Diplomarbeit

Describing complicated skin and soft tissue infections in a tertiary referral dermatological centre

eingereicht von

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zur Erlangung des akademischen Grades

Doktor der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Dermatologie & Venerologie

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Graz, am ..... (Sebastian Volc)

Eidesstattliche Erklärung

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Acknowledgement

First of all, I want to thank my primary mentor, Univ. Ass. Alexandra Maria Giovanna Brunasso-Vernetti, MD. During my dermatology classes at the university, I had the idea of writing my thesis on an infectious disease subject. Giovanna helped me organise my thoughts and together we defined the outline of this project. She always made time for our study and me, despite the fact, that she was working full-time at the department and even after her daughter was born. She wormed her way to the heap of data I had collected, pointed out certain difficulties and offered a lot of advice. When I was at loss with the details of my work, she made me see the bigger picture and taught me the value of clinical research and pride in my work.

I also want to thank my secondary mentor, Univ. Prof. Werner Aberer, MD, for chaperoning our study and offering his professional perspective. Furthermore, I would like to thank the doctors and nurses of Station B of the department for letting me use the workstations and offering the occasional cup of coffee.

For his help with my statistical analysis, I want to thank Mr. Matteo Puntoni, PhD.

I owe my parents a debt of gratitude for making my university studies possible in the first place and offering advice as well as challenging my ideas throughout my studies. Their approach to medicine inspired me at a very young age and after I had convinced them of my decision to go into this profession myself, they gave me the opportunity to gather experience in their respective fields. While I was working on this thesis, my mother provided me with her knowledgeable insights into the field.

I also want to thank my friends, Clara and Maximilian, for pointing out various organisational issues and their help with statistical and IT-related problems. Their supportive friendship and our shared ideals always motivated me during our memorable time at the university.

And I thank my girlfriend Nadja, who supported me and stood by me throughout medical school. Her attentive last minute corrections made me trust in my work and gave me the final push to finish this thesis.

Abstract

Background: Skin and soft tissue infections (SSTIs) are a group of infections localised in the skin and/or subcutaneous tissue and are among the most frequent infectious diseases in a dermatological emergency consultation setting. Although the mortality rate of SSTIs is low in general, the number of hospitalisations caused by them is rather high. They are responsible for quality of life reduction (QOL) in many of our patients and have a significant economical impact on the health care system.

Materials and methods: We performed a retrospective study to evaluate the frequency and risk profiles of patients with SSTIs. Patient-data of 221 patients, treated in 2009 at the ward A of the Department of Dermatology and Venerology of the Medical University Hospital Graz, Austria, was obtained from the hospital information system Medocs and categorised with a standardised protocol.

Results: 117 women and 104 men were included and the mean age was 61,2 years ± 18,1. Lower extremity SSTIs were the major site of infection, women showed a tendency towards facial infections, while men were more often afflicted at the upper extremities. The most common risk factors were obesity (34,8%), fungal foot infections (24,9%), diabetes mellitus (23,1%) and the most common comorbidities were arterial hypertension (31,2%) and chronic heart disease (9,9%). The only variables significantly associated with an increase in the days of admission were chronic lower extremity ulcers (mean increase of 7 days), bullous and/or haemorrhagic infections (mean increase of 5 days), thyroid diseases (mean increase of 5,5 days) and obesity (mean increase of 3,6 days). *S.aureus* was the most frequently isolated pathogen (39%). *S.aureus* and *P.aeruginosa* were the only detected multiresistant strains of bacteria. *S.pyogenes* was only detected in 4,9% of cases. The patients were stratified according to a modified version of the Eron classification into five classes of infection: 19,9% in class 1, 43,0% in class 2A, 19,0% in class 2B, 12,2% in class 3 and 3,6% in class 4. Infection class 1 patients were of younger age, but showed a tendency towards prolonged hospitalisation in comparison with other classes. The most frequent complications observed were antibiotic skin reactions in 7,2% and liver enzyme elevations (4,9%), sepsis was rarely seen. 20,8% of the patients relapsed and 16,3% presented with either a bullous or haemorrhagic form of SSTI. 2 patients (0,9%) died during their treatment.

Conclusions: Our study shows a comprehensive summary of a big cohort of patients, their demographics and the treatment schedules. We attribute the, in comparison to other infection classes, prolonged hospitalisation of class 1 patients to the possible QOL-impairment resulting from infections of the hands, face or anogenital region. Obesity appeared to be the only significant risk factor for prolonged hospitalisation as well in the general cohort as in patients with recurrent episodes of SSTIs. The Eron classification proofed to be a very useful tool for efficient patient-stratification, which could be improved in the future by taking the site of infection into account of

severity assessment. It is necessary to review SSTIs from a dermatological point of view, because, while internationally they are usually seen, treated and therefore scientifically discussed by non-dermatologists, in german speaking countries, these diseases are traditionally treated by dermatologists.
Keywords: Complicated skin and soft tissue infections, SSTI, cellulitis, erysipela, stratification, risk factors

Zusammenfassung

Hintergrund: Haut- und Weichteilinfektionen zählen zu den häufigsten infektiösen Erkrankungen, die man in einer dermatologischen Ambulanz antreffen kann. Obwohl die Mortalität für gewöhnlich sehr niedrig ist, führen sie dennoch zu sehr vielen stationären Aufenthalten. Sie sind für eine verringerte Lebensqualität vieler Patienten verantwortlich und haben einen signifikanten ökonomischen Einfluss auf das Gesundheitssystem.

Methoden: Wir führten eine retrospektive Studie durch, um die Frequenz und Risikoprofile von Patienten mit Haut- und Weichteilinfektionen zu evaluieren. Die Patientendaten von 221 Patienten, welche 2009 an der Bettenstation A der Universitätsklinik für Dermatologie und Venerologie der Medizinischen Universität Graz in stationärer Behandlungen waren, wurden dem Krankenhausinformationssystem Medocs entnommen und anhand eines standardisierten Protokolls kategorisiert.

Ergebnisse: 117 Frauen und 104 Männer wurden in die Studie eingeschlossen. Das durchschnittliche Alter betrug 61,2 Jahres ± 18,1. Die meisten Infektionen waren an den unteren Extremitäten lokalisiert, bei Frauen zeigte sich ein Trend zu Gesichtsinfektionen, während Männer öfter an den oberen Extremitäten betroffen waren. Die häufigsten Risikofaktoren waren Adipositas (34,8%), Fußpilzinfestationen (24,9%), Diabetes mellitus (23,1%) und die häufigsten Komorbiditäten waren arterielle Hypertension (31,2%) und koronare Herzkrankheit (9,9%). Die einzigen Variablen, welche mit einer statistisch signifikanten Verlängerung des stationären Aufenthalts einhergingen waren chronische Ulzera der unteren Extremitäten (durchschnittliche Verlängerung um 7 Tage), bullöse und/oder hämorrhagische Infektionen (durchschnittliche Verlängerung um 5 Tage), Schilddrüsenerkrankungen (durchschnittliche Verlängerung um 5,5 Tage) und Adipositas (durchschnittliche Verlängerung um 3,6 Tage). *S.aureus* war das am häufigsten isolierte pathogene Bakterium (39%). *S.aureus* und *P.aeruginosa* waren die einzigen multiresistenten Bakterienstämme. Eine Infektion mit *S.pyogenes* konnte in nur 4,9% der Fälle bestätigt werden. Die Patienten wurden anhand einer modifizierten Version der Eron-Klassifikation für Haut- und Weichteilinfektionen in fünf Klassen unterteilt: 19,9% in Klasse 1, 43,0% in Klasse 2A, 19,0% in Klasse 2B, 12,2% in Klasse 3 und 3,6% in Klasse 4. Patienten mit Klasse 1 Infektionen waren jünger, zeigten aber eine Tendenz zu verlängerter Hospitalisierung in Vergleich mit anderen Klassen. Die häufigsten dokumentierten Komplikationen waren Hautreaktionen nach Antibiotikagabe (7,2%) und Lebertransaminasenerhöhung (4,9%), Sepsis wurde sehr selten beobachtet. 20,8% der Patienten erlitten einen Rückfall und 16,3% zeigten entweder eine bullöse oder hämorrhagische Form einer Haut- und Weichteilinfektion. 2 Patienten (0,9%) verstarben während ihres stationären Aufenthalts.

Diskussion: Unsere Studie stellt umfangreiche Zusammenfassung eines großen Patientenkollektivs dar, sowie deren demographische Charakteristiken und Behandlungsschemata. Die, im Vergleich zu anderen Infektionsklassen verlängerte Hospitalisierung der Patienten der Klasse 1, führen wir auf die möglichen Einschränkungen der Lebensqualität zurück, welche sich aus Infektionen der Hände, des Gesichts oder der Anogenitalregion ergeben. Adipositas stellte sich als der einzige signifikante Risikofaktor für einen verlängerten Krankenhausaufenthalt heraus, sowohl in der gesamten Studienpopulation als auch bei rezidivierenden Haut- und Weichteilinfektionen. Die Eron-Klassifikation bewährte sich als nützliches Hilfsmittel zur effizienten Patienten-Stratifizierung, könnte aber in Zukunft noch durch das Einbeziehen der Infektionsstelle zur Abschätzung des Schweregrades verbessert werden. Es ist notwendig Haut- und Weichteilinfektionen von einem dermatologischen Standpunkt aus zu betrachten, da sie international zwar von Nicht-Dermatologen, in deutschsprachigen Ländern allerdings von Dermatologen behandelt und wissenschaftlich diskutiert werden.
Keywords: Komplizierte Haut- und Weichteilinfektionen, SSTI, Erysipel, Stratifizierung, Risikofaktoren

Table of contents

Glossary and Abbreviations

AA	Atrial arrythmia
AMA	Against Medical Advice
BMI	Body mass index
CHD	Chronic heart disease
CI	Convidence interval
CKD	chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CREST	Clinical Resource Efficiency Support Team (Department of Health of Northern Ireland)
cSSTI	complicated SSTI
CVI	Chronic venous insufficiency
DM	Diabetes mellitus
DVT	Deep vein thrombosis
E. coli	*Escherichia coli*
H. influenza	*Haemophilus influenza*
HIV	Human immunodeficiency virus
ICU	Intensive care unit
MCI	Myocardial infarction
MOF	Multi Organ Failure
MRSA	Methicillin resistant *S. aureus*, also Multi-RSA
MUG	Medical University Graz
NSAIDs	Non-steroidal antiinflammatory drugs
OR	Odds ratio
p	P-value
P. aeruginosa	*Pseudomonas aeruginosa*
PAE	Pulmonary artery emboly
PAOD	Peripheral artery occlusive disease
Pr. mirabilis	*Proteus mirabilis*
PTCA	Percutaneous coronary intervention
QOL	Quality of life
S. agalactiae	*Streptococcus agalactiae*
S. aureus	*Staphylococcus aureus*
S. pyogenes	*Streptococcus pyogenes*
SD	Standard deviation
SEWS	Standardized early warning score
spp.	Species
SSTI	Skin and soft tissue infection
-TEP	Total endoprothesis
TIA	Transient ischaemic attack
Tr. rubrum	*Trichophyton rubrum*
Tr. interdigitale	*Trichophyton interdigitale*
VRSA	Vancomycin resistant *S. aureus*

1. Introduction

Complicated skin and soft tissue infections (cSSTIs) are among the most frequent infectious diseases in the dermatological emergency consultation setting.

Worldwide they are often treated by infectious diseases specialists or surgical departments, compared to Germany, Austria and Switzerland, where they are part of the dermatologists‘ domain.

Although the mortality rate of SSTIs is low in general, the number of hospitalisations caused by them is rather high. This is mainly due to an ageing patient population with an increasing number of co-morbidities, such as diabetes mellitus (DM), obesity or prior surgery in the affected area. Therefore, they are still responsible for quality of life impairment (QOL) in many of our patients and have a significant economical impact on the health care system.

SSTIs are a group of infections localised in the epidermis and dermis and/or subcutaneous tissue. In general, diseases like impetigo contagiosa, erysipela or cellulitis are defined as SSTIs (1). cSSTIs require hospital admission for intravenous antibiotic therapy and strict medical follow-up. In our work, we will consider erysipela and/or cellulitis that require hospital admission as cSSTIs and we will avoid using specific terms to define the different clinical manifestations of this infections.

The severity of infectious diseases relies on two main factors: the etiological agent and the clinical setting. Therefore, addressing the focus, identifying the responsible micro-organisms and correctly diagnosing SSTIs are necessary to start treatment immediately (2).

The aim of our study was to categorise the patients admitted with the diagnosis of SSTIs such as infectious cellulitis with or without either abscess, ulcer or lymphangitis or necrotising fasciitis to the dermatology ward A of the Department of Dermatology and Venerology of the Medical University of Graz from December 2008 until January 2010 to evaluate disease severity, length of admission, class of infection according to the Eron classification, predisposing factors, aggravating factors, response to therapy, complications, recurrences, and mortality as well as to compare our data with previous studies performed by other medical disciplines (3).

1.1 Epidemiology

SSTIs are among the most frequent indications for a consultation in a dermatological setting. As Ki and Rotstein reported, the estimated incidence rate of cellulitis is 24,6 per 1000 person-years, individuals are aged between 45–64 years, but it can occur at all ages. They reported a higher incidence among males, which was indicated by other studies as well, but has not been confirmed worldwide (4-7).

cSSTIs are responsible for a major part of all infections in hospitalised patients, their estimated prevalence being as high as 7 to 10%. According to Eron et al., cSSTIs represent the third most common diagnosis after chest pain and asthma. The lower extremities predominate as site of

infection, followed by the face and trunk, whereas the upper extremities and the anogenital region are least often infected. (3,8,9)

1.2 Predisposing factors

Predisposing factors may not only increase the risk of contracting an infection, but can also prolong their course or affect the response to treatment.

Ki and Rotstein distinguish between patient related and etiological risk factors. The first category includes critical illness, elderly age, immunocompromised state, liver and kidney disease, and vascular (lymphatic or venous) insufficiency. The second category includes not only the usual suspected microbes, but also more recently emerging resistant bacteria. (5)

Table 1 illustrates the most frequent pathogens associated with specific risk factors. (3)

Table 1: Risk factors for specific pathogens causing SSTIs

Risk factor	Characteristic pathogen
Diabetes mellitus	*S. aureus*, group B streptococci, anaerobes, Gram-negative bacilli
Cirrhosis	*Klebsiella pneumoniae, E. coli*, other Gram-negative bacilli,
Neutropenia	*P. aeruginosa*
Hot tub exposure	*P. aeruginosa*
Intravenous drug abuse	MRSA, *P. aeruginosa*

Other common risk factors include: Obesity (defined as a body mass index (BMI) > 30) or Overweight (BMI between 25 and 30), fungal infections (Tinea pedis), recent or past local trauma, as well as surgery, neoplasms, human or animal bites, leg or foot ulcers, peripheral arterial occlusive disease (PAOD) and peripheral neuropathy.

SSTIs (in particular erysipela and/or cellulitis) can prepare the ground for venous ulcers in the lower extremities and vice versa, leading into a vicious cycle (10).

1.3 Microbial aetiology

The pathogenesis usually involves direct inoculation of microbial agents through skin disruption, traumatic or artificial in nature. cSSTIs are caused by a great variety of pathogens, especially *Staphylococcus aureus*, the most commonly isolated pathogen. Classically, *Streptococcus pyogenes* is the most mentioned responsible pathogen for cellulitis in the literature. However, since it usually is quite difficult to isolate, other microorganisms are more often detected at infection sites, such as *S.aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and others. For instance, Ki and Rotstein explained, that *S.pyogenes* and *S.aureus* are the most frequent pathogens found above the waist, while as below there is a much more mixed flora, especially due to faecal contamination (5).

In German-speaking countries, there is no differentiation made between the terms „cellulitis“ and „erysipela“. This overlapping is not present in the English-speaking countries, where erysipela, a more superficial infection, localised in the dermis is usually caused by group A streptococci and less often by group G, B, C and D streptococci, *S.aureus*, *Pneumococcus* spp, *Klebsiella pneumonia*, *Yersinia enterocolitica*, and *Haemophilus influenza B*. Cellulitis is the deeper form of infection, located in the deep dermis and subcutaneous tissue and is caused by *S.pyogenes* and *S.aureus*, sometimes complicated by a combination of various other microbial agents (11). From a clinical point of view, it is very difficult to differentiate between cellulitis and erysipela, that is why we prefer the term SSTIs.

Recent publications acknowledged the increase of *S.aureus* and *P.aeruginosa* related SSTIs (12).

Since 1997 the SENTRY Antimicrobial Surveillance Program has been monitoring SSTIs. Moet et al. presented data from three continents (North America, Latin America and Europe) over a 7-year period (1998-2004). Each year, participating medical centres were directed to send 50 consecutive pathogen samples from hospitalised patients determined to be significant causes of SSTIs. The program had found a rising incidence of antibiotic resistance among *S.aureus to methicilin* (26,2% to 47,4%), to vancomycin (from 8,6% to 14,8%) and extended-spectrum beta-lactamase (ESBL) production among *Klebsiella* spp (from 4,9% to 16,3%) and *E.coli* (from 3,5% to 12,8%). On the global scale, S. aureus was the most frequently occurring pathogen from SSTIs with methicilin-resistant *Staphylococcus aureus* (MRSA) being the greatest resistance concern. Community-associated MRSA had increased markedly to become the greatest problem facing therapy for SSTIs in the outpatient setting. The variability of MRSA rates observed among nations was most dramatic in Europe. The European Antimicrobial Resistance Surveillance System report from 1999 to 2002 compared an overall MRSA rate of 20%, with Sweden at 0,8% and Portugal at 34,7%. The second most frequently isolated Gram-positive organisms were enterococcal species, where the prevalence remained high in North America as did the occurrence of vancomycin resistant enterococcus (VRE, usually against vancomycin A). Among non-Enterobacteriaceae Gram-negative bacilli, *P.aeruginosa* had the highest occurrence in SSTI in all geographic regions. These results demonstrated the diversity of SSTI pathogens routinely monitored by the SENTRY program. This ongoing surveillance has provided researchers with an understanding of longitudinal trends in pathogen occurrences and how resistance to commonly used antimicrobial agents may develop. (23)

1.4 Classification

There are some classifications available to objectively stratify the severity of SSTIs. For our study, we used a modified version of the classification proposed by Eron et al., as shown in Table 2. According to this classification, we can consider class 1 infections as uncomplicated forms that can

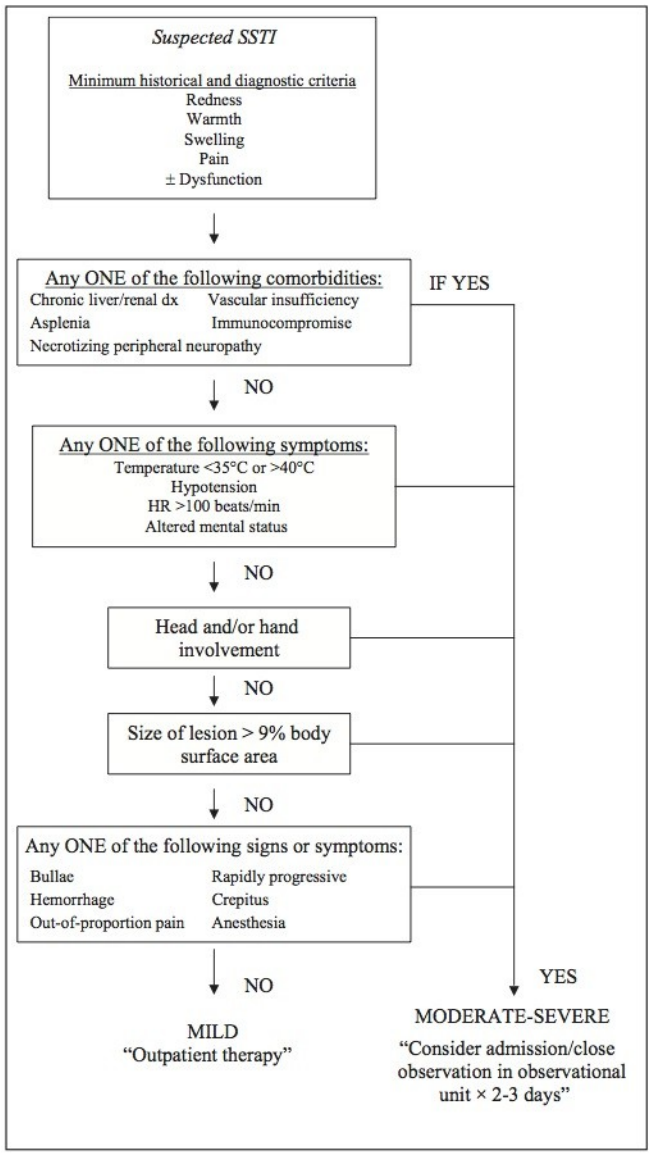
be treated safely in an outpatient setting. Class 1 infections usually make up a small percentage of patients in the hospital setting, because they are most likely treated by general physicians or in an outpatient setting. Infections categorised as class 2 can be considered complicated in some patients where the compliance, the clinical picture and the co-morbidities represent a threat for the successful ambulant treatment. Examples of cSSTIs may include the presence of risk factors or co-morbidities like diabetes mellitus, chronic ulcers, obesity and immunosuppression, as well as complicated forms like bullous or haemorrhagic cellulitis, burns, major abscesses, necrotising fasciitis, surgical site infections or combinations of the aforementioned maladies, i.e. diabetic foot infections or infected ulcers. Class 3 and 4 infections should always be considered as cSSTIs. (3)

Table 2: Infection classes

Class 1	Afebrile and healthy other than SSTI
Class 2 a	SSTI, afebrile, ≥1 stable co-morbidities that may complicate or delay resolution(e.g. DM, obesity)
Class 2 b	≥1 stable co-morbidities that may complicate or delay resolution(e.g. DM, obesity), appear systemically ill (temperature between 37° and 38,5°C)
Class 3	Appear toxic and unwell (fever, tachycardia, tachypnoea and/or hypotension) and/or unstable co-morbidities that may complicate or delay resolution (e.g. DM, obesity)
Class 4	Sepsis and/or multisystemic organ failure; needed to be admitted to the ICU and/or surgical emergency assessment

Other classifications include Ki and Rotstein‘s assessment scheme based on the primary infection site (see Figure 1) as well as the „Guidelines on the Management of Cellulitis in Adults“ by the Clinical Resource Efficiency Support Team (CREST) of the Department of Health of Northern Ireland which is very similar to the modified Eron Classification (see Figure 2: CREST). In 2010, Marwick et al. presented their „Dundee classification“, which was based upon the CREST-Guidelines but also included a standardised early warning score (SEWS) derived from the measurement of physiological parameters (5,13,14).

Figure 1: Evaluation algorithm for severity of SSTIs (according to (4))



dx Dysfunction; HR Heart rate

CREST
CLINICAL RESOURCE EFFICIENCY SUPPORT TEAM

CREST Management of Cellulitis In Adults

Diagnosis

Flu-like symptoms, malaise
onset of unilateral swelling, pain, redness

Decide Classification

Class I	Class II	Class III	Class IV
Patients have no signs of systemic toxicity, have no uncontrolled co-morbidities and can usually be managed with oral antimicrobials on an outpatient basis	Patients are either systemically ill or systemically well but with a co-morbidity such as peripheral vascular disease, chronic venous insufficiency or morbid obesity which may complicate or delay resolution of their infection	Patients may have a significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or may have unstable co-morbidities that may interfere with a response to therapy or have a limb threatening infection due to vascular compromise	Patients have sepsis syndrome or severe life threatening infections such as necrotizing fasciitis

Lab Investigations

Class II - IV	Selected Patients
FBC ESR or CRP U+E Culture any ulceration or blister fluid	• Blood cultures only Class III or Class IV • Streptococcal serology only in refractory cases where diagnosis is in doubt • Skin biopsy where differential diagnosis includes other inflammatory lesions

Treatment

	First line	Second line
Class I	Flucloxacillin 500mg qds po	Penicillin allergy - Clarithromycin 500mg bd po
Class II	Flucloxacillin 2g qds IV or *Ceftriaxone 1g od IV (OPAT)	Penicillin allergy - Clarithromycin 500mg bd IV or Clindamycin 600mg tds IV
Class III	Flucloxacillin 2g qds IV	Penicillin allergy - Clarithromycin 500mg bd IV or Clindamycin 900mg tds IV
Class IV	Benzylpenicillin 2.4 g 2-4 hourly IV +Ciprofloxacin 400mg bd IV +Clindamycin 900mg tds IV (If allergic to penicillin use Ciprofloxacin and Clindamycin only). **NB Discuss with local Medical Microbiology Service**	

***Must not be used in penicillin anaphylaxis**

Suggested Criteria For Oral Switch and/or Discharge

- Pyrexia settling
- Co-morbidities stable
- Less intense erythema
- Falling inflammatory markers

Suitable Agents for Oral Switch Therapy

- Flucloxacillin 500mg qds

If penicillin allergy-

- Clarithromycin 500mg bd
- Clindamycin 300mg qds

Prophylaxis for Recurrent Cellulitis

- 2 or more episodes at the same site
- Penicillin V 250mg bd or Erythromycin 250mg bd for up to 2 years

JUNE 2005

Figure 2: CREST-Guidelines (13).

1.5 Differential diagnoses

Not only are SSTIs common diseases, but they are also easily mistaken for other common illnesses, such as: irritant contact dermatitis, eczema, superficial thrombophlebitis, acute lymphangitis, localised angioedema, insect bite reactions, stasis dermatitis, deep vein thrombosis, panniculitis, erythema nodosum, Sweet‘s syndrome, vasculitis, cutaneous lymphoma and erysipela carcinomatosum (a clinical picture that appears after radiotherapy treatment for breast cancer mainly in the upper extremity and/or shoulder) (15).

1.6 Defining complicated SSTIs

Complicated skin infections are defined as those that require admission to the hospital due to patients-associated factors, as involvement of deeper soft tissues, presence of risk factors, co-morbidities and absence of compliance and aetiology-associated factors such as multiresistant bacteria, necrotising infections and infections following a potentially contaminated trauma (human/animal bites or animal associated trauma). Surgical intervention may be required in some cases of cSSTIs. In the clinical setting, all infections are considered as cSSTIs, when they are life-threatening and/or polymicrobial and/or rapidly progressive. Therefore, infected ulcers, burns, major abscesses or an underlying disease compromising the immune system or response to treatment, e.g., diabetes mellitus, humane immunodeficiency virus (HIV), neoplasms, chronic kidney insufficiency, PAOD etc. should always be considered as complicated and potentially life threatening infections.

Some non complicated SSTIs, in particular cellulitis or erysipela can develop into several complicated forms, such as: recurrent, haemorrhagic, bullous or necrotising. Furthermore, if the infection is situated at some sites like the anogenital region or at the face or hands, where a persistent disfiguration or an important functional compromise would cause the patient significant impairment of QOL and psychological and social discomfort and/or disability, it may as well be classified as complicated. Aggravating co-morbidities like diabetes mellitus, obesity and immunosuppression should also come into consideration, when distinguishing between an uncomplicated or a complicated form of infection.

Recurrent cSSTIs (mainly erysipela and/or cellulitis) bear the danger of obliterating the lymphatic vessels and can lead to secondary lymphedema, sclerosis, pigment alterations, pachydermia, and inflammatory elephantiasis. Anecdotal experience and evidence suggest that lymphedema occurs more often in genital SSTIs, where it causes considerable QOL impairment and poses a specific problem in the threat of faecal contamination due to the anatomical vicinity. Leclerc et al. examined

a cohort of 47 patients who presented with recurrent erysipela (two or more episodes). They concluded, that recurrence is the most frequent complication of erysipela (6).

A haemorrhagic or bullous component should be seen as a complication, because it can hide a phlegmonous form or necrotising fasciitis. We should also pay attention to rapidly evolving localised and systemic signs and symptoms. Rapidly progressive, necrotising infections more frequently involve pathogens that may be highly virulent (e.g. *Streptococcus* spp. and *Clostridium* spp.), produce a variety of exotoxins and have a rapid growth rate. Chronic wounds and nosocomial infections may involve highly resistant pathogens not commonly seen, e.g. MRSA, vancomycin resistant *S.aureus* (VRSA), ESBL and resistant strains of *P.aeruginosa*.

Life threatening-SSTIs can be classified in subgroups: necrotising infections, nosocomial and chronic infections, bite and water associated infections and MRSA-infections (community-acquired or nosocomial). Prompt antibiotic therapy is mandatory and empirical treatment is performed hours to days before appropriate culture and sensitivity data are available. Thus, selection of an appropriate antibiotic is based on knowledge of the pathogens likely involved in a particular infection and the comorbidities of the patient.

1.7 Complications

SSTIs can cause a number of localised complications, such as lymphangitis, formation of superficial or deep abscesses, skin necrosis and/or thrombosis.

Systemically, SSTIs can lead to bacteraemia, systemic inflammatory response syndrome (SIRS) and sepsis, especially those caused by *S.aureus*. These have been shown to be associated with the development of metastatic foci of infection and can therefore be responsible for other infections, i.e. endocarditis, deep-seated abscesses, osteomyelitis etc. To give another example of the lurking dangers of SSTIs, Petti and Fowler reported an increase in *S.aureus*-associated endocarditis and deduced, that partly, it might be due to an increased incidence of cellulitis. Furthermore, in rare cases, SSTIs can lead to acute glomerulonephritis, especially those caused by group A streptococci. (11,16,17)

1.8 Diagnosis and Treatment

Cellulitis is primarily diagnosed through clinical examination, the clinical presentation is typical in most cases with the triad of erythema, fever and lymphadenitis, but not all the symptoms need to be present to make the diagnosis. If the clinical is suspicious for a complicated or life-threatening infection, the diagnosis should be confirmed with swabs and blood cultures. Cultures from aspirates and lesions do not always reveal the causative organism(s) and, therefore, many diagnoses are based on the clinical presentation and morphology of the lesions (18).

The choice of treatment depends on the current guidelines and the local clinical experience. If the patient has already suffered from cellulitis before, not only has this to be taken into account as a recurrence, but also the kind of treatment administered before.

Current antibiotic and surgical treatment of cSSTIs is based mainly on the evidence provided from studies regarding non-necrotising soft tissue infections and few studies support guidelines for necrotising infections. Penicillin G is the most used first-line antibiotic agent, closely followed by clindamycin. Amoxicillin in combination with clavulanic acid (Augmentin ®) is also frequently administered. In more severe cases and where a polymicrobial aetiology is suspected, piperacillin in combination with tazobactam (Tazonam ®) is used as a second or third line antibiotic.

In Table 3, we list a comprehensive summary of antibiotic treatment options adapted from Altmeyer‘s „Enzyklopädie Dermatologie, Allergologie, Umweltmedizin“ (19).

Most cases of SSTIs can be treated effectively, using empirical antimicrobial therapy. The increasing prevalence of resistance among some bacterial strains, especially *S.aureus* and *P.aeruginosa*, highlights the paramount need of research for new treatment options. However, more potent antibiotics also have their disadvantages, as Eisenstein reported: „In addition to the decreasing efficacy of antibiotics against most resistant bacterial strains, the potential toxicity of many antibiotics is of clinical concern. For example, treatment with vancomycin can lead to potentially serious disorders such as nephrotoxicity and treatment with quinopristin-dalfopristin[1] is also problematic because of unfavourable adverse event profiles and high cost.“ (2)

For patients presenting with cellulitis and shock, initial empirical therapy should include antibiotic agents active against *P.aeruginosa* and Gram-positive organisms (20).

Adjuvant therapy, such as antithrombotic treatment, should always be administered together with the antibiotic treatment. In general, the patient needs bed-rest, the inflamed limb should be cooled and elevated. Local treatments include cool packs with antiseptic additives like polihexanid or potassium manganate, which should be changed several times a day.

The use of non-steroidal antiinflammatory drugs (NSAIDs) or paracetamol for pain relief is a controversial topic, because they might mask rapidly progressive and potentially life-threatening SSTIs, but we have to face the reality that they are used in the day to day clinical practice even without supporting evidence. To our knowledge, up to this point there have been no randomised controlled trials in this regard.

To support Hippocrates‘ basic principle, „ubi pus, ibi evacua“[2], Moran et al. concluded that the most simple abscesses, even those caused by resistant strains like MRSA, can be cured with drainage alone. Therefore, appropriate surgical care is also of critical importance. (21)

1 Streptogramin antibiotics used in vancomycin resistant infections.

2 „Where there is pus, drain it.“

Table 3: Treatment options of cellulitis (adapted from (19))			
	Medication	***Dosage***	***Length of therapy***
Uncomplicated case	Penicillin V	1.5-3 million units/die p.o. in 3-4 single doses	10 days
Penicillin-resistance	Dicloxacillin or 3rd genaration cephalosporins		
Therapy resistance	Combination of a cephalosporin and an aminoglykoside		
Complicated course or chronic recurrence	Penicillin G	15-30 million unitis/die i.v. in 3-4 single doses (max. 30 mio/die)	until the infection resolves
Complicated course combined with hypersensitivity to Penicillin	Vancomycin	40-60 mg/die i.v. in 2-3 single doses	until the infection resolves
Polymicrobial infections	Oxacillin	4 x 1 g/die i.v./i.m. (max. 8 g/die)	10 days
	Amoxicillin + clavulanic acid	2 x 4,4 g/die i.v.	until the infection resolves
	Cephalosporins (i.e. Cefotaxim)	2-3 x 2 g/die i.v.	until the infection resolves
	Cefuroxim + Gentamicin	2 x 1.5 g/die i.v. + 240 mg/die i.v.	until the infection resolves
Hypersensitivity to Penicillin	Erythromycin	4 x 0,5-1 g/die p.o.	10 days
	Clarithromycin	2 x 250-500 mg/die p.o	10 days

2. Materials and Methods

We performed a retrospective study in order to evaluate frequency, risk and aggravating factors, length of hospital admission, evolution, complications and response to treatment in patients admitted with the diagnosis of erysipela, cellulitis or complicated SSTIs in a tertiary dermatological centre. We obtained the approval of the ethical committee (23-331 ex 10/11) of the Medical University Graz (MUG).

The study involved 221 patients treated from December 2008 until January 2010 at the Department of Dermatology and Venerology of the Medical University Hospital Graz, Austria. Patients' data were obtained from the hospital‘s information system Medocs and categorised with a standardised protocol. Only patients that were between the age of 18 and 100 and who satisfied the diagnosis „infectious cellulitis“ (ICD-10 A46) with or without either abscess (L02, L03), ulcer (L97) or lymphangitis (I89.1) as well as necrotising fasciitis (M72.6) were included.

All patients, who were under 18 years of age or were part of a ethically protected group, were excluded from the study.

Statistical methods

Descriptive statistics included numbers and percentages for categorical factors and mean (or median) and standard deviation (or interquartile range) for continuous variables.

Due to the highly skewed distribution of the main outcome variable (number of days of admission), the relationships between the study outcome and all potentially associated socio-demographic, health-related and clinical-pathological factors were examined using non-parametric statistics.

The distribution of days of admission in each factor (i.e. sex, smoking habits, infection class, infection type, risk factors and co-morbidities) was explored using box-plot graphs, testing the difference between categories using the two-sample Wilcoxon rank-sum (Mann-Whitney) test or the Kruskal-Wallis equality-of-populations rank test.

Spearman's rho correlation coefficient was calculated to test correlation with age as a continuous variable.

To test the independence of the association between the outcome and all factors considered, we built a multivariate linear regression model, considering days of admission as the dependent variable and adjusting for all others factors.

A logistic regression model was also adopted to study the association between the presence or absence or recurrences (dependent binary variable) and the socio-demographic, health-related and clinical-pathological factors. Wald test was used to assess the statistical significance of independent factors included in the model.

All analyses were conducted using Stata (version 11; StataCorp., College Station, TX) software. Two-tailed probabilities were reported and the p-value of 0.05 was used to define nominal statistical significance.

3. Results

3.1 General information, Risk factors and Comorbidities

221 patients were evaluated. 117 (52,9%) women and 104 (47,1%) men were included. The mean age was 61,2 years with a standard deviation of 18,1 and ranging from 18 to 95 years. The most common risk factors were obesity (34,84%), fungal foot infections (24,9%), Diabetes mellitus (23,08%), overweight (22,17%), local scars (13,57%) and local surgery (12,67%). The most common co-morbidities were arterial hypertension (31,2%) and chronic heart disease (9,9%).

Table 4 shows the characteristics of the whole study population concerning co-morbidities, risk factors and site of infection.

Table 4: Characteristics of 221 patients with SSTIs

Characteristic	*No. (%)*	*Characteristic*	*No. (%)*
Sex		Age in years (mean ± SD)	61,2 ± 18,1
Female	117 (52,9)	Mean length of stay (days)	12,3 ± 7,9
Male	104 (47,1)	**Most common risk factors**	
Co-morbidities		Obesity (BMI>30)	77 (34,84)
arterial Hypertension	69 (31,22)	Fungal foot infection *	55 (24,89)
Chronic heart disease	22 (9,95)	Diabetes mellitus	51 (23,08)
knee/hip-TEP/Arthrosis	20 (9,05)	Overweight (BMI<30)	49 (22,17)
Thyroid disease / dysfunction	17 (7,69)	Scars	30 (13,57)
COPD, Asthma	16 (7,24)	Surgery	28 (12,67)
St.p. MCI, Bypass, PTCA	16 (7,24)	Ulcus cruris	20 (9,05)
Chronic kidney disease	14 (6,33)	Chronic venous insufficiency	20 (9,05)
Atrial arrhythmia	13 (5,88)	Liver cirrhosis	20 (9,05)
St.p. Stroke /TIA	12 (5,43)	Immunosuppression	19 (8,60)
Hypercholesterinemia	11 (4,98)	Varicosis	19 (8,60)
Electrolyte imbalance	9 (4,07)	PAOD	17 (7,69)
Osteoporosis	9 (4,07)	Trauma	13 (5,88)
St.p.PAE, internal thrombosis	8 (3,62)	Peripheral neuropathy	9 (4,07)
Parkinson's, Restless legs syndrome	8 (3,62)	Insect bite	8 (3,62)
		Chronic light damage	8 (3,62)

Abbreviations: BMI (Body Mass Index), COPD (Chronic obstructive pulmonary disease), MCI (Myocardial infarction), PAE (Pulmonary artery embolism), PAOD (Peripheral arterial occlusive disease), PTCA (Percutaneous transluminal coronary angioplasty), TEP (total endoprothesis), TIA (Transient ischaemic attack)
* see also Table 12 (Fungal foot infections)

3.2 Site of involvement

The lower extremities were the most commonly affected site with a total of 162 cases (70,7%). Only in 13 cases (5,7%) the upper extremities were affected. The face and the genital area were affected in 27 (11,8%) and 4 (1,7%) cases, respectively. 11 cases (4,8%) presented at more than one site. (Figures 3 and 4)

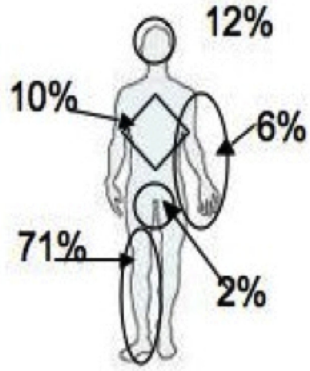
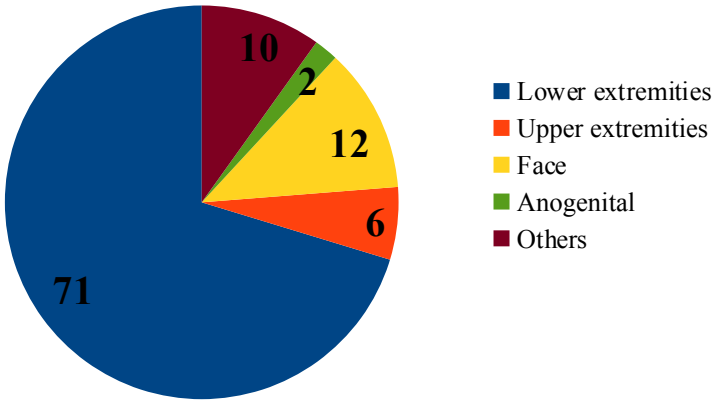


Figure 3: Distribution of infection sites (%)

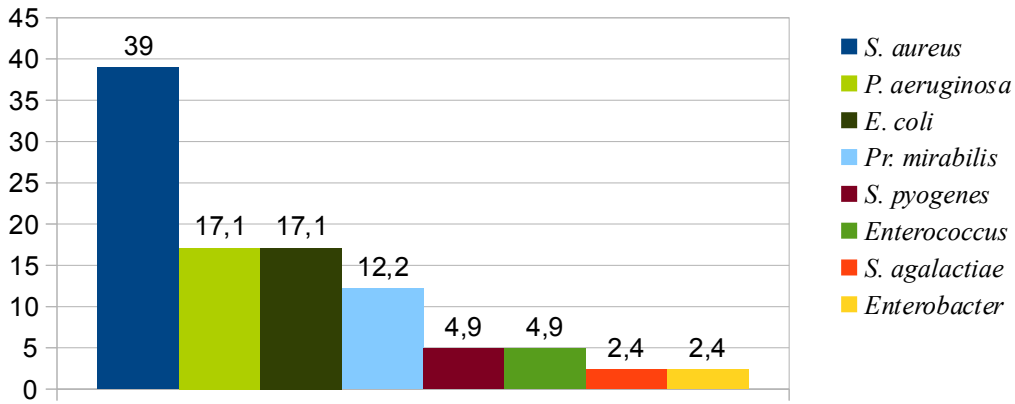
Figure 4: Site of infection (%)



3.3 Detected pathogens

We were able to identify the pathogen (using swabs for bacterial cultures and blood cultures) in 41 cases of 221 patients (18,6%). The most commonly isolated species, as shown in Figure 5, were *S.aureus* (39%), *P.aeruginosa*, *E.coli* (each 17,1%), *Proteus mirabilis* (12,2%), β-haemolytic group A *Streptococcus* (*S.pyogenes*), *Enterococcus* spp. (each 4,9%), *Streptococcus agalactiae* and *Enterobacter* (each 2,4%). Of the Staphylococci, resistance to penicillin, ampicillin and amoxillin combined with clavulanic acid was only shown in one case. No cases of MRSA were identified. Two out of seven *P.aeruginosa* infections (28,6%) were defined as multi-resistant by the treating physicians, mainly against ciprofloxacin, piperacillin combined with tazobactam and meropenem.

Figure 5: Identified microbial agents (%)



In terms of fungal infections our findings were as follows: 55 of 221 patients (24,9%) presented with fungal foot infections. Of these 34,5% were associated with Tr. rubrum, 14,5% with Tr. interdigitale and 30,9% were unspecified hyphae. There were fewer yeast infections with only 10% in total (Table 5).

Table 5: Fungal foot infections		
Hypha	*Trichophyton rubrum*	19 (34,5)
(80%)	*Trichophyton interdigitale*	8 (14,5)
	others	17 (30,9)
Yeast	*Candida krusei*	1 (1,8)
(10%)	*Malassezia furfur*	1 (1,8)
	others	9 (16,4)

3.4 Treatment and Outcome

The mean duration of hospital admission was 12,3 days and was correlated with the duration of intravenous administration of antibiotics. In most cases, patients were empirically treated either with penicillin G (52,9%) or clindamycin (24%) as a first-line regimen.

21 patients (9,5%) were considered as lost in follow-up, after they had left the hospital against medical advice (AMA) or had been transferred to other services, such as surgery, internal medicine, orthopaedics, the ICU or to the prison infirmary (1 patient). The transferrals lead to a problem because of limited patient data access. This limitation resulted from the narrow parameters of the ethical committee agreement, that did not allow us to inspect patient files from other services. Table 6 shows in detail the medical outcomes recorded for our patients. Table 6 shows in detail the medical outcomes recorded in our patients.

Table 6: Medical outcome & complications	
Mean length of hospitalisation	12,3 ± 7,9 days
Surgical debridement	22 (10,05%)
Directly related recurrence	5 (2,3)
Systemic complications	
Antibiotic related skin reaction	16 (7,2%)
Liver enzyme elevation	11 (5%)
Mortality	2 (0,9%)
Patients transferred to the department of … (*)	

Table 6: Medical outcome & complications	
Surgery	8 (3,6)
Internal medicine	4 (1,8)
Orthopaedics	2 (0,9)
ICU	2 (0,9)
back to prison infirmary	1 (0,45)
Lost in follow up	2 (0,9%)
Patients, who left AMA	2 (0,9%)
* Considered as lost in follow-up due to limited patient data access.	

3.4.a Mean length of admission

Patients stratified by general findings

Female patients were statistically significant longer hospitalised than men (p=0,0376), 13,1 days (± 7,7 SD), versus 11,4 days (± 8,1 SD) (Figure 6).

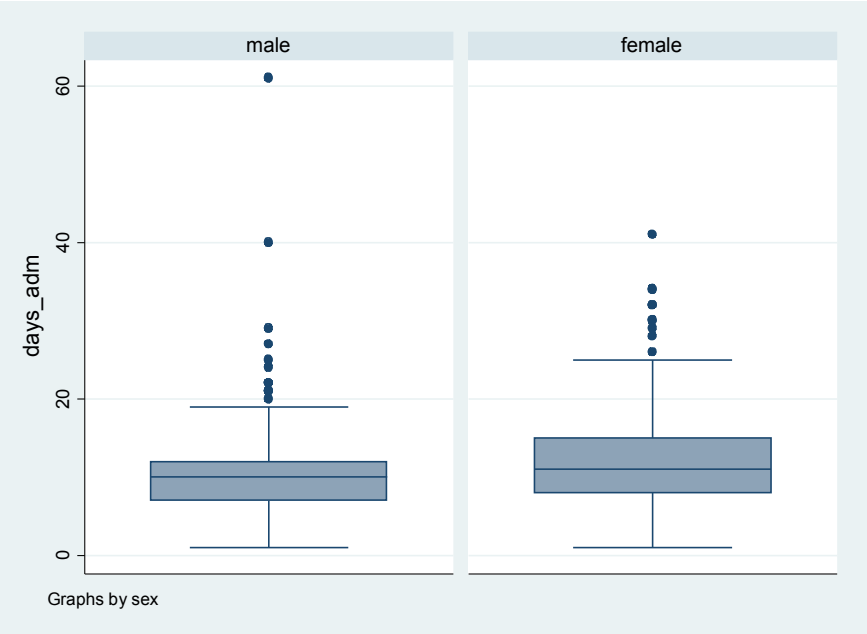


Figure 6: Length of admission stratified by sex.

The length of admission was positively correlated with increasing patient age (Spearman's rho = 0,3136, p<0,0001) (Figure 7).

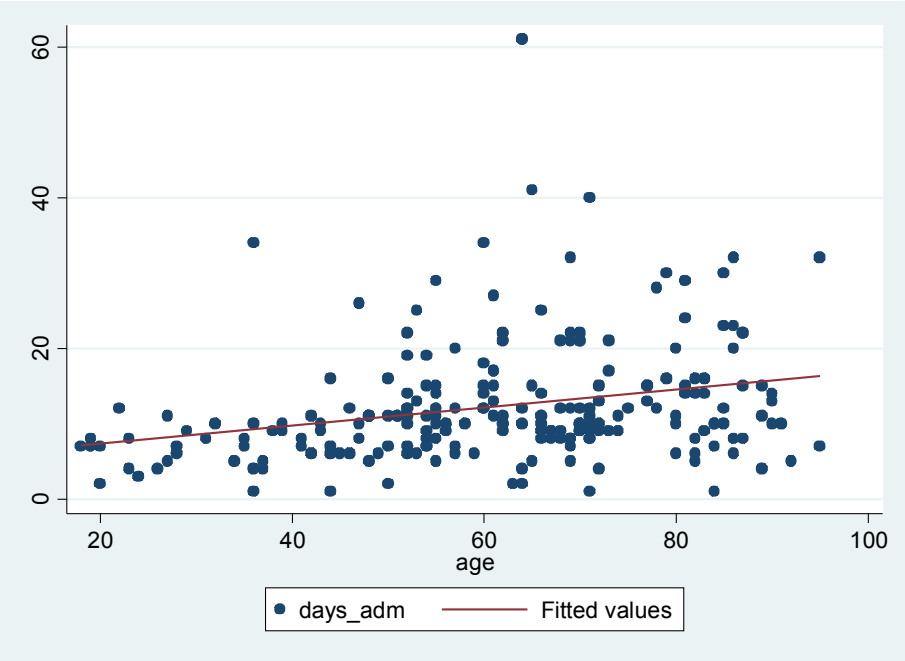


Figure 7: Correlation of age and length of admission.

The length of admission was also increased in the cohorts afflicted with a bullous or haemorrhagic form of cSSTIs and those aggravated by abscesses or other complications (p=0,048) (Figure 8).

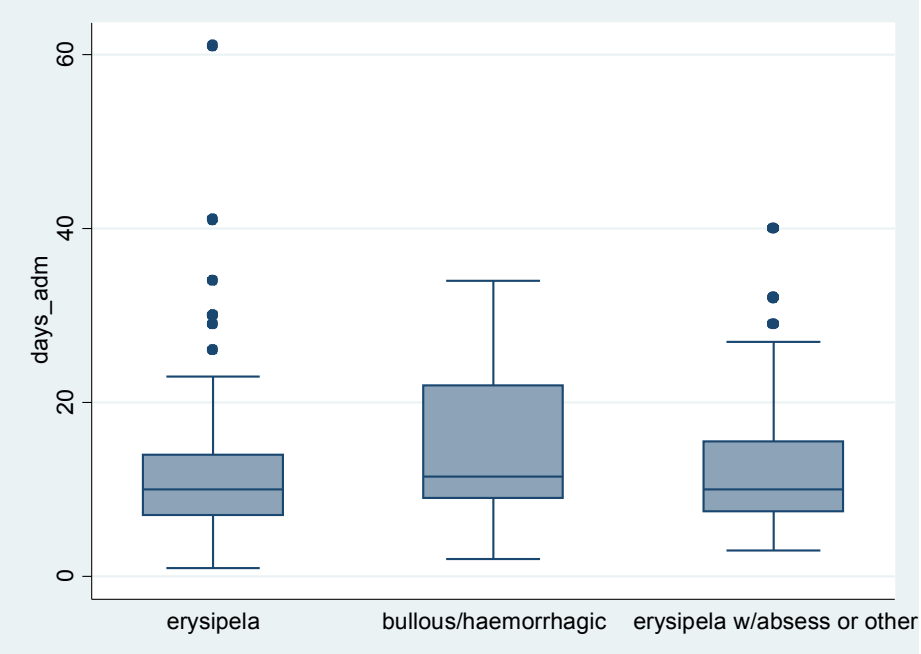


Figure 8: Complicated vs. uncomplicated forms (Length of admission).

We could not discern a statistically significant difference between smokers, ex-smokers and non-smokers regarding the length of admission (p=0,3843) (Figure 9).

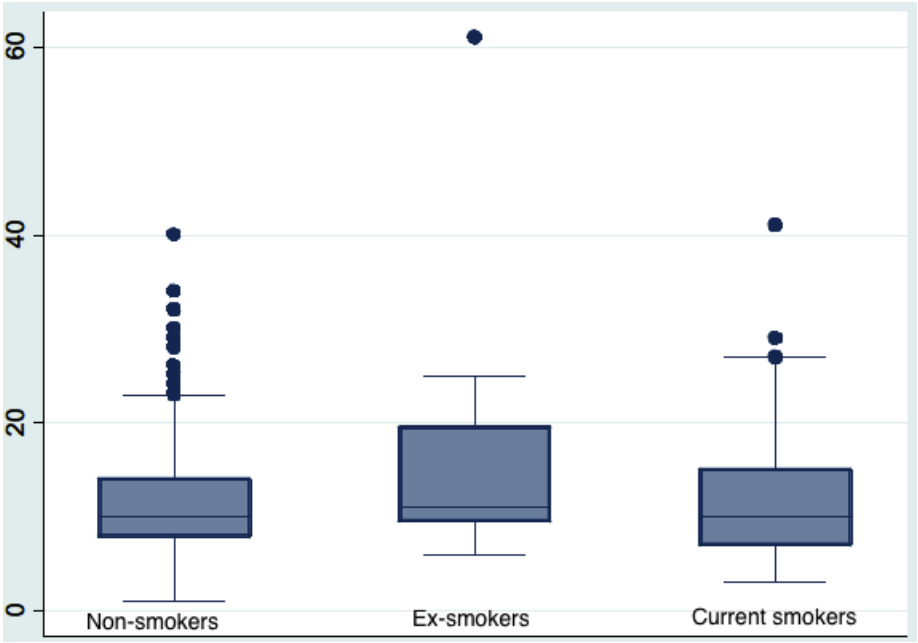
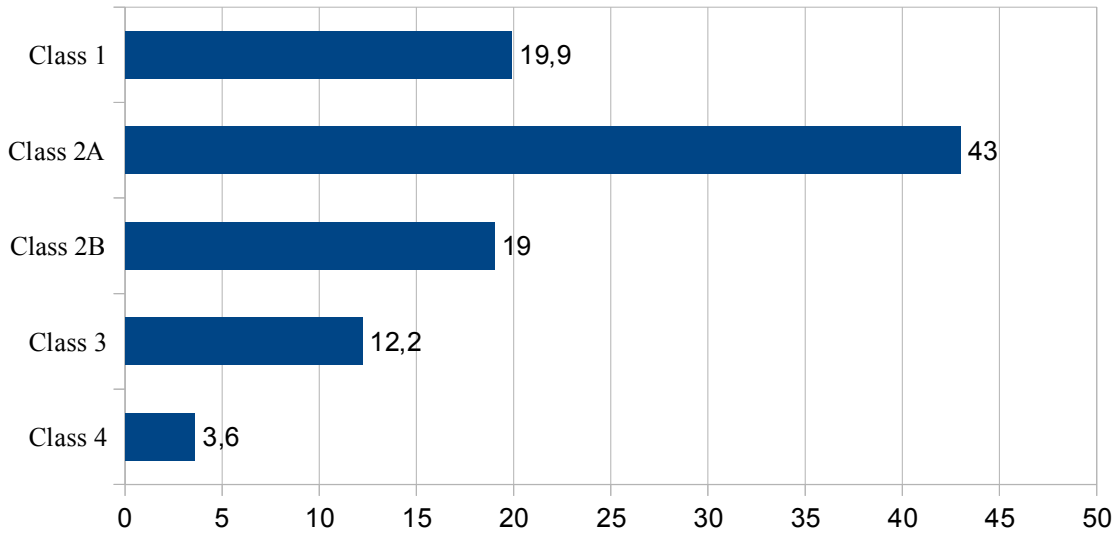


Figure 9: Smoking habits correlated with length of admission.

Patients stratified by infection class

We stratified the patients in five different infection classes, using a modified version of the Eron classification, as explained in the introduction. There were 49 cases (19,9%) in class 1, 95 (43,0%) in class 2 A, 42 (19,0%) in class 2 B, 27 (12,2%) in class 3 and 8 (3,6%) in class 4 (Figure 10).

Figure 10: Infection classes (%)



The number of patients was lower in class 1 compared to the classes 2 and 3.

Cases classified as class 1 infections were statistically significantly longer hospitalised than other forms (p=0,046). The average duration of hospitalisation was longest in class 1 (14,5 days ± 7,26

days SD) and shortest in class 2A (11,1 ± 6,09) (p=0,005). (Table 7: Comparison of mean length of admission according to infection class (days)) and Figure 11)

Table 7: Comparison of mean length of admission according to infection class (days)					
Class 1	***Class 2 a***	***Class 2 b***	***Class 3***	***Class 4***	***Overall***
14,5 ± 7,26	11,1 ± 6,09	11,7 ± 9,11	13,3 ± 11,2	13,0 ± 9,04	12,3 ± 7,9 days

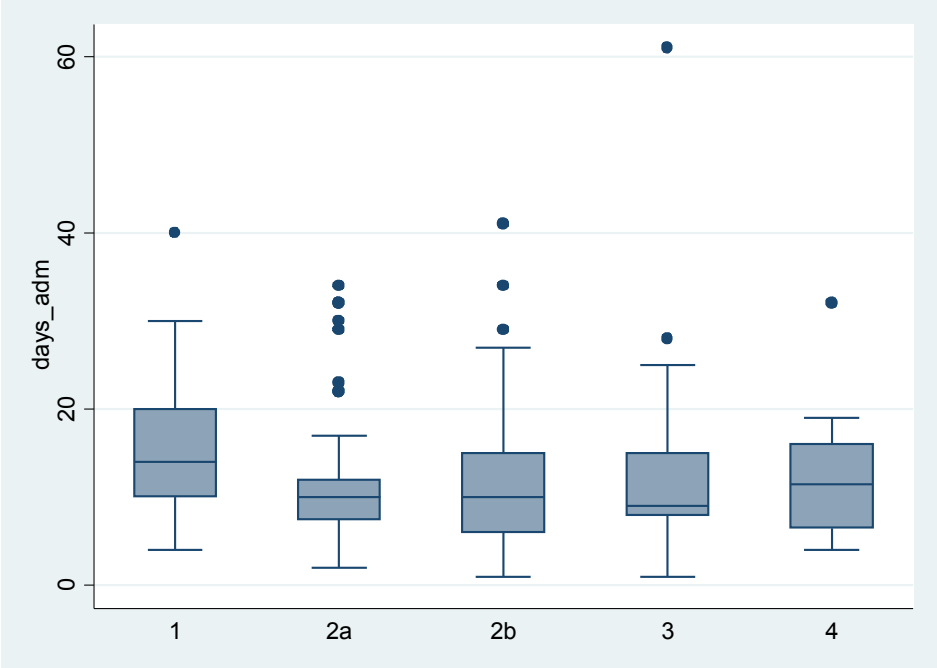


Figure 11: Infection classes correlated with Length of admission.

Patients stratified by most frequent co-morbidities

Prolonged hospitalisation was significantly correlated with arterial hypertension (p<0,0001), atrial arrhythmia (p=0,0054) and thyroid disease (p=0,0081), whereas it did not correlate with hypercholesterinaemia (p=0,6486), chronic heart (p=0,2068) or kidney disease (p=0,1303).

Patients stratified by risk factors

Length of hospitalisation increased in significant correlation with obesity (p<0,0001), diabetes mellitus (p<0,0001) and leg or foot ulcers (p=0,0001). It did however not correlate with tinea pedis (p=0,5965), overweight (p=0,7694), immunosuppression (p=0,6289), varicosis (p=0,8804), trauma or surgery (p=0,7185).

3.4.b Complications

40 patients (18,1%) experienced complications. Of these 22,5% were local complications, 40% were systemic and 45% were documented as related to therapy. The sum of these percentages is more than 100%, because in some of these patients more than one complication was present. The

most frequent complications observed were antibiotic skin reactions (mainly macular-papular rash or urticaria) in 16 cases (7,2%) and liver enzyme elevation in 11 (4,9%) cases. Approximately 10,1% of the patients required surgical debridement, 1% of patients developed sepsis and the mortality rate was below 1%.

3.4.c Mortality

Overall, the observed mortality rate was low, but unfortunately, for two of our patients the disease proofed fatal (0,9%). Both were elderly, presented with multiple co-morbidities and/or risk factors and were treated with various antibiotic regimens. Microbial identification could only be achieved in one case where it proofed to be S. aureus. Their characteristics are listed in Table 8.

Table 8: Mortality (Patients' characteristics)

Age / Sex	Comorbid conditions	Infection class	Identified microbe	Therapy (1st, 2nd, 3rd line)	Cause of death	Time to death (days)
89 / ♀	Arterial Hypertension, Ulcus cruris	4	S. aureus	1. Clin 2. Fos +Ave+Flo 3. Taz	refused amputation, acute renal failure and septic shock	15
80 / ♂	Arterial Hypertension, CKD, CHD, Tinea pedis, Obesity	4	none	1. Pen G 2. Clin + Ave	underlying disease	6

Abbreviations: Ave (Avelox), CHD (chronic heart disease), CKD (chronic kidney disease), Clin (Clindamycin), Flox (Floxapen), Fos (Fosfomycin), Pen G (Penicillin G), Taz (Tazonam)

3.5 Complicated Clinical Forms

All forms of complicated SSTIs lead to a prolonged hospitalisation as shown in Table 9: Comparison of length of admission (days).

Table 9: Comparison of length of admission (days)

General cohort	Recurrent cases	Bullous form	Haemorrhagic form
12,3 ± 7,9	15,5 ± 8,6	14,2 ± 6,34	15,8 ± 9,3

We took a closer look at the patients who presented either with relapse, bullous or haemorrhagic cellulitis. Their characteristics are shown in Tables 10 and Figure 11.

3.5.a Recurrence

46 patients (20,8%) relapsed in total. Such patients were older (average of 4 years), needed approximately 3 more days of admission and presented with a higher class of infection than the general study population. They also showed a higher percentage of most risk factors. Adjusting for age, sex and smoking habits, only obesity was significantly associated with recurrence, obese patients were two and half times more at risk of recurrence than other patients (OR=2,55, 95% CI: 1,03-6,30, p=0,04). Overweight (BMI between 25 and 30) and atrial arrhythmia were associated with a higher risk of recurrence as well, but statistical significance was not achieved (p=0,075 and 0,190, respectively).

Table 10: Characteristics of 46 patients who presented with relapsed SSTIs

Characteristic	No. (%)	overall	Characteristic	No. (%)	overall
Age in years (mean ± SD)	65,2 ± 11,4	61,2 ± 18,1	Most common risk factors		
Sex			Obesity (BMI>30)	21 (45,7)	77 (34,8)
Female	28 (60,89)	117 (52,9)	Fungal foot infection	12 (26,1)	55 (24,9)
Male	18 (39,1)	104 (47,1)	Diabetes mellitus	12 (26,1)	51 (23,1)
Mean length of stay (days)	15,5 ± 8,6	12,3 ± 7,9	Overweight (BMI<30)	12 (26,1)	49 (22,2)
Infection class			Scars	9 (19,6)	30 (13,6)
Class 1	1 (2,2)	49 (19,9)	Chronic venous insuffi-ciency	9 (19,6)	20 (9,1)
Class 2 a	22 (47,8)	95 (43)	Surgery	7 (15,2)	28 (12,7)
Class 2 b	10 (21,7)	42 (19)	Ulcus cruris	6 (13)	20 (9,1)
Class 3	9 (19,6)	27 (12,2)	Liver cirrhosis	5 (10,9)	20 (9,1)
Class 4	4 (8,7)	8 (3,6)	Varicosis	4 (8,7)	19 (8,6)
Abbreviations: MCI (Myocardial infarction), PAE (Pulmonary artery emboly), PAOD (Peripheral arterial obstructive disease), PTCA (Percutaneous transluminal coronary angioplasty), TEP (total endoprothesis), TIA (Transient ischaemic attack)			PAOD	4 (8,7)	17 (7,7)
			Immunosuppression	2 (4,3)	19 (8,6)
			Peripheral neuropathy	2 (4,3)	9 (4,1)
			Chronic light damage	2 (4,3)	8 (3,62)

3.5.b Bullous & haemorrhagic cellulitis

Approximately 16,3% of our patients were diagnosed with a hemorrhagic or bullous form of cellulitis with a mean length of admission of 17,4 days compared to 11,1 days in patients with uncomplicated forms of SSTIs (p=0,02). 25 cases (11,3%) presented with a haemorrhagic, 6 (2,7%) with a mixed bullous-haemorrhagic and 5 (2,3%) with a bullous form of cellulitis. The mixed form was more frequent in women (83,3%), while the sole presentation of either bullous (80%) or haemorrhagic (56%) forms were more often observed in men. There was a statistically significant

increase of length of admission as well in bullous and/or haemorrhagic cellulitis (15,6 ± 8,8 SD) as in cellulitis with abscesses (12,9 ± 8,2 SD) compared to the simple cases of cellulitis (11,4 ± 7,5 SD) (p=0,048). (see Figure 7, p.17)

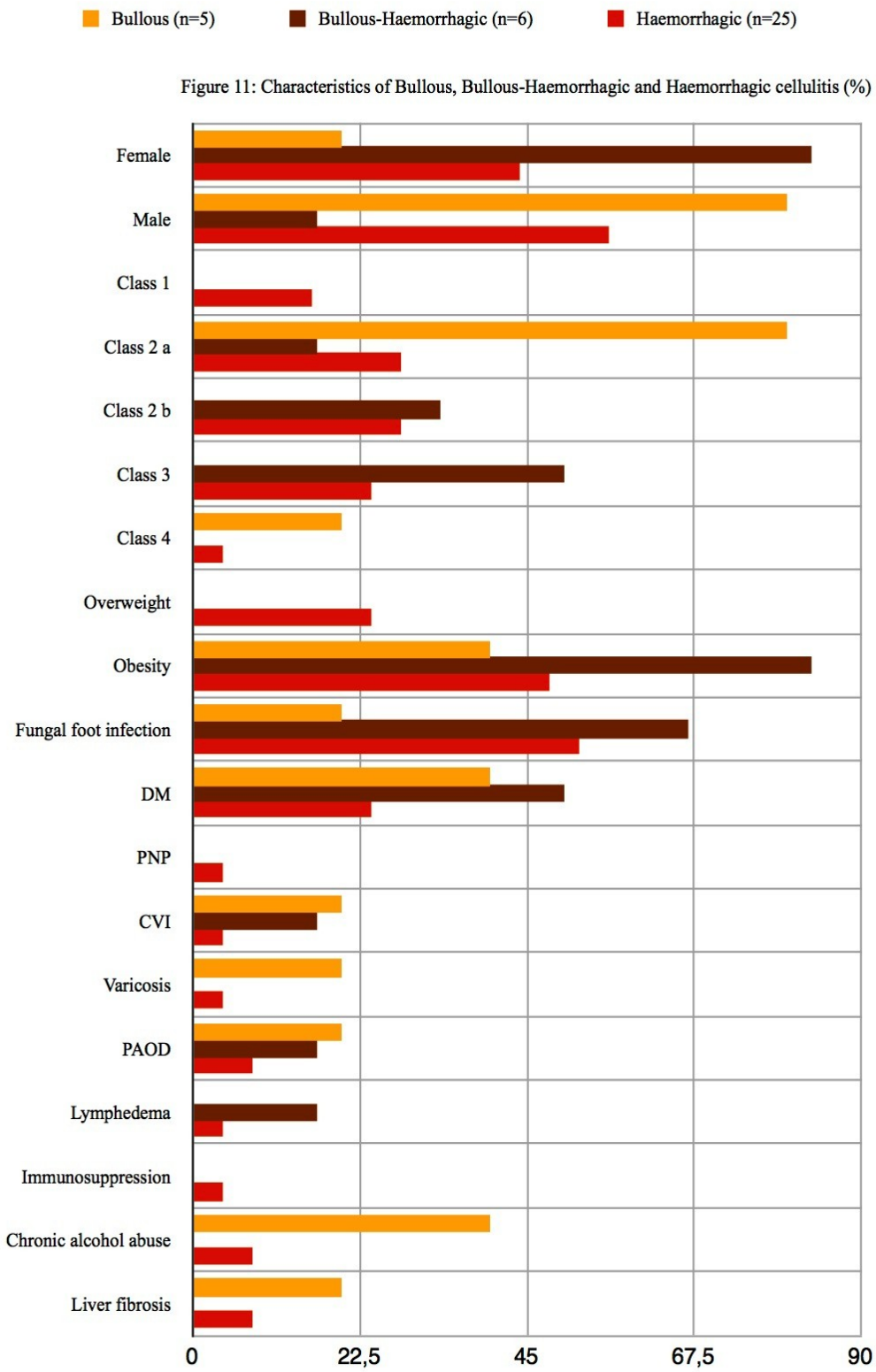


Figure 11: Characteristics of Bullous, Bullous-Haemorrhagic and Haemorrhagic cellulitis (%)

4. Discussion

SSTIs constitute a large portion of cases in the dermatological setting. There were 354 admissions to the wards of the Department of Dermatology and Venerology of the Medical University Graz with the diagnosis of SSTIs in 2009, this approximates 10% of total admissions. These numbers correspond with those of other tertiary referral centres in Austria. This underlines the importance of SSTIs in the dermatological field and emphasises the importance of these diseases not only to dermatologists but also in other fields such as internal medicine, surgery and infectious diseases.

Our study shows a comprehensive summary of a big cohort of patients, their demographics and the treatment schedules.

We decided to use the length of admission as a prognostic marker together with the rate of complications in order to categorise our patients and analyse their outcomes. The mean length of admission in the whole study population was 12,3 ± 7,9 days.

During our investigation, we were able to discern certain key variables of our patient population. The average age was 61,2 years ± 18,1 and the ratio between men and women was 47,1 : 52,9. The most common risk factors and co-morbidities were obesity, diabetes mellitus, venous ulcers in the lower extremity, arterial hypertension, atrial arrhythmia and thyroid diseases.

The only variables significantly associated with an increase in the days of admission were (adjusted for age, sex and smoking habits):

- Chronic lower extremity ulcer: mean increase of 7 days;
- Bullous and/or haemorrhagic infection type (compared with erysipela): mean increase of 5 days;
- Thyroid disease: mean increase of 5,5 days;
- Obesity: mean increase of 3,6 days.

The rate of microbial identification in the studied population was low (18,6%), because skin biopsies were not regularly performed in patients affected with cSSTIs and deep punctures were carried out only in the case of abscess or when there is a suspect of purulent material. In most of the cases, invasive procedures like these in order to isolate the pathogen were not performed at the time of initial diagnostics and treatment. The most commonly isolated species, were *S.aureus* (39%), *P.aeruginosa*, *E.coli* (each 17,1%), *Pr.mirabilis* (12,2%), *S.pyogenes* and *Enterococcus* spp. (each 4,9%).

A high incidence of stable risk factors and/or co-morbidities was observed between recurrent cases and the general study population, that can be treated only with the compliance of patients to adjuvant therapies.

In our cohort of patients, 49 cases (20%) were classified as class 1 according to the modified Eron classification. We were very surprised about the fact, that patients with class 1 infections were

hospitalised longer (14,5 ± 7,26 days) than those within classes 2A, 2B and 3 (11,1 ± 6,09, 11,7 ± 9,11 and 13,3 ± 11,2 days, respectively). We could discern that those patients were of younger age (44,9 years ± 21,8) and the gender ratio tipped towards the males (60%:40%). The site of infection was either in a high risk location (e.g. the face, hands or the anogenital region) or the patients showed diminished compliance to an oral administration of antibiotic agents and follow-up visits. We attribute the prolonged hospital stay in this group to the possible QOL-impairment due to the high risk location, combined with important psychosocial factors, such as stress and anxiety in a cohort of younger patients. (5)

Regarding further differences between the infection classes, we found, that the gender ratio tipped towards the males in class 1 and 4 (60% : 40% and 18,1% : 80,9% respectively) while females dominated the classes 2A, 2B and 3 (56,3% : 43,7%, 58,1% : 41,9% and 64,3% : 35,7%). The mean length of hospitalisation in the general cohort was 11,4 ± 8,1 days for men and 13,1 ± 7,7 days for women. While lower extremity SSTIs were the major site of infection in both sexes and all classes, we could distinguish that women were more prone to facial SSTIs, while men showed tendencies towards upper extremity and anogenital infections. In class 2B we showed, in accordance with clinical experience, that women were afflicted more frequently with obesity and lower extremity ulcers (60% : 24% and 12% : 6%, respectively).

Many of our findings were similar to other studies regarding the site of involvement, co-morbidities, risk factors, mean length of hospital admission and type of systemic antibiotics used, however there were some differences. The average age was 61,2 ± 18,1 years compared data reported by Carratala et al. (59,7 ± 16,7 years), Figtree (70,6 ± 18,8 years), Leclerc (62 years) and Pavlotsky (58,5 years). Men and women were equally (47,1 : 52,9%) affected, but female sex was associated with longer hospitalisation. Carratala et al. reported a similiar ratio (48 : 52%) as did Figtree et al. (43 : 57%), while the findings of Leclerc et al. (26 : 21%) and Pavlotsky et al. (53,1 : 46,9%) were reversed. (5-7,20,22)

In terms of microbial aetiology, *S.aureus* was the most often confirmed microbial specimen in our patient cohort (39%). This is in accordance with the data presented by Carratala et al. (35,9%), Figtree et al. (69,1%) and Ki and Rotstein (45,9%) (5,20,22). *P.aeruginosa* was the second most often confirmed microbial specimen (17,1%). This is in accordance with the data from the SENTRY programme presented by Moet et al. (12% in Europe) as well as the data by Ki and Rotstein (10,8%) and Carratala et al. (10,2) (5,20,23).

We did not find any cases of MRSA in our cohort of patients, only in one case resistance to penicillin, ampicillin and amoxillin combined with clavulanic acid was shown. Two out of seven (28,6%) *P.aeruginosa* infections were multi-resistant.

We found *S.pyogenes* in only 4,9% of all collected microbial samples. Ki and Rotstein and Moet et al. described corresponding numbers (2,3% and 4,7% in Europe, respectively), while Carratala et al. and Figtree et al. presented significantly higher figures (17,2% and 29,5%, respectively). This is curious, because in the literature, group A streptococci are the most often mentioned causative agents (5,11,19,20,22-24).

Our low detection rate might have been due to the fact, that streptococci are usually not found in swabs and blood cultures and punch biopsies would need to be performed to get a positive deep tissue sample. Such were not performed at the time of initial diagnosis and treatment. With swabs, it is easier to isolate staphylococci from open skin lesions, such as wounds, ulcers and chronic cutaneous conditions as maceration associated with tinea pedis.

Obesity appears as the only significant factor associated with risk of recurrence, as was shown in our cohort of patients with relapsing SSTIs. It was found in 34,8% of our whole patient cohort, which is very high, compared to the findings of other studies, i.e. Figtree et al. 6,8%, Carratala et al. 7% and Pavlotsky et al. 14,2. It is noteworthy, that Pavlotsky et al. did not differentiate between overweight (BMI between 25 and 30) and obesity, as we did. Leclerc et al. reported it in all of their patients, but those presented all with at least their first episode of recurrence (6,7,20,22).

Diabetes mellitus was found in 23,1% of our patients, which is similar to the range of 18,2% to 25% reported by other researchers, such as Leclerc et al., Pavlotsky et al., Carratala et al. and Figtree et al. The same was true for peripheral arterial occlusive disease (PAOD) (7,7% compared to 4,4%-15,4%), immunosuppression (8,6% compared to 3-21,3%) and venous ulcers (9,5% compared to 6,2%-33,7%). (6,7,20,22)

In contrast to the studies performed by Leclerc et al., Pavlotsky et al., Carratala et al. and Figtree et al. we encountered chronic venous insufficiency (CVI) (9,1% compared to 11,8%-44,7%) and chronic heart disease (CHD) (9,9% compared to 11-27,2%) less often. (6,7,20,22)

The main complications observed in our cohort of patients were related to antibiotic skin reactions (7,2%; mainly maculo-papular rash). Skin rash as a form of adverse reaction to antibiotics has not been documented in previous studies, probably because they had not been performed in dermatological wards. Liver enzyme elevation occurred in a considerable number of cases (4,9%), which lead to discontinuation of the causative antibiotic treatment. If there was still the need for an antimicrobial regimen, the caregiving physicians switched to next line of antibiotic treatment. An increase in similar adverse reactions has been pointed out by Eisenstein. Finch et al. noted as well, that last line antibiotics, such as vancomycin and others can lead to potentially dangerous events, e.g. nephrotoxicity. Sepsis was rarely seen in our cohort of patients (0,9%), in contrast to a range of 1,5-5,1% reported by previous similar studies followed in internal medicine and surgical divisions. This might have been due to class 3 and 4 patients being rushed to the ICU or surgical department,

which could have created a virtual bypass around a necessary dermatological consultation. For instance, Pavlotsky et al., who performed a study on 574 patients with recurrent SSTIs in a dermatological setting, also reported a sepsis rate of 0,9% in their patient-cohort. (2,5-7,20,22,25)

The mortality rate in our patient cohort was lower than in previous studies: 0,9% compared to 1,7% (Musette et al.), 2,5% (Carratala et al.) and 5% (Figtree et al.), showing a more favourable prognosis. This may have been related to an earlier diagnosis, because of higher diagnostical skills of dermatologists in skin related disorders. (20,22,26)

Due to the retrospective nature of our study, we had to rely on preexisting data, which had been obtained to diagnose, admit and treat patients. Because of this, we had to superimpose our objective stratification on subjectively written patient information, which showed a great variety of quality and quantity. It was impossible to attain missing informations when we performed the primary investigation of patient data several months later. For instance, patients‘ smoking habits had not been documented in all cases at the time of admission. The missing statistical significant difference between smokers, ex-smokers and non-smokers could have been due to that fact and was therefore - regrettably - not deemed viable information.

The insignificant correlation of immunosuppression with prolonged hospital stay may be due to the fact, that we did not distinguish between different classes of immunosuppression, e.g. the concurrent administration of systemic corticosteroids, methotrexate, cyclosporine or underlying immunodeficiencies such as acquired immunodeficiency syndrome (AIDS).

Another problem was the impossibility to attain the patients‘ data once they had been transferred to other services, e.g. internal medicine, surgery or the ICU, without violating the ethical committee agreement concerning sensible data. We were allowed only to investigate patient files from the dermatology department and not, for example, from the surgical department. The same occurred concerning in-hospital consultations of the dermatological service by other departments. Those were still, for instance, surgical patients and we were not given access to their files.

The significantly prolonged hospital stay of class 1 SSTI patients, in comparison to other classes, was probably caused by those patients in other classes, who were only admitted to the ward for one or two days and were either discharged early because of instant improvement or who had to be transferred to another service, i.e. surgery, internal medicine or the ICU, or who were lost to follow up for other reasons. Similarly, we expected a bigger difference in the length of hospitalisation of the classes 2A and 2B in comparison to 3 and 4. The only slightly prolonged length of admission in the latter two classes, which are defined as more complicated by the Eron classification, surprised us. Sooner referrals to the other aforementioned specialities could have been the reason for this. This major bias could be due to the non-selective approach to the patient-cohort, because the main inclusion criterion was the diagnosis „erysipela“ and not the outcome itself, which had often not

been documented. It may well be, that patients with class 1 infections represent the typically inhomogenous patient population of SSTIs. And thirdly, there may be a problem with the Eron classification being used on patients diagnosed in German-speaking countries. This results from the missing differentiation of SSTIs into „erysipela“ and „cellulitis“ in the German language. The former is considered a superficial and the latter a deeper form of infection, and therefore more likely complicated, form in anglo-american countries.

Closing remarks

In retrospect, whenever one or more additional conditions exist, e.g. Obesity, diabetes mellitus or leg ulcers, which may delay the recovery of the patient, the case should be considered as complicated SSTI. Hemorrhagic and bullous forms of cellulitis should always be classified as complicated and particular attention should be paid to patients with systemic signs and symptoms. Hospital admission has to be considered in patients with complicated SSTIs.

We could show, that class 2A infections constituted the major part of our study population. We also were able to show, that those patients were hospitalised for the shortest period of time in comparison to patients in other infection classes and despite the presence of various risk factors. Obesity was identified as a major risk factor in more than a third of our whole patient population and as the only risk factor, that lead to a statistically significant prolonged hospital stay. The mortality rate in our patient-cohort was below 1%, which is very low compared to previous studies, as we have shown. All this leads us to believe, that patients, who are afflicted with SSTIs, have a better prognosis if they are seen by a dermatologist.

Our hope is, that in the future, these findings can be incorporated into a database, which will offer reliable data to dermatologists, general practitioners, emergency care physicians and the scientific community on SSTIs.

The Eron classification proofed a useful and uncomplicated tool to stratify patients with SSTIs quickly and effectively. However, in our opinion it could be improved by adding the site of infection as a stratification criterion for different classes. Facial and hand SSTIs, for instance, should be considered automatically as class 2A, even if there are no other risk factors or co-morbidities present. Another possibility would be to assign specific factors to different infection classes. It stands to reason, that, if our findings should be made comparable with those of international researchers in the future, there is need of an internationally unified and validated classification.

Insufficient data access due to the limitations of the ethical committee agreement emerged as a problem regarding follow-up of patients, who had been transferred to other services, such as internal medicine, surgery or the ICU. In future study designs, access to patients‘ data should be granted

to researching scientists and students, as it does not create an ethical dilemma in our opinion, but would further the cause of scientific research and therefore, the quality of care given to our patients. In the future, we deem it necessary, that further investigation should focus on the outcome of patients with SSTIs as a main inclusion criterion to gain more precise data.

To guarantee an interdisciplinary approach to a patient‘s ailments and also in accordance with the biopsychosocial model[3] taught at the MUG, it is necessary to review SSTIs from a dermatological point of view, especially since, in German-speaking countries, these diseases are traditionally treated by dermatologists, while internationally they are usually seen, treated and therefore scientifically discussed by non-dermatologists.

During the work on this study, I experienced, how easily applicable clinical research can be, when you are working with patients on a day to day basis. For instance, the practicality of the Eron classification, helped me to develop an intuitive assessment of patients with SSTIs I was seeing on the ward. I also became aware, that medicine is not only about following algorithms, doctors also need to think about a case and in the best interest for the patient. This might seem obvious, but it was very surprising, how fast such a seemingly simple principle can be forgotten in everyday practice. While I was writing my thesis, my mentor, Giovanna Brunasso, taught me the importance of clear rules and an organised process in clinical research. If you have been focussing on a lot of details, it is important to take a step back from time to time and look a the bigger picture.

3 See http://en.wikipedia.org/wiki/Biopsychosocial_model (Access February 2nd, 2012).

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