Acute Bacterial Cellulitis:
Emergency Department Management, Aetiological Epidemiology
and Clinical Risk Factors for Antibiotic Treatment Failure

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A thesis submitted to the School of Postgraduate Studies, Faculty of
Medicine and Health Sciences, Royal College of Surgeons in Ireland, in
fulfilment of the degree of Doctor of Medicine (MD).

Principal Supervisor: Dr. Abel Wakai

October 2017
I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree of Doctor of Medicine, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed

Student Number 13125036

Date October 10th, 2017
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<tr>
<td>A&amp;E</td>
<td>Accident and Emergency</td>
</tr>
<tr>
<td>ABSSSIs</td>
<td>Acute Bacterial Skin And Skin Structure Infections</td>
</tr>
<tr>
<td>ANP</td>
<td>Advanced Nurse Practitioner</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BH</td>
<td>Beaumont Hospital</td>
</tr>
<tr>
<td>BIC</td>
<td>Bayesian Information Criterion</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>C &amp; S</td>
<td>Culture and Sensitivity</td>
</tr>
<tr>
<td>CAGE</td>
<td>Acronym for “Cut-down”, “Annoyed”, “Guilty” and “Eye Opener”</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>Community-Associated, Methicillin Resistant <em>Staphylococcus Aureus</em></td>
</tr>
<tr>
<td>CART</td>
<td>Classification and Regression Tree Analysis</td>
</tr>
<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
</tr>
<tr>
<td>CENTRAL</td>
<td>Cochrane Central Register of Controlled Trials</td>
</tr>
<tr>
<td>CHB</td>
<td>Connolly Hospital Blanchardstown</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CPCI-S</td>
<td>Conference Proceedings Citation Index-Science</td>
</tr>
<tr>
<td>CPG</td>
<td>Clinical Practice Guideline</td>
</tr>
<tr>
<td>CPR</td>
<td>Clinical Prediction Rule</td>
</tr>
<tr>
<td>CREST</td>
<td>Clinical Resource Efficiency Support Team</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CTR</td>
<td>Clinical Trials Registry</td>
</tr>
<tr>
<td>DRG</td>
<td>Diagnosis-Related Group</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>EDIS</td>
<td>ED Information System</td>
</tr>
<tr>
<td>EDOU</td>
<td>ED Observation Unit</td>
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<tr>
<td>EP</td>
<td>Emergency Physician</td>
</tr>
<tr>
<td>EPMS</td>
<td>Electronic Patient Management System</td>
</tr>
<tr>
<td>EWS</td>
<td>Early Warning Score</td>
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</table>
FDA  Food and Drug Administration
GP   General Practitioner
HES  Hospital Episode Statistics
HIPE Hospital In-Patient Enquiry
HPO  Healthcare Pricing Office, Ireland
HR   Heart rate
HSE  Health Service Executive
I & D Incision and Drainage
ICD-10-AM International Classification of Diseases, Australian Modification, 10th revision
ICD-9-CM International Classification of Diseases, Clinical Modification, 9th Revision
IDSA Infectious Diseases Society of America
IQR  Interquartile Range
IV   Intravenous
JCI  Joint Commission International
MRSA Methicillin-Resistant *Staphylococcus aureus*
MRHM Midlands Regional Hospital Mullingar
MRHP Midlands Regional Hospital Portlaoise
MRHT Midlands Regional Hospital Tullamore
MSSA Methicillin-Sensitive *Staphylococcus aureus*
MMUH Mater Misericordiae University Hospital
MOOSE Meta-analyses Of Observational Studies in Epidemiology
MVLR Multivariate Logistic Regression
NAMCS National Ambulatory Medical Care Survey
NHAMCS National Hospital Ambulatory Medical Care Survey
NHS  National Health Service, UK
NOS  Newcastle Ottawa Scale
NPLC Non-Purulent Leg Cellulitis
NPSS Numerical Pain Scale Score
NPV  Negative Predictive Value
OPAT Outpatient Parenteral Antimicrobial Treatment
OR   Odds Ratio
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>OU</td>
<td>Observation Unit</td>
</tr>
<tr>
<td>PCN</td>
<td>Penicillin</td>
</tr>
<tr>
<td>PO</td>
<td>Per os (oral)</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PVL</td>
<td><em>Panton Valentin Leukocidin</em> toxin</td>
</tr>
<tr>
<td>Rx</td>
<td>Treatment</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>ROB</td>
<td>Risk of Bias</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
</tr>
<tr>
<td>SAC</td>
<td>Staphylococcal Abscess Community</td>
</tr>
<tr>
<td>SCI-E</td>
<td>Science Citation Index – Expanded</td>
</tr>
<tr>
<td>SEWS</td>
<td>Scottish Early Warning Score</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic Inflammatory Response Syndrome</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>SRMA</td>
<td>Systematic review and meta-analysis</td>
</tr>
<tr>
<td>SSTI</td>
<td>Skin and Soft Tissue Infection</td>
</tr>
<tr>
<td>Sulfa</td>
<td>Sulfamethoxazole</td>
</tr>
<tr>
<td>TA</td>
<td>Treatment amendment</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>TF</td>
<td>Treatment failure</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VHI</td>
<td>Voluntary Health Insurance</td>
</tr>
<tr>
<td>WCC</td>
<td>White Cell Count</td>
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<tr>
<td>WOS</td>
<td>Web of Science</td>
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<td>WP</td>
<td>Workpackage</td>
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Summary

This thesis consists of 6 work-packages (WPs) that describe the Emergency Department (ED) management of cellulitis; it’s aetiological epidemiology, and risk factors for antibiotic treatment failure.

In order to provide a context for this thesis, I performed a scientometric analysis of research output related to skin and soft tissue infections (SSTIs) between 1945 and 2014. Overall, research output was low but increased as a result of the community associated methicillin-resistant Staphylococcus aureus (CA-MRSA) epidemic in North American settings.

My observational research work began with two studies describing the ED incidence of cellulitis, antibiotic prescribing practices and physician adherence to cellulitis treatment guidelines. The incidence of cellulitis ranged from 6.8-12 per 1000 ED patient attendances. Lower limb cellulitis among males accounted for the majority of cases. There was poor adherence to published guideline recommendations with between 32.9-43.5% of patients treated with intravenous (IV) antibiotics despite guideline recommendation for oral treatment. This finding suggested that a clinical prediction rule (CPR) may help clinicians to risk stratify ED patients with “uncomplicated” cellulitis. I therefore focused on investigating the risk factors for oral antibiotic treatment failure among adult ED patients with “uncomplicated” cellulitis in the remaining WPs of my thesis.

In order to define potential risk factors for cellulitis treatment failure, a systematic review and meta-analysis (SRMA) of published case-control studies examining risk factors for the development of non-purulent leg cellulitis was performed. The SRMA revealed that local risk factors may be more important than systemic risk factors, including diabetes, in the pathogenesis of non-purulent leg cellulitis.

I then performed a retrospective cohort study aimed at identifying risk factors for adjustment in type, duration and setting of prescribed IV antibiotic treatment for adult patients with cellulitis, treated in the largest outpatient parenteral antimicrobial therapy (OPAT) service in Ireland. I found that OPAT was an effective and safe treatment option for cellulitis, with hospital admission occurring in...
4.8% of patients and treatment adjustment in 11.7%. Increased patient age was a consistent risk factor for adjustment of OPAT and prolongation of treatment beyond 7 days, indicating the need for heightened vigilance among patients aged over 65 years.

My final study (WP-6) was a multicentre prospective cohort study describing the prevalence and predictors of oral antibiotic treatment failure among adult ED patients with cellulitis. Inter-observer reliability for patient risk factor assessment, and assessment of the eligibility and loss to follow-up rate was also performed in order to pilot study methods for any future, larger CPR derivation study. This study revealed that, depending on how treatment failure was defined, the rate of oral antibiotic treatment failure among adults discharged from 3 urban EDs with cellulitis was between 8.9% and 24.8%. Increased surface area of infection was associated with both definitions of treatment failure used in the study, and further risk factors for treatment failure are described.

This thesis concludes that, in current clinical practice, the risk stratification and antibiotic treatment of adult ED patients with cellulitis is not evidence-based. It also concludes that there is a need for a consensus definition of treatment failure for cellulitis in order to provide reliable comparison of treatment failure rates between studies, and to accurately associate risk factors with treatment failure. A number of implications for future research are discussed.
Acknowledgements

I wish to acknowledge the guidance, expertise and commitment of Dr. Abel Wakai, Principal Supervisor, without whom this body of research would not have been possible. I wish to thank Professor Arnold Hill for his support and mentorship during this project, Professor Tom Fahey for pointing the project in the correct direction at an early stage, and finally Professor Ronan O’ Sullivan for sharing his expertise.

I wish to thank Dr. Fiona Boland for her statistical support for WP-6 in particular, and for the overall direction of the thesis in general. I also wish to thank Mr Patrick O’ Kelly for his assistance with the analysis of WP-5 and Dr. Jean Saunders for her assistance with the statistical analysis of WP-2 and WP-3. I am also grateful to Professor Gerry McElvaney for his assistance with facilitating the completion of WP-5. Emma May Curran was an invaluable asset to WP-5 and through her role with the RCSI Summer Research School worked hard to complete data compilation on time.

I wish to thank all of the EPs and ANPs who helped with patient enrolment. During WP-2 and WP-3, Dr. Fahd Butt, Dr. Paul Staunton, Dr. David Menzies, Dr. Jameel Ahmed, Dr. Sinéad Ni Bhraoináin and Dr. Milenkovski were integral to the success of these projects. For WP-4, Mr. Firas Ayoub was a constant help and dedicated many hours helping me complete this project. For WP-6, I particularly wish to thank Mr. Stephen Kelly, Dr. Jarlath Varley, Dr. Niamh Mitchell, Dr. Adrian Moughty and Mr. Joe McKeever. In particular, I wish to thank Mary McKeown in the BH ED Dressing Clinic for her help with patient enrolment.

Finally, I wish to thank all of the many patients with cellulitis who consented to be enrolled into each of the WPs contributing to this thesis. Individually, they provided me with the opportunity to better understand how the ED treatment of cellulitis can be improved for patients in the future.
Dedication

To my wife Síona, and my three children Muireann, Marcus and Conor.
Published manuscripts


5) **Quirke M**, Wakai A. Treatment outcome measures for randomized controlled trials of antibiotic treatment for acute bacterial skin and skin structure infections in the emergency department setting. *Int J Emerg Med* 2015; 22(8):11


Manuscript in preparation


Conference presentations

1) Prevalence and predictors of initial oral antibiotic treatment failure in adult emergency department patients with cellulitis: a pilot study

   • Oral presentation at the Irish Association for Emergency Medicine Annual Scientific Meeting, Galway 2017

2) Risk factors for amendment in type, duration and setting of prescribed OPAT for adult patients with cellulitis: a retrospective cohort study and CART analysis

   • Oral presentation at the Irish Association for Emergency Medicine Annual Scientific Meeting, Galway 2017

3) “Risk factors for the development of cellulitis”.

   • Oral presentation at the Shephard Prize Meeting, Beaumont Hospital, 2015.

4) “Factors associated with failure of outpatient intravenous antibiotic treatment for acute bacterial skin and skin structure infections.”

   • Poster presentation at the RCSI Research Day 2016

5) “A systematic review and meta-analysis of risk factors for non purulent leg cellulitis.”
• Poster presentation at the European Society of Emergency Medicine Meeting, Turin, Italy 2015
• Poster presentation at the RCSI Research Day 2016

6) A Pilot Cross Sectional Study of Patients Presenting with cellulitis to Emergency Departments”.

• Poster presentation at the Irish Association for Emergency Medicine ASM, 2012

7) “Skin and soft tissue infections 1945-2015: A scientometric analysis.”

• Poster presentation at the Sheppard Prize Meeting 2015
• Poster presentation at the European society of emergency Medicine Meeting, Turin, Italy 2015
• Poster presentation at the RCSI Research Day 2016

8) “The management of cellulitis in emergency departments: antibiotic prescribing practices and adherence to practice guidelines in Ireland”.

• Oral presentation at the Shephard Prize Meeting, Beaumont Hospital, 2014.
• Oral presentation at the Royal College of Emergency Medicine, Annual Scientific Meeting, London, 2013.
Chapter 1: Cellulitis in the emergency department setting – background and context.

1.1 Introduction

Acute bacterial cellulitis is a spreading, suppurative infection of the dermal and subdermal tissues that induces a host response (1). It most commonly affects the leg, which has unique risk factors for bacterial entry, proliferation and spread of infection (2). Clinically, cellulitis is characterised by erythema, oedema, induration, tenderness and warmth. Inflammation within draining lymphatic tissues may also result in lymphangitis and regional lymphadenopathy (3). Most episodes of cellulitis are treatable with oral antibiotics active against gram-positive organisms, however prolonged inpatient treatment, recurrence, chronic oedema, tissue ulceration and necrotising infection are potential complications (2, 4). Figure 1.1 is a graphical representation of the types of infection affecting each anatomical layer of the skin and soft tissues.

Figure 1.1 Anatomical classification of SSTIs

From Green at al (5)
1.2 Nomenclature

The nomenclature utilised to describe the spectrum of skin, skin structure and soft tissue infections is confusing. Phenomenological descriptions of different types of infection (cellulitis, erysipelas, abscess), predisposing conditions (diabetic foot ulcer), eponymous diseases (Fournier’s gangrene) and microbiological causes of infection (clostridial myonecrosis) have resulted in heterogeneous terminology, much of which has only historical relevance (6, 7). Furthermore, there are inconsistencies between classifications of skin and structure infections issued by the FDA and the IDSA in the US which have contributed to confusion in terminology (3, 8). For the purposes of clinical trial design, the US FDA groups cellulitis, erysipelas, wound infections and abscesses together as ABSSSIs and in this classification, cellulitis and erysipelas are considered to be synonymous with the same pathophysiologic process. The CPG issued by the IDSA, utilises the term SSTI, and advises clinicians to consider the management of SSTIs as either “purulent” (associated with purulent drainage, discharge or exudate) or “non-purulent” (not associated with purulent drainage discharge or exudate). Purulent SSTIs therefore refer to conditions such as furuncles, carbuncles and abscesses, whereas non-purulent SSTIs refer to conditions such as cellulitis / erysipelas and necrotising fasciitis.

In the US and Canada, CA-MRSA infection has been identified as the most common identifiable cause of SSTIs in EDs. The IDSA CPG is therefore most relevant to clinicians working in areas where CA-MRSA is endemic (9). Table 1.1 details the definitions issued by the US FDA, CDER between 1998-2013, and definitions issued by IDSA between 2011-2014.
<table>
<thead>
<tr>
<th>Source-year</th>
<th>Descriptor</th>
<th>Clinical conditions included</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-1998 (10)</td>
<td>Uncomplicated skin and skin structure infections</td>
<td>Abscesses, cellulitis, impetigo, furuncles</td>
</tr>
<tr>
<td>FDA-1998</td>
<td>Complicated skin and skin structure and soft tissue infections</td>
<td>Infections of deeper soft tissue or requiring significant surgical intervention (infected ulcers, burns, major abscess) or a significant underlying disease state that complicates response to treatment</td>
</tr>
<tr>
<td>IDSA-2014 (3)</td>
<td>Purulent skin and soft tissue infections</td>
<td>Abscess, furuncle, carbuncle, inflamed epidermoid cyst</td>
</tr>
<tr>
<td></td>
<td>Non-purulent skin and soft tissue infections</td>
<td>Cellulitis, erysipelas, necrotising fasciitis</td>
</tr>
<tr>
<td>IDSA-2011 (11)</td>
<td>Purulent cellulitis</td>
<td>Cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess</td>
</tr>
<tr>
<td></td>
<td>Non-purulent cellulitis</td>
<td>Cellulitis with no purulent drainage or exudate and no associated abscess</td>
</tr>
<tr>
<td>FDA-2010 (12)</td>
<td>Acute bacterial skin and skin structure infections</td>
<td>Bacterial infection of the skin with a minimal size of &gt; 75 cm². Includes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cellulitis / erysipelas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wound infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major cutaneous abscess</td>
</tr>
</tbody>
</table>
Based on its current clinical use, the term “erysipelas” is used to describe three different clinical entities. Firstly, erysipelas is often used to describe a superficial streptococcal invasion of the skin and upper subcutaneous tissues, its hallmark being a well-defined raised edge reflecting dermal involvement (13). Secondly, it may be used to describe an infectious process involving only the face. Thirdly, the term erysipelas is often used interchangeably with cellulitis, particularly in continental Europe, to describe a dermo-hypodermatitis of the leg (14-16). Since cellulitis may extend superficially and erysipelas may extend deeply, the term erysipelas is usually considered synonymous with cellulitis by researchers (13), and specifically, by the US FDA for the purposes of clinical trial design (8).

Figure 1.2 details the IDSA CPG for the clinical management of SSTIs (3). Table 1.2 details the definitions utilised by IDSA in more detail.

1.3 Terminology used in this thesis

For the purposes of this thesis, and in order to maintain relevance to daily clinical practice in Ireland and the UK, the term cellulitis will be used to denote a superficial spreading infection of the dermal and subdermal tissues that may arise from abscesses, wounds, or “de novo” from an unrecognised cause. The descriptor “ABSSSI” is arguably a more accurate representation of these three potentially different conditions. However this term was specifically derived for the purposes of performing RCTs of antibiotic therapies for the treatment of cellulitis, wound infections and abscesses. Also, the term “cellulitis” was used to identify suitable study participants for potential enrolment into the observational studies performed for this thesis.

The term non-purulent cellulitis is used in Chapter 5 (WP – 4) of this thesis to describe the studies included in the SRMA of case control studies. This is because each of the case control studies examined patients with acute bacterial cellulitis or erysipelas and did not include patients with purulent infections from abscess or wound infections. The term SSTI is also used in my scientometric analysis in order to capture the maximum amount of relevant literature for the purposes of citation analysis, as this term is a commonly used descriptor for these infections internationally.
Figure 1.2: The IDSA CPG for the management of SSTIs.

From Stevens et al (3).

1Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.
Table 1.2: Definitions used in the IDSA CPG, 2014

* temperature > 38 °C, heart rate > 90 beats per minute, respiratory rate > 24 breaths per minute, abnormal white blood cell count (> 12,000 or < 200 cells/μL)

<table>
<thead>
<tr>
<th>Purulent SSTI</th>
<th>Non purulent SSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td><strong>Mild</strong></td>
</tr>
<tr>
<td></td>
<td>Typical cellulitis, no purulence</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td></td>
<td>Typical cellulitis with systemic signs of infection</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td><strong>Severe</strong></td>
</tr>
<tr>
<td></td>
<td>Failed oral antibiotic treatment, or</td>
</tr>
<tr>
<td></td>
<td>Systemic signs of infection, or</td>
</tr>
<tr>
<td></td>
<td>Immunocompromised patients, or</td>
</tr>
<tr>
<td></td>
<td>Suspected deep soft tissue infection (bullae, skin sloughing, hypotension, organ dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Systemic signs of infection *</td>
</tr>
<tr>
<td></td>
<td>Failed incision and drainage plus oral antibiotics, or</td>
</tr>
<tr>
<td></td>
<td>Immunocompromised patients.</td>
</tr>
</tbody>
</table>

1.4 Epidemiology

Cellulitis represents a considerable and evolving burden to healthcare systems internationally. Point prevalence surveys of antibiotic use in Irish and other European hospitals, have shown that “skin, wound or soft tissue infections” are second only to lower respiratory tract infections as the most common indication for inpatient antibiotic treatment (17, 18). In a study of the prevalence and economic costs associated with bacterial cellulitis of the leg in the Netherlands, where comprehensive data is available for patients admitted to all Dutch hospitals through their National Morbidity Registration system, it was shown that the community based incidence was 179 cases / 100,000 population. The proportion of patients treated in the community was noted to be 10-times higher than the number of patients treated in hospital settings (15.2/100,000 population) (15).
In Ireland, data regarding hospital admissions for medical conditions and cost are obtained from the Healthcare Pricing Office which governs information from the HIPE system. HIPE utilises the ICD-10-AM classification. In Ireland, annual hospital admission rates for erysipelas, cellulitis, cutaneous abscess, furuncle, carbuncle and bursitis, have increased yearly between 2009 and 2014, from 5,603 to 7,161 persons. Hospital admissions for cellulitis and erysipelas increased by 25% during this time-period (19). It is important to note that HIPE only records patient details once they are admitted to a hospital from an ED setting. There is no national integrated EDIS that gathers and maintains data on the treatment and disposition (admission or discharge) of patients attending EDs in Ireland.

Epidemiological data from the UK NHS is collected by the Health and Social Care Information Centre through a HES resource. This resource records data both for patients who are admitted to hospital, and for patients attending A&E departments. When A&E attendances are examined for 2013-2015, patients categorised as having a “local infection” accounted for 1.5% of all ED attendances nationally (20). Unfortunately, the coding system utilised gives no further breakdown as to infection type. Furthermore, since 14.2% and 15.3% of all A&E attendances in 2013-14 and 2015-15 respectively, are “not classifiable”, this figure may not be a true indication of the incidence of “local infection” in A&E settings in the UK. Using HES data from England, 87,749 people were admitted for on average of 7.1 days with cellulitis, costing £172.4 to £254.8 million to treat (21). By 2014, this number had increased to 116,882 patients who were admitted to hospital with cellulitis, abscesses and localised SSTIs for on average 6 days (20).

In the US, large population based surveys have been performed annually by the National Center for Health Statistics, creating accurate epidemiological data for patients attending diverse healthcare settings with cellulitis and other SSTIs. Data for patients attending community-based ambulatory healthcare settings is gathered using the NAMCS, and data for patients attending outpatient and ED settings are gathered using the NHAMCS. These surveys gather information about presenting diagnoses based on the ICD-9-CM, types of medications prescribed, and patient demographic characteristics. From these datasets, SSTIs are estimated to account for up to 3% of ED attendances (22). Combined NAMCS and NHAMCS datasets have shown that visits by patients with SSTIs to EDs and
community-based practices increased from 32.1 to 48.1 visits per 1,000 population between 1997 and 2005 (23). Using NHAMCS data between 1992 and 2005, it has been shown that annual ED attendances for SSTIs increased from 1.2 million patient visits (1.35% of all ED visits) to 3.4 million patient visits (2.98% of all ED visits) (22). This three-fold increase in the rate of presentation of SSTIs to EDs in the US occurred contemporaneous with research showing that CA-MRSA was the most common identifiable cause of SSTI among ED patients in the US (24).

In addition to increased ED attendances, increased hospital admissions secondary to SSTI was also noted between 2000-2004. Using the *US Healthcare Cost and Utilization Project National Inpatient Sample*, which is a stratified random sample from 20% of all US community hospitals, a 29% increase in hospital admissions for SSTIs was seen (25). Patients younger than 65 years of age with cellulitis and abscesses accounted for the majority of hospital admissions. Rather than substituting for methicillin-sensitive *S. aureus* as a primary cause of SSTI, the advent of CA-MRSA was associated with an epidemic of “new” disease.

Whether CA-MRSA caused an increase in the frequency of presentation of abscesses or cellulitis has been a subject of debate. Since population based prospective studies have not been published, trends on hospital attendance and admission figures have been derived from retrospective studies of hospital databases (26). The ICD-9-CM diagnostic coding system in use in the US and Ireland until its replacement with the ICD-10-CM coding system in October 2015, unfortunately conflated cellulitis and abscess as the same condition. As a result epidemiological data on the increasing incidence of SSTIs across different US healthcare settings, failed to differentiate between abscess and cellulitis. It has been shown in one study that the frequency of presentation of abscesses to one US ED increased by 11% per year between 1997 and 2007, while the frequency of “non-abscess” SSTIs remained relatively stable (26). Expert consensus and evidence from a limited number of epidemiological studies suggests that the epidemic of CA-MRSA caused a disproportionate increase in the presentation of abscesses to EDs in the US, while the frequency of non-purulent SSTIs remained relatively unchanged (3, 26, 27).

The burden of CA-MRSA in European ED settings was the subject of a recent prospective cross-sectional study. In this study of 7 European EDs performed
over a 3-month period in 2015, the prevalence of MRSA in community-acquired SSTIs was 15.1% (28). Of all infections culturing *S. aureus* in this study, 51 (24.9%) were PVL toxin producing. PVL toxin was present in both methicillin-sensitive and methicillin-resistant *S. aureus*. There was diverse clonal heterogeneity, with no predominant clone found across the 7 countries in this study, although the authors did note an increasing “north-to-south European gradient” in the ED prevalence of MRSA (28). In contrast, the ED prevalence of CA-MRSA associated SSTI in the US has been shown to be as high as 78%, where the “USA300” clone of MRSA predominates (24).

1.5 Healthcare costs

There is a lack of data concerning the economic burden of cellulitis both in Ireland and internationally, particularly when attempting to calculate the economic burden in ED settings. In Ireland, even the calculation of total inpatient costs associated with the treatment of cellulitis is inaccurate, and only approximations are possible (19). The Healthcare Pricing Office generates costs and prices at the DRG level and not for individual ICD-10-AM codes. DRGs are groups of clinically similar cases, which are expected to consume similar amounts of resources. The assignment of a case to a DRG takes into account each of the top 30 diagnoses within the group. Since several diagnoses are grouped together, providing cost estimates for individually coded ICD-10-AM conditions is not possible (19).

Regarding cellulitis, the majority of conditions coded through HIPE fall into two DRGs, one broadly describing “complicated cellulitis” (J64A: *Cellulitis with catastrophic or severe complications and / or co-morbidities*) and the other describing “uncomplicated cellulitis” (J64B: *Cellulitis without catastrophic or severe complications and / or comorbidities*). In Ireland in 2014, there were 7,452 cases of inpatient care assigned to the above two DRGs. The ICD-10-AM code for “cellulitis” was estimated to account for 77% of inpatient cases. “Complicated cellulitis” (DRG-J64A) cost €5,908 per inpatient case, while “uncomplicated cellulitis” (DRG-J64B) cost €2,575 per inpatient case (29).

In England in 2011, limb cellulitis was estimated to account for 52,654 hospital admissions at an approximate cost of £120 million to the exchequer (21). In the
Netherlands, where accurate national coding of healthcare costs related to DRG exists, it has been shown in a large retrospective cohort study that the average cost per hospitalisation for cellulitis of the leg was €5,346 (15). In this study it was shown that only 7% of all patients with leg cellulitis were admitted to hospital for treatment. However, this cohort of admitted patients accounted for 83% of the total costs of treatment (15). The results of this study also indicate that cellulitis was managed primarily in primary care settings, where the rate of treatment was shown to be at least 10-fold greater than inpatient treatment (15).

In the US, the epidemic of CA-MRSA has led to significantly increased costs associated with the treatment of SSTIs. An economic simulation model designed to quantify the costs associated with CA-MRSA infection from societal and third party payer perspectives, showed an annual burden of between $478 million to $2.2 billion on third party payers and $1.4–$13.8 billion on society (30). A substantial proportion of unmeasured cost is estimated to arise from productivity losses and the small proportion of patients with CA-MRSA who die as a result of their illness. A retrospective cohort study, also from the US, showed that the mean total cost of care for patients admitted with SSTIs was $13,313, whereas those treated as outpatients cost $413 (31).

Given the significant healthcare burden associated with the treatment of cellulitis, it is surprising that there is a lack of research-based data to risk stratify patients with cellulitis according to infection severity. Risk stratification of patients with cellulitis based on research evidence may permit a more evidence-based approach to the prescription of oral or IV antibiotic treatment and may lead to the avoidance of unnecessary hospital admission of patients who can be safely managed with oral antibiotics. Evidence-based risk stratification of cellulitis patients may also lead to healthcare cost savings by avoiding expensive IV antibiotic treatment options and hospital admission costs. In this thesis, I describe the current ED management of patients with cellulitis in Ireland and describe a prospective observational cohort study which examines risk factors for empirically prescribed antibiotic treatment failure among patients with cellulitis, wound infections and abscesses.
1.6 Pathogenesis

The skin is the first-line defence against microbial infection. It is a physical barrier to infection, inhibits growth of pathogens by virtue of its low pH, sebaceous fluid and fatty acids, and is colonised by its own bacterial flora to inhibit growth of pathogens (32, 33). Usually, a break in epithelial integrity is required in order for infection to develop (14). Normal skin flora or indigenous flora from the instrument of penetration gain access to the subdermal space and colonise different layers of the skin architecture. Other routes of penetration include contiguous spread from an adjacent infection (osteomyelitis), entry of water into skin pores (e.g. hot-tub folliculitis) and rarely haematogenous seeding (1, 3, 32, 34). Bacterial adherence to host cells, invasion of tissues and release of toxins then occur. Endotoxins and exotoxins released into surrounding tissues act as chemo-attractants, and lead to local tissue damage through enzymatic reactions, cellular dysregulation, and cell lysis. Virulent strains of S. aureus and S. pyogenes in particular, produce superantigens which result in widespread T-lymphocyte activation and inflammatory response (33).

Abscess formation, a common sequela of infection with S. aureus in particular, has recently been postulated to develop in four stages (35). Firstly, staphylococci attract immune cells and replicate in their presence to eventually replace physiological epithelia with distinctive lesions. Within four days, a SAC forms, which allows the pathogen to shield itself from host immune cells by a surrounding fibrin pseudocapsule. Thirdly, rupture of the SAC from soft tissues or solid organs then allows the process to repeat itself (35). This phenomenon is supported by the fact that approximately 20% of staphylococcal abscesses flare up at a future time point, despite effective antibiotic treatment (35).

MRSA strains were first described in the 1960s from nosocomial infections (36), and in the late 1990s SSTIs culturing community-associated MRSA emerged in the US (37). These strains of CA-MRSA have distinct genetic lineages that differentiate them from traditional healthcare-associated MRSA strains (28). In particular the USA300 clone has emerged as the most common subtype of CA-MRSA causing SSTIs in the US (24). The USA300 clone has unique virulence factors, the most important of which is the pore-forming PVL-exotoxin, which has also been associated with necrotising pneumonia and osteomyelitis (38). A cross
sectional study of 7 European EDs, showed that the USA300 MRSA clonal genotype was detected in only 1 out of 205 samples of S. aureus associated infections (28). PVL toxin producing strains were distributed among methicillin-sensitive and methicillin-resistant S. aureus, except in Greece, where a predominant circulating clone of CA-MRSA (clonal genotype ST80), is endemic (39).

1.7 Risk factors

It is apparent that access of bacteria to the subcutaneous space through a break in epithelial continuity does not result in cellulitis in every instance. The presence of certain host risk factors may potentiate an episode of infection, alter the course of the infectious process, or dictate response to treatment (1).

Host risk factors for developing cellulitis are the subject of WP-4 of this thesis. Published research from case-control studies has described a wide range of host risk factors for developing cellulitis. Host risk factors may be either local or general. Local risk factors that have been implicated in the development of cellulitis include previous cellulitis, wounds, lymphoedema, ulceration, skin disease, tinea pedis and interdigital maceration of the toe-web spaces (40). Often, the port-d’entrée for bacteria is clinically not apparent (3). General (systemic) risk factors for developing cellulitis that are commonly reported include elevated BMI, diabetes and immunocompromise (32). Although diabetes mellitus does not appear to be a risk factor for developing non purulent leg cellulitis (40), it may be associated with purulent infections (41).

Aetiological risk factors, such as exposure to a specific type of bacteria or specific mechanisms of injury, increases the likelihood of infection caused by specific bacteria (1). Table 1.3 lists specific aetiological risk factors for cellulitis and their associated bacterial pathogens.
Table 1.3: Aetiological risk factors for developing cellulitis.

Adapted from Eron et al (1)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Characteristic aetiological agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bite wounds</td>
<td></td>
</tr>
<tr>
<td>2. Cat</td>
<td>2. P. multocida</td>
</tr>
<tr>
<td>3. Dog</td>
<td>3. C. canimorsus, P. multocida</td>
</tr>
<tr>
<td>Animal contact</td>
<td>Campylobacter spp.</td>
</tr>
<tr>
<td>Fresh water exposure</td>
<td>A. hydrophila</td>
</tr>
<tr>
<td>Sea or fish tank exposure</td>
<td>V. vulnificus, M. marinum</td>
</tr>
<tr>
<td>Hot tub exposure</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>Drug use</td>
<td></td>
</tr>
<tr>
<td>1) Intravenous</td>
<td>3) MRSA, P. aeruginosa</td>
</tr>
<tr>
<td>2) Subcutaneous</td>
<td>4) Anaerobes, E. corrodens</td>
</tr>
</tbody>
</table>

1.8 Clinical presentation

Cellulitis typically presents with a rapidly spreading area of erythema, swelling, induration, tenderness, warmth and lymphadenopathy with variable lymphangitis. Induration of the skin can result in a classic *peau-d’orange* appearance. Destruction of skin and skin structures may result in the formation of skin vesicles and bullae. Haemorrhage into the skin may result in skin petechiae and ecchymoses. The development of systemic toxicity is variable and may depend on underlying risk factors such as immunocompromise (3). Fever, tachycardia, tachypnoea, alterations in blood pressure and WCC are manifestations of SIRS, which may occur with severe infections and result in sepsis (1, 3, 33).
Skin abscesses are collections of pus within the dermis and upper dermal tissue (3). They are painful, red fluctuant nodules encircled by an area of skin inflammation. This area of inflammatory change is often mistakenly termed cellulitis. *S. aureus* causes the majority of skin abscesses although they may be polymicrobial and contain bacteria associated with the mechanism of injury (3) (see Table 1.3).

### 1.9 Cellulitis mimics

Evidence from observational studies and audits of practice indicate that general clinicians are often erroneous when making a diagnosis of cellulitis. One UK study which examined the transfer of care of cellulitis from general physicians to dermatologists in a general hospital found that 33% of the 635 patients referred with lower limb cellulitis had alternative diagnoses which did not require admission, 28% had an underlying skin condition which required dermatological treatment and 407 of 435 patients enrolled over the 40 month period were managed in their own homes using OPAT for their episode of cellulitis (21). It has also been shown that 13.6% of patients enrolled to a RCT which examined the appropriate duration of antibiotic treatment for cellulitis, were cellulitis “mimics” (42). Table 1.4 depicts a number of alternative diagnoses which should be distinguished from cellulitis by treating clinicians, with more frequent and important entities highlighted in bold (34).
Table 1.4: Differential diagnoses to cellulitis ("cellulitis mimics").

Adapted from Ki et al, Swartz et al and Hirshmann et al (32, 34, 43)

<table>
<thead>
<tr>
<th>Process</th>
<th>Clinical Clues to Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
</tr>
<tr>
<td>Necrotising fasciitis</td>
<td>Acute rapidly spreading infection; marked pain, tenderness, swelling; possible crepitus, bullae and necrosis of underlying skin.</td>
</tr>
<tr>
<td>Cutaneous anthrax</td>
<td>Gelatinous oedema surrounding eschar; epidemiologic factors.</td>
</tr>
<tr>
<td>Vaccinia reaction</td>
<td>Induration and erythema around vaccination site peaks at day 10-12; little toxicity; cell-mediated response to vaccine.</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic venous disease</td>
<td></td>
</tr>
<tr>
<td>Dependent rubor</td>
<td>Ischaemic process; disappears on elevation of the limb</td>
</tr>
<tr>
<td>Acute stasis dermatitis</td>
<td>Sharply demarcated erythema, papules, weeping, crusting, fissuring.</td>
</tr>
<tr>
<td>Acute lipodermatosclerosis</td>
<td>Red, indurated, warm and tender plaque; very painful; gradual onset, typically over medial malleolus; may be bilateral.</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>Erythema, hot, tender; linear pattern along vessel. Inflammation may extend beyond thrombosed vessel mimicking cellulitis.</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>Erythema only seen with proximal DVT over anteromedial thigh as vein becomes superficial</td>
</tr>
<tr>
<td>Eczema/dermatitis</td>
<td>Unlike typical cellulitis, there will be pruritis, tiny vesicles, crusting, fissuring, weeping and scaling.</td>
</tr>
<tr>
<td>Eosinophilic cellulitis (Wells’ syndrome)</td>
<td>Dermal eosinophil infiltration; eosinophilia; multiple, pruritic, erythematous plaques; recurrent.</td>
</tr>
<tr>
<td>Acute febrile neutrophilic dermatosis (Sweet’s syndrome)</td>
<td>Idiopathic neutrophilic skin plaque eruption; associated with haematological malignancy; Erythematous, tender plaques on face, neck, arms; fever.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Process</th>
<th>Clinical Clues to Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoedema</td>
<td>May resemble cellulitis, but lower limb is not as warm as typical cellulitis. Elevation and compression therapy causes erythema to disappear.</td>
</tr>
<tr>
<td>Carcinoma erysipelatoides</td>
<td>Malignancy affecting the lymphatics of the lower extremities can closely mimic cellulitis</td>
</tr>
<tr>
<td>Erythromelalgia</td>
<td>Rare disorder; episodes of heat burning redness provoked by heat and dependency and relieved by elevation and cooling.</td>
</tr>
<tr>
<td>Hereditary periodic fevers</td>
<td></td>
</tr>
<tr>
<td>Familial Mediterranean Fever</td>
<td>Rare, periodic fevers, arthritis, chest pain, well demarcated warm tender plaques on legs and feet. May be bilateral.</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>Ulcerative condition of skin; Inflammatory bowel disease, leukaemia, rheumatoides; papule progresses to ulcer with violaceous borders.</td>
</tr>
<tr>
<td>Eosinophilic cellulitis (Wells’ syndrome)</td>
<td>Dermal eosinophil infiltration; eosinophilia; multiple, pruritic, erythematous plaques; recurrent.</td>
</tr>
<tr>
<td>Acute febrile neutrophilic dermatosis (Sweet’s syndrome)</td>
<td>Idiopathic neutrophilic skin plaque eruption; associated with haematological malignancy; Erythematous, tender plaques on face, neck, arms; fever.</td>
</tr>
</tbody>
</table>
1.10 Complications

Most episodes of cellulitis are treatable with oral antibiotics active against gram-positive organisms, however prolonged inpatient treatment, infection recurrence, chronic oedema, tissue ulceration and necrotising infection are potential complications (2, 4). Recurrent infections occur in up to 57% of patients with cellulitis, predisposing to post-cellulitic oedema and further episodes of recurrence (4, 44, 45).

In a review of the population-based mortality rate from erysipelas spanning pre-and post- antibiotic eras it was shown that the introduction of sulfonamide antibiotic treatment followed by penicillin, dramatically reduced the mortality rate associated with “erysipelas, major abscesses, wound infections and ulcer infections” (46). Figure 1.3 demonstrates this reduction in mortality rate described in two different population-based studies. The first study was from the US between 1929-1938, and the second study was from Norway.

More recent data concerning the mortality rate associated with infections of the skin and deeper soft tissues (surgical site infections and diabetic foot infections) has been shown to range from 0.4% to 5.2% depending on the study population (47, 48).
Figure 1.3: Mortality rates associated with erysipelas before and after the introduction of antibiotic treatment

A: Cook County Hospital (US) 1929-1938 (49); B: National Registry in Norway (50). Figures from Spellberg B et al (46).

Sulfa: Sulfonamide; PCN: Penicillin
1.11 Microbiological diagnosis

The diagnosis of cellulitis is based on clinical impression (32). Ancillary investigations have been shown to be of little utility. Of the few CPGs pertaining to the diagnosis and management of cellulitis that exist (1, 3, 32, 34, 51, 52), none recommends ancillary investigations for diagnostic purposes, while two (3, 52) recommend serum WCC measurement for the purposes of risk stratifying mild and severe infections.

It has been shown that attempts to culture bacteria from cellulitis has a low yield. Culture of needle aspiration from inflamed skin yields positive cultures in between 5% to 40% of cases (53-55). Culture of punch biopsy specimens yield bacterial growth in less than 30% of cases (55). A systematic review of the published literature, which included adult patients with bacteraemia secondary to cellulitis and erysipelas, showed that between 4.6% and 7.9% of patients with erysipelas and cellulitis respectively, had positive blood cultures (56). Combined data from specimen cultures, serologic studies, and immunohistochemical staining suggest that the majority of infections arise from streptococci, in particular group A streptococci (3, 57).

*S. aureus* is believed to be a less common cause of cellulitis, but may be associated with open wounds or penetrating injury, including from injection sites among IV drug users (2, 3, 13). In a prospective study of 173 patients with non-purulent cellulitis who were admitted to a US hospital from a community with endemic CA-MRSA, beta-haemolytic streptococci were detected using anti-streptolysin-O and anti-DNAse-B assays in 73% of cases. Since almost 98% of cases responded to beta-lactam antibiotics, the authors concluded that beta-haemolytic streptococci appeared to account for most cases of non-purulent cellulitis, even in the presence of endemic CA-MRSA infection (57). As discussed above, CA-MRSA is believed to be associated with purulent infections such as abscesses, wound infections and septic bursitis rather than non-purulent cellulitis.

The CPG issued by the IDSA group recommends that cultures of blood, tissue or skin are unnecessary for cellulitis (3). In patients with malignancy, severe systemic features of infection, and unusual predisposing factors such as immersion injury, animal bites, neutropenia and cell-mediated immunodeficiency,
blood cultures should be obtained and cultures of aspirate or skin biopsy considered (3).

1.12 Management strategies

A variety of treatment strategies exist for cellulitis, both in terms of healthcare settings and antibiotic treatment options. Traditionally, patients attending an ED with cellulitis were either discharged to the community on oral antibiotic treatment, or admitted to hospital for IV antibiotic treatment. Over the past two decades however, alternative pathways for treating ED patients with cellulitis have evolved. OPAT programs and EDOUs are well established in many countries worldwide, and provide effective alternatives to hospital admission (58).

1.13 ED management of cellulitis

EDOUs provide an alternative to hospital admission for selected patients with cellulitis. OUs are useful for the short-term treatment and management of patients with a variety of medical conditions, including chest pain, asthma, syncope and cellulitis, which are believed to comprise between 1-5% of all EOU patients (59). Predicting which patients with cellulitis (termed SSTIs in most of the published US literature) will require more than 24 hours of treatment in an OU is most commonly based on the clinical judgment of the treating clinician (60). There are few studies which have examined objective criteria that may be used to predict which patients will require greater than 24 hours of OU treatment for cellulitis (60, 61).

1.14 OPAT for cellulitis

OPAT is increasingly being used to shorten or avoid hospital admission for ED patients with cellulitis (62). It usually consists of daily visits by a health care provider and the administration of IV antibiotics in the patient’s home. Given its increasing use in European healthcare settings and more recently in Ireland, knowledge of which patient-specific risk factors are associated with the requirement for hospital admission or change in type or duration of antibiotic treatment prescribed is important in order to design and configure service delivery appropriately (63). WP-5 of this thesis measures the rate of adjustment of empiric
IV antibiotic treatment and hospital readmission among patients enrolled to an Irish OPAT service (the VhiHomeCare service). Additionally, risk factors for adjustment of empiric IV antibiotic treatment, IV antibiotic treatment for more than seven days and antibiotic treatment regimens prescribed to patients enrolled to the service are described.

In addition to OPAT, some EDs may provide daily outpatient IV treatment review clinics (64). Two studies from Canada have examined the management of cellulitis treated in ED daily review clinics (64, 65). To the best of my knowledge, this model of care does not currently exist in EDs in Ireland.

1.15 Antibiotic therapy

Empirically prescribed antibiotic therapies for cellulitis vary significantly in type, route and duration among EPs (66) and inpatient hospital physicians (52). Adherence to published guideline recommendations for the management of patients with cellulitis has also been shown to be poor (32, 51, 67). A recent audit of 23 acute NHS Trusts in the UK, revealed that there was significant heterogeneity in the choice of antibiotics utilised for the treatment of cellulitis, the mode of administration, and the duration of therapy (68).

Penicillin, either as flucloxacillin alone or combined with penicillin V, is the standard antibiotic regimen for the treatment of cellulitis in Ireland, the UK and France (2, 51, 69). Clinicians, in both the UK and Ireland commonly prescribe a combination of flucloxacillin and penicillin V for the treatment of cellulitis despite a lack of RCT-based evidence for or against this combination therapy (2, 70). A Cochrane Review that examined 25 RCTs of cellulitis therapy, found no clearly superior, single treatment for cellulitis (13). Figure 1.2 describes the IDSA-recommended antibiotic treatment options for purulent and non-purulent SSTIs, which necessarily accounts for a high endemic rate of CA-MRSA.

A retrospective observational study of the management of cellulitis performed in a UK hospital, showed that hospital physicians frequently over-treated infections defined as “mild” on an established CPG and undertreated infections defined as “severe” (52). This equipoise in terms of which type and route of antibiotic therapy to administer to patients with cellulitis indicates a lack of objective evidence with which to risk stratify patients with cellulitis in acute clinical settings.
Several expert panel recommendations and practice guidelines for the management of cellulitis exist, although none have been formulated specifically for ED use (1, 3, 32, 51, 67). In this thesis, I report the management of cellulitis in a cross section of Irish EDs, and physician adherence to existing CPGs.

1.16 The importance of measuring antibiotic treatment failure

Failure of empirically prescribed antibiotic treatment for cellulitis is dependent on several different host and infection-related factors (71). Host factors, such as adherence to the prescribed antibiotic treatment regimen, social determinants of health, and reduced immunity in an ageing population may be contributory (71). Poor adherence to prescribed antibiotic therapy has been shown to lead to antibiotic treatment failure and the encouragement of selection of resistant bacteria (72). Factors related to the type of antibiotic prescribed, such as allergy, changing antibiotic dose and duration of treatment, also influences treatment failure (71). Finally, pathogen-related factors such as changing virulence and antibiotic resistance are important (71, 73).

When initiating treatment for an episode of cellulitis, clinicians attempt to minimise the risk of treatment failure while containing the costs of care and the risk of fostering antibiotic resistance (3). It has been shown that antibiotic treatment failure for “complicated” cellulitis in hospitalised patients is associated with a three-fold increased mortality rate (OR 2.91; 95% CI 2.34-3.62), prolonged duration of antibiotic treatment, longer hospital length of hospital stay and significantly increased costs (74).

The rate of antibiotic treatment failure for cellulitis treated in ED settings in Ireland is unknown. Furthermore, the association between patient risk factors and treatment failure has not been previously described in our setting. Knowledge of which patient-specific risk factors are associated with empirically prescribed oral antibiotic treatment failure, would provide an evidence-based approach for EPs to risk-stratify patients with cellulitis during their initial ED attendance.

In WP-6 of this thesis, I report a multicentre prospective observational cohort study of adult patients attending three EDs with cellulitis. It is the first study in Ireland to
measure the rate of empirically prescribed oral antibiotic treatment failure for patients presenting to the ED with cellulitis. The study defined treatment failure in two ways. The first definition, the primary outcome measure of the study, defined treatment failure as the requirement for IV antibiotic treatment after an initial course of empirically prescribed oral antibiotic treatment, to achieve a treatment response. The second definition of treatment failure, a secondary outcome measure of the study, was a change in the initial course of empirically prescribed oral antibiotic to another course of oral antibiotic, or a change in the prescribed dose of the initial course of empirically prescribed oral antibiotic to a higher dose of the same antibiotic. The other secondary outcome measures included inter-observer reliability for patient risk factor assessment and assessment of the eligibility and loss to follow-up rate among enrolled patients. This was performed as a pilot study to assess the feasibility of developing a CPR regarding the appropriateness of empirically prescribed oral or IV treatment for ED patients presenting with acute cellulitis.
1.17 Thesis aims and objectives

The overarching aim of this thesis is to describe the rate and risk factors for empirically prescribed oral antibiotic treatment failure for adult ED patients presenting with acute cellulitis.

The specific aims of this thesis are to:

1) describe the global research output pertaining to SSTIs and the impact of the CA-MRSA epidemic on research output;
2) describe the current ED management of cellulitis, physician adherence to CPGs for cellulitis and prescribing practices for cellulitis in Irish EDs;
3) describe the aetiological epidemiology of cellulitis in order to cohere the existing evidence base;
4) identify which patient-specific risk factors should be measured for an association with empirically prescribed initial oral antibiotic treatment failure;
5) describe the rate and risk factors for adjustment of empirically prescribed IV antibiotic treatment for cellulitis among patients treated in an OPAT service;
6) describe the treatment failure rate and patient specific risk factors associated with empirically prescribed oral antibiotic ED treatment failure of cellulitis;
7) assess the feasibility of developing a CPR regarding the appropriateness of empirically prescribed oral or IV treatment for ED patients presenting with acute cellulitis.
1.1.1 WP-1: Research output relevant to SSTIs, 1945-2014 a scientometric analysis

*Aim:* To set the scene for the thesis by evaluating the global breadth of research relevant to SSTIs and establish possible future research directions.

*Specific Objectives:*

1) to establish the importance of SSTIs in the context of research yield using scientometric indices;
2) to identify the most cited publications of the past 65 years;
3) to identify events associated with temporal trends in research output;
4) to determine the association between the CA-MRSA epidemic and research output relevant to SSTIs.

1.1.2 WP-2: A pilot cross-sectional study of patients presenting with cellulitis to EDs

*Aims:* To assess the feasibility of a large, full-scale study aimed at characterising the patients who present with cellulitis to EDs in Ireland.

*Specific Objectives:*

1) to measure the prevalence of patients presenting with cellulitis to EDs in Ireland;
2) to measure adherence to the CREST guideline recommendations in terms of predicting the ED management of patients presenting with cellulitis;
3) to determine clinical and epidemiological factors which may predict route of antibiotic therapy;
4) to describe antibiotic prescribing practices for the ED treatment of cellulitis.
1.1.3 WP-3: The management of cellulitis in EDs: antibiotic-prescribing practices and adherence to practice guidelines in Ireland

**Aim:** To perform a larger, full-scale study aimed at characterising the antibiotic prescribing practices for the treatment of patients who present with cellulitis to EDs in Ireland.

**Specific Objectives:**

1) to identify patient variables associated with the prescription of IV antibiotics.

2) to describe the potential utility of three published guidelines for the management of cellulitis in the ED setting.

1.1.4 WP-4: A systematic review and meta-analysis of risk factors for non-purulent leg cellulitis

**Aim:** To identify and cohere all studies which have examined risk factors for the development of leg cellulitis that may be relevant to measuring antibiotic treatment failure in the ED management of cellulitis.

**Specific Objectives:**

1) to perform a systematic literature review of relevant controlled observational studies;

2) to perform quality assessment of the identified studies using the NOS;

3) to perform data synthesis and meta-analysis;

4) to cohere the existing evidence base concerning risk factors for developing cellulitis for future research, especially in relation to antibiotic treatment failure in the ED management of cellulitis;
1.1.5 WP-5: Risk factors for amendment in type, duration and setting of prescribed IV antibiotics for adult patients with cellulitis: a retrospective cohort study and CART analysis

*Aim:* To measure the factors associated with treatment failure of IV antibiotics in the management of patients with cellulitis.

**Specific Objectives:**

1) to measure the rate of IV treatment amendment, defined *a priori* as hospital admission, change in dose or type of antibiotic, or addition of antibiotic in order to achieve response;

2) to identify risk factors for IV treatment amendment;

3) to describe risk factors for duration of IV treatment of more than 7 days;

4) to describe physician IV antibiotic prescribing practices for the management of cellulitis;

5) to perform a CART analysis aimed at predicting IV antibiotic treatment adjustment risk factors in cellulitis.

1.1.6 WP-6: Prevalence and predictors of initial oral antibiotic treatment failure in adult ED patients with cellulitis: a pilot study.

*Aim:* To identify the treatment failure rate of empirically prescribed oral antibiotic therapy for ED patients discharged with cellulitis.

**Specific Objectives:**

1) to pilot a standardised clinical assessment for ED patients with cellulitis, incorporating variables from medical history, clinical examination and
investigation, including a pain numerical rating scale and physician-reported assessment scale;

2) to determine the treatment failure rate, the loss-to-follow-up rate and the proportion of eligible patients who enrol in the study;

3) to investigate the relationship between patient specific risk factors and treatment failure.

4) To evaluate reasons why patients are not eligible in order to determine if eligibility criteria needs to be changed for a larger, full-scale study.

5) To assess interobserver reliability regarding the assessment of patient specific risk factor.
1.18 Thesis outline

This thesis consists of 6 different WPs. It is presented in 8 chapters. Chapter 2 provides a description of the research methods utilised in the 6 WPs contributing to this thesis and a brief introduction to CPR research methodology. Chapter 3 reports an evaluation of the global breadth of research relevant to SSTIs and establishes possible future research directions (WP-1). Chapter 4 describes the current ED incidence, antibiotic prescribing practices and adherence to guideline recommendations relevant to the ED treatment of cellulitis in Ireland. Two observational studies are described (WP-2 and WP-3). Chapter 5 is a SRMA of case control studies examining risk factors for the development of cellulitis (WP-4). This SRMA identified several clinical risk factors for developing cellulitis which were also chosen for investigation as possible risk factors for antibiotic treatment failure. Chapter 6 describes a retrospective cohort study of risk factors for adjustment in type, duration and setting of prescribed IV antibiotics for adult patients with cellulitis (WP-5). Chapter 7 is a prospective cohort study examining the prevalence and predictors of oral antibiotic treatment failure among adult ED patients with cellulitis (WP-6). Finally, chapter 8 is a discussion of the thesis findings and recommendations for future research.
Chapter 2: Methods

In this chapter I begin with a brief discussion of a scientometric analysis of research relevant to SSTIs followed by a discussion of the methods used in WP-1. A brief introduction to CPR methodology then follows. In this section the hierarchy of evidence for developing and evaluating CPRs is described. In addition, techniques for deriving CPRs are briefly described in order to contextualise the subsequent thesis WPs.

I then describe WP-2, a pilot cross-sectional study for WP-3 aimed at measuring the prevalence of cellulitis in Irish EDs and characterising the antibiotic prescribing practices for the treatment of patients who present with cellulitis to EDs in Ireland. Study methodology for WP-4, a SRMA of observational research aimed at identifying risk factors for cellulitis, then follows.

Study methodology for WP-5, a retrospective cohort study of risk factors for the adjustment of initial empirically prescribed IV antibiotic treatment for adult patients with cellulitis is described. In addition, risk factors for IV antibiotic treatment of cellulitis for more than 7-days, IV antibiotic prescribing practices for cellulitis among OPAT physicians, and a CART analysis for predicting amendment of IV antibiotic treatment are described.

Finally, the study methodology for WP-6, a prospective cohort study of the prevalence and predictors for initial empirically prescribed oral antibiotic treatment failure among adult ED patients with cellulitis, is described.

2.1 WP-1 Methodology: Research output relevant to SSTIs (1945-2014): a scientometric analysis.

Scientometrics is concerned with the measurement of science, it’s growth, structure, inter-relationship and productivity (75). It involves the quantitative study of scientific activity including publication, and so overlaps with bibliometric analysis (76). The importance of quantitative and qualitative assessment of scientific output has increased in tandem with increased research output across all disciplines, and these assessments now play an important role in terms of grant funding and resource prioritisation (77). Additionally scientometric analyses
provide an important context for the temporal evolution of a disease over time. Findings from scientometrics can help researchers to realise the breadth of research in the field and establish possible future research directions (78).

For WP-1, data was retrieved from the WOS SCI-E database from 1945 to 2014 and CPCI-S from 1990 to 2014, produced by Thomson Reuters. I employed a broad search strategy aimed at capturing the overall number of published items on SSTIs as follows: (cellulitis) OR (erysipelas) OR (skin and soft tissue infection$) OR (skin infection$) OR (soft tissue infection) OR (cutaneous abscess) OR (skin abscess) OR (necroti$ing fasciitis) where $ = any character. There were no restrictions in the search strategy used in terms of document type, language or geographical region. The search was from 1945 to 2014. The search was performed on the 20th May 2015, however 2015 was not included in our results as database entries for 2015 were not complete at the time of the search.

The search was restricted to articles relevant to human life sciences only.

A second search using the terms (community-associated methicillin-resistant Staphylococcus aureus) OR (community-onset methicillin-resistant Staphylococcus aureus) OR (CA-MRSA) was also performed and combined with the primary search results. I included only those research publications that assessed CA-MRSA-associated SSTIs by performing a title and abstract review. SSTIs arising from hospital-acquired MRSA were therefore not included.

Publications were analysed using WOS Citation Report Manager. Journals containing the most highly cited articles were categorised using Microsoft Excel. This was performed yearly between 1990 and 2015, for each decade between 1950 and 1989 and for the 5 years between 1945 and 1950. I assessed the number of citations per year and the citation rate per item as a proxy of research productivity. I also measured the h-index. The h-index is based on the depth of years of the product registration in a selected timespan. For example, a h-index of “20” means that there were 20 items with at least 20 citations. The advantage of this metric is that it discounts disproportionate weight of highly cited papers or papers that have not yet been cited.
2.2 CPR methodology

CPRs are clinical tools that quantify the contribution of the history, physical examination and diagnostic tests and assist in the stratification of patients according to the probability of having a target disorder (79). They are designed to reduce clinical uncertainty in an outcome by assessing the strength of association between the risk of the outcome occurring and baseline characteristics (79), and should incorporate 3 or more variables from the history, physical examination or simple tests (80). CPRs were originally intended to “help physicians interpret clinical information...(and) know what clinical data are important to obtain” (81).

The distinction between “CPRs” and “clinical decision rules” is important to recognise (82). CPRs only become clinical decision rules once clinicians use the predictive models to help make decisions for patients (79). The 4 levels of evidence characterising CPRs have been defined by the Evidence Based Medicine Working Group, and adapted by Reilly et al in the table displayed below (Table 2.1).
### Table 2.1 Developing and Evaluating CPRs
Adapted from Reilly et al (79) and McGinn et al (83)

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Definition and Standards of Evaluation</th>
<th>Implications for Clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1: Derivation of prediction rule</strong></td>
<td>Identification of predictors using multivariable model; blinded assessment of outcomes</td>
<td>Needs validation and further evaluation before used for patient care</td>
</tr>
<tr>
<td><strong>Level 2: Narrow validation of prediction rule</strong></td>
<td>Verification of predictors when tested prospectively in one setting; blinded assessment of outcomes</td>
<td>Needs validation in varied settings; may use predictors cautiously in patients similar to sample studied</td>
</tr>
<tr>
<td><strong>Level 3: Broad validation of prediction rule</strong></td>
<td>Verification of predictive model in varied setting with wide spectrum of patients and physicians</td>
<td>Needs impact analysis; may use prediction with confidence in their accuracy</td>
</tr>
<tr>
<td><strong>Level 4: Narrow impact analysis of prediction rule used as decision rule</strong></td>
<td>Prospective demonstration in one setting that use of the prediction rule improves physicians decisions (quality or cost-effectiveness of patient care)</td>
<td>May use cautiously to inform decisions in settings similar to that studied</td>
</tr>
<tr>
<td><strong>Level 5: Broad impact analysis of prediction rule used as decision rule</strong></td>
<td>Prospective demonstration in varied settings that use of prediction rule improves physicians decisions for a wide spectrum of patients</td>
<td>May use in varied settings with confidence that its use will benefit patient care, quality or effectiveness</td>
</tr>
</tbody>
</table>

### 2.3 Types of prediction models

In 2006, Grobman et al (84) described five methods of CPR derivation which are summarised in Table 2.2.
Table 2.2: Techniques for the development of a CPR

From Grobman et al (84)

<table>
<thead>
<tr>
<th>Type of model</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoring system derived from univariate analysis</td>
<td>Simple statistical models usually allocated a &quot;score&quot;</td>
<td>Arbitrary manner of weighting scores and inclusion of non-independent risk factors;</td>
</tr>
<tr>
<td>Prediction model based on multivariable logistic regression</td>
<td>Use of logistic regression analysis in observational research; more accurate assessment of association between variable and outcome</td>
<td>Assumption of linear relationship between dependent and independent variables; time-consuming</td>
</tr>
<tr>
<td>Predictive nomograms</td>
<td>Of variable complexity; accounts for interaction of multiple independent variables and presents these in a graphic form to the clinician</td>
<td>Complex interactions can be made simple to analyse</td>
</tr>
<tr>
<td>Classification and Regression Tree analysis</td>
<td>Recursive partitioning technique</td>
<td>Accounts for complex relationships; simple presentations of data; binary decision processes can lead to inaccuracies</td>
</tr>
<tr>
<td>Artificial neural networks</td>
<td>Complex mathematical models based on biological neural networks</td>
<td>Require significant computational resources; may not transfer to bedside setting; over-fitting; new technique with limited experience.</td>
</tr>
</tbody>
</table>

In WP-5, I assessed risk factors for initial empirically prescribed IV antibiotic treatment failure using CART analysis. CART is a data-mining tool based on recursive binary partitioning. The term “binary” implies that each group of patients, represented by a “node” in a decision tree, can only be split into two groups (85). Thus, each node can be split into two child nodes, in which case the original node is called a parent node. The term “recursive” refers to the fact that the binary partitioning process can be applied over and over again. A tree is grown until further splitting cannot reduce the residual sum of squares. One of the principal advantages of regression trees over more traditional techniques is that if a covariate has no influence on the outcome, it will not be included in the fitted tree.
CART analysis is intuitively useful for the clinician to use. In the CART displayed in Figure 2.1, the clinician simply follows the paths of the tree that describe the characteristics of the patient being evaluated and arrives at the prediction of the outcome of interest. However an important restriction to the utility of CART analysis occurs if there are too few instances of the outcome of interest occurring to obtain reliable predictions, or “too few leaves on the trees” as termed by Bellazzi et al (86). Sabbaj et al reported a useful CART analysis of predictors for prolonged EDOU stay in ED patients with a diagnosis of nonfacial soft tissue infection (60). A diagrammatic representation of their high sensitivity CART figure is included below; it clearly displays the intuitive decision process that may assist bedside clinical decision-making and clinician’s decisions about patient disposition.
Figure 2.2 High sensitivity decision tree for identifying patients requiring greater than 24-hours of EDOU stay

From Sabbaj et al (60)
2.4 WP-2 Methodology: A pilot cross sectional study of patients presenting with cellulitis to EDs

This cross-sectional study was performed in the EDs of the MRHT, MRHM and MRHP. The combined annual census of the three participating EDs is approximately 87,000. The HSE Midlands Area REC approved the study.

Consecutive adult patients aged > 18 years presenting with cellulitis over a one-month period, were invited to participate and written consent obtained. Cellulitis was diagnosed when any 2 of the following signs were present in any body part: erythema, warmth, tenderness, swelling and regional lymphadenopathy. The treating EP completed a study-specific data collection form during the clinical assessment (Appendix file 1). Demographic and epidemiological data on patient age, gender, patient referral source, previous episodes of cellulitis, pre-ED antibiotic treatment, and discharge or admission antibiotic treatment were recorded. Assessment for causes of cellulitis and local risk factors predisposing to the development of cellulitis included examination for tinea pedis or evidence of interdigital maceration of the feet (athlete’s foot), lymphoedema (defined as a chronic swelling of the leg with premorbid pitting oedema), and venous disease (manifesting as venous ulcers, venous eczema and/or varicose veins). The presence or absence of general risk factors for cellulitis (BMI > 30kg/m², diabetes mellitus, previously diagnosed peripheral vascular disease, chronic renal and liver disease, chronic steroid use and asplenia) was recorded. This clinical data was retrieved from the patient referral documentation (for example, GP referral letter), the patient history or any existing hospital chart at the time of patient recruitment to participate in the study. Information on lesion location, lesion size and duration of symptoms was also recorded. Each patient was allocated to a disease severity class based on the CREST guidelines by the treating doctor (see Table 4.1 for description of CREST guideline).

2.4.1 Data and statistical analysis

Descriptive statistics using odds ratios with 95% CIs was planned. I also planned to perform CART analysis, provided there were sufficient occurrences of each outcome to allow analysis. MVLR analysis was used to model outcomes and find predictors for each of the outcome variables. Descriptive statistics were
performed, and ORs were calculated, using SPSS statistical software (Version 20.0).
2.5 WP-3 Methodology: The management of cellulitis in EDs: antibiotic prescribing practices and adherence to practice guidelines in Ireland

This was a multicentre, prospective cohort study. Consecutive patients were recruited from 6 EDs in Ireland, each with an annual census of 30-50,000 patients, over a one-month period. The recruiting EDs were located in the Irish Midlands (MRHT), the west (University Hospital Limerick) and south coasts of Ireland (Cork University Hospital and Waterford University Hospital) and Dublin (Connolly Hospital Blanchardstown and Beaumont Hospital). Outpatient IV antibiotic therapy programs were not in use in any of the participating EDs at the time of enrolment. I therefore used the prescription of IV antibiotics, instead of hospital admission, as a surrogate marker of infection severity. REC approval was obtained from the hospital of each participating ED. At enrolment, written informed consent was obtained.

Consecutive patients aged over 18 years presenting to the participating EDs with cellulitis of any body part, were considered eligible for enrolment on a 24/7 basis. The recruiting EP prospectively collected study data by interview with the patient and physical examination. CRFs detailing each of the predictor variables for infection severity were completed in a prospective, unblinded fashion by the recruiting EP at the patient’s bedside. All predictor variables were based on a literature review, agreed upon by the investigative team, and had been previously piloted in WP-2 (see Appendix file 1).

2.5.1 Patient selection and outcome measurement

Cellulitis was diagnosed as recent onset of typical features of cellulitis including any 2 of the following: erythema, warmth, tenderness, swelling and regional lymphadenopathy. Patients with an abscess without co-existing signs of cellulitis were excluded. Patient vital signs were recorded. Fever was defined as tympanic membrane temperature reading exceeding 37.5°C. A description of each of the guidelines used in this study is described on Table 4.1. The CREST score and SEWS were fully transcribed on the CRF and recruiting EPs were asked to record specific scores for each patient enrolled. The modified-CREST and Ki-Rotstein scores were calculated from the recorded CREST score and SEWS.
2.5.2 Data and statistical analysis

Descriptive statistics were performed. For each significant risk factor ORs and 95% CIs were calculated. Predictor variables chosen for inclusion in the MVLR model were selected by using multiple 2X2 analyses in those variables that emerged from the univariate analysis. Univariate analyses were carried out for all variables where there were sufficient occurrences of the event to be meaningful (> 1-2 occurrences). Forward and backward step-wise regression analysis was performed. A significance level of 0.05 was used to include a variable to the model and a P-value of 0.1 was used before excluding a variable from the model. Statistical analysis was performed using SPSS software, version 20.0 (Chicago, Illinois, USA).
2.6 WP-4 Methodology: Risk factors for the development of leg cellulitis - a SRMA of case-control studies.

2.6.1 Study design

This was a SRMA of case control studies examining risk factors for the development of non-purulent cellulitis of the leg. The design of this review conforms to the MOOSE and PRISMA guidelines (87, 88). Details of the study protocol for this systematic review were prospectively registered on PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009693.

2.6.2 Study setting and population

The study population included all patients with a clinical diagnosis of non-purulent cellulitis treated in an inpatient or outpatient healthcare setting. Non-purulent cellulitis was defined as a spreading infection of the dermal and subdermal tissues of the leg due to a suspected or presumed bacterial aetiology (13).

2.6.3 Literature search

A systematic literature search was performed from 1945 up to July 2015 using the following electronic databases: CENTRAL, MEDLINE and EMBASE. Searching of grey literature databases (OpenGrey, NLM gateway, Google Scholar) was supplemented by hand searching the references of retrieved articles. I searched for ongoing studies relevant to our research question in the 5 trial registries recommended by the Cochrane Skin Group: The Australia New Zealand CTR, World Health Organisation CTR, The EU CTR, The US National Institutes of Health Ongoing Trials Registry, and the metaRegister of Controlled Trials.

I generated the search strategy with a medical librarian. Keywords and medical subject heading terms including “cellulitis” OR “erysipelas” OR “skin infection” OR “skin and soft tissue infection” OR “Soft tissue infection” OR “soft” AND “tissue” AND “infection” OR “acute bacterial skin and skin structure infection” OR “ABSSSI” AND “risk factor” were used in the search strategy. There were no language restrictions imposed. Google Translate ™ was used to translate relevant journals.
to English where necessary. All results were exported to EndNote™. Duplicates were detected using EndNote software.

2.6.4 Selection process

Titles and abstracts of potentially eligible studies were independently screened for the inclusion criteria by two study investigators. Cohen’s kappa was used to assess inter-observer reliability. Full-text versions of potentially eligible studies were obtained if it was felt a potentially eligible study met the inclusion criteria, or if it could not be decided after the initial screening of the title and abstract whether the study met the inclusion criteria. Any disagreement between the two investigators was resolved by discussion and consensus with a third investigator.

2.6.5 Inclusion and exclusion criteria

Epidemiological studies have shown that non-purulent cellulitis is the most common form of cellulitis encountered in acute care settings in the UK and Ireland (19, 89-91). Therefore the study population was restricted to patients with non-purulent cellulitis. Furthermore, although there has been a significant increase in the ED incidence of purulent cellulitis secondary to the CA-MRSA epidemic in the US, it is notable that non-purulent cellulitis, which is not associated with purulent discharge, exudate or abscess, is still a major burden in those areas where CA-MRSA is endemic (7, 66). Any controlled observational study that assessed at least 1 risk factor for the development of non-purulent leg cellulitis was eligible for inclusion. Studies that used a control group were selected in order to allow calculation of the relative importance of each predictor variable, and to allow for the calculation of ORs. The literature search was limited to cellulitis of the leg for two reasons. Firstly, it is the body part most commonly affected by cellulitis. Secondly, summary estimates of the effect of risk factors for cellulitis affecting other anatomical sites would have made it impossible to validly pool the studies due to significant heterogeneity of the included studies.

Uncontrolled observational studies, case reports, letters, surveys, conference proceedings, and review articles were excluded. In addition, studies of risk factors for the following conditions were excluded:

a. Purulent cellulitis;
b. Cellulitis in specific populations (e.g. cirrhosis, lymphoedema, rheumatoid arthritis);

c. Recurrent cellulitis, furunculosis alone or necrotising fasciitis;

d. Studies of antibiotic treatment failure.

2.6.6 Quality assessment

The methodological quality of included studies was evaluated using the NOS (92). The NOS is based on a cumulative score in each of three categories: selection of study groups, comparability of cases and controls, and ascertainment of the outcome / exposure in cases and controls. If a study fulfills the criteria for an item, a score of 1 star is allocated, with the exception of comparability which can score up to 2 stars, resulting in a maximum score of 9 stars. Studies were classified as having a high ROB if the total score was 1–3 stars, medium ROB if the total was 4–5 stars, or low ROB if there were 6–9 stars. Two investigators independently assessed methodological quality, with any disagreement resolved by discussion and consensus. The NOS and coding manual is available in the Appendix (Appendix file 2 and Appendix file 3)

2.6.7 Data synthesis and statistical analysis.

For each included study two investigators independently extracted the following data using a study-specific data abstraction form: first author, publication year, country, study design and setting, number of cases and controls, patient characteristics, type and location of infection(s), risk-factors measured, and authors conclusions. I contacted the authors by email to find out if further information relevant to the systematic review was available. The risk factors chosen for meta-analysis were required to be present in at least 50% of included studies and similar in terms of their clinical definition(s). The $I^2$ statistic was used to describe the percentage of total variation across studies that was due to heterogeneity rather than chance (93). Significant statistical heterogeneity was considered to be present if the $I^2$ statistic was greater than 50%. Both fixed and random effects models were used to analyse results. When the $I^2$ statistic was
greater than 50%, the random effects model was applied. When the $I^2$ was less than 50%, the fixed effects model was applied. The random effects model takes into account between-study, and within-study, variability. Individual study characteristics were also reviewed for potential sources of heterogeneity. Results are reported as OR and 95% CI. Additionally, funnel plot analysis was used to assess publication bias. The statistical analysis was conducted using the Cochrane Collaboration’s Review Manager (94).
2.7 WP-5 Methodology: Risk factors for amendment in type, duration and setting of prescribed IV antibiotics for adult patients with cellulitis: a retrospective cohort study and CART analysis.

OPAT is often used shorten or avoid hospital admission for patients with cellulitis and other ABSSSIs (62, 63). It is well established in many healthcare systems internationally, and has been shown to be practical, safe, well-tolerated and efficacious (95). The Vhi HomeCare Service provides the largest OPAT service to patients in the east of Ireland and is accredited by the JCI (96). The service treats on average 127 patients with cellulitis per year, with referrals for cellulitis accounting for 13% of all referrals to the service. Patients may be referred directly from EDs, the community or following hospital admission in order to complete treatment at home.

This was a retrospective cohort study of a prospectively maintained database, owned and operated by Vhi Homecare. This study was approved by Beaumont Hospital REC in June 2015 (Ref 15/53), and by the Board of Directors of Vhi HomeCare in July 2015.

2.7.1 Study setting and population

Consecutive patients with cellulitis referred to the Vhi HomeCare Service between 2010 and 2015 by GPs, EPs or hospital clinicians, were eligible for enrolment. Patients referred from hospital wards or EDs for completion therapy at home are assessed pre-discharge, with follow-up physician assessment within 24 hours. GP referrals are assessed at home within 24 hours.

At the time of writing, first-line treatment was with IV flucloxacillin 1 - 2 grams four times daily, either alone or combined with IV benzylpenicillin 1.2 - 2.4g four times daily at the treating OPAT-physician’s discretion. Patients allergic to beta-lactam antibiotics were administered IV clindamycin 300mg four times daily. Treatment for confirmed MRSA isolated from an infected wound was with IV vancomycin 1 g twice daily.
An EPMS was prospectively maintained for each patient enrolled. The EPMS is a secure online database containing physician and nursing care plans, both as binary prompts for each of the relevant descriptor elements of the patient’s history and examination, and as a free text source. Laboratory investigations including WCC and CRP were monitored at least every 3 days. Treatment success and IV to oral switch was clinically determined using physician discretion based on clinical signs, symptoms and laboratory results.

2.7.2 Study protocol and measurements

Excluded patients included those with diabetic foot ulcer, pressure sores, bilateral cellulitis, suspected osteomyelitis, septic arthritis, necrotising fasciitis, abscesses and those who refused to consent to third party information sharing. I created a study-specific data abstraction form containing 40 clinical variables including demographic information, vital signs, general and local cellulitis risk factors, laboratory results and cellulitis mechanism (Appendix file 4). Data was abstracted from the EPMS by an independent study researcher who was blinded to patient outcome measures.

The primary outcome for the study was to measure the rate of TA, defined a priori as hospital admission, change in dose or type of antibiotic, or addition of antibiotic in order to achieve response. Secondary outcomes were to identify risk factors for TA and duration of treatment exceeding 7 days. Physician antibiotic prescribing practices were also described.

2.7.3 Statistical methods

Categorical variables were reported in terms of number of items in a category and percentages. Continuous variables were reported as medians and IQRs. The primary outcome was assessed for risk factors using univariate logistic regression followed by MVLR to test for independence of association. An optimal parsimonious model was derived using the BIC and was tested for goodness-of-fit with the Homer-Lemeshow method. CART analysis was also performed in order to derive and cross-validate a decision rule for predicting OPAT amendment. The predictive tree was assessed for sensitivity and specificity, and compared with
logistic regression using ROC curve analysis. Duration of OPAT was assessed using linear regression. Univariate, followed by MVLR analysis was conducted to assess variables for association with duration. Only independently significant results in the multifactorial models were presented in the tables. A P value less than 0.05 was considered statistically significant.

Statistical analyses were performed using Stata (version 13, College Station, Texas) and R (version 2.10 The R Foundation) software.
2.8 WP-6 Methodology: Prevalence and predictors of initial oral antibiotic treatment failure in adult ED patients with cellulitis: a pilot study.

2.8.1 Study design and setting

A prospective observational cohort study of consecutive patients attending three urban EDs (BH, MMUH and CHB) in Dublin, Ireland, was performed. The combined annual ED patient attendance of the three EDs is approximately 150,000 patients. The protocol was approved by each hospital’s REC, published in an open access, peer-reviewed journal (study protocol), and registered with ClinicalTrials.gov (NCT02230813).

Consecutive patients aged over 16 years attending the study EDs with cellulitis suitable for outpatient treatment with oral antibiotics were considered eligible for enrolment on a 24/7 basis. Patients were identified by their treating EP or ANP.

Cellulitis was defined as the appearance of a typical area of erythema over any body part excluding the perineum, within the preceding 5 days. Two of the following signs were also required for diagnosis: Increased warmth, swelling or induration, pain over the affected area and regional lymphadenopathy. We included patients with cellulitis arising *de novo* and secondary to wound infections and abscesses (ABSSSI). Patients with cellulitis secondary to abscess required clinical evidence of co-existing cellulitis, that in the opinion of the treating EP required antibiotic treatment. A minimum diameter of erythema was not used to include patients to this observational study. Standard therapy for abscess including incision, drainage and packing was permitted.

Patients were recruited by EPs and ANPs, both of whom were required to have at least 2 years postgraduate experience in EM. Treating EPs or ANPs who initially screened and recruited patients to the study (‘first study recruiters’) were explicitly told not to alter their usual practice, in terms of patient care, for the purpose of this study. Suitable patients meeting the pre-specified inclusion criteria were invited to participate in the study by the first study recruiter. An information leaflet and verbal explanation of the study procedure was conveyed to each patient and written...
consent was obtained from the patient. Consenting patients were given a study questionnaire to complete. The first study recruiter completed the listed predictor variables in a standardised, closed-response, written CRF by interview and examination of the patient.

Whenever feasible, a second EP or ANP (‘second study recruiter’) examined the patient and recorded the presence of potential risk factors for TF. After assessment, the second study recruiter gave their opinion as to whether they would recommend oral or IV antibiotic therapy for the patient. The second study recruiter was required to have at least 2 years postgraduate experience in EM and was asked to remain blinded and independent of the first recruiter’s patient assessment. It was pre-specified that at least 10% of all patient assessments were to be completed by a second study recruiter. In order to ensure standardised data collection, all enrolling EPs and ANPs were provided with a 30 min individual training session regarding the study procedures. Throughout the duration of the study there were regular site visits and educational workshops to sustain patient recruitment.

The patient risk-factors selected for assessment in this study were chosen based on previous observational research, a systematic review of risk factors for developing cellulitis (40), and on input from study investigators. I assessed demographic and historical variables, medical and social history, history of recorded fever at home, rigors, vital signs recorded at triage, laboratory investigations whenever these were taken as part of routine care, diameter and surface area of cellulitis, systemic and local risk factors for infection, and a visual analogue pain scale. The CRF utilised in this WP is available in the appendix (Appendix file 8).

### 2.8.2 Interventions

All patients enrolled to this study were suitable only for treatment with outpatient oral antibiotic therapy. Patients were discharged on a 7-14 day course of flucloxacillin 500mg -1 g four times daily, or in the case of penicillin-allergic
patients, either doxycycline, clindamycin or erythromycin as specified by local hospital prescribing guidelines. Patients were discharged from the ED to the care of their GP, but were advised to attend the treating ED in case of clinical deterioration.

2.8.3 Follow-up

After 2 weeks of treatment patients were contacted by telephone to evaluate response to treatment (whether the area of redness had decreased in diameter by at least 50% and if they felt the infection was cured or not), need for antibiotic adjustment (further oral or IV antibiotics), side effects and whether they wished to receive study results. Patients describing deteriorating symptoms at this visit were advised to attend their ED and were recorded as a TF.

2.8.4 Outcome measures

The primary outcome measure was TF defined as a change in the route of antibiotic administration from oral antibiotic to IV treatment in order to elicit treatment response. The main secondary outcome measure was TF defined as a change in the type or dose of oral antibiotic treatment. TF did not include admission to hospital for an unrelated condition. Additional secondary outcome measures were assessment of inter-observer reliability for each patient risk factor and assessment of the eligibility and loss to follow up rate.

2.8.5 Analysis

For measurement of the primary outcome the number of patients who failed oral antibiotic treatment were expressed as a percentage of the total number of patients prescribed oral antibiotic treatment. For the secondary outcome the percentage of patients whose oral antibiotic prescribed in the ED was changed to another oral antibiotic, or whose dose of oral antibiotic was changed to a higher dose of the same antibiotic, was calculated. Univariate associations between
explanatory variables and TF was examined. These results were expressed as ORs with 95% CIs.

Explanatory variables considered of prior clinical importance or having a threshold p value of ≤ 0.15 in the univariate analysis were planned for inclusion in a MVLR. Before the study began, it was planned that at least 10% of all patient assessments were to be completed by a second study recruiter (97). The inter-observer agreement for each variable was assessed by calculating the κ coefficient along with 95% CIs. A variable was deemed to have an acceptable agreement if the κ coefficient had a value of at least 0.6. For continuous variables (lesion length, width and surface area) Lin’s concordance coefficient was calculated. Feasibility was assessed in terms of recruitment, response rates, loss to follow-up and eligibility.

The sample size of this pilot study was estimated based on determining the proportion of patients failing oral antibiotic treatment. Using a 95% CI for the proportion of patients failing oral antibiotic treatment, a margin of error of 0.05 and an expected proportion of 10% based on an educated guess, and two recent studies suggesting that at least 6.8%, and up to 20% of ED patients with cellulitis fail initially prescribed antibiotic therapy, the required sample for the pilot study would be at least 152 patients. Data was collected using hard copy CRFs and analysed using Microsoft Excel. Statistical analysis was performed using Stata 13.
Chapter 3: WP 1: Research output relevant to skin and soft tissue infections (1945-2014): a scientometric analysis

This chapter describes WP-1, a scientometric analysis of global research output relevant to SSTIs. It then describes the impact of the CA-MRSA epidemic on global scientometric indices of research output.

3.1 Introduction

SSTIs represent a heterogeneous group of infections which include cellulitis, abscesses, furuncles and carbuncles, wound infections and necrotising soft tissue infections, and myonecrosis (3). Given the ubiquity, varying severity and diverse microbiological causes of SSTIs, they constitute a constant and significant burden to healthcare systems globally. Prior to the advent of antibiotics, sepsis from SSTIs was a major cause of death. Spellberg et al recently calculated that the mortality rate of erysipelas was 11-17%, while that of major complicated abscess was 6% (46) (Figure 1.3). It is perhaps unsurprising that one of the first clinical trials of antibiotic therapy in humans performed in 1936 evaluated sulfanilimide versus ultraviolet light for the treatment of erysipelas (98), while the first therapeutic administration of penicillin was for a man with disseminated facial abscess and osteomyelitis, precipitated by a simple ulcer on his lip the previous year (99).

3.2 The growth of CA-MRSA

Recently, several unique factors have combined to increase the burden of SSTIs on global healthcare systems. The epidemic of CA-MRSA in the US and Canada has resulted in it becoming the most common identifiable cause of SSTI in a cross section of EDs in the US (24). This epidemic has been associated with increased ED attendance and hospital admissions secondary to SSTIs (25). Data from the SENTRY antimicrobial surveillance program, which monitors pathogen prevalence
and resistance patterns of SSTIs, revealed that *S. aureus* was present in 44.6% of isolates in North America of which 35.9% were methicillin-resistant (100). Latin America (29.4%) and Europe (22.8%) also had a high prevalence of MRSA-associated SSTI. Meanwhile, global healthcare budgetary constraints, decreased hospital capacity and a diminishing pipeline of novel antibiotic drugs have changed how we need to manage these common infections, both currently and into the future (101).

Given these shifting influences on the epidemiology of SSTIs and the current importance of SSTIs in the context of antimicrobial resistance, we evaluated the global research output relevant to SSTIs by performing a scientometric analysis. The aim of this analysis was to evaluate the research yield relevant to SSTI globally from 1945 to 2014 using bibliometric indicators of research production and quality.

### 3.3 Results

#### 3.3.1 Total number of published items

The number of published items was used as an index of research productivity. Between 1945 and 2014, 46,567 items were published which examined the research question. 38,229 were research articles, 4,204 were review articles, and 2,387 were papers from proceedings. The earliest record is from 1945, when 7 publications were recorded on WOS. Many of these items were isolated case reports describing penicillin treatment for erysipelas. Between 1945 and 1949 (n=65), SSTI-related research was almost double that recorded between 1955-1959 (n=35). Between 1965-69 (91 items), the amount of research items produced exceeded the quantity recorded between 1945-49. Research output increased exponentially from the early 1990’s, breaking 1,000 published items in 1995, to reach a maximum output in 2014 (n=3,321; 7.3% of total).
3.3.2 Total number of citations

The 46,567 items have been cited 1.1 million times since 1945. There was a parallel increase in the number of citations in tandem with the increase in published items relevant to SSTIs. Articles published in 2005 were responsible for more citations than those published in any other year (n=54,462) and also generated the highest h-index (n = 99). Of the five most highly cited articles in 2005 alone, 3 dealt with the epidemic of CA-MRSA in the US (102-104). Overall the 5 most-highly cited articles were published between 2003 and 2009, and all dealt with the epidemic of CA-MRSA in the US (Table 3.1). Since 2005, the yearly sum of citations per item has gradually declined.
Table 3.1 Five most highly cited articles since 1945

<table>
<thead>
<tr>
<th>Author</th>
<th>Article title</th>
<th>Journal title</th>
<th>Year</th>
<th>Total citation</th>
<th>Average per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klevens, R; Morrison, M; Nadle J.</td>
<td>Invasive methicillin-resistant <em>Staphylococcus aureus</em> infections in the United States (105)</td>
<td><em>Journal of the American Medical Association</em></td>
<td>2007</td>
<td>1,545</td>
<td>171.7</td>
</tr>
<tr>
<td>Moran, GJ; Krishnadasan, A; Gorwitz, RJ et al.</td>
<td>Methicillin-resistant <em>S aureus</em> infections among patients in the emergency department (24)</td>
<td><em>New England Journal of Medicine</em></td>
<td>2006</td>
<td>1,200</td>
<td>120</td>
</tr>
<tr>
<td>Boucher, HW; Talbot, GH; Bradley, JS.</td>
<td>Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America (106)</td>
<td><em>Clinical Infectious Diseases</em></td>
<td>2009</td>
<td>1,072</td>
<td>153.1</td>
</tr>
<tr>
<td>Fridkin, SK; Hageman, JC; Morrison, M.</td>
<td>Methicillin-resistant <em>staphylococcus aureus</em> disease in three communities (102)</td>
<td><em>New England Journal of Medicine</em></td>
<td>2005</td>
<td>812</td>
<td>73.8</td>
</tr>
<tr>
<td>Diep B; Gill SR; Chang RF.</td>
<td>Complete genome sequence of USA300, an epidemic clone of community acquired methicillin-resistant <em>Staphylococcus aureus</em> (107)</td>
<td><em>Lancet</em></td>
<td>2006</td>
<td>675</td>
<td>67.5</td>
</tr>
</tbody>
</table>

3.3.3 Country of origin

In total, 167 countries contributed to the literature on SSTIs during the study period. The US alone accounted for 36% (16,759 items) of total research output followed by Germany (n = 3,833), England (n=3,348), France (n=2,974), Italy (n=2,135) and Spain (n=1,613), which cumulatively contributed 28.1% of the total research output. In total, 22 countries contributed between 1 and 36% of total research output while 145 countries contributed items that amounted to less than 1% of the total research output.
In addition to producing the highest volume of published items, the US also has the highest average citation rate per item (n=51). Denmark (2nd), Sweden (3rd) and the Netherlands (4th) produced the next most highly cited items, yet in terms of publications produced on a yearly basis, ranked 23rd, 17th and 11th respectively (Table 3.2).

Table 3.2: Leading countries by research output and average citations per item (1945-2014)

<table>
<thead>
<tr>
<th>TOP COUNTRIES – OUTPUT</th>
<th>TOP COUNTRIES - AVERAGE CITINGS PER ITEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank</td>
<td>Country</td>
</tr>
<tr>
<td>1</td>
<td>USA</td>
</tr>
<tr>
<td>2</td>
<td>GERMANY</td>
</tr>
<tr>
<td>3</td>
<td>ENGLAND</td>
</tr>
<tr>
<td>4</td>
<td>FRANCE</td>
</tr>
<tr>
<td>5</td>
<td>JAPAN</td>
</tr>
<tr>
<td>6</td>
<td>ITALY</td>
</tr>
<tr>
<td>7</td>
<td>SPAIN</td>
</tr>
<tr>
<td>8</td>
<td>AUSTRALIA</td>
</tr>
<tr>
<td>9</td>
<td>CANADA</td>
</tr>
<tr>
<td>10</td>
<td>BRAZIL</td>
</tr>
</tbody>
</table>
3.3.4 Publishing journals

A total of 2,926 journals have published at least one item on SSTIs. The top 5 journals contributing the most items are summarised in order in Table 3.3. These journals only accounted for 14.6% of the total amount of journals publishing research relevant to SSTIs.

Table 3.3: Leading journals publishing SSTI-related items (1945-2014)

<table>
<thead>
<tr>
<th>Journal Title</th>
<th>Item published</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clinical Infectious Diseases</em></td>
<td>827</td>
</tr>
<tr>
<td><em>Journal of the American Academy of Dermatology</em></td>
<td>629</td>
</tr>
<tr>
<td><em>British Journal of Dermatology</em></td>
<td>606</td>
</tr>
<tr>
<td><em>The Public Library of Science (PLOS One)</em></td>
<td>566</td>
</tr>
<tr>
<td><em>International Journal of Dermatology</em></td>
<td>558</td>
</tr>
</tbody>
</table>

The 10 most frequently cited articles and their publishing journal were categorised between 1990 to 2013 for each year of publication. The same process was performed on a 10-yearly basis between 1950-1989 and for the 5 years between 1945 and 1949. The journal titles which published the most highly cited items are summarized in Table 3.4. *Clin Infect Dis, J Infect Dis* and *N Eng J Med* published the most highly cited articles (total 61,107) yet contributed only 978 items (1.7% of total).
### Table 3.4: Journals producing most highly cited items (1945-2014)

<table>
<thead>
<tr>
<th>Journal name</th>
<th>Items published</th>
<th>Times cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Infectious Diseases</td>
<td>803</td>
<td>38,392</td>
</tr>
<tr>
<td>The Journal of Infectious Diseases</td>
<td>280</td>
<td>12,617</td>
</tr>
<tr>
<td>New England Journal of Medicine</td>
<td>175</td>
<td>22,715</td>
</tr>
<tr>
<td>Lancet</td>
<td>160</td>
<td>17,463</td>
</tr>
<tr>
<td>Journal of the American Medical Association</td>
<td>138</td>
<td>10,164</td>
</tr>
</tbody>
</table>

### 3.4 Research output relevant to SSTIs associated with CA-MRSA

Our second search resulted in 1,119 research items. After excluding research items that did not examine either SSTIs or CA-MRSA, 808 items remained. Original research articles accounted for 652 items (80.5%) and review articles for 103 (12.7%). The remainder were proceedings papers (48; 5.9%), letters (20; 1.9%) and meeting abstracts (13; 1.6%). The majority of items were produced in the US (490; 60.6%) followed by France (37; 4.6%), Spain (29; 3.6%), Australia (28; 3.5%) and England (24; 3%). From the early 1990s several case reports and case series from various global settings were reported in the literature. From 2003 (8 items), research output increased exponentially until 2008 (101 items), after which research output decreased again to 2005 levels.
Prior to 2004, articles examining CA-MRSA associated SSTI were rarely cited. Since then, the number of yearly citations increased in tandem with the number of items produced in a linear fashion. The yearly citation rate peaked 2 years after the peak of items produced. The 808 items have been cited 27,656 times in total with an average 34.2 citations per item. Robert Daum (McGill University) produced the largest number of items (16; 2%). The most highly cited articles were by Klevens et al (105) and Moran et al (24) (Table 3.5). The most common subject areas publishing research items were infectious diseases (321; 40%), microbiology (239; 30%), immunology (111; 14%), pharmacology (12.5%) and general internal medicine (95; 12%).

Figure 3.2: Yearly research output relevant to CA-MRSA associated SSTIs (1990-2014)
Table 3.5: Five most highly cited articles produced relevant to CA-MRSA and SSTIs (1990-2014)

<table>
<thead>
<tr>
<th>Author</th>
<th>Article title</th>
<th>Journal title</th>
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<td>Lancet</td>
<td>2006</td>
<td>675</td>
<td>67.5</td>
</tr>
<tr>
<td>Dielema DJ; Pfaller MA; Scmitz FJ.</td>
<td>Survey of infections due to Staphylococcus species: Frequency of occurrence and antimicrobial susceptibility of isolates in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999</td>
<td>Clinical Infectious Diseases</td>
<td>2001</td>
<td>552</td>
<td>36.8</td>
</tr>
<tr>
<td>Miller L; Remington F; Rieg G.</td>
<td>Necrotising fasciitis caused by community-associated methicillin resistant Staphylococcus aureus in Los Angeles</td>
<td>New England Journal of Medicine</td>
<td>2005</td>
<td>524</td>
<td>47.6</td>
</tr>
</tbody>
</table>

3.5 Discussion

This scientometric analysis provides some unique insights into the quantity and quality of SSTI-related research output produced over the past 70 years. I have attempted to contextualise variations in this research output by identifying key points in the historical timeline of SSTI-related research. There were two relative increases in the amount of research produced, one between 1945-49 and a second from 1990 onwards. Between 1945-49, research items chiefly took the form of case reports or expert opinion, issued shortly after the widespread use of
penicillin (108-110). One interesting review described the major burden of cutaneous infections on troop numbers during the World War II; 42-80 per 1,000 troop-strength per-year were affected by wound infections, with an average hospital stay of 5.5 months (111).

SSTI-related research output increased exponentially from 1990 onwards, a finding which is in common with other scientometric analyses (77, 112). General research output across all health science disciplines increased from the 1980s onwards, with one study showing a 4% annual increase in output between 1957 and 2007 (113). This increased output may be due to the provision of additional, more accessible scientific data sources, including databases and journals. Furthermore, the concept of producing the “smallest publishable research unit” in order to advance publication status for funding reasons may partly explain this overall increased output (114). Nevertheless, the number of SSTI-related research items retrieved (n=46,567) is significantly less when compared to the research output of other medical conditions. For example, a recent bibliometric analysis of breast cancer research output, also using WOS only, retrieved 180,126 publications, over 4 times greater than our total publication number (77). This supports the opinion held by several authors in the field, that SSTIs are poorly researched in general (1, 46, 67)

The distribution of SSTI-related research output between countries was unequal. The significant contribution of the US to research output in this field is notable, both in terms of publication number and citation count. Although the former is a measure of quantity, citation count has been used as a proxy measure of quality (77). The overall citation rate per item increased in parallel with the number of items produced, a finding mirrored in other scientometric studies (77, 114). It is also notable that using measures of qualitative research output, articles concerning the epidemic of CA-MRSA in North America during the 2000s were consistently the most highly cited items retrieved.

When I performed a second search, combining CA-MRSA search terms with SSTI-related research output, the quantity of items produced from 2000 to 2008 increased exponentially (figure 3.2). The US was over-represented in terms of the quantity of items produced, far in excess of their representation for the primary search (60.6% versus 36%). It is interesting to see that the number of items
produced gradually decreased between 2008 and 2014, while the citation rate per item also stabilised in the same time period. Although it is difficult to draw any firm conclusions from this finding, it may indicate a stabilisation of research output as CA-MRSA became endemic in many areas of the US. A recent meta-analysis of published studies that included trend data from 4 large population cohorts in the US, showed that the estimated epidemic curve for each cohort appears to be approaching a plateau, while one population cohort showed a levelling-off of the epidemic curve in 2007 (115). Interestingly, this paper also describes the appearance of CA-MRSA in geographically disparate areas across the USA in the early and mid-1980s, earlier than most published studies would suggest, which was followed by a “rapid, consistent nation-wide shift in the genetic background of S. aureus strains”, which occurred between 2000 and 2008 (115).

The large range of journals in which SSTI-related research is published and the large number of countries producing research in this field, points to the interdisciplinary nature of the treatment of SSTI and its global burden. Although research from the US predominates, Asia, central Europe and South America appear to be underrepresented. Since WOS incorporates 45 different languages in its catalogue, it is difficult to attribute this underrepresentation to language barrier alone. Interestingly, Denmark, Sweden and the Netherlands contribute high citation counts despite ranking lower in terms of number of publications produced, reflecting a high-quality, low-volume research output.

As expected, many different journals publish literature relevant to SSTIs and we were unable to focus research output to a select few. This poses difficulties for clinicians and researchers with an interest in SSTIs to keep updated with recent literature in this field. We identified the top 5 journals associated with the highest citation rate per item, indicating a core of highly relevant journals, albeit producing a small fraction of total research output.

Although this scientometric analysis evaluated the impact of the current CAMRSA epidemic on research output was examined, the future emergence of multidrug resistant organisms is cause for major concern (116). Given that the development of antimicrobial drug therapy was arguably the defining moment of modern medicine (117), the possibility exists that the evolution of further drug resistant microorganisms will reverse decades of progress in antibiotic treatments. In
contemplating a future without antibiotic treatments, it is most likely that a combination of renewed industry interest in novel drug development, investment in alternatives to antibiotic treatments, physician prescribing habit change and altered public perception of antibiotic treatment will be necessary to limit the impact of large scale antibiotic resistance (116). Recently, several novel antibiotic treatments effective for the treatment of SSTIs have been developed. These include antibiotics such as oritavancin and dalbavancin delivered as a single IV infusion and which have been comparable to 7-10 days of IV vancomycin and linezolid (118, 119). In addition, the advent of high potency oxazolidinediones such as tedizolid, which also have excellent oral bioavailability, may play a role in altering the way we treat conditions such as cellulitis(120). The threat of antibiotic resistance has highlighted the essential role antibiotic stewardship plays in order to improve the quality of antibiotic prescribing and reduce inappropriate antibiotic use (121). How we decide to utilise these novel antibiotic treatments in place of current therapies will be equally as important as their discovery (122).

3.6 Limitations

I focused on entries contained in WOS only. Although Pubmed focuses mainly on medicine and biomedical sciences, it does not offer a citation analysis and only covers a time period from 1950 – present (123). Therefore, the use of Pubmed, Scopus or Google Scholar could have yielded different results to ours.

Several case reports relevant to the growing epidemic of CA-MRSA in the early 1980s and 1990s, dealt with non-SSTI medical conditions and were therefore not retrieved using our search criteria (124-126). Furthermore, I assessed for year of publication as an index of temporal trends in research output. Some items which were published in the late 2000s, in fact dealt with historical databases from the early 1990s.

3.7 Conclusion

To the best of my knowledge this is the first scientometric analysis of the quality and quantity of SSTI-associated research output. Overall, the total number of
retrieved publications was low. The results have demonstrated a recent exponential increase in research output from the US, where the most highly cited articles dealt with the epidemic of SSTIs secondary to CA-MRSA. Similarly there was a temporal association between research output and the exponential increase in CA-MRSA cases between 2000 and 2008. There is mounting evidence to suggest that the future evolution of multi-drug resistant bacteria will significantly impact the aetiological epidemiology of common medical conditions, including SSTI. Future research into novel antibiotic therapies for SSTI and alternatives to antibiotic treatments will likely ensure that the prominent role the antibiotic treatment of SSTI had in the past, will also continue into the future.
Chapter 4: WP-2 and WP-3. Incidence, prescribing practices and disposition of patients with cellulitis in Irish EDs

4.1 Introduction

This chapter describes two WPs evaluating the current ED management of cellulitis in Ireland. The overarching aims of these two studies were to:

1) measure the incidence of ED cellulitis among adult patients;

2) assess EP adherence to established clinical practice guidelines;

3) define preliminary clinical and epidemiological factors which may predict route of antibiotic therapy;

4) evaluate the antibiotic prescribing practices of EPs treating cellulitis.

The results of these two studies highlight significant knowledge gaps concerning the risk stratification of ED patients with cellulitis in Ireland. For simplicity, both studies will be described in the order in which they were performed. WP-3 was a pilot study which informed the methodology of WP-4, and will therefore be described first. Note that although the term cellulitis is used, the population of patients enrolled to these studies had cellulitis arising de novo, secondary to ulcer, abscess and wound infections.
4.2 WP 2: A pilot cross sectional study of patients presenting with cellulitis to EDs

4.2.1 Introduction

The incidence of cellulitis presenting to EDs in Ireland is unknown. As described in section 1.3 and 1.4, only inpatient episodes are coded and costed by the HPO in Ireland. There is currently no nationally integrated EDIS in Ireland, with significant discrepancy in how diagnostic categories are coded among patients attending, and subsequently discharged from ED settings nationally.

There is a lack of research-based data to guide the risk stratification and management of cellulitis, particularly in ED settings. Existing CPGs have generally been derived by expert opinion and consensus (1, 3, 32, 51, 67). The CREST guideline is commonly used in the NHS to guide the treatment of cellulitis (51). This guideline stratifies patients according to co-morbidities and signs of infection, and recommends antibiotic treatment ranging from oral therapy in CREST Class 1 to IV therapy in CREST Classes 2-4. The modified CREST guideline was devised by Marwick et al (52). It is based on the CREST guideline but also applies objective measures of infection severity by utilising accepted sepsis definitions and the SEWS. It was further assessed in a prospective cohort of patients admitted to a general hospital in Dundee, Scotland, and compared with the guideline issued by Ki et al (32, 67). The CREST guideline, Modified CREST guideline, and CPG issued by Ki et al are summarised in Table 4.1. The Modified CREST and CPG issued by Ki et al, are further described in the text of WP 4.
Table 4.1: CPGs for the management of cellulitis

* Peripheral vascular disease, chronic venous disease, morbid obesity;

<table>
<thead>
<tr>
<th>Guideline</th>
<th>CREST</th>
<th>Antibiotic therapy suggested by CREST group</th>
<th>Modified CREST</th>
<th>Ki et al</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td>No signs of systemic toxicity / uncontrolled co-morbidities</td>
<td><strong>First line:</strong> Flucloxacillin 500mg qds PO&lt;br&gt;Penicillin allergy&lt;br&gt;Clarithromycin 500 mg bd PO</td>
<td>No comorbidity*&lt;br&gt;No sepsis&lt;br&gt;SEWS &lt; 4</td>
<td>Any one of the following comorbidities?</td>
</tr>
<tr>
<td></td>
<td>Usually treat with oral antimicrobials as outpatient</td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td><strong>Group 1</strong></td>
<td><strong>First line:</strong> Flucloxacillin 2 g qds IV, or&lt;br&gt;Ceftriaxone 1 g od IV (OPAT)</td>
<td>&gt;1 comorbidity&lt;br&gt;No sepsis&lt;br&gt;SEWS &lt; 4</td>
<td>Any one of the following symptoms:</td>
</tr>
<tr>
<td></td>
<td>Systemically ill&lt;br&gt;or&lt;br&gt;Systemically well with co-morbidity e.g. peripheral vascular disease, chronic venous insufficiency, morbid obesity</td>
<td>Penicillin allergy&lt;br&gt;Clarithromycin 500 mg bd IV /&lt;br&gt;Clindamycin 600 mg tds IV</td>
<td></td>
<td>Temp &lt;35 C or &gt;40 C&lt;br&gt;Hypotension&lt;br&gt;HR &gt;100/min&lt;br&gt;Altered mental status</td>
</tr>
<tr>
<td></td>
<td>Significant systemic upset (acute confusion, tachycardia, tachypnoea, hypotension), or&lt;br&gt;Unstable co-morbidities interfering with response to therapy, or&lt;br&gt;Limb threatening infection from vascular compromise</td>
<td><strong>First line:</strong> Flucloxacillin 2 g qds IV&lt;br&gt;Penicillin allergy&lt;br&gt;Clarithromycin 500 mg bd IV&lt;br&gt;Clindamycin 900 mg tds IV</td>
<td>Sepsis&lt;br&gt;SEWS &lt; 4</td>
<td>Bullae, Haemorrhage, Out of proportion pain, Rapidly progressive, Crepitus, Anaesthesia</td>
</tr>
</tbody>
</table>

If YES to any of the above: “Moderate/...”
The primary aim of this study was to measure the incidence of cellulitis presenting daily to three EDs in Ireland. The secondary aims were to determine:

(1) the clinical utility of the CREST guideline in predicting the ED disposition of patients presenting with cellulitis;

(2) preliminary clinical and epidemiological factors which may predict route of antibiotic therapy; and

(3) prescribing practices for the ED treatment of cellulitis.

### 4.2.2 Results

#### 4.2.2.1 Incidence of cellulitis

Over the one-month study period there were 59 patients enrolled in total, 39 from MRHT, 18 from MRHT and 2 from MRHP. After excluding MRHP from the analysis due to poor patient recruitment at that study site, the incidence of cellulitis
attending the 2 remaining EDs was 12 cases per 1,000 ED visits (95% CI, 9-15 per 1,000 ED visits).

4.2.2.2 Patient characteristics

Forty patients were male (67.8%) and the mean age (which was normally distributed) was 50.9 years. Female patients were significantly older than male patients (mean = 60.9 versus 46.2 years; p = 0.019). The majority of cases affected the lower limb (n=39, 71.3%). Thirty-five patients (59.3%) were referred by their GP, while the remainder were self-referrals to the ED. Overall, 27 (45.8%) patients were discharged on oral antibiotic treatment and 32 (54.2%) received IV antibiotic treatment. The majority were in CREST Class 1 (n=39; 66.1%). The remainder were in CREST Class 2 (n=20, 33.9%). There were no CREST Class 3 or 4 patients enrolled.

4.2.2.3 Predictors of oral antibiotic therapy

On MVLR analysis, the following were predictive of oral antibiotic therapy: self-referral (OR = 6.2, 95% CI 1.9 – 20.0, p=0.03), CREST Class 1 allocation (OR 6.81, 95% CI = 1.5-30.1, p=0.012) and duration of symptoms over 48 hours (OR 1.2, 95% CI = 1.0-1.5, p=0.049). Patients who had already received antibiotics prior to ED attendance (“Pre-ED therapy” group) were more likely to receive IV antibiotic therapy (OR 0.22, 95% CI 0.06-0.8, p=0.04). Seventeen patients (43%) in CREST Class 1 received IV antibiotics despite the guideline recommending oral antibiotic treatment. A CART analysis was not possible with the available set of predictors.

Table 4.2: Predictors of patient discharge on oral antibiotic therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED self-referral</td>
<td>6.2</td>
<td>1.9-20.0</td>
<td>0.030</td>
</tr>
<tr>
<td>CREST Class 1</td>
<td>6.81</td>
<td>1.52-30.58</td>
<td>0.012</td>
</tr>
<tr>
<td>Duration of infection &gt;48 hrs.</td>
<td>1.22</td>
<td>1.0-1.49</td>
<td>0.049</td>
</tr>
<tr>
<td>Pre-ED antibiotic therapy</td>
<td>0.22</td>
<td>0.08-0.8</td>
<td>0.040</td>
</tr>
</tbody>
</table>
4.2.2.4 Prescribing practices

Sixteen patients had pre-ED antibiotic therapy prescribed by their GP. There were no doses recorded. The breakdown of antibiotic type was as follows: flucloxacillin monotherapy (n=9), combined flucloxacillin and penicillin V therapy (n=4), combined flucloxacillin and co-amoxiclav (n=1), erythromycin (n=1) and co-amoxiclav (n=1).

Of the 27 patients discharged on oral antibiotic treatment, 63% (17/27) received flucloxacillin combined with penicillin V, and 26% received flucloxacillin alone, with the remainder receiving clindamycin (n=1) or co-amoxiclav (n=2). There were 3 different prescribed doses of flucloxacillin and 4 different doses of penicillin V. The cumulative daily dose of flucloxacillin ranged from 1.5 to 4 g; 2 patients (8.6%) received 4 g, 17 patients (74.0%) received 2 g and 4 patients (17.4%) received 1.5g. Regarding penicillin-V, the cumulative daily doses ranged from 2 – 2.6 g; 14 patients (82.4%) received 2 g and 3 patients (17.6%) received 2.6 g.

Of the 9 patients recorded as obese, 5 were discharged on oral antibiotic therapy. One patient was treated with a high dose of flucloxacillin 4g daily with penicillin-V 2.6g daily, while one other patient was treated with 1.5g of flucloxacillin daily. The remaining 3 patients received 2 g of flucloxacillin combined with 2g of penicillin-V.

Thirty-two patients received IV antibiotics: 27 received combined flucloxacillin and benzylpenicillin of 3 different doses, 3 received flucloxacillin and co-amoxiclav, 1 received co-amoxiclav alone and 1 received erythromycin alone.

4.3 Discussion

This is the first study to measure the ED incidence of cellulitis in Ireland. The ED incidence of cellulitis in this study was found to be approximately 12 per 1,000 ED attendances. This is also the first study to investigate the clinical utility of the CREST guideline in the ED setting. Patients who self-referred to the ED, who had not received antibiotic treatment in the community, who had a duration of symptoms exceeding 48 hours and who were in CREST Class 1, were more likely to be discharged from the ED on empiric oral antibiotic treatment. The majority of discharged patients (63%) were prescribed a combination of oral flucloxacillin and penicillin-V, while the majority of patients admitted to hospital (84%) received...
combined IV flucloxacillin and benzylpenicillin treatment. The local antimicrobial
prescribing guideline in use in the 3 recruiting EDs in 2012, recommended
prescription of combined flucloxacillin 500 mg four times daily with penicillin V 500
mg four times daily for patients suitable for oral antibiotic therapy. For patients
requiring IV antibiotic therapy, combined flucloxacillin and benzylpenicillin was
recommended. Although adherence to the local prescribing guideline occurred in
63% of patients, it is clear that physician prescribing preference varied as a further
26% of patients received flucloxacillin only. When considering the range of doses
prescribed, the majority (74.0 - 82.4%) received the dose recommended by the
local prescribing guidelines. Additionally, patients with obesity were treated with a
range of antibiotic doses, highlighting a patient population that perhaps would
benefit from selective antibiotic prescribing rather than in a “one-size-fits all” local
prescribing guideline.

Although EPs completed a separate CREST score for each patient, adherence to
the guideline was poor with 17 patients (43%) in CREST Class 1 admitted to
hospital for IV antibiotics, despite the guideline recommending oral treatment for
this patient subset. Marwick et al also showed that 47% of admitted in-patients
with cellulitis were in CREST Class 1, similarly indicating over-treatment of milder
infections (52).

Other factors require further examination in a larger study. That patients describing
over 48 hours of symptoms on ED arrival were more likely to be discharged may
indicate a subgroup of indolent infection suitable for oral treatment. It is intuitive
that patients who did not attend their GP prior to ED attendance were more likely
to be discharged from the ED on oral antibiotics. Oral flucloxacillin and penicillin V
were the most commonly prescribed antibiotics, with 63% of discharged patients
receiving both. Although combined antibiotic therapy was recommended by the
local antimicrobial prescribing policy, there is no RCT-based evidence to either
refute or support this practice (127). One small RCT showed no additional benefit
when IV benzylpenicillin was added to IV flucloxacillin for the treatment of lower
limb cellulitis (70).
4.4 Limitations

The sample size was small and the results may be imprecise. In the absence of any previous study documenting the epidemiology of ED cellulitis in Ireland, this study was a necessary starting point to generate information for sample size calculation in the larger, full-scale study described in WP4. Patients were not followed-up beyond their ED admission and since I am unaware of any adverse events, I cannot comment on the validity of the CREST guideline in the ED setting. The generalisability of the findings may be limited by geographical factors since both participating EDs serve mixed urban/rural populations and the findings may not be valid in urban (city centre) EDs. However, the main focus of this pilot study was on the processes of the main study, for example to ensure recruitment and follow-up assessments all run smoothly.
4.5 WP 3: The management of cellulitis in EDs: antibiotic prescribing practices and adherence to practice guidelines in Ireland.

4.5.1 Introduction

The primary aim of this study was to characterise antibiotic prescribing practices for the treatment of cellulitis in Irish EDs. Secondary aims were to identify patient variables associated with the prescription of IV antibiotics and to describe the utility of three published CPGs for the treatment of cellulitis in the ED setting. The CREST guideline has already been described in section 4.1. In addition, adherence to the Modified CREST guideline (52), which stratifies infection severity according to definitions of sepsis and the SEWS, was assessed. The CPG issued by Ki et al stratifies patients with SSTIs as “mild” or “moderate/severe” based on co-morbidities, vital signs and clinical findings (32). The three CPGs are summarised in Table 4.1.

4.5.2 Results

During the study period, 132 consecutive patients with cellulitis were enrolled. Fifteen patients were excluded; 11 due to incomplete data collection and 4 because they were younger than 18 years. Final analysis was completed on 117 patients.

4.5.2.1 Demographic and clinical data

Baseline characteristics of the study patients are summarised in Table 4.3. Almost 40% of patients were recorded as having wound infections, and only 4% had abscesses. The majority of patients were male (73 patients; 63.5%). The mean age was 52.1 ± 19.3 years and age range data was normally distributed. Sixty-five patients (55.6%) were referred to the ED by their GP (55.6%) and 52 self-referred (44.4%). The mean duration of symptoms prior to attendance was 4.5 days [107 hours (95% CI 88-126)] and mean duration of oral antibiotic therapy received was
3 days [80 hours (95% CI 62-98)]. Mean diameter of infection at presentation was 11.7 cm (SD 7.9cm). Twenty-six patients (22 %) had 1 previous episode of cellulitis, 3 (2.2%) had 2 previous episodes and 9 (7.7%) had 3 or more episodes. Fifty-eight patients (49.6%) were discharged from the ED on oral antibiotics and 59 (51.4%) were admitted for IV antibiotics.
### Table 4.3: Baseline characteristics of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (% of total)</th>
<th>I.V. treatment (% admitted)</th>
<th>Oral treatment (% discharged)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td></td>
<td>52.09</td>
<td>52.34</td>
</tr>
<tr>
<td>Male gender</td>
<td>73 (63.5)</td>
<td>38 (64.4)</td>
<td>35 (60.3)</td>
</tr>
<tr>
<td>Female gender</td>
<td>42 (36.5)</td>
<td>19 (32.2)</td>
<td>23 (39.7)</td>
</tr>
<tr>
<td>Self referral</td>
<td>48 (41.0)</td>
<td>18 (30.5)</td>
<td>30 (51.7)</td>
</tr>
<tr>
<td>Antibiotics prescribed in community</td>
<td>50 (42.7)</td>
<td>31 (52.2)</td>
<td>19 (32.8)</td>
</tr>
<tr>
<td>Obesity</td>
<td>20 (17.1)</td>
<td>12 (20.3)</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>6 (5.1)</td>
<td>5 (8.5)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Chronic pitting oedema</td>
<td>9 (7.7)</td>
<td>5 (8.5)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>Excoriating skin disease</td>
<td>8 (6.8)</td>
<td>4 (6.8)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>11 (9.4)</td>
<td>9 (15.3)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Venous eczema</td>
<td>11 (9.4)</td>
<td>6 (10.2)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>Venous ulcer</td>
<td>11 (9.4)</td>
<td>7 (11.9)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>9 (7.7)</td>
<td>5 (8.5)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>4 (3.4)</td>
<td>4 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (10.3)</td>
<td>10 (16.9)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>4 (3.4)</td>
<td>4 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (2.6)</td>
<td>2 (3.4)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1 (0.9)</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>3 (2.6)</td>
<td>2 (3.4)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Steroids</td>
<td>1 (0.9)</td>
<td>1 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Asplenia</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Site of infection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head/Neck</td>
<td>11 (9.4)</td>
<td>7 (11.9)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>Upper limb</td>
<td>36 (30.8)</td>
<td>17 (28.8)</td>
<td>19 (32.8)</td>
</tr>
<tr>
<td>Lower limb</td>
<td>67 (57.3)</td>
<td>33 (55.9)</td>
<td>34 (58.6)</td>
</tr>
</tbody>
</table>
4.5.2.2 Antibiotic prescribing practices

Flucloxacillin and pencillin V were the most commonly prescribed antibiotics (n=81; 69%). EPs prescribed a combination of oral flucloxacillin and penicillin V in approximately a third of patients, flucloxacillin alone in a third of patients, and an alternative antibiotic in a third of patients. Of those patients prescribed flucloxacillin (n=45), data concerning doses was available for 39. Thirty-seven patients received a cumulative daily dose of flucloxacillin of 2.0 g (94.8%). Two patients received 1.0 g and 2 other patients received 4.0 g in the 24-hour period. Among patients prescribed penicillin-V by EPs, data on cumulative daily dosing was available for all 21 patients who received between 2.0 (n=12; 52.4%) and 2.6 g (n=11; 47.6%).

Thirty-three patients (54%) were prescribed combined IV flucloxacillin and benzylpenicillin while 16 patients (27%) were prescribed IV flucloxacillin alone. All patients received between 1.0 to 2.0 g of flucloxacillin and between 1.2-2.4g of benzylpenicillin. Prescribed antibiotic regimens are summarised in Table 4.4.
Table 4.4: Antibiotic regimens prescribed for cellulitis

* Flucloxacillin added to therapy in 1 patient

<table>
<thead>
<tr>
<th>Name of antibiotic drug</th>
<th>Oral antibiotic prescribed in the community prior to ED presentation (n=49)</th>
<th>Oral antibiotic prescribed in the ED (n=58)</th>
<th>IV antibiotic prescribed in the ED (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin</td>
<td>23 (46.9%)</td>
<td>22 (37.9%)</td>
<td>16 (27.1%)</td>
</tr>
<tr>
<td>Flucloxacillin and penicillin V</td>
<td>13 (26.5%)</td>
<td>23 (35.4%)</td>
<td>32 (54.2%)</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>4 (8.1%)</td>
<td>2 (3.5%)</td>
<td>2 (3.3%) *</td>
</tr>
<tr>
<td>Erythromycin / clarithromycin</td>
<td>5 (10.2%)</td>
<td>5 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Cefaclor, cefalexin or cefradine</td>
<td>3 (6.1%)</td>
<td>1 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1 (2.0%)</td>
<td>1 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0</td>
<td>3 (5.2%)</td>
<td>5 (8.5%) *</td>
</tr>
<tr>
<td>Missing data</td>
<td></td>
<td>3 (5.2%)</td>
<td>4 (6.7%)</td>
</tr>
</tbody>
</table>

4.5.2.3 Factors associated with IV antibiotic prescription

Univariate analysis of predictor variables associated with prescription of IV antibiotics are summarised in Table 4.5.
Table 4.5: Univariate analysis of predictor variables associated with prescription of IV antibiotics.

Only variables with sufficient occurrences underwent univariate analysis. Significant variables are in bold italics.

*Cut off of 9 cm taken as most useful cut-point.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (% of total)</th>
<th>ORs for IV antibiotic therapy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-referral</td>
<td>48 (42.9)</td>
<td>0.4 (0.2-0.9)</td>
</tr>
<tr>
<td>Antibiotics prescribed in community</td>
<td>50 (43.5)</td>
<td>2.5 (1.2 - 5.2)</td>
</tr>
<tr>
<td><strong>Local variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>34 (29.1)</td>
<td>0.7 (0.33-1.64)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>13 (11.3)</td>
<td>1.73 (0.53-5.6)</td>
</tr>
<tr>
<td>Diameter of erythema &gt; 9 cm*</td>
<td>69 (59.0)</td>
<td>OR=5.32 95%CI (2.34, 12.1)</td>
</tr>
<tr>
<td><strong>General variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>20 (17.1)</td>
<td>1.67 (0.63-4.5)</td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>11 (9.6)</td>
<td>5.3 (1.1-25.5)</td>
</tr>
<tr>
<td>Venous eczema</td>
<td>11 (9.6)</td>
<td>1.3 (0.365-4.43)</td>
</tr>
<tr>
<td>Venous ulcer</td>
<td>11 (9.6)</td>
<td>1.89 (0.53-6.85)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (10.3)</td>
<td>6.0 (1.2-28.0)</td>
</tr>
<tr>
<td>Fever</td>
<td>12 (10.3)</td>
<td>2.4 (1.5-4.0)</td>
</tr>
<tr>
<td>&gt; 2 previous episodes of cellulitis</td>
<td>9 (7.8)</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td><strong>Cellulitis guideline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREST Score &gt; 1</td>
<td>39</td>
<td>6.7 (2.8-16.0)</td>
</tr>
<tr>
<td>Modified CREST Score &gt;1</td>
<td>36</td>
<td>2.5 (1.3-4.7)</td>
</tr>
<tr>
<td>SEWS &gt; 0</td>
<td>21</td>
<td>7.3 (1.7-31.2)</td>
</tr>
</tbody>
</table>
On MVLR analysis, fever (OR 2.4 (95% CI 1.4 - 4.4)), toe-web maceration due to tinea pedis (OR 14.2 (95% CI 1.4 - 145.2)) and diameter of infection (OR 1.1 for each cm increase, 95% CI 1.0 -1.2) were significantly associated with EP prescription of IV antibiotics.

4.5.2.4 Guideline adherence
The number of patients allocated to each treatment guideline, and the number prescribed IV antibiotics in each group, is summarised in Table 4.6. Between 32.9 and 43.5% of patients in CREST and Modified CREST group 1 and Ki et al “mild” infections, were prescribed IV antibiotics despite the guideline recommending oral treatment.

Table 4.6: Total number of study participants in each guideline group
The number and percentage of study participants prescribed IV antibiotics are in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST guideline</td>
<td>76 (25; 32.9%)</td>
<td>33 (27; 81.8%)</td>
<td>6 (5; 83.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Modified CREST guideline</td>
<td>79 (34; 43.0%)</td>
<td>25 (12; 48.0%)</td>
<td>8 (8; 100%)</td>
<td>3 (3; 100%)</td>
</tr>
<tr>
<td>Guideline by Ki et al</td>
<td>62 (27; 43.5%)</td>
<td>51 (29; 56.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.6 Discussion

4.6.1 ED incidence
This multicentre study described the management of cellulitis in adults attending 6 Irish EDs, and builds upon the work performed in WP-2. In WP-2 the ED incidence of cellulitis was 12 per 1000 (95% CI 9-15) ED attendances, and in WP 3 the incidence was 6.3 per 1000 (95% CI, 5.1-7.4) ED attendances.

Both studies show that over 50% of all patients attending the ED with cellulitis were referred by their GP. This indicates a high level of community-directed treatment in Ireland and is consistent with data from the Netherlands where community based treatment has been shown to be 10-fold greater than hospital based treatment for cellulitis (15). Consistent with previously published studies (23, 66) most ED attendances in this study consisted of men aged 30-50 years with lower limb cellulitis due to a wound. Since only 5 cases of abscess were enrolled in this study, the incidence of “purulent cellulitis” appears to be comparatively low in Irish EDs.

4.6.2 Prescribing practices

Similar to WP-2, this study revealed heterogeneous prescribing practices for cellulitis. Almost 75% of patients were prescribed either flucloxacillin alone or combined with penicillin V by their GP or treating EP, despite a lack of evidence to either support or refute this practice. Flucloxacillin is most commonly administered as a 500 mg capsule four times daily resulting in a cumulative daily dose of 2.0 g. In only 2 cases did EPs prescribe a higher dose of 1.0 g four times daily. Penicillin V is available either as a 500 mg or 666 mg tablet. Depending on EP preference, penicillin V was prescribed between 3 and 4 times daily, resulting in a daily dose between 2.0 to 2.6 g. One retrospective study of patients admitted to a US hospital with cellulitis showed that “low antibiotic dosing” at patient discharge was associated with clinical treatment failure (OR 3.64; 95% CI 1.41-9.41) (128). In addition, this paper showed higher rates of clinical treatment failure among morbidly obese (body mass index > 40) and overweight (weight > 100kg) patients. The role of obesity both as an independent risk factor for treatment
failure, and the relationship between antibiotic dosing among obese patients and treatment failure, is deserving of further study.

4.6.3 Predictors of IV treatment

I examined the association between patient variables and the treating EPs decision to prescribe IV antibiotics. This contrasts with the chosen outcome measure on WP-2 where patient variables predictive of oral antibiotic treatment were examined. Fever, diameter of the area of erythema and maceration of the toe web spaces due to tinea pedis, were associated with a decision to prescribe IV antibiotics. Fever has previously found significance as a predictor of empirically prescribed antibiotic treatment failure in the ED and observation unit setting (60, 64). Infection diameter is an intuitive measure of cellulitis severity, but has not previously been shown to predict antibiotic treatment failure. Toe web maceration is a recognised risk factor for developing cellulitis. However, the width of the CI reported for this variable is very wide which indicated imprecision regarding its accuracy as a risk factor for IV treatment (14, 16). Patients with diabetes were more likely to be prescribed IV antibiotics on univariate analysis, but the number of diabetic patients in the study was too small on MVLR analysis to permit me to draw any firm conclusions whether diabetes is a determinant of infection severity.

4.6.4 CPG utility in the ED setting

This study found that, contrary to guideline recommendations, a high proportion of CREST Group 1 patients (25; 32.9%) were prescribed IV antibiotics. However, 68% of these patients had been prescribed oral antibiotics in the community and so may have been considered to have antibiotic TF by the treating EP. Based on guideline recommendations, all groups 3 and 4 patients were appropriately prescribed IV antibiotics. The Modified CREST guideline uses contemporary definitions of sepsis and an early warning score, intuitively reflecting a useful stratification tool (67). In contrast, the CREST guideline was published in 2005 and
uses outdated definitions and descriptions for sepsis. The clinical decision to prescribe IV antibiotics depends on multiple factors, including failed oral therapy in the community, socioeconomic factors and physician or patient preference. These factors may not correlate with the actual risk of antibiotic TF, without which such guideline recommendations cannot be validated. Furthermore, the TF rate for cellulitis outside of the North American ED setting, is unknown. In WP 5, I describe the prevalence and predictors of empiric oral antibiotic TF for adult patients attending 3 EDs in Dublin.

The strengths of this study includes its contribution to characterising the management of cellulitis in the Irish ED setting and its prospective design, which ensured the appropriate primary diagnosis for recruitment in a pragmatic way.

4.7 Limitations

The sample size was relatively small and the imprecision of some of the data suggests the study may be underpowered. A convenience sample was used in this study, and may not be representative of all ED patients with cellulitis. However, the study population was pragmatically defined to minimise selection bias. Since the patients were not followed up after they left the ED, it is not possible to draw definitive causal inference regarding the predictor variables examined. The SEWS score is not in use in the EDs assessed in this study therefore no firm conclusions can be drawn regarding its use.
4.8 Summary conclusions for WP 2 and WP 3

- In 2012, the incidence of cellulitis was approximately 6-12 per 1000 ED attendances.
- Between 62.5 - 67.8% of patients attending EDs were male, and between 57.3 to 71.3% of cases involved the lower limb.
- Between 55.9 - 59.3% of patients attending the ED with cellulitis were referred by their GP.
- Between 45.8 - 49.6% of patients were discharged on oral antibiotic therapy while the remainder received IV antibiotic therapy.
- Flucloxacillin either alone or combined with penicillin V accounts for between 73 - 89% of oral antibiotics prescribed by EPs and 73% of antibiotics prescribed by GPs.
- EPs prescribed a combination of oral flucloxacillin and penicillin V in approximately a third of patients, flucloxacillin alone in a third of patients, and an alternative antibiotic in a third of patients.
- Flucloxacillin either alone or combined with benzylpenicillin accounts for between 81-83% of prescribed IV antibiotics prescribed by EPs.
- Fever (OR 2.4, 95% CI 1.5–4.0), diameter of the area of erythema over 9 cm (OR 5.32, 95% CI 2.3-12.1), maceration of the toe web spaces due to tinea pedis (OR 5.3, 95% CI 1.1–25.5) and “pre-ED antibiotic therapy” (OR 0.22, 95% CI 0.06-0.8) were associated with a decision to prescribe IV antibiotics.
- Self-referral (OR = 6.2, 95% CI 1.9 – 20.0), CREST Class 1 allocation (OR 6.81, 95% CI = 1.5-30.1) and duration of symptoms over 48 hours (OR 1.2, 95% CI = 1.0-1.5) were associated with a decision to prescribe oral antibiotics.
- Current ED prescribing practices are poorly adherent to guideline recommendations, particularly for the management of patients in CREST and Modified CREST groups 1 and 2.
- In WP-2, 17 patients (43%) in CREST Class 1 were prescribed IV antibiotics, despite the guideline recommending oral treatment for this patient subset.
• In WP 3, 25 patients (32.9%) in CREST Class 1 were prescribed IV antibiotics. However, 68% of these patients had been prescribed oral antibiotics in the community and so may have been considered as having antibiotic TF by the treating EP.
Chapter 5: WP-4: Risk factors for the development of leg cellulitis - a systematic review and meta-analysis of case-control studies.

5.1 Introduction

The first three thesis WPs have examined trends in global research output relevant to cellulitis, the ED management and prescribing practices for patients with cellulitis in Ireland, risk factors influencing patient disposition, and EP adherence to existing CPGs. The overarching aim of this thesis is to describe patient-specific risk factors for empirically prescribed, antibiotic TF in order to risk-stratify patients with cellulitis attending EDs to oral or IV treatment for cellulitis. I have demonstrated that patients in CREST Groups 1 and 2 are equally likely to be disposed to either oral or IV treatment for their episode of cellulitis. It is therefore this group of “systemically well” patients for whom risk stratification appears to be most necessary.

In this chapter, I describe a SRMA of controlled observational studies which examine risk factors for the development of leg cellulitis. I performed this SRMA in order to cohere the existing published evidence concerning risk factors for developing cellulitis. Also, in WP-5 these risk factors are subjected to further study in a retrospective cohort study examining the rate and risk factors associated with amendment of prescribed antibiotic treatment for patients treated with OPAT for cellulitis, and in WP-6, I assess the utility of these risk factors as predictors of oral antibiotic treatment failure in a prospective observational cohort study of adult ED patients with cellulitis.

It was important and timely to cohere the existing evidence base concerning risk factors for developing cellulitis for two other reasons. Firstly, it is both intuitive and supported by consensus opinion that treatment of risk factors promotes resolution of the index episode of infection (3, 129). Secondly, risk factor modification is also likely to reduce the risk of complications, the most important of which is recurrent cellulitis (1) (3). Recurrent infections occur in up to 57% of patients with cellulitis, predisposing to post-cellulitic oedema and further episodes of recurrence (4, 130,
Knowledge of which risk-factors merit targeted modification or treatment in clinical practice would be of value to emergency physicians and researchers, both to reduce the cost and morbidity of complications, and to promote healing of the index episode of infection.

Therefore the objectives of this WP were to:

1) identify and critically appraise all controlled observational studies that have examined risk factors for the development of cellulitis;

2) identify a set of risk factors for cellulitis suitable for analysis in two proposed studies of empirically prescribed antibiotic TF among patients with cellulitis.

5.2 Results

5.2.1 Article selection

A PRISMA diagram is displayed in Figure 5.1. In total, 3,572 potentially eligible studies were identified. After removal of duplicates, 2,611 studies were screened and 46 potentially eligible studies were identified for inclusion. There was excellent agreement between the two investigators responsible for independently screening the title and abstract of potentially eligible studies against the inclusion criteria (Cohen’s Kappa 0.93). One potentially eligible study required translation to English from German (132). In order to provide data concerning risk factors exclusively for leg cellulitis, the authors of three studies were contacted (16, 133, 134) of whom two provided the required data.
Figure 5.1: PRISMA flow diagram.

Records identified through electronic database searching = 2976
Medline = 1171
EMBASE = 1329
Cochrane = 476

Additional records identified through other sources = 596
Grey literature = 8
NLM gateway = 69
Google search = 1
Reference lists of primary articles = 6
Trial registries = 512

Records after duplicates removed = 2611

Records screened = 2611

Records excluded = 2565
Number of studies excluded after screening full-text versions and reason for exclusion = 39
- Uncontrolled study design (n=9)
- MRSA/CAMRSA only (n=6)
- Recurrent cellulitis (n=6)
- MRSA only (n=7)
- Specific population (cirrhosis (n=1); lymphoedema (n=2); diabetes (n=1); RA (n=1).
- Necrotising fasciitis only (n=2)
- Antibiotic prophylaxis study (n=1)
- Review article (n=1)
- Furunculosis only (n=1)
- Not leg cellulitis (n=1)

Studies included in qualitative synthesis = 7

Studies included in quantitative synthesis (meta-analysis) = 6

High risk of bias (n=1)
5.2.2 Methodological quality assessment

Table 5.1 summarises the characteristics of the included studies. Detailed results of NOS quality assessment are summarised in the appendix (Appendix file 5). All included studies scored a low ROB except for one (135).

After performing a methodological quality assessment on 7 potentially eligible studies (14, 16, 129, 133-137), 6 were selected for inclusion, which examined 40 different risk factors (16, 129, 133, 134, 136, 138). One study was excluded from further analysis due to a high ROB (135).

In order to provide summary estimates for each of the risk factors, a meta-analysis was performed. Of the 40 risk factors, 8 local (anatomically in the leg), and 4 general (anatomically not on the leg and related to the patient’s general health) risk factors were identified. A table summarising the frequency of occurrence of risk factors in the 6 case control studies is displayed in the appendix (Appendix file 6).

5.2.3 Study characteristics

All studies evaluated patients admitted to hospital with non purulent leg cellulitis in a case-control design. Five were conducted in Western Europe and one in Tunisia. Three of the included studies were multi-centre and three single-centre studies. All the included studies examined hospitalised cases of NPLC while one examined community and hospitalised cases (136). In total there were 874 cases and 1,597 controls. Apart from two of the included studies (16, 134), controls were age and sex-matched hospital inpatients admitted for a condition unrelated to non purulent leg cellulitis. All studies had independent validation of cases by a hospital dermatologist.
Table 5.1: Summary of the characteristics of the included case-control studies.

*Site of entry: combination of leg ulcer, wound, excoriated leg dermatosis, pressure ulcer or intertrigo; ^ Overweight: Lorentz formula > 120%; ¯ Leg lesions; ! Traumatic wounds <1 month, skin disease, toe-web intertrigo, and chronic ulcers

<table>
<thead>
<tr>
<th>Authors and Countries</th>
<th>n</th>
<th>Design &amp; Setting</th>
<th>Results of Multivariate Analysis (Odds Ratios (95% CI))</th>
<th>Conclusion</th>
<th>Limitations</th>
<th>Newcastle Ottawa Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupuy et al, 1999, France</td>
<td>167 cases, 294 controls</td>
<td>Prospective multicentre, case control</td>
<td>Lymphoedema: 71.2 (5.6-908.0), Site of entry*: 23.8 (10.7-52.5), Leg oedema: 2.5 (1.2-5.1), Venous insufficiency: 2.9 (1.0-8.7), Overweight*: 2.0 (1.1-3.7).</td>
<td>Local risk factors highly associated with leg cellulitis.</td>
<td>Hospitalised cases and controls</td>
<td>low</td>
</tr>
<tr>
<td>Mokni et al, 2004, Tunisia</td>
<td>124 cases 267 controls</td>
<td>Prospective multicentre, case control</td>
<td>Lymphoedema: 19.1 (1.1-331.0), Site of entry*: 13.6 (6.3-31.0), Leg oedema: 7.0 (1.3-38.0), Venous insufficiency: 0.7 (0.3-1.6), Overweight*: 1.3 (0.6-2.9), Sedentary work: 0.6 (0.3-1.4)</td>
<td>Site of entry and leg oedema contribute significant risks for erysipelas. General risk factors were not significant.</td>
<td>Hospitalised cases and controls</td>
<td>low</td>
</tr>
<tr>
<td>Bjornsdottir et al, 2005, Iceland</td>
<td>100 cases 200 controls</td>
<td>Prospective single-centre, case control</td>
<td>Toe web bacteria: 69.6 (9.61-504.8), Previous cellulitis: 21.8 (4.4 - 108.9), Leg lesions 21.2 (5.2-85.5), Prior saphenectomy: 12.2 (2.4-60.9).</td>
<td>Colonisation of the toe webs by pathogenic bacteria is a greater risk factor than intertrigo alone</td>
<td>Hospitalised cases and controls; unknown if bacterial pathogens cause or result of cellulitis;</td>
<td>low</td>
</tr>
<tr>
<td>Roujeau et al, 2004, France, Austria, Germany, Iceland</td>
<td>243 cases 467 controls</td>
<td>Prospective multicentre case control</td>
<td>Disruption of cutaneous barrier: 22 (9.4-51.5), Raised BMI: 2.8 (1.5-6.0), Tinea pedis: 3.2 (1.6-6.3), Previous cellulitis: 24 (7.1-81.2), Chronic leg oedema: 4.5 (1.3-15.6)</td>
<td>Tinea pedis and onychomycosis are significant, modifiable risk factors</td>
<td>Hospitalised cases, included recurrent cases; mixed community and hospital controls;</td>
<td>low</td>
</tr>
<tr>
<td>Authors and Countries</td>
<td>n</td>
<td>Design &amp; Setting</td>
<td>Results of Multivariate Analysis (Odds Ratios (95% CI))</td>
<td>Conclusion</td>
<td>Limitations</td>
<td>Newcastle Ottawa Score</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>------------------------------------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Halpern et al., 2008, England</td>
<td>150 cases 300 controls</td>
<td>Prospective single-centre, case control Hospital cases and controls</td>
<td>White ethnicity: 2.95 (1.8-4.8). Previous cellulitis: 0.03 (0.01-0.07). Previous leg surgery: 0.3 (0.2-0.6). Leg injury blunt and open: 0.1 (0.06-0.17). Preceding rash: 0.08 (0.03,0.22). Previous DVT: 0.1 (0.03-0.35). Toe web disease: 0.32 (0.21-0.48). Oedema or lymphoedema: 0.1 (0.06-0.17). Ulcer: 0.05 (0.02,0.12)</td>
<td>White ethnicity in the UK associated with leg cellulitis. Local risk factors are significant.</td>
<td>Hospitalised cases and controls; uncontrolled for recurrence;</td>
<td>low</td>
</tr>
<tr>
<td>Karpellin et al., 2010, Finland</td>
<td>90 cases 90 controls</td>
<td>Prospective single-centre, case control Hospital cases and community controls</td>
<td>Chronic leg oedema: 11.5 (1.2-114.4). Disruption of cutaneous barrier*: 6.2 (1.9, 20.2). BMI &gt; 30: 5.2 (1.3,20.9). Malignant disease: 2.0 (0.5-18.9). Current smoking: 1.4 (0.4-5.3)</td>
<td>Leg oedema, broken skin and obesity are risk factors for acute cellulitis.</td>
<td>Hospitalised cases</td>
<td>low</td>
</tr>
</tbody>
</table>

5.2.4 Local risk factors identified

Eight local risk factors related anatomically to the leg were identified:

1) Lymphoedema / chronic leg oedema (Figure 5.2)

Lymphoedema and chronic leg oedema, pooled as variables, were analysed in all included studies (OR: 2.66; 95% CI: 1.71-4.12; p<0.05). One study did not show a positive association having enrolled only 4 cases (136). Summary estimate for lymphoedema/chronic leg oedema are shown in Figure 5.2.
2) Previous cellulitis (Figure 5.3)

Previous cellulitis was associated with NPLC in three included studies, with meta-analysis showing a positive association (OR: 40.40; 95% CI 22.59-71.90; p<0.05) (16, 129, 133).

3) Wound (Figure 5.4)

Four included studies provided evidence for the presence of a leg wound as a risk factor for NPLC (129, 134, 136, 138). Two included traumatic wounds [25, 29], with one of these specifying a wound of less than 1-month’s duration (134). One study combined blunt injury, insect bite and open wound (129), and one study gave no description of the wound (138). A meta-analysis indicated an increased risk of NPLC (OR: 19.11; 95% CI 9.13-39.98; p < 0.05).
Figure 5.4: Summary estimates for wound

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cases Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupuy 1999</td>
<td>47</td>
<td>82</td>
<td>21</td>
<td>294</td>
<td>28.0%</td>
</tr>
<tr>
<td>Halpern 2008</td>
<td>65</td>
<td>85</td>
<td>21</td>
<td>300</td>
<td>52%</td>
</tr>
<tr>
<td>Karpellin 2010</td>
<td>15</td>
<td>75</td>
<td>4</td>
<td>90</td>
<td>19.3%</td>
</tr>
<tr>
<td>Mokni 2004</td>
<td>35</td>
<td>79</td>
<td>7</td>
<td>208</td>
<td>24.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>321</td>
<td>892</td>
<td>100.0%</td>
<td></td>
<td>19.11 [9.13, 39.98]</td>
</tr>
<tr>
<td>Total events</td>
<td>162</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.39; Chi² = 10.29; df = 3 (P = 0.02); I² = 71%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.83 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4) Current leg ulcer (Figure 5.5)

Five included studies reported data on leg ulcers being present at the time of assessment as a risk factor for NPLC. Three studies indicated an increased risk of developing leg cellulitis (16, 129, 138), while 2 studies did not (134, 136). Only 6 patients (134), and 1 patient (136), were enrolled to these studies again indicating possible patient selection bias (OR 13.65; 95% CI 7.890-23.59; p<0.05).

Figure 5.5: Summary estimates for current leg ulcer

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cases Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjornsdottir 2005</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Dupuy 1999</td>
<td>17</td>
<td>129</td>
<td>2</td>
<td>294</td>
<td>11.9%</td>
</tr>
<tr>
<td>Halpern 2008</td>
<td>40</td>
<td>150</td>
<td>5</td>
<td>300</td>
<td>27.5%</td>
</tr>
<tr>
<td>Karpellin 2010</td>
<td>6</td>
<td>76</td>
<td>0</td>
<td>76</td>
<td>5.2%</td>
</tr>
<tr>
<td>Mokni 2004</td>
<td>1</td>
<td>114</td>
<td>1</td>
<td>208</td>
<td>7.9%</td>
</tr>
<tr>
<td>Roujeau 2004</td>
<td>29</td>
<td>243</td>
<td>7</td>
<td>467</td>
<td>47.5%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>712</td>
<td>1345</td>
<td>100.0%</td>
<td></td>
<td>13.65 [7.89, 23.59]</td>
</tr>
<tr>
<td>Total events</td>
<td>93</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 4.27; df = 4 (P = 0.37); I² = 6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 9.36 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5) Tinea pedis causing toe-web disease (Figure 5.6)

Fungal foot infection was classified differently in the 6 included studies. Toeweb intertrigo (133, 134, 136, 138), toe-web disease causing dermatomycosis, intertrigo and cracking or fissuring (129), and toe-web scaling, fissuring or maceration (16), were considered the one entity. Two studies used microscopy and culture to confirm the diagnosis (16, 133). All 6 studies reported an increased risk of cellulitis in the presence of toe-web disease secondary to tinea pedis (n=375), while meta-analysis also indicated an association between the two conditions (OR 3.16; 95% CI 1.9-5.2; p<0.05).
6) Excoriating skin diseases (Figure 5.7)
Excoriating skin disease described any break in epithelial integrity. Skin conditions were described differently in the 6 included studies (Table 1). Excoriated dermatoses (136, 138), eczema and psoriasis (129) and undefined “skin disease” (134), were pooled. Dry skin, varicose eczema and venous stasis dermatitis were excluded where reported. All 4 reported an association with cellulitis (129, 134, 136, 138) (OR 4.37; 95% CI 2.70-7.08; p<0.05).

7) Previous history of ulcer (Figure 5.8)
A previous history of leg ulcer was reported in 3 included studies (133, 136, 138). Although the pooled OR was significant, one study showed a negative association between previous leg ulcer and the development of leg cellulitis (136) (OR 4.47; 95% CI 1.60-12.51; p<0.05).
8) Previous leg surgery (Figure 5.9)

All 6 included studies reported data on patients who underwent any previous leg surgery (n=165). No further specific descriptions of the type of surgery were reported. Three studies (129, 136, 138) reported that previous leg surgery was associated with leg cellulitis, while three did not (16, 133, 134). Meta-analysis showed a positive association (OR 2.66; 95% CI 1.71-4.12; p<0.05).

5.2.5 General risk factors

I identified the following 4 general risk factors:

1) Diabetes mellitus (Figure 5.10)

All 6 included studies examined diabetes as a risk factor. No study reported an association between the two conditions, which was confirmed on meta-analysis (OR 1.16; 95% CI 0.92-1.47; p=0.22).
2) Obesity (Figure 5.11)

Two included studies (136, 138) utilised Lorentz formula >120% to define patients as "overweight". One study defined obesity as a body mass index (BMI) > 25 (133), one as BMI > 27 (16), and 3 as BMI > 30 (129, 133, 134). When BMI > 25 and Lorentz score > 120% were pooled, there was a weak association with the development of leg cellulitis (OR 1.87; 95% CI 1.26-2.79; p<0.05). When BMI > 30 was analysed exclusively, this association increased further (OR 2.37; 95% CI 1.39-4.05; p< 0.05).

Figure 5.11: Summary estimates for obesity / overweight
3) Smoking (Figure 5.12)

Smoking was defined as “any current or recent smoking” in all 6 included studies, apart from one study which did not provide any explicit definition (134). There was no association between smoking and developing leg cellulitis in any study individually or on meta-analysis (OR 0.90; 95% CI 0.66-1.24; p = 0.54).

**Figure 5.12: Summary estimates for smoking**

![Graph showing summary estimates for smoking]

4) Alcohol consumption (Figure 5.13)

Any social or medical problem related to the overuse of alcohol (134), number of units consumed per week (129, 134), 2 or more items on the CAGE questionnaire (136, 138), and “any alcohol consumption” (16) were used as definitions in the included studies. One included study reported an association between alcohol consumption and developing leg cellulitis (136). Meta-analysis did not indicate any association (OR 1.14; 95% CI 0.81-1.60; p = 0.45).

**Figure 5.13: Summary estimates for alcohol consumption**

![Graph showing summary estimates for alcohol consumption]
5.2.6 Publication bias

Visually there was evidence of publication bias. However, it is usual to perform tests for funnel plot asymmetry only when there are at least 10 studies included in the meta-analysis. Funnel plots are shown in the appendix (Appendix file 7).

5.3 Discussion

The principal finding of this SRMA is that local risk factors appear to be more significant than general risk factors in the pathogenesis of NPLC. Previous cellulitis, previous leg surgery, a “site of bacterial entry” from wound, ulcer, excoriating skin disease or toe web intertrigo, and chronic leg oedema were the most frequently described risk factors in the 6 included studies. This supports recent opinion that cellulitis is predominantly a disease of local risk factors which should be controlled in order to promote healing and reduce the rate of complications (129, 134, 139).

Patients with diabetes are more likely to present with suppurative cellulitis from infected diabetic foot ulcers or wounds, and may have been excluded from the studies reviewed (16, 41). One case-control study examining the rate of S. aureus and MRSA colonisation of patients hospitalised with non-purulent cellulitis, found that diabetics were more likely to have cellulitis than matched hospital controls (adjusted OR 3.3; 95% CI 1.4-7.8) (140). Since this study did not specify patients with leg cellulitis, it was excluded from our systematic review.

There is an important differentiation to be made concerning patient risk factors for developing cellulitis and risk factors that may be predictive of antibiotic treatment failure. This study provides evidence that certain local risk factors are highly associated with developing cellulitis and that measurement of these risk factors among patients with cellulitis is feasible. Interestingly, the small amount of literature concerning risk factors for TF that exist, also support the importance of local risk factors in determining response to treatment. What role systemic risk factors play in determining treatment response is less clear and will be further studied in WP 5 of this thesis.
Cellulitis is thought to develop when disruption of the cutaneous barrier creates a “site of entry” for commensal or environmental bacteria to colonise different layers of the skin architecture (3). The clinical presentation of cellulitis results from the interaction of bacteria with host defences. Bacterial adherence to host cells, invasion of tissue and release of toxins is followed by host innate and adaptive immune responses, which usually results in local containment of infection (32, 33).

Along with wounds, ulcers and excoriating skin diseases, toe web disease from tinea pedis is a potential site of entry. Two studies included in this review reported that the greater the number of toe web spaces affected by tinea pedis, the greater the risk of developing cellulitis (16, 138). Positive culture of bacteria from toe-web intertrigo is also associated with developing cellulitis (OR: 69.6; 95% CI 9.61–504.86) (133). However, given the ubiquity of tinea pedis in the general population, it is intuitive that other factors are involved in the pathogenesis of leg cellulitis (141).

Lymphoedema is a unique risk factor for leg cellulitis. Lymphoscintigraphic studies have shown that the lymphatic supply of the leg affected by cellulitis shows abnormalities in 50% to 77% of patients (142, 143). Two further studies demonstrated abnormal lymphatic drainage in the unaffected leg of 79% to 86% of patients who underwent lymphoscintigraphy after a previous episode of cellulitis, suggesting that some patients presenting with leg cellulitis may have a pre-existing undiagnosed primary lymphatic abnormality (141, 144).

The lymphatic system plays an essential role in interstitial fluid balance and immunological function (4, 145). Each episode of cellulitis further damages the lymphatic system, thereby perpetuating a cycle of recurrence and infection (4). In addition to antibiotics graduated leg compression stockings, massage therapy and consideration of lymphoscintigraphy in patients with recurrent episodes, is advocated (141, 144).

The treatment of risk factors such as interdigital maceration, fungal nail infection, skin ulceration, and dry skin is supported by expert opinion but has not been
subject to rigorous study (3, 4, 146). Recent evidence has also shown the utility of antibiotic prophylaxis for preventing recurrence of leg cellulitis in patients with at least two episodes within the previous three years (147). Of note, a BMI > 33 kg/m², and pre-existing leg oedema were associated with a poorer response to prophylactic treatment.

5.4 Limitations

Like all systematic reviews the conclusions of this review are limited by the quality of existing studies. The use of hospitalised cases and controls in most studies introduces Berkson bias. This limits the external validity of this review’s findings to other settings, for example primary care. Hospital controls were used in four of the six the included studies, rendering comparison of risk factors potentially less valid (sampling bias). Most authors attempted to control for this by excluding patients with a chronic disease related to any of the risk factors under study (129, 136, 138), or by only enrolling patients hospitalised for an acute condition other than cellulitis (134). Conversely, community controls may have biased results towards healthier individuals who volunteered to respond to the study (selection bias).

Mokni et al (2004) showed lower rates of toe-web intertrigo and lymphoedema in their study conducted in Tunisia when compared to the study by Dupuy et al (1999) conducted in France, reflecting differences in disease definition (“leg oedema” versus “lymphoedema”) between clinicians working in different settings.

The NOS was used to assess the quality of non-randomised studies. However, validity of the NOS has recently been questioned (148). Meta-analyses of observational studies present particular challenges because of inherent biases and differences in study design (87). Ultimately, a meta-analysis was performed despite this heterogeneity, because an overall measure of the effects of these risk factors would be clinically useful, and performing a meta-analysis coheres the current evidence underpinning the topic in a scientifically valid way.
On examination of funnel plots, there was some evidence of publication bias.

5.5 Conclusions

Local risk factors appear to play a more significant role in the development of leg cellulitis than systemic risk factors. Disruption of epithelial integrity, accumulation of dermal and subdermal fluid and disruption of lymphatics are the most plausible, common pathophysiological pathways for the variety of risk factors identified. Although not a risk factor for developing leg cellulitis, diabetes may play a role in determining host response to infection. Further studies are required in order to fully clarify the role general risk factors have to play in determining response to treatment. Concurrent with antibiotic treatments, compression therapy for leg oedema and the treatment of other potential sites of bacterial entry should be considered a standard of care. Finally, researchers should consider the use of these risk factors as part of a standardised patient assessment tool in future studies of leg cellulitis.
Chapter 6: WP-5: Risk factors for amendment in type, duration and setting of empirically prescribed IV antibiotics for adult patients with cellulitis: a retrospective cohort study and CART analysis.

6.1 Introduction

This chapter describes a retrospective cohort study of the management of cellulitis among patients enrolled to an OPAT service. The primary objective was to measure the rate of OPAT failure among patients with cellulitis enrolled to the service. The secondary objective was to identify risk factors for amendment in the type, setting or duration of treatment among patients with cellulitis who were treated in the service. Given the safety and efficacy of OPAT as an alternative to hospital admission, I decided not to describe changes to initially prescribed antibiotic therapy as “treatment failure”. As a result in this chapter I elected to use the term “treatment amendment” to describe any change to the dose or type of antibiotic, or the addition of a second antibiotic to the initially prescribed regimen in order to achieve clinical response. In the final WP, I use the term “treatment failure” to describe IV antibiotic therapy administered to ED patients who deteriorate while on oral antibiotic therapy for their episode of cellulitis, as this can be considered an accurate description of true events.

OPAT is globally accepted as a well-established method to shorten or avoid hospital admission for patients with cellulitis (62, 63). Outpatient parenteral antimicrobial therapy (OPAT) is a well-established, effective alternative to hospital admission, and in the UK is most commonly used for the treatment of cellulitis and other SSTIs (149, 150). The benefits of OPAT include hospital admission avoidance and increased inpatient capacity, reduced length of hospital stay, significant cost savings compared with inpatient care, reduction in risk of healthcare-associated infection and improved patient choice and satisfaction (151). OPAT is administered to patients who require parenteral antibiotic treatment for severe or deep-seated infection but who are otherwise well enough
to be managed in the community (152). Antibiotics delivered by the IV route are one-hundred per cent bioavailable and as a result steady state concentrations of antibiotic may be more reliably achieved within four to five half-lives of drug therapy (153, 154). Oral antibiotics undergo absorption and distribution while being variably absorbed from the gastrointestinal tract, resulting in delayed peak plasma concentrations which are usually than those achieved with IV therapy (153).

A recent consensus document from the British Society for Antimicrobial Chemotherapy outlines several good practice recommendations for OPAT units (151). Unplanned readmission, treatment failure and adverse effects of antimicrobial treatment are potential risks of OPAT that require close patient monitoring. In addition to careful patient selection and safety of the home environment for visiting healthcare professionals, clear shared responsibility between the referring clinician and the OPAT service lead is also necessary for safe patient care (151).

The Vhi HomeCare Service provides the largest OPAT service to patients in the east of Ireland. This privately operated service treats on average 127 patients with cellulitis per year, with referrals for cellulitis accounting for 13% of all referrals. Patients may be referred directly from EDs, the community or following hospital admission in order to complete treatment at home. Vhi Homecare is accredited by the Joint Commission International and operates under robust clinical governance structures (96).

In order to optimise outcomes for patients treated for cellulitis with OPAT, an evidence-based approach to patient selection is required. This is dependent on knowledge of the percentage of patients who undergo TA in the opinion of a clinician and secondly, on knowledge of risk factors for TA in cellulitis (58, 60). Although TA is predicated on variables such as antibiotic adherence, type, route of therapy and pathogen virulence (71), knowledge of patient-centred risk factors for TA may permit better patient selection for OPAT.
The primary outcome measure for the study was to measure the rate of TA, defined \textit{a priori} as hospital admission, change in dose or type of antibiotic, or addition of antibiotic in order to achieve response.

Secondary outcomes were as follows:

1. to identify risk factors for TA;
2. to identify risk factors for duration of OPAT exceeding 7 days;
3. to describe physician IV antibiotic prescribing practices for cellulitis.

6.2 Results

A total of 313 OPAT-managed patients for cellulitis were identified. Two did not commence OPAT, and 4 had an alternative diagnosis recorded, leaving a total of 307 patients who were analysed for this study. Baseline clinical characteristics of included patients are summarised in Table 6.1.
Table 6.1: Baseline characteristics of patients treated with OPAT for cellulitis

**Diabetes:** Type 1 or 2 diabetes mellitus, impaired glucose tolerance;

**Cardiovascular disease:** ischaemic heart disease, hypertension, stroke, aortic aneurysm repair, coronary artery bypass graft;

**Kidney disease:** acute or chronic kidney disease defined by RIFLE guidelines at enrolment;

**Recurrent cellulitis:** > 1 previous episode of cellulitis in the same limb;

**Chronic ulcer:** Ulcer present for > 3 months;

**Immunocompromise:** HIV, chemotherapy, current cancer, splenectomy.

Data is reported in n(%) unless otherwise specified.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients (n = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [median (IQR)]</td>
<td>62 (48 - 73)</td>
</tr>
<tr>
<td>Weight (kg) [median (IQR)]</td>
<td>84 (72 - 102)</td>
</tr>
<tr>
<td>Female sex</td>
<td>123 (40.1)</td>
</tr>
<tr>
<td>Smoker current/ex - smoker</td>
<td>36 (11.7)/ 46 (15.0)</td>
</tr>
<tr>
<td>Referral source</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>153 (49.8)</td>
</tr>
<tr>
<td>ED *</td>
<td>99 (32.3)</td>
</tr>
<tr>
<td>GP b</td>
<td>42 (13.7)</td>
</tr>
<tr>
<td>OPD c</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Prior oral antibiotic</td>
<td>122 (39.7)</td>
</tr>
<tr>
<td>Diabetes d</td>
<td>42 (13.7)</td>
</tr>
<tr>
<td>Cardiovascular disease * and kidney disease f</td>
<td>144 (46.9)</td>
</tr>
<tr>
<td>Recurrent cellulitis *</td>
<td>77 (25.1)</td>
</tr>
<tr>
<td>Chronic ulcers b</td>
<td>16 (5.2)</td>
</tr>
<tr>
<td>Immunocompromised f</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>15 (4.7)</td>
</tr>
<tr>
<td>Obesity (Body Mass Index &gt; 25kg/m²)</td>
<td>60 (19.4)</td>
</tr>
<tr>
<td>Infection type</td>
<td></td>
</tr>
<tr>
<td>Laceration</td>
<td>38 (12.4)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>28 (9.2)</td>
</tr>
<tr>
<td>Surgical wound</td>
<td>24 (7.8)</td>
</tr>
<tr>
<td>Non penetrating injury</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Animal bite</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Insect bite</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Burns</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Infected IV access site</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Unspecified cause</td>
<td>191 (62.4)</td>
</tr>
</tbody>
</table>

TA occurred in 36 patients (11.7%). Fifteen patients (4.8%) required hospital admission, 9 due to clinical deterioration, 2 due to treatment non-compliance, 1 due to adverse effects of treatment and 3 due to unrelated medical conditions. Twenty-one (6.9%) patients were successfully treated in the community by change in antibiotic dose, type or by the addition of another antibiotic.
6.2.1 Risk factors for treatment amendment

Risk factors for treatment amendment are summarised in Table 6.2. Age at presentation and NPSS were significant at the 5% level on univariate analysis. When correcting for confounding variables on MVLR, increased age, increased NPSS and immunocompromise were independently associated with treatment amendment. Using the BIC statistic, a best-fit likelihood model comprising age, NPSS and immunocompromise was obtained, and the Homer-Lemeshow goodness-of-fit statistic confirmed no reason to reject this model (p = 0.933).

Table 6.2: Risk factors for OPAT amendment in cellulitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate logistic regression OR (95% CI)</th>
<th>p value</th>
<th>Multifactorial logistic regression OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.044 (1.019 - 1.069)</td>
<td>0.001</td>
<td>1.063 (1.026 - 1.101)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.946 (0.464 - 1.929)</td>
<td>0.878</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>0.828 (0.496 - 1.382)</td>
<td>0.470</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Prior antibiotic received
d | 0.732 (0.351 - 1.524)                     | 0.405   |                                               |         |
| Temperature (°C)                | 1.671 (0.837 - 3.334)                     | 0.145   |                                               |         |
| **NPSS**                        | 1.227 (1.038 - 1.450)                     | 0.017   | 1.326 (1.072 - 1.641)                         | 0.009   |
| HR (bpm)\(^{c}\)                | 1.023 (0.992 - 1.055)                     | 0.147   |                                               |         |
| RR (breaths / min)\(^{d}\)      | 1.217 (0.957 - 1.549)                     | 0.109   |                                               |         |
| Systolic blood pressure         | 1.015 (0.992 - 1.038)                     | 0.193   |                                               |         |
| Diastolic blood pressure        | 0.986 (0.951 - 1.023)                     | 0.451   |                                               |         |
| WCC (mmol/L)\(^{e}\)           | 1.033 (0.973 - 1.096)                     | 0.286   |                                               |         |
| CRP \(^{f}\)                   | 1.002 (0.998 - 1.006)                     | 0.346   |                                               |         |
| Diabetes \(^{g}\)              | 1.992 (0.839 - 4.726)                     | 0.118   |                                               |         |
| Obesity                         | 1.203 (0.518 - 2.793)                     | 0.667   |                                               |         |
| CVD \(^{h}\)                   | 1.685 (0.833 - 3.407)                     | 0.147   |                                               |         |
| Immunocompromise \(^{i}\)      | 3.263 (0.967 - 11.00)                     | 0.057   | 4.452 (1.118 - 17.73)                         | 0.034   |
| Lymphoedema                     | 2.955 (0.888 - 9.827)                     | 0.077   |                                               |         |
| Chronic ulcers                  | 2.698 (0.821 - 8.866)                     | 0.102   |                                               |         |
| Recurrent cellulitis            | 0.995 (0.446 - 2.221)                     | 0.990   |                                               |         |

* Antibiotic received prior to commencing OPAT; \(^{a}\) Numerical Pain Scale Score rated from 0 ("no pain") to 10 ("worst pain ever"); \(^{b}\) HR: heart rate in beats per minute; \(^{c}\) RR: respiratory rate; \(^{d}\) WCC: White cell count; \(^{e}\) CRP: C-Reactive Protein; \(^{f}\) Type 1 or 2 diabetes mellitus, impaired glucose tolerance; \(^{g}\) CVD: cardiovascular disease (ischaemic heart disease, hypertension, stroke, aortic aneurysm repair, coronary artery bypass graft); \(^{h}\) Immunocompromise: HIV, chemotherapy, current cancer, splenectomy; \(^{i}\) NPSS among patients with TA was mean 2.28 (range 0-8) versus mean 1.42 (range 0-9) among patients treated successfully.
6.2.2 Risk factors associated with prolonged OPAT duration

Variables associated with OPAT duration exceeding 7 days are summarised in Table 6.3. The median OPAT duration was 7 days (range 1 – 24 days). Obesity, cardiovascular disease, increased age, HR, WCC and CRP were significant on univariate analysis. Increased age, HR and CRP remained independently significant on MVLR analysis.

Table 6.3: Risk factors for duration of OPAT greater than 7 days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate model OR (95% CI)</th>
<th>P value</th>
<th>Multifactorial model OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.050 (0.022 - 0.078)</td>
<td>0.001</td>
<td>0.056 (0.022 - 0.090)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.190 (-1.195 - 0.814)</td>
<td>0.710</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>0.380 (-0.283 - 1.042)</td>
<td>0.260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior antibiotic</td>
<td>-0.439 (-1.443 - 0.564)</td>
<td>0.390</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>0.174 (-0.900 - 1.248)</td>
<td>0.751</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain score</td>
<td>0.192 (-0.069 - 0.453)</td>
<td>0.149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>0.054 (0.010 - 0.099)</td>
<td>0.016</td>
<td>0.060 (0.013 - 0.106)</td>
<td>0.012</td>
</tr>
<tr>
<td>RR (breaths/min)*</td>
<td>0.272 (-0.070 - 0.615)</td>
<td>0.119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP b</td>
<td>0.027 (-0.006 - 0.059)</td>
<td>0.105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP b</td>
<td>0.008 (-0.043 - 0.058)</td>
<td>0.761</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCC (mmol/L)</td>
<td>0.135 (0.011 - 0.259)</td>
<td>0.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.011 (0.005 - 0.018)</td>
<td>0.000</td>
<td>0.010 (0.003 - 0.017)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.612 (-0.886 - 2.109)</td>
<td>0.422</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>1.361 (0.131 - 2.592)</td>
<td>0.030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD f</td>
<td>1.148 (0.168 - 2.129)</td>
<td>0.022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompromise</td>
<td>0.965 (-1.454 - 3.383)</td>
<td>0.433</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>0.361 (-1.900 - 2.622)</td>
<td>0.753</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic ulcers</td>
<td>-0.051 (-2.244 - 2.142)</td>
<td>0.963</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurent cellulitis</td>
<td>1.222 (0.093 - 2.352)</td>
<td>0.034</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.2.3 Antibiotic prescribing practices

Prescribed antibiotic regimens are summarised in Table 6.4. The most commonly prescribed antibiotic was flucloxacillin, prescribed alone (n=35; 11.4%) or in combination with benzylpenicillin (n=147; 47.8%). Over half of all patients received 2 different antibiotics (n=170; 55%), with 9 patients (2.9%) receiving 3 different antibiotics.
### Table 6.4: Antibiotic regimens prescribed for OPAT-managed patients with cellulitis

<table>
<thead>
<tr>
<th>Antibiotic name</th>
<th>Full sample number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin and benzylpenicillin</td>
<td>147</td>
<td>47.8</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>35</td>
<td>11.4</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>23</td>
<td>8.5</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>17</td>
<td>5.5</td>
</tr>
<tr>
<td>Flucloxacillin and clindamycin</td>
<td>8</td>
<td>2.6</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>7</td>
<td>2.2</td>
</tr>
<tr>
<td>Flucloxacillin/Benzyl / Clindamycin</td>
<td>6</td>
<td>1.9</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/piperacillin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin and Clindamycin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cefazolin and clindamycin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Meropenem and vancomycin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Levofoxicin and daptomycin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin and co-amoxiclav</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin and cefuroxime</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin and daptomycin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin, benzylpenicillin, clindamycin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin, metronidazole clindamycin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin, clindamycin, piperacillin/tazobactam</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin, metronidazole, cefazolin</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

#### 6.2.4 CART Analysis

A CART decision tree is presented in Figure 6.1. Numbers in the centre of each branch are the overall treatment success and treatment adjustment numbers. The numbers to the left side of each branch of the decision tree indicates patients selected by CART analysis as low-risk for treatment adjustment, and with numbers to the right indicating the opposite.

In the first branch, CART predicted that all patients aged less than 64.5 years would be treated successfully. Of the 171 patients aged less than 64.5 years, 162
had treatment success and 9 had treatment adjustment (Negative Predictive Value (NPV) for treatment adjustment = 94.7%). In the next branch of the decision tree, age < 89.5 years was selected. There were 7 patients to the right of this branch and 4 of these had treatment adjustment (Positive Predictive Value (PPV) for treatment adjustment = 57.1%). The low-risk group to the left aged less than 89.5 years but greater than 64.5 years, produced a further low-risk branch for female gender. Of the 63 patients in this branch, 56 had treatment success and 7 had treatment amendment, resulting in a NPV value of 89% for females in this age category.

Of the 66 remaining male patients, 55 had a NPSS < 2.5 and 45 of these patients had treatment success. This resulted in a NPV value of 82% for male gender with NPSS < 2.5 (45/55). Of the remaining 11 patients with NPSS > 2.5, only 6 of these are correctly classified resulting in a PPV of 54.5% for treatment adjustment (6/11).

Overall, the decision tree predicted only 10 of the 36 patients with treatment adjustment correctly (sensitivity 27.8%), but correctly predicted 263 of the 272 patients treated successfully with OPAT (specificity 97.1%).
Figure 6.1: CART analysis of risk factors associated with amendment of OPAT

6.2.5 ROC curve analysis

Results of the fitted logistic regression and CART models for treatment adjustment were compared for sensitivity and specificity using post-hoc ROC analysis (figure 6.2). The area generated combining sensitivity and 1-specificity, show the superiority of the logistic regression model with an AUC of .7528 compared to the CART AUC of .6241 (Chi-squared = 8.31, p = 0.004).
6.3 Discussion

OPAT aims to provide safe, efficacious and cost-effective care while shortening or avoiding hospital admission (95). The rate of OPAT amendment described (11.6%) is consistent with previous studies, which range from 12% to 15.3% (63, 155, 156). In a Scottish retrospective database study involving 953 SSTI patients, the rate of “OPAT failure” was 13% (63). In 2002, a trial comparing OPAT with inpatient treatment for cellulitis described a hospital readmission rate of 12% (155). More recent evidence shows rates of hospital readmission as low as 5.5% (157). In our study, hospital admission was 4.8%, with the remainder of patients responding to amendments in antibiotic treatment in the community. Since 292 (95.1%) patients enrolled to this OPAT service were managed successfully in community settings, our study is further proof of the overall safety and effectiveness of OPAT for cellulitis.
In order to continually improve patient outcomes and OPAT service delivery, identification of patient-specific factors associated with hospital readmission, change in the dose or type of prescribed treatment and duration of treatment is important (158). In this study, increased age, increased NPSS and immunocompromise were identified as risk factors for hospital readmission and change in dose or type of antibiotic. Increased age has previously been shown to predict OPAT failure (63, 65) and longer lengths of ED observation unit treatment for cellulitis (60). Increased age was also predictive of 30-day hospital readmission in a retrospective analysis of an OPAT service treating various medical conditions (159). To the best of our knowledge, immunocompromise and increased NPSS have not previously been associated with OPAT amendment for cellulitis (63, 155, 160). Immunocompromise was associated with prolongation of OPAT for cellulitis in one retrospective study by Seaton et al, however it was not associated with “OPAT failure”. NPSS is an understudied measure of cellulitis severity making comparison with currently published studies difficult (161). Since NPSS was measured for all OPAT-managed patients, our findings are representative of a typical cohort of patients with cellulitis receiving OPAT. It is intuitive that increased pain would predict poorer patient outcomes and the association of this variable with TA is deserving of further investigation. Since guidelines for patient selection for OPAT generally require stable patient symptoms and comorbidities (158), it is likely that immunocompromise and increased NPSS have been underrepresented among patients enrolled to previous studies.

Increased age, heart rate and CRP were associated with prolonged OPAT duration, with both increased age and CRP having previously been shown to be a significant risk factor in two other studies (63, 160). Recent evidence from a prospective observational study of risk factors for non-response to antibiotic treatment for cellulitis among hospitalised patients, has shown that female sex, cardiovascular disease, higher BMI and acute onset of symptoms were associated with non-response at day 3 of treatment (162).

In keeping with other studies of the management of cellulitis in ED and inpatient settings (52, 66), antibiotic prescribing for cellulitis was disparate. Antimicrobial
selection for OPAT requires a balance between appropriate prescribing principles and dosing convenience (163). In the VhiHomeCare service, choice of antibiotic treatment is at the discretion of the treating OPAT physician. In this study the majority of patients received flucloxacillin, either alone or combined with benzylpenicillin. There is limited evidence based on one small ED-based trial, to show that IV flucloxacillin monotherapy is non-inferior to combination therapy with IV benzylpenicillin for cellulitis (70). However, flucloxacillin and benzylpenicillin, although narrow spectrum, require dosing four times daily which is inconvenient for patients and potentially costly for OPAT providers. IV antibiotics with once daily dosing such as ceftriaxone represent a more cost effective option. Ceftriaxone is a first-line antibiotic for the treatment of SSTIs using OPAT in the UK (63). Teicoplanin, since it is dosed thrice-weekly, is also a useful option when there is allergy to beta-lactams or where MRSA is suspected or proven as the cause of infection (63). Given the risk of *C. difficile* infection associated with broad-spectrum antibiotics such as ceftriaxone, local antimicrobial stewardship programs, particularly in the UK, have limited the prescription of broad-spectrum agents (164). Although OPAT faces these unique challenges, early IV to oral switch and strict adherence to antimicrobial stewardship structures are recommended (163).

The recent discovery of novel antibiotics for cellulitis and other SSTIs may significantly alter the way OPAT is delivered in the future (122). Oritavancin and dalbavancin are both delivered as a single IV infusion and have been shown to be non-inferior to 7-10 days of daily vancomycin and linezolid (118, 119). Linezolid, and the more recently available drug tedizolid, have excellent oral bioavailability and may also prove comparable to currently used drugs for OPAT management of cellulitis (120). Although further research comparing these drug therapies with currently used drugs for OPAT in terms of cost, ease of use and “real-world” efficacy are required, these new drugs may improve antimicrobial stewardship through a reduction in inappropriate antibiotic use and higher quality prescribing. (163).
Decision trees are a simple, but powerful form of multivariable analysis. The CART created a decision tree based on age, gender and NPSS. Although the decision tree may appear crude, the binary decision analysis used in CART analysis can yield some clinically useful results. In our model, age was selected as the first variable of interest, with a high NPV recorded for patients younger than 64.5 years. As an initial screening tool for patient suitability we suggest that age less than 64.5 years is a clinically useful cut-point. As a next step, clinicians may consider patients aged between 64.5 and 89.5 years. In this group of patients, a second branch of the tree was formed in which female gender was associated with a NPV of 89%, indicating that female patients in this age category appear to be at a lower risk of TF than males. The role of male gender as a risk factor for TF is less clear, and it is most likely that unmeasured confounders (comorbidity status, social supports) may have influenced this result.

In the final branch of the CART analysis, NPSS was selected for the remaining (male only) patients. Although the presence of a high NPSS is an intuitive predictor of treatment amendment, it contributed to a model which overall lacked sufficient sensitivity for the CART analysis to be clinically useful. Comparison with the logistic regression model using ROC curves confirmed these limitations and affirmed the superiority of traditional methods of analysis.

As a machine learning tool the CART model is optimized for selecting and splitting variables. At each stage (node) the CART algorithm selects the explanatory variable and splitting value that gives the best discrimination between two outcomes. Given this optimization process, the CART model represents the best possible result, and no alternative models of CART analysis were generated in this WP.

6.4 Limitations

Although the data used for the study was prospectively collected at each patient encounter, ascertainment and reviewer bias during database review was possible. Independent confirmation of patient diagnosis and risk factors used to predict treatment amendment was not performed and misdiagnosis may have occurred. I
combined documented patient variables to fit broader comorbidity subtypes for the purposes of analysis, which may have introduced bias. I attempted to mitigate against this by using a standardised patient data collection form and by remaining blinded to the recorded outcome measures during data acquisition. Also the variables described on MVLR are less likely to be subject to recording bias.

Although the clinical variables reported to influence the outcome of interest were comprehensively analysed, it is not possible to exclude the possibility that unknown confounding variables, such as social support and affordability of care, may have influenced the findings of this study.

The Vhi Homecare Service is a privately operated OPAT service in Ireland and results may not be generalisable to non-privately operated OPAT services. This was a study of patients older than 18 years with cellulitis only and is not applicable to children.

6.5 Conclusions

Over 88% of patients with cellulitis were treated successfully with OPAT, while a further 6.8% required treatment amendment to elicit response. Only 4.8% of patients were hospitalised from the OPAT service. Increased patient age was associated with both OPAT amendment and prolonged OPAT duration. Increased NPSS and immunocompromise were risk factors for amendment of OPAT, while increased HR and CRP were associated with OPAT prolongation. Using CART analysis, a high specificity tool based primarily on patient age was created, with patient age < 64.5 years associated with a 95% NPV for OPAT amendment. These risk factors may be used to support an evidence-based approach to patient selection for IV antibiotic treatment in cellulitis.

7.1 Introduction

In this final thesis WP, I describe a prospective cohort study examining the prevalence and predictors of empiric oral antibiotic treatment failure among adult ED patients with cellulitis. The study methodology was subjected to external peer review and published in an Open Access journal in order to ensure internal study validity (97). Since the overarching aim of this thesis was to pilot study methodology for a larger CPR derivation project, I evaluate the recruitment, response rates, loss to follow-up and eligibility of patients with cellulitis enrolled from three EDs in Dublin, and describe the projected sample size required for a future CPR derivation study.

7.1.1 Uncomplicated cellulitis – a management dilemma

I have demonstrated from WP-2 and WP-3, that uncomplicated cellulitis constitutes the majority of patients presenting to EDs with cellulitis, yet it is this group of patients for whom treatment appears to be most heterogeneous (91, 165). When the CREST guideline is considered (51), I have shown that CREST Groups 1 and 2 do not appear to adequately discriminate between patients with cellulitis who, in the opinion of a treating EP, require either oral or IV antibiotic treatment to elicit a treatment response. It is therefore this group of “systemically well” patients for whom risk-stratification appears to be most necessary. During the process of risk-stratifying patients, the treating EP could decide whether or not to administer oral or IV antibiotic treatment at the patient’s initial presentation and so reduce the risk of treatment failure and its associated negative outcomes. The objective acquisition of clinical signs and symptoms, laboratory investigation results and demographic characteristics at the time of clinical decision making, is a valid method for determining risk factors for treatment failure (79). This process of
quantifying risk factors for antibiotic treatment failure with patient characteristics is one potential method of CPR derivation.

7.1.2 Importance of examining antibiotic treatment failure
Recent evidence has highlighted important differences in European MRSA epidemiology when compared with the US, such that CA-MRSA associated ABSSSIs are comparatively rare in Northern European ED settings (28). To the best of my knowledge there are no prospective studies in the published literature which have examined risk factors associated solely with oral antibiotic treatment failure for cellulitis in Europe. Since previous studies were performed in CA-MRSA endemic areas, the generalisability of positive risk factors for treatment failure to settings where the endemic rate of CA-MRSA is low is unknown.

Two cohort studies performed in Canadian EDs have focused on the assessment of risk factors associated with treatment failure of empirically prescribed antibiotics for cellulitis (64, 65). These studies have assessed outcome in patients who have received oral and IV antibiotic treatment at their initial ED presentation. However, knowledge of which patient risk factors are associated exclusively with oral antibiotic treatment failure for uncomplicated cellulitis, would arguably provide EPs with more useful evidence to risk-stratify patients to either oral or IV treatment during their initial ED attendance.

In the study by Murray et al (65) which combined ED patients receiving oral and IV antibiotic treatment, the overall rate of cellulitis treatment failure was 18.7% (95% CI 11.0 – 28.0%). The rate of oral antibiotic treatment failure was 6.8% (95% CI: 2.0 – 22.0%). Treatment failure was defined as specialist consultation, hospital admission, a change in antibiotics, or a surgical procedure. Change in antibiotic therapy was defined as rescue IV therapy or a change from one IV antibiotic to another. In this small study, only 29 patients were treated exclusively with oral antibiotics. Older patients, prior antibiotic treatment and a large initial diameter of infection were associated with overall treatment failure. There were no risk factors reported exclusively for oral antibiotic treatment failure, and therefore the results describe patients who failed both oral and IV antibiotic treatment.
The second study by Peterson et al (64) was also performed in Canadian EDs. A total of 598 patients were analysed comprising 185 patients administered oral antibiotic therapy, 81 administered combined oral and IV antibiotic therapy and 231 patients administered only IV antibiotic therapy. In this study, treatment failure was defined as hospitalisation for cellulitis or change in antibiotic therapy. Change in antibiotic therapy was defined as follows: a change in oral antibiotic to another oral antibiotic, a change in IV antibiotic to another IV antibiotic, or “step-up” therapy from oral to IV antibiotic. The overall rate of treatment failure was 20.5% (95% CI 17.2 - 24.3%). The treatment failure rate for patients only prescribed oral antibiotic therapy was 21.1% (no CI reported). On MVLR analysis, the combined definition of treatment failure was associated with fever at triage (OR 4.3 (95% CI 1.6-11.7), chronic leg ulcers (OR 2.5 (95% CI 1.1-5.2), chronic oedema or lymphoedema (OR 2.5; 95% CI 1.5-4.2), prior cellulitis at the same site (OR 2.1; 95% CI 1.3-3.5) and cellulitis at a wound site (OR 1.9; 95% CI 1.2-3.0). There were no risk factors reported exclusively for oral antibiotic treatment failure.

7.2 Outcome measures

The primary outcome measure in this pilot study was treatment failure defined as a change in the route of antibiotic administration from oral antibiotic to IV antibiotic. The secondary outcome measures were treatment failure measured by change in prescribed oral antibiotic to another oral antibiotic, treatment failure measured by the change in prescribed dose of oral antibiotic to a higher dose of the same antibiotic, inter-observer reliability for patient risk factor assessment, and assessment of the eligibility and loss to follow-up rate in order to pilot study methods for a larger CPR derivation study. Treatment failure did not include admission to hospital for an unrelated condition.

7.3 Results

Two sites (CHB and BH) enrolled patients for 19 months (March 2015 to September 2016 inclusive). The third site (MMUH) enrolled patients for 11 months (November 2015-September 2016). Of 2,533 patients screened for enrolment, 2,374 were excluded and 159 patients were enrolled. Due to variations in ED coding of patients with cellulitis in the three study sites we were unable to provide accurate data regarding missed enrolments. Figure 7.1 displays a flow diagram.
There were 52 patients with infected wounds (35.86%), 27 patients with abscess (18.49%), and 67 patients with cellulitis (45.89%), resulting in 31 cases of “purulent” cellulitis (21.2%), and 115 cases of “non-purulent” cellulitis (79.8%).

### 7.3.1 Primary outcome

After exclusions 146 patients were analysed. Of these, 13 had a change in route of antibiotic administration from oral to IV (8.9%; 95% CI: 5.2%-14.8%). Increased WCC count (OR 1.32; 95% CI 1.05-1.67), lesion length (OR 1.09 (95% CI: 1.03-1.14), lesion surface area 1.74 (1.09-2.79), athletes foot (OR 8.00; 95% CI 2.31-27.71) and fungal toe nail infection (OR 7.25; 95% CI 1.99-26.35) were associated
with treatment failure requiring IV antibiotic therapy. Involvement of body parts excluding the lower limb and perineum was associated with treatment success on univariate analysis (OR 0.16; 95% CI 0.06-0.26). It was not possible to conduct MVLR analysis due to the small number of patients undergoing treatment failure (n=13).

Table 7.1 Patient variables associated with treatment failure requiring IV antibiotic treatment (primary outcome measure)

Significant variables analysed by univariate logistic regression in bold with asterix

*Unless otherwise stated

Chronic co-morbidity: Chronic kidney disease, chronic liver disease, chronic cardiac disease.

Chronic venous disease: 1 of leg ulcer and/or venous eczema and/or phlebitis;

Diabetes mellitus: Type 1 or Type 2 diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total number (%)**</th>
<th>Number of patients with treatment success (%)</th>
<th>Number of patients with treatment failure (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>146 (100)</td>
<td>133 (91.1)</td>
<td>13 (8.9)</td>
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</tr>
<tr>
<td>Age (years)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>29 (19.9)</td>
<td>27 (20.3)</td>
<td>2 (15.4)</td>
<td>1.00</td>
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<tr>
<td>30-39</td>
<td>32 (21.9)</td>
<td>31 (23.3)</td>
<td>1 (7.7)</td>
<td>0.44 (0.04 – 5.07)</td>
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<tr>
<td>40-49</td>
<td>24 (16.4)</td>
<td>21 (15.8)</td>
<td>3 (23.1)</td>
<td>1.93 (0.29 – 12.61)</td>
</tr>
<tr>
<td>50-59</td>
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<td>13 (9.8)</td>
<td>2 (15.4)</td>
<td>2.08 (0.26 – 16.44)</td>
</tr>
<tr>
<td>60-69</td>
<td>21 (14.4)</td>
<td>18 (13.5)</td>
<td>3 (23.1)</td>
<td>2.25 (0.34 – 14.83)</td>
</tr>
<tr>
<td>70-79</td>
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<td>12 (9.0)</td>
<td>2 (15.4)</td>
<td>2.25 (0.28 – 17.91)</td>
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<tr>
<td>&gt;=80</td>
<td>11 (7.5)</td>
<td>11 (8.3)</td>
<td>0</td>
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</tr>
<tr>
<td>Demographic and historical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>95 (65.1)</td>
<td>86 (64.7)</td>
<td>9 (69.2)</td>
<td>0.81 (0.24-2.78)</td>
</tr>
<tr>
<td>Self referral</td>
<td>70 (47.9)</td>
<td>64 (48.1)</td>
<td>6 (46.1)</td>
<td>0.87 (0.28-2.73)</td>
</tr>
<tr>
<td>Variable</td>
<td>Total number (%)**</td>
<td>Number of patients with treatment success (%)</td>
<td>Number of patients with treatment failure (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>--------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Pre-ED antibiotic treatment</td>
<td>35 (24.0)</td>
<td>32 (24.1)</td>
<td>3 (23.1)</td>
<td>0.89 (0.23-3.44)</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>57 (46.7)</td>
<td>53 (39.8)</td>
<td>4 (30.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>&gt;=25</td>
<td>65 (53.3)</td>
<td>60 (45.1)</td>
<td>5 (38.5)</td>
<td>1.10 (0.28-4.33)</td>
</tr>
<tr>
<td>Missing</td>
<td>24 (16.4)</td>
<td>20 (15.0)</td>
<td>4 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Active smoker</td>
<td>45 (33.3)</td>
<td>41 (30.8)</td>
<td>4 (30.8)</td>
<td>1.00 (0.28-3.52)</td>
</tr>
<tr>
<td>Chronic co-morbidity</td>
<td>28 (19.2)</td>
<td>23 (17.3)</td>
<td>5 (38.5)</td>
<td>2.99 (0.90-9.97)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>4 (2.8)</td>
<td>3 (2.3)</td>
<td>1 (7.7)</td>
<td>3.53 (0.34-36.60)</td>
</tr>
<tr>
<td>Chronic Venous Disease</td>
<td>21 (14.7)</td>
<td>17 (12.8)</td>
<td>4 (30.8)</td>
<td>2.95 (0.82-10.66)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (5.5)</td>
<td>7 (5.3)</td>
<td>1 (7.7)</td>
<td>1.64 (0.18-14.53)</td>
</tr>
<tr>
<td>Active intravenous drug use</td>
<td>6 (4.14)</td>
<td>4 (3.0)</td>
<td>2 (15.4)</td>
<td>5.82 (0.96-35.40)</td>
</tr>
<tr>
<td>History of cellulitis in past year</td>
<td>18 (12.6)</td>
<td>7 (5.3)</td>
<td>1 (7.7)</td>
<td>0.55 (0.68-4.54)</td>
</tr>
<tr>
<td>Previous surgery to affected body part</td>
<td>22 (15.3)</td>
<td>20 (15.0)</td>
<td>2 (15.4)</td>
<td>1.00 (0.20-4.90)</td>
</tr>
<tr>
<td>Rigor / Self reported fever</td>
<td>32 (22.2)</td>
<td>28 (21.1)</td>
<td>4 (30.8)</td>
<td>1.63 (0.47-5.70)</td>
</tr>
<tr>
<td>Objectively self-diagnosed fever prior</td>
<td>34 (23.5)</td>
<td>30 (22.6)</td>
<td>4 (30.8)</td>
<td>1.51 (0.43-5.26)</td>
</tr>
<tr>
<td>Fever at triage</td>
<td>17 (11.6)</td>
<td>17 (12.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Average (SD) heart rate at triage</td>
<td>81.0 (13.0)</td>
<td>80.6 (13.3)</td>
<td>84.75 (9.3)</td>
<td>1.05 (0.98-1.07)</td>
</tr>
<tr>
<td>Average (SD) systolic blood pressure</td>
<td>131.5</td>
<td>130.4 (20.2)</td>
<td>140.3 (17.0)</td>
<td>1.03 (0.99-1.06)</td>
</tr>
<tr>
<td>Average (SD) capillary blood glucose</td>
<td>6.4 (3.3)</td>
<td>5.7 (1.4)</td>
<td>11.3 (6.1)</td>
<td>1.67 (0.97-2.89)</td>
</tr>
<tr>
<td>C reactive protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>12 (8.2)</td>
<td>11 (8.3)</td>
<td>1 (7.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>10–&lt;20</td>
<td>8 (5.5)</td>
<td>7 (5.3)</td>
<td>1 (7.7)</td>
<td>1.57 (0.08 – 29.4)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>28 (19.2)</td>
<td>24 (18.1)</td>
<td>4 (30.8)</td>
<td>1.83 (0.18 – 18.4)</td>
</tr>
<tr>
<td>Missing values</td>
<td>98 (67.1)</td>
<td>91 (68.4)</td>
<td>7 (53.9)</td>
<td></td>
</tr>
<tr>
<td>Average (SD) WCC count (x 10^9) *</td>
<td>10.1 (3.7)</td>
<td>9.5 (3.4)</td>
<td>13.4 (4.2)</td>
<td>1.32 (1.05-1.67)</td>
</tr>
<tr>
<td>Variables locally related to the site of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average (SD) lesion surface area (cm^2) *</td>
<td>124.8 (194.4)</td>
<td>110.9 (165.1)</td>
<td>286.6 (390.4)</td>
<td>1.74 (1.09-2.79)</td>
</tr>
<tr>
<td>Purulent discharge</td>
<td>31 (21.2)</td>
<td>28 (21.1)</td>
<td>3 (23.1)</td>
<td>1.13 (0.29-4.37)</td>
</tr>
<tr>
<td>Variable</td>
<td>Total number (%)**</td>
<td>Number of patients with treatment success (%)</td>
<td>Number of patients with treatment failure (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>--------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Fluctuance from abscess</td>
<td>27 (18.5)</td>
<td>23 (17.3)</td>
<td>4 (30.8)</td>
<td>2.13 (0.60-7.50)</td>
</tr>
<tr>
<td>Wound</td>
<td>52 (35.6)</td>
<td>50 (37.6)</td>
<td>2 (15.4)</td>
<td>0.30 (0.06-1.40)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>15 (10.3)</td>
<td>13 (9.8)</td>
<td>2 (15.4)</td>
<td>1.66 (0.33-8.34)</td>
</tr>
<tr>
<td>Athlete’s foot *</td>
<td>18 (12.3)</td>
<td>12 (9.0)</td>
<td>6 (46.2)</td>
<td>8.00 (2.31-27.71)</td>
</tr>
<tr>
<td>Fungal nail infection *</td>
<td>15 (10.3)</td>
<td>10 (7.5)</td>
<td>5 (38.5)</td>
<td>7.25 (1.99-26.35)</td>
</tr>
<tr>
<td>Lymphangitis</td>
<td>13 (8.9)</td>
<td>11 (8.3)</td>
<td>2 (15.4)</td>
<td>2.02 (0.396-10.27)</td>
</tr>
<tr>
<td>Skin breakdown due to skin</td>
<td>27 (18.5)</td>
<td>25 (18.8)</td>
<td>2 (15.4)</td>
<td>0.75 (0.16-3.60)</td>
</tr>
<tr>
<td>Chronic limb oedema including</td>
<td>16 (11.0)</td>
<td>14 (10.5)</td>
<td>2 (15.4)</td>
<td>1.48 (0.30-7.38)</td>
</tr>
</tbody>
</table>

**Numerical pain scale score**

- NPSS 0-50 mm | 68 (46.6) | 64 (48.1) | 4 (30.8) | 1.00
- NPSS 60-100 mm | 78 (53.4) | 69 (51.9) | 9 (69.2) | 2.087 (0.61-7.11)

**Anatomical location of infection**

- Leg | 79 (52.6) | 70 (52.6) | 9 (69.23) |
- Foot | 18 (11.3) | 15 (11.3) | 3 (23.1) |
- Thigh | 5 (3.8) | 5 (3.8) | 0 |
- Upper limb | 29 (19.9) | 28 (21.0) | 1 (7.69) |
- Face | 9 (6.8) | 9 (6.8) | 0 |
- Torso | 4 (3.0) | 4 (3.0) | 0 |
- Abdominal wall | 2 (1.5) | 2 (1.5) | 0 |

### 7.3.2 Secondary outcome

The 13 patients requiring a change in route of antibiotic administration from oral to IV were excluded from this analysis, leaving 133 patients. Of these, 33 required a change in type and/or dose of oral antibiotic resulting in a treatment failure rate of 24.8% for the secondary outcome measure (95% CI: 18.1%-33.0%). Univariate associations between patient risk factors and the secondary outcome measure for treatment failure are summarised in Table 7.2. Lesion length, lesion surface area, chronic limb oedema and purulent discharge were associated with treatment
failure requiring a change in the type or dose of oral antibiotic therapy. MVLR analysis was not performed also due to the small number of observations.

**Table 7.2 Explanatory variables associated with treatment failure requiring a change in dose or type of oral antibiotic (secondary outcome measure)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length; mean/SD (cm) (n=145)</td>
<td>1.06 (1.01-1.11)</td>
</tr>
<tr>
<td>Lesion surface area (cm²) (n=145)</td>
<td>1.00 (0.99-1.00)</td>
</tr>
<tr>
<td>Log lesion surface area</td>
<td>1.34 (1.02-1.73)</td>
</tr>
<tr>
<td>Purulent discharge (n=146)</td>
<td>3.68 (1.51-8.95)</td>
</tr>
<tr>
<td>Chronic limb oedema including lymphoedema (n=141)</td>
<td>3.96 (1.26-12.41)</td>
</tr>
</tbody>
</table>

**7.3.3 Inter-observer reliability**

Of the 146 patients recruited, 80 (55%) had dual completion of risk factors by an independent second study recruiter. An assessment of inter-observer reliability is displayed in Table 7.3. All variables had \( \kappa > 0.6 \) apart from the following: fluctuance (\( \kappa = 0.57 \) (95% CI 0.32-0.82), lymphangitis (\( \kappa = 0.44 \), 95% CI: 0.12-0.77), wound (\( \kappa = 0.48 \), 95% CI 0.27-0.69) and chronic venous disease (\( \kappa = 0.57 \), 95% CI 0.32-0.82).
**Table 7.3 Interobserver reliability assessment for explanatory variables examined**

*Bootstrap estimation used to calculate the CI; ** Lin's concordance coefficient

***Example interpretation (Purulent discharge): we would expect the two raters/recruiters to agree on 67/1% of the patients. In fact, they agreed on 92.2% of the patients, or 76.3% (95% CI: 58.3% - 94.3%) of the way between random agreement and perfect agreement. The amount of agreement indicates that we can reject the hypothesis (p<0.001) that they are making their determinations randomly.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Agreement - κ coefficient (unless otherwise stated)</th>
<th>κ coefficient &gt; 0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of infection *</td>
<td>73</td>
<td>0.95 (95% CI: 0.87 – 1.00)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lesion length (cm)</td>
<td>75</td>
<td>0.971 (95% CI: 0.958 – 0.984)**</td>
<td>Yes</td>
</tr>
<tr>
<td>Lesion Width (cm)</td>
<td>74</td>
<td>0.913 (95% CI: 0.875 – 0.951)**</td>
<td>Yes</td>
</tr>
<tr>
<td>Lesion surface area (cm²)</td>
<td>68</td>
<td>0.977 (95% CI: 0.966 – 0.988)**</td>
<td>Yes</td>
</tr>
<tr>
<td>Purulent discharge***</td>
<td>77</td>
<td>0.76 (95% CI: 0.58 – 0.94)</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluctuance</td>
<td>78</td>
<td>0.57 (95% CI: 0.32 – 0.82)</td>
<td>No</td>
</tr>
<tr>
<td>Lymphangitis</td>
<td>77</td>
<td>0.44 (95% CI: 0.12 – 0.77)</td>
<td>No</td>
</tr>
<tr>
<td>Ulcer</td>
<td>78</td>
<td>0.62 (95% CI: 0.36 – 0.88)</td>
<td>Yes</td>
</tr>
<tr>
<td>Wound</td>
<td>76</td>
<td>0.48 (95% CI: 0.27 – 0.69)</td>
<td>No</td>
</tr>
<tr>
<td>Athletes foot</td>
<td>75</td>
<td>0.77 (95% CI: 0.69 – 0.96)</td>
<td>Yes</td>
</tr>
<tr>
<td>Fungal nail infection</td>
<td>75</td>
<td>0.72 (95% CI: 0.51 – 0.93)</td>
<td>Yes</td>
</tr>
<tr>
<td>Skin breakdown</td>
<td>74</td>
<td>0.67 (95% CI: 0.47 – 0.86)</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic limb oedema</td>
<td>75</td>
<td>0.79 (95% CI: 0.59 – 0.99)</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic co-morbidity</td>
<td>76</td>
<td>0.83 (95% CI: 0.68 – 0.99)</td>
<td>Yes</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>73</td>
<td>0.79 (95% CI: 0.40 – 1.00)</td>
<td>Yes</td>
</tr>
<tr>
<td>Venous disease</td>
<td>74</td>
<td>0.57 (95% CI: 0.32 – 0.82)</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>76</td>
<td>0.79 (95% CI: 0.50 – 1.00)</td>
<td>Yes</td>
</tr>
<tr>
<td>Current intravenous drug use</td>
<td>76</td>
<td>0.74 (95% CI: 0.39 – 1.00)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
7.3.4 Adverse events and side effects of treatment
There were no adverse events. Fifteen patients (9.87%) reported side effects of antibiotic therapy. Vaginal thrush (n=1), rash (n=2), nausea (n=2), vomiting (n=2), abdominal pain (n=3) and diarrhoea (n=5) were described.

7.3.5 Exploratory analysis
In order to allow comparison with the definition of treatment failure utilised by Petersen et al (64), I combined both of the primary and secondary outcome measures (treatment failure for which further courses of IV or oral antibiotics were required to achieve response). In this exploratory analysis, 46 patients had treatment failure (31.5%; 95% CI 24.4%-39.6%). Statistically significant univariate associations between explanatory variables and the combined primary and secondary outcome measures are summarised in Table 7.4.

Table 7.4 Exploratory analysis of explanatory variables associated with both primary and secondary outcome measures of treatment failure

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate at triage; mean (SD)</td>
<td>1.03 (1.00-1.06)</td>
</tr>
<tr>
<td>Lesion surface area (cm²)</td>
<td>1.002 (1.00-1.005)</td>
</tr>
<tr>
<td>Log lesion surface area</td>
<td>1.33 (1.03-1.73)</td>
</tr>
<tr>
<td>Purulent discharge</td>
<td>3.02 (1.33-6.85)</td>
</tr>
<tr>
<td>Chronic limb oedema including lymphoedema</td>
<td>3.22 (1.19-9.97)</td>
</tr>
</tbody>
</table>

7.3.6 Reasons for treatment failure
“Persistent signs and symptoms of infection” (n=28; 66%), “abscess re-incision and drainage” (n=5; 11.9%), “MRSA growth” (n=4; 9.5%) and “extension of the area of infection” (n=5; 11.9%) were the reasons for treatment failure given at patient telephone follow-up. For treatment failure requiring IV antibiotic therapy (primary outcome measure), “extension of infection” (5/13), and “abscess re-incision and drainage” (4/13) were most commonly described. For treatment failure
requiring further oral therapy (secondary outcome measure) most patients described “persistent signs and symptoms of infection” (n=25; 80.6%).

There were four cases of purulent cellulitis where MRSA was cultured, and all of these were successfully treated with further oral antibiotics. Three of these were acquired in community settings and one was acquired from a healthcare setting. MRSA clonal typing was not performed.

7.4 Discussion

The primary outcome measure of this research study was to determine the treatment failure rate among ED patients prescribed oral antibiotic therapy for cellulitis, defined as a change in route of antibiotic administration from oral to IV antibiotic. This is the first prospective study to measure the prevalence and predictors of initial antibiotic treatment failure among patients with cellulitis in European EDs where CA-MRSA is not endemic. I have shown that 8.9% of ED patients with cellulitis required a change in the initial empirically prescribed oral antibiotic to IV antibiotic treatment. However, due to inconsistent definitions for ED cellulitis treatment failure in the published literature, this treatment failure rate is not directly comparable with other studies.

In a longitudinal analysis of first line antibiotic treatments for SSTI from 700 general practices in the UK, the treatment failure rate was 12.8% (73). In this study, treatment failure was defined as prescription of a different antibiotic with 30 days, hospital admission, and ED visit within 3 days. A retrospective analysis of cellulitis management in Canada showed a treatment failure rate of 13% (66), where failure was defined as change in antibiotic therapy or relapse of infection, and another retrospective study of outpatients with “uncomplicated” SSTIs from the US quoted a treatment failure rate of 24% (166).

To the best of my knowledge, there are only two published prospective cohort studies reporting the predictors of oral antibiotic treatment failure in adult ED patients with cellulitis, both performed in Canada (64, 65). In the first study where treatment failure was defined as “specialist consultation, hospital admission, requirement for IV antibiotics, or a surgical procedure”, the treatment failure rate
was 6.8% among 29 patients treated only with oral antibiotic therapy (65). In the second study, the treatment failure rate was 21.1% among 185 patients treated with oral antibiotics (64). However, treatment failure was defined as change in antibiotic therapy from one oral antibiotic to another, from oral to IV antibiotic, or hospital admission, a composite of both our primary and secondary outcomes.

The decision to prescribe oral as opposed to IV antibiotics for cellulitis is based on clinical “gestalt”. It is therefore intuitive that patients treated with oral antibiotics in the ED setting usually have less severe symptoms and signs of infection than those receiving IV antibiotics. Therefore, combining explanatory variables from both groups of patients in a composite definition of treatment failure, may lead to biased results. I contend that change in route of antibiotic administration from oral to IV, is a more meaningful outcome than a further course of oral antibiotics, both from the patient and healthcare provider’s perspective. I also believe it is important that future studies carefully define antibiotic treatment failure in order to permit the comparability and reliability of reported treatment failure rates across studies.

In my univariate analysis of risk factors for the primary outcome measure of treatment failure, I found that increasing WCC count, increasing lesion surface area, athlete’s foot and fungal nail infection were predictive of antibiotic treatment failure. Since my study population was small, I was unable to perform MVLR. Increased surface area of infection is an intuitive predictor of treatment failure and was significant for both my primary and secondary outcome measures. The mean surface area of erythema in this study (126.64 cm²) was relatively large, indicating a high decision threshold for administering IV antibiotic therapy among the recruiting physicians. In WP-3 increased diameter of infection was also associated with increased odds of prescription of IV antibiotic therapy for cellulitis among EPs (OR 5.32; 95% CI 2.34-12.1) (165). It should be noted that WCC count was only taken in 35% of the patient cohort as part of their routine care, and not specifically for this research study. Athlete’s foot and fungal nail infection are recognised risk factors for developing cellulitis, however the low number of occurrences in my study means the association of athlete’s foot and fungal nail infection with treatment failure, is unreliable.
The treatment failure rate defined as change in dose or type of prescribed oral antibiotic was higher (24.8%) than previously reported (6.8%-20.5%). In addition, the rate of treatment failure in the exploratory analysis combining both primary and secondary outcome measures was over 10% higher than that seen by Petersen et al (TF rate = 21.1% vs. 31.5%) (64). In both my exploratory analysis and analysis of patient specific risk factors for the secondary outcome measure, purulent discharge, lymphoedema, and increased infection surface area were associated with antibiotic treatment failure. It is interesting that patients with chronic leg oedema and lymphoedema were more likely to be disposed to further courses of oral antibiotic therapy, rather than IV therapy. Guidelines from the British Lymphology Society recommend administration of oral antibiotic therapy for at least 14 days from the time of onset of clinical response to infection in patients with lymphoedema complicated by cellulitis, and that this treatment should be prolonged in many cases, to courses of 1-2 months duration (167). It is therefore unsurprising that more than 7 days of oral antibiotics are administered to this group of patients. More importantly, this point highlights the limitations of interpreting a composite outcome of treatment failure among patients failing oral and IV treatment.

It is notable that patients who required IV antibiotic treatment most frequently described extension of infection and abscess re-incision and drainage as reasons for treatment failure. This contrasts with patients who were administered further courses of oral antibiotic treatment (secondary outcome measure), who described persistent signs and symptoms of infection. From these results it can be inferred that patients requiring IV antibiotic treatment described more “severe” infections, whereas patients requiring further oral antibiotic therapy described “Persisting” symptoms. Whether these cases of “persistent infection” represented true bacterial cellulitis or persisting infection erythema is unknown, and was not the focus of this WP.

Only 4 patients (2.5%) in the cohort cultured MRSA, 3 of which were community-associated. Two of these cases occurred in patients visiting one of the study EDs from CA-MRSA endemic areas. A recent ED based cross sectional study has shown that CA-MRSA accounts for only 15.1% of all S aureus associated ABSSSIs in Western Europe with only sporadic cases of PVL- toxin producing
MRSA isolated (28). In contrast, CA-MRSA accounts for up to 78% of all ABSSSI in US EDs, where the USA-300 clone predominates (24).

As shown by Murray et al (65), EPs agreed poorly on the presence of subjective cellulitis characteristics such as fluctuance, lymphangitis, the presence or absence of a wound and chronic venous disease, but had higher inter-observer agreement for objectively measured variables such as diameter of infection, chronic co-morbidity and diabetes. These results highlight heterogeneity in clinical measures of severity and cellulitis risk factors when performed by EPs. Previous studies have shown that “non-dermatologists” erroneously dispose 28-30% of patients to treatment for cellulitis, when a cellulitis mimic is in fact causing the patients’ symptoms (21).

I aimed to use the findings from this pilot study to possibly inform a larger, full-scale CPR derivation study (97). In that context, I measured over 40 explanatory variables for treatment failure. A CPR derivation study measuring only 10 explanatory variables for treatment failure would require a minimum of 1,600 patients, possibly indicating a prohibitively large sample size in a prospective study design. By recruiting patients on a 24/7 basis using experienced ED clinicians, I believe the findings of this pilot study are generalisable. Loss to follow up was low (n=8; 5%), the inter-observer reliability completion rate of 55% was higher than specified in my published protocol (10%), and measurement of outcomes at day 14 was again shown to be feasible (65, 97). I was unable to accurately describe the number of missed enrolments due to inaccuracies in hospital coding of discharged patients at the study sites. Missing data also impacted on my ability to perform MVLR, highlighting the need for funding of dedicated research assistants if a larger CPR derivation study were to be performed.

7.5 Conclusion

In this pilot study, treatment failure, defined as a change in route of antibiotic administration from oral to IV, was 8.9%. Treatment failure defined as a change in dose or type of prescribed antibiotic was 24.8%. Increasing lesion surface area was consistently associated with both definitions of treatment failure. Increased odds for IV treatment were also seen with increasing WCC, athlete’s foot and
fungal nail infection. Purulent discharge and lymphoedema were associated with further oral treatment. Telephone follow-up and inter-observer reliability assessment for cellulitis risk factors were feasible in this study. Based on the findings of this pilot study, and given the significant research investment required to perform a definitive CPR derivation study, it is crucial that a meaningful and reliable definition of treatment is agreed a priori, and a composite measurement of antibiotic treatment failure avoided.
Chapter 8: Discussion

Acute bacterial cellulitis is in many ways an enigma in modern healthcare. Despite its ubiquity, significant healthcare burden and evolving microbiological epidemiology, it remains poorly researched in terms of its aetiological epidemiology, management, risk stratification and treatment. Our approach – like the condition itself – has being broad. In this chapter, I summarise several important research outcomes from my work and consider priority issues for future research.

8.1 Aims of the dissertation

The overarching aim of this thesis was to describe the rate and risk factors for empirically prescribed oral antibiotic treatment failure among adult ED patients with cellulitis.

The specific aims of this thesis were to:

1) describe the global research output pertaining to SSTIs and the impact of the CA-MRSA epidemic on research output;

2) describe the current ED management of cellulitis, physician adherence to CPGs for cellulitis and prescribing practices for cellulitis in Ireland;

3) describe the aetiological epidemiology of cellulitis in order to cohere the existing evidence base and to pilot which patient risk factors should be studied for association with treatment failure;

4) describe the rate and risk factors for adjustment of IV antibiotic treatment for cellulitis;

5) describe the treatment failure rate and patient risk factors associated with oral antibiotic treatment failure for ED patients with cellulitis;

6) pilot study methodology for a possible future CPR derivation project.
8.2 Summary of findings

8.2.1 WP 1: Research output relevant to skin and soft tissue infections, 1945-2014: a scientometric analysis

For WP-1, a scientometric analysis was performed. Key points in the historical timeline of SSTI-related research were identified showing two relative increases in the amount of research produced; the first increase coinciding with the discovery of penicillin between 1940-45, and the second increase from 1990 onwards. The number of SSTI-related research items retrieved (n=46,567) was relatively low, supporting the opinion held by several authors in the field that SSTIs are poorly researched (1, 46, 67). A large range of journals published SSTI-related research, which highlights the interdisciplinary nature of the treatment of SSTIs. The majority of research output originated from the US.

When I performed a second search, combining CA-MRSA search terms with SSTI-related research output, the quantity of items produced from 2000 to 2008 increased exponentially. The US was over-represented in terms of the quantity of items produced.

8.2.2 WP 2: A pilot cross-sectional study of patients presenting with cellulitis to EDs

In WP-2, I performed a one-month cross-sectional study of patients attending three Irish EDs with cellulitis. I showed that the ED incidence of cellulitis was 12 per 1000 ED attendances. Almost 70% of patients were male, with over 70% of cases affecting the lower limb. The majority of patients were systemically well, with 66% of all patients in CREST Class 1. Overall, 45.8% of patients were discharged on oral antibiotic treatment and 54.2% received IV antibiotic treatment. CREST guideline adherence was poor, with 43% of patients in CREST Class 1 receiving IV antibiotic treatment despite the guideline recommending oral treatment.
I identified 3 clinical and epidemiological risk factors associated with EP decision to prescribe oral antibiotic treatment. These were self-referral (OR = 6.2, 95% CI 1.9 – 20.0, p=0.03), CREST Class 1 allocation (OR 6.81, 95% CI = 1.5-30.1, p=0.012) and duration of symptoms over 48 hours (OR 1.2, 95% CI = 1.0-1.5, p=0.049). I identified one risk factor associated with IV antibiotic treatment, which was pre-ED oral antibiotic therapy (OR 0.22, 95% CI 0.06-0.8, p=0.04). The majority of patients (89%) received oral flucloxacillin either alone or combined with penicillin V.

8.2.3 WP-3: The management of cellulitis in EDs: antibiotic-prescribing practices and adherence to practice guidelines in Ireland

In WP-3, an observational study of consecutive patients attending 6 Irish EDs was performed. The incidence of cellulitis in the 6 EDs was 6.3 per 1000 ED attendances. Patients were mostly male (63.5%), with 57.3% of cases affecting the lower limb. Fifty-eight patients (49.6%) were discharged from the ED on oral antibiotics and 59 (51.4%) were admitted for IV antibiotics.

This study also found that EP adherence to guidelines was poor. Between 32.9% and 43.5% of patients in CREST and Modified CREST group 1, and Ki-Rostein group “mild”, were prescribed IV antibiotics despite the guidelines recommending oral treatment.

I identified 3 clinical variables on MVLR analysis that were associated with the administration of IV antibiotic treatment for cellulitis by EPs. These were fever (OR 2.4 (95% CI 1.4 - 4.4)), toe-web maceration due to tinea pedis (OR 14.2 (95% CI 1.4 - 145.2)) and diameter of infection (OR 1.1 for each cm increase, 95% CI 1.0 - 1.2).

EPs prescribed a combination of oral flucloxacillin and penicillin V in approximately a third of patients, flucloxacillin alone in a third of patients, and an alternative antibiotic in a third of patients.
8.2.4 WP 4: A SRMA of Risk Factors for non-purulent leg cellulitis

This SRMA of case control studies examining risk factors for developing cellulitis was performed in order to identify clinical variables suitable for future study as risk factors for antibiotic treatment failure. In addition, I believe it was timely to cohere the existing evidence base regarding risk factors for developing cellulitis and classify this evidence into a clinically useful format of general and local risk factors. The impact of risk factor treatment has not been studied. However it is both intuitive and supported by consensus opinion, that treatment of risk factors promotes resolution of the index episode of infection and likely reduces the risk of complications, the most important of which is recurrent cellulitis (1, 3).

Of 3,059 potentially eligible studies retrieved and screened, 6 case-control studies were included. An increased risk of developing leg cellulitis was associated with previous cellulitis (OR 40.3, 95% CI 22.6 – 72.0), wound (OR 19.1, 95% CI 9.1 – 40.0), current leg ulcers (OR 13.7, 95% CI 7.9 – 23.6), lymphoedema/chronic leg oedema (OR 6.8, 95% CI 3.5-13.3), excoriating skin diseases (OR 4.4, 95% CI 2.7-7.1), tinea pedis (OR 3.2, 95% CI 1.9-5.3) and BMI > 30 (OR 2.4, 95% CI 1.4-4.0). Diabetes, smoking and alcohol consumption were not associated with leg cellulitis. Although diabetics may have been underrepresented in the included studies, local risk factors appear to play a more significant role in the development of leg cellulitis than systemic risk factors. Treatment of modifiable risk-factors including leg oedema, wounds, ulcers, areas of skin breakdown and toe web intertrigo should be performed while administering antibiotic treatment for leg cellulitis. The roles these risk factors play in determining response to treatment were studied in WP-5 and WP-6.

8.2.5 WP-5: Risk factors for amendment in type, duration and setting of prescribed IV antibiotic treatment for adult patients with cellulitis: a retrospective cohort study and CART analysis.

This retrospective cohort study of the VhiHomecare OPAT service was performed in order to measure the percentage rate and risk factors for IV antibiotic amendment for the treatment of cellulitis. Since over 95% of patients were treated
successfully with OPAT I elected to avoid the term “treatment failure” in reporting of this study’s results.

The primary outcome measure for the study was to measure the rate of treatment amendment, defined *a priori* as hospital admission, change in dose or type of antibiotic, or addition of antibiotic in order to achieve response. Secondary outcomes were to identify risk factors for treatment amendment, to identify risk factors for duration of OPAT exceeding 7 days and to describe OPAT physician prescribing practices.

CART analysis was also performed in order to derive and cross-validate a prediction rule for treatment amendment. The predictive tree was assessed for sensitivity and specificity, and compared with logistic regression using ROC curve analysis. Duration of OPAT was assessed using linear regression.

Of the 307 patients enrolled, treatment amendment occurred in 36 patients (11.7%). However, hospital admission was only 4.8%, with the remainder of patients responding to amendments in antibiotic treatment in the community. Since 292 (95.1%) patients enrolled to this OPAT service were managed successfully in community settings, this study is further proof of the overall safety and effectiveness of OPAT for cellulitis.

Significant risk factors for treatment amendment on MVLR were increased age, increased NPSS and immunocompromise. The median OPAT duration was 7 days. Increased age, HR and CRP were associated with treatment prolongation. CART analysis selected age < 64.5 years, female gender and NPSS < 2.5 in the final model, generating a low sensitivity (27.8%), high specificity (97.1%) decision tree. My findings, along with other published research, indicate that increasing age is a significant risk factor for treatment amendment in OPAT. I also identified two novel risk factors for treatment amendment - NPSS and immunocompromise. To the best of my knowledge, this is the first study to examine the association of NPSS with patient outcome for the treatment of cellulitis.

The CART algorithm yielded some interesting results and displayed good specificity but lacked sensitivity. Overall, its clinical utility is limited beyond the first “tree branch” indicating insufficient numbers of patients with treatment amendment.
for each variable measured. CART was shown to be inferior to logistic regression
modeling using ROC curve analysis.

8.2.6 WP-6: Prevalence and predictors of empiric oral antibiotic treatment
failure among adult emergency department patients with cellulitis: a
pilot study.

In this prospective cohort study of adult ED patients with cellulitis empirically
treated with a 7-day course of oral antibiotics, the primary aim was to describe the
rate of treatment failure. I used two definitions of treatment failure. The first
definition, the primary outcome measure, was the requirement for IV antibiotic
treatment in patients discharged on oral treatment. The second definition, and the
main secondary outcome measure, was defined as change in oral antibiotic to
another oral antibiotic or change in the prescribed dose of oral antibiotic to a
higher dose of the same antibiotic. Additional secondary outcome measures were
assessment of interobserver reliability for relevant clinical variables, and
assessment of the eligibility and loss-to-follow-up rate.

Follow-up assessment was performed by telephone contact 14 days after study
enrolment. Risk factors measured for association with oral antibiotic treatment
failure were generated from three previous observational studies (WP-2, WP-3
and WP-5) and a SRMA of case control studies (WP-4).

I enrolled 159 patients, 8 were lost to follow up, and 5 were excluded. Interrater
agreement for the relevant clinical variables occurred in 55% of patients. Change
to IV antibiotic treatment occurred in 13 patients (8.9%; 95% CI 5.2%-14.8%), and
33 patients required further oral treatment (24.8%; 95% CI 18.1%-33.0%).
Increased lesion surface area was associated with both primary (OR 1.74; 95% CI
1.09-2.79) and secondary outcome definitions of treatment failure on univariate
analysis (OR 1.00; 95% CI 0.99-1.00). Interrater agreement was poor for
fluctuance, lymphangitis, wound, and chronic venous disease.
Depending on how it was defined, the oral antibiotic treatment failure rate for ED patients with cellulitis varied from 8.9% to 24.8% in this study. Association of positive risk factors for treatment failure using the methods piloted would require a large sample size. A consensus definition of treatment failure is needed prior to conducting a larger definitive study.

8.3 Implications of results

From my scientometric analysis we have highlighted the important role the treatment of SSTIs have in our medical history. Recent shifts in microbiological epidemiology particularly in North America have greatly impacted the clinical manifestations and treatment of these infections. It is therefore all the more surprising that research output has remained relatively low, particularly when compared to research output in other medical fields. As has been recognised by other researchers in the field, there has been inadequate research to date regarding the treatment and risk stratification of cellulitis and other SSTIs (1, 52).

As evidenced in WP-2 and WP-3, cellulitis is a significant ED burden (91, 165). To the best of my knowledge, these two WPs were the first to measure the ED incidence of cellulitis in Ireland. However, in the absence of a nationally integrated EDIS that permits the accurate coding of patients who are discharged from ED settings, the acquisition of data regarding the ED incidence of cellulitis is currently opportunistic in Ireland. An integrated EDIS is long overdue in Ireland and was one of the key recommendations of the National Emergency Medicine Programme Report from 2012 (168).

I have shown that the management of cellulitis in Irish EDs is at variance with established CPGs, particularly when patients with “uncomplicated” cellulitis are considered. When the CREST guidelines is considered, I have shown that CREST Groups 1 and 2 do not appear to adequately discriminate between patients with cellulitis who, in the opinion of a treating EP, require either oral or IV antibiotic treatment to elicit a treatment response. It is therefore this group of systemically well patients for whom risk stratification appears to be most necessary, and for whom current treatment has been shown to be heterogeneous and without evidence. Therefore, I support the conclusion of Marwick et al/ that CREST Class 1
and 2 should be combined (67). A CPR operating for patients who are in CREST Class 1 and 2 would contribute substantially to the management of ED patients with cellulitis.

The majority of patients discharged from EDs in WP-2 and WP-3 received either flucloxacillin alone or combined with penicillin V. From WP-3, I showed that a third received flucloxacillin, a third received combined flucloxacillin and penicillin V and a third received a variety of other antibiotics. I have previously highlighted the lack of RCT-based evidence to either recommend or refute combined oral flucloxacillin and penicillin V treatment for uncomplicated cellulitis (127). As detailed below in section 7.4, a non-inferiority RCT comparing both antibiotic treatments for cellulitis would provide important evidence in order to rationalise existing antibiotic prescribing practices.

In WP-4, I have cohered the existing evidence base concerning risk factors for developing cellulitis. In my SRMA of case control studies, I have highlighted several risk factors which are worthy of modification during the patients initial attendance to the ED. It is accepted that the treatment of risk factors for developing cellulitis reduces the severity of the index episode of infection and decreases the risk of infection recurrence (2, 134). Given the significant role EPs play in the daily treatment of cellulitis, and with the advent of more OPAT services under the clinical governance of the ED, it is important that risk factor modification is undertaken at the initial ED attendance. Along with antibiotic treatment for cellulitis, I recommend that cellulitis mimics should be specifically assessed for and risk factors for developing cellulitis treated. In addition, I suggest that future researchers include these risk factors in standardised assessments of patients with cellulitis risk factors. A CPG incorporating these three facets of “cellulitis risk stratification”, “assessment for mimics” and “treatment of underlying causes” would intuitively be a useful tool for practicing ED clinicians (Appendix file 9).

By highlighting the effectiveness of OPAT for cellulitis, I have contributed to the growing body of evidence concerning the role of OPAT as a safe and efficacious alternative to hospital admission. I have identified novel risk factors associated with prolonged duration of empirically prescribed IV antibiotics and adjustment of empirically prescribed IV antibiotics for cellulitis. Increased patient age was a consistent risk factor for adjustment of empirically prescribed IV antibiotics and
prolongation of treatment beyond 7 days, indicating the need for heightened vigilance among patients older than 65 years with cellulitis. Knowledge of patient risk factors for treatment adjustment has important implications for the governance and planning of OPAT services. Finally, I also believe it was important to draw a distinction between empirically prescribed IV antibiotic “treatment failure” and empirically prescribed IV antibiotic “treatment adjustment”, and suggest that future researchers are cognisant of the important differences in this context. Extending or altering the dose or type of prescribed IV antibiotic treatment for cellulitis in an OPAT setting, differs substantially to the requirement for readmission to hospital for IV antibiotic treatment. As such I elected to utilise the term treatment failure in WP-6 rather than treatment adjustment.

I did not consider WP-5 as a potential validation set for WP-6. The most important reason is that WP-5 examined the association of patient risk factors for IV antibiotic treatment adjustment, whereas WP-6 was a study of risk factors for oral antibiotic treatment failure. Secondly, WP-5 was performed in a privately operated OPAT service in the patients own home, while WP-6 was performed in 3 urban EDs. There were also important methodological differences between the two studies. Given the disparate data-set which was retrieved from retrospectively interrogating the VHIHomecare EPMS, I was forced to combine predictor varaibles in order to conveniently measure their association with our primary outcome measure. For example, the predictor variable “immunocompromise” included patients who had HIV, chemotherapy, current cancer and splenectomy. Since WP-6 was a prospective cohort study, this limitation was obviated. Given the differing populations under study and the methodological differences between the two studies, I believe that a separate derivation study examining only oral antibiotic treatment failure among ED patients with cellulitis was necessary.

By identifying the oral antibiotic treatment failure rate associated with the ED management of “uncomplicated” cellulitis, wound infections and abscesses in Ireland, patients may be given clear, evidence-based information regarding their risk of requiring further courses of oral antibiotic treatment (24.8%) or requiring hospital re-admission for IV treatment due to treatment failure (8.9%).

The risk factors associated with oral antibiotic treatment failure are not ready for implementation in routine clinical practice. Further analysis of these explanatory
variables in a CPR derivation and validation project would be required before recommendations for use can be made. By contributing to the small body of research utilising prospective observational research techniques to describe risk factors for oral antibiotic treatment for cellulitis, my work provides important new information that may be utilised in a number of different ways. Firstly, future experts in the field may collaborate to issue consensus opinion regarding the appropriate ED risk stratification of cellulitis. Secondly, future researchers may elect to perform a CPR derivation project, enrolling several thousand ED patients with cellulitis in a prospective design. This may well be feasible in the setting of emergency care research networks where pooled resources may provide achievable sample size in a feasible time-frame. However, based on the findings of the pilot study, and given the significant research investment required to perform a definitive CPR derivation study, it is crucial that a meaningful and reliable definition of treatment failure is agreed \textit{a priori}, and a composite measurement of antibiotic treatment failure avoided.

Finally, readers of this thesis should note that the studies performed are valid only in settings where CA-MRSA is not endemic. Given the major differences in the microbiological epidemiology of cellulitis and other ABSSSIs internationally, risk factors for treatment failure may differ across different healthcare settings. Readers should also note that the results of WP-2, WP-3, WP-5 and WP-6 only apply to patients attending EDs in Ireland and may not be generalisable to other ED settings.

\subsection*{8.4 Future research}

Recently several antibiotic therapies suitable for the treatment of cellulitis, wound infections and abscesses have been developed. Oritavancin, when given in a single dose, has been shown to be non-inferior to 7-10 days of vancomycin in adults with ABSSSI caused by gram-positive bacteria including MRSA (118). Similarly dalbavancin, given once by IV infusion has been shown to be non-inferior to IV vancomycin followed by linezolid for ABSSI (119). The role of both of these agents for OPAT has not yet been evaluated. However, they have the potential to dramatically reduce the costs of OPAT, reduce the rate of line-associated infection and improve patient satisfaction(122). Although these antibiotic treatment have
proven efficacy in RCTs, there is no real-world data to recommend their administration in place of conventional therapies.

In addition to oritavancin and dalbavancin, linezolid and tedizolid offer the advantage of excellent oral bioavailability (120). Although they have been subjected to rigorous evaluation in RCTs, they have not been compared with standard beta-lactams and macrolides for the treatment of cellulitis. Further studies comparing these oral agents with standard IV antibiotics for the treatment of cellulitis using OPAT would be valuable (122).

In addition, the WPs contributing to this thesis have highlighted obvious clinical equipoise between the use of oral flucloxacillin alone or combined with penicillin V for the ED treatment of cellulitis as evidenced by current disparate prescribing practices (91, 165). A systematic literature review previously published by this research group has shown that there is no evidence from RCTs to either refute or support the combined treatment of cellulitis with penicillin V and flucloxacillin (127). Based on my work for this thesis, a successful application for funding was made to the Health Research Board, Ireland to perform a multicentre, placebo-controlled non-inferiority RCT, comparing combined flucloxacillin and penicillin V with flucloxacillin and placebo for the oral outpatient treatment cellulitis (Grant code: Heath Research Board- Health Research Award – Definitive Intervention Panel – 2015 – 1297). The RCT will be one of the first clinical trials to compare the US FDA outcome measure of early clinical response to antibiotic treatment measured at 48-72 hours post patient enrolment, with the traditional test of cure measured 14-21 days after patient enrolment, and still the outcome measure of choice issued by the European Medicines Agency (169). The WPs contributing to this thesis and in particular WP 2,3 and 4, contributed significantly to the background and feasibility sections of the grant application.
Chapter 9: References


20. NHS HESonline. *Hospital Episode Statistics*. Available at: http://content.digital.nhs.uk/hes


29. Kearns K. Healthcare Pricing Office, Hospital Inpatient Enquiry (HIPE): E-mail to Michael Quirke (michaelquirke@rcsi.ie) 2017 Feb 13.


116. Laupland KB, Ruppé E, Harbarth S. In 2035, will all bacteria be multidrug resistant? We are not sure. *Intensive Care Med* 2016; 42(12):2021-3.


139. Halpern JS. Fungal infection, not diabetes, is risk factor for cellulitis. *BMJ* 2012; 345: e5877; author reply e5881.


151. Chapman AL, Seaton RA, Cooper MA *et al.* Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in


Chapter 10: Appendix
Appendix file 1: Data collection sheet utilised in WP-2 and WP-3

DATA COLLECTION SHEET: E.D. Cellulitis Study

This study is aimed at documenting the demographic and clinical characteristics of patients presenting to the ED with cellulitis. It is also aimed at determining the ED disposition of these patients.

Please fully complete the form.

Patient Number:

Hospital Name: ___________________________________________

Date of visit: _____/____/_____ Time of visit _____: _____

1. Demographic Information

Male ☐ Female ☐ Year of birth: 19____ Occupation ___________________

2. Referral to ED

Self-referral ☐ GP referral

3. Cause of cellulitis

<table>
<thead>
<tr>
<th>Wound</th>
<th>Folliculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal bite</td>
<td>Abscess</td>
</tr>
<tr>
<td>Insect bite</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Other
______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
4. Physical Risk factors for cellulitis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Other Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Venous eczema</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>Venous ulcer</td>
</tr>
<tr>
<td>Toe web maceration +/- fungal infection</td>
<td>IVDU</td>
</tr>
<tr>
<td>Eczema</td>
<td></td>
</tr>
</tbody>
</table>

Other

5. Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Other Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Peripheral Vasc Dse</td>
<td>Chronic liver failure</td>
</tr>
<tr>
<td></td>
<td>Asplenia</td>
</tr>
</tbody>
</table>

Other

6. Location of cellulitis

7. Maximum diameter of erythema in cm

8. Duration of symptoms

9. Details of any previous cellulitis
10. **CREST Classification (Severity Stratification Score)**

   I  Afebrile, Healthy

   II  Febrile, III no co-morbidity OR systemically well with comorbidity (PVD, obesity, chronic venous disease)

   III  hypotension, confusion, tachycardia, tachypnea OR unstable comorbidities that may interfere with response OR limb threatening infection

   IV  sepsis syndrome, necrotising fasciitis

11. **Scottish early warning score:** (AVPU = alert / responds to voice / pain / unresponsive)

<table>
<thead>
<tr>
<th>Resp rate:</th>
<th>Temp:</th>
<th>Heart rate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2:</td>
<td>Systolic BP:</td>
<td>AVPU scale:</td>
</tr>
</tbody>
</table>

12. **Pre-ED treatment**

<table>
<thead>
<tr>
<th>Antibiotic Name</th>
<th>Antibiotic Dose</th>
<th>Treatment Duration</th>
</tr>
</thead>
</table>

13. **Admission to hospital:** Yes ☐ No ☐

   **Admission Antibiotic(s)**

<table>
<thead>
<tr>
<th>Antibiotic Name (s)</th>
<th>Antibiotic dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.V.:</td>
<td></td>
</tr>
</tbody>
</table>

14. **Discharge from ED:** Yes ☐ No ☐

   **Discharge Antibiotic Name**

<table>
<thead>
<tr>
<th>Antigiotic Name</th>
<th>Antibiotic Dose</th>
<th>Treatment Duration</th>
</tr>
</thead>
</table>
NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE: CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ★
   b) Yes, eg record linkage or based on self-reports
   c) No description

2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases ★
   b) Potential for selection biases or not stated

3) Selection of Controls
   a) Community controls ★
   b) Hospital controls
   c) No description

4) Definition of Controls
   a) No history of disease (endpoint) ★
   b) No description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) Study controls for _______________ (Select the most important factor.) ★
b) Study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) Secure record (e.g. surgical records) *
   b) Structured interview where blind to case/control status *
   c) Interview not blinded to case/control status
   d) Written self report or medical record only
   e) No description

2) Same method of ascertainment for cases and controls
   a) Yes *
   b) No

3) Non-Response rate
   a) Same rate for both groups *
   b) Non respondents described
   c) Rate different and no designation
CODING MANUAL FOR CASE-CONTROL STUDIES

SELECTION

Is the Case Definition Adequate?

Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records)

Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record

No description

Representativeness of the Cases

All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample)

Not satisfying requirements in part (a), or not stated.

Selection of Controls

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

Community controls (i.e. same community as cases and would be cases if had outcome)

Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population

No description

Definition of Controls
If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded.

No mention of history of outcome

**COMPARABILITY**

Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = ★, Other controlled factors = ★

**EXPOSURE**

Ascertainment of Exposure

Allocation of stars as per rating sheet

Non-Response Rate

Allocation of stars as per rating sheet
Appendix file 4: Data extraction form utilised in WP - 5

Please destroy this form after the data has been uploaded to the excel file.

Data abstractors should be blinded to final ED disposition, patient outcome, and chart information (laboratory tests and radiographs) that may bias record abstraction.

Demographic Information

• Age > 18 years
• Gender
• Weight
• Referral from home
• Nursing home referral

Vital parameters / Laboratory results

• Temperature (degrees C)
• Heart Rate beats per minute
• Respiratory Rate
• Systolic Blood Pressure
• Diastolic Blood Pressure
• SpO2
• Numerical pain scale score
• White Cell Count x 10$^9$/L
• C Reactive Protein

Local Risk factors for increased infection severity

• Lymphoedema
• Chronic ulcers undefined
• Recurrent cellulitis
• Peripheral Vascular Disease / amputation on affected limb
• Excoriating skin disease (psoriasis, eczema, dermatitis )
• Recent surgery to affected area / lymph node removal at an affected limb
• Mastectomy / lumpectomy
• Tinea pedis
• Chronic Venous Disease (varicose veins/ thrombophlebitis/ DVT)

Systemic Risk Factors for increased infection severity

• Diabetes (type 1 / type 2 / impaired glucose tolerance)
• Chronic cardiovascular disease (Ischaemic heart disease / hypertension / stroke or transient ischaemic attack, abdominal aortic aneurysm repair, atrial fibrillation, coronary artery bypass graft, implantable cardioverter defibrillator
• Kidney disease (acute or chronic)
• Immunocompromised (HIV, chemotherapy, current cancer, splenectomy)
• Smoking status
• Obesity
• Alcohol abuse

**Mechanism**

• Penetrating injury/ laceration
• Surgical wound
• Animal Bite
• Insect bite
• Burn
• Infected IV access
• Non penetrating injury
• No obvious cause/ unspecified
• Ulcer/ blister

**First antibiotic treatment**

• Antibiotic name
• Antibiotic dose and frequency
• Antibiotic duration

**Treatment success / failure**

Primary outcome

Referral to hospital for further management

**Secondary outcomes: change in prescribed antibiotic regimen in order to achieve cure**

Change of antibiotic or addition of second antibiotic to first antibiotic prescribed

Change in dose of prescribed antibiotic

**Overall duration of treatment days**

__________________
Appendix file 5: Quality assessment of included studies from WP-4 using the NOS

<table>
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</thead>
<tbody>
<tr>
<td>1. Is the case definition adequate? (&gt;1 person/record/time/process …)</td>
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<td>Yes, with independent</td>
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<tr>
<td>Yes, eg record linkage or</td>
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<td>No description (no star)</td>
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<tr>
<td>2. Representativeness of the cases</td>
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<td>Consecutive or obviously representative series of cases*</td>
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<tr>
<td>Potential for selection biases or not stated</td>
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<tr>
<td>3. Selection of controls</td>
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<tr>
<td>Community controls (same community as cases and would be case if had cellulitis)*</td>
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<tr>
<td>Hospital controls, within same community as cases (ie not another city) but hospitalised.</td>
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<td>No description</td>
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<tr>
<td>4. Definition of controls</td>
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<tr>
<td>Controls can have a previous episode of cellulitis if the cases involve patients with previous episodes *</td>
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</table>

* Selection: max one star
<table>
<thead>
<tr>
<th>Study controls for age, gender, lymphoedema, tinea etc</th>
<th>study controls for any additional factor?</th>
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<tbody>
<tr>
<td>**  ** **  ** **  *  *  *  *</td>
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</table>

**EXPOSURE: max 1 star for each section**

**1. Ascertainment of exposure**

<table>
<thead>
<tr>
<th>Secure record (surgical record/ notes) *</th>
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<tbody>
<tr>
<td>Structured interview where blind to case / control status *</td>
</tr>
<tr>
<td>Unblinded interview</td>
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<tr>
<td>Written self report</td>
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**2. Same method of ascertainment for cases and controls**

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</table>

**3. Non response rate**

<table>
<thead>
<tr>
<th>Same for both groups *</th>
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<tbody>
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<td>Non-respondants described</td>
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<td>Rate different and no</td>
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<td>designation</td>
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<tr>
<td>Risk of bias judgement</td>
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<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
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<td></td>
</tr>
</tbody>
</table>
Appendix file 6: Frequency of occurrence of risk factors in the 6 included studies (WP-4).

Risk factors included in the meta-analysis are highlighted in bold font.

1 Risk factor measured in the study

0 Risk factor not measured in the study.

* Assessed previous cellulitis only in cases with previous cellulitis vs cases with no previous cellulitis

** Eczema and psoriasis

^ Undefined skin disease

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>General Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Overweight</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2. Obesity</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3. Diabetes</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4. Alcohol</td>
<td>1</td>
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<td>1</td>
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<td>5. Smoking</td>
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<td>1</td>
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<td>6. Malignant disease</td>
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<td>8. Neurological disorder</td>
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</tr>
<tr>
<td>9. Peripheral Arterial Disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td><strong>Local risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Previous cellulitis</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11. Previous phlebitis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12. History of leg ulcers</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13. Current leg ulcers</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>14. Previous saphenectomy</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>15. Previous leg surgery</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16. Previous DVT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>17. Lymphoedema or chronic leg oedema</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>-----</td>
<td>----------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>-------------------</td>
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| 18  | 1              | 0         | 1                  | 0                 | 1               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 19  | 1              | 0         | 1                  | 0                 | 1               | 1                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 20  | 1              | 0         | 0                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 21  | 0              | 0         | 1                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 22  | 1              | 1         | 1                  | 1                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 23  | 0              | 1         | 0                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 24  | 0              | 0         | 0                  | 1                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 25  | 0              | 0         | 0                  | 1                 | 1               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 26  | 1              | 0         | 1                  | 1                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 27  | 1              | 0         | 1                  | 1                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 28  | 0              | 0         | 0                  | 0                 | 1               | **                     | 1                    | ^                       |                             |                          | 1             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 29  | 0              | 1         | 0                  | 1                 | 1               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 30  | 0              | 0         | 0                  | 0                 | 1               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 31  | 0              | 1         | 1                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 32  | 0              | 1         | 1                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 33  | 0              | 0         | 0                  | 0                 | 1               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 34  | 0              | 0         | 0                  | 1                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 35  | 1              | 1         | 1                  | 1                 | 0               | 1                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 36  | 0              | 1         | 0                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 37  | 0              | 1         | 0                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 38  | 1              | 0         | 1                  | 0                 | 0               | 1                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 39  | 0              | 0         | 0                  | 1                 | 0               | 1                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0
| 40  | 1              | 1         | 1                  | 0                 | 0               | 0                      |                      |                        |                             |                          | 0             | 0             | 0                 | 0                      | 0     |                          | 1                       | 0             | 1             | 0             | 0                        | 0

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Appendix file 7: Funnel plots of risk factors for non-purulent leg cellulitis (WP-4)

Local Risk Factors

Lymphoedema / chronic leg oedema

Previous cellulitis

Wound
Current leg ulcer

Tinea pedis causing toe-web disease

Excoriating skin disease
Previous history of ulcer

Previous history of surgery

General risk factors

Diabetes
1. **10% of all study forms must be completed by a second study recruiter.**

2. The second study recruiter must fulfil the following criteria:

   1. Be independent and blinded to the first recruiter’s case report form.

   2. Be blinded to the final decision to prescribe oral or IV antibiotics for the patient.
First Study Recruiter

Please complete the following in addition to your ED clinical records and assist the patient with the questionnaire as needed.

Date: ___/____/_______

Time: ______________

Consent obtained? Yes ☐ No ☐

If no, what is the reason for not enrolling the patient?

Refused consent?

No telephone?

Social reasons (e.g. homeless)?

____________________________________________________________________________

____________________________________________________________________________

Patient enrolment ID number: __________________________________________

Was the patient taking oral antibiotics prior to ED attendance? ____________Yes ☐ No ☐

If yes, Name ______________________ Dose _________________ Duration ________ in days

<table>
<thead>
<tr>
<th>Temp</th>
<th>Capillary blood glucose (if done)</th>
</tr>
</thead>
<tbody>
<tr>
<td>____</td>
<td>mmol/L</td>
</tr>
<tr>
<td>HR</td>
<td>CRP (if done)</td>
</tr>
<tr>
<td>____</td>
<td>mmol/L</td>
</tr>
<tr>
<td>BP</td>
<td>WCC (if done)</td>
</tr>
<tr>
<td>____</td>
<td>mmol/L</td>
</tr>
<tr>
<td>RR</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td></td>
</tr>
<tr>
<td>SpO2</td>
<td></td>
</tr>
<tr>
<td>____</td>
<td></td>
</tr>
</tbody>
</table>

Level of awareness: Alert ☐ Voice ☐ Pain ☐ Unresponsive ☐
Patient enrolment ID number: ________________________________

<table>
<thead>
<tr>
<th>Location of infection</th>
<th></th>
</tr>
</thead>
</table>

Lesion size:

<table>
<thead>
<tr>
<th>Length (“aligned head to toe”)</th>
<th>Width (“maximum diameter”)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

- Purulent discharge
- Fluctuance from abscess
- Lymphangitis
- Ulcer
- Wound (surgical or traumatic)
- Please specify ________________________________

<table>
<thead>
<tr>
<th>Athletes’ Foot</th>
<th></th>
</tr>
</thead>
</table>

- (Interdigital skin breakdown/exudate in >1 web space)
- Fungal nail infection in affected leg (if applicable)
- Skin breakdown due to underlying skin condition
- Chronic limb oedema (including lymphoedema)

**Medical History**

- Chronic underlying co-morbidity (chronic kidney/liver/cardiac disease)
- Peripheral Vascular Disease
- Venous Insufficiency (1 of leg ulcer, venous eczema, phlebitis)
- Diabetes mellitus (either Type 1 or 2)
- Intravenous Drug Use
Patient Questionnaire:

Please complete the following questionnaire to the best of your ability. Details about this study will have been given to you in the information leaflet. If you have any queries regarding the questions asked, please ask for help from the doctor or nurse treating you.

Your phone no.: Mobile _____________________ Landline _____________________

Next-of-kin phone no.: Mobile _____________________ Landline _____________________

GP name: ___________________________

Age: _______ years | Gender: Female ☐ Male ☐ | Snooker? Yes ☐ No ☐

Your weight: _______ | your height: _______________

(Circle: kg or stones or lb.) (Circle: ft. or cm)

What part of your body is affected by this infection? _____________________________

In the past year, have you had a similar infection in the same part of your body as now? ____________________________________________ Yes ☐ No ☐

Have you ever had surgery, of any kind, to the same part of your body that is now infected? ____________________________________________ Yes ☐ No ☐

Were you referred by your GP? ____________________________________________ Yes ☐ No ☐

Did you notice any uncontrolled shivering of your body? __________________________ Yes ☐ No ☐

Did you have a fever at home prior to coming to hospital? __________________________ Yes ☐ No ☐

Choose a number from 0 to 10 that best describes your current pain.

"0" would mean ‘No pain’ and 10 would mean ‘Worst possible pain’.

Mark the chart below at the number that best describes your current pain.
Second Study Recruiter

Please examine the patient and complete the following variables

Patient enrolment ID number: ___________________________________________

Location of infection ____________________________________________________________________________________

Length (“aligned head to toe”) _______ cm Width (“max diameter”)________

Purulent discharge ☐ ☐

Fluctuance from abscess ☐ ☐

Lymphangitis ☐ ☐

Ulcer ☐ ☐

Wound (surgical or traumatic) ☐ ☐

Please specify ________________________________

Athletes’ Foot ☐ ☐

(Interdigital skin breakdown/exudate in >1 web space) ☐ ☐

Fungal nail infection in affected leg (if applicable) ☐ ☐

Skin breakdown due to underlying skin condition ☐ ☐

Chronic limb oedema (including lymphoedema) ☐ ☐

Medical History

Chronic underlying co-morbidity (chronic kidney/liver/cardiac disease) ☐ ☐

Peripheral Vascular Disease ☐ ☐

Venous Insufficiency (1 of leg ulcer, venous eczema, phlebitis) ☐ ☐

Diabetes mellitus (either Type 1 or 2) ☐ ☐

Intravenous Drug Use ☐ ☐

In your opinion, what is the most likely diagnosis?________________________________________

In your opinion, will cure be achieved with oral antibiotics? Yes ☐ No ☐
Telephone follow-up

Day post enrolment: Day___________

Regarding the infection for which you were treated with antibiotics, has there been a decrease in the size of the area of infection by at least 50% from when you were first treated?

Increase ☐ Decrease ☐

Do you believe your infection has been cured?

Yes ☐ No ☐

Have you received antibiotic injections directly into a vein (intravenously) for your infection since your first assessment?

Yes ☐ No ☐

Have you required a second course of antibiotic tablets from your GP or from another doctor since you were first treated in the Emergency Department with this infection?

Yes ☐ No ☐

How have you felt since your first visit?

Well ☐ Unwell ☐

(Any adverse events should be recorded at this point in time. Describe in detail any untoward (unexpected or inappropriate) medical event regardless of its causal relationship to study treatment.)

Adverse event description _____________________________

Date of onset ________________________________________

Duration ____________________________________________

Resolution __________________________________________

Severity _____________________________________________

Outcome (Recovery, continuing, worsening, death)_________

Relationship to treatment for cellulitis?
Unrelated/Possible/Probable/Definite ____________________________

Did you require a change in your antibiotic prescription due to a skin rash or other side effect (such as diarrhoea, nausea, vomiting, thrush)?

Please specify ____________________________________________

Does the patient wish to receive the final study results?

Yes ☐ No ☐
Appendix file 9: Draft cellulitis pathway in use in Beaumont Hospital ED

Appendix 3

Non-Thrombotic Limb Pathway

Exclusions:
- Hand / Face
- Bite Wounds
- Diabetic foot
- Pregnant
- Immunocompromised

Consider mimics:
- bilateral cellulitis
- venous stasis dermatosis
- lipodermatosclerosis

Risk stratify:
- Age > 65?
- Prior oral antibiotic therapy?
- Diameter > 15 cm?
- WBC > 15?
- Bullae / Pain / Severe Lymphangitis?

Treat the Cause:
- Wound - clean, dress, topical antiseptic.
- Lymphoedema - compression therapy.
- Ulcer - debride, antiseptics.
- Athlete’s foot - topical Lamasil cream, hygiene advice.

Diagnose

Cellulitis

Abscess

Wound Infection

NO SEPSIS
ERON I/II

SEPSIS
ERON III/IV

Consider I.V. therapy

O.P.A.T. (under Surgical team on call)

- 08:00 - 15:00 (C.I.T.)
- 8:00 - 16:00 (V.H.I.)
- 16:00 - 08:00
- O.P.A.T. will be notified the following day

Surgical referral

I.V. Therapy:
FLUCLOXACILLIN 1-2g QDS if hospital admission
OR
CEFAZOLIN 2g BD/TDS if O.P.A.T.

P.O. Therapy:
FLUCLOXACILLIN 500 mg QDS x 7-10 days.
Enroll into PEDOCELL RCT
<table>
<thead>
<tr>
<th>Process</th>
<th>Clinical Clues to Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotising fasciitis</td>
<td>Acute rapidly spreading infection; marked pain, tenderness, swelling; possible crepitus, bullae and necrosis of underlying skin.</td>
</tr>
<tr>
<td>Chronic venous disease</td>
<td></td>
</tr>
<tr>
<td>Dependent rubor</td>
<td>Ischaemic process; disappears on elevation of the limb</td>
</tr>
<tr>
<td>Acute stasis dermatitis</td>
<td>Sharply demarcated erythema, papules, weeping, crustig, fissuring.</td>
</tr>
<tr>
<td>Acute lipodermatosclerosis</td>
<td>Red, indurated, warm and tender plaque; very painful; gradual onset, typically over medial malleolus; may be bilateral.</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>Erythema, hot, tender; linear pattern along vessel. Inflammation may extend beyond thrombosed vessel mimicking cellulitis.</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>Erythema only seen with proximal DVT over anteromedial thigh as vein becomes superficial</td>
</tr>
<tr>
<td>Eczema/dermatitis</td>
<td>Unlike typical cellulitis, there will be pruritis, tiny vesicles, crustig, fissuring, weeping and scaling.</td>
</tr>
<tr>
<td>Acute gout</td>
<td>Joint inflammation causing erythema, warmth, tenderness, mild fever; urate crystals.</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>May resemble cellulitis, but lower limb is not as warm as typical cellulitis. Elevation and compression therapy causes erythema to disappear.</td>
</tr>
<tr>
<td>Carcinoma erysipelatoides</td>
<td>Malignancy affecting the lymphatics of the lower extremities can closely mimic cellulitis.</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>Ulcerative condition of skin; Inflammatory bowel disease, leukaemia, rheumatoides; papule progresses to ulcer with violaceous borders.</td>
</tr>
</tbody>
</table>

NB: This is a non-exhaustive list

| Table 2: ERON’s classification of cellulitis. |
|---------------------------------------------|-----------------------------------------------|
| ERON                                        | I                                             | II                                           | III                                          | IV                                           |
| Systemic toxicity                          | No Signs                                      | systemically ill; or systemically well       | acute confusion                             | sepsis syndrome                              |
| Comorbidities                              | None                                          | o peripheral vascular disease               | o unstable co-morbidities                   | severe life threatening infection, e.g. necrotizing fasciitis. |
| Oral vs IV Antibiotics                     | Oral                                          | IV                                           | IV                                          | IV +/- Surgical debriement                    |
| In-patient vs Out-patient                  | Out-patient                                   | Hospital for 48-hours, then out-patient.     | Hospital                                    | Hospital                                     |