Division of Infectious Diseases
Inflammation Center
Helsinki University Hospital

Doctoral Programme in Clinical Research
University of Helsinki

POPULATION-BASED STUDIES ON COMPLICATED SKIN AND SKIN STRUCTURE INFECTION

Iiro Jääskeläinen

ACADEMIC DISSERTATION

To be presented, with permission of the Faculty of Medicine, University of Helsinki,
for public examination in Auditorium 2, Haartman Institute, Haartmaninkatu 3,
on November 3th, 2017, at 12 noon.
Helsinki, Finland 2017

Supervisor

Docent Asko Järvinen, MD, PhD
Division of Infectious Diseases, Inflammation Center
Helsinki University Central Hospital
Helsinki, Finland

Reviewers

Docent Ulla Hohenthal, MD, PhD
Department of Infectious Diseases, Division of Medicine
Turku University Hospital
Turku, Finland

Docent Heikki Kauma, MD, PhD
Department of Medicine, Division of Infectious Diseases
Oulu University Hospital
Oulu, Finland

Opponent

Docent Jaana Syrjänen, MD, PhD
Department of Medicine, Division of Infectious Diseases
Tampere University Hospital
Tampere, Finland

ISBN 978-951-51-3669-5 (paperback)
ISBN 978-951-51-3670-1 (PDF)

Unigrafia
Helsinki 2017

CONTENTS

To my family

ABSTRACT

Introduction. Skin and skin structure infections (SSSI) are among the most frequent human bacterial infections and an increasing indication for antimicrobial treatment both in the hospital and in the outpatient setting. In 1998, The U.S. Food and Drug Administration (FDA) classified SSSI as complicated (cSSSI) if it involves deep subcutaneous tissues, needs surgery in addition to antimicrobial therapy or affects a patient with severe co-morbidities like diabetes. Presently, practically all new antimicrobials against Gram-positive bacteria are studied before licensing on patients with SSSI. FDA recommended in 2013 that in these studies, the early treatment response (within 48–72 hours after initiation of therapy) should be used as the primary outcome measure.

The aims of this population based retrospective observational study were: (1) to assess the present characteristics and outcome of patients with cSSSI in low resistance area, (2) to analyse the factors associated with the time to clinical stability and to evaluate the association of early response to outcome, (3) to compare the microbiological aetiology and treatment practices between diabetics and nondiabetics, and (4) to compare the treatment practises of cSSSI between two cities with similar public health care structure and low incidence of antimicrobial resistance.

Study population. The study population consisted of all adult residents from two cities with nearly equal size of population (Helsinki, Finland and the Gothenburg area, Sweden) who were treated in hospital because of cSSSI in 2008–2011. First patient selection from hospital databases with specific ICD10 codes revealed 3315 patients with SSSI, of which 460 cases were severe enough to meet the above FDA criteria for cSSSI. These 460 patients constituted the final analysis population of the study.

Main results. In the final analysis population, bacteraemia was detected in 13%, treatment failure in 38%, initial antibiotic treatment modification in 39% but a switch to narrower-spectrum antibiotic treatment (streamlining) only in 5% of patients. *Staphylococcus aureus* (21%) and streptococci (16%) were the most common etiologies in monomicrobial infections. The overall mortality within 30 days was 4.1% and a recurrence within 12 months was experienced by 16% of patients.

In study II (n=402), 59% of patients had clinical stability within 3 days. In multivariable analysis, late (≥4 days) clinical stability was statistically significantly associated with admission to ICU (OR 10.1, 95% CI 4.01–25.3), posttraumatic wound infection (OR 3.17, 95% CI 1.31–7.69), bacteraemia

(OR 3.09, 95% CI 1.36–7.02), surgical intervention after diagnosis (OR 2.64, 95% CI 1.36–5.11), diabetes (OR 2.33, 95% CI 1.28–4.25) and initial broad-spectrum antibiotic therapy (OR 3.03, 95% CI 1.43–6.40). Early stabilization (within 3 days) was associated with previous hospitalization (OR 0.47, 95% CI 0.22–0.99) and empirical antimicrobial therapy covering the initial pathogens (OR 0.38, 95% CI 0.18–0.80). Patients with clinical stability within 3 days were less likely to have treatment modifications and antimicrobial changes and had shorter hospital stay and antimicrobial treatment than those who stabilized later.

In study III, after exclusion of patients with diabetic foot infection (DFI), there was no difference in the microbiological aetiology or initial antimicrobial treatment of cSSSI between diabetics and nondiabetics. Yet, diabetes was the only baseline characteristic associated with broad-spectrum antimicrobial use and long (≥17 days) antibiotic treatment duration.

In study IV, patients in Helsinki, as compared to those in Gothenburg, were treated more often with antimicrobials with Gram-negative coverage (in initial treatment 96% versus 47%, $p<0.001$), had more treatment modifications (mean 4.3 versus 2.7, $p<0.001$) and longer median duration of antimicrobial therapy (29 days versus 12 days, $p<0.001$) and longer in-hospital stay (17 days versus 11 days, $p<0.001$). During their hospital stay, 57% of patients in Helsinki visited more than one department while in Gothenburg 85% of patients were treated in only one department. These observations were unlikely explained by the differences detected between the cities in the baseline and disease characteristics of the patients.

Conclusions. In this population based real-life study, bacteraemia, clinical failures, recurrences and treatment modifications (other than streamlining) were more common than in previous non-population-based studies. The study observations suggest that time to treatment response depends on several baseline and disease related characteristics other than treatment related factors and that early treatment response was associated to better outcome. This study also suggests that diabetics without DFI, as compared to nondiabetics, are not different in the causative agents of cSSSI, but they were more exposed to antimicrobial therapy of inappropriate extended spectrum and long duration. Furthermore, this study revealed remarkable differences in the treatment and management of cSSSI between two Nordic cities. Importantly, the real-life observations of our study have detected several targets for antimicrobial stewardship.

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following four original studies, which are referred to in the text by their Roman numerals I–IV.

I Jääskeläinen IH, Hagberg L, From J, Schyman T, Lehtola L, Järvinen A. Treatment of complicated skin and skin structure infections in areas with low incidence of antibiotic resistance- a retrospective population based study from Finland and Sweden. Clin Microbiol Infect. 2016 Apr;22(4):383.e1,383.e10.

II Jääskeläinen IH, Hagberg L, Forsblom E, Järvinen A. Factors associated with time to clinical stability in complicated skin and skin structure infections. Clin Microbiol Infect. 2017 Sep;23(9):674.e1, 674.e5.

III Jääskeläinen IH, Hagberg L, Forsblom E, Järvinen A. Microbiological Etiology and Treatment of Complicated Skin and Skin Structure Infections in Diabetic and Nondiabetic Patients in a Population-Based Study. Open Forum Infect Dis. 2017 Mar 10;4(2):ofx044.

IV Jääskeläinen IH, Hagberg L, Schyman T, Järvinen A. A potential benefit from infectious disease specialist and stationary ward in rational antibiotic therapy of complicated skin and skin structure infections. Infect Dis (Lond). 2017 Aug 08:1-10.

ABBREVIATIONS

AIC	Akaike information criteria
ABSSSI	Acute bacterial skin and skin structure infection
ANOVA	The analysis of variance
BHS	β-hemolytic streptococci
BMI	Body mass index
CA-MRSA	Community-associated methicillin resistant *Staphylococcus aureus*
CDC	The Center for Disease Control and Prevention, USA
CI	Confidence interval
CRP	C-reactive protein
cSSSI	Complicated skin and skin structure infection
CT	Computed tomography
DFI	Diabetic foot infection
FDA	The U.S. Food and Drug Administration
GAS	Group A *Streptococcus pyogenes*
HA-MRSA	Health-care associated methicillin resistant *Staphylococcus aureus*
HAI	Health-care associated infection
ICD-10	International statistical classification of diseases and related health problems
ICU	Intensive care unit
IDSA	The Infectious Disease Society of America
IDU	Intravenous drug user
LOS	Length of hospital stay
MRI	Magnetic resonance imaging
MRSA	Methicillin resistant *Staphylococcus aureus*
MSSA	Methicillin sensitive *Staphylococcus aureus*
NSTI	Necrotizing soft tissue infection
OR	Odds ratio
PCT	Procalcitonin
PS	Propensity-score
PTE	Post-treatment evaluation
PVD	Peripheral vascular disease
SD	Standard deviation
SEWS	Standardized early warning score
SSI	Surgical site infection
SSSI	Skin and skin structure infection
SSTI	Skin and soft tissue infection
uSSSI	Uncomplicated skin and skin structure infection
WBC	White blood cell
WSES	The World Society of Emergency Surgery

1 INTRODUCTION

The skin together with the subcutaneous tissue is the largest organ of the human body, accounting for 15–25% of the total body weight [1]. As the outermost layer of the body one of its main function is to serve as a physical barrier and to protect from an invasion of microbes [1]. The human skin is colonized by a variety of microorganisms, including bacteria, fungi, viruses and mites [2]. Most of those microbes of the normal flora are harmless or even beneficial and they may act as a competitive inhibitor of pathogenic microbes [2].

Skin and skin structure infection (SSSI) reflects an invasion of microbes, usually after damage to skin, and the causative inflammatory reaction in any of the three layers of skin – epidermis, dermis or subcutaneous tissue – or to fascia between subcutaneous tissue and muscle. SSSIs are usually classified according to the anatomical site of infection (Figure 1) but classifications by severity, purulence or microbial aetiology of infection have also been utilized [3,4]. Gram-positive aerobic cocci – particularly streptococci and *Staphylococcus aureus* – are the most common causative agents of SSSIs, but in complicated cases also Gram-negative rods and anaerobic bacteria are frequently detected [5-8].

SSSIs are among the most frequent human bacterial infections and antimicrobial treatment is increasingly used for them for both in the hospital and in the outpatient setting [9-14]. The mildest SSSIs can be treated without systemic antimicrobial therapy, either by topical treatment (e.g. local impetigo) or by incision and drainage (e.g. simple abscess) [4]. In the United States, the annual incidence of clinically diagnosed SSSI was calculated as 496/10'000 inhabitants [11]. During a 7-year period totally 4'891'187 hospital admissions with a primary diagnosis of SSSI were identified in the U.S. [15]. In Finnish health care centers during 1998–2002, SSSIs were the sixth most common infection, accounting for 6% of all infection-related doctor's appointments [16]. These figures have not been bypassed unseen by the medical industry and practically all new antimicrobial agents against Gram-positive bacteria are currently studied in patients with SSSI before licensing.

SSSI is generally regarded as complicated (cSSSI) if it involves deep subcutaneous tissues, needs surgery in addition to antimicrobial therapy or affects a patient with severe co-morbidities [17]. Our population-based survey was conducted in Helsinki and Gothenburg during 2008–2011, and the above criteria were utilized to find patients with cSSSI. Our objective was to evaluate the background and disease characteristics, treatment and outcome of cSSSIs in real-life population-based setup. High affinity to public health-care in the Nordic countries enabled the population-based approach with more comprehensive patient material, in contrast to clinical trials with selected patients and to observational studies made in selected hospitals.

2 REVIEW OF THE LITERATURE

2.1 DEFINITIONS OF SSSI

A skin and skin structure infection (SSSI) is an infection affecting skin and/or subcutaneous connective tissue. Several classification systems have been used to describe SSSIs but none of them is universally accepted [18]. In general, SSSIs can be classified to purulent or non-purulent infections and on the other hand by the depth of infection. Purulent SSSIs include folliculitis, furuncle, carbuncle, abscess and inflamed epidermoid cyst (Table 1) and non-purulent SSSIs comprise, from the most superficial to the deepest infection, impetigo/ecthyma, erysipelas, cellulitis and necrotizing fasciitis (Table 1 and Figure 1). Although it may be anatomically incorrect infectious (necrotizing) myositis is often included in SSSIs.

Table 1 *Overview of the different skin and skin structure infections according to anatomical site of infection (wound infections not included)* [4].

	Infection	Infected structure or layer of the skin	Most common causative agent(s)	Treatment
purulent	folliculitis	hair follicle	*S. aureus*	topical antimicrobial
	furuncle	hair follicle, dermis and subcutaneous tissue	*S. aureus*	incision and drainage (systemic antimicrobial [a])
	carbuncle	multiple hair follicle, dermis and subcutaneous tissue	*S. aureus*	incision and drainage (systemic antimicrobial [a])
	abscess	any layer of the skin	*S. aureus*	incision and drainage (systemic antimicrobial [a])
	inflamed epidermoid cyst	epidermoid cyst	normal skin flora	incision and drainage (systemic antimicrobial [a])
non-purulent	impetigo	superficial epidermis	*S. aureus* and streptococci	topical (or oral [b]) antimicrobial
	ecthyma	deeper epidermis	*S. aureus* and streptococci	systemic (oral) antimicrobial
	erysipelas [c]	superficial dermis	streptococci	systemic antimicrobial
	cellulitis [c]	deeper dermis and subcutaneous tissue	streptococci (*S. aureus*)	systemic antimicrobial
	necrotizing fasciitis	fascia between subcutaneous tissue and muscle	usually polymicrobial	surgical debridement and systemic antimicrobial

[a] For patients with severely impaired host defenses or signs or symptoms of systemic infection
[b] For patients with numerous lesions or in outbreaks affecting several people
[c] In European countries, cellulitis and erysipelas are used often as synonyms

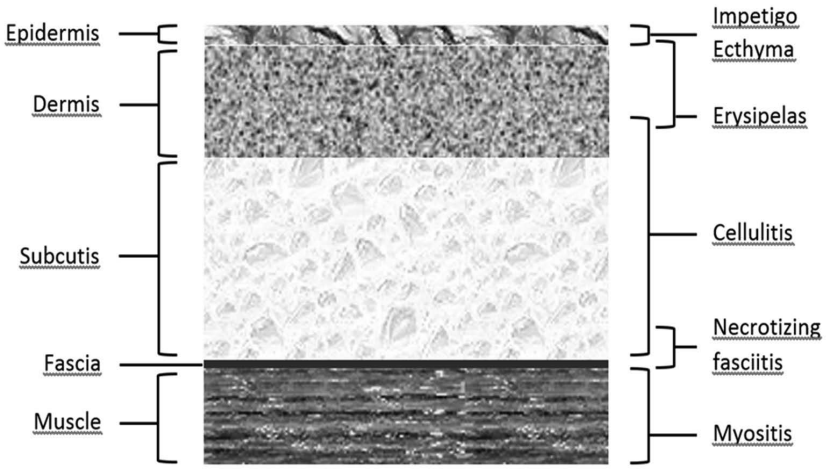

Figure 1 *Schematic picture of the skin and localization of the different types of non-purulent infections.*

The skin consists of several layers (Figure 1) and structures each of which can be affected by an infection (Table 1). Evaluation of the depth of SSSI – particularly distinction between erysipelas and cellulitis – is not so clear-cut in practise, therefore clinicians often use the term erysipelas as a synonym to cellulitis, beyond the classic definition [19,20]. When compared to cellulitis, erysipelas affects only the superficial part of dermis and the skin lesion is slightly elevated and sharply demarcated from the surrounding unaffected skin [21]. In clinical practise, the distinction between erysipelas and cellulitis is usually not crucial since they have similar risk factors and mostly similar aetiology and treatment [4-6,22,23].

2.1.1 DEFINITIONS OF SSSI USED IN CLINICAL STUDIES AND GUIDELINES

Initially for the purpose of clinical trials for new drugs for SSSIs, in 1998 The US Food and Drug Administration (FDA) divided SSSIs into two categories: Complicated (cSSSI) and uncomplicated (uSSSI, Table 2). SSSI was considered as complicated if it involves deeper soft tissue (e.g. fascia or muscle) or rectal area, requires significant surgical intervention or affects a patient with a significant underlying disease that complicates the treatment response [17]. Therefore, the umbrella of cSSSI covers a variety of infections sharing common microbiological features, such as infected ulcers and burns, major abscesses, deep subcutaneous infections and infections in diabetics or patients with vascular insufficiency. In contrast, simple abscesses, impetiginuous lesions, folliculitis, furuncles and superficial cellulitis are

examples of uSSSIs. The disease process of SSSI is not rigid and uSSSI may escalate to cSSSI if not managed properly.

A definition "acute bacterial skin and skin structure infection" (ABSSSI), was introduced in 2013 by the FDA in guideline on developing drugs for treatment of SSSI, and included cellulitis/erysipelas, acute wound infections and major skin abscesses with a minimum lesion surface area of 75 cm^2 (Table 2) [24]. For example, diabetic foot infections (DFI), deep subcutaneous and necrotizing infections are excluded from the umbrella of ABSSSI.

Table 2 *The characteristics of different classifications used in clinical trials of skin and skin structure infections.*

Classification	Characteristic	Infections included in the classification
uSSSI	Superficial skin infections or infections that can be treated by incision and drainage alone	Simple abscesses, impetigo, folliculitis, furuncles and superficial cellulitis
cSSSI	Skin infection that involves deeper soft tissue or rectal area, requires significant surgical intervention or affects a patient with significant underlying disease that complicates the response to treatment	Infected ulcers and burns, major abscesses, deep subcutaneous infections and diabetic foot infection
ABSSSI	Bacterial skin infection, minimum lesion area 75 cm^2	Cellulitis/erysipelas, acute wound infection and major skin abscess

uSSSI, uncomplicated skin and skin structure infection
cSSSI, complicated skin and skin structure infection
ABSSSI, acute bacterial skin and skin structure infection

The Infectious Disease Society of America (IDSA) has retained the term "skin and soft tissue infection" (SSTI), a synonym to SSSI, in their nomenclature [4]. Particularly in the perspective of treatment, in their recent guideline IDSA classifies SSTIs into two broad categories, non-purulent and purulent and further identifies 10 different types of SSTIs (Table 1) [4].

A clinical management oriented classification of SSTI suggested by Eron et al includes four levels of severity: 1. Patients with no signs or symptoms of systemic toxicity or co-morbidities; 2. Patients that are systemically unwell with stable co-morbidities or systemically well but have a comorbidity that may complicate the course of disease; 3. Patients appear toxic (e.g. tachycardia, tachypnea or hypotension) or non-toxic but have unstable comorbidities that may delay response to therapy; 4. Patients with sepsis syndrome or life-threatening infection, e.g. necrotizing fasciitis [3]. In the

Eron classification cSSSIs are located in Classes 2–4. Marwick et al. modified the Eron classification by utilizing sepsis criteria and standardized early warning score (SEWS) in particular to separate severity classes 3 and 4 [25-27]. SEWS scoring system includes following parameters: respiratory rate, blood oxygen saturation, body temperature, blood pressure, heart rate and level of consciousness [27].

The World Society of Emergency Surgery (WSES) used three categories in their recent guideline for the treatment of SSTI: Surgical site infections (SSI), non-necrotizing SSTIs and necrotizing SSTIs (NSTI) [28]. Non-necrotizing SSSIs usually involve the superficial layers of the skin (epidermis and dermis) and subcutaneous tissue, while necrotizing SSSIs most usually affect the deeper fascia and muscle [29]. In literature some terms of necrotizing SSSIs are also based either on anatomical site (necrotizing fasciitis of anogenital region, i.e. Fournier´s gangrene) or on microbiological aetiology (e.g. clostridial gas gangrene).

Health-care associated infections (HAI), including SSIs, are important groups of SSSI. The Center for Disease Control and Prevention (CDC) divides health-care associated SSSIs into skin (skin and subcutaneous tissue) and soft tissue (fascia and muscle) infections [30]. When SSI is at issue, the former group constitutes superficial and the latter deep incisional SSIs, respectively [31]. The deepest of SSIs – organ space infections – are not SSSIs.

In conclusion, SSSIs can be classified from many perspectives and no universally adopted classification system exists. Complicated SSSIs represent a heterogeneous group of disorders ranging from severe infection in a patient with no co-morbidities to relatively minor infection in patient with major co-morbidities that may complicate treatment response. Although initially designed for the purpose of clinical trials, the umbrella term cSSSI used in this thesis is still valid and useful in the detection of the most severe forms of SSSIs [32]. In our studies the goal was to catch the patients with the most serious infection, therefore we did not exclude any severe entities (e.g. necrotizing fasciitis) that are usually left out in clinical trials among patients with cSSSI.

2.2 EPIDEMIOLOGY OF CSSSI

2.2.1 INCIDENCE OF CSSSI

Several studies have detected an increasing incidence of SSSIs and rate of hospital admissions for SSSI during the last decades [9-12], while the

hospital admissions for pneumonia has remained relatively constant [12]. Most recently, the annual incidence of clinically diagnosed SSSI in the United States was calculated as 496/10'000 [11] and hospital admissions due to SSSI increased from 1.6% (2005) to 2.0% (2011) of the total hospital admissions [15]. In contrast, Miller et al found the incidence of SSSI to been relatively constant among persons less than 65 years in the U.S. population during 2005–2010 [33]. They detected the annual incidence of SSSIs around 480/10'000, approximately two and ten-fold higher than the incidences of urinary tract infection and pneumonia in the same study population [33]. In the United Kingdom, three-fold increase was found in the annual hospital admissions due to abscess or cellulitis during 1990–2004 and up to four to five-fold higher hospitalization rate was detected in the oldest (≥85 years) patients in comparison to the younger age groups (15–44 years and 45–64 years) – the annual hospitalization rates due to SSSI were 634/100'000 and 123/100'000 among them in 2003–2004, respectively [13]. The incidence of SSSIs has been consistent with the reported increase of community-associated methicillin-resistant *S. aureus* (CA-MRSA) infections [10,12].

In a European point-prevalence survey, SSSIs combined with bone and joint infections were the second most common indication of antimicrobial treatment after pneumonia and comprised 18% of the total antibiotic use [34]. In the U.K., a rise in the amount of antibiotic prescriptions for SSSI among out-patients was detected during 1991–2012 [14]. After pneumonia and intra-abdominal infections, SSSIs are the third most frequent cause of severe sepsis or septic shock, accounting for about 10% of all cases of septic shock [35-37]. SSIs are the most common HAI in U.S. affecting overall 1.9% of the patients after surgical procedure during 2006–2008 [38].

Due to heterogeneity of the disease entity and lack of population based studies the incidence of cSSSI in general population is largely unknown. Miller et al suggest the incidence of cSSSI to be as high as 20/1000 person years, yet their criteria for complication differed from the original FDA criteria [17,33].

2.2.2 RISK FACTORS OF CSSSI

To the best of my knowledge, any case-control studies comparing patients with cSSSI to general population to evaluate risk factors specifically for cSSSI have not been made. However, in addition to diseases defining SSSI as complicated, case-control studies made in patients with cellulitis have detected several risk factors to skin infection: obesity, chronic leg oedema, prior saphenectomy, history of previous cellulitis, skin lesion as a possible site of bacterial entry and bacterial colonization of toe-webs as risk factors for cellulitis of the lower extremity [22,23,39,40]. The incidence of cellulitis increases with age [41]. In a Danish observational study, obesity was detected

as a risk factor for skin abscess in both sexes and for other types of SSSI in men [42].

Patients' background characteristics (e.g. co-morbidities) have been evaluated in the observational studies of cSSSI. The most frequent comorbidities observed among patients with cSSSI have been diabetes mellitus (24%–35%) and peripheral vascular disease (PVD, 7%–21%) [43-47]. Malignancy (4.0%–20% of patients with cSSSI), chronic renal disease (10%–17%), immunosuppression (3.5%–15%), intravenous drug abuse (2.3%–14%), chronic pulmonary disease (3.0%–13%), chronic liver disease (4.0%–12%), and congestive heart disease (3.7%–12%) have also been pointed out as usual comorbidities in patients with cSSSI [43-47].

In comparison to general population, patients with diabetes are more susceptible to variety of infectious diseases, have more community-based antibiotic prescriptions and increasing rates of hospitalizations due to infection, including SSSI [48-51]. Diabetes predisposes to the development of SSSI through multiple mechanisms. First, *in vitro* studies have shown that neutrophil function is reduced and that humoral immunity and antioxidant systems may be impaired in diabetes [52-54]. Second, due to peripheral polyneuropathy diabetics are prone to the development of foot ulcers, which offer a site of entry to pathogens. The lifetime risk for a diabetic patient to develop an ulcer is estimated to be as high as 25% [55]. Third, patients with diabetes have up to four-fold higher risk of developing PVD compared to patients without diabetes [56]. The combination of PVD and infection was observed to have a major impact on the healing rate of foot ulcer [57] and in another study PVD was an independent predictor of infection-related mortality [58].

Subcutaneous or intramuscular, instead of intravenous, injections are major risk factors for abscesses and SSSIs are the most common cause of hospital admission among intravenous drug users (IDU) [59,60]. In the U.K. in 2009, 28% of IDUs reported an injection site infection with a variable severity [61].

2.3 DIAGNOSIS AND PATHOGENESIS OF CSSSI

Typical presentation of a skin and skin structure infection incudes the four classical local signs of inflammation described in the first century by Celcus – calor, rubor, tumor and dolor (heat, redness, swelling and pain). A fifth local sign (fluor, discharge), systemic signs of inflammation (fever, tachycardia and tachypnea) and lymphangitis with inflammation of regional lymph nodes are also frequently present in cSSSI. Systemic signs may sometimes be present before the local signs of infection appears.

SSSIs arise usually by a direct microbial invasion after a disruption of the skin surface and rarely by a haematogenous spread of microbes from a remote infection focus. The portal of entry of the microbes may be obvious, such as ulceration or trauma, or small and difficult to detect, or even not located in the site of SSSI. Compared to intact skin, breaks in the skin allow colonization with a broader range of microbes [2]. Clinically important, microbial colonization of damaged skin does not usually result in inflammation or infection and therefore is not an indication of antimicrobial treatment [32]. In the pre-antibiotic era, the most typical location of erysipelas was the face, but currently erysipelas most likely affects the lower extremity, wherein cSSSIs are also typically located [45,62].

In contrast to abscess with high microbial density, cellulitis is a paucibacillary infection, characterized by an intensive inflammatory response and more scattered microbial spread in the tissue [63]. Important from the point of therapeutic view, inflammation surrounding a collection of pus (e.g. abscess) is not regarded as a cellulitis [4]. Necrotizing fasciitis is an aggressive infection affecting usually the superficial fascia between the subcutaneous tissue and muscle, which allows the rapid spreading of the infection. Pain "out of proportion" and swelling beyond the area of apparent skin involvement and signs of systemic toxemia are the most distinctive features of necrotizing fasciitis [64]. Recognition of abscess – and especially necrotizing infection – is of paramount importance, since the primary treatment of these entities is surgical [28,64].

2.3.1 BIOMARKERS

Eder et al. found PCT and CRP levels to be higher in patients with cSSSI than in patients with SSSI, median PCT levels 0.3 ng/ml versus 2.0 ng/ml and CRP 135 mg/l versus 263 mg/l, respectively [65]. In a study on group A streptococcal (GAS) skin infection, patients with invasive infection had more likely blood neutrophil percentages of above 80 (81% versus 48%) and higher CRP level (mean 205 mg/l versus 78 mg/l) than patients with noninvasive infection [66].

PCT has been observed to have a high discriminatory value for differentiation of erysipelas from deep venous thrombosis with clearly higher PCT level (median PCT 0.17 μg/l vs 0.08 μg/l, p=0.001) [67]. In contrast, statistically significant differences between these groups in CRP (median 76 mg/l versus 33 mg/l, p=0.200) or WBC (median 10.7 versus 8.6, p=0.140) were not detected [67].

In one study PCT, WBC, CRP and erythrocyte sedimentation rate showed a positive correlation with the length of hospital stay in patients with cellulitis [68], while another study found no correlation between PCT and length of in-hospital treatment in patients with SSSI [65]. According to the

studies by Lipsky et al and Karppelin et al, CRP has no prognostic value on treatment failure of cSSSI [69] or recurrence of cellulitis [70].

2.3.2 RADIOLOGY

In Denver (U.S.), Jenkins et al. detected frequent use of imaging studies among hospitalized patients with SSTI but a low yield (4%) for identification of deep infection [71]. Imaging studies were performed in total to 82%, plain film radiograph to 61%, ultrasonography to 25%, CT to 15% and MRI to 7% of the patients, respectively [71]. Furthermore, in the study by Gundersen et al ultrasonography was conducted to 73% of the patients with cellulitis and ipsilateral deep venous thrombosis was found only in 1% of the patients [72].

In necrotizing fasciitis, the routine use of computed tomography (CT) or magnetic resonance imaging (MRI) is not recommended – although they may show edema extending along the fascial plane [4,28,73]. If necrotizing fasciitis is suspected, one should rather perform a deep diagnostic incision instead of extensive imaging to prevent the delay to definitive surgical treatment [74]. In diabetic foot infection MRI is superior to other imaging modalities in diagnosis of osteomyelitis [75] and it is also frequently used in the evaluation of need for any kind of surgical intervention [76].

2.4 AETIOLOGY OF CSSSI

Streptococci and *S. aureus* are the most common causative agents of non-purulent and purulent SSSIs, respectively [5,6]. In complicated cases also Gram-negative rods and anaerobic bacteria may play a role, as the definition of cSSSI suggests [7,8]. The microbiological aetiologies of the various infection entities under the umbrella of cSSSI are to be reviewed below in detail.

Bacterial culture is the primary method for detecting the microbiological aetiology of SSSI. The sensitivity of bacterial culture is generally higher in purulent infections, but in cellulitis only 10–40% of needle aspirations [63,77-79] and 20%–30% of punch biopsy specimens [63,80] of the inflamed skin were positive. Blood cultures are generally positive in ≤5% of patients with cellulitis [81], and in observational studies of cSSSI 4%–6.3% of the patients have been reported to be blood culture positive [44,71]. Bacterial cultures – especially those of superficial swabs – may detect also bacterial colonization in addition to causative microbiological agents and therefore tissue specimens from the deeper tissues are preferred to prevent unnecessary broad-spectrum antimicrobial treatment [4]. Cultures of blood or cutaneous aspirates, biopsies or swabs are not routinely recommended in

uncomplicated SSSI [4]. However, in patients with severe infection or in patients with risk factors for Gram-negative infection, such as malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites cultures of blood are recommended and cultures and microscopic examination of cutaneous aspirates, biopsies, or swabs should be considered [4].

2.4.1 CELLULITIS

β-haemolytic streptococci (BHS), particularly group A and G streptococci, are the most common microbiological aetiologies in non-purulent cellulitis [5,6,63,82]. Though *S. aureus* is frequently isolated from skin breaks associated to non-purulent cellulitis, it may represent merely a colonization and it´s role as a causative agent of non-purulent cellulitis is controversial [6,83]. On the contrary, the role of *S. aureus* has been demonstrated in cellulitis associated with an abscess, wound infection or previous penetrating trauma [4,84]. Numerous other organisms can also cause cellulitis in special circumstances, typically in patients with freshwater (*Aeromonas* spp.) or saltwater (*Vibrio* ssp.) injuries, neutropenia (Enterobacteria, *Pseudomonas aeruginosa*, *Acinetobacter* spp.) or severe cell-mediated immunodeficiency (Fungi) [4,19,85-87].

2.4.2 ABSCESS

Microbiological aetiology of skin and subcutaneous abscesses can be polymicrobial and differ according to the microbiological flora of the skin or mucous membranes on the originating site of infection [4,88,89]. Therefore a variety of micro-organisms can be isolated from abscesses, including Gram-positive cocci, Gram-negative bacteria, anaerobes and *Clostridium* species although *S. aureus* alone is detected in a large percentage of these infections [88,90]. In addition to skin flora, IDUs can have an infection caused by microbes of oral or faecal flora or environmental contamination [28,89].

2.4.3 BITES

Microbes isolated from infected bite wounds are most often reflective of the oral flora of the biting animal or human but may also originate from the victim's own skin or the physical environment at the time of injury [4,91]. Bite wound infections with purulence are usually polymicrobial. *Pasteurella* species are the most commonly isolated bacteria in infections after dog or cat bite and streptococci and staphylococci are the next common isolates [92]. Anaerobes are common but rarely the only bacteria found in infected cat or dog bite [92]. *Capnocytophaga canimorsus* infection after a dog bite

warrants a special mention due to high risk of systemic complications in immunocompromised (particularly in splenectomised) patients [91]. Microbiology of infection after human bite is usually complex, frequently detected organisms include streptococci, *S. aureus*, *Eikenella corrodens* and anaerobes, such as *Fusobacterium*, *Prevotella* and *Peptostreptococcus* species [93].

2.4.4 BURN WOUND INFECTION

The majority of burn wound infections are polymicrobial with Gram-positive bacteria dominance initially but Gram-negative bacteria usually colonize burn wounds within a week after injury [28]. In a recent Swedish study among patients treated in burn center, the most frequently detected microbes were coagulase-negative staphylococci (20%), *S. aureus* (19%), Enterobacteria (16%), enterococci (10%), streptococci (10%), *P. aeruginosa* (4.6%), and *Candida* spp. (3.9%) [94]. Burn wound infections are frequently caused by non-fermenting Gram-negative rods with a high potential to antimicrobial resistance. In a South African study, *Acinetobacter baumannii* and *P. aeruginosa* were the most common microbes isolated in patients with severe burns [95].

2.4.5 PRESSURE ULCER INFECTION

Pressure ulcer infections are usually polymicrobial and anaerobic bacteria may also play a role, as severely infected pressure ulcers are usually associated with a tissue necrosis of some degree [28]. *Staphylococcus aureus*, *Proteus mirabilis*, *P. aeruginosa*, and *Enterococcus faecalis* were the most frequently isolated organisms in a recent meta-analysis of the microbiology of pressure (decubitus) ulcers among patients with spinal cord injury [96]. Similarly, in a very recent Italian study on patients with spinal cord injury, *S. aureus* (31%), *P. mirabilis* (27%) and *P. aeruginosa* (16%) were the most common bacterial isolates [97]. In addition, they found only 22% concordance between cultures of superficial swabs and intra-operative specimens [97].

2.4.6 DIABETIC FOOT INFECTION

Although usually not detected alone, *S. aureus* is the major and most frequently isolated pathogen in diabetic foot infection (DFI) [8,98,99]. The vast majority of moderate-to-severe DFIs are polymicrobial [8,98,99]. Detection of Gram-negative bacteria is associated in particular to chronic ulcers and prior antibiotic use, detection of *P. aeruginosa* to some form of hydrotherapy or warm climate and detection of anaerobes to limb ischemia

[98,100]. Enterococci are frequently isolated in DFI, but they often represent colonizers rather than true pathogens [98]. Similarly, bacteria commonly considered as contaminants, such as coagulase-negative staphylococci and corynebacteria, may occasionally be true pathogens in DFI [76].

2.4.7 SURGICAL SITE INFECTION

The rarely occurring very early (<48 hours after operation) emerging surgical site infections (SSI) are almost always caused by *Streptococcus pyogenes* or *Clostridium* spp [4]. SSIs after a clean surgical procedure in areas not involving axilla or perineum are most commonly caused by *S. aureus* or streptococcal species, whereas the risk for infection due to Gram-negative organism is significant in SSIs after surgery of axilla or perineal region [4,101]. In the latter occasion anaerobic bacteria are also frequently detected [4,101]. SSIs following operation of intestinal tract or female genitalia have a high probability of mixed infection with Gram-positive, Gram-negative and anaerobic bacteria [4,102,103].

2.4.8 NECROTIZING INFECTIONS

Necrotizing SSSIs are caused basically by the same microbes as non-necrotizing SSSIs, but particularly streptococcal and clostridial species are isolated more frequently in necrotizing as compared to non-necrotizing infections [7,104]. The majority of necrotizing SSSIs are polymicrobial, on the average 4.4 microbes per infection were detected by Elliot et al [7] and 54% of infections were polymicrobial in an Indonesian study [105]. In the latter study GAS (24%) was the most common aetiology among monomicrobial infections which commonly arise after minor nonpenetrating trauma or without a recognized precipitating factor [4,64,105]. Polymicrobial infections are most commonly associated with anogenital infection site (Fournier´s gangrene), penetrating abdominal trauma, surgical procedures involving the bowel, pressure ulcers and injection site infection in IDUs [4]. Highly virulent pathogens, such as GAS, *S. aureus*, *Clostridium* spp, *Pasteurella* spp (animal bites), *Vibrio* spp (salt water exposure) and *Aeromonas hydrophila* (freshwater exposure), have a capacity to cause fulminant monomicrobial infection also in an immunocompetent host [106-108].

2.4.9 MICROBIOLOGICAL FINDINGS IN OBSERVATIONAL STUDIES AND CLINICAL TRIALS OF CSSSI

The microbiology of cSSSI have been evaluated in several observational studies (Table 3) and clinical trials (Table 4). These studies are not directly

comparable due to different inclusion and exclusion criteria and differences in the presentation of microbiological data. Yet, some general remarks of the microbiology of cSSSI can be made. First, microbiological diagnosis is obtained for less than half of the patients in observational studies, in comparison to two thirds of that in clinical trials. Second, Gram-positive pathogens are detected more often than Gram-negative or anaerobic bacteria; Gram-positive, Gram-negative and anaerobic bacteria constituted altogether 61%–97%, 13%–45% and 2.6%–58% of the microbiological diagnoses in the studies, respectively (Tables 3 and 4). Third, in the majority of infections a single microbe was detected whereas polymicrobial infections were found in 15%–49% of the patients (Tables 3 and 4). Fourth, when reported, mixed polymicrobial infections including both Gram-positive and Gram-negative microbes constituted usually less than half of the polymicrobial infections. Fifth, *S. aureus* is the most commonly isolated pathogen, found in 37%–81% of the cases, of which 5.0%–76% were resistant to methicillin (MRSA).

The percentage of methicillin resistance among staphylococcal SSSIs has increased during the last decades particularly due to the increase of community-acquired MRSA (CA-MRSA) infections [10,12]. CA-MRSA strains are genetically and phenotypically different from health-care associated MRSA (HA-MRSA) strains, therefore, some significant differences exists between CA-MRSA and HA-MRSA. First, CA-MRSA infections occur typically in young otherwise healthy patients without a prior contact to health-care whereas HA-MRSA infections affect patients with recent hospitalization or other contact to health-care facilities [109]. Second, CA-MRSA strains often produce Panton-Valentine leucocidin, a toxin that destroys white blood cells and is a potent virulence factor [110]. Third, CA-MRSA strains are typically more susceptible to anti-staphylococcal antibiotics than HA-MRSA strains, some strains of CA-MRSA are resistant only to β-lactams [111].

In a multi-center study, it was found that MRSA was present in one-third of cSSSI infections [112]. They detected younger age groups to be more likely infected with MRSA as compared to the older ones [112]. Furthermore, number of comorbidities and traditional risk factors for healthcare-associated infection were lower among patients with MRSA infection in comparison to patients with non-MRSA infection [112].

Globally, the reported resistance rates of *S. aureus* to methicillin vary considerably; based on national registration data the rates were 51% in the U.S. and between 0.3% (Norway) and 55% (Portugal) in Europe 2011 [113]. The prevalence of MRSA has stayed low in the Nordic countries, 2.8% and 0.8% of *S. aureus* isolates were resistant to methicillin in Finland and Sweden in 2011, respectively [114,115].

Table 3 *Microbiological findings of observational studies on complicated skin and skin structure infection (includes only studies with comprehensive microbiological data)* [44,46,47,71,116,117].

Study	Garau	Jenkins [a]	Li	Lipsky	Zervos [b]	Zilberberg [c]
Data collection, years	2010-11	2007	2008-13	2008-09	2005-08	2006-07
Geographical region	Europe	US	China	US	US	US
No of patients / hospitalizations	1995	322	575	1033	1096	717
No of patients with microbiological dg	1001	150	184	525	449	717
Gram-positive bacteria	70	74 [d]	61	68 [d]	84 [d]	75
Staphylococci	49	65	46	65	66	53
MSSA	28	19	31	31	16	18
MRSA	10	43	8	35	50	35
Streptococci	14	40	12		26	6
Enterococci	11	3	8		3	15
Gram-negative bacteria	46	13	49	13 [e]	10 [e]	33
Enterobacteriacae	34		34		13	22
Pseudomonas			11		4	9
Other Gram-negative	12		5		3	3
Anaerobic bacteria	3	19				3
Other microorganism	8	3			2	6
Polymicrobial infections	30		18		15	32
Mixed				19	4	10

Numbers are percentages (%) of the patients with microbiological diagnosis.
[a] Superficial swabs excluded
[b] Only cultures obtained <24 h from hospitalisation were included
[c] Only patients with positive culture <24 h from hospitalisation were included, 52% of the patient bacteraemic on admission, 74% of the patient had HAI
[d] Patients with only Gram-positive bacteria
[e] Patients with only Gram-negative bacteria

Table 4 *Microbiological findings of selected clinical trials for antimicrobial treatment in complicated skin and skin structure infection (includes only studies with comprehensive microbiological data)* [118-123].

Study	Graham	Ellis-Grosse	Noel	Corey	Gyssens	Matthews
Data collection, years	1998-99	2001-04	2005-06	2007	2006-08	2006-08
Geographical region	America	Global	Global	Global	Global	Global
No of patients / hospitalizations	359		828	1378		531
No of patients with microb. dg	306	540	590	914	511	301
Gram-positive bacteria	97	85	75	79 [c]	65	
Staphylococci	46	59	66	81	37	58
MSSA	44	47	42	51	33	29
MRSA	2	12	21	30	4	29
Streptococci	39	19	9	17	14	
Enterococci	6	7		5	12	
Gram-negative bacteria	45		28	6 [d]	28	42
Enterobacteriacae	34	11 [a]	21	12	25	
Pseudomonas	5		7	4		
Other Gram-negative	6				1	
Anaerobic bacteria	58	2 [b]			7	5
Polymicrobial infections	40			30	49	43
Mixed				15		19

Numbers are percentages (%) of the patients with microbiological diagnosis.
[a] Only number of *E. coli* infections reported
[b] Only number of *B. fragilis* infections reported
[c] Only Gram-positive bacteria detected
[d] Only Gram-negative bacteria detected

2.5 ANTIMICROBIAL TREATMENT OF CSSSI

The effective management of cSSSIs frequently involves a combination of antimicrobial therapy and surgical source control [32]. The choice of empirical antimicrobial treatment depends mainly on the clinical presentation (see aetiology, page 18) and on the antimicrobial susceptibility of the potential pathogens – particularly the local prevalence of methicillin-resistance among *S. aureus* strains. Exchange of the initial empirical treatment to targeted antimicrobial therapy is generally advisable once the microbiological aetiology has been determined. Management of infection should be initiated as soon as possible. Failure to initiate an antibiotic with activity against causative bacteria was the only independent predictor of treatment failure in a study of patients with SSSI due to MRSA [124]. Prospective randomised studies evaluating the optimal duration of antimicrobial treatment in cSSSI have not been made. In a prospective randomised study of 121 patients with uncomplicated cellulitis no difference was detected in the treatment efficacy between 5 and 10 days course of

levofloxacin – if patient was responding to treatment at day 5 [125]. On the other hand, viable streptococci were detected in the tissue specimens of patients with necrotizing fasciitis up to 20 days after the initiation of effective antimicrobial treatment [126]. An overview of the clinical trials, retrospective studies and guidelines evaluating the antimicrobial treatment of cSSSI is presented below.

2.5.1 EVALUATION OF TREATMENT RESPONSE

Currently, almost all new antimicrobials against Gram-positive bacteria are studied before licencing in patients with ABSSSIs. Previously, clinical trials on antibiotics covering also Gram-negative and anaerobic bacteria have been made under the umbrella of cSSSI (table 5). Traditionally, treatment response in clinical trials of cSSSI have been evaluated – typically 7 to 14 days – after the completion of antimicrobial therapy. Clinical cure was usually defined as resolution or near-resolution of signs/symptoms at post-treatment evaluation (PTE) such that no further antimicrobial therapy was required. However, two historical trials [127,128] comparing antibiotic and ultraviolet therapy found the difference between treatment arms to be most prominent 2–3 days after start of treatment – suggesting that early response is a more treatment-specific measure than PTE [129]. Therefore, in 2013 FDA recommended in their guidance for the development of antimicrobials used in ABSSSI the treatment response to be evaluated at 48 to 72 hours after initiation of the therapeutic agent instead of traditional post-treatment evaluation [24]. The new primary endpoint has also been criticized, mainly because early response is not the ultimate goal of antibiotic therapy [130]. European guideline still recommends PTE as the primary endpoint [131]. The recommended primary endpoint by FDA is ≥20% reduction in infection lesion area from baseline [24]. Clinical trials of ABSSSI exploiting the new primary endpoint are presented in table 6.

When the lesion size is evaluated it mainly measures the size of the visible inflammatory area instead of measuring the whole infection area. Thus, reduction in lesion size may not correspond to reduced bacterial burden or to need for antibiotic therapy. This may further complicate the use of measurement of the lesion size as the surrogate for treatment response. In addition, local and also systemic symptoms of infection may worsen after initiation of therapy probably due to sudden destruction of bacteria and consequent release of potent cytokines that enhance local inflammation [4].

2.5.2 CLINICAL TRIALS ON ANTIMICROBIAL TREATMENT IN PATIENTS WITH CSSSI

Phase three clinical trials on patients with cSSSI and ABSSSI are presented in tables 5 and 6, respectively. Except for one study that included only patients with MRSA infection, studies on cSSSI have compared antimicrobial therapies covering both Gram-positive and Gram-negative bacteria – or at least addition of an antibiotic with Gram-negative coverage was allowed beside the study drug that covered only Gram-positive bacteria (Table 5). In contrast, studies on ABSSSI have mainly compared antimicrobial agents with effect only to Gram-positive bacteria (Table 6). In studies on patients with cSSSI, clinical response rates at PTE have varied between 68%–98% (Table 5). In studies on patient with ABSSSI, clinical response rates at PTE were similar (81%–97%) to those of cSSSI and similar or higher than early 48–72 hours response rates (Table 5 and 6).

In a clinical trial linezolid was found to be superior to vancomycin in PTE of the clinically evaluable population, but patients with linezolid were treated statistically significantly longer than patients with vancomycin [132]. Friedland et al. conducted a retrospective analysis of two phase 3 clinical trials in cSSSI using an early response to treatment as primary endpoint [133]. They found ceftaroline to have numerically higher early clinical response rates than vancomycin–aztreonam, the difference was not detected in the primary analyses using PTE as endpoint [121,133]. Otherwise, the efficacy of all the new antimicrobials studied in clinical trials on cSSSI and ABSSSI (tables 5 and 6) met the margins for non-inferiority, i.e. were equivalent to the comparator drug. This also applies to the single-dose treatment with oritavancin, a novel semisynthetic glycopeptide antibiotic. The reported mean/median durations of antimicrobial treatment in clinical trials of cSSSI and ABSSSI have varied between 6.5 to 14.5 and 6 to 10 days, respectively (tables 5 and 6).

In sub-analyses of clinical trials on patients with cSSSI, lower clinical success rates at PTE have been detected in patients with diabetes [134,135] or PVD [136] in comparison to patients without these characteristics. Vascular insufficiency have shown to decrease antibiotic concentration in peripheral tissues which, together with the impaired neutrophil function in diabetics, may explain the lower response rates in these patients [137].

Table 5 *Clinical trials (phase 3) on patients with complicated skin and skin structure infection* [119-123,132,138-149].

Study	**Antimicrobials**	**PTE** [a]	**Response rate at PTE** [b]	**Duration of antimicrobial treatment** (days)
Matthews 2012 n=405	tigecyclin vs ampicillin-sulbactam	8-50	77.5% vs 77.6% (95% CI: -8.7, 8.6)	mean 8 vs 8
Noel 2012 n=188	omadacycline vs linezolid (±aztreonam)	10-17	98.0% vs 93.2% (95% CI: -1.7, 11.3)	mean 10.0 vs 9.6 (mean iv 4.3 vs 4.3)
Gyssens 2011 n=668	moxifloxacin vs piperacillin-tazobactam (+ amoxicillin-clavulanate po)	14-28	88.6% vs 89.6% (p=0.758)	7–21 (DFI 14.5 vs 14.2)
Wilcox 2010 n=586	ceftaroline vs vancomycin+aztreonam	8-15	92.2% vs 92.1% (95% CI: -4.4, 4.5)	median 6.5 vs 6.5
Corey 2010 n=616	ceftaroline vs vancomycin+aztreonam	8-15	91.1% vs 93.3% (95% CI: -6.6, 2.1)	median 7 vs 7
Itani [c] 2010 n=436	linezolid vs vancomycin	6-28	84% vs 80% (95% CI: -3, 11.5)	mean 8.8 vs 7.6
Vick-Fragoso 2009 n=632	moxifloxacin vs amoxicillin-clavulanate	14-28	80.6% vs 84.5% (95% CI: -9.4, 2.2)	mean (SD) 13.5 (4.8) vs 14.1 (4.8), iv 6.2 (4.1) vs 6.6 (3.9)
Stryjewski 2008 n=1683	telavancin vs vancomycin	7-14	88% vs 87% (95% CI: -2.1, 4.6)	median 10 vs 11 (study 0017) and 8 vs 9 (study 0018)
Noel 2008 n=729	ceftobiprole vs vancomycin+ceftazidim	7-14	90.5% vs 90.2% (95% CI: -4.2, 4.9)	mean 9.0 and 9.1
Jauregui 2005 n=660	dalbavancin vs linezolid	12-16	88.9% vs 91.2% (p = NS)	fixed duration 14
Giordano 2005 n=367	moxifloxacin vs piperacillin-tazobactam (+ amoxicillin-clavulanate po)	10-42	79% vs 82% (95% CI: -12.0, 3.3)	mean iv 6 vs 6
Fabian 2005 n=548	meropenem vs imipenem-cilastatin	7-28	86.2% vs 82.9% (95% CI: -2.8, 9.3)	mean(SD) iv 5.8(3.2) vs 6.0(3.4), switch to po 48% vs 51%, for those 9.3(6.6) vs 9.0(5.2)
Ellis-Grosse 2005 n=833	tigecycline vs vancomycin+aztreonam	12-92	86.5% vs 88.6% (p = 0.4233)	mean 8
Weigelt 2005 n=898	linezolid vs vancomycin	7	94.4% vs 90.4% (p = 0.023)	mean (SD) 11.8 (4.9) vs 10.9 (5.3) (p = 0.004)
Graham 2002 n=270	levofloxacin vs ticarcillin-clavulanate (+ amoxicillin-clavulanate po)	7	84.1% vs 80.3% (95% CI: -13.3, 5.8)	mean (SD) 10.1 (4.7) vs 12.1 (4.9)
Graham 2002 n=359	ertapenem vs piperacillin-tazobactam	10-21	82.4% vs 84.4% (95% CI: -10.2, 6.2)	mean (SD) 9.1 (3.1) vs 9.8 (3.3), median 9 vs 9
Stevens 2000 n=600	linezolid vs oxacillin (+dicloxacillin po)	15-21	88.6% vs 85.8% (CI: −2.5, 8.2)	mean (SD) 14.3 (4.6) vs 14.1 (4.6)
Nichols 1999 n=562	quinupristin-dalfopristin vs cefazolin, oxacillin or vancomycin	14-28	68.2% vs 70.7% (95% CI: −10.1, 5.1)	mean (SD) 7.0 (3.2) vs 8.4 (3.4) in US (p<0.001), 7.7 (3.5) vs 8.7 (3.3), global study (p = 0.005)

[a] Post treatment evaluation, days after the end of treatment
[b] In clinically evaluable population
[c] Only patients with MRSA infection included

Table 6 *Clinical trials (phase 3) on patients with acute bacterial skin and skin structure infection* [133,150-154].

Study [a]	**Antimicrobials**	**Clinical response at 48–72 hours**	**Clinical response at PTE**	**Correlation of responses at 48-72 hours and at PTE**	**Duration of antimicrobial treatment** (days)
Kingsley 2016 n=256	delafloxacin vs linezolid vs vancomycin	cessation of spread and afebrile 78.2% vs 74.7% vs 72.6% (p = NS)	cured or improved 84% vs 81.8% vs 80.6%		mean 7.6 vs 7.4 vs 7.8
Corey 2015 n=1005	oritavancin vs vancomycin	cessation of spread and afebrile 80.1% vs 82.9% (95% CI:-7.5, 2.0)	cured or improved 82.7% vs 80.5% (95% CI: -2.6, 7.0)	"high"	single-dose vs mean (SD) 8.4 (2.1)
Moran 2014 n=666	tedizolid vs linezolid	improvement of overall clinical status 92% vs 90% (95% CI: −3.3, 5.6)	cured or improved 88% vs 88% (95% CI: -4.8, 5.3)	10% early non-responders but success at PTE, 2.3% early responders, but failures at PTE	fixed 6 vs 10
Boucher 2014 n=1312	dalbavancin vs vancomycin (+linezolid po)	cessation of spread and afebrile 79.7% vs 79.8% (95% CI: -4.5, 4.2)	cured or improved 96.0% vs 96.7% (95% CI: -3.0, 1.5)		10–14
Prokocimer 2013 n=667	tedizolid vs linezolid	cessation of spread and afebrile 79.5% vs 79.4% (95% CI: −6.1, 6.2)	cured or improved 85.5% vs 86.0% (p = NS)	7% early non-responders but success at PTE, 2% early responders, but failures at PTE	fixed 6 vs 10
Friedland [b] 2012 n=616	ceftaroline vs vancomycin+ aztreonam	cessation of spread and afebrile 74.0% vs 66.2% (95% CI: 1.3, 14.0)	cured or improved 91.6% vs 92.7% (95% CI: −4.2, 2.0)		median 7 vs 7

PTE, post-therapy evaluation
[a] n = intension-to-treat population
[b] Retrospective analysis of two clinical trials in patient with cSSSI

2.5.3 OBSERVATIONAL STUDIES ON PATIENTS WITH CSSSI

In retrospective studies the initial (empiric) antimicrobial treatment was clearly divided according to MRSA coverage (table 7). β-lactam antibiotics were the most frequently used antimicrobials in areas with low prevalence of MRSA, whereas vancomycin dominated in areas with high prevalence of MRSA (table 7). In a multinational European survey Garau et al. found a wide variation in the selection of antimicrobial therapy as during treatment 54 different antibiotic agents were used as monotherapy or in combinations [44]. The reported mean/median total durations of antimicrobial treatment varied between 11 and 16.7 days (table 7).

Table 7 *The most frequently used initial antibiotics and mean/median total durations of antimicrobial therapy in observational studies on patients with complicated skin and skin structure infections* [43-45,47,71,155].

Study	Region	MRSA (%)	The most frequently used antimicrobials in initial treatment	Antibiotic treatment duration	Length of hospital stay
Garau 2013 n=1995	Europe	10	penicillin+β-lactamase inhibitor (29%) broad-spectrum antibiotic [a] (12%) cephalosporins (6.7%)	median 11 days	median 12 days
Jenkins 2010 n=322	US	43	vancomycin (74%) penicillin+β-lactamase inhibitor (63%) clindamycin (27%)	median 13 days	median 4 days
Li 2016 n=575	China	7.6	3rd generation cephalosporins (22%) 2nd generation cephalosporins (14%) 1st generation cephalosporins (7.7%)		median 13 days
Lipsky 2012 n=1033	US	35	vancomycin (61%) penicillin+β-lactamase inhibitor (37%) cephalosporins (18%)	mean 2.2 – 3.4 days (iv)	median 5 days
Carratala 2003 [b] n=332	Spain	0	amoxicillin-clavulanate (72%) penicillin (4%) cloxacillin (3%)	mean (SD) 16.7 (11.1) days	mean (SD) 11.8 (11.3) days
Nathwani 2014 n=1542	Europe	100	vancomycin (50%) linezolid (15%) clindamycin (11%)	mean (SD) 14.8 (9.9) days	mean (SD) 20.6 (17.4) days

MRSA, methicillin resistant *Staphylococcus aureus*
[a] Carbapenems or piperacillin-tazobactam
[b] Study included only patients with cellulitis, 31% of infections were complicated

2.5.4 TREATMENT GUIDELINES FOR SSSI

Overview of the Finnish and Swedish national guidelines for the treatment of mild-to-moderate SSSIs are presented in table 8 which includes also two guidelines with an international importance [4,76,156-159]. In the empirical treatment of erysipelas and cellulitis guidelines consistently suggest treatment targeted to Gram-positive bacteria, except for severe cases (IDSA) [4]. In purulent infections (e.g. abscess) coverage of *S. aureus* is recommended and in the areas of high MRSA prevalence (IDSA) an empirical antibiotic active against MRSA is suggested [4]. For treatment of DFI, Finnish and IDSA guidelines identically suggest antimicrobial treatment targeted only to Gram-positives in mild infection and broad-spectrum therapy in moderate-to-severe infections (Table 8). The greatest variation between guidelines can be found in the recommended duration of antimicrobial therapy. For erysipelas and cellulitis, total treatment durations of 14–21, 10–14 and 5 (if improving) days are suggested by Finnish, Swedish and IDSA guidelines, respectively (Table 8). Based on empirical data, for treatment of DFI the IDSA guideline suggests duration of antimicrobial therapy between 2 days to ≥3 months based on disease severity, presence of osteomyelitis and nature of retained infected tissue after surgical intervention [76].

Table 8 *Recommended empirical antimicrobial agents and durations of antimicrobial treatment in selected treatment guidelines for skin and soft tissue infections* [4,76,156-159].

Infection	**Finland** [a]	**Sweden** [b]	**IDSA** [c]	**WSES** [d]
Erysipelas / cellulitis	Penicillin 14–21 days	Penicillin 10–14 days	Moderate: penicillin G or ceftriaxone or cefazolin or clindamycin Severe: vancomycin + piperacillin-tazobactam 5 days if patient responding to treatment	Antimicrobial therapy against Gram-positives
Abscess [e]	1st generation cephalosporin	Penicillin or cefadroxil 7–10 days	Moderate: trimetoprim-sulfamethoxazole or doxycycline Severe: vancomycin or daptomycin or linezolid or telavancin or ceftaroline	Antimicrobial therapy against the likely pathogens
Bites		Amoxicillin-clavulanate	Amoxicillin-clavulanate	
Necrotizing fasciitis [f]			Vancomycin or linezolid AND piperacillin-tazobactam or carbapenem or ceftriaxone + metronidazole	Linezolid + piperacillin-tazobactam or daptomycin + piperacillin-tazobactam + clindamycin
Surgical site infection [g]			Clean operation, trunk, head, neck, extremity: antimicrobial therapy against staphylococci Operation on the axilla, perineum, gastrointestinal or female genital tract: antimicrobial therapy against Gram-positives, Gram-negatives and anaerobes	Clean operation: antimicrobial therapy against Gram-positives Procedure on gastrointestinal or genitourinary tract: antimicrobial therapy against Gram-positives and Gram-negatives
Diabetic foot infection	Mild: antimicrobial against Gram-positives Moderate-to-severe: broad-spectrum [h]		Mild: antimicrobial against Gram-positives 7–14 days Moderate-to-severe: broad-spectrum [h] 14–21 days	

[a] Bacterial skin infections. Current Care Guidelines. Duodecim 2010. Diabetic foot infections. Current Care Guidelines. Duodecim 2009.
[b] Farmakologisk behandling av bakteriella hud- och mjukdelsinfektioner. Läkemedelsverket och Strama. 2009.
[c] Infectious Diseases Society of America Clinical Practice Guidelines. Skin and soft tissue infections 2014, diabetic foot infections 2012.
[d] World Society of Emergence Surgery guidelines for management of skin and soft tissue infections. 2014.
[e] Incision & Drainage is the primary treatment, adjunctive antimicrobials recommended only for moderate-to-severe cases.
[f] Antimicrobial therapy in adjunction to early aggressive surgical source control recommended.
[g] Opening of the surgical incision, adjunctive antimicrobials if systemic signs of infection (IDSA and WSES), erythema > 5 cm from incision or any necrosis (IDSA), source control incomplete (WSES) or immunocompromised patient (WSES).
[h] Antimicrobial treatment covering Gram-positive cocci, common Gram-negative and obligate anaerobic bacteria.

2.6 SURGICAL TREATMENT OF CSSSI

Need for surgical treatment was included as one of the criteria of cSSSI in the FDA guidance document for the development of new antimicrobials [17]. Early and aggressive surgical treatment – debridement or drainage – is the cornerstone in the management of cutaneous abscess, surgical site infection, diabetic foot infection and especially necrotizing infections [4,76,159]. In retrospective studies on patients with cSSSI, totally 36%–44% of patients had significant surgical intervention(s) after the diagnosis of cSSSI [44,45,47,160].

2.6.1 CUTANEOUS ABSCESS

Incision and evacuation of pus and debris is the primary treatment of cutaneous abscesses [4]. Incision and drainage of skin abscesses were compared to ultrasonographically guided needle aspiration in a randomized trial [161]. At day 7 the overall success rates of incision and drainage compared to ultrasonographically guided needle aspiration were 80% and 26%, respectively, indicating that the latter is insufficient therapy for skin abscesses [161]. The addition of systemic antibiotics to incision and drainage has usually not improved cure rates in randomized studies [162-164], but a preventive effect on recurrence of other abscesses have been detected [162,164]. In two recent U.S. study among patients with drained cutaneous abscess, however, adjunctive trimethoprim-sulfamethoxazole (93%) and clindamycin treatment (93%) resulted in a statistically significantly higher cure rate than placebo (81–86%) in per-protocol population [165,166]. IDSA guideline suggests systemic antibiotics to be given for patients with severely impaired host defenses or signs or symptoms of systemic infection [4].

2.6.2 SURGICAL SITE INFECTION (SSI)

Based on empirical data, for SSIs guidelines (IDSA and WSES) suggest to open the incision, evacuate the infected material, and continue dressing changes until the wound heals by secondary intention [4,28]. In the single prospective randomized trial on patients with SSI statistically significant effect of adjunctive antibiotic treatment was not detected [167]. However, adjunctive systemic antimicrobial therapy is recommended if systemic signs of infection are present (IDSA and WSES), or erythema reaches >5 cm from incision margins (IDSA), or any wound necrosis (IDSA), or source control is incomplete (WSES) or patient is immunocompromised (WSES) [4,28].

2.6.3 DIABETIC FOOT INFECTION

In addition to antimicrobial therapy, surgical interventions are frequently needed in patients with moderate-to-severe DFI, and in life- or limb-threatening infections or if the affected limb is ischemic the need for those is mostly urgent [76]. These surgical procedures can be minor, such as drainage of abscess or debridement of devitalized tissue, or major, such as amputation. In an American survey among diabetics, cSSSI accounted for 59% of lower limb amputations [168]. Bone resection has been regarded as integral part of treatment in DFI with chronic osteomyelitis [169] but this view has been challenged by the reports from retrospective studies that have demonstrated success rates of 65%–80% with prolonged (3–6 months) antibiotic treatment alone [170-174]. Vascular surgeon should be consulted if ischemia of the infected limb is suspected [175].

2.6.4 NECROTIZING INFECTIONS

Early recognition and urgent surgical debridement were the most critical factors for reducing mortality in retrospective analysis of patients with necrotizing infections [176]. Repeated daily debridement is recommended until the surgical team finds no further need for debridement [4,28]. In the empirical antimicrobial treatment of necrotizing fasciitis a broad-spectrum antimicrobial treatment is recommended in guidelines [4,28]. In the treatment of GAS necrotizing fasciitis an addition of protein synthesis inhibitor (high dose clindamycin or linezolid) to cell-wall active antibiotic (β-lactam) therapy has been associated to better outcome in retrospective studies [177,178]. Similar desirable effect of protein synthesis inhibitors to exotoxin production of Gram-positive bacteria was detected also in *S. aureus* [179]. However, in a recent prospective randomized study on patients with limb cellulitis the addition of a short course of clindamycin to flucloxacillin treatment did not improve outcome at day 5 [180].

Despite the theoretically desirable effects, the role of intravenous immunoglobulin and hyperbaric oxygen therapies in the treatment of necrotizing fasciitis is controversial; no high quality evidence is supporting their use. In a small randomized study on 21 patients with GAS necrotizing fasciitis, a significant decrease was detected among patients with intravenous immunoglobulin treatment in the sepsis-related organ failures at day 2–3, but not in the primary outcome (mortality at 28 days) [181]. The expert panel of WSES supports the use of early intravenous immunoglobulin therapy in patients with severe sepsis or septic shock and the use of hyperbaric oxygen therapy in those hospitals where the hyperbaric chamber is available – as an adjunctive therapy, not replacing the surgical treatment [28].

2.7 OUTCOME AND THE USE OF RESOURCES IN CSSSI

In real-life observational studies of cSSSI the 30-day mortality rates have been 0.4%–9.0% and recurrences have been detected in 3.7%–8.6% of the patients [25,43-46,71]. Necrotizing fasciitis has significantly higher mortality rate; mean mortality was 21.5% in a recent review with 1463 patients [182]. In observational studies higher mortality rate has also been detected among patients with nosocomial infection, co-morbidities and age over 65 years as compared to patients without these characteristics [44,46,117].

In practice, patients with cSSSI who survive eventually have their infection cured and chronically persistent symptoms of active infection do not exist. Therefore, the frequency of recurrence and length of hospital stay and length of antimicrobial treatment may be used as indicators for treatment efficacy – and for the use of resources. A great difference in the mean/median length of hospital stay between U.S. and Europe have been detected in the retrospective studies on patients with cSSSI: 4–5 days in U.S. and 11.8–20.6 days in Europe (Table 5). Important to note when estimating the costs of infection management, is that the costs of hospitalization constitute the majority of total costs – up to 81% in a Canadian study on patients with MRSA [183-185]. The total median costs of cSSSI hospitalization have varied from 1'643 USD in China to 13'240 USD in U.S. [47,71]. Furthermore, in an American study higher median total costs were observed among patients with Gram-positive infection (19'894 USD) than those with mixed infection (26'935 USD) [186]. In observational studies, intensive care unit (ICU) admissions are reported in 4.0–6.5% of cases [44,71].

3 AIMS OF THE STUDY

The objectives of this study were:

I To assess the treatment reality of patients with a complicated skin and skin structure infection in two low resistance areas in focus of patient, disease and treatment characteristics and outcome.

II To study the feasibility of early treatment response criteria in a population-based real-life setting and to evaluate factors associated with the time to clinical stability and the association of early response with outcome in patients with complicated skin and skin structure infection.

III To evaluate differences in microbiological aetiology and treatment practices between diabetics and nondiabetics in a population-based set-up of complicated skin and skin structure infection.

IV To compare the characteristics and treatment practises of complicated skin and skin structure infection between two areas with low incidence of antimicrobial resistance, Helsinki in Finland and Gothenburg in Sweden.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

The design was an observational retrospective cohort study. The study population consisted of all adult residents from cities with nearly equal population (Helsinki, Finland population of 588'000 and the Gothenburg area, Sweden population 600'000) who were treated in hospital because of cSSSI during 2008–2011. The study hospitals, Helsinki University Central Hospital and Helsinki City Hospital in Finland and Sahlgrenska University Hospital, Gothenburg area in Sweden, have the only emergency departments on their catchment area and are thus responsible for treatment of almost all hospitalized SSSI infections. Data for the study was collected from the electronic patient medical record databases of these hospitals by IJ in Helsinki and by LH and trained nurses in Gothenburg.

First, medical records of all patients with ICD-10 codes possibly suitable for SSSI (table 9) were reviewed and patients who met the inclusion criteria for cSSSI (Table 10) were included in the analysis. For the final analysis population, data was collected on patient demographics, microbiology, signs and courses of the disease. Co-morbidities of interest were diabetes, peripheral vascular disease, congestive heart disease and chronic renal, liver or respiratory disease, malignancy, human immunodeficiency virus infection or any other disease with immune system impairment. In addition, data about patient care, antimicrobial and other treatments in various departments, treatment response and one-year post-cSSSI diagnosis follow-up information was collected.

4.2 STUDY DEFINITIONS

The classification of cellulitis/fasciitis was harmonized between centers post-hoc; patient had cellulitis/fasciitis if there was no abscess, diabetic foot/leg ulcer or peripheral vascular ulcer. The definition of DFI was based on typical clinical presentation with infected (traumatic) wound or (neuropathic) ulceration. Due to requirement of systemic sings of infection in the study, the DFIs of were classified as severe on IDSA classification [76]. Clinical stability was assessed from patient records and it was defined as improvement of systemic symptoms such as fever and vital signs (pulse rate, blood pressure) along with local signs of infection. Criteria for treatment failure were: need for unplanned surgery due to infection, no improvement in clinical situation after 5 days of treatment or treatment failure registered in patient records by treating physician.

Infection was defined as health-care associated (nosocomial) if the patient had undergone invasive surgery or had been hospitalized within the previous three months. Microbiological diagnosis was obtained by routine bacterial cultures of blood, tissue specimens or superficial swabs. Results of deep tissue samples were preferred in case of multiple specimens yielding potential aetiological agents. In the microbiological analysis of studies II and III, candida and coagulase negative staphylococci were not regarded as true pathogens. Carbapenems and piperacillin-tazobactam were considered as broad-spectrum antimicrobial therapy in the analysis. To enable the comparison between the cities, departments Helsinki City hospital was combined to the department of Medicine and treatment at Home hospital (Helsinki) was regarded as home-based care in the analyses. Since the Home hospital had treatment facilities similar to in-patient treatment (e.g. intravenous antibiotics) the treatment was included to the total LOS. Home-based care included follow up of cure, wound care or other forms of nursing. The study was approved by both study sites in local conventional manner and the ethical committee of Sahlgrenska University Hospital.

Table 9 *ICD-10 diagnostic codes used in the primary patient selection from hospital databases.*

ICD-10 codes	Diagnosis in text
A46	Erysipelas
A48.0	Gas gangrene
L02	Cutaneous abscess, carbuncle and furuncle
L03	Cellulitis
L04	Acute lymphadenitis
L05.0	Pilonidal cyst with abscess
L08	Other local infections of skin and subcutaneous tissue
L97	Ulcer of lower limb, not elsewhere classified
M72.6	Necrotizing fasciitis
O86.0	Infection of obstetric surgical wound
T79.3	Posttraumatic wound infection, not elsewhere classified
T81.4	Postoperative infection
T82.7	Infection due to other vascular device, implant and graft
T87.4	Infection of amputation stump

Table 10 *Inclusion and exclusion criteria for the final analysis population, i.e. criteria of complicated skin and skin structure infection in the study.*

Inclusion criteria
The patient's age was ≥18 years at the time of hospitalization
The patient was hospitalized
The patient required treatment with antimicrobials
The infected lesion fitted at least one of the following descriptions: • It affected deeper soft tissue (e.g. cellulitis, fasciitis, etc) • It required significant surgical intervention (such as wound infection – surgical or traumatic) • It developed on a lower extremity in a subject with diabetes mellitus or well-documented peripheral vascular disease • It was a major abscess, infected ulcer or deep and extensive cellulitis.
The patient had at least two local signs of cSSSI (purulent or seropurulent drainage/discharge, erythema, fluctuance, heat/localized warmth, pain/tenderness to palpation, swelling/induration) plus at least one systemic sign (temperature of >38 or <36°C, white blood cell count of >10,000/mm^3 or <4,000/mm^3, or >10% immature neutrophils).
Exclusion criteria
The patient was participating in other clinical trial or interventional study
The patient had an uncomplicated SSSI such as simple abscesses, impetiginous lesions, superficial cellulitis, furunculosis, carbunculosis, or folliculitis. Or the patient had skin and skin-structure infections with a high cure rate after surgical incision alone or after aggressive local skin care (e.g., surgical wound infection with less than 5 cm of erythema surrounding the wound margin).
Definitions
Wound infection: purulent / seropurulent discharge or >5 cm of erythema (i.e. cellulitis) surrounding the wound margin. Abscess: loculated fluid collection with >2 cm of erythema (i.e. cellulitis) extending from the abscess margin. A "major abscess" either extended to deeper soft tissue or required significant surgical intervention. Cellulitis: advancing erythema, oedema and heat. "Deep and extensive cellulitis" involved deeper soft tissue and had a surface area > 10 cm^2. Significant surgical intervention: a major operative procedure, not including commonly performed minor procedures such as incision and drainage of abscesses performed at the bedside, suture removal, needle aspiration, superficial debridement of devitalized tissue, or routine wound care. Deeper soft tissue: a subdermal tissue, including subcutaneous fat; for example, extension of infection to muscle or fascia constitutes evidence of deeper soft tissue involvement.

4.3 STATISTICAL METHODS

Categorical variables were summarized using counts and percentages and continuous variables using means, standard deviation, median, first and third quartile, min and max values.

Study I. Due to low frequency of a number of variables in some subgroups, p-values for differences between subpopulations have been calculated using Fisher's exact test. A two sample t-test was used to test for difference between two subgroups while for difference between three or more subgroups the analysis of variance (ANOVA) with subgroup as a fixed factor was utilized. If assumption of normal distribution was violated Wilcoxon rank-sum test was used.

Study II. The main outcome measure was time to clinical stability. Patients were divided into two groups according to time from diagnosis of cSSSI to clinical stability – within 0–3 days or >3 days – in line with the FDA recommendation [24]. In addition, a subgroup of 4–5 days to clinical stability was defined to test whether this subgroup of patients shared similarities with the patients of 0–3 days or ≥6 days groups. Patients who died before they reached clinical stability or those with day of clinical stability unknown were excluded from the analyses.

On univariable analysis categorical variables were compared with the Pearson's X^2- or the Likelihood ratio –test and for continuous variables the Mann-Whitney U -test was utilized. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Multivariable logistic regression analysis with backward selection was performed including 1) all clinically relevant variables and 2) those having univariable p-values less than 0.15 and 3) were not multicollinear [187]. The model with lowest Akaike information criteria (AIC) was the final multivariable model [188]. All tests were two-tailed and p-value <0.05 was considered as significant. SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) were used for analyses.

Study III. Patients were divided into three separate groups: diabetics, non-diabetics and patients with diabetic foot infection (DFI). Pearson´s X^2 test and Mann-Whitney U -test were applied in the analyses of categorical variables and non-parametric data, respectively. Odds ratios (OR) with 95% confidence intervals (CI) were calculated and univariate factors with p-value ≤0.1 were included into binary logistic regression multivariate analysis.

To verify the stability of the main results, a Propensity-score (PS) was calculated by logistic regression for the assignment of either i) broad-spectrum or non-broad-spectrum or ii) short (<17 days) or long (≥17 days) definitive antimicrobial treatment. Variables interpreted as relevant for this assignment were age >60, chronic renal failure, respiratory disease and injection drug abuse. Next, a PS-adjusted binary logistic regression multivariate analysis was performed to estimate treatment characteristics specific for patients with a diagnosis of diabetes. All tests were two-tailed and p-value <0.05 was considered as significant. Analyses were done using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

Study IV. The Fischer´s exact test and Cochran-Mantel-Haenszel statistics, controlling for age, were utilized in the statistical analyses of categorical variables. For continuous variables a two sample t-test or the analysis of variance (ANOVA) were used to test for difference between two subgroups and if assumption of normal distribution was violated, also Wilcoxon rank-sum test was used.

5 RESULTS

5.1 CHARASTERISTICS OF CSSSI IN TWO NORDIC CITIES (STUDY I)

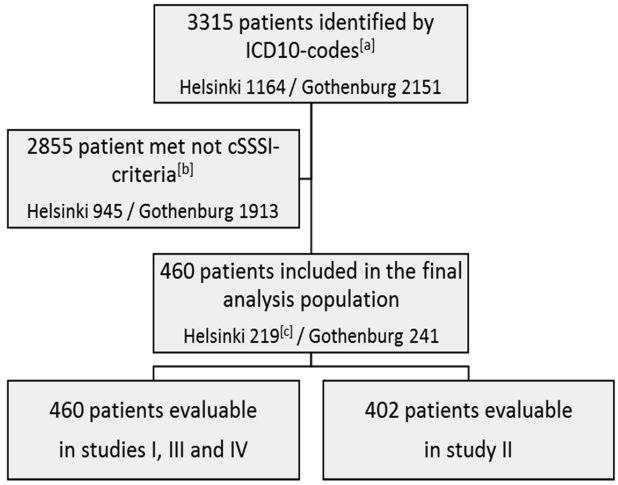

Figure 2 The study flowchart. Footnotes: [a] See table 9. [b] See table 10. [c] Of the 219 patients in Helsinki, 191 were identified at Helsinki University Central Hospital and 28 at Helsinki City Hospital.

5.1.1 PATIENT POPULATION

Totally, 3315 patients were identified by ICD10-codes and 460 patients met the inclusion criteria for the final analysis population (Figure 2). Within the study period, the average annual incidences of cSSSI were 9/100'000 and 11/100'000 in Helsinki and Gothenburg, respectively. The patients' mean age was 60.8 years and the majority (61%) of them were male (Study I, Table 1). The minority of patients (24%) had no underlying diseases, whereas 38%, 26% and 12% of patients had 1, 2 and ≥3 co-morbidities, respectively. The most common chronic underlying conditions were diabetes (41%), peripheral vascular disease (29%), congestive heart disease (9.3%), chronic renal disease (8.7%), malignancy (7.8%) and respiratory disease (7.4%) (Study I, Table 1). Alcohol and injection drug abuse were detected in 8.7% and 7.0% of patients, respectively. Totally 25% of infections were classified as healthcare-associated, 18% of patients had previous hospitalization and 16% had underwent an invasive surgical procedure. Thirty-three persent of patients had received antibiotic treatment within the previous three months before cSSSI. After the onset of symptoms of infection but before fulfillment of the

used diagnostic criteria of cSSSI, antibiotic treatment was given orally to 23% and intravenously to 6.1% of patients.

5.1.2 CLINICAL DIAGNOSIS

Diagnosis of cSSSI was made in 28% of patients within 2 days, in 50% between days 2 to 7 and in 20% later than 7 days after the symptoms appeared. Bacteraemia was detected in 13% of patients and the average maximal CRP level was 222 (SD 129) mg/L. At the time of diagnosis or later, 16% of patients were admitted to Intensive Care Unit (ICU), 5.0% met the criteria for septic shock and 28% needed blood pressure support (fluid resuscitation or vasopressor therapy). The majority of patients had cellulitis (42%) or abscess (40%) and infections of post-surgical wound (17%), diabetic foot/leg ulcer (15%), peripheral vascular disease ulcer (12%), and post-traumatic wound (11%) were also frequently detected types of infection (Study I, Table 2).

5.1.3 MICROBIOLOGICAL DIAGNOSIS

Microbiological tests were taken from 94% and diagnosis was obtained in 69% of the total patient population. Microbiological diagnosis was based on the culture of blood, tissue sample or superficial swab in 17%, 6.3% and 77% of the patients, respectively. Monomicrobial infections (50%) were more common than polymicrobial infections (24%, Study I, Table 3). *Staphylococcus aureus* and streptococci were the most commonly isolated pathogens in monomicrobial infections, identified in 21% and 16% of the microbiologically tested patients, respectively (Study I, Table 3). Among staphylococcal infections, methicillin sensitive *S. aureus* (21%) was the most common, coagulase-negative staphylococci (3.2%) and methicillin resistant *S. aureus* (0.7%) were detected less often. *Streptococcus pyogenes* (9.3%) and other β-hemolytic streptococci (5.6%) were the most frequently detected streptococci. Gram-negative and anaerobic bacteria were less common – and if detected – they were found more often in conjunction with other microbe (16%) than as a single pathogen (6.0%). β-hemolytic streptococci (51%) and *S. aureus* (31%) constituted the majority of bacteraemic infections.

5.1.4 ANTIMICROBIAL THERAPY

Data on antimicrobial treatment was available for 458 patients. Initial antimicrobial therapy after diagnosis of cSSSI was intravenous in 92% of patients and mainly classified as empirical (89% of patients). Totally 23 different antibacterial agents were used in initial therapy, among which cephalosporins (49%) were the most frequently used (Study I, Table 4). In

subsequent therapy, 29 different agents in total were used. Again, cephalosporins (23%) were the most utilized antibiotics, whereas clindamycin was the most common single agent (15%). Antibiotics with MRSA-coverage (vancomycin, linezolid or tigecycline) were rarely used in the study, for initial therapy in 0.4% and for subsequent therapy in 3.9% of patients.

During treatment with antibiotics, in average 3.5 (SD 2.1) different antimicrobial agents were used per patient and the median overall duration of antimicrobial therapy was 17 days. The median durations of intravenous and oral antimicrobial treatment were 9 days (range 1–372 days) and 14 days (range 2–570 days), respectively. In subgroup analysis, factors associated to longer total duration of antimicrobial treatment were the presence of co-morbidities, diabetes, bacteraemia, higher peak CRP level and initial antimicrobial treatment with a broad-spectrum antibiotic (Table 11).

During the period of intravenous therapy, initial treatment was modified to another intravenous drug in 39% of cases and in 5% of patients the reason for modification was direction of therapy according to microbiological results (streamlining). In comparison to patients without these characteristics, patients with surgical intervention after diagnosis of cSSSI, bacteraemia, admission to ICU and higher peak CRP level had more often their treatment streamlined (Table 11). The median time from diagnosis to the first modification was 3 days (mean 4.7 days, SD 6.5) (Study I, Figure 1). Only 5.4% of patients completed their therapy with the same agent that the treatment was started with (Study I, Table 2). Oral antimicrobials were prescribed for 64% of patients after intravenous treatment. Cephalexin (33%), clindamycin (25%), fluoroquinolones (15%) and flucloxacillin (14%) were the most common antibiotics used after discharge.

Surgical intervention after diagnosis of cSSSI was conducted to 52% of the patients and 20% had more than one intervention during their disease course. Patients with surgical intervention after diagnosis of cSSSI had in average longer LOS than patients without surgical intervention (16 versus 11 days), but statistically significant difference was not found in the total duration of antimicrobial treatment (Table 11).

5.1.5 CLINICAL OUTCOME

The median time to clinical stability was 3 days (Study I, Figure 1) and treatment failure was detected in 38% of patients – in 82% of cases it was due to cSSSI. Clinical failure occurred more often in patients with surgical intervention after diagnosis of cSSSI, bacteraemia, admission to ICU, higher peak CRP-level and initial antimicrobial treatment with a broad-spectrum agent when compared to patients without these characteristics. In the total analysis population, the median LOS was 13 days, but nearly half (46%) of

patients had home-based care after discharge. Bacteraemia, higher peak CRP level, admission to ICU and need for surgical intervention after diagnosis of cSSSI were the factors associated to longer LOS (Table 11).

The overall mortality in 30 days was 4% and in 12 months 12%. Admission to ICU was the only factor associated to higher mortality in 30 days (13% versus 2.6%, p=0.0015). Sixteen percent of patients were hospitalized again due to SSSI within 12 months after initial discharge and the presence of a co-morbidity (20% versus 5.6%, p=0.0003) was the only factor associated to the higher risk of recurrence. Patients with a recurrence had been treated longer for their primary episode of cSSSI (median total durations of antibiotic treatment 25 days) than patients without a recurrence; (20 days, p=0.0012, n=294). In the analysis of the association of microbiological aetiology to outcome, pathogens were grouped as follows: only methicillin sensitive *S. aureus*, only streptococci, multiple bacteria and microbiological diagnosis negative or unknown. In this analysis, microbiological aetiology had no statistically significant association to clinical outcomes presented in table 11. In subgroup analysis, higher peak CRP level was associated with longer LOS and total duration of antimicrobial therapy, higher rate of treatment modifications, streamlining, and treatment failures (Table 11).

Table 11 *Clinical outcome according to patients´ baseline, disease and treatment characteristics.*

Character	**Initial antibiotic treatment modification** [g], n (%)	**Streamlining** [h] n (%)	**Clinical failure due to cSSSI** n (%)	**Length of hospital stay**, days [i] median	**Total duration of antibiotic treatment**, days (IV + PO only) median
No co-morbidity (n=112)	42 (37.5%)	8 (7.1%)	21 (18.8%)	8 (n=105)	16 (n=81)
>1 co-morbidities (n=348)	135 (38.8%)	15 (4.3%)	85 (24.4%)	14 (n=313)	22 (n=223)
p-value	0.8243	0.2226	0.2465	0.1072	0.0326
Diabetes (n=187)	72 (38.5%)	8 (4.3%)	50 (26.7%)	15 (n=167)	26 (n=118)
No diabetes (n=273)	105 (38.5%)	15 (5.5%)	56 (20.5%)	11 (n=251)	17 (n=186)
p-value	1.0000	0.6655	0.1427	0.1977	0.0106
Nosocomial [a] (n=114)	43 (37.7%)	7 (6.1%)	33 (28.9%)	13 (n=102)	18 (n=78)
Non-nosocomial [a] (n=346)	134 (38.7%)	16 (4.6%)	73 (21.1%)	13 (n=316)	22 (n=226)
p-value	0.9118	0.6198	0.0956	0.9762	0.7080
Surgical intervention (n=240)	100 (41.7%)	18 (7.5%)	86 (35.8%)	16 (n=215)	19.5 (n=156)
No surgical interv. (n=220)	77 (35.0%)	5 (2.3%)	20 (9.1%)	11 (n=203)	21.5 (n=148)
p-value	0.1510	0.0103	<.0001	<.0001	0.8799
Bacteraemia (n=61)	37 (60.7%)	10 (16.4%)	21 (34.4%)	21 (n=52)	29.5 (n=38)
No bacteraemia (n=399)	140 (35.1%)	13 (3.3%)	85 (21.3%)	12 (n=366)	19 (n=266)
p-value	0.0002	0.0002	0.0328	0.0012	0.0058
Admitted to ICU (n=73)	55 (75.3%)	10 (13.7%)	39 (53.4%)	31 (n=55)	33 (n=44)
Not admitted to ICU (n=387)	122 (31.5%)	13 (3.4%)	67 (17.3%)	11 (n=363)	19 (n=260)
p-value	<.0001	0.0011	<.0001	<.0001	0.1005
Highest CRP <100 (n=81)	8 (9.9%)	1 (1.2%)	4 (4.9%)	6.5 (n=78)	16.5 (n=56)
Highest CRP 100-200 (n=138)	38 (27.5%)	3 (2.2%)	27 (19.6%)	12 (n=127)	18 (n=87)
Highest CRP >200 (n=232)	129 (55.6%)	19 (8.2%)	72 (31.0%)	17 (n=207)	26.5 (n=158)
p-value	<.0001	0.0107	<.0001	0.0002	0.0038
MSSA only (n=90)	31 (34.4%)	2 (2.2%)	20 (22.2%)	9.5 (n=82)	17 (n=56)
Streptococci only (n=72)	35 (48.6%)	6 (8.3%)	15 (20.8%)	14 (n=64)	21 (n=45)
Negative/unknown (n=113)	50 (44.2%)	5 (4.4%)	25 (22.1%)	14 (n=105)	24 (n=86)
Multiple bacteria (n=92)	38 (41.3%)	9 (9.8%)	31 (33.7%)	13 (n=84)	21 (n=70)
p-value	0.3031	0.1142	0.1716	0.3429	0.8658
Broad-spectrum [b] (n=87)	35 (40.2%)	4 (4.6%)	32 (36.8%)	17.5 (n=78)	29 (n=49)
Cefalosporins [c] (n=224)	99 (44.2%)	13 (5.8%)	56 (25.0%)	14 (n=208)	23 (n=168)
Other [d] (n=42)	11 (26.2%)	2 (4.8%)	6 (14.3%)	7 (n=34)	12.5 (n=26)
Penicillins [e] (n=53)	20 (37.7%)	1 (1.9%)	8 (15.1%)	13 (n=50)	21 (n=33)
Pen. with staph. ef.[f] (n=52)	10 (19.2%)	3 (5.8%)	4 (7.7%)	7.5 (n=46)	16 (n=28)
p-value	0.0057	0.8704	0.0004	0.003	0.025

Fishers exact test have been used to calculation of p-values for categorical values.
T-test have been used for calculation of p-values for difference between two subgroups,
one-way ANOVA for difference between three or more subgroups for continuous variables.
CRP, C-reactive protein. MSSA, Methicillin sensitive *Staphylococcus aureus*.
[a] Patient had been hospitalized or had undergone invasive surgery within previous 3 months
[b] Carbapenem and Piperacillin-Tazobactam
[c] Cefadroxil, Cefotaxim, Ceftazidim, Ceftriaxone, Cefuroxime, Cephalexin and Cefazolin
[d] Aztreonam, Clindamycin, Colistin, Doxycyklin, Fluoroquinolone, Fusidic Acid, Linezolid, Metronidazol, Netilmycin, Rifampicin, Tetracyclin, Tigecyclin, co-trimoxazole, Tobramycin, Unknown and Vancomycin
[e] Amoxicillin, Ampicillin, Benzylpenicillin and Phenoxymethylpenicillin
[f] Amoxicillin + Clavulanic Acid, β-lactamasestable Penicillin, Cloxacillin, Dicloxacillin and Flucloxacillin
[g] Only IV to IV modifications
[h] Initial treatment modification, reason: Directed antimicrobial treatment according to microbiological results
[i] Time from diagnosis of cSSSI to discharge from hospital

5.2 FACTORS ASSOCIATED WITH TIME TO CLINICAL STABILITY IN CSSSI (STUDY II)

Totally 402 patients were included in the analysis of clinical stability and time to clinical stability varied between 0–50 days. Two hundred thirty-nine (59%) patients reached stability in 0–3 days and 163 (41%) after 3 or more days (Figure 3, Table 12).

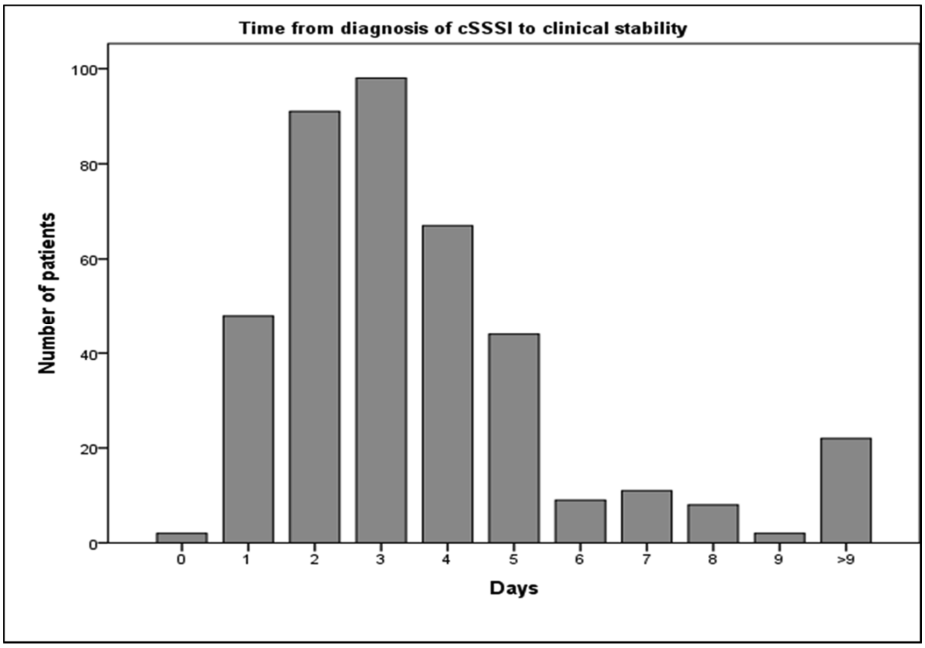

Figure 3 Time to clinical stability from the day of cSSSI diagnosis (n=402).

5.2.1 CLINICAL STABILITY ON 0–3 VERSUS ≥4 DAYS

On multivariable analysis (n=308), factors statistically significantly associated to clinical stability on ≥4 days were as follows: posttraumatic wound infection, bacteraemia, diabetes, a short (<2 days) time from onset of symptoms to diagnosis of cSSSI, admission to ICU, a surgical intervention after diagnosis of cSSSI and initial treatment with a broad-spectrum antimicrobial agent (Table 12). On the contrary, previous hospitalization within the three months before infection and initial antimicrobial treatment covering initial pathogens were the factors that remained statistically significantly associated with stabilization on 0–3 days on multivariable analysis (Table 12).

Table 12 *Baseline and disease characteristics, microbiological diagnosis and antimicrobial treatment of 402 patients with cSSSI categorized according to time to clinical stability.*

Variable	Clinical stability 0-3 days	Clinical stability ≥4 days	Clinical stability ≥4 vs 0-3 days		Clinical stability ≥4 vs 0-3 days Multivariable analysis [a]	
Full analysis population (N=402)	239	163	OR (95% CI)	p [b]	OR (95% CI)	p
Baseline characteristics						
Male gender (n=240)	127 (53)	113 (69)	1.99 (1.31-3.03)	0.001	---	
Age > 60 years (n=253)	146 (61)	107 (66)	1.22 (0.80-1.84)	0.35	---	
Injection drug abuse (n=31)	22 (9)	9 (6)	0.58 (0.26-1.29)	0.17		
Alcohol abuse (n=33)	13 (5)	20 (12)	2.43 (1.17-5.04)	0.015	---	
Congestive heart disease (n=29)	16 (7)	13 (8)	1.21 (0.57-2.58)	0.63		
Respiratory disease (n=31)	15 (6)	16 (10)	1.63 (0.78-3.39)	0.20		
Chronic renal failure (n=26)	13 (5)	13 (8)	1.51 (0.68-3.34)	0.31		
Liver disease (n=21)	10 (4)	11 (7)	1.66 (0.69-4.00)	0.26		
Cancer/Malignancy (n=31)	22 (9)	9 (6)	0.58 (0.26-1.29)	0.17		
Diabetes (n=158)	81 (34)	77 (47)	1.75 (1.16-2.63)	0.007	2.33 (1.28-4.25)	0.006
Peripheral vascular disease (n=97)	49 (21)	48 (29)	1.62 (1.02-2.57)	0.041	1.82 (0.93-3.58)	0.08
Hospitalization within 3 months (n=76)	53 (23)	23 (14)	0.58 (0.34-0.99)	0.040	0.47 (0.22-0.99)	0.047
Inv. surgery within 3 months (n=67)	47 (20)	20 (13)	0.57 (0.32-1.01)	0.047	---	
Disease characteristics						
Abscess (n=172)	121 (51)	51 (31)	0.44 (0.29-0.67)	<0.001	0.55 (0.29-1.04)	0.07
Cellulitis/fasciitis (n=171)	86 (36)	85 (52)	1.94 (1.29-2.91)	0.001	---	
Posttraumatic wound (n=42)	19 (8)	23 (14)	1.90 (1.00-3.62)	0.05	3.17 (1.31-7.69)	0.011
Postsurgical wound (n=76)	46 (19)	30 (18)	0.95 (0.57-1.58)	0.83		
Decubitus/pressure ulcer (n=10)	8 (3)	2 (1)	0.36 (0.08-1.71)	0.16		
Diabetic foot/leg ulcer (n=53)	24 (10)	29 (18)	1.94 (1.08-3.47)	0.026	---	
Perip. vascular disease ulcer (n=35)	22 (9)	13 (8)	0.86 (0.42-1.75)	0.67		
Antibiotic treatment before dg (n=108)	68 (28)	40 (25)	0.82 (0.52-1.29)	0.38		
Symptoms <2 days before dg (n=117)	56 (24)	61 (38)	1.95 (1.26-3.02)	0.003	2.01 (1.02-3.94)	0.043
Bacteraemia (n=50)	15 (6)	35 (21)	4.08 (2.15-7.77)	<0.001	3.09 (1.36-7.02)	0.007
Admission to intensive care unit (n=58)	9 (4)	49 (30)	11.0 (5.21-23.2)	<0.001	10.1 (4.01-25.3)	<0.001
Surgical intervention after dg (n=211)	114 (48)	97 (60)	1.61 (1.08-2.41)	0.020	2.64 (1.36-5.11)	0.004
Initial microbiological diagnosis						
Staphylococci (n=99)	70 (29)	29 (18)	0.52 (0.32-0.85)	0.008	---	
Streptococci (n=90)	48 (20)	42 (26)	1.38 (0.86-2.22)	0.18		
Gram-negative bacteria (n=24)	15 (6)	9 (6)	0.87 (0.37-2.05)	0.75		
Polymicrobial infection (n=79)	40 (17)	39 (24)	1.57 (0.95-2.57)	0.08	---	
Other microbe (n=12)	5 (2)	7 (4)	2.10 (0.66-6.74)	0.21		
Negative/unknown (n=98)	61 (26)	37 (23)	0.86 (0.54-1.37)	0.52		
Initial antimicrobial treatment						
Broad-spectrum [c] (n=79)	34 (14)	45 (28)	2.28 (1.38-3.75)	0.001	3.03 (1.43-6.40)	0.004
Cephalosporins [d] (n=202)	119 (50)	83 (51)	1.03 (0.69-1.53)	0.89		
Penicillin with staph. effect [e] (n=46)	36 (15)	10 (6)	0.37 (0.18-0.76)	0.004	---	
Penicillin without staph. effect [f] (n=38)	21 (9)	17 (10)	1.20 (0.61-2.35)	0.60		
Other antimicrobials [g] (n=35)	27 (11)	8 (5)	0.40 (0.18-0.91)	0.020		
Initial pathogen(s) covered by initial antimicrobial treatment (n=256/310)	155 (86)	101 (78)	0.56 (0.31-1.01)	0.05	0.38 (0.18-0.80)	0.011

Data are no. (column-%) of patients unless otherwise specified. OR, odds ratio.
[a] Logistic regression analysis (Method: Backward/Likelihood ratio/Akaike information criteria, n=308)
[b] Likelihood ratio -test
[c] Carbapenem and Piperacillin-Tazobactam
[d] Cefadroxil, Cefotaxim, Ceftriaxone, Cefuroxime and Cephalexin
[e] Cloxacillin, Flucloxacillin and other β-lactamase-stable Penicillin
[f] Amoxicillin, Benzylpenicillin and Phenoxymethylpenicillin
[g] Clindamycin, Doxycyclin, Fluoroquinolone, Fusidic Acid, Linezolid, Metronidazole, Cotrimoxazole, Tobramycin and Vancomycin

5.2.2 CLINICAL STABILITY ON 0–3 VERSUS 4–5 DAYS

To further evaluate the factors associated with time to clinical stability, we compared patients who reached clinical stability on days 4–5 (n=111, 28%) after the diagnosis of cSSSI to patients with clinical stability reached in 3 days (n=239, 59%). In univariable analyses, clinical stability on days 4–5 was associated with ICU treatment [OR 7.05 (3.15–15.77), p<0.001], bacteraemia [OR 3.90 (1.95–7.83), p<0.001], diabetic foot infection [OR 2.47 (1.33–4.59), p=0.003], diabetes [OR 2.14 (1.35–3.38), p=0.001], male gender [OR 2.00 (1.24–3.22), p=0.004] and cellulitis/fasciitis [OR 1.69 (1.07–2.66), p=0.024]. In contrast, abscess [OR 0.45 (0.28–0.72), p=0.001] or surgery within prior three months [OR 0.50 (0.25–0.98), p=0.039] were the factors that were associated with clinical stability within 3 days.

Of the 52 patients (13%) who stabilized after 5 days, a significant proportion had been treated in ICU (48%) or had polymicrobial aetiology (37%) – and they were treated on an average with 5.5 different antimicrobials during their disease course (Study II, Table 1).

5.2.3 ASSOCIATION OF TIME TO CLINICAL STABILITY TO OUTCOME AND TO THE USE OF RESOURCES

Patients with late (>3 days) clinical stability were more likely to have their initial treatment modified and had longer LOS and antimicrobial treatment duration as compared to patients with clinical stability in 3 days – and they also had more different antibiotic agents used and clinics visited during their disease course (Table 13).

Table 13 *Clinical outcomes and resource use of 402 patients with cSSSI categorized by time to clinical stability.*

Variable	Clinical stability 0-3 days	Clinical stability ≥4 days	Clinical stability ≥4 vs 0-3 days	
Full analysis population (N=402)	239	163	OR (95% CI)	p
Hospitalized again due to cSSSI (n=66/391)	39 (17%)	27 (17%)	1.03 (0.60-1.76)	0.93 [a]
Initial treatment modification [c] (n=116/397)	37 (16%)	79 (49%)	5.18 (3.25-8.27)	<0.001 [a]
Length of hospital stay, days (n=378), median (IQR25, 75)	7 (4, 13)	20 (12, 37)	---	<0.001 [b]
Duration of antibiotics, days (n=395), median (IQR25, 75)	12 (7, 23)	28 (16, 43)	---	<0.001 [b]
No. of antibiotic courses (n=401), mean (SD)	2.8 (1.4)	4.6 (2.4)	---	<0.001 [b]
No. of clinics during hospital stay (n=402), mean (SD)	1.3 (0.7)	2.1 (1.4)	---	<0.001 [b]

Data are number (%) of patients unless otherwise specified. OR, Odds ratio; IQR, interq. range.
[a] Pearson's X^2 –test
[b] Mann-Whitney *U* –test
[c] Only iv to iv modifications

5.3 COMPARISON OF DIABETICS AND NONDIABETICS (STUDY III)

5.3.1 PATIENT POPULATION

Of the total 460 patients with cSSSI, the main comparison was performed between patients with diabetes (n=119) and without it (n=271). Patients with diabetic foot infection (DFI, n=70) were analyzed as a separate group. When compared to nondiabetics, diabetics were found to be significantly older [mean age 71 (SD 15) versus 64 (20) years, p=0.001], have more often chronic renal failure (13% versus 2.2%) or a respiratory disease (13% versus 6.3%), infection localized in the lower extremity (68% versus 49%, p=0.001) or classified as cellulitis (65% versus 43%) and to seek treatment earlier from the onset of symptoms (Table 14). In contrast, diabetics were detected to have less injection drug abuse (0.8% versus 11%) than nondiabetics (Table 14).

5.3.2 ANTIMICROBIAL TREATMENT AND MICROBIOLOGICAL DIAGNOSIS

Initial antimicrobial therapy and initial microbiological aetiology of patients with cSSSI are presented in tables 15 and 16, respectively. Initial antibiotic agents and pathogens were analyzed between diabetics and nondiabetics in the main categories and statistically significant differences were not found (Tables 15 and 16). Gram-positive aerobic bacteria accounted for 70% of microbiological diagnoses in diabetic patients and 69% in nondiabetics and the empirical antibiotic treatment covered the initial bacterial pathogen(s) in 81% and 86% (p=0.250) of diabetics and nondiabetics, respectively.

When the total period of antimicrobial treatment was analyzed, broad-spectrum antibiotic agents were used more often in diabetics than in nondiabetics (42% versus 28%, OR 1.83, p=0.008). In multivariable analysis, polymicrobial aetiology of infection (OR 3.76, p<0.001), invasive surgery within the previous three months (OR 2.79, p=0.001), admission to ICU (OR 2.65, p=0.001) and bacteraemia (OR 2.55, p=0.002) were the other factors associated to use of broad-spectrum therapy at any time during the course of treatment. Only character that was found to be inversely associated to broad-spectrum therapy in multivariate analysis was staphylococcal infection (OR 0.37, p=0.001). After PS-adjusted analysis, diabetes was the only background characteristic that was a risk factor for broad-spectrum therapy (OR 1.75, p=0.022).

Table 14 *Background and disease characteristics of cSSSI among diabetics and nondiabetics.*

Character		Patients with diabetes (n=119)	Patients without diabetes (n=271)	Diabetics vs nondiabetics	
				OR (95% CI)	p [a]
Male gender		70 (59)	157 (58)	1.04 (0.67-1.61)	0.870
Age >60 years		93 (78)	149 (55)	2.93 (1.78-4.81)	<0.001
Human immunodeficiency virus infection		3 (3)	4 (1)	1.73 (0.38-7.84)	0.474
Other disease with immunodeficiency		3 (3)	10 (4)	0.68 (0.18-2.50)	0.554
Cancer / Malignancy		10 (8)	22 (8)	1.04 (0.48-2.27)	0.925
Chronic renal failure		15 (13)	6 (2)	6.37 (2.41-16.9)	<0.001
Congestive heart disease		10 (8)	25 (9)	0.90 (0.42-1.94)	0.794
Liver disease		4 (3)	16 (6)	0.55 (0.18-1.70)	0.295
Peripheral vascular disease		32 (27)	67 (25)	1.12 (0.69-1.83)	0.651
Respiratory disease		16 (13)	17 (6)	2.32 (1.13-4.77)	0.019
Alcohol abuse		6 (5)	25 (9)	0.52 (0.21-1.31)	0.160
Injection drug abuse		1 (1)	29 (11)	0.07 (0.01-0.53)	0.001
Hospitalization within previous 3 months		30 (25)	50 (18)	1.49 (0.89-2.49)	0.128
Invasive surgery within previous 3 months		23 (19)	47 (17)	1.14 (0.66-1.99)	0.638
Treatment with antibiotics before dg		25 (21)	72 (27)	0.74 (0.44-1.23)	0.242
Abscess		42 (35)	124 (46)	0.65 (0.41-1.01)	0.054
Cellulitis/fasciitis		77 (65)	116 (43)	2.45 (1.57-3.83)	<0.001
Post-surgical wound		29 (24)	48 (18)	1.50 (0.89-2.52)	0.128
Post-traumatic wound		10 (8)	37 (14)	0.58 (0.28-1.21)	0.143
Number of days between symptoms start and diagnosis	<2 days	50 (42)	74 (27)	1.93 (1.23-3.03)	0.004
	2-7 days	53 (45)	139 (51)	0.76 (0.50-1.18)	0.219
	>7 days	16 (13)	50 (18)	0.69 (0.37-1.26)	0.225
	Unknown	0 (0)	8 (3)	0.97 (0.95-0.99)	0.058
Highest C-reactive protein level [n=451, mean (SD)]		240 (116)	222 (140)		0.056 [b]
Bacteraemia		18 (15)	34 (13)	1.24 (0.67-2.30)	0.490
Septic shock		2 (2)	6 (5)	0.76 (0.15-3.80)	0.732
Admitted to ICU		15 (13)	52 (19)	0.61 (0.33-1.13)	0.113

Data are number (%) of patients unless otherwise specified.
[a] Pearson's X^2 –test
[b] Mann-Whitney U -test

Table 15 *Initial antimicrobial agents in the treatment of cSSSI among diabetics and nondiabetics.*

Antimicrobial agent	Patients with diabetes (n=118)	Patients without diabetes (n=270)	Diabetics vs nondiabetics	
			OR (95% CI)	p [a]
Broad-spectrum [b]	26 (22)	39 (14)	1.67 (0.96-2.91)	0.066
Cephalosporins [c]	60 (51)	133 (49)	1.07 (0.69-1.64)	0.773
Other [d]	11 (9)	31 (11)	0.79 (0.38-1.64)	0.529
Penicillins [e]	12 (10)	29 (11)	0.94 (0.46-1.91)	0.866
Penicillins with staph. effect [f]	9 (8)	38 (14)	0.50 (0.24-1.08)	0.073

Data are number (%) of patients unless otherwise specified.
[a] Pearson's X^2 –test
[b] Carbapenem and Piperacillin-Tazobactam
[c] Cefadroxil, Cefotaxim, Ceftriaxone, Cefuroxime and Cephalexin
[d] Clindamycin, Doxycyclin, Fluoroquinolone, Fusidic Acid, Linezolid, Metronidazole, Cotrimoxazole, Tobramycin and Vancomycin
[e] Amoxicillin, Benzylpenicillin and Phenoxymethylpenicillin
[f] Cloxacillin, Flucloxacillin and other β-lactamase-stable Penicillin

Table 16 *Microbiological diagnosis of cSSSI among diabetics and nondiabetics.*

Pathogen	Patients with diabetes (n=119)	Patients without diabetes (n=271)	Diabetics vs nondiabetics	
			OR (95% CI)	p [a]
Staphylococci	27 (23)	77 (28)	0.74 (0.45-1.22)	0.239
Methicillin-sensitive *S. aureus*	26 (22)	75 (28)		
Methicillin-resistant *S. aureus*	1 (1)	2 (1)		
Streptococci	27 (23)	67 (25)	0.89 (0.54-1.49)	0.665
Streptococcus pyogenes	8 (7)	46 (17)		
Streptococcus agalactiae	4 (3)	2 (1)		
β-hemolytic streptococci	14 (12)	8 (3)		
Streptococcus pneumoniae	1 (1)	2 (1)		
Alfa-hemolytic streptococci	0 (0)	9 (3)		
Gram-negative bacteria	8 (7)	13 (5)	1.43 (0.58-3.55)	0.438
Enterobacteriacae	5 (4)	8 (3)		
Pseudomonas	3 (3)	2 (1)		
Other gram-negative bacteria	0 (0)	3 (1)		
Other microorganism	3 (3)	10 (4)	0.68 (0.18-2.50)	0.554
Anaerobic bacteria	2 (2)	8 (3)		
Enterococci	1 (1)	2 (1)		
Polymicrobial infections	19 (16)	45 (17)	0.95 (0.53-1.71)	0.875
Only Gram-positive bacteria	4 (3)	19 (7)		
Only Gram-negative bacteria	0 (0)	1 (0)		
Mixed	15 (13)	25 (9)		
Negative / Unknown	35 (29)	59 (22)	1.50 (0.92-2.44)	0.104

Data are number (%) of patients unless otherwise specified.
[a] Pearson's X^2 –test

Table 17 *Clinical outcomes and the use of resources of cSSSI among diabetics and nondiabetics.*

Outcome	Patients with diabetes (n=119)	Patients without diabetes (n=271)	Diabetics vs nondiabetics	
			OR (95% CI)	p
Clinical failure due to cSSSI (n=457)	31 (26)	56 (21)	1.33 (0.81-2.21)	0.262 [a]
Hospitalized again due to cSSSI (n=439)	16 (13)	38 (14)	0.93 (0.50-1.75)	0.825 [a]
Mortality in 30 days (n=460)	6 (5)	11 (4)	1.26 (0.45-3.48)	0.662 [a]
Mortality in 12 months (n=451)	23 (19)	25 (9)	2.35 (1.27-4.34)	0.005 [a]
Time to clinical stability, days (n=402, mean (SD)	4.1 (3.5)	3.9 (4.2)		0.038 [b]
Duration of antimicrobial therapy, days (n=448, median (IQR25, 75)	21 (12, 38)	14 (8, 28)		<0.001 [b]
Number of antibiotic therapy courses (n=457, mean (SD)	3.6 (2.2)	3.3 (1.9)		0.560 [b]
Length of hospital stay, days (n=416, median (IQR25, 75)	13 (6, 21)	10 (5, 20)		0.090 [b]
Number of clinics during hospital stay (n=460, mean (SD)	1.7 (1.0)	1.5 (1.0)		0.022 [b]

Data are number (%) of patients unless otherwise specified.
[a] Pearson's X^2 –test
[b] Mann-Whitney U –test

5.3.3 PATIENTS WITH DIABETIC FOOT INFECTION

When compared to nondiabetics, patients with DFI were observed to have more often Gram-negative (13% versus 4.8%; OR 2.93, p=0.014) or polymicrobial infections (31% versus 17%; OR 2.30, p=0.005) and broad-spectrum antimicrobial as initial therapy (30% versus 14%; OR 2.54, p=0.002) – and less often staphylococcal infection (13% versus 28%; OR 0.37, p=0.008). The median duration of antimicrobial treatment (21 versus 14 days; p=0.005) and hospital stay (14 versus 10 days; p=0.006) were found to be longer in patients with DFI than in nondiabetics – nevertheless patients with DFI had more recurrences than patients without diabetes (26% versus 14%; OR 2.12, p=0.020).

5.4 COMPARISON OF MANAGEMENT PRACTICES BETWEEN HELSINKI AND GOTHENBURG (STUDY IV)

5.4.1 PATIENT POPULATION

Totally 460 patients were included in the analyses out of which 219 were from Helsinki and 241 from Gothenburg (Figure 2). Compared to patients in Helsinki, patients in Gothenburg were older [mean (SD) age 63 (19) vs. 59 (18) years; p=0.0117] and had less often diabetes (32% versus 50%, p<0.0001), chronic renal failure (2.9% versus 11%, p=0.0004), respiratory disease (5.0% versus 10%, p=0.0273), or a prior hospitalization (14% versus 23%, p=0.0235; Study IV, Table 1). In contrast, patients in Gothenburg had more often congestive heart disease (14% versus 4.6%, p=0.0077) and were treated more often with antibiotics before their infection met the cSSSI criteria (34% versus 24%, p=0.0293; Study IV, Table 1).

Bacteraemic infection was more common in Helsinki (18% of patients) than in Gothenburg (9.1% of patients, p=0.0102), but statistically significant differences were not detected in the other measures of disease severity: WBC count, peak CRP level, occurrence of septic shock, and in the need for blood pressure support (Study IV, Table 2). Both in Helsinki and Gothenburg, patients were categorized to have mainly cellulitis (43% and 41%) or abscess (43% and 41%), respectively (Study IV, Table 2). Infections related to peripheral vascular disease (16% versus 6.4%, p=0.0208) or pressure ulcers (5.4% versus 0.5%, p=0.0022) were more common in Gothenburg, whereas postsurgical wound infections (23% versus 12%, p=0.0026) were more common in Helsinki (Study IV, Table 2).

5.4.2 MICROBIOLOGICAL DIAGNOSIS

Microbiological testing was conducted for 97% and 91% of patients and microbiological diagnosis was obtained in 65% and 73% of the patients in Helsinki and Gothenburg, respectively. Polymicrobial infections were more frequently reported in Helsinki (34%) than in Gothenburg (13%, p<0.0001) although in monomicrobial infections the proportions of main pathogens – staphylococci (46% versus 50%) and streptococci (33% versus 31%) were similar (Study IV, Table 3).

5.4.3 ANTIMICROBIAL THERAPY

Initial antimicrobial therapy was analysed between cities in the main categories: broad-spectrum, cephalosporins, penicillins, penicillins with staphylococcal effect and other antibiotics (Study IV, Table 5). When compared to Gothenburg, initial antimicrobial therapy in Helsinki consisted

almost exclusively of cephalosporins (69% versus 31%) and broad-spectrum antibiotics (27% versus 12%) whereas penicillins with staphylococcal effect (0.0% versus 22%) and without it (0.9% versus 21%) were used more often in Gothenburg, respectively (p<0.0001; Study IV, Table 5). Flowcharts of antibiotic treatment are presented in figure 4. Initially cultured pathogens were covered by initial antimicrobial treatment in 79% and 87% of the patients in Helsinki (data available for 184 patients) and Gothenburg (data available for 169 patients, p=0.056), respectively.

The median overall durations of antimicrobial therapy were 29 days in Helsinki and 12 days in Gothenburg (p<0.0001) and each patient was treated in an average with 4.3 different antibiotics in Helsinki and 2.7 in Gothenburg (p<0.0001) (Study IV, Table 4). While on intravenous therapy, initial antibiotic treatment was modified to another intravenous drug in 55% and 31 % of the patients (p<0.0001) and the median time from diagnosis to the first modification was 3 and 4 days (p=0.0507) in Helsinki and Gothenburg, respectively (Study IV, Table 4). The majority of patients – 77% of the patients in Helsinki and 53% in Gothenburg – continued with an (mainly oral) antibiotic after hospital discharge (Study IV, Table 5).

5.4.4 CLINICAL MANAGEMENT AND OUTCOME

The median LOS was 17 days in Helsinki and 11 days in Gothenburg (p<0.0001) and home-based care after discharge was given to 32% and 57% of patients (p<0.0001), respectively (Study IV, Table 4). Statistically significant difference between cities was detected in the number and the distribution of the different departments that the patient visited during the hospital stay (Study IV, Table 4 and Figure 1). In Helsinki, 57% of the patients visited two or more departments during the hospital stay while in Gothenburg 85% of the patients were treated in one department only (Study IV, Table 4 and Figure 1). Patients were treated most frequently on a surgical ward in Helsinki (64%) and on an infectious disease ward in Gothenburg (48%; Study IV, Table 4). Surgical intervention after diagnosis of cSSSI was conducted on 64% of patients in Helsinki and on 40% of patients in Gothenburg (p<0.0001). The mean time from diagnosis to clinical stability was 4.4 days in Helsinki and 3.4 days in Gothenburg (p=0.0204) and treatment failure (of any kind) occurred in 37% and 38% of the patients (p=0.8430), respectively. Recurrence of infection was detected in 16% of the patients in Helsinki and 19% in Gothenburg within 12 months after initial discharge (p=0.3776). In comparison to patients in Gothenburg, patients in Helsinki had higher mortalities within 30 days (5.5% versus 2.1%, p=0.0326) and within 12 months (16% versus 7.5%, p=0.0003).

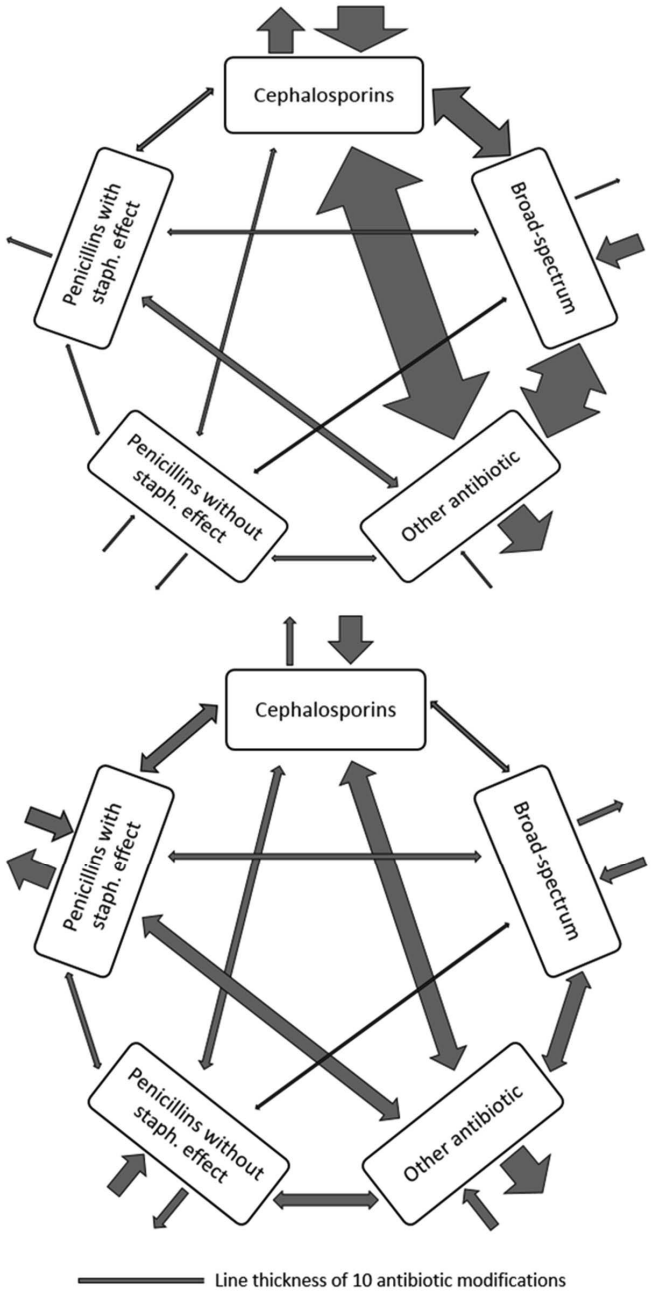

Figure 4 The flow of antibiotics in patients with cSSSI in Helsinki (above) and in Gothenburg (below). The thickness of arrow indicates the number of treatment modifications between the main classes of antimicrobials. The arrows outside the circle pointing inside indicate the initial antibiotic and the outward arrow the antibiotic at the end of treatment.

6 DISCUSSION

6.1 CHARASTERISTICS OF CSSSI IN TWO NORDIC CITIES (STUDY I)

High rates of bacteraemia and clinical failure, high number of antibiotic treatment modifications – but rare streamlining – was revealed in our population-based patient material. The median duration of antimicrobial therapy (17 days) in our study was longer when compared both to previous observational studies in cSSSI (11–15 days) [44,45,71,155] and to treatment guidelines [4,156,158]. Further, the use of broad-spectrum antimicrobial therapy was high in comparison to recommendations [4,156,158] and also in relation to microbiological findings of this study.

The REACH study, with similar inclusion criteria as in our study, was performed in 2010–2011 in a number of European countries with variable incidences of MRSA [44]. The baseline characteristics of patients in REACH were very similar to those of our study; both had a male predominance (61% in our study and 58% in REACH) and median age was the same (62 years). Similarly, only 24% of patients in our study and 22% in REACH had no comorbidities and the most common underlying diseases were diabetes (41% and 34%) and peripheral vascular disease (29% and 21%), respectively [44]. These co-morbidities have been reported as the most common also in other real-life studies in patients with cSSSI [43,45-47].

However, a notable difference in the proportion of patients with bacteremic infection was detected between our study (13%) and REACH (6.3%) which cannot be explained by differences in the frequency of blood cultures taken (53% of patients in both studies) [44]. The occurrence of bacteraemia detected in our study on patients with cSSSI was also higher in comparison to previous studies on patients with cellulitis (≤5%) [19,81]. Further, the low prevalence of bacteremic cases in many clinical trials on patients with cSSSI suggests that many patients with more severe cSSSI have not been included [122,139,189]. The presence of bacteraemia is clinically important since in our study patients with bacteremic infection reached clinical stability significantly later (median 4 versus 3 days), had significantly higher clinical failure rate (34% versus 21%), longer total antibiotic treatment duration (median 30 versus 19 days), and longer LOS (median 21 versus 12 days) as compared to patients without bacteraemia.

Both in the REACH and in our study, Gram-positive bacteria accounted for the majority of microbiological diagnoses in patients with cSSSI. In the REACH, 70% of microbiological diagnoses were due to Gram-positive bacteria [44] and microbiological aetiology was Gram-positive aerobic

bacteria in 81% of monomicrobial infections in our study which is consistent with proportions of Gram-positive infection (61%–84%) reported also in other real-life studies on patients with cSSSI [46,47,71,116,117]. In light of this, we were somewhat surprised about the high use of broad-spectrum antibiotics (19%) and cephalosporins with Gram-negative coverage (49%) in the empirical antibiotic treatment. Further, higher failure rate was detected among patients with initial broad-spectrum (37%) or cephalosporin (25%) therapy as compared to patients initially treated with penicillins (15%), penicillins with staphylococcal effect (14%) or other antibiotics (7.7%, Table 11) – probably mostly reflecting the phenomenon of "confounding by indication". That is, patients with severe conditions more likely receive broad spectrum antimicrobial treatment as compared to patients with an optimistic prognosis [190].

IDSA guideline suggests empirical treatment coverage for Gram-negative (and anaerobic bacteria) mainly in infections associated with diabetic foot, peripheral vascular insufficiency, bites, prior contact to health care and in necrotizing infections [4]. Although many patients of our study belonged to these groups, the majority of patients would not have needed Gram-negative coverage because 49% of the microbiologically tested patients had only Gram-positive bacteria detected. In our material only 29% of the antibiotics used in initial therapy had coverage limited mainly to Gram-positives, which is in accordance with the results of REACH (20%) [44] and the American study by Jenkins et al. (26%) [71].

According to microbiological results, 45% of patients in our study could have been treated with or streamlined to narrow spectrum agents since they had monomicrobial MSSA, streptococcal, enterococcal or polymicrobial Gram-positive infection. However, only 5% of patients had their treatment streamlined which did not differ from that in REACH (5.6%) [44]. In our study, streamlining was associated with bacteraemia, surgical intervention after diagnosis, admission to ICU, and higher CRP level (Table 11). Probably, bacteraemia or surgical intervention with deep tissue specimens enabled more reliable microbiological diagnosis and therefore led to more frequent streamlining among these patients. The low rate of streamlining was contradicted by the higher frequency of other treatment modifications. In total, initial treatment was modified to another intravenous drug in 39% of cases and the median time to initial treatment modification was only 3 days (Study I, Figure 1).

In our study, the total duration of antimicrobial therapy was longer than in previous real-life studies (Table 7) and clinical trials (Table 5) on patients with cSSSI and guideline recommendation [4], maybe partly explained by the high occurrence of bacteraemia and more severe infections. Duration of intravenous antimicrobial therapy in this study was comparable to the total treatment time in previous studies [44,45,71,155] – resulting in longer LOS in

our study (median 13 days) as compared to real-life studies in Europe (median 12 days) [44] and in U.S. (median 4–5) [45,71]. Opportunities to an earlier switch to oral treatment has been detected also in other European studies [155,160,191].

Interestingly, the higher peak CRP level was associated with longer LOS and total duration of antimicrobial therapy, higher rate of treatment modifications, streamlining, and treatment failures (Table 11). Of the analysed outcomes, only the risk for recurrence was not associated with the maximal CRP level and association with mortality was not statistically significant. To the best of our knowledge, studies evaluating CRP in connection to cSSSI has not been made previously, except for one prospective clinical study on patients with DFI that found no independent prognostic effect on treatment failure [69].

Clearly higher recurrence-rate (16%) was detected in our study as compared to other studies (3.7%–8.6%) [44,71] – possibly explained by the longer (12 month) observation period of our study. Higher risk of recurrence was associated with presence of co-morbidity and interestingly also with longer duration of antimicrobial treatment which suggests that longer treatment might not protect from recurrence. Thirty day mortality (4.1%) in our study was not different from the mortality reported in REACH (3.4%) [44] and in other studies on cSSSI (0.4%–9.0%) [25,43,45,46]. Admission to ICU was the only factor associated to higher mortality in 30 days (Study I, Table 5). In addition we observed high mortality (12%) within 12 months most probably reflecting the severe chronic conditions in the study population.

6.2 FACTORS ASSOCIATED WITH TIME TO CLINICAL STABILITY IN CSSSI (STUDY II)

In our study, 59 % of patients had their condition stabilised within 3 days after diagnosis, that is, within 72 hours which is suggested by FDA as a new primary endpoint for clinical trials in SSSI [129]. Later clinical stability was associated with many patient´s baseline conditions and disease characteristics – not only with treatment related factors. Further, patients with no treatment response within 72 hours had eventually more antimicrobial treatment modifications and transfers between departments – and longer antimicrobial and in-hospital treatment duration.

As in our study, diabetes was more common among late responders in another retrospective European study on patients with cSSSI [192]. They also found patients with more severe disease to have more likely late treatment response [192] – also in our study bacteraemia and admission to ICU were associated to later stabilization. In a prospective study on patients with

cellulitis, Bruun et al. found late treatment response to be associated with female sex, high body mass index (BMI) and cardiovascular disease [193]. Clinical trials on patients with ABSSSI have detected trends toward later treatment responses in patients with high age, high BMI, and diabetes [133,151-154]. Patients with wound infection were found to have more initial treatment failures in studies on patients with cSSSI [194] and with ABSSSI [195] which is in line with our findings. As in the study by Bruun et al. on patients with cellulitis [193], patients with shorter duration of symptoms before diagnosis stabilized later also in our study. This probably reflects the natural course of disease, or perhaps, patients with more severe disease seek treatment earlier.

Patients with early clinical stability were compared to those who stabilized on days 4–5. The same risk factors for late response (Table 12) were all significant also in this analysis except peripheral vascular disease, posttraumatic wound and surgical interventions – a tendency towards later response was detected among those also. That is, the differences detected between patients with early (0–3 days) and late (≥4 days) stability are not explained only by the subpopulation of patients with very late stability (≥6 days) – the patients with the most complicated course of disease. Indeed, this suggests indirectly that the ideal time point for evaluation of early treatment response might be 48–72 hours, as recommended by FDA [129].

The association of early treatment response with post-treatment clinical cure has been studied in clinical trials (Table 6) [151,152,154,196] and in observational studies [192,193]. In general, patients with early response have eventually high cure rate in post-treatment evaluation, but many of the patients with early nonresponse have also treatment response at the end of treatment. In our study, early responders had shorter median lengths of hospital stay (7 versus 21 days) and shorter antimicrobial treatment (12 versus 28 days) as compared to late responders. The association of early treatment response to LOS and duration of antimicrobial treatment are consistent with the findings of a previous European study [192] and studies from the USA [194,195,197,198].

In our study, clinical stability was reached earlier if the empiric antimicrobial treatment covered the initial pathogen(s) (Table 12) – this suggests that the treatment effect of antimicrobial therapy may be evaluated by early response, as recommended by FDA. Due to the dominance of Gram-positive bacteria (62 % of patients with microbiological diagnosis), low proportion of MRSA (1%) and high use of antimicrobials comprising also Gram-negative coverage, initial pathogens were covered by empirical treatment in the vast majority of our patients (83% of patients with microbiological diagnosis). In contrast, Bruun et al. found no correlation between discordant initial treatment and early nonresponse in patients with cellulitis, but their effective sample size was small – only 13/216 of patients

had initial treatment that did not cover the pathogens (mainly β-hemolytic streptococci) [193]. Yet, in 34% of patients initial treatment was escalated to more broad-spectrum therapy in their study, mostly within 2 days after admission [193]. This is in line with our findings (Study I); 34% of patients had initial treatment modification other than streamlining and median time to modification was 3 days.

In contrast, initial treatment with a broad-spectrum antibiotic – that is, antimicrobial therapy that covers almost all pathogens in our low antimicrobial resistance environment – was associated with a late treatment response. Similar trends were detected by Garau et al, who observed that patients treated with piperacillin-tazobactam or ampicillin-sulbactam were less likely to have an early response [192]. Further, in the study by Jenkins et al. on hospitalized patients with cellulitis or abscess, two thirds of patients received broad-spectrum therapy, but the failure rate was not different regardless of spectrum of treatment [71]. Together these data suggest that broad spectrum empiric coverage would not guarantee early response but might even postpone the treatment response. Naturally, this argument cannot be proved by observational retrospective studies. Again, patients with severe conditions more likely receive broad spectrum antimicrobial treatment as compared to patients with an optimistic prognosis [190].

The above findings suggest that background and infection related factors ought to be controlled when early treatment response is used for comparison of various treatment options. Prospective studies are needed to elucidate early response dynamics of different patient groups. Until then, what to do for the antibiotic treatment of a patient without treatment response in 48–72 hours? Referring to the above, if patient is not immediately deteriorating or antimicrobial treatment is not clearly discordant, do not rush with treatment escalation – at least in patients with risk factors for later clinical stability.

6.3 COMPARISON OF DIABETICS AND NONDIABETICS (STUDY III)

Diabetes is one of the main risk factors for cSSSI which is substantiated by that diabetics constituted 37% of patient populations in our and 25%–35% in other studies on patients with cSSSI [43-47]. In accordance with previous studies on less severe SSSI, in our cSSSI population diabetics were older, had more likely infection classified as cellulitis or infection localized into a lower extremity, had more often chronic renal failure but less injection drug abuse in comparison to nondiabetics [134,135,199,200]. However, time from onset of symptoms to diagnosis of cSSSI was shorter in diabetics than in nondiabetics. Maybe diabetic patients had been educated to seek treatment earlier or had easier access to their primary care physician and were also

send more often to hospital evaluation than nondiabetics. No statistically significant differences were detected in the objective markers of disease severity – maximal CRP level, rate of bacteraemia, septic shock, or admission to ICU – between diabetics and nondiabetics.

Statistically significant differences in the microbiological aetiology between diabetics (without DFI) and nondiabetics were not found in our study nor in the study of Jenkins et al. on patients with less severe SSSI [199]. Gram-positive aerobic bacteria accounted for 70% and 69% of the microbiological diagnoses in diabetics and nondiabetics, respectively, which is consistent with the study by Jenkins et al. [199] and also to other studies on patients with diabetes [201] and cSSSI [44,46,71]. Yet, both in our study and in the study by Jenkins et al., broad-spectrum antibiotics were used more often in diabetics than in nondiabetics [199]. In our study a trend toward more frequent use of broad-spectrum therapy was detected already in initial treatment among diabetics (p=0.066, Table 15) but it seemed also that the antibiotics were changed to broad-spectrum more often among diabetics than in nondiabetics. Interestingly, in the study of Jenkins et al. broad spectrum agents were not used more frequently in the empirical antibiotic choice but only when the total antimicrobial treatment period was analyzed [199]. In Study II we found diabetics to have in the average later treatment response than nondiabetics which could be a possible explanation for the more frequent treatment escalations among them.

Our results in cSSSI and those of Jenkins et al in SSSI are in line with the IDSA guideline recommendation on antimicrobial treatment covering only *S. aureus* and streptococci in the treatment of a cellulitis or an abscess irrespective of the presence of diabetes [4]. Empirical antimicrobial therapy covering also Gram-negative (and anaerobic) bacteria is recommended only in the most severe forms of SSSI [4] and in patients with DFI for moderate-to-severe infections [76] (Study III, Figure 1).

In our study the median total duration of antimicrobial treatment was longer in diabetics (21 days) than in nondiabetics (14 days) which was also observed in SSSI by Jenkins et al [199]. Interestingly, no difference was found in the length of hospital stay between diabetics and nondiabetics. That is, the difference in the duration of antimicrobial treatment reflected mainly antibiotics prescribed at the time of discharge due to unknown reason longer for diabetics than nondiabetics.

Only 15% of our study population had DFI and on IDSA classification they would have been classified as severe since signs of systemic infection were required for inclusion [76]. In the analyses, patients with DFI were separated from other cSSSI among diabetics and they seemed to differ substantially from nondiabetics. In comparison to nondiabetics, patients with DFI had more often Gram-negative or polymicrobial but less often staphylococcal infection and their treatment was started more often with a broad-spectrum

antibiotic. In addition, patients with DFI had more recurrences, longer median time of hospital stay and longer total antimicrobial treatment duration than nondiabetics. These are characteristics that have been detected also in previous studies in DFI [8,57,202,203].

6.4 COMPARISON OF MANAGEMENT PRACTICES BETWEEN HELSINKI AND GOTHENBURG (STUDY IV)

Remarkable differences in the treatment and management of patients with cSSSI were revealed between Helsinki and Gothenburg despite the centers' similar public healthcare structure and low incidence of antimicrobial resistance. Patients in Helsinki were predisposed more frequently to antimicrobials with Gram-negative coverage, had more treatment modifications, longer median duration of antimicrobial therapy and longer hospital stay than patients in Gothenburg. In addition, during their hospital stay 57% of patients in Helsinki were transferred between departments while in Gothenburg 85% of patients were treated in one department, most commonly in the department of Infectious Diseases.

Helsinki and Gothenburg area have near equal number of inhabitants and after two-step inclusion process we ended up eventually to final patient populations with almost equal size (Helsinki 219 and Gothenburg 241 patients, Figure 2). In the first step, more patients were identified with ICD10-codes in Gothenburg (2151 patients) than in Helsinki (1164 patients). This might indicate that in Gothenburg more patients with ICD10-code possibly related to SSSI had been hospitalized (or evaluated in emergency department). Naturally some differences may have been between cities in the practices of diagnostic coding. In total, only 460 (14%) of 3315 patients initially identified by ICD10-codes met our criteria for cSSSI probably indicating that we have caught the patients with the most severe disease. Annual incidence of cSSSI was higher in Gothenburg (11/100'000) than in Helsinki (9/100'000) which might reflect that more patients with milder disease have been included in Gothenburg than in Helsinki.

Although we tried to apply strict criteria for patient data collection there was some differences in the patient populations between the cities. In both cities, patients had a high number of co-morbidities and a male predominance but patients in Gothenburg were older than in Helsinki (Study IV, Table 1). Of the co-morbidities, diabetes, chronic renal failure and respiratory disease were more common among patients in Helsinki but congestive heart disease among patients in Gothenburg. In both cities, patients were classified to have mainly cellulitis or abscess. Post-surgical wound infections were more common in Helsinki instead infected peripheral

vascular disease ulcers or infected decubitus ulcers were more prevalent in Gothenburg.

Importantly, no significant differences were found between study groups among the objective measures of disease severity like WBC count at the time of diagnosis, highest CRP level or in the amount of patients admitted to ICU, patients with septic shock or in need for blood pressure support. However, blood culture positive infections were twice more common in Helsinki (18% of patients) than in Gothenburg (9.1% of patients).

Gram-positive cocci accounted for the majority of infections, however, in Helsinki they were detected more often in conjunction with Gram-negative or anaerobic bacteria. The higher prevalence of diabetes and previous hospitalization may explain in part the higher proportion of polymicrobial infections in Helsinki. Yet, in both cities only 15% of patients had DFI and in Study III it was observed that diabetics without DFI and nondiabetics had similar microbiological aetiologies of infection. Differences in laboratory reporting practices between countries cannot be ruled out either since the known risk factors for Gram-negative, anaerobic or polymicrobial infection were not that different between the cities. In both cities, the majority of microbiological diagnoses were detected by superficial swabs which may detect also bacterial colonization.

Although some differences existed between the cities in the patient and disease characteristics, differences out of proportion were observed in clinical practices between the study centers. Gram-negative or anaerobic bacteria were present only in the minority of patients both in Helsinki (33%) and in Gothenburg (18%). However, 96% of patients in Helsinki and 47% in Gothenburg had Gram-negative bacteria covered in their initial antimicrobial therapy. Even after the first treatment modification – that is, while the microbiological results are usually available – 61% of patients in Helsinki and 33% in Gothenburg had still Gram-negative coverage. Cephalosporin-based treatment was significantly more common in Helsinki and explains the main part of the more common Gram-negative coverage used in Helsinki whereas more penicillin-based therapies (without Gram-negative coverage) were used in Gothenburg. The more common cephalosporin use in cSSSI seems to reflect the general use of antimicrobials in hospital setting. In nationwide statistics in 2011, the use of non-penicillin β-lactam antibiotics (most of which were cephalosporins) was five times more common in Finland as compared to Sweden [204]. In light of the microbiological results, staphylococcal penicillins might have been used more often both empirically as well as in streamlining. Experience in open care treatment of SSSI in U.K. supports this with almost two fold increase in the use of flucloxacillin within 10 years and no increase in treatment failures related to it [14]. Furthermore, the use of antimicrobials with broader spectrum in Helsinki did not result in better coverage of the cultured pathogens with the initial antimicrobial

treatment which were 87% and 79% in Gothenburg and Helsinki, respectively.

Significant differences were found between the cities also in the number of different departments the patient was treated in, the number of antimicrobial treatment modifications and the length of hospital stay. During their hospital stay, 57% of patients in Helsinki were treated in more than one department while in Gothenburg 85% of patients stayed in one department. In Helsinki, patients were treated most frequently in the department of Surgery but in Gothenburg in the department of Infectious Diseases. Not surprisingly patients in Helsinki had more surgical interventions after diagnosis. Infectious disease specialist consultation has been shown to improve the treatment of *S. aureus* -bacteraemia [205], but unexpectedly, it was detected to be an independent risk factor for broad-spectrum antimicrobial therapy in SSSI [199]. To the best of our knowledge, the effect of Infectious disease specialist -based treatment on the outcome of patients with cSSSI has not been studied. The number of different antibiotic courses used per patient was significantly higher in Helsinki (mean 4.3) than in Gothenburg (mean 2.7) and also the time from diagnosis to the first antibiotic modification was almost statistically significantly longer in Gothenburg (median 4 days) than in Helsinki (3 days, p=0.0507). The longer average time to clinical stability in Helsinki (4.4 days) compared to Gothenburg (3.4 days) may have had an impact to more frequent antibiotic modifications in Helsinki. Possibly more frequent transfer of the patient to another department (Study IV, Figure 1) has affected to the earlier and more frequent modifications in antibiotic treatment in Helsinki and perhaps explains partly the longer lengths of hospital stay and total antimicrobial treatment duration also. In addition, patients in Gothenburg had more often home-based care after in-hospital treatment which may have enabled earlier discharge and led to shorter LOS in Gothenburg.

The most striking difference was the more than double longer total antimicrobial treatment in Helsinki (median 29 days) compared to Gothenburg (12 days). The median duration of antimicrobial therapy in Helsinki also far exceeds the duration detected in clinical trials (Table 5 and 6), previous real-life studies (Table 7) and recommended in guidelines (Table 8) while duration in Gothenburg falls within the range detected in previous studies and recommendation in their national guideline. Again, although there were differences in patients' baseline or disease characteristics they hardly explain totally the difference in the antimicrobial treatment duration between the cities.

The more Gram-positive oriented antimicrobial treatment with fewer modifications and shorter duration in Gothenburg did not have a negative association to treatment outcome. On the contrary, the 30-day mortality was significantly higher in Helsinki (5.5%) than in Gothenburg (2.1%) which may

also reflect the differences in patient material between the cities. The mortalities in both cities fall within the range from 0.4% to 9.0% that has been previously reported for cSSSI [25,43-46]. No differences between cities were detected in the number of total treatment failures or recurrences.

6.5 STRENGTHS AND LIMITATIONS OF STUDIES I–IV

The major strength of this study was its population based approach which was enabled by the high affinity to public health care in the Nordic countries. That is, patients with an infection severe enough to be included in our study have been treated in public hospitals and we were able to catch all cSSSI patients from hospital databases as long as patient had the diagnostic ICD10-code used in our study. Naturally, we may have missed some patients due to coding errors. Population based approach may give comprehensive real-life data in contrast to clinical trials in which patients with the most severe illness commonly have been excluded and also in contrast to retrospective cohort studies gathered from selected hospitals. The data were collected in two countries which makes it more generalizable. On the other hand, different interpretations of patients' medical records may have potentially biased the study data. This study was also conducted in the area of low prevalence of MRSA (2011: Finland 2.8%, Sweden 0.8%) [114,115], ruling out one possible confounding factor of antimicrobial treatment.

However, retrospective real-life design was also the main limitation of our study because it led to complete dependence on medical records, not initially made for research purposes. In the study II, insufficient recording of local signs of infection made it impossible to fully evaluate the patients' treatment response in a manner recommended by FDA [24]. The retrospective nature led also to missing data in some parameters. The main reason for missing data was the common problem in all SSSI studies: due to low sensitivity of bacterial cultures especially in cellulitis microbiological documentation is not possible in all patients. To control for the missing microbiological data in the study II, multivariable analysis was repeated without the covariate "Initial pathogen(s) covered by initial antimicrobial treatment" practically with no changes in the results. In addition, microbiological diagnosis was based mainly on superficial swabs, which may detect also bacterial colonization in addition to causative microbiological agents – although this probably did not biased intergroup analyses of the study.

Furthermore, the phenomenon "confounding by indication" is a source for bias in retrospective cohort analyses [190]. In our study that is, patients with severe conditions, as compared to patients with an optimistic prognosis, probably more likely have received broad-spectrum antimicrobial treatment. In the study III, the main results were observed in Propensity-score adjusted

(PS) analysis correcting for significant differences between diabetics and nondiabetics which may reduce the potential bias associated to retrospective analyses [206].

The definition of DFI was critical in study III. The classification of infection was made by two experienced clinicians who collected the data and ended up to similar proportions of DFI between cities (Helsinki 32/219, Gothenburg 37/241). In our study, only minority of infections in the lower extremities of diabetics were classified as DFI. In theory, the inclusion criteria of our study may have allowed patients with diabetes (or peripheral arterial disease) with less severe infections of lower extremities to be included. Yet, no statistically significant differences were detected between patients with DFI and nondiabetics in the level of highest CRP or in the occurrence of bacteraemia or septic shock.

7 CONCLUSIONS

7.1 CHARACTERISTICS OF CSSSI IN TWO NORDIC CITIES (STUDY I)

Bacteraemia, treatment failure and recurrences in cSSSI were more common in this population based real-life study than in previous non-population based studies. Gram-positive bacteria constituted 66% of the microbiological diagnoses which indicated that the frequent use of antimicrobials with Gram-negative coverage was most often unnecessary. Treatment modifications – other than streamlining – were frequent and the treatment duration was longer than previously reported and recommended in the guidelines. Higher maximal CRP level seemed to be associated with worse outcome but further studies are needed to evaluate the role of CRP as a prognostic tool in cSSSI. This study supports the use of narrow spectrum antibiotic therapy for cSSSI patients in Finland and Sweden.

7.2 FACTORS ASSOCIATED WITH TIME TO CLINICAL STABILITY IN CSSSI (STUDY II)

Time to treatment response seemed to depend on several baseline characteristics and disease related factors other than treatment related factors in this retrospective real-life population-based study. This suggests that these factors ought to be controlled when early treatment response is used for comparison of various treatment options. Even more importantly, these findings might be helpful in clinical practice to reduce unnecessary early antimicrobial treatment modifications. Time to treatment response was associated with outcome i.e. patients with clinical stability within 3 days were less likely to have treatment modifications and had shorter hospital stay and shorter antimicrobial treatment than those who stabilized later.

7.3 COMPARISON OF DIABETICS AND NONDIABETICS (STUDY III)

After exclusion of patients with diabetic foot infection, no statistically significant differences in the microbiological aetiology of cSSSI was found between diabetics and nondiabetics. Yet, diabetics were treated significantly more often with broad-spectrum antibiotics covering also Gram-negative and

anaerobic bacteria and their antibiotic treatment lasted longer than in nondiabetics. These results point out that merely Gram-positive antimicrobial coverage is usually enough also in diabetics without DFI.

7.4 COMPARISON OF MANAGEMENT PRACTICES BETWEEN HELSINKI AND GOTHENBURG (STUDY IV)

Striking differences were observed in the management of cSSSI between the two Nordic cities with similar public healthcare structure and low prevalence of antimicrobial resistance. Unnecessary Gram-negative antimicrobial coverage was common in both cities though it was more common in Helsinki. Compared to mainly Infectious Disease Specialist guided treatment in Gothenburg, the more frequent transfer from one department to another in Helsinki was linked to longer antimicrobial therapy and hospital stay and to more frequent changes in antimicrobial treatment. This study suggests that infectious disease specialist-guided therapy and avoidance of transfers between wards may have a role in the optimizing of antimicrobial treatment.

8 ACKNOWLEDGEMENTS

These studies were carried out at the Inflammation Center, Division of Infectious Diseases, Helsinki University Hospital, during 2012–2017.

Firstly, I owe my deepest gratitude to my supervisor Docent Asko Järvinen, Head of Division of Infectious Diseases, for his patient and comprehensive guidance throughout my research project. I felt always that my project was a special one among his many projects. This work would have never been accomplished without his creativeness and sense for the essential.

Half of the patient material in our study was collected from Gothenburg. I would like to express my greatest appreciation to Professor Lars Hagberg, Department of Infectious Diseases, Sahlgrenska University Hospital – not only for collecting the material but also for his contributions to the designing and the reporting of the study. I warmly thank also the medical staff who helped Lars in Gothenburg.

I am deeply grateful to all of my co-authors. I wish to express my great thanks to Dr Laura Lehtola for the contact to Helsinki City Hospital and also for her clinical perspective in writing process. My sincere thanks go also to the Medical Evidence Manager Jesper From at AstraZeneca Nordic–Baltic who had a crucial role in the managing of the entire research project. During the study I was priviledged to work with three skilled statisticians. I wish to thank BSc Tommy Schyman for his precise analyses, PhD Jukka Ollgren for his invaluable statistical consultations, and especially Dr Erik Forsblom for guiding me to statistics in practise.

I am most indebted to Docent Ulla Hohenthal and Docent Heikki Kauma for their thorough reviews of the manuscript – with comments that significantly improved it.

Most of my practical work of the study was carried out under the ever-helpful and stimulating atmosphere of Aurora Hospital. I owe warmest thanks to my colleagues in Aurora Hospital, especially to the closest ones Docent Jussi Sutinen and Dr Eero Mattila, all of them were always ready for an instant assistance in practical matters – and if needed – for more profound discussions also. Special thanks go to secretaries Minna Ollikainen and Virve Vahterkoski–Sjöblom for running the current matters of the study.

Finally, I wish to give my deepest thanks to my family – most of all to my lovely wife Arja and dear kids Nuutti and Unna – for their loving support and encouragement throughout the work.

These studies were financially supported by AstraZeneca Nordic–Baltic and I would like warmly thank AZ also for the initiation and managing of the study project, not to mention for the reviewing of the articles. This work was financially supported also by grants from the special Finnish governmental subsidy for health sciences (EVO), the Faculty of Medicine at Helsinki University and Suomen Infektiolääkärit ry.

9 REFERENCES

1. Nienstedt W, Hänninen O, Arstila A, Björkqvist S: Ihmisen fysiologia ja anatomia. 1992, WSOY, Porvoo.

2. Grice EA, Segre JA: The skin microbiome. Nat Rev Microbiol 2011, 9(4):244-253.

3. Eron LJ, Lipsky BA, Low DE, Nathwani D, Tice AD, Volturo GA, Expert panel on managing skin and soft tissue infections: Managing skin and soft tissue infections: expert panel recommendations on key decision points. J Antimicrob Chemother 2003, 52 Suppl 1:i3-17.

4. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC: Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014, 59(2):e10-52.

5. Karppelin M, Siljander T, Haapala AM, Aittoniemi J, Huttunen R, Kere J, Vuopio J, Syrjanen J: Evidence of streptococcal origin of acute non-necrotising cellulitis: a serological study. Eur J Clin Microbiol Infect Dis 2015, 34(4):669-672.

6. Jeng A, Beheshti M, Li J, Nathan R: The role of beta-hemolytic streptococci in causing diffuse, nonculturable cellulitis: a prospective investigation. Medicine (Baltimore) 2010, 89(4):217-226.

7. Elliott DC, Kufera JA, Myers RA: Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg 1996, 224(5):672-683.

8. Citron DM, Goldstein EJ, Merriam CV, Lipsky BA, Abramson MA: Bacteriology of moderate-to-severe diabetic foot infections and in vitro activity of antimicrobial agents. J Clin Microbiol 2007, 45(9):2819-2828.

9. Hersh AL, Chambers HF, Maselli JH, Gonzales R: National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. Arch Intern Med 2008, 168(14):1585-1591.

10. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA,Jr: Increased US emergency department visits for skin and soft

tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant Staphylococcus aureus. Ann Emerg Med 2008, 51(3):291-298.

11. Ray GT, Suaya JA, Baxter R: Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study. BMC Infect Dis 2013, 13:252-2334-13-252.

12. Edelsberg J, Taneja C, Zervos M, Haque N, Moore C, Reyes K, Spalding J, Jiang J, Oster G: Trends in US hospital admissions for skin and soft tissue infections. Emerg Infect Dis 2009, 15(9):1516-1518.

13. Hayward A, Knott F, Petersen I, Livermore DM, Duckworth G, Islam A, Johnson AM: Increasing hospitalizations and general practice prescriptions for community-onset staphylococcal disease, England. Emerg Infect Dis 2008, 14(5):720-726.

14. Currie CJ, Berni E, Jenkins-Jones S, Poole CD, Ouwens M, Driessen S, de Voogd H, Butler CC, Morgan CL: Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. BMJ 2014, 349:g5493.

15. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K: Rising United States Hospital Admissions for Acute Bacterial Skin and Skin Structure Infections: Recent Trends and Economic Impact. PLoS One 2015, 10(11):e0143276.

16. Rautakorpi UM, Huikko S, Honkanen P, Klaukka T, Makela M, Palva E, Roine R, Sarkkinen H, Varonen H, Huovinen P, MIKSTRA Collaborative Study Group: The Antimicrobial Treatment Strategies (MIKSTRA) program: a 5-year follow-up of infection-specific antibiotic use in primary health care and the effect of implementation of treatment guidelines. Clin Infect Dis 2006, 42(9):1221-1230.

17. Center for Drug Evaluation and Research, Food and Drug Administration: Guidance for industry: uncomplicated and complicated skin and skin structure infections—developing antimicrobial drugs for treatment. 1998.

18. Esposito S, Noviello S, Leone S: Epidemiology and microbiology of skin and soft tissue infections. Curr Opin Infect Dis 2016, 29(2):109-115.

19. Swartz MN: Clinical practice. Cellulitis. N Engl J Med 2004, 350(9):904-912.

20. Hirschmann JV, Raugi GJ: Lower limb cellulitis and its mimics: part I. Lower limb cellulitis. J Am Acad Dermatol 2012, 67(2):163.e1-12; quiz 175-6.

21. Bisno AL, Stevens DL: Streptococcal infections of skin and soft tissues. N Engl J Med 1996, 334(4):240-245.

22. Bjornsdottir S, Gottfredsson M, Thorisdottir AS, Gunnarsson GB, Rikardsdottir H, Kristjansson M, Hilmarsdottir I: Risk factors for acute cellulitis of the lower limb: a prospective case-control study. Clin Infect Dis 2005, 41(10):1416-1422.

23. Karppelin M, Siljander T, Vuopio-Varkila J, Kere J, Huhtala H, Vuento R, Jussila T, Syrjanen J: Factors predisposing to acute and recurrent bacterial non-necrotizing cellulitis in hospitalized patients: a prospective case-control study. Clin Microbiol Infect 2010, 16(6):729-734.

24. U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER): Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. 2013.

25. Marwick C, Broomhall J, McCowan C, Phillips G, Gonzalez-McQuire S, Akhras K, Merchant S, Nathwani D, Davey P: Severity assessment of skin and soft tissue infections: cohort study of management and outcomes for hospitalized patients. J Antimicrob Chemother 2011, 66(2):387-397.

26. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992, 101(6):1644-1655.

27. Paterson R, MacLeod DC, Thetford D, Beattie A, Graham C, Lam S, Bell D: Prediction of in-hospital mortality and length of stay using an early warning scoring system: clinical audit. Clin Med (Lond) 2006, 6(3):281-284.

28. Sartelli M, Malangoni MA, May AK, Viale P, Kao LS, Catena F, Ansaloni L, Moore EE, Moore FA, Peitzman AB, Coimbra R, Leppaniemi A, Kluger Y, Biffl W, Koike K, Girardis M, Ordonez CA, Tavola M, Cainzos M, Di Saverio S, Fraga GP, Gerych I, Kelly MD, Taviloglu K, Wani I, Marwah S, Bala M, Ghnnam W, Shaikh N, Chiara O, Faro MP,Jr,

Pereira GA,Jr, Gomes CA, Coccolini F, Trana C, Corbella D, Brambillasca P, Cui Y, Segovia Lohse HA, Khokha V, Kok KY, Hong SK, Yuan KC: World Society of Emergency Surgery (WSES) guidelines for management of skin and soft tissue infections. World J Emerg Surg 2014, 9(1):57-7922-9-57. eCollection 2014.

29. Howell GM, Rosengart MR: Necrotizing soft tissue infections. Surg Infect (Larchmt) 2011, 12(3):185-190.

30. CDC/NHSN surveillance definitions for specific type of infections. 2016. http://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdefcurrent.pdf

31. CDC/NHSN definitions for surgical site infections. 2016. https://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf

32. Dryden MS: Complicated skin and soft tissue infection. J Antimicrob Chemother 2010, 65 Suppl 3:iii35-44.

33. Miller LG, Eisenberg DF, Liu H, Chang CL, Wang Y, Luthra R, Wallace A, Fang C, Singer J, Suaya JA: Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005-2010. BMC Infect Dis 2015, 15:362-015-1071-0.

34. Ansari F, Erntell M, Goossens H, Davey P: The European surveillance of antimicrobial consumption (ESAC) point-prevalence survey of antibacterial use in 20 European hospitals in 2006. Clin Infect Dis 2009, 49(10):1496-1504.

35. Shen HN, Lu CL: Skin and soft tissue infections in hospitalized and critically ill patients: a nationwide population-based study. BMC Infect Dis 2010, 10:151-2334-10-151.

36. Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, Gruendling M, Huhle G, Jaschinski U, John S, Mayer K, Oppert M, Olthoff D, Quintel M, Ragaller M, Rossaint R, Stuber F, Weiler N, Welte T, Bogatsch H, Hartog C, Loeffler M, Reinhart K: Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive Care Med 2007, 33(4):606-618.

37. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006, 34(6):1589-1596.

38. Mu Y, Edwards JR, Horan TC, Berrios-Torres SI, Fridkin SK: Improving risk-adjusted measures of surgical site infection for the national healthcare safety network. Infect Control Hosp Epidemiol 2011, 32(10):970-986.

39. Dupuy A, Benchikhi H, Roujeau JC, Bernard P, Vaillant L, Chosidow O, Sassolas B, Guillaume JC, Grob JJ, Bastuji-Garin S: Risk factors for erysipelas of the leg (cellulitis): case-control study. BMJ 1999, 318(7198):1591-1594.

40. Roujeau JC, Sigurgeirsson B, Korting HC, Kerl H, Paul C: Chronic dermatomycoses of the foot as risk factors for acute bacterial cellulitis of the leg: a case-control study. Dermatology 2004, 209(4):301-307.

41. McNamara DR, Tleyjeh IM, Berbari EF, Lahr BD, Martinez JW, Mirzoyev SA, Baddour LM: Incidence of lower-extremity cellulitis: a population-based study in Olmsted county, Minnesota. Mayo Clin Proc 2007, 82(7):817-821.

42. Kaspersen KA, Pedersen OB, Petersen MS, Hjalgrim H, Rostgaard K, Moller BK, Juul-Sorensen C, Kotze S, Dinh KM, Erikstrup LT, Sorensen E, Thorner LW, Burgdorf KS, Ullum H, Erikstrup C: Obesity and risk of infection: results from the Danish Blood Donor Study. Epidemiology 2015, 26(4):580-589.

43. Carratala J, Roson B, Fernandez-Sabe N, Shaw E, del Rio O, Rivera A, Gudiol F: Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. Eur J Clin Microbiol Infect Dis 2003, 22(3):151-157.

44. Garau J, Ostermann H, Medina J, Avila M, McBride K, Blasi F, REACH study group: Current management of patients hospitalized with complicated skin and soft tissue infections across Europe (2010-2011): assessment of clinical practice patterns and real-life effectiveness of antibiotics from the REACH study. Clin Microbiol Infect 2013, 19(9):E377-85.

45. Lipsky BA, Moran GJ, Napolitano LM, Vo L, Nicholson S, Kim M: A prospective, multicenter, observational study of complicated skin and soft tissue infections in hospitalized patients: clinical characteristics, medical treatment, and outcomes. BMC Infect Dis 2012, 12:227-2334-12-227.

46. Zervos MJ, Freeman K, Vo L, Haque N, Pokharna H, Raut M, Kim M: Epidemiology and outcomes of complicated skin and soft tissue

infections in hospitalized patients. J Clin Microbiol 2012, 50(2):238-245.

47. Li X, Chen Y, Gao W, Ouyang W, Wei J, Wen Z: Epidemiology and Outcomes of Complicated Skin and Soft Tissue Infections among Inpatients in Southern China from 2008 to 2013. PLoS One 2016, 11(2):e0149960.

48. Shah BR, Hux JE: Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003, 26(2):510-513.

49. Mor A, Berencsi K, Nielsen JS, Rungby J, Friborg S, Brandslund I, Christiansen JS, Vaag A, Beck-Nielsen H, Sorensen HT, Thomsen RW: Rates of Community-based Antibiotic Prescriptions and Hospital-treated Infections in Individuals With and Without Type 2 Diabetes: A Danish Nationwide Cohort Study, 2004-2012. Clin Infect Dis 2016, 63(4):501-511.

50. Korbel L, Spencer JD: Diabetes mellitus and infection: an evaluation of hospital utilization and management costs in the United States. J Diabetes Complications 2015, 29(2):192-195.

51. Simonsen JR, Harjutsalo V, Jarvinen A, Kirveskari J, Forsblom C, Groop PH, Lehto M, FinnDiane Study Group: Bacterial infections in patients with type 1 diabetes: a 14-year follow-up study. BMJ Open Diabetes Res Care 2015, 3(1):e000067.

52. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B: Impaired leucocyte functions in diabetic patients. Diabet Med 1997, 14(1):29-34.

53. Alexiewicz JM, Kumar D, Smogorzewski M, Klin M, Massry SG: Polymorphonuclear leukocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function. Ann Intern Med 1995, 123(12):919-924.

54. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW: Infections in patients with diabetes mellitus. N Engl J Med 1999, 341(25):1906-1912.

55. Singh N, Armstrong DG, Lipsky BA: Preventing foot ulcers in patients with diabetes. JAMA 2005, 293(2):217-228.

56. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, Wolfson SK: Ankle-arm index as a marker of atherosclerosis in the

Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation 1993, 88(3):837-845.

57. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, Uccioli L, Urbancic V, Bakker K, Holstein P, Jirkovska A, Piaggesi A, Ragnarson-Tennvall G, Reike H, Spraul M, Van Acker K, Van Baal J, Van Merode F, Ferreira I, Huijberts M: Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008, 51(5):747-755.

58. Cardoso CR, Salles GF: Macro and microvascular complications are determinants of increased infection-related mortality in Brazilian type 2 diabetes mellitus patients. Diabetes Res Clin Pract 2007, 75(1):51-58.

59. Murphy EL, DeVita D, Liu H, Vittinghoff E, Leung P, Ciccarone DH, Edlin BR: Risk factors for skin and soft-tissue abscesses among injection drug users: a case-control study. Clin Infect Dis 2001, 33(1):35-40.

60. Ebright JR, Pieper B: Skin and soft tissue infections in injection drug users. Infect Dis Clin North Am 2002, 16(3):697-712.

61. Lavender TW, McCarron B: Acute infections in intravenous drug users. Clin Med (Lond) 2013, 13(5):511-513.

62. Ronnen M, Suster S, Schewach-Millet M, Modan M: Erysipelas. Changing faces. Int J Dermatol 1985, 24(3):169-172.

63. Hook EW,3rd, Hooton TM, Horton CA, Coyle MB, Ramsey PG, Turck M: Microbiologic evaluation of cutaneous cellulitis in adults. Arch Intern Med 1986, 146(2):295-297.

64. Anaya DA, Dellinger EP: Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis 2007, 44(5):705-710.

65. Eder J, Hlavin G, Haushofer A, Trubert-Exinger D, Trautinger F: Correlation of serum procalcitonin with the severity of skin and skin structure infections - a pilot study. J Dtsch Dermatol Ges 2012, 10(8):564-571.

66. Lin JN, Chang LL, Lai CH, Lin HH, Chen YH: Clinical and molecular characteristics of invasive and noninvasive skin and soft tissue infections caused by group A Streptococcus. J Clin Microbiol 2011, 49(10):3632-3637.

67. Rast AC, Knobel D, Faessler L, Kutz A, Felder S, Laukemann S, Steiner D, Haubitz S, Fux CA, Huber A, Mueller B, Schuetz P: Use of procalcitonin, C-reactive protein and white blood cell count to distinguish between lower limb erysipelas and deep vein thrombosis in the emergency department: A prospective observational study. J Dermatol 2015, 42(8):778-785.

68. Noh SH, Park SD, Kim EJ: Serum Procalcitonin Level Reflects the Severity of Cellulitis. Ann Dermatol 2016, 28(6):704-710.

69. Lipsky BA, Sheehan P, Armstrong DG, Tice AD, Polis AB, Abramson MA: Clinical predictors of treatment failure for diabetic foot infections: data from a prospective trial. Int Wound J 2007, 4(1):30-38.

70. Karppelin M, Siljander T, Aittoniemi J, Hurme M, Huttunen R, Huhtala H, Kere J, Vuopio J, Syrjanen J: Predictors of recurrent cellulitis in five years. Clinical risk factors and the role of PTX3 and CRP. J Infect 2015, 70(5):467-473.

71. Jenkins TC, Sabel AL, Sarcone EE, Price CS, Mehler PS, Burman WJ: Skin and soft-tissue infections requiring hospitalization at an academic medical center: opportunities for antimicrobial stewardship. Clin Infect Dis 2010, 51(8):895-903.

72. Gunderson CG, Chang JJ: Overuse of compression ultrasound for patients with lower extremity cellulitis. Thromb Res 2014, 134(4):846-850.

73. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A: Current concepts in the management of necrotizing fasciitis. Front Surg 2014, 1:36.

74. Eckmann C: The importance of source control in the management of severe skin and soft tissue infections. Curr Opin Infect Dis 2016, 29(2):139-144.

75. Kapoor A, Page S, Lavalley M, Gale DR, Felson DT: Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis. Arch Intern Med 2007, 167(2):125-132.

76. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, Deery HG, Embil JM, Joseph WS, Karchmer AW, Pinzur MS, Senneville E, Infectious Diseases Society of America: 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and

treatment of diabetic foot infections. Clin Infect Dis 2012, 54(12):e132-73.

77. Leppard BJ, Seal DV, Colman G, Hallas G: The value of bacteriology and serology in the diagnosis of cellulitis and erysipelas. Br J Dermatol 1985, 112(5):559-567.

78. Sigurdsson AF, Gudmundsson S: The etiology of bacterial cellulitis as determined by fine-needle aspiration. Scand J Infect Dis 1989, 21(5):537-542.

79. Newell PM, Norden CW: Value of needle aspiration in bacteriologic diagnosis of cellulitis in adults. J Clin Microbiol 1988, 26(3):401-404.

80. Duvanel T, Auckenthaler R, Rohner P, Harms M, Saurat JH: Quantitative cultures of biopsy specimens from cutaneous cellulitis. Arch Intern Med 1989, 149(2):293-296.

81. Perl B, Gottehrer NP, Raveh D, Schlesinger Y, Rudensky B, Yinnon AM: Cost-effectiveness of blood cultures for adult patients with cellulitis. Clin Infect Dis 1999, 29(6):1483-1488.

82. Siljander T, Karppelin M, Vahakuopus S, Syrjanen J, Toropainen M, Kere J, Vuento R, Jussila T, Vuopio-Varkila J: Acute bacterial, nonnecrotizing cellulitis in Finland: microbiological findings. Clin Infect Dis 2008, 46(6):855-861.

83. Eells SJ, Chira S, David CG, Craft N, Miller LG: Non-suppurative cellulitis: risk factors and its association with Staphylococcus aureus colonization in an area of endemic community-associated methicillin-resistant S. aureus infections. Epidemiol Infect 2011, 139(4):606-612.

84. Moran GJ, Krishnadasan A, Gorwitz RJ, Fosheim GE, McDougal LK, Carey RB, Talan DA, EMERGEncy ID Net Study Group: Methicillin-resistant S. aureus infections among patients in the emergency department. N Engl J Med 2006, 355(7):666-674.

85. Carey CF, Dall L: Diagnosis of cellulitis in the immunocompromised host. Can J Infect Dis 1990, 1(4):133-135.

86. Van Grieken SA, Dupont LJ, Van Raemdonck DE, Van Bleyenbergh P, Verleden GM: Primary cryptococcal cellulitis in a lung transplant recipient. J Heart Lung Transplant 2007, 26(3):285-289.

87. Thomas N, Brook I: Animal bite-associated infections: microbiology and treatment. Expert Rev Anti Infect Ther 2011, 9(2):215-226.

88. Brook I, Finegold SM: Aerobic and anaerobic bacteriology of cutaneous abscesses in children. Pediatrics 1981, 67(6):891-895.

89. Talan DA, Summanen PH, Finegold SM: Ampicillin/sulbactam and cefoxitin in the treatment of cutaneous and other soft-tissue abscesses in patients with or without histories of injection drug abuse. Clin Infect Dis 2000, 31(2):464-471.

90. Rajendran PM, Young D, Maurer T, Chambers H, Perdreau-Remington F, Ro P, Harris H: Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant Staphylococcus aureus infection. Antimicrob Agents Chemother 2007, 51(11):4044-4048.

91. Abrahamian FM, Goldstein EJ: Microbiology of animal bite wound infections. Clin Microbiol Rev 2011, 24(2):231-246.

92. Talan DA, Citron DM, Abrahamian FM, Moran GJ, Goldstein EJ: Bacteriologic analysis of infected dog and cat bites. Emergency Medicine Animal Bite Infection Study Group. N Engl J Med 1999, 340(2):85-92.

93. Talan DA, Abrahamian FM, Moran GJ, Citron DM, Tan JO, Goldstein EJ, Emergency Medicine Human Bite Infection Study Group: Clinical presentation and bacteriologic analysis of infected human bites in patients presenting to emergency departments. Clin Infect Dis 2003, 37(11):1481-1489.

94. Fransen J, Huss FR, Nilsson LE, Rydell U, Sjoberg F, Hanberger H: Surveillance of antibiotic susceptibility in a Swedish Burn Center 1994-2012. Burns 2016, 42(6):1295-1303.

95. Bahemia IA, Muganza A, Moore R, Sahid F, Menezes CN: Microbiology and antibiotic resistance in severe burns patients: A 5 year review in an adult burns unit. Burns 2015, 41(7):1536-1542.

96. Dana AN, Bauman WA: Bacteriology of pressure ulcers in individuals with spinal cord injury: What we know and what we should know. J Spinal Cord Med 2015, 38(2):147-160.

97. Tedeschi S, Negosanti L, Sgarzani R, Trapani F, Pignanelli S, Battilana M, Capirossi R, Ventura DB, Giannella M, Bartoletti M, Tumietto F, Cristini F, Viale P: Superficial swab versus deep tissue biopsy for the microbiological diagnosis of local infection in advanced-stage pressure ulcers of spinal cord injured patients: a prospective study. Clin Microbiol Infect 2017 Apr 19. pii: S1198-743X(17)30226-4.

98. Lipsky BA: Empirical therapy for diabetic foot infections: are there clinical clues to guide antibiotic selection? Clin Microbiol Infect 2007, 13(4):351-353.

99. Wheat LJ, Allen SD, Henry M, Kernek CB, Siders JA, Kuebler T, Fineberg N, Norton J: Diabetic foot infections. Bacteriologic analysis. Arch Intern Med 1986, 146(10):1935-1940.

100. Esposito S, Leone S, Noviello S, Fiore M, Ianniello F, Felaco FM, Romagnoli F, Sarli E: Foot infections in diabetes (DFIs) in the out-patient setting: an Italian multicentre observational survey. Diabet Med 2008, 25(8):979-984.

101. Brook I, Frazier EH: Aerobic and anaerobic bacteriology of wounds and cutaneous abscesses. Arch Surg 1990, 125(11):1445-1451.

102. Steinberg JP, Braun BI, Hellinger WC, Kusek L, Bozikis MR, Bush AJ, Dellinger EP, Burke JP, Simmons B, Kritchevsky SB, Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) Study Group: Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. Ann Surg 2009, 250(1):10-16.

103. Ramcharan AA, den Heijer CD, Smeets EE, Rouflart MM, van Tiel FH, Bruggeman CA, Breukink SO, Tordoir JH, Baeten CG, Stobberingh EE: Microbiology of surgical site infections after gastrointestinal surgery in the south region of The Netherlands. Future Microbiol 2014, 9(3):291-298.

104. Moet GJ, Jones RN, Biedenbach DJ, Stilwell MG, Fritsche TR: Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998-2004). Diagn Microbiol Infect Dis 2007, 57(1):7-13.

105. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO: Necrotizing fasciitis: clinical presentation, microbiology, and

determinants of mortality. J Bone Joint Surg Am 2003, 85-A(8):1454-1460.

106. Vinh DC, Embil JM: Rapidly progressive soft tissue infections. Lancet Infect Dis 2005, 5(8):501-513.

107. May AK: Skin and soft tissue infections. Surg Clin North Am 2009, 89(2):403-20, viii.

108. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, Tang AW, Phung TO, Spellberg B: Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. N Engl J Med 2005, 352(14):1445-1453.

109. Nathwani D, Morgan M, Masterton RG, Dryden M, Cookson BD, French G, Lewis D, British Society for Antimicrobial Chemotherapy Working Party on Community-onset MRSA Infections: Guidelines for UK practice for the diagnosis and management of methicillin-resistant Staphylococcus aureus (MRSA) infections presenting in the community. J Antimicrob Chemother 2008, 61(5):976-994.

110. Genestier AL, Michallet MC, Prevost G, Bellot G, Chalabreysse L, Peyrol S, Thivolet F, Etienne J, Lina G, Vallette FM, Vandenesch F, Genestier L: Staphylococcus aureus Panton-Valentine leukocidin directly targets mitochondria and induces Bax-independent apoptosis of human neutrophils. J Clin Invest 2005, 115(11):3117-3127.

111. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, Liassine N, Bes M, Greenland T, Reverdy ME, Etienne J: Community-acquired methicillin-resistant Staphylococcus aureus carrying Panton-Valentine leukocidin genes: worldwide emergence. Emerg Infect Dis 2003, 9(8):978-984.

112. Zilberberg MD, Chaudhari P, Nathanson BH, Campbell RS, Emons MF, Fiske S, Hays HD, Shorr AF: Development and validation of a bedside risk score for MRSA among patients hospitalized with complicated skin and skin structure infections. BMC Infect Dis 2012, 12:154-2334-12-154.

113. World Health Organization: Antimicrobial resistance: global report on surveillance. 2014.

114. Jaakola S, Lyytikäinen O, Rimhanen-Finne R, Salmenlinna S, Vuopio J, Roivainen M, Löflund J, Kuusi M, Ruutu P: Tartuntataudit Suomessa 2011. 2012.

115. Johnson AP: Methicillin-resistant Staphylococcus aureus: the European landscape. J Antimicrob Chemother 2011, 66 Suppl 4:iv43-iv48.

116. Lipsky BA, Napolitano LM, Moran GJ, Vo L, Nicholson S, Kim M: Inappropriate initial antibiotic treatment for complicated skin and soft tissue infections in hospitalized patients: incidence and associated factors. Diagn Microbiol Infect Dis 2014, 79(2):273-279.

117. Zilberberg MD, Shorr AF, Micek ST, Hoban AP, Pham V, Doherty JA, Ramsey AM, Kollef MH: Epidemiology and outcomes of hospitalizations with complicated skin and skin-structure infections: implications of healthcare-associated infection risk factors. Infect Control Hosp Epidemiol 2009, 30(12):1203-1210.

118. Graham DR, Lucasti C, Malafaia O, Nichols RL, Holtom P, Perez NQ, McAdams A, Woods GL, Ceesay TP, Gesser R: Ertapenem once daily versus piperacillin-tazobactam 4 times per day for treatment of complicated skin and skin-structure infections in adults: results of a prospective, randomized, double-blind multicenter study. Clin Infect Dis 2002, 34(11):1460-1468.

119. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E, Tigecycline 300 cSSSI Study Group, Tigecycline 305 cSSSI Study Group: The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis 2005, 41 Suppl 5:S341-53.

120. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS: A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin Infect Dis 2008, 46(5):647-655.

121. Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, Critchley I, Das AF, Thye D: Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010, 51(6):641-650.

122. Gyssens IC, Dryden M, Kujath P, Nathwani D, Schaper N, Hampel B, Reimnitz P, Alder J, Arvis P: A randomized trial of the efficacy and safety of sequential intravenous/oral moxifloxacin monotherapy versus intravenous piperacillin/tazobactam followed by oral

amoxicillin/clavulanate for complicated skin and skin structure infections. J Antimicrob Chemother 2011, 66(11):2632-2642.

123. Matthews P, Alpert M, Rahav G, Rill D, Zito E, Gardiner D, Pedersen R, Babinchak T, McGovern PC, Tigecycline 900 cSSSI Study Group: A randomized trial of tigecycline versus ampicillin-sulbactam or amoxicillin-clavulanate for the treatment of complicated skin and skin structure infections. BMC Infect Dis 2012, 12:297-2334-12-297.

124. Ruhe JJ, Smith N, Bradsher RW, Menon A: Community-onset methicillin-resistant Staphylococcus aureus skin and soft-tissue infections: impact of antimicrobial therapy on outcome. Clin Infect Dis 2007, 44(6):777-784.

125. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC: Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med 2004, 164(15):1669-1674.

126. Thulin P, Johansson L, Low DE, Gan BS, Kotb M, McGeer A, Norrby-Teglund A: Viable group A streptococci in macrophages during acute soft tissue infection. PLoS Med 2006, 3(3):e53.

127. Snodgrass WR, Anderson T: Prontosil in Erysipelas. Br Med J 1937, 2(3993):101-104.

128. Snodgrass WR, Anderson T: Sulphanilamide in the Treatment of Erysipelas. Br Med J 1937, 2(4014):1156-1159.

129. Talbot GH, Powers JH, Fleming TR, Siuciak JA, Bradley J, Boucher H, CABP-ABSSSI Project Team: Progress on developing endpoints for registrational clinical trials of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections: update from the Biomarkers Consortium of the Foundation for the National Institutes of Health. Clin Infect Dis 2012, 55(8):1114-1121.

130. Shlaes DM, Sahm D, Opiela C, Spellberg B: The FDA reboot of antibiotic development. Antimicrob Agents Chemother 2013, 57(10):4605-4607.

131. European Medicines Agency: Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. 2011.

132. Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch C, Linezolid CSSTI Study Group: Linezolid versus vancomycin in treatment of

complicated skin and soft tissue infections. Antimicrob Agents Chemother 2005, 49(6):2260-2266.

133. Friedland HD, O'Neal T, Biek D, Eckburg PB, Rank DR, Llorens L, Smith A, Witherell GW, Laudano JB, Thye D: CANVAS 1 and 2: analysis of clinical response at day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. Antimicrob Agents Chemother 2012, 56(5):2231-2236.

134. Lipsky BA, Itani KM, Weigelt JA, Joseph W, Paap CM, Reisman A, Myers DE, Huang DB: The role of diabetes mellitus in the treatment of skin and skin structure infections caused by methicillin-resistant Staphylococcus aureus: results from three randomized controlled trials. Int J Infect Dis 2011, 15(2):e140-6.

135. Embil JM, Soto NE, Melnick DA: A post hoc subgroup analysis of meropenem versus imipenem/cilastatin in a multicenter, double-blind, randomized study of complicated skin and skin-structure infections in patients with diabetes mellitus. Clin Ther 2006, 28(8):1164-1174.

136. Duane TM, Weigelt JA, Puzniak LA, Huang DB: Linezolid and vancomycin in treatment of lower-extremity complicated skin and skin structure infections caused by methicillin-resistant Staphylococcus aureus in patients with and without vascular disease. Surg Infect (Larchmt) 2012, 13(3):147-153.

137. Stein GE, Schooley S, Peloquin CA, Missavage A, Havlichek DH: Linezolid tissue penetration and serum activity against strains of methicillin-resistant Staphylococcus aureus with reduced vancomycin susceptibility in diabetic patients with foot infections. J Antimicrob Chemother 2007, 60(4):819-823.

138. Noel GJ, Draper MP, Hait H, Tanaka SK, Arbeit RD: A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother 2012, 56(11):5650-5654.

139. Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T, CANVAS 2 investigators: CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010, 65 Suppl 4:iv53-iv65.

140. Itani KM, Dryden MS, Bhattacharyya H, Kunkel MJ, Baruch AM, Weigelt JA: Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant Staphylococcus aureus. Am J Surg 2010, 199(6):804-816.

141. Vick-Fragoso R, Hernandez-Oliva G, Cruz-Alcazar J, Amabile-Cuevas CF, Arvis P, Reimnitz P, Bogner JR, STIC Study Group: Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. Infection 2009, 37(5):407-417.

142. Stryjewski ME, Graham DR, Wilson SE, O'Riordan W, Young D, Lentnek A, Ross DP, Fowler VG, Hopkins A, Friedland HD, Barriere SL, Kitt MM, Corey GR, Assessment of Telavancin in Complicated Skin and Skin-Structure Infections Study: Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis 2008, 46(11):1683-1693.

143. Jauregui LE, Babazadeh S, Seltzer E, Goldberg L, Krievins D, Frederick M, Krause D, Satilovs I, Endzinas Z, Breaux J, O'Riordan W: Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. Clin Infect Dis 2005, 41(10):1407-1415.

144. Giordano P, Song J, Pertel P, Herrington J, Kowalsky S: Sequential intravenous/oral moxifloxacin versus intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate for the treatment of complicated skin and skin structure infection. Int J Antimicrob Agents 2005, 26(5):357-365.

145. Fabian TC, File TM, Embil JM, Krige JE, Klein S, Rose A, Melnick D, Soto NE: Meropenem versus imipenem-cilastatin for the treatment of hospitalized patients with complicated skin and skin structure infections: results of a multicenter, randomized, double-blind comparative study. Surg Infect (Larchmt) 2005, 6(3):269-282.

146. Graham DR, Talan DA, Nichols RL, Lucasti C, Corrado M, Morgan N, Fowler CL: Once-daily, high-dose levofloxacin versus ticarcillin-clavulanate alone or followed by amoxicillin-clavulanate for complicated skin and skin-structure infections: a randomized, open-label trial. Clin Infect Dis 2002, 35(4):381-389.

147. Graham DR, Lucasti C, Malafaia O, Nichols RL, Holtom P, Perez NQ, McAdams A, Woods GL, Ceesay TP, Gesser R: Ertapenem once daily versus piperacillin-tazobactam 4 times per day for treatment of complicated skin and skin-structure infections in adults: results of a prospective, randomized, double-blind multicenter study. Clin Infect Dis 2002, 34(11):1460-1468.

148. Stevens DL, Smith LG, Bruss JB, McConnell-Martin MA, Duvall SE, Todd WM, Hafkin B: Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2000, 44(12):3408-3413.

149. Nichols RL, Graham DR, Barriere SL, Rodgers A, Wilson SE, Zervos M, Dunn DL, Kreter B: Treatment of hospitalized patients with complicated gram-positive skin and skin structure infections: two randomized, multicentre studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin. Synercid Skin and Skin Structure Infection Group. J Antimicrob Chemother 1999, 44(2):263-273.

150. Kingsley J, Mehra P, Lawrence LE, Henry E, Duffy E, Cammarata SK, Pullman J: A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. J Antimicrob Chemother 2016, 71(3):821-829.

151. Corey GR, Good S, Jiang H, Moeck G, Wikler M, Green S, Manos P, Keech R, Singh R, Heller B, Bubnova N, O'Riordan W, SOLO II Investigators: Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis 2015, 60(2):254-262.

152. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P: Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2014, 14(8):696-705.

153. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW: Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med 2014, 370(23):2169-2179.

154. Prokocimer P, De Anda C, Fang E, Mehra P, Das A: Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure

infections: the ESTABLISH-1 randomized trial. JAMA 2013, 309(6):559-569.

155. Nathwani D, Eckmann C, Lawson W, Stephens JM, Macahilig C, Solem CT, Simoneau D, Chambers R, Li JZ, Haider S: Pan-European early switch/early discharge opportunities exist for hospitalized patients with methicillin-resistant Staphylococcus aureus complicated skin and soft tissue infections. Clin Microbiol Infect 2014, 20(10):993-1000.

156. Skin and soft tissue infections (online). Current Care Guidelines. Working group appointed by the Finnish Medical Society Duodecim and the Finnish Dermatological Society. Helsinki: The Finnish Medical Society Duodecim, 2010.

157. Diabetes-related foot problems (online). Current Care Guidelines. A working group appointed by the Finnish Medical Society Duodecim, the Medical Advisory Board of the Finnish Diabetes Society, the Finnish Endocrine Society and the Finnish Dermatological Society. Helsinki: The Finnish Medical Society Duodecim, 2009.

158. The Swedish guideline for management of skin and soft tissue infections. Läkemedelsverket and Strama. 2009.

159. Russo A, Concia E, Cristini F, De Rosa FG, Esposito S, Menichetti F, Petrosillo N, Tumbarello M, Venditti M, Viale P, Viscoli C, Bassetti M: Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. Clin Microbiol Infect 2016, 22 Suppl 2:S27-36.

160. Nathwani D, Eckmann C, Lawson W, Solem CT, Corman S, Stephens JM, Macahilig C, Simoneau D, Chambers R, Li JZ, Haider S: Influence of real-world characteristics on outcomes for patients with methicillin-resistant Staphylococcal skin and soft tissue infections: a multi-country medical chart review in Europe. BMC Infect Dis 2014, 14:476-2334-14-476.

161. Gaspari RJ, Resop D, Mendoza M, Kang T, Blehar D: A randomized controlled trial of incision and drainage versus ultrasonographically guided needle aspiration for skin abscesses and the effect of methicillin-resistant Staphylococcus aureus. Ann Emerg Med 2011, 57(5):483-91.e1.

162. Duong M, Markwell S, Peter J, Barenkamp S: Randomized, controlled trial of antibiotics in the management of community-acquired skin

abscesses in the pediatric patient. Ann Emerg Med 2010, 55(5):401-407.

163. Macfie J, Harvey J: The treatment of acute superficial abscesses: a prospective clinical trial. Br J Surg 1977, 64(4):264-266.

164. Schmitz GR, Bruner D, Pitotti R, Olderog C, Livengood T, Williams J, Huebner K, Lightfoot J, Ritz B, Bates C, Schmitz M, Mete M, Deye G: Randomized controlled trial of trimethoprim-sulfamethoxazole for uncomplicated skin abscesses in patients at risk for community-associated methicillin-resistant Staphylococcus aureus infection. Ann Emerg Med 2010, 56(3):283-287.

165. Talan DA, Mower WR, Krishnadasan A, Abrahamian FM, Lovecchio F, Karras DJ, Steele MT, Rothman RE, Hoagland R, Moran GJ: Trimethoprim-Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess. N Engl J Med 2016, 374(9):823-832.

166. Daum RS, Miller LG, Immergluck L, Fritz S, Creech CB, Young D, Kumar N, Downing M, Pettibone S, Hoagland R, Eells SJ, Boyle MG, Parker TC, Chambers HF, DMID 07-0051 Team: A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses. N Engl J Med 2017, 376(26):2545-2555.

167. Huizinga WK, Kritzinger NA, Bhamjee A: The value of adjuvant systemic antibiotic therapy in localised wound infections among hospital patients: a comparative study. J Infect 1986, 13(1):11-16.

168. Pecoraro RE, Reiber GE, Burgess EM: Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care 1990, 13(5):513-521.

169. Lipsky BA: Osteomyelitis of the foot in diabetic patients. Clin Infect Dis 1997, 25(6):1318-1326.

170. Eneroth M, Larsson J, Apelqvist J: Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. J Diabetes Complications 1999, 13(5-6):254-263.

171. Senneville E, Lombart A, Beltrand E, Valette M, Legout L, Cazaubiel M, Yazdanpanah Y, Fontaine P: Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study. Diabetes Care 2008, 31(4):637-642.

172. Senneville E, Yazdanpanah Y, Cazaubiel M, Cordonnier M, Valette M, Beltrand E, Khazarjian A, Maulin L, Alfandari S, Caillaux M, Dubreuil L, Mouton Y: Rifampicin-ofloxacin oral regimen for the treatment of mild to moderate diabetic foot osteomyelitis. J Antimicrob Chemother 2001, 48(6):927-930.

173. Pittet D, Wyssa B, Herter-Clavel C, Kursteiner K, Vaucher J, Lew PD: Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. Arch Intern Med 1999, 159(8):851-856.

174. Bamberger DM, Daus GP, Gerding DN: Osteomyelitis in the feet of diabetic patients. Long-term results, prognostic factors, and the role of antimicrobial and surgical therapy. Am J Med 1987, 83(4):653-660.

175. Lepantalo M, Biancari F, Tukiainen E: Never amputate without consultation of a vascular surgeon. Diabetes Metab Res Rev 2000, 16 Suppl 1:S27-32.

176. McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA: Determinants of mortality for necrotizing soft-tissue infections. Ann Surg 1995, 221(5):558-63; discussion 563-5.

177. Zimbelman J, Palmer A, Todd J: Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection. Pediatr Infect Dis J 1999, 18(12):1096-1100.

178. Mulla ZD, Leaverton PE, Wiersma ST: Invasive group A streptococcal infections in Florida. South Med J 2003, 96(10):968-973.

179. Stevens DL, Ma Y, Salmi DB, McIndoo E, Wallace RJ, Bryant AE: Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant Staphylococcus aureus. J Infect Dis 2007, 195(2):202-211.

180. Brindle R, Williams OM, Davies P, Harris T, Jarman H, Hay AD, Featherstone P: Adjunctive clindamycin for cellulitis: a clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis. BMJ Open 2017, 7(3):e013260-2016-013260.

181. Darenberg J, Ihendyane N, Sjolin J, Aufwerber E, Haidl S, Follin P, Andersson J, Norrby-Teglund A, StreptIg Study Group: Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a

European randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2003, 37(3):333-340.

182. Goh T, Goh LG, Ang CH, Wong CH: Early diagnosis of necrotizing fasciitis. Br J Surg 2014, 101(1):e119-25.

183. Nathwani D: Impact of methicillin-resistant Staphylococcus aureus infections on key health economic outcomes: does reducing the length of hospital stay matter? J Antimicrob Chemother 2003, 51 Suppl 2:ii37-44.

184. Goetghebeur M, Landry PA, Han D, Vicente C: Methicillin-resistant Staphylococcus aureus: A public health issue with economic consequences. Can J Infect Dis Med Microbiol 2007, 18(1):27-34.

185. Wright BM, Eiland EH,3rd: Retrospective Analysis of Clinical and Cost Outcomes Associated with Methicillin-Resistant Staphylococcus aureus Complicated Skin and Skin Structure Infections Treated with Daptomycin, Vancomycin, or Linezolid. J Pathog 2011, 2011:347969.

186. Itani KM, Merchant S, Lin SJ, Akhras K, Alandete JC, Hatoum HT: Outcomes and management costs in patients hospitalized for skin and skin-structure infections. Am J Infect Control 2011, 39(1):42-49.

187. Hosmer DW, Lemeshow S, Sturdivant RX: Applied Logistic Regression: Third Edition ed. John Wiley & Sons, Inc., Hoboken, New Jersey.; 2013.

188. Akaike H: A new look at the statistical model identification. IEEE transactions on automatic control 1974, 19(6):716-723.

189. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI, Daptomycin 98-01 and 99-01 Investigators: The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004, 38(12):1673-1681.

190. Psaty BM, Koepsell TD, Lin D, Weiss NS, Siscovick DS, Rosendaal FR, Pahor M, Furberg CD: Assessment and control for confounding by indication in observational studies. J Am Geriatr Soc 1999, 47(6):749-754.

191. Eckmann C, Lawson W, Nathwani D, Solem CT, Stephens JM, Macahilig C, Simoneau D, Hajek P, Charbonneau C, Chambers R, Li JZ, Haider S: Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant

Staphylococcus aureus: a plea for implementation of early switch and early discharge criteria. Int J Antimicrob Agents 2014, 44(1):56-64.

192. Garau, J., Blasi, F., Medina, J., McBride, K., Ostermann, H.: Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study. BMC Infectious Diseases 2015, 15:78.

193. Bruun T, Oppegaard O, Hufthammer KO, Langeland N, Skrede S: Early Response in Cellulitis: A Prospective Study of Dynamics and Predictors. Clin Infect Dis 2016, 63(8):1034-1041.

194. Berger A, Oster G, Edelsberg J, Huang X, Weber DJ: Initial treatment failure in patients with complicated skin and skin structure infections. Surg Infect (Larchmt) 2013, 14(3):304-312.

195. Amara S, Adamson RT, Lew I, Huang X: Clinical response at Day 3 of therapy and economic outcomes in hospitalized patients with acute bacterial skin and skin structure infection (ABSSSI). Curr Med Res Opin 2013, 29(7):869-877.

196. Nathwani D, Corey R, Das AF, Sandison T, De Anda C, Prokocimer P: Early Clinical Response as a Predictor of Late Treatment Success in Patients With Acute Bacterial Skin and Skin Structure Infections: Retrospective Analysis of 2 Randomized Controlled Trials. Clin Infect Dis 2017, 64(2):214-217.

197. Edelsberg J, Berger A, Weber DJ, Mallick R, Kuznik A, Oster G: Clinical and economic consequences of failure of initial antibiotic therapy for hospitalized patients with complicated skin and skin-structure infections. Infect Control Hosp Epidemiol 2008, 29(2):160-169.

198. Zilberberg MD, Shorr AF, Micek ST, Chen J, Ramsey AM, Hoban AP, Pham V, Doherty JA, Mody SH, Kollef MH: Hospitalizations with healthcare-associated complicated skin and skin structure infections: impact of inappropriate empiric therapy on outcomes. J Hosp Med 2010, 5(9):535-540.

199. Jenkins TC, Knepper BC, Jason Moore S, Saveli CC, Pawlowski SW, Perlman DM, McCollister BD, Burman WJ: Comparison of the microbiology and antibiotic treatment among diabetic and nondiabetic patients hospitalized for cellulitis or cutaneous abscess. J Hosp Med 2014, 9(12):788-794.

200. Suaya JA, Eisenberg DF, Fang C, Miller LG: Skin and soft tissue infections and associated complications among commercially insured patients aged 0-64 years with and without diabetes in the U.S. PLoS One 2013, 8(4):e60057.

201. Lipsky BA, Tabak YP, Johannes RS, Vo L, Hyde L, Weigelt JA: Skin and soft tissue infections in hospitalised patients with diabetes: culture isolates and risk factors associated with mortality, length of stay and cost. Diabetologia 2010, 53(5):914-923.

202. Fincke BG, Miller DR, Christiansen CL, Turpin RS: Variation in antibiotic treatment for diabetic patients with serious foot infections: a retrospective observational study. BMC Health Serv Res 2010, 10:193-6963-10-193.

203. Richard JL, Lavigne JP, Got I, Hartemann A, Malgrange D, Tsirtsikolou D, Baleydier A, Senneville E: Management of patients hospitalized for diabetic foot infection: results of the French OPIDIA study. Diabetes Metab 2011, 37(3):208-215.

204. ECDC.ESACnetdatabase.2017. http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-consumption/esac-net-database/Pages/consumption-rates-by-country.aspx

205. Forsblom E, Ruotsalainen E, Ollgren J, Jarvinen A: Telephone consultation cannot replace bedside infectious disease consultation in the management of Staphylococcus aureus Bacteremia. Clin Infect Dis 2013, 56(4):527-535.

206. Rosenbaum PR RD: The central role of the propensity score in observational studies for causal effects. Biometrika 1983, 70:41-55.