure a Satisfactory End-Bearing Stump. I. *Can J Surg.* 1963;6:456-69 CONTD.
195. Westberry DE, Davids JR, Pugh LI. The Boyd amputation in children: indications and outcomes. *J Pediatr Orthop.* 2014;34(1):86-91.
196. Bhat S. Amputations. In: Bhat S, editor. *SRB's Surgical Operations.* p. 252.
197. Lindqvist C, Riska EB. Chopart, Pirogoff and Syme amputations. A survey of twenty-one cases. *Acta Orthop Scand.* 1966;37(1):110-6.
198. Lindqvist C, Riska EB. Results after amputations of Chopart, Pirogoff and Syme. *Acta Orthop Scand.* 1965;36(3):344-5.
199. Harris JP, Page S, Englund R, May J. Is the outlook for the vascular amputee improved by striving to preserve the knee? *The Journal of cardiovascular surgery.* 1988;29(6):741-5.
200. Chetter I. Lower leg Magnetic resonance Angiogram In: *Manual TAC,* editor. London: The Royal College of Surgeons of England; 2013.
201. Verduin PA. *Nouvelle Méthode pour Amputer Les Membres* Amsterdam: Wolters; 1697.
202. Hey W, Pearson J, Clift W, Basire J, Cadell & Davies (Firm), Guy's Hospital. Physical Society. *Practical observations in surgery, illustrated by cases.* Third edition ed. London: printed by Luke Hansard & Sons, ..., for T. Cadell and W. Davies, ... 1814. xiv, 1-204, 5-577, 15 p., 15 plates p.
203. Stahel PF, Oberholzer A, Morgan SJ, Heyde CE. Concepts of transtibial amputation: Burgess technique versus modified Bruckner procedure. *ANZ J Surg.* 2006;76(10):942-6.
204. Dudek NL, Marks MB, Marshall SC. Skin Problems in an Amputee Clinic. *American Journal of Physical Medicine & Rehabilitation.* 2006;85(5):424-9.
205. Humzah MD, Gilbert PM. Fasciocutaneous blood supply in below-knee amputation. *J Bone Joint Surg Br.* 1997;79(3):441-3.
206. Robinson KP, Hoile R, Coddington T. Skew flap myoplastic below-knee amputation: a preliminary report. *Br J Surg.* 1982;69(9):554-7.
207. Robb HJ, Jacobson LF, Jordan P. Midcalf Amputation in the Ischemic Extremity. Use of Lateral and Medial Flap. *Archives of surgery.* 1965;91:506-8.
208. Termansen NB. Below-knee amputation for ischaemic gangrene. Prospective, randomized comparison of a transverse and a sagittal operative technique. *Acta Orthop Scand.* 1977;48(3):311-6.
209. Robinson KP. Skew flap method of transtibial amputation. In: G. Murdoch ABWJ, editor. *Amputation Surgical Practice and Patient Management.* Oxford: Butterworth Heinemann; 1996. p. 63-8.
210. Bates B, Stineman MG, Reker DM, Kurichi JE, Kwong PL. Risk factors associated with mortality in veteran population following transtibial or transfemoral amputation. *J Rehabil Res Dev.* 2006;43(7):917-28.
211. Tisi PV, Callam MJ. Type of incision for below knee amputation. *Cochrane Database Syst Rev.* 2004(1):CD003749.
212. Executive HaS. Structure and function of the Skin Great Britain [Available from: <http://www.hse.gov.uk/skin/professional/causes/structure.htm>].
213. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. *Nature.* 2008;453(7193):314-21.

214. Young A, Macnaught, C. The physiology of wound healing. *Surgery*. 2011;29(10):475-9.
215. Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. *J Int Med Res*. 2009;37(5):1528-42.
216. Ueno C, Hunt TK, Hopf HW. Using physiology to improve surgical wound outcomes. *Plast Reconstr Surg*. 2006;117(7 Suppl):59S-71S.
217. Khalil RA vBC. Mechanisms of calcium mobilization and homeostasis in vascular smooth muscle and their relevance to hypertension. In: Laragh JH BB, editor. *Hypertension: Pathophysiology, Diagnosis and Management*. 2nd ed ed. New York: Raven Press; 1995. p. 523-40.
218. Chee YL. Coagulation. *J R Coll Physicians Edinb*. 2014;44(1):42-5.
219. Zarbock A, Polanowska-Grabowska RK, Ley K. Platelet-neutrophil-interactions: linking hemostasis and inflammation. *Blood Rev*. 2007;21(2):99-111.
220. Smyth SS, McEver RP, Weyrich AS, Morrell CN, Hoffman MR, Arepally GM, et al. Platelet functions beyond hemostasis. *J Thromb Haemost*. 2009;7(11):1759-66.
221. Broughton G, 2nd, Janis JE, Attinger CE. The basic science of wound healing. *Plast Reconstr Surg*. 2006;117(7 Suppl):12S-34S.
222. Kaplan MJ, Radic M. Neutrophil extracellular traps: double-edged swords of innate immunity. *J Immunol*. 2012;189(6):2689-95.
223. Peterson JM, Barbul A, Breslin RJ, Wasserkrug HL, Efron G. Significance of T-lymphocytes in wound healing. *Surgery*. 1987;102(2):300-5.
224. Nathan C. Points of control in inflammation. *Nature*. 2002;420(6917):846-52.
225. Yang J, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. *Dev Cell*. 2008;14(6):818-29.
226. De Donatis A, Ranaldi F, Cirri P. Reciprocal control of cell proliferation and migration. *Cell Commun Signal*. 2010;8:20.
227. Hinz B. Masters and servants of the force: the role of matrix adhesions in myofibroblast force perception and transmission. *Eur J Cell Biol*. 2006;85(3-4):175-81.
228. Campos AC, Groth AK, Branco AB. Assessment and nutritional aspects of wound healing. *Curr Opin Clin Nutr Metab Care*. 2008;11(3):281-8.
229. Bhutani S, Vishwanath G. Hyperbaric oxygen and wound healing. *Indian J Plast Surg*. 2012;45(2):316-24.
230. Kurz A, Sessler DI, Lenhardt R. Perioperative Normothermia to Reduce the Incidence of Surgical-Wound Infection and Shorten Hospitalization. *New England Journal of Medicine*. 1996;334(19):1209-16.
231. Henriksen NA, Yadete DH, Sorensen LT, Agren MS, Jorgensen LN. Connective tissue alteration in abdominal wall hernia. *Br J Surg*. 2011;98(2):210-9.
232. Berrios-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surg*. 2017.
233. Agency HP. Surgical Site Infection surveillance in England October 1997 - September 2005. In: Health Do, editor. London: Department of Health; 2006.
234. Barnes R, Souroullas P, Chetter IC. A survey of perioperative management of major lower limb amputations: current UK practice. *Ann Vasc Surg*. 2014;28(7):1737-43.
235. Sadat U, Chaudhuri A, Hayes PD, Gaunt ME, Boyle JR, Varty K. Five day antibiotic prophylaxis for major lower limb amputation reduces wound infection rates and the length of in-hospital stay. *Eur J Vasc Endovasc Surg*. 2008;35(1):75-8.
236. Hirsemann S, Sohr D, Gastmeier K, Gastmeier P. Risk factors for surgical site infections in a free-standing outpatient setting. *American journal of infection control*. 2005;33(1):6-10.
237. Hayden A, Holdsworth J. Complications following re-exploration of the groin for recurrent varicose veins. *Annals of the Royal College of Surgeons of England*. 2001;83(4):272-3.

238. HPA. Surgical Site Infection Surveillance in England October 1997- September 2005. In: Agency HP, editor. 2006.
239. Doherty GM. Current diagnosis & treatment surgery. 13th ed. New York ; London: McGraw-Hill Medical; 2010. xii, 1312 p. p.
240. Newsom B. Surgical wound infections: A historical review. *International Journal of Infection Control* [Internet]. 2008; 4(1). Available from: [www.ijic.info/article/download/3028/2211](http://www.ijic.info/article/download/3028/2211).
241. Erichsen JE. Hospitalism and the causes of death after an operation. *British Medical Journal*. 1874;(-):65-7.
242. Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. *Infect Control Hosp Epidemiol*. 1999;20(11):725-30.
243. Eagye KJ, Kim A, Laohavaleeson S, Kuti JL, Nicolau DP. Surgical site infections: does inadequate antibiotic therapy affect patient outcomes? *Surg Infect (Larchmt)*. 2009;10(4):323-31.
244. Haley RW, Schaberg DR, Crossley KB, Von Allmen SD, McGowan JE, Jr. Extra charges and prolongation of stay attributable to nosocomial infections: a prospective interhospital comparison. *Am J Med*. 1981;70(1):51-8.
245. Mahmoud NN, Turpin RS, Yang G, Saunders WB. Impact of surgical site infections on length of stay and costs in selected colorectal procedures. *Surg Infect (Larchmt)*. 2009;10(6):539-44.
246. Smyth ET, McIlvenny G, Enstone JE, Emmerson AM, Humphreys H, Fitzpatrick F, et al. Four country healthcare associated infection prevalence survey 2006: overview of the results. *J Hosp Infect*. 2008;69(3):230-48.
247. Astagneau P, Rioux C, Golliot F, Brucker G, Group INS. Morbidity and mortality associated with surgical site infections: results from the 1997-1999 INCISO surveillance. *J Hosp Infect*. 2001;48(4):267-74.
248. Bayat A, McGrouther DA, Ferguson MW. Skin scarring. *BMJ*. 2003;326(7380):88-92.
249. Coello R, Charlett A, Wilson J, Ward V, Pearson A, Borriello P. Adverse impact of surgical site infections in English hospitals. *J Hosp Infect*. 2005;60(2):93-103.
250. Plowman R, Graves N, Griffin MA, Roberts JA, Swan AV, Cookson B, et al. The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. *J Hosp Infect*. 2001;47(3):198-209.
251. Anderson DJ. Surgical site infections. *Infect Dis Clin North Am*. 2011;25(1):135-53.
252. Burke JP. Infection control - a problem for patient safety. *N Engl J Med*. 2003;348(7):651-6.
253. Liau KH, Aung KT, Chua N, Ho CK, Chan CY, Kow A, et al. Outcome of a strategy to reduce surgical site infection in a tertiary-care hospital. *Surg Infect (Larchmt)*. 2010;11(2):151-9.
254. Gaynes R, Richards C, Edwards J, Emori TG, Horan T, Alonso-Echanove J, et al. Feeding back surveillance data to prevent hospital-acquired infections. *Emerg Infect Dis*. 2001;7(2):295-8.
255. Imperatori A, Rovera F, Rotolo N, Nardecchia E, Conti V, Dominioni L. Prospective study of infection risk factors in 988 lung resections. *Surg Infect (Larchmt)*. 2006;7 Suppl 2:S57-60.
256. Korol E, Johnston K, Waser N, Sifakis F, Jafri HS, Lo M, et al. A systematic review of risk factors associated with surgical site infections among surgical patients. *PLoS One*. 2013;8(12):e83743.
257. Royal College of Obstetricians and Gynaecologists W, Andrew, Health NCCfWsaCs. NICE Guidance 74 - Surgical site infection prevention and treatment of

- surgical site infection. In: Excellence NifHaC, editor. London: Royal College of Obstetricians and Gynaecologists; 2008.
258. (WHO) WHO. WHO guidelines on hand hygiene in health care. Geneva, Switzerland: World Health Organisation; 2009.
259. Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. *JAMA*. 2005;294(16):2035-42.
260. Krizek TJ, Robson MC. Evolution of quantitative bacteriology in wound management. *Am J Surg*. 1975;130(5):579-84.
261. Dohmen PM. Influence of skin flora and preventive measures on surgical site infection during cardiac surgery. *Surg Infect (Larchmt)*. 2006;7 Suppl 1:S13-7.
262. Tourmousoglou CE, Yiannakopoulou E, Kalapothaki V, Bramis J, St Papadopoulos J. Adherence to guidelines for antibiotic prophylaxis in general surgery: a critical appraisal. *J Antimicrob Chemother*. 2008;61(1):214-8.
263. Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AFT, Lipman J. Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction: Insights From a Prospective Database of ED Patients With Infection. *Chest*. 2017;151(3):586-96.
264. Barchitta M, Matranga D, Quattrocchi A, Bellocchi P, Ruffino M, Basile G, et al. Prevalence of surgical site infections before and after the implementation of a multimodal infection control programme. *J Antimicrob Chemother*. 2012;67(3):749-55.
265. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery*. 1961;50:161-8.
266. Edwards PS, Lipp A, Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev*. 2004(3):CD003949.
267. Berry AR, Watt B, Goldacre MJ. A comparison of the use of povidone-iodine and chlorhexidine in the prophylaxis of post-operative wound infection. *J Hosp Infect*. 1982;3(4):402.
268. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database Syst Rev*. 2007(2):CD004985.
269. Lee I, Agarwal RK, Lee BY, Fishman NO, Umscheid CA. Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol*. 2010;31(12):1219-29.
270. Darouiche RO, Wall MJ, Jr., Itani KM, Otterson MF, Webb AL, Carrick MM, et al. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. *N Engl J Med*. 2010;362(1):18-26.
271. Spigelman AD, Swan JR. Skin antiseptics and the risk of operating theatre fires. *ANZ J Surg*. 2005;75(7):556-8.
272. A clinician's guide to surgical fires. How they occur, how to prevent them, how to put them out. *Health devices*. 2003;32(1):5-24.
273. Patel R, Chavda KD, Hukkeri S. Surgical field fire and skin burns caused by alcohol-based skin preparation. *Journal of emergencies, trauma, and shock*. 2010;3(3):305.
274. NRES N. Risk of skin-prep related fire in operating theatres: Signal. In: system NNraL, editor. <http://www.nrls.npsa.nhs.uk/resources/?EntryId45=132981> 2012.
275. Bruce J, Russell EM, Mollison J, Krukowski ZH. The measurement and monitoring of surgical adverse events. *Health Technol Assess*. 2001;5(22):1-194.
276. Wilson AP, Treasure T, Sturridge MF, Gruneberg RN. A scoring method (ASEPSIS) for postoperative wound infections for use in clinical trials of antibiotic prophylaxis. *Lancet*. 1986;1(8476):311-3.
277. Armitage P, Berry, G., Matthews, J.N.S. Statistical methods in medical research. 4th Edition ed. Oxford: Blackwell; 2001.

278. Byrne DJ, Malek MM, Davey PG, Cuschieri A. Postoperative wound scoring. *Biomed Pharmacother.* 1989;43(9):669-73.
279. Bui KM, Raugi GJ, Nguyen VQ, Reiber GE. Skin problems in individuals with lower-limb loss: literature review and proposed classification system. *J Rehabil Res Dev.* 2009;46(9):1085-90.
280. Dudek NL, Marks MB, Marshall SC, Chardon JP. Dermatologic conditions associated with use of a lower-extremity prosthesis. *Arch Phys Med Rehabil.* 2005;86(4):659-63.
281. Meulenbelt HE, Geertzen JH, Dijkstra PU, Jonkman MF. Skin problems in lower limb amputees: an overview by case reports. *J Eur Acad Dermatol Venereol.* 2007;21(2):147-55.
282. Ruocco V. The immunocompromised district: How the pieces of the puzzle gradually fell into place. *Clinics in Dermatology.* 32(5):549-52.
283. Lin CH, Ma H, Chung MT, Chou J. Granulomatous cutaneous lesions associated with risperidone-induced hyperprolactinemia in an amputated upper limb. *Int J Dermatol.* 2012;51(1):75-8.
284. Traballesi M, Delussu AS, Fusco A, Iosa M, Averna T, Pellegrini R, et al. Residual limb wounds or ulcers heal in transtibial amputees using an active suction socket system. A randomized controlled study. *Eur J Phys Rehabil Med.* 2012;48(4):613-23.
285. Meulenbelt HE, Geertzen JH, Jonkman MF, Dijkstra PU. Determinants of skin problems of the stump in lower-limb amputees. *Arch Phys Med Rehabil.* 2009;90(1):74-81.
286. Singh SK, Manchanda K. Acroangiokeratosis (Pseudo-Kaposi sarcoma). *Indian Dermatol Online J.* 2014;5(3):323-5.
287. Levy SW. Amputees: skin problems and prostheses. *Cutis.* 1995;55(5):297-301.
288. Highsmith MJH, J. T.; Kahle, J. T. . Identifying and Managing Skin Issues With Lower-Limb Prosthetic Use. *InMotion.* 2011;21(1):41-3.
289. Buikema KES, Meyerle JH. Amputation stump: Privileged harbor for infections, tumors, and immune disorders. *Clinics in Dermatology.* 32(5):670-7.
290. Meulenbelt HE, Geertzen JH, Dijkstra PU, Jonkman MF. Skin problems in lower limb amputees: an overview by case reports. *Journal of the European Academy of Dermatology and Venereology.* 2007;21(2):147-55.
291. Habif TP. *Skin disease : diagnosis and treatment.* St. Louis, London: Mosby; 2001. x,557 p p.
292. Ruocco V, Ruocco E, Brunetti G, Baroni A. The correct meaning of the term 'immunocompromised': a necessary explanation. *J Eur Acad Dermatol Venereol.* 2011;25(10):1242.
293. Ruocco V, Brunetti G, Puca RV, Ruocco E. The immunocompromised district: a unifying concept for lymphoedematous, herpes-infected and otherwise damaged sites. *J Eur Acad Dermatol Venereol.* 2009;23(12):1364-73.
294. McIntosh J, Earnshaw JJ. Antibiotic prophylaxis for the prevention of infection after major limb amputation. *Eur J Vasc Endovasc Surg.* 2009;37(6):696-703.
295. Akinyoola AL, Ojo OD, Oginni LM. Microbiology of amputation wound infection in a Nigerian setting. *J Wound Care.* 2008;17(5):202, 4-6.
296. Friis H. Penicillin G versus cefuroxime for prophylaxis in lower limb amputation. *Acta Orthop Scand.* 1987;58(6):666-8.
297. Huizinga WK, Robbs JV, Bhamjee A, Kritzing NA. Wound infection after major lower-limb amputation--the role of antibiotic prophylaxis. *S Afr J Surg.* 1986;24(3):98-102.
298. Huizinga WK, Robbs JV, Kritzing NA. Prevention of wound sepsis in amputations by peri-operative antibiotic cover with an amoxicillin-clavulanic acid combination. *S Afr Med J.* 1983;63(3):71-3.
299. Moller BN, Krebs B. Antibiotic prophylaxis in lower limb amputation. *Acta Orthop Scand.* 1985;56(4):327-9.

300. Norlin R, Fryden A, Nilsson L, Ansehn S. Short-term cefotaxime prophylaxis reduces the failure rate in lower limb amputations. *Acta Orthop Scand.* 1990;61(5):460-2.
301. Sonne-Holm S, Boeckstyns M, Menck H, Sinding A, Leicht P, Dichmann O, et al. Prophylactic antibiotics in amputation of the lower extremity for ischemia. A placebo-controlled, randomized trial of cefoxitin. *J Bone Joint Surg Am.* 1985;67(5):800-3.
302. Thomsen S, Jakobsen BW, Wethelund JO, Dalsgaard J, Gregersen HN, Lucht U. Antibiotic prophylaxis in lower-extremity amputations due to ischemia. *Archives of Orthopaedic and Trauma Surgery.* 1990;109(2):72-4.
303. Berridge DC, Slack RCB, Hopkinson BR, Makin GS. A bacteriological survey of amputation wound sepsis. *Journal of Hospital Infection.* 13(2):167-72.
304. Rubinovitch B, Pittet D. Screening for methicillin-resistant *Staphylococcus aureus* in the endemic hospital: what have we learned? *J Hosp Infect.* 2001;47(1):9-18.
305. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. *Clin Infect Dis.* 2003;36(2):131-9.
306. Tacconelli E. New strategies to identify patients harbouring antibiotic-resistant bacteria at hospital admission. *Clin Microbiol Infect.* 2006;12(2):102-9.
307. Tacconelli E, Venkataraman L, De Girolami PC, D'Agata EMC. Methicillin-resistant *Staphylococcus aureus* bacteraemia diagnosed at hospital admission: distinguishing between community-acquired versus healthcare-associated strains. *Journal of Antimicrobial Chemotherapy.* 2004;53(3):474-9.
308. Richards T, Pittathankel AA, Pursell R, Magee TR, Galland RB. MRSA in lower limb amputation and the role of antibiotic prophylaxis. *The Journal of cardiovascular surgery.* 2005;46(1):37-41.
309. Scriven JM, Silva P, Swann RA, Thompson MM, Naylor AR, Bell PR, et al. The acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) in vascular patients. *Eur J Vasc Endovasc Surg.* 2003;25(2):147-51.
310. Grimble SA, Magee TR, Galland RB. Methicillin resistant *Staphylococcus aureus* in patients undergoing major amputation. *Eur J Vasc Endovasc Surg.* 2001;22(3):215-8.
311. Bob Phillips CB, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes. Oxford Centre for Evidence-based Medicine – Levels of Evidence [Electronic / Online]. Centre for Evidence Based Medicine - University of Oxford; 1998 [updated March 2009. Available from: <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>).
312. Mekako AI, Chetter IC, Coughlin PA, Hatfield J, McCollum PT, Hull Antibiotic pRophylaxis in varicose Vein Surgery T. Randomized clinical trial of co-amoxiclav versus no antibiotic prophylaxis in varicose vein surgery. *Br J Surg.* 2010;97(1):29-36.
313. General Assembly of the World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent.* 2014;81(3):14-8.
314. DoH. Research Governance Framework for Health and Social Care. 2nd Edition. In: Health Do, editor. 2005.
315. Data Protection Act. In: HMSO, editor. Great Britain 1998.
316. DoH. The Caldicott Committee: Report on the review of patient- identifiable information. 1997.
317. Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ.* 1996;313(7057):570-1.
318. Robbs JV, Kritzinger NA, Mogotlane KA, Odell JA, Huizinga WH. A clinical trial of a combination of amoxicillin and flucloxacillin in amputations for septic ischaemic lower limb lesions. *S Afr Med J.* 1981;60(24):932-4.
319. Choudhury Y, Hussain I, Parsons S, Rahman A, Eldridge S, Underwood M. Methodological challenges and approaches to improving response rates in population surveys in areas of extreme deprivation. *Prim Health Care Res Dev.* 2012;13(3):211-8.

320. Harrison RA, Holt D, Elton PJ. Do postage-stamps increase response rates to postal surveys? A randomized controlled trial. *Int J Epidemiol.* 2002;31.
321. Patel MX, Doku V, Tennakoon L. Challenges in recruitment of research participants. *Advances in Psychiatric Treatment.* 2003;9(3):229-38.
322. Collins AS. Preventing Health Care-Associated Infections. In: Hughes RG, editor. *Patient Safety and Quality: An Evidence-Based Handbook for Nurses.* Advances in Patient Safety. Rockville (MD)2008.
323. Berry AR, Watt B, Goldacre MJ, Thomson JW, McNair TJ. A comparison of the use of povidone-iodine and chlorhexidine in the prophylaxis of postoperative wound infection. *J Hosp Infect.* 1982;3(1):55-63.
324. Murphy PG, Tadros E, Cross S, Hehir D, Burke PE, Kent P, et al. Skin closure and the incidence of groin wound infection: a prospective study. *Ann Vasc Surg.* 1995;9(5):480-2.
325. Biancari F, Tiozzo V. Staples versus sutures for closing leg wounds after vein graft harvesting for coronary artery bypass surgery. *Cochrane Database Syst Rev.* 2010(5):CD008057.
326. Coulthard P, Esposito M, Worthington HV, van der Elst M, van Waes OJ, Darcey J. Tissue adhesives for closure of surgical incisions. *Cochrane Database Syst Rev.* 2010(5):CD004287.
327. Coulston JE, Tuff V, Twine CP, Chester JF, Eysers PS, Stewart AH. Surgical factors in the prevention of infection following major lower limb amputation. *Eur J Vasc Endovasc Surg.* 2012;43(5):556-60.
328. Squires JW, Johnson WC, Widrich WC, Nabseth DC. Cause of wound complications in elderly patients with above-knee amputation. *American journal of surgery.* 1982;143(4):523-7.
329. Sir William Stokes, M.D., F.R.C.S.I. *British Medical Journal.* 1900;2(2070):609-12.
330. Harbarth S, Samore MH, Lichtenberg D, Carmeli Y. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation.* 2000;101(25):2916-21.
331. Wymenga AB, Hekster YA, Theeuwes A, Muytjens HL, van Horn JR, Slooff TJ. Antibiotic use after cefuroxime prophylaxis in hip and knee joint replacement. *Clin Pharmacol Ther.* 1991;50(2):215-20.
332. Fearon KC, Luff R. The nutritional management of surgical patients: enhanced recovery after surgery. *Proc Nutr Soc.* 2003;62(4):807-11.
333. Hennessey DB, Burke JP, Ni-Dhonocho T, Shields C, Winter DC, Mealy K. Preoperative hypoalbuminemia is an independent risk factor for the development of surgical site infection following gastrointestinal surgery: a multi-institutional study. *Annals of surgery.* 2010;252(2):325-9.
334. Lupo L, Pannarale O, Altomare D, Memeo V, Rubino M. Reliability of clinical judgement in evaluation of the nutritional status of surgical patients. *Br J Surg.* 1993;80(12):1553-6.
335. Beltramini AM, Salata RA, Ray AJ. Thermoregulation and risk of surgical site infection. *Infect Control Hosp Epidemiol.* 2011;32(6):603-10.
336. Seamon MJ, Wobb J, Gaughan JP, Kulp H, Kamel I, Dempsey DT. The effects of intraoperative hypothermia on surgical site infection: an analysis of 524 trauma laparotomies. *Annals of surgery.* 2012;255(4):789-95.
337. Woodburn KR, Sockalingham S, Gilmore H, Condie ME, Ruckley CV, Scottish Vascular Audit G, et al. A randomised trial of rigid stump dressing following trans-tibial amputation for peripheral arterial insufficiency. *Prosthetics and orthotics international.* 2004;28(1):22-7.
338. Dumville JC, Walter CJ, Sharp CA, Page T. Dressings for the prevention of surgical site infection. *Cochrane Database Syst Rev.* 2011(7):CD003091.

339. Kumar KLPS. The Joint Commission's Implementation Guide for NPSG.07.05.01 on Surgical Site Infections: The SSI Change Project. America: The Joint Commission; 2013.
340. Cataife G, Weinberg DA, Wong HH, Kahn KL. The effect of Surgical Care Improvement Project (SCIP) compliance on surgical site infections (SSI). *Med Care*. 2014;52(2 Suppl 1):S66-73.
341. Focht J, Klietmann W, Heilmann HD. In-vitro activity of augmentin against clinically important gram-positive and gram-negative bacteria in comparison with other antibiotics. *Zentralbl Bakteriol Mikrobiol Hyg A*. 1984;256(4):523-30.
342. University G. Evidence-based Medicine Resource Guide - Types of Clinical Questions Georgetown, USA2018 [updated 21/07/2018. Available from: <http://guides.dml.georgetown.edu/ebm/ebmclinicalquestions>.
343. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ*. 2001;323(7308):334-6.
344. Melsen WG, Bootsma MCJ, Rovers MM, Bonten MJM. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clinical Microbiology and Infection*. 2014;20(2):123-9.
345. National Nosocomial Infections Surveillance S. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control*. 2004;32(8):470-85.
346. Siah CJ, Childs C. A systematic review of the ASEPSIS scoring system used in non-cardiac-related surgery. *J Wound Care*. 2012;21(3):124, 6-30.
347. A systematic review of surgical infection scoring systems used in surgical patients. *JB Libr Syst Rev*. 2011;9(60):2627-83.
348. Dunkel N, Belaieff W, Assal M, Corni V, Karaca S, Lacraz A, et al. Wound dehiscence and stump infection after lower limb amputation: risk factors and association with antibiotic use. *J Orthop Sci*. 2012;17(5):588-94.
349. Toursarkissian B, Hagino RT, Khan K, Schoolfield J, Shireman PK, Harkless L. Healing of transmetatarsal amputation in the diabetic patient: is angiography predictive? *Ann Vasc Surg*. 2005;19(6):769-73.
350. Landry GJ, Silverman DA, Liem TK, Mitchell EL, Moneta GL. Predictors of healing and functional outcome following transmetatarsal amputations. *Archives of surgery*. 2011;146(9):1005-9.
351. Blume P, Salonga C, Garbalosa J, Pierre-Paul D, Key J, Gahtan V, et al. Predictors for the healing of transmetatarsal amputations: retrospective study of 91 amputations. *Vascular*. 2007;15(3):126-33.
352. Silverstein P. Smoking and wound healing. *Am J Med*. 1992;93(1A):22S-4S.
353. Heughan C, Grislis G, Hunt TK. The effect of anemia on wound healing. *Annals of surgery*. 1974;179(2):163-7.
354. Yuwen P, Chen W, Lv H, Feng C, Li Y, Zhang T, et al. Albumin and surgical site infection risk in orthopaedics: a meta-analysis. *BMC Surg*. 2017;17(1):7.
355. Chai FY, Jiffre D. Preoperative Hypoalbuminemia is an Independent Risk Factor for the Development of Surgical Site Infection Following Gastrointestinal Surgery. *Annals of surgery*. 2011;254(4):665.
356. Kim JL, Park J-H, Han S-B, Cho IY, Jang K-M. Allogeneic Blood Transfusion Is a Significant Risk Factor for Surgical-Site Infection Following Total Hip and Knee Arthroplasty: A Meta-Analysis. *The Journal of Arthroplasty*. 32(1):320-5.
357. Kaneko M, Sasaki S, Ishimaru K, Terai E, Nakayama H, Watanabe T. The impact of perioperative allogeneic blood transfusion on survival in elderly patients with colorectal cancer. *Anticancer Res*. 2015;35(6):3553-8.
358. Stone PA, Flaherty SK, Aburahma AF, Hass SM, Jackson JM, Hayes JD, et al. Factors affecting perioperative mortality and wound-related complications following major lower extremity amputations. *Ann Vasc Surg*. 2006;20(2):209-16.

359. Ridgeway S, Wilson J, Charlet A, Kafatos G, Pearson A, Coello R. Infection of the surgical site after arthroplasty of the hip. *J Bone Joint Surg Br.* 2005;87(6):844-50.
360. Bailey IS, Karran SE, Toyn K, Brough P, Ranaboldo C, Karran SJ. Community surveillance of complications after hernia surgery. *Bmj.* 1992;304(6825):469-71.
361. Slim H, Tiwari A, Ahmed A, Ritter JC, Zayed H, Rashid H. Distal versus ultradistal bypass grafts: amputation-free survival and patency rates in patients with critical leg ischaemia. *Eur J Vasc Endovasc Surg.* 2011;42(1):83-8.
362. Belmont PJ, Jr., Davey S, Orr JD, Ochoa LM, Bader JO, Schoenfeld AJ. Risk factors for 30-day postoperative complications and mortality after below-knee amputation: a study of 2,911 patients from the national surgical quality improvement program. *J Am Coll Surg.* 2011;213(3):370-8.
363. Abou-Zamzam AM, Jr., Teruya TH, Killeen JD, Ballard JL. Major Lower Extremity Amputation in an Academic Vascular Center. *Annals of Vascular Surgery.* 17(1):86-90.
364. Aulivola B, Hile CN, Hamdan AD, Sheahan MG, Veraldi JR, Skillman JJ, et al. Major lower extremity amputation: outcome of a modern series. *Archives of surgery.* 2004;139(4):395-9; discussion 9.
365. Burgess EM, Marsden F. Major lower extremity amputations following arterial reconstruction. *Archives of surgery.* 1974;108(5):655-60.
366. Cruz CP, Eidt JF, Capps C, Kirtley L, Moursi MM. Major lower extremity amputations at a Veterans Affairs hospital. *American journal of surgery.* 2003;186(5):449-54.
367. Ploeg AJ, Lardenoye JW, Vrancken Peeters MP, Breslau PJ. Contemporary series of morbidity and mortality after lower limb amputation. *Eur J Vasc Endovasc Surg.* 2005;29(6):633-7.
368. Kazmers M, Satiani B, Evans WE. Amputation level following unsuccessful distal limb salvage operations. *Surgery.* 1980;87(6):683-7.
369. Johansen K, Burgess EM, Zorn R, Holloway GA, Jr., Malchow D, Bach A. Improvement of amputation level by lower extremity revascularization. *Surg Gynecol Obstet.* 1981;153(5):707-9.
370. Faglia E, Clerici G, Caminiti M, Curci V, Clerissi J, Losa S, et al. Mortality after major amputation in diabetic patients with critical limb ischemia who did and did not undergo previous peripheral revascularization Data of a cohort study of 564 consecutive diabetic patients. *Journal of diabetes and its complications.* 2010;24(4):265-9.
371. Van Niekerk LJ, Stewart CP, Jain AS. Major lower limb amputation following failed infrainguinal vascular bypass surgery: a prospective study on amputation levels and stump complications. *Prosthetics and orthotics international.* 2001;25(1):29-33.
372. Feinglass J, Sohn MW, Rodriguez H, Martin GJ, Pearce WH. Perioperative outcomes and amputation-free survival after lower extremity bypass surgery in California hospitals, 1996-1999, with follow-up through 2004. *J Vasc Surg.* 2009;50(4):776-83 e1.
373. Chetter IC, Spark JI, Scott DJA, Kent PJ, Berridge DC, Kester RC. Prospective analysis of quality of life in patients following infrainguinal reconstruction for chronic critical ischaemia. *British Journal of Surgery.* 1998;85(7):951-5.
374. Nehler MR, Coll JR, Hiatt WR, Regensteiner JG, Schnickel GT, Klenke WA, et al. Functional outcome in a contemporary series of major lower extremity amputations. *J Vasc Surg.* 2003;38(1):7-14.
375. Jaar BG, Astor BC, Berns JS, Powe NR. Predictors of amputation and survival following lower extremity revascularization in hemodialysis patients. *Kidney Int.* 2004;65(2):613-20.
376. Simsir SA, Cabellon A, Kohlman-Trigoboff D, Smith BM. Factors influencing limb salvage and survival after amputation and revascularization in patients with end-stage renal disease. *American journal of surgery.* 1995;170(2):113-7.
377. Gregg RO. Bypass or amputation? Concomitant review of bypass arterial grafting and major amputations. *American journal of surgery.* 1985;149(3):397-402.

378. Hallett JW, Jr., Byrne J, Gayari MM, Ilstrup DM, Jacobsen SJ, Gray DT. Impact of arterial surgery and balloon angioplasty on amputation: a population-based study of 1155 procedures between 1973 and 1992. *J Vasc Surg.* 1997;25(1):29-38.
379. Heikkinen M, Saarinen J, Suominen VP, Virkkunen J, Salenius J. Lower limb amputations: Differences between the genders and long-term survival. *Prosthetics and orthotics international.* 2007;31(3):277-86.
380. Hobson RW, 2nd, Lynch TG, Jamil Z, Karanfilian RG, Lee BC, Padberg FT, Jr., et al. Results of revascularization and amputation in severe lower extremity ischemia: a five-year clinical experience. *J Vasc Surg.* 1985;2(1):174-85.
381. Schlenker JD, Wolkoff JS. Major amputations after femoropopliteal bypass procedures. *American journal of surgery.* 1975;129(5):495-9.
382. Tentolouris N, Al-Sabbagh S, Walker MG, Boulton AJ, Jude EB. Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study. *Diabetes Care.* 2004;27(7):1598-604.
383. Tsang GMK, Crowson MC, Hickey NC, Simms MH. Failed femorocrural reconstruction does not prejudice amputation level. *British Journal of Surgery.* 1991;78(12):1479-81.
384. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339.

---

# Appendices

# *Appendix 1 : Health Protection Agency- Surgical wound healing post discharge questionnaire*

Study Number: \_\_\_\_\_

## **Surgical wound healing post discharge questionnaire**

Type of procedure: \_\_\_\_\_

Date of operation \_\_\_/\_\_\_/\_\_\_

Date form to be completed \_\_\_/\_\_\_/\_\_\_

### **Dear Patient,**

*As part of the clinical trial you have entered to look at wound infections following amputation surgery we would be grateful if you would complete the following questionnaire and return it in the envelope provided.*

**Please fill in the date you completed this questionnaire \_\_\_/\_\_\_/\_\_\_**

**Have you had any problems with the healing of your wound?**

YES  NO

If you have answered **NO** you do not need to continue with the rest of the form but it is very important that you return it to the hospital in the envelope provided. Thank you for taking the time to do this. **If you have answered YES, please read the following carefully and complete the rest of the form.**

**Since your surgery have you noticed any of the following symptoms?**

**Was there any discharge or leakage of fluid from any part of the wound?**

Yes  No

If yes, was it either;

Clear or blood stained

Yellow/green (pus)

Other-please specify \_\_\_\_\_

**Please tick any of the following additional symptoms that applied to your wound:**

Pain or soreness in addition to the discomfort experienced following the operation.

Redness or inflammation spreading from the edges of the wound.

The area around the wound felt warmer/hotter than the surrounding skin.

The area around the wound became swollen

The edges of any part of the wound separated or gaped open.

**Did any health care worker take a sample from your wound to send to the laboratory?**

Yes  No

**If you saw a health care worker because of these symptoms, please indicate who you saw from the list below-**

- GP
- District nurse
- Midwife
- Doctor or nurse at the hospital
- Other – please specify
- Did not see one about my wound

**Please tell us the date you noticed these symptoms.**

If you cannot remember the exact date, please give an approximate date  
\_\_\_\_/\_\_\_\_/\_\_\_\_

**Have you been prescribed antibiotics for an infection in the wound?**

Yes  No

If yes, who prescribed them? \_\_\_\_\_

**Have you been re-admitted to hospital with an infection of the surgical wound?**

To the hospital at which the operation was carried out?  Yes  No

To another hospital?  Yes  No

If yes, which one? \_\_\_\_\_

**Other comments** \_\_\_\_\_

**For Office Use Only: (To be completed by surveillance co-ordinator only)**

Patient reported SSI meets definition  Yes  No

*If yes enter criteria for SSI-*

- Criterion 1 Discharge pus + antibiotics prescribed
- Criterion 2 Clinical signs\* + dehiscence
- Criterion 3 Clinical signs\* + antibiotics prescribed

\*Clinical signs- at least 2 of pain, heat, redness or swelling.

**Note:** Do not report stitch abscess (discharge confined to points of suture penetration, minimal inflammation)

## *Appendix 2 Patient Information Leaflet*

### **Part 1**

#### **Invitation**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Your consultant believes you may be a suitable/ willing participant for a research study being carried out at Hull Royal Infirmary. The study is being carried out by a Doctor attached to the Department of Vascular Surgery, undertaking a research degree at Hull University. You are being asked to take part in this study because you need an amputation.

Amputations are a relatively common operation with approximately 5,000 operations being performed per year in the NHS in England & Wales.

Development of a wound infection after amputation can result in delayed wound healing and as such increase the length of time you stay in hospital and delay your rehabilitation. Infections can also mean that you require further treatments such as antibiotics, repeated surgery etc. It is therefore important for us to look at ways that we can reduce how often wound infections occur.

You have been invited to take part in a clinical trial to see whether a more prolonged course of antibiotics around the time of your surgery reduces the number of wound infections which occur.

To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part and also who to contact if you would like to discuss the study or ask any questions.

### **Do I have to take part?**

No. It is up to you to decide whether or not to take part. If you do decide to participate you will be given this information sheet to keep and be asked to sign a Consent form. You are still free to withdraw at any time and without giving a reason. Your non-participation or dropping out of the study will not affect your planned treatment and care in any way.

### **Before you can begin the study**

The recruiting researcher will tell you about any potential adverse events that could occur in this study. You will be told exactly what the study entails and what will be required of you. You are encouraged to ask questions of the researchers conducting the recruitment interview until you are satisfied that you fully understand the nature of the study and the requirements.

### **What happens in the study?**

If you think you might be interested in taking part in the study, you will have a short interview with one of the researchers so we can collect some details from you and make sure there is no reason not to include you in the trial.

Once you are enrolled in the trial we will ask you to complete a short questionnaire and we will perform a physical examination.

Your operation will proceed as normal but at the time of the surgery rather than your surgeon deciding you will be randomly assigned to either a 24 hour course of antibiotics or a 5 days course. You will also be randomly assigned to one of three groups according to the type of skin cleanser used. These will be aqueous iodine (iodine in a water base), or alcoholic iodine (iodine in an alcoholic base), or alcoholic chlorhexidine (chlorhexidine in an alcoholic base). If you are allergic to any of these skin cleansers, then you will be excluded from the study and a suitable skin cleanser will be chosen for you. This will be done primarily for your own safety and secondarily to avoid introducing flaws in the study.

Your post-operative care will at all times be managed by the surgeon caring for you.

After your procedure you will be given short questionnaires to fill in 7 days after your operation and again at 30 days after your operation. If you have left hospital at the time these will be sent to you. The questionnaires will ask you to describe any problems you have had with your wound and how you are feeling in general.

On around day 14 you will be reviewed in the hospital and be seen by a nurse or doctor who will ask you a few questions about how you have been and will look at your wound. You will also be given a short questionnaire to complete at this time.

### **Are there any risks to participating in the study?**

Taking part in the trial will not alter the operation or treatment that you will receive. The only difference is that instead of the surgeon deciding the duration of antibiotic treatment you will receive this will be randomly assigned as will the skin cleanser and closure method. All the techniques used are already in use by our surgeons.

### **What are the possible benefits of taking part?**

We hope that we may be able to reduce the number of wound infections in the future.

### **What happens when the research study stops?**

When the study is complete, you will continue to be followed up by the vascular team as usual.

### **What if there is a problem?**

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in part 2.

If you have a complaint, please contact the following in the first instance: Mr Panos Souroullas.

Any complaints about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

A contact number for complaints will be given.

### **Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

### **Contact Details:**

If you require any further information please contact:

Research team contact;

Panos Souroullas, Clinical Research Fellow,

Academic Vascular Surgery Unit,

Vascular Laboratory,

Hull Royal Infirmary, Hull. HU3 2JZ

Tel: 01482 674178

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

## **Part 2**

### **What if relevant new information becomes available?**

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

### **What will happen if I don't want to carry on with the study?**

If you withdraw from the study we will need to use the data collected up to your withdrawal.

### **What if there is a problem?**

If you have a concern about any aspect of this trial, you should first ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain, you can do this via the NHS Complaints Procedure. Details can be obtained from;

Bridget Wainman, Head of Complaints Department, Hull Royal Infirmary.

Tel: 01482 674924

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Hull and East Yorkshire Hospitals NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. In the highly unlikely event that

you suffer from injury or illness as a result of participation in this study, indemnity will be provided by the Hull and East Yorkshire hospitals NHS Trust. Compensation will be by the usual NHS procedures.

### **Will my taking part in this study be kept confidential?**

All the information obtained about you in the course of the study is confidential and will be kept in a secure locked room. The researchers performing the study and a study Monitor will have access to the data collected in this study. They may also be looked at by representatives of regulatory authorities and by authorised people from Hull Royal Infirmary to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

### **What will happen to the results of the research study?**

The results of this study may be published or presented at meetings. You will not be identified in any report / publication or presentation. We would be happy to supply you with a copy of the results on request.

### **Who is organising and funding the study?**

This study is organised and funded through the Academic Vascular Surgery Unit, Hull Royal Infirmary.

### **Who has reviewed this study?**

The ethics behind this study have been reviewed and supported by the National Research Ethics Committee and the Medicine and Healthcare Products Regulatory Agency.

### **Further information/independent advice**

Independent advice regarding this study or any other aspect of your care can be obtained from the Patients Advisory Liaison Service (PALS) using the details below;

PALS Office: Patient Experience Service

1st Floor

Alderson House

Hull Royal Infirmary

Anlaby Road

Hull

HU3 2JZ

Tel. 01482 675508

Email: [pals@hey.nhs.uk](mailto:pals@hey.nhs.uk)

### **What happens next?**

Please discuss this information with your family, friends or GP if you wish. Any questions can be answered then or please do not hesitate to contact the research team on the number below. Thank you very much for taking the time to read this information sheet and considering taking part in our research.

## ***Appendix 3 Patient Consent Form***

### **Consent to participate in:**

### The Amputation Surgical Site Infection Trial (ASSIT)

A randomised controlled trial to determine whether a 5 day course of antibiotics is more clinically and cost effective than a 24 hour prophylactic course for the prevention of surgical site infection following major lower limb amputation surgery.

Study ID and Patient INITIALS:

	Participants Initials
I confirm that I have been given adequate time to read and understand the Patient Information Sheet version 2; Dated 12th February 2014 relating to the trial. I have had the opportunity to ask any questions and have understood the responses.	
I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records	
I understand that participation in the trial is entirely voluntary and that I have the right to withdraw at any time without giving my reasons.	
I consent to my general practitioner and consultant vascular surgeons being informed of my participation in the trial.	
I agree to take part in the trial	
I consent to have details stored by the research team and understand that my details will not be available to anyone other than the research staff or database administrator.	
I understand that the results of the study may be presented at medical conferences and published in medical literature in an anonymous form. No identifiable details will be released to anyone outside of the research team without my permission.	
To be included on consent form for other participating sites. I agree that a copy of this consent form will be faxed/emailed to Hull and East Yorkshire Hospitals NHS Trust.	

Participant Name \_\_\_\_\_ date \_\_/\_\_/\_\_

Signature \_\_\_\_\_

Researcher Name \_\_\_\_\_ date \_\_/\_\_/\_\_ Signature \_\_\_\_\_

## Appendix 6 Level of evidence <sup>(311)</sup>

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR” validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR” with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval”i)	Individual inception cohort study with > 80% follow-up; CDR” validated in a single population	Validating** cohort study with good” ” ” reference standards; or CDR” tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts” “	All or none case-series	Absolute better-value or worse-value analyses ” ” ” “
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR” or validated on split-sample§§§ only	Exploratory** cohort study with good” ” ” reference standards; CDR” after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	“Outcomes” Research; Ecological studies	“Outcomes” Research		Ecological studies	Audit or outcomes research

3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on economic theory or “first principles”

## Appendix 7      *The PRISMA Checklist*<sup>(384)</sup>



### PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	



## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

**Appendix 8 Hull and East Yorkshire Hospitals Local Antibiotic guideline**

Amputation	Recommended	<p>Co-amoxiclav 1.2g IV <b>plus</b> Metronidazole 500mg IV at induction (repeat at 4 hours if operation <math>\geq</math>4 hours) followed by, <b>IF</b> high lower limb or trauma related amputation, oral Co-amoxiclav 625mg/8h <b>plus</b> oral Metronidazole 400mg/8h for 5 days (<b>Note:</b> doxycycline cannot be given in pregnancy)</p> <p><b>Penicillin allergy</b> – Vancomycin 1g IV once only 100 minutes before induction <b>plus</b> Gentamicin 5mg/kg IV (maximum 480mg) at induction only <b>plus</b> Metronidazole 500mg IV at induction (repeat Metronidazole at 4 hours if operation <math>\geq</math>4 hours) followed by, <b>IF</b> high lower limb or trauma related amputation, oral Doxycycline 100mg/12h <b>plus</b> oral Metronidazole 400mg/8h for 5 days (<b>Note:</b> doxycycline cannot be given in pregnancy)</p>
------------	-------------	---

---

# *List of Abbreviations/Index*

---

## **A**

AC: Antibiotic Course · **209, 218, 222, 228**

AD: Anno Domini · **20, 21, 22**

AFMA: Automated Fabrication of Mobility Aids · **46**

AKA: Above Knee Amputation · **195, 214, 215**

ASA: American Society of Anaesthesiology · **54, 55**

ASSIT: Amputation Surgical Site Infection Trial · **199, 208, 210, 211, 246**

---

## **B**

BC: Before Christ · **19**

BKA: Below Knee Amputation · **195, 214, 215**

---

## **C**

CAD-CAM: Computer Aided Design and Manufacture · **46**

CDC: Centre for Disease Control · **130**

---

## **G**

GLEA: Global Lower Extremity Amputation Study · **48, 49**

---

## **H**

HPA: Health Protection Agency · **142**

---

## **I**

ICF: Informed Consent Form · **137**

IPOP: Immediate Post-Operative Prosthetic Group · **45**

IWH: Impaired Wound Healing · **177, 179, 183, 184, 186, 188, 189, 191, 208, 209, 210, 211, 212, 213**

---

## **L**

LLA: Lower Limb Amputation · **1, 2, 3, 47, 48, 208, 48, 208, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 61, 72, 104, 105, 119, 121, 122, 123, 126, 130, 133, 134, 137, 138, 146, 156, 160, 165, 184, 188, 194, 198, 203, 206, 208, 210, 213, 216, 217**

---

## **M**

MA: Meta-Analysis · **203, 204, 205, 206, 207, 216**

MRSA: Methicillin Resistant Staphylococcus Aureus · **113, 114, 125, 126**

---

## **N**

NCEPOD: National Confidential Enquiry into Patient Outcome and Death · **55**

NICE: National Institute for Health and Care Excellence · **109**; National Institute of Health and Clinical Excellence · **118, 133, 199, 109, 208**

---

## **O**

OR: Odds Ratio · **117, 129, 148, 150, 179, 184, 199, 209, 210**

---

## **P**

PI: Povidone Iodine · **117, 199**

PIS: Patient Information Sheet · **137**

POF: Prosthetics Outreach Organisation · **46, 47**

PRS: Prosthetics Research Study · **45, 46**

PVD: Peripheral Vascular Disease · **119, 120, 123, 124**

---

## **R**

RCT: Randomised Controlled Trial · 117, 126, 131, 134, 136, 151, 152, 172, **204, 217, 260**

---

## **S**

SR: Systematic Review · **203, 204, 216, 260, 261**

SSI: Surgical Site Infection · **1, 2, 3, 24, 63, 77, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 125, 128, 130, 133, 134, 136, 142, 145, 147, 148, 164, 165, 168, 169, 171, 177, 179, 181, 182, 184, 186, 188, 189, 191, 192, 193, 199, 200, 201, 202, 203, 204, 206, 207, 208, 209, 210, 211, 212, 213, 216, 217, 234, 238**

---

## **V**

VA: Veterans Association · **45, 46**

VAMC: Veterans Affairs Medical Centre · **46**

VSGBI: Vascular Society of Great Britain and Ireland · **55**