IMPROVING OUTCOMES

for patients with

NECROTIZING SOFT TISSUE INFECTIONS

Femke Nawijn

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Improving outcomes for patients with necrotizing soft tissue infections

Het verbeteren van de uitkomsten voor patiënten met necrotiserende weke delen infecties

(met een samenvatting in het Nederlands)

Proefschrift

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te Amersfoort

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General introduction and thesis outline

Necrotizing soft tissue infections (NSTIs) are rare, invasive and life-threatening infections. Partly due to its rarity, these infections are currently underrepresented in international literature due to a lack of high-quality studies covering knowledge gaps regarding topics such as incidence, diagnostics options and treatment. NSTIs are notorious for their acute onset and rapidly spreading nature causing sepsis and necrosis of the fascia often extending into the skin, subcutaneous tissue and muscles [1-3].

Currently, NSTI is the internationally accepted umbrella term for these kind of necrotizing infections, but a broad range of other terms are still used, such as severe necrotizing soft tissue disease (SNSTD), the "flesh-eating infection" by layman's terms, Fournier gangrene if it affects the perineum or external genitalia, and the most commonly known term when the fascia is involved being necrotizing fasciitis [2-3]. The estimated incidences of NSTIs vary geographically from 1.3 cases per 100,000 person-year in New Zealand to 10.3 per 100,000 person-year in the United States to 32.6 per 100,000 person-years in Thailand [4-6]. However, these incidence studies on NSTIs are limited in numbers and no European incidence rates are known. Not only vary the reported incidence rates widely, but also reported mortality rates have a large variance, ranging from 0% to as high as 64% [7-10]. These extreme differences in reported incidence and outcomes, mostly based on relatively small (retrospective) cohort studies, makes it difficult to not only comprehend the exact size of the problem and consequences of NSTIs, but also makes it difficult to formulate and validate diagnostic and treatment algorithms and to provide patients with a realistic prognosis.

NSTIs are not only a medical problem of the modern times, but were already first described and studied by Hippocrates in the 5th century BC. He noticed the heterogeneity in presentation, which remains current since no pathognomic symptoms are known for NSTIs [11]. Edema, erythema and severe pain or tenderness (e.g. out of proportion and/or crescendo pain) are among the non-specific symptoms often seen upon presentation of NSTI patients, while only in a minority of cases skin necrosis, bullae or crepitus are seen [2,12,13]. The atypical presentation entails one of the biggest challenges for successful and timely treatment of NSTIs by causing high rates of mis- or delayed diagnosis allowing further spreading of the infection [14-16]. Some attempts were made to improve the diagnostic process for NSTIs, such as the Laboratory Risk Indicator for Necrotizing infections (LRINEC) score or the use of imaging techniques (e.g. computed tomography (CT) scans, magnetic resonance imaging (MRI) or ultrasound) to differentiate necrotizing soft tissue infection from non-necrotizing soft tissue infections [17-21]. However, subsequent studies validating these diagnostic options are scarce and report conflicting results.

Another diagnostic option recently proposed, is the use of intra-operative diagnostics during surgical exploration to confirm or rule out the diagnosis NSTI [22,23]. Patients with macroscopic signs of NSTIs upon surgical exploration, such as dishwater pus or grey necrotic tissue, undergo immediately surgical source control. On the other hand, patients without any distinct signs of NSTIs upon surgical exploration, will not undergo debridement and will be re-evaluated very closely, while the patients with ambivalent signs, such as perifascial edema, might undergo adjunct intra-operative diagnostic tests [22]. However, this technique of triple diagnostics (macroscopic evaluation followed by, if needed, a Gram stain and frozen section) has not yet been rigorously investigated and the use of frozen sections for NSTIs is often deemed impractical [22,24,25]. Due to this sparsity of studies assessing the diagnostic process of NSTIs and the conflicting results, no substantial advancements in the diagnostic process have been made in the past decade and the discussion on adjuncts for diagnosing NSTIs remains ongoing.

On the other hand, not much discussion exists surrounding the well-established belief that prompt source control by resection of all infected and necrotic tissue reduces further progression of the infection and therefore reduces mortality rates [13,25-27]. The initial treatment of NSTIs consists of three vital pillars that all need to be initiated immediately and simultaneously: 1) start broad-spectrum intravenous antibiotics (most commonly a combination of β-lactam antibiotics, clindamycin and gentamycin), 2) adequate resuscitation if the patient is septic and 3) emergency surgery for source control [3,25,27]. Currently, debridement within 12 hours after presentation is advised in international guidelines, which supports the longstanding assumption that “time is fascia” [25,26]. However, the exact time frame in which the surgical treatment should be initiated to obtain the most optimal outcome is still unsure. Nevertheless, NSTI is considered a time sensitive disease, which requires diagnosis and treatment as soon as possible. As in most time sensitive emergency surgical diseases, treatment of NSTIs should focus on four primary outcomes which are prioritized as follows:

1) Survival
2) Limb salvage
3) Optimization of cognitive and physical function (quality of life)
4) Optimization of (objective and subjective) aesthetics

This thesis investigated all these NSTI outcomes, but mainly focusses on the first two priorities, being survival and limb salvage, as they are inevitable necessities to achieve any functional and aesthetic outcomes. This resulted in the aim of this thesis to gain insight in how outcomes (e.g. mortality, quality of life) of NSTIs can and

should be improved by increasing knowledge of the incidence, diagnostic options, importance of time and factors influencing these outcomes of NSTIs.

Thesis outline

Within the first three chapters the consequences in terms of mortality and morbidity of NSTIs in the Netherlands are outlined. First, in chapter 2, the population-wide incidence and mortality rate of NSTIs in the Netherlands were evaluated by combining nationwide databases and previously published Dutch studies. In chapter 3 the cause of death in NSTI patients and the factors associated with mortality stratified by pre-existing physical status were investigated to gain knowledge on how the mortality rate can further be reduced and to which extent comorbidities impact outcome. Chapter 4 focusses on the differences in mortality caused by difference in causative micro-organisms of the NSTI. This chapter also describes the hypothesis of an exhaustion of the immune system by a common causative micro-organism of NSTIs in the Netherlands, the Group A Streptococcus.

The following two chapters investigates potential improvements for the NSTI diagnostic process. Chapter 5 illustrates a potential adjunct to the diagnostics tools for diagnosing NSTIs, being intra-operative assessed frozen sections as part of the triple diagnostics approach (macroscopic evaluation, Gram stain and frozen section) for ambivalent NSTI cases. Subsequently, the added value of the implementation of this triple diagnostics approach for NSTI patients is discussed in chapter 6.

The importance of early diagnosis to facilitate prompt surgical treatment is further evaluated in the meta-analysis in chapter 7 by identifying the most optimal time between presentation and the initial debridement to reduce mortality. The essence of time was further investigated in chapter 8 by evaluating if the principles of damage control surgery are applicable to NSTIs by investigating if the operative time influences outcomes.

Next, the factors influencing all four of the primary outcomes of NSTIs are outlined, while focusing on a specific subtype of NSTIs to limit heterogeneity within the NSTI population, being NSTIs of the upper extremity. Chapter 9 describes the factors associated with short term outcomes (mortality and amputation), while chapter 10 describes the long-term outcomes (long term survival, quality of life and content with aesthetics of wounds) of NSTIs affecting the upper extremity.

Finally, chapter 11 outlines one of the important remaining knowledge gaps. It focuses on the heterogeneity in presentation of NSTIs and the potential pitfalls entailing from unawareness of this matter. Both types of presentation, the critically ill patient with evident pain out of proportion, erythema, necrotic skin and bullae as

well as the patient with nonspecific symptoms without systemic toxicity at presentation should be diagnosed and treated equally efficient to ultimately optimize outcome of all NSTI patients.

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2

Incidence and mortality of necrotizing fasciitis in the Netherlands: the impact of Group A Streptococcus

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Abstract

Purpose: To gain insight in the incidence of necrotizing fasciitis in the Netherlands and the associated mortality and health care burden.

Methods: This nationwide retrospective database study used three distinct data sources to map the incidence of necrotizing fasciitis in the Netherlands between 2014 - 2019, being data from the Dutch Hospital Data (DHD) foundation, data from Osiris-AIZ, which is a database of notifiable diseases managed by regional Public Health Services (GGD) and the National Institute for Public Health and the Environment (RIVM), and previously published studies on necrotizing fasciitis conducted in the Netherlands.

Results: The incidence of necrotizing fasciitis in the Netherlands is estimated to be approximately 1.1 to 1.4 cases per 100,000 person-years, which corresponds to 193 – 238 patients per year. Of all necrotizing fasciitis infections, 34% to 42% are caused by the group A Streptococcus. Annually, 56 patients die as a result of a necrotizing fasciitis infection (mortality of 23 – 29%) and 26 patients undergo an amputation for source control (11 – 14%). Patients stay a mean of six to seven days at the intensive care unit and have a mean hospital length of stay of 24 to 30 days.

Conclusion: The combination of nationwide databases provides reliable insight in the epidemiology of low-incidence and heterogenic diseases. In the Netherlands, group A streptococcus was the most common causative micro-organism of necrotizing fasciitis. Necrotizing fasciitis is associated with substantial morbidity and morbidity, risk at amputation and health care burden characterized by prolonged ICU and hospital stay.

Introduction

Necrotizing fasciitis is a rare, bacterial infection of the fascia, characterized by rapidly progressive soft tissue necrosis and (impending) sepsis [1]. Umbrella terms such as necrotizing soft tissue infections (NSTI) or severe necrotizing soft tissue disease (SNSTD) are becoming more commonly used terms to denote necrotizing fasciitis, but also refer to other necrotizing infectious diseases such as gas gangrene, necrotizing cellulitis, necrotizing myositis and combination diseases. However, necrotizing fasciitis remains the most notorious and most common form of a NSTI [2,3]. The mortality rate of these NSTIs declined by almost half since the beginning of the 21st century compared to the 20th century, however, the mortality rate remained stable around 20% during the past two decades [4]. Achieving further decrease in mortality rates still seems to be limited by delay in diagnosis and therefore treatment [2,4,5]. Timely diagnosis is especially difficult due to the low incidence of necrotizing fasciitis and its heterogeneous presentation [6–8].

These same factors of heterogeneity and low incidence also hinder the conduct of sufficiently powered and generalizable studies to gain knowledge into how timely diagnosis and treatment can be improved.

On one hand, available studies on necrotizing fasciitis are often small single or multicenter (retrospective) cohort studies performed by institutes with particular interest in the disease. This might introduce selection bias with potentially relatively higher incidences and lower mortality rates (due to extra awareness and special interest).

On the other hand, to gain true insight in the incidence of this rare disease, nationwide studies might provide more accurate information, However, most of these studies are based on only one nationwide database, most often an hospital imbursement database, and are mostly conducted in Asia or the United States [8–10]. It is difficult to interpreter such large, nationwide, finance-based databases as, for example, there is a risk of over- or underreporting and heterogeneity in registration of the data. There are a few studies available that have reported the incidence of necrotizing fasciitis: 0.86 cases per 100,000 person-years in South Korea, 1.3 cases per 100,000 person-years in New Zealand and 4 to 10.3 cases per 100,000 person-years in the United States [6–8,11]. These incidence rates are not directly applicable to the Netherlands, due to known geographic heterogeneity in causative micro-organisms involved in necrotizing fasciitis infections and the corresponding differences in, for example, age distribution and mortality [12–18]. Therefore, the incidence of necrotizing fasciitis in the Netherlands remains uncertain, resulting in the aim of this study to map the incidence, mortality rate and hospital course of necrotizing fasciitis infections in the Netherlands by using

different types of nationwide databases, a hospital imbursement database and a notifiable diseases database, and previous published cohort studies conducted on necrotizing fasciitis in the Netherlands to enable correcting for over- and underreporting of each source.

Methods

To map the nationwide incidence of necrotizing fasciitis in the Netherlands, three distinct data sources were used, being (1) data from the Dutch Hospital Data (DHD) foundation, (2) data from Osiris-AIZ, which is a national database of notifiable diseases managed by regional Public Health Services (GGD) and the National Institute for Public Health and the Environment (RIVM), and (3) previously published studies on necrotizing fasciitis conducted in the Netherlands (Table 1) [12–14].

The DHD foundation registers data from all (both peripheral and academic) hospitals with an emergency department in the Netherlands by using a standardized diagnosis- and procedure thesaurus, directly linked to hospital imbursement systems, with as aim to support health care quality, decision-making and management. From the DHD foundation, the number of registered necrotizing fasciitis patients (based on international classification of Diseases (ICD) 9 and 10 codes and procedure codes, protocol available upon request at DHD foundation) within the Netherlands between January 1st, 2014, and December 31st, 2019, were obtained, including the frequency in which mortality and amputations occurred, the number of operative procedures, and the length of hospital and intensive care (ICU) stay. Importantly, the data from the DHD foundation might overestimate the incidence, considering that transferred patients might be registered in duplicate in the database (this cannot be corrected for, since the data supplied by the DHD foundation was aggregated and pseudo-anonymized).

In the Netherlands, invasive group A streptococcal (GAS) infections are notifiable diseases which have to be reported to and registered by the GGD in the national Osiris-AIZ database managed by the RIVM. For this study, all reported GAS necrotizing fasciitis cases between January 1st, 2011, and December 31st, 2019, were requested, including age distribution of the patients and registered mortality. The registered mortality in Osiris-AIZ is commonly underreported since it is not obligatory for health care workers to report if a patient died after the notification of the infection has already been made. Furthermore, the GGD of the region Utrecht was asked for the registered cases of GAS necrotizing fasciitis within the same time period, including year of notification, patient's age at time of diagnosis and notifying hospital. These extra variables are not registered within the national Osiris-AIZ database. By obtaining these variables, the patients reported to the GGD in the region Utrecht could be matched to a previous by our own study group published

Table 1 Data sources used to gain insight in the incidence of necrotizing soft tissue infection in the Netherlands

Database	Obtained information	Period
Dutch Hospital Data (DHD) Foundation		
	All necrotizing fasciitis cases registered based on International Classification of Disease (ICD) 9 and 10 diagnosis and procedural codes in this nationwide registry linked to hospital imbursements systems, including data on mortality rates, amputation rates, number of operative procedures, length of intensive care unit stay and length of hospital stay	January 2014 – January 2020
National Institute for Public Health and the Environment (RIVM)		
• Osiris-AIZ	Nationwide registry containing all cases of notifiable diseases registered anonymously by the regional public health services (GGD), including GAS necrotizing fasciitis cases and the associated mortality per age category	January 2011 – January 2020
• Regional Public Health Services (GGD) of the Utrecht region	Number of registered Group A Streptococcal necrotizing fasciitis cases within the region of the GGD Utrecht, including year of notification, patient's age at time of diagnosis and notifying hospital.	January 2009 – July 2016
Published Dutch retrospective databases		
• Nawijn et al. (2019)	Patients with necrotizing fasciitis presenting to two different hospitals within the region of Utrecht (one academic medical center and one large peripheral teaching hospital)	August 2002 – September 2016
• Van Stigt et al. (2016)	Patients with necrotizing fasciitis presenting to four different hospitals within the region on Gelderland (one academic medical center and three peripheral teaching hospitals)	January 2003 – December 2013
• Suijker et al. (2020)	Patients with necrotizing soft tissue infection presenting to a large academic medical center within Amsterdam.	2000 - 2012

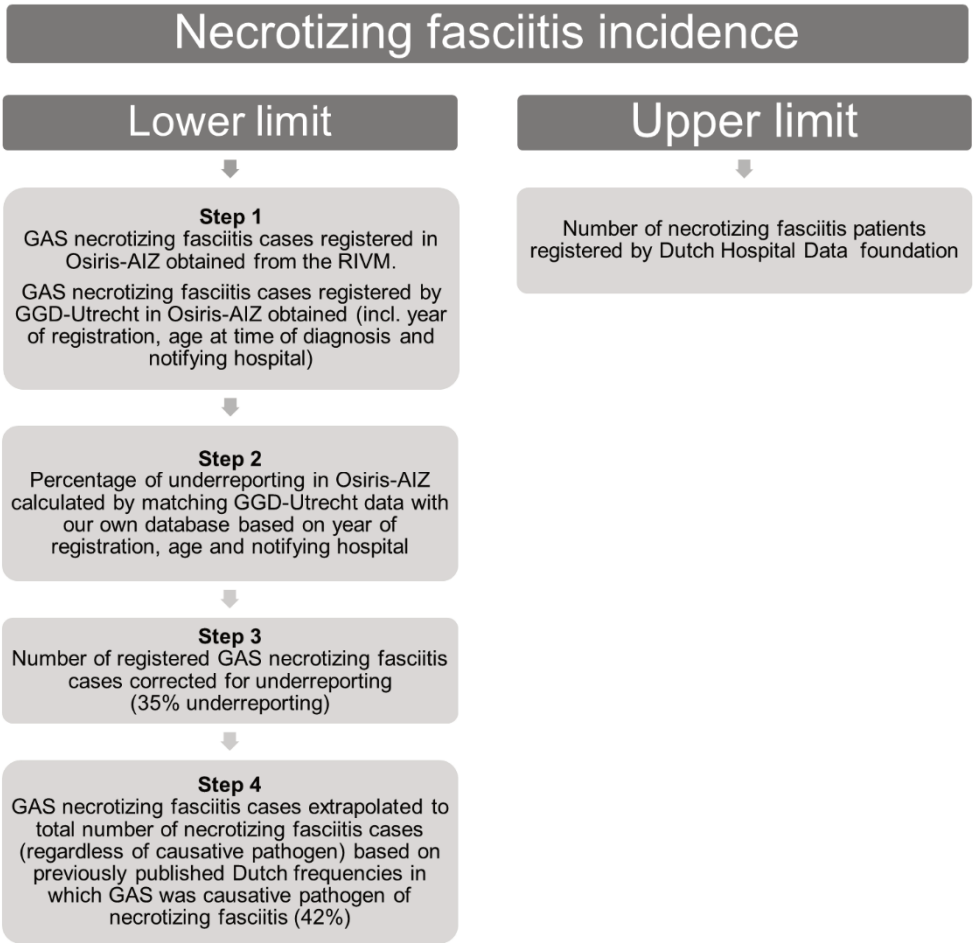

Figure 1 Methods used to map incidence of necrotizing fasciitis in the Netherlands
Legend: GAS = Group Streptococcal; GGD = Regional Public Health Services; Osiris-AIZ = nationwide database of notifiable infectious diseases managed by GGD and RIVM; RIVM = National Institute for Public Health and Environment.

database of necrotizing fasciitis patients between January 2002 and August 2016 performed at two of the hospitals within the same region (an academic hospital and a large peripheral hospital) to estimate the (in)completeness of the Osiris-AIZ database (step 2 of figure 1) [12]. This incompleteness was anticipated, since even though GAS necrotizing fasciitis is a notifiable disease, it is likely that in some cases the GGD was not notified. During this matching process, six patients were identified that were reported to the GGD of the region Utrecht, but were not included in our own database, and fourteen patients with GAS necrotizing fasciitis were included in

our own database but were not registered by the GGD. This resulted in a total of 40 registered, unique cases between 2011 and 2016 at the two study hospitals. To correct for this underreporting, the reported GAS necrotizing fasciitis cases were extrapolated using the estimated percentage of incompleteness of the Osiris-AIZ database (14/40 not reported to the GDD; 35% underreporting, 95% confidence interval (CI) 20 – 50%).

Due to the potential under- and overreporting within the different databases, the choice was made to present the Dutch incidence as an extreme estimate of the actual incidence of necrotizing fasciitis in the Netherlands. The upper limit of the estimated incidence is based on the data from the DHD foundation. The lower limit is based on the data from Osiris-AIZ corrected for the estimated incompleteness of the database and extrapolated to all necrotizing fasciitis cases (regardless of the causative micro-organism) based on previous published studies reporting frequencies in which GAS was the causative micro-organism of necrotizing fasciitis in the Netherlands (overall 42%, 95% CI 34 - 49%) (Step 3 and 4, Figure 1) [12–14].

To illustrate the age distribution of reported GAS necrotizing fasciitis cases, the age distribution was standardized to the age distribution in the Netherlands using the population age distribution from the Dutch Central Bureau for Statistics, illustrating the incidence of GAS necrotizing fasciitis cases per 100,000 person-years per age category [19]. Dichotomous variables were analyzed using the Fisher's exact test. For all analyses, a two-sided *p*-value <0.05 was considered statistically significant. Data were analyzed using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

Estimated incidence

The incidence of necrotizing fasciitis in the Netherlands is estimated to be approximately 1.1 to 1.4 cases per 100,000 person-years, which corresponds to 193 – 238 patients per year in the Netherlands (Table 2 and Figure 2). Per year, 81 of these patients had necrotizing fasciitis caused by GAS (34 – 42%), with a peak in incidence within the age category of 65 years and older (Table 3 and Figure 3). The DHD foundation data showed that most necrotizing fasciitis patients were treated in peripheral hospitals (81% of all registered patients), however, it is with the currently available information unknown how many patients of those patients were transferred to academic (in case of critical illness) or burn centers (in case of extensive reconstructions).

Table 2 Incidence, mortality and health care burden of necrotizing fasciitis in the Netherlands (2014 – 2019)

Year	Number of necrotizing fasciitis cases[a]	Mortality[b]	Amputations[b]	Number of operative procedures[b]	Length of ICU stay in days[b]	Length of hospital stay in days[b]
2014	185 - 205	46 (22 - 25%)	19 (9 - 10%)	346	1029	4600
2015	179 - 234	61 (26 - 34%)	30 (13 - 18%)	416	1122	5967
2016	205 - 236	51 (22 - 25%)	23 (10 - 11%)	429	1463	5945
2017	245 - 256	62 (24 - 25%)	24 (9 - 10%)	522	1394	6097
2018	155 - 243	62 (26 - 40%)	42 (17 - 27%)	470	1416	5589
2019	186 - 252	53 (21 - 28%)	19 (8 - 10%)	468	1420	5885
Total	1155 - 1426	335 (23 - 29%)	157 (11 - 14%)	2651	7844	34083
Yearly average	193 - 238	56 (23 - 29%)	26 (11 - 14%)	442	1307	5681
Average per patient	NA	NA	NA	1,9 – 2,3	6 - 7	24 – 30

ICU = Intensive Care Unit. Data sources: [a] Lower limit based on cases registered in Osiris-AIZ, on cases registered by the GGD Utrecht combined with previous Dutch retrospective databases, upper limit based on data from the Dutch Hospital Data (DHD) Foundation; [b] DHD Foundation

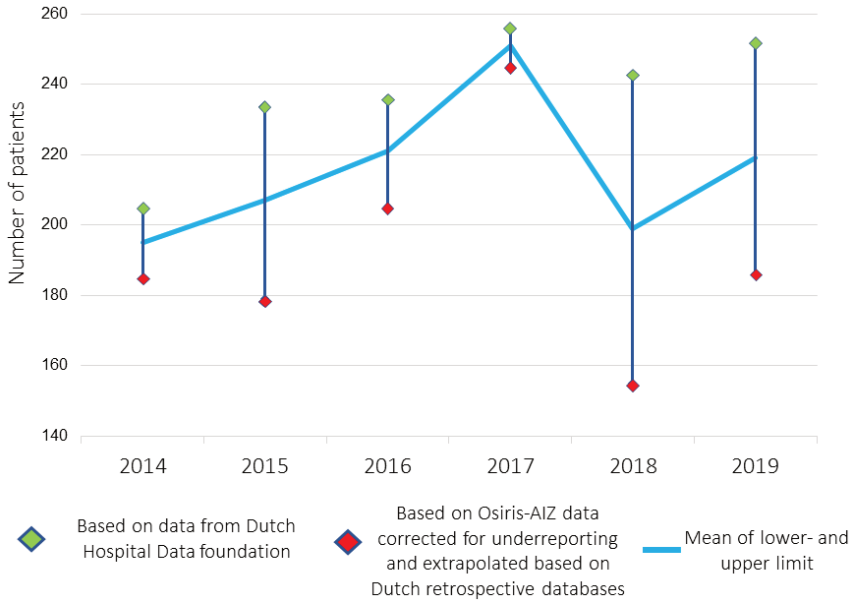

Figure 2 Incidence of necrotizing fasciitis in the Netherlands (2014 – 2019)

Table 3 Incidence and mortality of (non-) Group A Streptococcal necrotizing fasciitis in the Netherlands (2014 – 2019)

Year	Number of necrotizing fasciitis cases[a]	GAS necrotizing fasciitis cases registered in Osiris-AIZ[b]	Number of GAS necrotizing fasciitis cases corrected for underreporting [c]	Number of non-GAS necrotizing fasciitis cases[d]	Overall mortality[e]	Mortality of GAS necrotizing fasciitis registered in Osiris-AIZ[b]	Mortality of GAS necrotizing fasciitis corrected for underreporting[c]	Mortality of non-GAS necrotizing fasciitis[d]
2014	185 - 205	51	78 (38 - 42%)	107 - 127 (58 - 62%)	46 (22 - 25%)	11	17 (22%)	29 (23 - 27%)
2015	179 - 234	49	75 (32 - 42%)	104 - 159 (58 - 68%)	61 (26 - 34%)	5	8 (11%)	53 (33 - 51%)
2016	205 - 236	56	86 (36 - 42%)	119 - 150 (58 - 64%)	51 (22 - 25%)	14	22 (26%)	29 (19 - 24%)
2017	245 - 256	67	103 (40 - 42%)	142 - 153 (58 - 60%)	62 (24 - 25%)	8	12 (12%)	50 (33 - 35%)
2018	155 - 243	42	65 (27 - 42%)	90 - 178 (58 - 73%)	62 (26 - 40%)	7	11 (17%)	51 (29 - 57%)
2019	186 - 252	51	78 (31 - 42%)	108 - 174 (53 - 69%)	53 (21 - 28%)	9	14 (18%)	39 (22 - 36%)
Total	1155 - 1426	316	485 (34 - 42%)	670 - 941 (58 - 66%)	335 (23 - 29%)	54	84 (17%)	251 (27 - 37%)
Yearly average	193 - 238	53	81 (34 - 42%)	112 - 157 (58 - 66%)	56 (23 - 29%)	9	14 (17%)	42 (27 - 37%)

GAS = Group A Streptococcus. Data sources: [a] Lower limit based on cases registered in Osiris-AIZ, on cases registered by the GGD Utrecht combined with previous Dutch retrospective databases, upper limit based on data from the Dutch Hospital Data (DHD) Foundation; [b] Osiris-AIZ; [c] Number of registered cases in Osiris-AIZ corrected for underreporting by using data from the GGD-Utrecht and our own retrospective database from the same geographic region; [d] Based on data source 1 and 3; [e] DHD Foundation

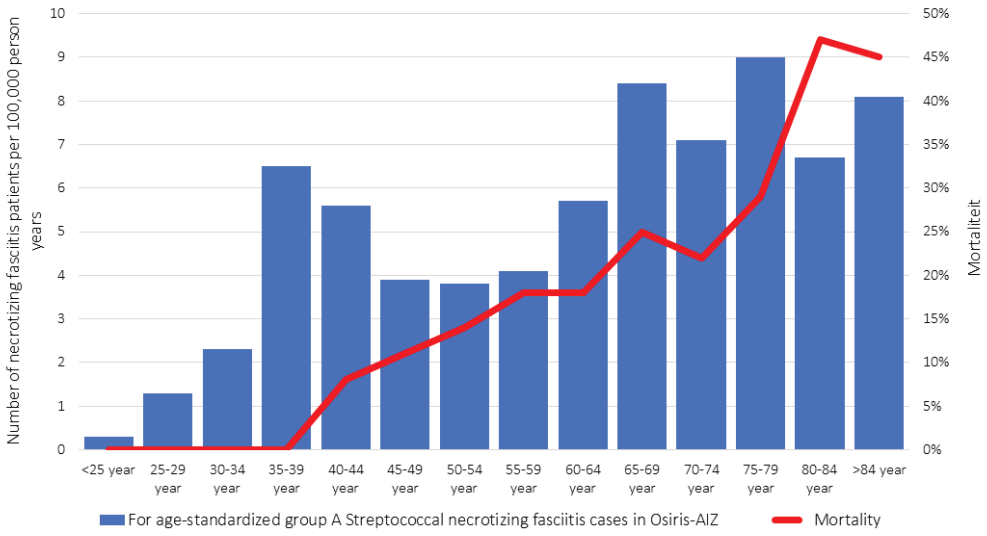

Figure 3 Incidence of group A Streptococcal fasciitis necroticans patients reported in Osiris-AIZ per age category and associated mortality (2009 – 2019)

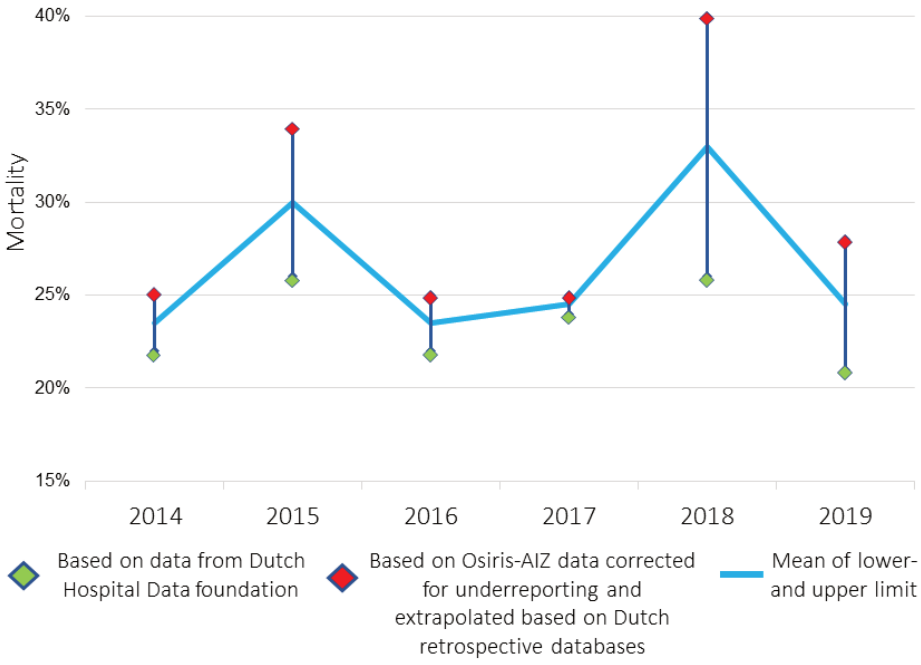

Figure 4 Mortality of necrotizing fasciitis in the Netherlands (2014 – 2019)

Mortality

Between January 2014 and December 2019, a total of 335 patients died as result of necrotizing fasciitis (on average 56 patients per year), representing a mortality rate of 23 – 29%. During those 6 years, the incidence and mortality of necrotizing fasciitis in the Netherlands remained stable (Figure 4). Of the 81 GAS necrotizing fasciitis patients per year, an average of 14 patients per year died as result of the infection (average mortality rate of 17%). Older age was associated with an increased risk at mortality in GAS necrotizing fasciitis patients, with a mortality rate of 46% in the age category of 80 years and older (Figure 3). Necrotizing fasciitis patients caused by other micro-organisms than GAS (for example, polymicrobial infection with anaerobic and aerobic bacteria, *Staphylococcus aureus*, *Clostridium* spp.) had a mortality rate of 27 – 37% (Table 3). Based on the DHD foundation data, no difference in mortality was found between academic and peripheral hospitals (57/265 (22%) vs. 278/1161 (24%), $p = 0.423$).

Hospital course

Dutch patients with necrotizing fasciitis undergo on average 1,9 to 2,3 operative procedures, which also includes patients who did not undergo any surgical procedures, for example due to withdrawal of care. Annually, 26 patients undergo an amputation as treatment for a necrotizing fasciitis (11 - 14%). Amputations were more often performed at academic hospitals compared to peripheral hospitals (48/265 in academic hospitals (18%) vs. 109/1161 in peripheral hospitals (9%), $p < 0.001$). Patients had a mean ICU stay of six to seven days (incl. patients without ICU admission) and a mean hospital length of stay of 24 to 30 days.

Discussion

The estimated incidence of necrotizing fasciitis in the Netherlands is approximately 1.1 – 1.4 cases per 100,000 person-years. The Dutch mortality rate of necrotizing fasciitis (23 - 29%) is slightly higher than the reported mortality rate of 18 – 21% in recent international literature from selected centers. The Dutch mortality rate for GAS necrotizing fasciitis (17%) is comparable to that found in other European studies on GAS necrotizing fasciitis (10 – 22%) [4,12,20,21]. In the current study a higher mortality rate was observed in non-GAS necrotizing fasciitis patients compared to GAS necrotizing fasciitis patients, which is most likely due to the fact that non-GAS necrotizing fasciitis patients tend to be older and to have more severe and/or multiple comorbidities compared to GAS necrotizing fasciitis patients [12,22]. Factors such as age, comorbidities (e.g. diabetes mellitus, renal failure, history of malignancy) and laboratory results upon presentation (e.g. creatinine, lactate) are frequently reported to be potential predictors for mortality in these patients

[15,23,24]. Nonetheless, the most important, potentially modifiable predictor for mortality remains time to treatment [4]. Early recognition, followed by prompt (preferable within 6 hours) and adequate surgical and antibiotic treatment is of utmost importance due to the progressive nature of the infection [2,4]. However, initiating prompt treatment is frequently hindered by a delayed diagnosis caused by a misdiagnosis upon presentation, with reported rates as high as 70%, due to its low incidence and the absence of pathognomic symptoms upon presentation [5]. To obtain prompt and acquired diagnosis and treatment, it requires a multidisciplinary approach with involvement of surgeons, medical microbiologists, pathologists, intensive care physicians, and often also plastic surgeons, infectious disease physicians, otolaryngologists, urological surgeons, and within the phase of rehabilitation also involve physiatrists [3,25].

In the Netherlands, notable more patients underwent an amputation in an academic hospital than in a peripheral hospital, while there was no difference in mortality between both types of hospitals. The Dutch healthcare system is constructed in such a way, that it is tempting to speculate that necrotizing fasciitis patients who present to academic hospitals (primarily or secondarily) had more comorbidities, a more severely extended infection (potential due to delay in presentation) and/or had a higher degree of physiological derangement upon presentation warranting a more aggressive surgical approach to obtain source control. A previous meta-analysis showed that treatment delay does not necessarily result in a higher rate of amputations, however other studies have shown that factors such as sepsis and transfer to another hospital are predictors for amputation as treatment [4,15,26,27].

Nowadays, there is a growing interest in the skin sparing approach for necrotizing fasciitis based on the hypothesis that it would results in less reconstructive surgeries and less wound healing complications [28]. Those advantages would contribute to a shorter hospital stay, which has been associated with a better quality of life after necrotizing fasciitis, but could also lower health care costs [28,29]. Unfortunately, studies on the outcomes of the skin sparing technique remain scarce. One of the few studies showed that wounds can be closed earlier on and that fewer patients required skin grafts [30]. However, in most studies on the skin sparing approach the technique was mainly used during the secondary debridement in transferred patients (85%) and in patients in who the initial debridement was not performed skin sparing (32-71%), limiting conclusion to be drawn about outcomes of the approach if it is used during the initial debridement [30,31]. Preventing mortality by performing adequate source control remains the primary goal with extra consideration for long-term function and aesthetics as secondary goals.

One of the previous mentioned advantages of the skin-sparing technique was the possibility to reduce health care costs. Currently, the exact health care costs linked

to a necrotizing fasciitis infection in the Netherlands remain unknown, while costs of approximately $50,000 per patient have been reported by two prior studies (Australia and United States) [11,32]. Mapping the Dutch health care costs is especially difficult due to the great variety of health care codes used to declare costs for these patients. For example, in the Netherlands, the DHD foundation found 483 different procedure codes declared for necrotizing fasciitis patients. Furthermore, not all these diagnosis- and procedure codes cover the full costs entailing the treatment for necrotizing fasciitis. Unambiguously registration would undoubtedly improve research into, knowledge about and insight in health care costs related to necrotizing fasciitis.

The results should be interpreted considering the study's limitations, especially the uncertainty caused by under- and overreporting in the different databases. For example, the percentage of underreporting of GAS necrotizing fasciitis patients in Osiris-AIZ. Potentially, patients were not reported to the GGD or coded as streptococcal toxic shock syndrome instead of necrotizing fasciitis. Nonetheless, this is the first study introducing a method for combing nationwide databases containing necrotizing fasciitis patients, with different data sources (in this case a nationwide hospital billing database and the notifiable disease database by the National Institute for Public Health), with previously publish literature from the same geographic region to map the incidence of necrotizing fasciitis within a country. This method aimed for the highest accuracy of the estimated incidence as possible based on the available data by acknowledging the possibility of under- and overreporting within the databases and correcting for this, and by recognizing the uncertainty by providing interval estimates instead of point estimates.

Conclusion

The combination of nationwide databases provides reliable insight in the epidemiology of low-incidence and heterogenic diseases. In the Netherlands, group A streptococcal is the most common causative micro-organism of necrotizing fasciitis. Necrotizing fasciitis is still associated with substantial morbidity and morbidity, risk at amputation and health care burden characterized by prolonged ICU and hospital stay. The main focus should be to further reduce mortality by improving and facilitating prompt recognition of necrotizing fasciitis, followed by reducing the morbidity and improving long-term function and quality of life.

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3

Cause of death by necrotizing soft tissue infections with focus on patients previously considered healthy: a retrospective cohort study

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Submitted

Abstract

Purpose: To identify the cause of death of necrotizing soft tissue infections (NSTIs) stratified by patients with and without multiple and/or severe pre-existing comorbidities (American Society of Anesthesiologists (ASA) classification III/IV vs. ASA I/II). Secondly, differences in presentation, mortality rate and factors associated with mortality between those two comorbidity groups is investigated.

Methods: A retrospective multicenter study was conducted of patients with NSTIs between January 2010 and January 2020. The primary outcome was the cause of death within the first 30 days. The secondary outcomes were length of ICU and hospital stay and sepsis. Furthermore, factors associated with mortality were identified. All analysis were stratified by severity of comorbidities (ASA I/II or ASA III/IV).

Results: Of the 187 included patients, 39 patients (21%) died within 30 days after presentation. ASA I/II patients (overall mortality rate: 11% (12/106) / mortality rate directly related to infection: 10% (11/106)) died more often as direct result of the infection compared to ASA III/IV patients (overall mortality rate 33%, 27/81) (92% vs. 48%, p = 0.013). ASA III/IV patients died more often due to withdrawal of care based on assumed poor outcome (52% vs. 8%, p = 0.013).

Conclusion: Mortality rates in NSTI patients varied from 10% in previously healthy patients to 33% in patients with comorbidities. The predominant cause of mortality was overwhelming infection and associated sepsis in healthy patients while in patients with multiple and/or severe preexisting medical disease, death most often followed after treatment limitations based on patient's wishes and prognosis.

Introduction

The reported mortality rate of necrotizing soft tissue infections (NSTIs) only hardly declined the past two decades, as it remained stable around 20% in current literature [1]. Further decline of the mortality rate depends on multiple factors. One of these known factors associated with high mortality rates in NSTIs is the presence of pre-existing comorbidities; patients with multiple and/or severe comorbidities (indicating worse physical status) have a higher risk of dying of NSTIs compared to patients with no or minor comorbidities (indicating good physical status). For those patients with no or only minor comorbidities, mortality rates of 12% (range 3 - 25%) have been reported and for patients with multiple and/or severe comorbidities mortality rates around 37% (range 20 - 55%) [2–4]. The reason for this difference can be assumed, but is not fully elucidated. A frequently suggested reason is that the requirement of emergency surgery to treat the NSTI leaves only limited room for pre-operative optimization of a patients physical status or comorbidities to limit the risk of post-operative complications and mortality, especially for patients with a pre-existing suboptimal physical status [5]. Nonetheless, patients without severe and/or multiple comorbidities do not necessarily require this pre-operative optimization other than treatment of their sepsis, but still have mortality rates reported ranged up to 25% [2–4]. It is unclear what the exact cause of the death is in NSTI patients with no or only minor comorbidities and if this cause of death differs from patients with pre-existing multiple and/or severe comorbidities. Therefore, this study investigates the cause of death of NSTIs stratified by the ASA classification, but also investigates if there is a difference in presentation, mortality rate and factors associated with mortality between those two groups, with as aim to identify in which regards patients with and without pre-existing multiple and/or severe comorbidities (ASA I/II vs. ASA III/IV) differ from each other to provide all NSTI patients with a more patient-tailored prognosis aiding in the decision regarding proportionality and consequences of treatment

Methods

The institutional review board of the initiating hospital (academic medical center) provided a waiver (WAG/mb/20/012110) for retrospective data collection. This article was written in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [6]. A protocol was a priori written and stored, however, not published.

Study design

All patients with confirmed NSTIs admitted to one of the four hospitals participating in this study (three large peripheral teaching hospitals and one academic medical

center) between January 2010 and January 2020 were eligible for inclusion in this retrospective cohort study. NSTI is the collective name for necrotizing forms of fasciitis, myositis and cellulitis. The diagnosis of NSTI had to be confirmed by either operative findings and/or microbiology results and/or histopathologic tissue findings [7,8]. Patients younger than 18 years upon presentation to the hospital were excluded, as well were patients who were lost to follow-up (e.g. due to transfer of patient to another hospital without correspondence to referring hospital at discharge). Eligible patients were identified using different methods per hospital which are outlined in Appendix 1. The study size was determined by the number of eligible patients in the aforementioned study period.

Data collection

The patient demographics were extracted from the medical charts (ER, IC, OR, ward, outpatient c), including the ASA classification and comorbidities. If the ASA classification was unknown, the ASA classification was based on comorbidities reported prior to the NSTI. Patients were grouped as previously healthy patients if they had an ASA I or II classification, representing no or mild systemic diseases, and grouped as patients with pre-existent multiple and/or severe comorbidities in case of an ASA III or IV classification, representing multiple and/or severe systemic disease(s). Morbid obesity was defined as a body mass index (BMI) of 30 kg/m^2 or greater. If a patient had no other comorbidities but a BMI between 30 and 40 kg/m^2, they were still classified as ASA II, based on the ASA classification system [9]. The extracted disease-related characteristics were location of the infection, hours from onset symptoms to presentation, estimated total body surface area (TBSA) affected using the rule of nine for burn injuries [10], cultured micro-organisms, hemodynamic parameters upon hospital admission and laboratory results upon hospital admission. If possible, based on the available hemodynamic parameter and laboratory results, the Laboratory Risk Indicator for Necrotizing fasciitis (LRINEC), (Portsmouth) physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM) scores, the quick sequential organ failure assessment (qSOFA) score and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score were calculated upon presentation [11–14]. Patients were determined to be septic prior to surgery if either the qSOFA was scored two or higher or if the patient was reported to be septic in the patient's chart [15]. For the laboratory results and hemodynamic parameters upon presentation, only values reported within twelve hours after presentation were used. The treatment-related variables extracted include time to diagnosis, surgical variables (e.g. amputation, intra-operative assessed diagnostics, skin-sparing operative technique based on operative notes, number of surgeries) and length of ICU and hospital stay. The primary outcome of this study was the cause of death of NSTIs within the first 30 days of presentation.

The secondary outcomes were length of ICU and hospital stay and sepsis, furthermore factors associated with mortality were identified. All analysis were stratified by severity of comorbidities (ASA I/II or ASA III/IV).

Statistical analysis

Normally distributed continuous variables are presented with means and standard deviations (SD), and, if more appropriate based on normality, presented with medians and interquartile ranges (IQR). Categorical variables are presented with frequencies and percentages. Missing data were handled using pairwise deletion. Statistical tests used to assess the difference in presentation, mortality and cause of death between ASA I/II and III/IV patients and for analyses to assess factors associated with mortality were the Fisher's exact test for dichotomous dependent variables, the Kruskall Wallis for nominal dependent variables, the Chi-squared test for trend for ordinal dependent variables and the Students t-test or Mann-Whitney U test for continuous dependent variables (depending on normality). For all analyses, a two-sided *p*-value <0.05 was considered statistically significant. Data was analyzed using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

NSTI patient characteristics

A total of 187 patients were included in this study: 36 ASA I (19%), 70 ASA II (37%), 63 ASA III (34%) and ASA IV (10%) patients. Hypertension (n = 50, 27%), morbid obesity (n = 43, 24%) and diabetes mellitus (n = 40, 21%) were common comorbidities. The mean age was 57 ± 17 years, most patients were male (n = 121, 65%) and the lower extremities were most commonly affected (n = 81, 43%). Group A *Streptococcus* (GAS) was the most often found causative micro-organism (n = 83, 44%) (Table 1). Of the 99 patients with available blood gasses, 27 patients (27%) had a metabolic acidosis upon presentation. The median LRINEC score was 7 (IQR 5 - 9), the median APACHE II score was 12 (IQR 8 - 17), 21 patients (of 124, 17%) scored a qSOFA score of 2 or greater, the median POSSUM physiological score was 26 (IQR 21 – 35) and median POSSUM operative severity score was 22 (IQR 22 - 22), which has an associated median predicted morbidity of 92% (IQR 83 - 98) and median predicted mortality of 24% (11 - 64) (Table 2).

Outcomes of all NSTI patients

Patients stayed a median of 25 days (IQR 15 – 42) in the hospital, of which 142 patients (76%) were admitted to the ICU with a median length of ICU stay of 4 days (IQR 2 – 11 days). Patients with NSTI of the trunk (100% ICU admission rate, *p* =

Table 1 Patient and disease characteristics of necrotizing soft tissue infection patients

	Total n = 187 (100%)	ASA I/II n = 106 (57%)	ASA III/IV n = 81 (43%)	*p*-value
Age in years, mean ± SD	57 ± 17	53 ± 16	62 ± 16	**<0.001**
Male sex, n (%)	121 (65)	72 (68)	49 (60)	0.354
Comorbidities, n (%)				
Diabetes mellitus	40 (21)	12 (11)	28 (35)	**<0.001**
Malignancy in medical history	29 (16)	9 (8)	20 (25)	**0.004**
Auto-immune disease	28 (15)	9 (8)	19 (23)	**0.007**
Hypertension	50 (27)	15 (14)	35 (43)	**<0.001**
Heart failure	10 (5)	0 (0)	10 (12)	**<0.001**
Renal failure	8 (4)	0 (0)	8 (10)	**0.001**
Morbid obesity (BMI ≥30 kg/m^2)[a]	43 (24)	19 (19)	24 (32)	0.076
Surgery within past 30 days	30 (16)	15 (14)	15 (19)	0.429
Current smoker[b]	49 (31)	28 (32)	21 (30)	0.863
Current intra-venous drugs user[b]	3 (2)	0 (0)	3 (4)	0.091
Location of NSTI, n (%)				0.743
Head/neck	10 (5)	5 (5)	5 (6)	0.748
Trunk	17 (9)	10 (9)	7 (9)	1.000
Perineum	50 (27)	26 (25)	24 (30)	0.505
Upper extremity	22 (12)	18 (17)	4 (5)	**0.012**
Lower extremity	81 (43)	45 (42)	36 (44)	0.882
Multiple body areas involved	7 (4)	2 (2)	5 (6)	0.242
Hours from onset symptoms to presentation at hospital[c], n (%)				0.163
≤24 hours	65 (39)	33 (34)	32 (45)	0.153
25 - 48 hours	41 (24)	25 (26)	16 (23)	0.717
49 - 72 hours	14 (8)	11 (11)	3 (4)	0.156
>72 hours	48 (29)	28 (29)	20 (28)	1.000
Estimated TBSA affected in %[d], median (IQR)	4 (2 – 6)	4 (2 – 6)	3 (2 – 6)	0.638
0 – 5%	121 (68)	70 (67)	51 (69)	0.871
6 – 10%	39 (22)	29 (28)	10 (14)	**0.027**
>10%	18 (10)	5 (5)	13 (17)	**0.010**
Cultured micro-organism from incisional biopsy[e], n (%)				
Monomicrobial	123 (68)	72 (71)	51 (64)	0.336
Group A Streptococcus	83 (67)	56 (78)	27 (53)	**0.006**
Other *Streptococcus spp.*	11 (9)	5 (7)	6 (12)	0.523
Staphylococcus aureus	9 (7)	5 (7)	4 (8)	1.000

Continuation of table 1

Escherichia coli	8 (7)	0 (0)	8 (15)	**0.001**
Pseudomonas spp.	2 (2)	2 (3)	0 (0)	0.511
Clostridium spp.	1 (1)	0 (0)	1 (2)	0.415
Other[f]	9 (7)	4 (5)	5 (10)	0.487
Polymicrobial	58 (32)	29 (29)	29 (36)	0.336
Escherichia coli involved	21 (36)	9 (31)	12 (41)	0.585
Pseudomonas spp. involved	3 (5)	2 (7)	1 (3)	1.000
Clostridium spp. involved	8 (14)	6 (21)	2 (7)	0.253

ASA = American Society of Anesthesiologists; IQR = Interquartile Range; NSTI = Necrotizing Soft Tissue Infection; TBSA = Total Body Surface Area; SD = standard deviation. [a] 11 missing cases; [b] 28 missing cases; [c] 19 cases missing; [d] 9 missing cases; [e] 4 cases with negative cultures and 2 in which no cultures were obtained; [f] *Acinetobacter baumannii, Acinetobacter guillouiae, Bacteroides fragilis, Enterobacter cloacae, Klebsiella pneumoniae, Morganella morganni, Neisseria meningitidis, Proteus vulgaris, Vibrio parahaemolyticus.* **Bold** font indicates significant result.

0.014) or patients with a greater TBSA ($p < 0.001$) were more often admitted to the ICU. In 22 patients (12%) an amputation was performed. Thirty-nine patients (21%) died within 30 days after presentation (Figure 1). Per ASA classification the mortality rates differed: ASA I 14% (5/36), ASA II 10% (7/70), ASA III 22% (14/63) and ASA IV 72% (13/18) (p <0.001). If mortality occurred, this was at a median of two days (IQR 1 – 7) after presentation (Table 3).

Cause of death

Within the first 30 days, 12 of the 106 ASA I/II patients (11%) died due to NSTIs. The cause of death was in most cases (92%) a direct result of the infection (non-survivable dissemination of the infection or sepsis) or a complication (cardiac arrest in patient without history of cardiac problems). ASA I/II patients died more often as a direct result of the fulminant infection or related complication than ASA III/IV patients (11/12 (92%) vs. 13/27 (48%), $p = 0.013$), which resulted in a mortality rate of 10% (11/106) as a direct result of the infection in the ASA I/II group.

Of the 81 ASA III/IV patients, 27 died within the first 30 days (33%), which is significantly higher compared to ASA I/II patients (12 (11%) vs. 27 (33%), $p < 0.001$). The cause of death was in 52% due to withdrawal of care based on an estimated poor outcome (mortality and morbidity) considering pre-existing patient characteristics (e.g. comorbidities, age, prior quality of life and independence) in combination with NSTI severity. Withdrawal of care occurred more often in ASA III/IV patients compared to ASA I/II (14/27 (52%) vs. 1/12 (8%), $p = 0.013$). (Table 3 and Figure 1). Excluding the patients in which care was withdrawn, in the ASA III/IV group, the mortality rate as a direct result of the infection was 16% (13/81).

Table 2 Hemodynamic parameters and laboratory results upon presentation in necrotizing soft tissue infection patients

	Total		ASA I/II		ASA III/IV			
	n	Mean ± SD or Median (IQR)	n	Mean ± SD or Median (IQR)	n	Mean ± SD or Median (IQR)	*p*-value	Reference values
Hemodynamic parameters								
Systolic blood pressure	178	117 ± 23	102	119 ± 23	76	114 ± 22	0.221	90 – 120 mmHg
Diastolic blood pressure	178	69 ± 15	102	70 ± 15	76	67 ± 16	0.165	60 – 80 mmHg
Mean arterial pressure	178	85 ± 16	102	86 ± 16	76	82 ± 16	0.153	70 – 100 mmHg
Heart rate	180	101 (90 - 115)	102	102 (92 - 116)	78	101 (88 - 112)	0.226	60 – 100 beats/minute
Respiratory rate	126	20 (16 - 25)	68	19 (16 - 24)	58	21 (18 - 30)	**0.048**	12 – 20 breaths/minute
Temperature	181	37.7 ± 1.2	104	37.6 ± 1.2	77	37.9 ± 1.1	0.122	36 – 38 °C
Blood test results								
Hemoglobin	117	♂ 8.4 ± 1.5	71	♂ 8.8 ± 1.2	46	♂ 7.7 ± 1.7	**<0.001**	♂ 8.6 – 10.7 mmol/L
	64	♀ 7.6 ± 1.2	33	♀ 7.9 ± 0.9	31	♀ 7.4 ± 1.3	0.089	♀7.4 – 9.6 mmol/L
Hematocrit	180	38.9 ± 6.4	104	40.4 ± 5.4	76	36.9 ± 7.0	**<0.001**	41 – 50%
Platelet count	155	204 (151 – 267)	88	200 (151 – 254)	67	213 (147 - 288)	0.431	150 – 450 x10^9/L
White blood cell count	181	15.5 (9.4 – 22.3)	104	15.9 (10.3 - 22.7)	77	14.7 (9.1 – 21.5)	0.292	0.8 – 4.0 x10^9/L
Sodium	170	134 (131 - 137)	94	134 (131 - 137)	76	134 (130 - 136)	0.653	136 – 146 mmol/L
Potassium	170	4.0 (3.6 – 4.3)	94	4.0 (3.5 – 4.3)	76	4.0 (3.7 – 4.6)	0.165	3.8 – 5.0 mmol/L
Creatinine	176	128 (82 - 208)	100	115 (80 - 180)	76	136 (88 - 246)	0.118	64 – 104 µmol/L
Total bilirubin	117	16 (10 – 28)	64	16 (9 - 25)	53	16 (10 – 30)	0.378	3 – 21 mmol/L
Lactate	76	4.0 (2.8 – 5.7)	35	4.8 (3.0 – 6.2)	41	3.4 (2.7 – 5.4)	0.213	0.0 – 2.2 mmol/L
Lactate dehydrogenase	123	246 (194 – 365)	65	234 (194 - 363)	58	260 (204 - 365)	0.392	0 – 250 U/L
Creatine kinase	77	212 (66 – 768)	39	212 (66 - 1084)	38	181 (65 - 445)	0.454	0 – 170 U/L
C-reactive protein	180	302 (164 - 398)	102	318 (182 - 433)	78	263 (88 - 338)	**0.009**	0 – 10 mg/L
Glucose	154	7.2 (6.1 – 9.7)	82	7.4 (6.3 – 9.8)	72	7.0 (5.8 – 9.5)	0.273	3.6 – 5.6 mmol/L

Continuation of table 2

Arterial blood gas results[a]								
pH	99	7.42 (7.34 – 7.47)	54	7.42 (7.37 – 7.48)	45	7.43 (7.32 – 7.47)	0.471	7.37 – 7.45
PaO_2	85	86 (66 - 120)	48	96 (78 - 149)	37	73 (60 - 99)	**0.002**	70 – 100 mmHg
$PaCO_2$	85	28 (25 - 34)	48	27 (23 - 34)	37	30 (27 – 34)	0.114	35 – 45 mmHg
Bicarbonate	99	19 (15 - 23)	54	18 (15 - 23)	45	20 (16 – 23)	0.308	22.0 – 28.0 mmol/L
Base excess	99	-4 (-9 - 1)	54	-5 (-9 - -1)	45	-4 (-9 - -1)	0.728	-3.0 – 3.0 mmol/L
Risk scores								
LRINEC score	150	7 (5 - 9)	82	7 (6 - 9)	68	7 (4 - 9)	0.786	Range 0 – 13
POSSUM physiological score	154	26 (21 - 35)	88	23 (19 - 30)	66	32 (24 - 39)	**<0.001**	Range 12 – 88
Predicted morbidity POSSUM	154	92 (83 - 98)	88	89 (81 - 97)	66	97 (89 - 99)	**<0.001**	Range 0 – 100%
Predicted mortality P-POSSUM	154	24 (11 - 64)	88	18 (8 - 48)	66	48 (18 - 84)	**<.0.001**	Range 0 – 100%
APACHE II score	62	12 (8 – 17)	36	10 (6 – 15)	26	15 (11 – 17)	**0.004**	Range 0 - 67
qSOFA ≥2 points	124	21 (17)	68	11 (16)	56	10 (18)	0.815	
Septic upon admission, n (%)	179	60 (34)	102	29 (28)	77	31 (40)	0.111	

ASA = American Society of Anesthesiologists; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; IQR = Interquartile Range; LRINEC = Laboratory Risk Indicator for Necrotizing fasciitis; (P-)POSSUM = (Portsmouth) Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; qSOFA = Quick Sequential Organ Failure Assessment. SD = Standard Deviation. **Bold** font indicates significant result.

[a] If only a venous blood gas was available, only pH, bicarbonate and base deficit were extracted

Table 3 Outcomes of necrotizing soft tissue infections dived by ASA classification prior to the infection

	Total n = 187 (100%)	ASA I/II n = 106 (57%)	ASA III/IV n =81 (43%)	*p*-value
Treatment				
Admitting specialty				
Surgical (incl. urology, plastic surgery, ENT surgery)	153 (82)	88 (83)	65 (80)	0.703
Internal Medicine (incl. cardiology),	34 (18)	18 (17)	16 (20)	
Time from presentation at hospital to diagnosis in hours[a], median (IQR)	7 (4 - 29)	7 (4 - 31)	11 (4 - 29)	0.577
Amputation performed[b], n (%)	22 (12)	14 (13)	8 (10)	0.647
Skin sparing operating technique utilized, n (%)	35 (21)	19 (19)	16 (24)	0.442
Intra-operative assessed frozen section and/or Gram stain[c], n (%)	40 (23)	22 (22)	18 (24)	0.716
Frozen section, n (%)	23 (13)	12 (12)	11 (14)	0.657
Gram stain, n (%)	28 (16)	16 (16)	12 (16)	1.000
Number of surgeries for NSTI within first 30 days[d], median (IQR)	3 (2 - 5)	3 (2 - 5)	3 (2 - 5)	0.882
Days from initial surgery to definitive wound closure in days[d], median (IQR)	28 (11 – 56)	23 (10 - 55)	30 (13 - 61)	0.371
Postoperative phase				
Admitted to ICU, n (%)	142 (76)	79 (75)	63 (79)	0.602
Length of ICU stay in days[e], median (IQR)	4 (2 - 11)	4 (2 - 10)	4 (1 - 12)	0.563
Length of hospital stay in days, median (IQR)	25 (15 - 42)	23 (14 - 41)	27 (15 - 48)	0.334
Major complication during hospital course, n (%)				
Sepsis	109 (58)	57 (54)	52 (64)	0.179
Multiple organ dysfunction syndrome	21 (11)	12 (11)	9 (11)	1.000
Deceased within 30 days after presentation, n (%)	39 (21)	12 (11)	27 (33)	**<0.001**
Days from presentation to death in days, median (IQR)	2 (1 - 7)	3 (1 - 10)	2 (1 - 7)	0.611
Cause of death, n (%)				**<0.001**
Direct result of infection or complication	24 (62)	11 (92)	13 (48)	
Withdrawal of care based on assumed poor outcome	15 (38)	1 (8)	14 (52)	

Continuation of table 3

Abbreviations: ASA = American Society of Anesthesiologists; ENT= ear, nose and throat; ICU = Intensive Care Unit; IQR = Interquartile Range; NSTI = Necrotizing Soft Tissue Infection; SD = Standard Deviation. [a] 6 missing cases; [b] Lower extremity amputation n = 12, (hemi)scrotectomy n = 7, mastectomy n = 1, orchidectomy n = 1, finger n = 1; [c] Based on 177 surgeries; [d] Only patients who survived hospital stay; [e] Only patients who survived ICU stay. **Bold** font indicates significant result.

Table 4 Patient and disease characteristics of ASA I/II necrotizing soft tissue infection patients

	ASA I/II			ASA III/IV		
	Survived n = 94 (89%)	Deceased n = 12 (11%)	*p*-value	Survived n = 54 (67%)	Deceased n = 27 (33%)	*p -value*
Age in years, mean ± SD	51 ± 15	71 ± 13	**<0.001**	59 ± 17	67 ± 13	**0.027**
Male sex, n (%)	66 (70)	6 (50)	0.193	33 (61)	16 (59)	1.000
Comorbidities, n (%)						
Diabetes mellitus	11 (12)	1 (8)	1.000	17 (31)	11 (41)	0.462
Malignancy in medical history	8 (9)	1 (8)	1.000	11 (20)	9 (33)	0.275
Auto-immune disease	7 (7)	2 (17)	0.269	13 (24)	6 (22)	1.000
Hypertension	11 (12)	4 (33)	0.065	23 (43)	12 (44)	1.000
Morbid obesity (BMI ≥30 kg/m^2)[a]	17 (18)	2 (29)	0.615	19 (36)	5 (22)	0.288
Surgery within past 30 days	15 (16)	0 (0)	0.209	9 (17)	6 (22)	0.557
Current smoker[b]	27 (34)	1 (13)	0.427	12 (29)	9 (36)	0.423
Location of NSTI, n (%)			0.302			0.178
Head/neck	4 (4)	1 (8)	0.458	3 (6)	2 (7)	1.000
Trunk	8 (8)	2 (17)	0.315	5 (9)	2 (7)	1.000
Perineum	23 (25)	3 (25)	1.000	19 (35)	5 (19)	0.196
Upper extremity	16 (17)	2 (17)	1.000	2 (4)	2 (7)	0.597
Lower extremity	41 (44)	4 (33)	0.552	24 (44)	12 (45)	1.000
Multiple body areas involved	2 (2)	0 (0)	1.000	1 (2)	4 (15)	**0.040**

Continuation of table 4

Hours from onset symptoms to presentation at hospital[c], n (%)			0.658			0.245
≤24 hours	30 (34)	3 (30)	0.540	19 (41)	13 (54)	0.319
25 - 48 hours	20 (23)	5 (50)	0.076	11 (23)	5 (21)	1.000
49 - 72 hours	11 (13)	0 (0)	0.282	2 (4)	1 (4)	1.000
>72 hours	26 (30)	2 (20)	0.719	15 (32)	5 (21)	0.409
Estimated TBSA affected in %[d], median (IQR)	3 (2 - 6)	7 (5 - 10)	**0.002**	3 (2 - 5)	7 (3 - 15)	**0.003**
0 – 5%	67 (72)	3 (27)	**0.005**	42 (79)	9 (43)	**0.005**
6 – 10%	23 (25)	6 (55)	0.069	5 (9)	5 (24)	0.135
>10%	3 (3)	2 (18)	0.086	6 (12)	7 (34)	**0.040**
Cultured micro-organism from incisional biopsy[e], n (%)						
Monomicrobial	63 (70)	9 (82)	0.505	32 (59)	19 (73)	0.321
Group A Streptococcus	49 (78)	7 (77)	0.644	20 (63)	7 (37)	0.091
Other *Streptococcus spp.*	5 (8)	0 (0)	0.502	5 (16)	1 (5)	0.392
Staphylococcus aureus	5 (8)	0 (0)	1.000	1 (3)	3 (16)	0.140
Pseudomonas spp.	2 (3)	0 (0)	1.000	0 (0)	0 (0)	NA
Escherichia coli	0 (0)	0 (0)	NA	3 (9)	5 (26)	0.131
Polymicrobial	27 (30)	2 (18)	0.505	22 (41)	7 (27)	0.321
Escherichia coli involved	7 (26)	2 (100)	0.089	7 (32)	5 (71)	0.092
Pseudomonas spp. involved	1 (4)	1 (50)	0.135	1 (5)	0 (0)	1.000
Clostridium spp. involved	6 (22)	0 (0)	1.000	1 (5)	1 (14)	0.431

ASA = American Society of Anesthesiologists; IQR = Interquartile Range; NSTI = Necrotizing Soft Tissue Infection; TBSA = Total Body Surface Area; SD = Standard Deviation; [a] 6 missing cases; [b] 18 missing cases; [c] 9 missing cases; [d] 2 missing cases; [e] 4 cases with negative cultures and 1 in which no cultures were obtained. **Bold** font indicates significant result.

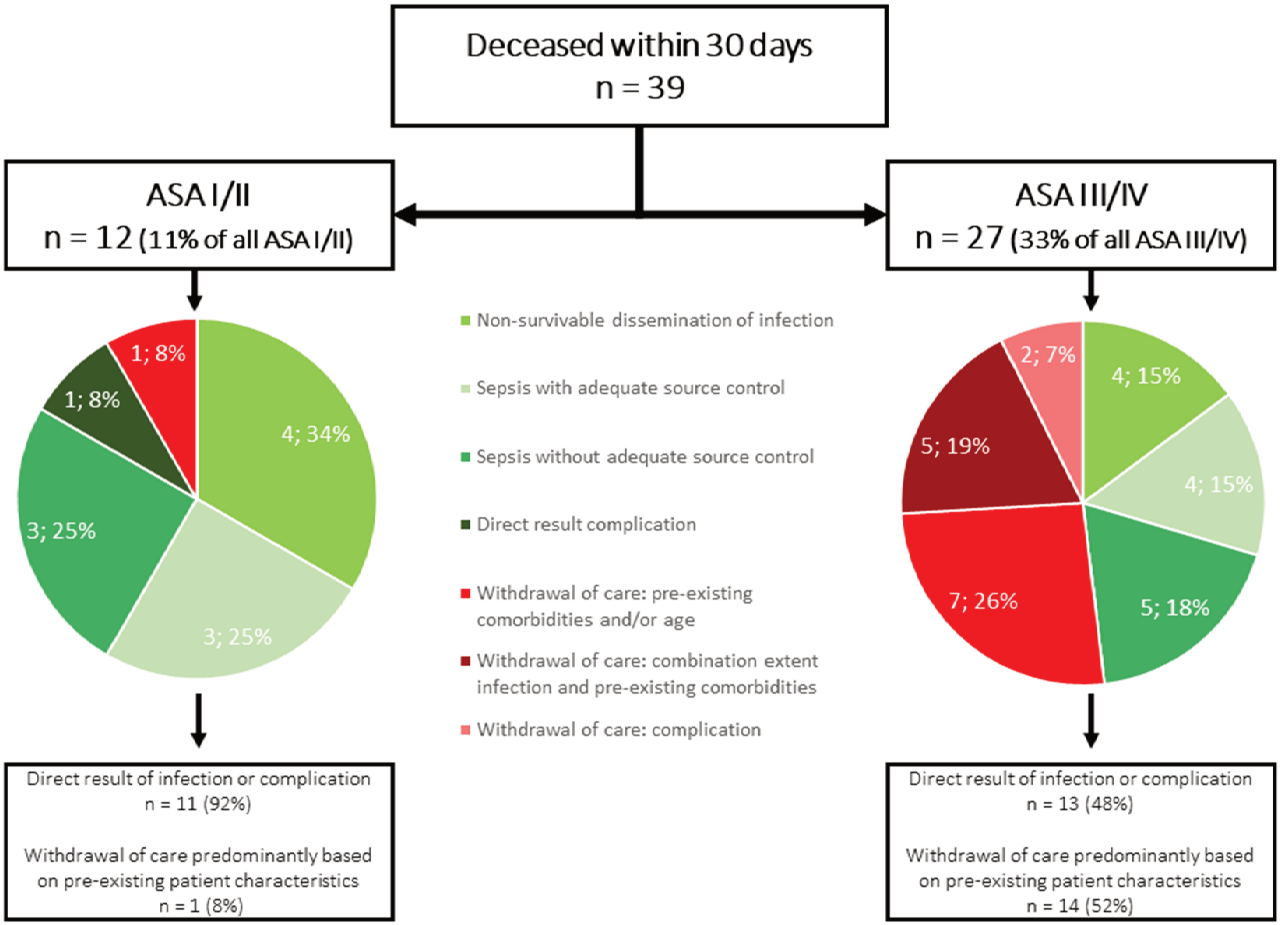

Figure 1 Cause of death of necrotizing soft tissue infection patients stratified by severity of comorbidities

Differences between ASA I/II and ASA III/IV patients

ASA I/II patients were significantly younger upon onset of the NSTI compared to ASA III/IV patients (53 ± 16 vs. 62 ± 16, $p < 0.001$), had more frequently NSTI of the upper extremity ($p = 0.012$), more frequently a TBSA ≤10% affected area ($p = 0.010$), more frequent monomicrobial GAS NSTIs ($p = 0.006$) and less frequent monomicrobial *E. coli* NSTIs ($p = 0.001$, no *E. coli* NSTIs occurred within the ASA I/II group) (Table 1). ASA III/IV patients had significantly higher respiratory rate ($p = 0.048$), lower hemoglobin levels ($p < 0.001$) and PaO_2 levels ($p = 0.002$). In addition, the POSSUM physiological score ($p < 0.001$) with associated predicted morbidity and mortality rates (both $p < 0.001$) and APACHE II score ($p = 0.004$) were also significantly higher compared to ASA I/II patients (Table 2). On the other hand, ASA III/IV patients had lower c-reactive protein (CRP) levels ($p = 0.009$).

Factors associated with mortality stratified per ASA group

ASA I/II patients who died were significantly older than the patients who survived ($p < 0.001$), had a greater TBSA affected ($p = 0.002$), higher lactate dehydrogenase (LD) levels ($p = 0.027$), higher creatine kinase (CK) levels ($p = 0.006$),had higher POSSUM physiological scores upon admission ($p = 0.029$) with higher associated predicted morbidity and mortality rates ($p = 0.021$ and $p = 0.023$), and had more often sepsis during hospital stay ($p = 0.005$). On the other hand, deceased ASA I/II patient had lower white blood cell count ($p = 0.042$).

ASA III/IV patients who died were significantly older than ASA III/IV patients who survived ($p = 0.027$), had more often a NSTI affecting multiple body regions ($p = 0.040$), higher TBSA affected ($p = 0.003$), higher potassium levels and creatinine levels upon admission ($p = 0.011$ and $p = 0.030$, respectively), had higher POSSUM physiological scores upon admission with higher associated predicted morbidity and mortality rates (all three $p < 0.001$) and developed more often sepsis during hospital stay ($p = 0.007$) (Table 4 and 5).

Discussion

This study describes a 30-day mortality rate in patients with no or only minor comorbidities of 11% and in patients with severe comorbidities of 33%. The reason for patients with no or minor comorbidities to decease was in almost all cases directly related to the infection (non-survivable dissemination of the infection or uncontrollable sepsis) or a related complication (92%). Based on the number of patients who died regardless of adequate source control or in who care was withdrawn based on pre-existing comorbidities and/or age, it can be hypothesized that the minimum achievable mortality rate of NSTIs lies around 10% in our current healthcare setting [1]. Currently, the worldwide mortality rate reported in literature

is around 20% (0 – 67%). However, there are a few large retrospective cohort studies (between 138 – 216 included patients) available with reported mortality rates around 10-15% [1,16–18]. There are to our knowledge no large studies with adequate follow-up that demonstrated mortality rates below 10%.

The pillars for successful management of NSTIs are early recognition, prompt and adequate surgical treatment combined with appropriate antibiotic therapy and resuscitation in case of sepsis [19]. Adequate execution of these pillars is vital for reduction of NSTI mortality rates [1,20]. The devastating consequences of this aggressive and rapidly spreading disease, which requires timely recognition and adequate treatment, were especially apparent in the group of patients with no or only minor comorbidities, with most patients dying as direct result of advanced dissemination of the infection, indicated by the greater TBSA affected in deceased patients, and/or uncontrollable sepsis. Besides the greater TBSA affected, which has been priorly linked to mortality in NSTIs, the deceased patients with no or only minor comorbidities had also higher LD and CK levels. These latter parameters are associated with greater tissue and muscle destruction, and/or sepsis [3,21]. Possible explanation for these differences in disease progression prior to presentation and the high rate of sepsis, with upon presentation already greater physiological derangement in eventually deceased patients, could be delay (either patient, diagnostic, treatment), or the ability of the causative pathogen to spread more [1,4,22,23]. However, this study was unable to determine such an association due to lack of power caused by the small group of deceased patients with no or only minor comorbidities.

In case of NSTI patients with multiple and/or severe comorbidities, the pillars for successful management of NSTIs remain even important, as more widespread NSTIs and sepsis were more common in deceased patients. However, the outcome of NSTIs in these patients are also influenced by the patient's pre-existing physical status. Comorbidities such as a history of malignancy, kidney failure and cirrhosis are known to increase mortality in NSTI patients [24–27]. Besides the presence of comorbidities, patients with multiple and/or severe comorbidities compose a different patient population than NSTI patients with no or only minor comorbidities, characterized by an older age. Furthermore, they presented differently with more anatomically extensive infections, other causative pathogens, higher POSSUM physiological and APACHE II scores upon admission. Also, the outcomes of the NSTI differed for patients with multiple and/or severe comorbidities with higher mortality rates (33% vs 11%) and withdrawal of care as common cause of death. The decision to withdraw care was made by the judgment of the treating multidisciplinary team based on an estimated poor outcome (mortality and morbidity) considering pre-

Table 5 Hemodynamic parameters and laboratory results upon presentation with necrotizing soft tissue infection divided by ASA classification

	ASA I/II				
	Survived		Deceased		
	n	Mean ± SD or Median (IQR)	n	Mean ± SD or Median (IQR)	*p*-value
Hemodynamic parameters					
Systolic blood pressure	90	119 ± 23	12	117 ± 25	0.756
Diastolic blood pressure	90	70 ± 14	12	67 ± 19	0.535
Mean arterial pressure	90	86 ± 16	12	84 ± 20	0.603
Heart rate	90	101 (90 – 119)	12	111 (96 - 115)	0.319
Respiratory rate	62	18 (16 - 24)	6	21 (16 - 25)	0.480
Temperature	92	37.7 ± 1.2	12	37.1 ± 1.3	0.165
Blood test results					
Hemoglobin	65	♂ 8.9 (8.1 – 9.5)	6	♂ 8.1 (6.6 - 10)	0.336
	27	♀ 8.1 (7.7 – 8.5)	6	♀ 7.5 (6.7 – 8.6)	0.640
Hematocrit	92	41 (38 - 43)	12	38 (32 - 44)	0.153
Platelet count	77	197 (151 - 249)	11	213 (151 - 273)	0.575
White blood cell count	92	16.1 (10.9 – 23.4)	12	11.8 (6.1 – 16.7)	**0.042**
Sodium	82	135 (131 - 137)	12	131 (131 - 135)	0.141
Potassium	82	4.0 (3.5 – 4.3)	12	3.8 (3.5 – 4.2)	0.281
Creatinine	88	112 (80 - 171)	12	131 (93 - 253)	0.233
Total bilirubin	56	16 (9 - 25)	8	18 (13 - 26)	0.509
Lactate	28	4.3 (3.0 – 5.5)	7	7.6 (3.0 – 9.8)	0.274
Lactate dehydrogenase	58	219 (178 - 352)	7	328 (269 - 624)	**0.027**
Creatine kinase	33	168 (58 – 714)	6	2001 (1029 - 13994)	**0.006**
C-reactive protein	90	310 ± 153	12	287 ± 126	0.633
Glucose	72	7.4 (6.3 – 9.6)	10	7.4 (5.5 – 9.8)	0.403
Arterial blood gas results[a]					
pH	48	7.42 (7.37 – 7.48)	6	7.41 (7.39 – 7.43)	0.700
PaO_2	42	96 (76 - 170)	6	92 (83 - 99)	0.445
$PaCO_2$	42	28 ± 7	6	29 ± 9	0.758
Bicarbonate	48	19 ± 6	6	16 ± 2	0.344
Base excess	48	-4 (-9 - -1)	6	-6 (-10 - -5)	0.164
Risk scores					
LRINEC score	72	7 (6 - 8)	10	9 (8 - 9)	0.147
POSSUM physiological score	76	23 (19 – 27)	12	32 (25 – 33)	**0.029**
Predicted morbidity P- POSSUM	76	88 (79 – 93)	12	97 (89 – 98)	**0.021**
Predicted mortality P-POSSUM	76	15 (8 – 28)	12	51 (21 – 63)	**0.023**
APACHE II score	32	10 (6 – 15)	4	13 (9 – 18)	0.434
qSOFA ≥2	62	10 (16)	6	1 (17)	1.000
Septic upon admission, n (%)	90	24 (27)	12	5 (42)	0.314
Sepsis during hospital stay, n (%)	94	46 (49)	12	11 (92)	**0.005**

Continuation of table 5

ASA III/IV					
Survived		Deceased			
n	Mean ± SD or Median (IQR)	n	Mean ± SD or Median (IQR)	*p*-value	Reference values
50	117 ± 22	26	109 ± 22	0.157	90 – 120 mmHg
50	67 ± 16	26	65 ± 16	0.627	60 – 80 mmHg
50	84 ± 16	26	80 ± 17	0.340	70 – 100 mmHg
51	103 (88 - 113)	27	96 (85 - 112)	0.475	60 – 100 beats/minute
37	20 (18 – 28)	21	23 (16 - 30)	0.727	12 – 20 breaths/minute
51	37.9 ± 1.1	26	37.8 ± 1.2	0.565	36 – 38 °C
30	♂ 7.8 (6.7 – 8.9)	16	♂ 7.3 (6.3 – 8.2)	0.204	♂ 8.6 – 10.7 mmol/L
20	♀ 7.2 (6.7 – 8.2)	11	♀ 8.1 (5.9 – 8.8)	0.885	♀7.4 – 9.6 mmol/L
49	37 (34 - 42)	27	37 (30 - 42)	0.309	41 – 50%
42	224 (175 - 288)	25	182 (147 - 285)	0.627	150 – 450 $x10^9$/L
50	14.6 (10.2 – 21.5)	27	15.9 (5.4 – 21.5)	0.212	0.8 – 4.0 $x10^9$/L
49	135 (130 - 136)	27	133 (131 - 137)	0.991	136 – 146 mmol/L
49	3.9 (3.6 – 4.3)	27	4.4 (3.8 – 5.2)	**0.011**	3.8 – 5.0 mmol/L
49	125 (82 - 188)	27	169 (91 - 280)	**0.030**	64 – 104 µmol/L
32	14 (10 - 28)	21	24 (12 - 43)	0.153	3 – 21 mmol/L
25	3.0 (2.5 – 5.2)	16	3.6 (2.8 – 6.2)	0.462	0.0 – 2.2 mmol/L
36	253 (205 - 331)	22	306 (203 - 465)	0.136	0 – 250 U/L
22	185 (80 - 521)	16	181 (55 - 337)	0.497	0 – 170 U/L
51	263 (127 - 348)	27	234 (58 - 332)	0.635	0 – 10 mg/L
48	6.9 (6.0 – 10.6)	24	7.3 (5.2 – 8.7)	0.507	3.6 – 5.6 mmol/L
27	7.44 (7.33 – 7.47)	18	7.35 (7.30 – 7.46)	0.354	7.37 – 7.45
21	74 (62 - 103)	16	65 (56 - 82)	0.304	70 – 100 mmHg
21	30 ± 6	16	32 ± 7	0.192	35 – 45 mmHg
27	19 ± 5	18	19 ± 4	0.800	22.0 – 28.0 mmol/L
27	-3 (-12 - -1)	18	-4 (-9 - -3)	0.728	-3.0 – 3.0 mmol/L
44	7 (5 - 9)	24	8 (4 - 10)	0.427	Range 0 – 13
43	28 (24 - 35)	23	39 (29 - 44)	**<0.001**	Range 12 - 88
43	94 (89 - 98)	23	99 (95 - 100)	**<0.001**	Range 0 – 100%
43	32 (18 - 64)	23	87 (36 - 91)	**<0.001**	Range 0 – 100%
15	15 (11 - 17)	11	16 (11 - 17)	0.834	Range 0 - 67
37	7 (19)	19	3 (16)	1.000	
50	16 (32)	27	15 (56)	0.054	
54	29 (54)	27	23 (85)	**0.007**	

Continuation of table 5

Abbreviations: ASA = American Society of Anesthesiologists; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; IQR = Interquartile Range; LRINEC = Laboratory Risk Indicator for Necrotizing fasciitis; (P-)POSSUM = (Portsmouth) Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity; qSOFA = Quick Sequential Organ Failure Assessment. SD = Standard Deviation. **Bold** font indicates significant result.[a] If only a venous blood gas was available, only pH, bicarbonate and base deficit were extracted

existing patient characteristics (e.g. comorbidities, age, prior quality of life and independence) in combination with NSTI extensiveness and severity. The decision for withdrawal of care is often culture dependent, and it is to realize this present study was performed in the Netherlands [28]. Within this subgroup of NSTI patients, other countries might have lower 30-day mortality rates and less often withdrawal of care as cause of death. Within its culture and ethical considerations, the proportionality of treatment should be debated in relation to the high predicted morbidity and mortality rate within this group of patients. As also seen in this study, NSTIs are known to have high risk of adverse short-term outcomes, lengthy recovery and suboptimal long-term outcomes, such as decreased physical function and long-lasting discomfort [1,29–32].

Withdrawal of care based on age remains a controversial decision, while advanced age (most commonly defined as age >60 years) is a known predictor for mortality in NSTI patients regardless of the presence of comorbidities, as also seen in this study [24–27,33]. Prior surgical ICU studies in elderly patients found that elder surgical patients form a select population. Brakenridge et al. found that these patients have early on already more severe physiological derangement and found that they have a high risk of adverse events (incl. mortality) within the first six months, furthermore, Owodunni et al. and Smith et al. found that the risk of losing independence (e.g. inability to live independently afterwards) significantly increases with age [34–36]. Unfortunately, age is not represented in the assessment of physical status using the ASA classification, while physical function and frailty are known to be age-associated [36,37]. On the other hand, mortality predictors scores, such of the POSSUM and APACHE II score, already include age as predictor. Age might also be an important adjuvant criterion to determine proportionality of NSTIs treatment and was and should be weighted in the decision to withdraw or continue care. For example, this study included a previously healthy patient, age 88, from who the care was withdrawn based on her age, the extent and severity of the NSTI and the resultant presumed lengthy recovery awaiting, which the physicians and family decided to be disproportional.

The results of this study should be analyzed considering its limitations. First, this study is a retrospective study which is associated with missing data, especially regarding availability of blood gas results, which limits the ability to calculate

POSSUM and APACHE II scores. Secondly, the group of deceased patients with no or only minor comorbidities consisted of only 12 patients which limits the power of the analysis regarding patients with no or only minor comorbidities who expired and survived. It is difficult to obtain a large enough database of this subgroup of NSTI patients. Third, patients who died outside the hospital (e.g. hospice or at home) were lost to follow-up, since this study had only access to hospital data, which also contributes to the relatively short follow-up period. However, the biggest strength of this study is the comprehensiveness of this database, by using multiple hospital registration databases, using multiple NSTI related registrations codes (appendix 1) and going through patients record by hand, we have great confidence that we found all patients diagnosed with a NSTIs within the study period, also the ones who did not underwent surgery. This is to date one of the largest and most comprehensive NSTI database in Europe and the first study investigating cause of death in NSTI patients with various degrees in comorbidities.

Conclusion

A major difference in mortality rates was found between previously healthy patients and patients with severe comorbidities (11 vs 33%). In addition to the patient's previous condition, age, anatomical extensiveness of the NSTI and physiological derangement at presentation were associated with mortality. This latter restates the importance of early recognition and prompt adequate treatment to prevent nonsurvivable dissemination of the infection and physiological derangement of the patient. Nevertheless, especially in patients with advanced age and/or serious preexisting medical diseases, goals of care should be discussed with the patient and their family early on to determine proportionality of treatment weighing the patient's wishes regarding life-sustaining therapies and prognosis enabling patient-centered care by shared decision making.

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Appendix 1 Methods of identifying patients with necrotizing soft tissue infections

University Medical Center Utrecht	Jan 2010 – Jan 2013	Patient sought using the International Code for Disease (ICD) 10 for necrotizing fasciitis (M72.6)
	Jan 2013 – Dec 2019	Prospective database of patients with necrotizing soft tissue infection
St. Antonius Hospital	Jan 2010 – Sept 2016	Patients identified using search terms necrotizing fasciitis, Fournier gangrene, myonecrosis in three databases: • Rare disease list kept by intensive care department • The consulting system of the microbiology department • The microbiology laboratory information management system for documented positive fascia cultures
	Oct 2016 – Dec 2019	Patient sought using the International Code for Disease (ICD) 10 for necrotizing fasciitis (M72.6) and Fournier gangrene (N49.3) and the Surgical Diagnosis Treatment Combination (DBC) codes for necrotizing fasciitis (164), soft tissue infections (160), large wounds (282) and Fournier gangrene (068 and 098)
Diakonessenhuis	Jan 2010 – Dec 2019	Patient sought using the International Code for Disease (ICD) 10 for necrotizing fasciitis (M72.6) and Fournier gangrene (N49.3) and the Surgical Diagnosis Treatment Combination (DBC) codes for necrotizing fasciitis (164), soft tissue infections (160), large wounds (282) and Fournier gangrene (068 and 098)
Meander Medical Center	Jan 2010 – Dec 2019	Patient sought using the Surgical Diagnosis Treatment Combination (DBC) codes for necrotizing fasciitis (164), soft tissue infections (160), large wounds (282) and Fournier gangrene (068 and 098)

4

Exhaustion of the immune system by Group A Streptococcus necrotizing fasciitis: the occurrence of late secondary infections in a retrospective study

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Abstract

Background: Necrotizing fasciitis is a potentially lethal condition for which early and adequate treatment with surgical debridement and broad-spectrum intravenous antibiotics are essential for survival. It is hypothesized that GAS necrotizing fasciitis causes exhaustion of the immune system, making these patients more susceptible for late secondary infections.

Methods: A retrospective study was conducted of all necrotizing fasciitis patients between 2002 - 2016. Patients with necrotizing fasciitis based on macroscopic findings, positive Gram-staining, culture or fresh frozen section of fascia biopsies were included. Necrotizing fasciitis patients were divided in two groups based on the presence of GAS. Of both groups, clinical course, outcome and occurrence of late secondary infections were analyzed. For the occurrence of secondary infections, pneumonia was chosen as reference for late secondary infections.

Results: Eighty-one necrotizing fasciitis patients were included of which 38 (47%) had GAS necrotizing fasciitis and 43 (53%) non-GAS necrotizing fasciitis. GAS necrotizing fasciitis patients were younger (50 vs. 61 years, p = 0.023) and more often ASA I (45% vs. 14%, p = 0.002) compared to non-GAS necrotizing fasciitis patients. In-hospital mortality rate for necrotizing fasciitis was 32%. Patients with comorbidities were more likely to die of necrotizing fasciitis compared to patients without comorbidities (OR 7.41, 95% CI 1.58 – 34.63). Twelve patients (39%) with GAS necrotizing fasciitis developed pneumonia compared to 4 patients (13%) with non-GAS necrotizing fasciitis (p = 0.017; OR 4.42, 95% CI 1.124 – 15.79). Median time from diagnosis to development of pneumonia in GAS necrotizing fasciitis patients was 10 days (IQR 9).

Conclusion: Patients with GAS necrotizing fasciitis have an increased risk to develop late secondary infections during initial treatment for necrotizing fasciitis compared to patients with necrotizing fasciitis without involvement of GAS. This suggests exhaustion of the immune system after severe GAS infection.

Background

Necrotizing Soft Tissue Infections (NSTIs or 'necrotizing fasciitis') are rare, severe and potentially lethal conditions for which early and adequate treatment with surgical debridement and broad-spectrum intravenous antibiotics are essential for survival [1]. Necrotizing fasciitis is associated with significant morbidities such as organ dysfunction and amputations [2–4]. Delay in diagnosis is associated with higher morbidity and mortality, but diagnosis can be challenging, as no early pathognomonic symptoms are known. [5–7]. When necrotizing fasciitis is suspected, triple diagnostics - based on per-operative macroscopic findings, Gram staining and analysis of fresh frozen sections - is proposed for fast and early conformation of the diagnosis and thus to reduce treatment delay [8].

All NSTIs (including necrotizing fasciitis, myonecrosis and necrotizing cellulitis) are commonly classified according to microbiologic findings, dividing it in type I (polymicrobial) and type II (monomicrobial) [4,9]. The organism isolated in type II necrotizing fasciitis is frequently Group A Streptococcus (GAS), but other streptococcal species or staphylococcal species can also be found [4,10]. Evident differences in clinical course and outcome between both types have not yet been clearly described in current literature. However, differences in patient demographics have been previously reported, stating that patients with type II necrotizing fasciitis tend to be healthier and younger compared to type I [11,12].

As a result of its often complicated disease course, necrotizing fasciitis is known to impose a high burden on the surgical and critical care and thus on the patient [11,13]. Specifically, GAS causes an excessive inflammatory response, and might induce a damaged and dysregulated immune system [11]. The fulminant course of GAS necrotizing fasciitis is due to the amplified systematic immune response caused by the release of GAS exotoxins (also known as superantigens), which can lead to toxic shock syndrome [11]. It is hypothesized that the massive release of pro-inflammatory cytokines causes exhaustion of the patient and the immune system, making these patients more susceptible for secondary infections [14].

The aim of this study was to assess the occurrence of late secondary infections, with pneumonia as reference, in patients hospitalized for initial treatment of GAS necrotizing fasciitis compared to patients with necrotizing fasciitis without involvement of GAS.

Methods

A study protocol was not registered nor published. This article was written in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [15].

Study Design

A retrospective observational multi-center study was performed in the University Medical Center Utrecht (UMCU) and St. Antonius Hospital, an academic medical center and a large peripheral teaching hospital in the Netherlands, respectively. The institutional review board of both centers provided a waiver. Patients diagnosed with necrotizing fasciitis from August 2002 until September 2016 in either of these centers were identified. In current literature, NSTI is defined as an infection of any of the layers within the soft tissue compartment with necrotizing changes of which necrotizing fasciitis is the most prominent infection [7,11]. Patients who presented at UMCU were identified using the associated ICD-10 code (International Classification of Diseases) for necrotizing fasciitis. As no official ICD-10 code existed for the diagnosis necrotizing fasciitis in the St. Antonius hospital, patients were searched using the search terms 'NSTI', 'fasciitis necroticans / necrotizing fasciitis', Fournier's gangrene' and 'myonecrosis'. To reduce selection bias, this search was performed in multiple databases; 1) rare disease lists kept by the intensive care department, 2) the consulting system of the microbiology department and 3) the microbiology laboratory information management system with documented positive fascia biopsies. All cases of necrotizing fasciitis from both centers were identified and data were independently collected by three researchers (FN, EW, FH). Patients were included if the diagnosis of necrotizing fasciitis (including Fournier's gangrene and myonecrosis) was confirmed by two out of three modalities: 1) macroscopic findings during surgery, 2) positive findings in the fascia fresh frozen section and 3) positive Gram staining or tissue cultures confirmed by the medical microbiology department. Macroscopic findings indicative for necrotizing fasciitis were lack of tissue resistance, grey necrotic tissue and non-contracting muscles [8,16,17]. Exclusion criteria were patients with a superficial infection (complex cellulitis or erysipelas) and out-of-hospital death before initial presentation at the hospital. For the occurrence of late secondary infections, pneumonia was chosen as reference infection as result of its evident clinical presentation. Other infectious complications such as multiple organ dysfunction syndrome and bacteremia usually are already present at admission, while it is the second hit that is of interest in the present study. This simultaneous presentation of these complications with necrotizing fasciitis makes it difficult to distinguish them as a primary infection combined with necrotizing fasciitis or as secondary complication with secondary sepsis after a few days [18]. Furthermore, it is challenging to objectively extract details on these complications and secondary infections such as surgical site infections from patient's charts. This is in contrast to the unambivalent description of pneumonia in radiology and microbiology reports, providing a suitable reference infection for late secondary infections.

Data collection

The number of cases found in both hospitals during the study period determined the sample size. For all identified patients, demographic characteristics (sex, age, ASA (American Society of Anesthesiologists) classification, medical history, date and time of presentation, medical microbiology, pathology and operation reports, length of hospitalization, length of Intensive Care Unit (ICU) stay and mortality were extracted from the hospitals' electronic medical charts. The variable time between first presentation and surgery was categorized in four time-categories (within 12 hours, 12 – 24 hours, 24 – 48 hours and over 48 hours). Furthermore, of all patients developing pneumonia, the date of pneumonia diagnosis, the causative agent of the pneumonia and antibiotic treatment received for the necrotizing fasciitis were extracted. The length of follow-up was the length of hospital stay for initial treatment of the necrotizing fasciitis. Patients were divided in two groups based on the isolated organism(s) in the fascia biopsy, resulting in a group in which GAS was isolated, either as single organism or as part of a polymicrobial infection. Patients with negative fascia cultures were excluded from the study. The second group consisted of patients in which other organisms than GAS was isolated.

The primary outcome of this study was the rate of late secondary infections during hospitalization for the initial treatment of necrotizing fasciitis, based on the occurrence of pneumonia, in patients with GAS necrotizing fasciitis compared to necrotizing fasciitis without involvement of GAS. Necrotizing fasciitis patients with (suspected) pneumonia were identified based on their medical charts and discussed in a consensus meeting between three researchers (FN, EW, FH) to determine compliance to the a priori defined definition of pneumonia, which was ''an alteration in treatment plan based on pulmonary complaints suspicious for pneumonia combined with supporting radiology finding and/or positive cultures for micro-organisms'' [19,20]. This definition was chosen since these results all can be extracted objectively and retrospectively from patients' charts. To assess if there was an association between necrotizing fasciitis and late secondary infections, patients who died within five days after diagnosis were excluded from all analysis involving pneumonia, since these patients did not have a chance to develop a pneumonia as a delayed consequence of the necrotizing fasciitis. For all other analysis, all identified patients were included, regardless of mortality within five days. A subgroup analysis was performed to assess the baseline characteristics and clinical outcomes of all patients with pneumonia compared to patients without pneumonia.

A second subgroup analysis was performed to assess the association between the ASA classification and the in-hospital mortality rate in patients with GAS necrotizing fasciitis and necrotizing fasciitis without involvement of GAS.

Statistical analysis

Continuous data were presented as means with standard deviation or medians with interquartile ranges (IQR). Categorical data were presented as frequencies with percentages. Missing data were handled using pairwise deletion to reduce information bias. Odds ratios (ORs) were presented with 95% confidence intervals (95% CI). Normally distributed data were compared using the independent samples t-test for continuous variables or the Chi-square test for categorical variables. The two-tailed Mann-Whitney-U test was used to compare not normally distributed continuous variables. The Fisher exact test for dichotomous variables or the Fisher-Freeman-Halton test, in case of categorical variables with more than two categories, was used when a cell count of five or less was observed. In none of the analysis was adjusted for confounding due to the small sample size. For all analyses, a two-sided p-value < 0.05 was considered statistically significant. Data were analyzed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Patient characteristics

A total of 84 patients with necrotizing fasciitis were identified. Three patients were excluded based on negative fascia cultures, resulting in 81 eligible patients for inclusion. GAS was isolated from fascia cultures in 38 patients (47%) and 43 patients (53%) had fascia cultures without isolation of GAS. The median age of patients with GAS necrotizing fasciitis was 50 (IQR 29), which was significantly younger compared to patients with non-GAS necrotizing fasciitis (61 years (IQR 20), p = 0.023). In both groups, most patients were male (66% and 70%). Patients with GAS necrotizing fasciitis were more often classified as ASA I compared to the non-GAS group (45% vs. 14%, p = 0.002). At baseline, patients with GAS necrotizing fasciitis had less frequently diabetes mellitus (21% vs. 43%, p = 0.038) and tended to have less cardiovascular diseases or recent surgery in their medical history compared to the non-GAS group. The primary site of infection affected most often the extremities in both the GAS (45%) and non-GAS group (50%). In patients with necrotizing fasciitis of the chest or axilla, GAS was significantly more frequent isolated (21% vs. 3%, p = 0.013). GAS was less frequent isolated in necrotizing fasciitis of the perineum (18% vs. 40%, p = 0.037). In both groups, most patients underwent surgery within twelve hours after presentation (62% in GAS group vs. 58% in non-GAS group). In the non-GAS necrotizing fasciitis group, surgical treatment tends to be more frequently delayed beyond 24 hours after initial presentation (24% vs. 33%). All baseline characteristics are presented in table 1.

Table 1 Baseline characteristics of patients with necrotizing fasciitis

	Total n = 81 (100%)	GAS necrotizing fasciitis n = 38 (47%)	Non-GAS necrotizing fasciitis n = 43 (53%)	*p*-value
Age (median, IQR)	56 (27)	50 (29)	61 (20)	**0.023**
Sex				
Male	55 (68%)	25 (66%)	30 (70%)	0.702
Female	26 (32%)	13 (34%)	13 (30%)	
ASA classification				0.017
I	23 (28%)	17 (45%)	6 (14%)	
II	36 (45%)	13 (34%)	23 (53%)	
III	14 (17%)	6 (16%)	8 (19%)	
IV	8 (10%)	2 (5%)	6 (14%)	
Comorbidities[a]				
Diabetes mellitus	26 (33%)	8 (21%)	18 (42%)	**0.038**
Cardiovascular disease	15 (19%)	6 (16%)	9 (21%)	0.519
Pulmonary disease	9 (11%)	5 (13%)	4 (10%)	0.729
Medical History[a]				
Malignancy	15 (19%)	7 (18%)	8 (19%)	0.943
Auto-immune disease	12 (15%)	6 (6%)	6 (6%)	0.851
Surgery within 30 days	17 (21%)	7 (18%)	10 (24%)	0.556
Localization necrotizing fasciitis[b]				
Abdomen	5 (6%)	2 (5%)	3 (7%)	1.000
Chest and axilla	9 (12%)	8 (21%)	1 (3%)	**0.013**
Head and neck	4 (5%)	4 (11%)	0 (0%)	0.052
Extremity	37 (48%)	17 (45%)	20 (50%)	0.642
Perineum	23 (29%)	7 (18%)	16 (40%)	**0.037**
Time between first presentation and surgery[c]				0.414
	42 (60%)	21 (62%)	21 (58%)	
<12 hours	8 (11%)	5 (15%)	3 (8%)	
12-24 hours	14 (20%)	7 (20%)	7 (20%)	
24-48 hours	6 (9%)	1 (3%)	5 (14%)	
>48 hours				

ASA = American Society of Anesthesiologists; GAS = Group A Streptococcus; IQR = Interquartile range; **Bold** font indicates significant result. [a] 1 (1%) missing case; [b] 3 (4%) missing cases; [c] 11 (14%) missing cases

Table 2 Clinical outcomes of patients with (non-) Group A Streptococcus necrotizing fasciitis

	Total n = 81 (100%)	GAS necrotizing fasciitis n = 38 (47%)	Non-GAS necrotizing fasciitis n = 43 (53%)	*p*-value
Total no. of surgeries (median, IQR)[a]	3 (4)	2 (2)	2 (1)	0.756
Amputation	15 (19%)	8 (21%)	7 (16%)	0.581
Hospital length of stay (median, IQR)	31 (35)	31 (33)	32 (47)	0.721
ICU admittance	68 (84%)	35 (92%)	33 (77%)	0.060
ICU length of stay (median days, IQR)[b]	5 (11)	6 (12)	4 (8)	0.406
Pneumonia[c]	16 (25%)	12 (39%)	4 (13%)	**0.017**
Time between diagnosis and pneumonia (median days, IQR)	11 (19)	10 (9)	33 (43)	0.063
Mortality	26 (32%)	7 (18%)	19 (44%)	**0.013**
Died within five days after necrotizing fasciitis diagnosis	18 (69%)	7 (100%)	11 (58%)	0.439
Time between diagnosis and death (median days, IQR)	3 (9)	1 (2)	4 (14)	0.055

GAS = Group A Streptococcus; ICU = Intensive Care Unit; IQR = Interquartile Range; **Bold** font indicates significant result. [a] 1 (1%) missing case; [b] 13 (16%) missing cases; [c] All patients who died within five days after necrotizing fasciitis diagnosis were excluded from this analysis.

Table 3 Association between ASA classification and mortality in patients with (non-) Group A Streptococcus necrotizing fasciitis

	Total n = 81 (100%)			GAS necrotizing fasciitis n = 38 (47%)			Non-GAS necrotizing fasciitis n = 43 (53%)		
	Died n = 26 (32%)	Survived n = 55 (68%)	*p*-value	Died n = 7 (18%)	Survived n = 31 (82%)	*p*-value	Died n = 19 (44%)	Survived n = 24 (56%)	*p*-value
ASA			**0.004**			0.427			**0.027**
I	2 (2%)	21 (26%)		2 (5%)	15 (39%)		0 (0%)	6 (14%)	
II-IV	24 (30%)	34 (42%)		5 (13%)	16 (42%)		19 (44%)	18 (42%)	

ASA = American Society for Anesthesiology; GAS = Group A Streptococcus; **Bold** font indicates significant result.

Overall outcome characteristics

On average, all patients required 3 (IQR 4) surgical debridements to treat the necrotizing fasciitis, 15 patients (19%) required amputation and 64 patients (84%) were admitted to the ICU with a median length of stay of 5 (IQR 11) days. Total length of hospital stay was 31 (IQR 35) days. The overall rate of late secondary infections, measured as pneumonia rate during initial hospitalization for treatment of necrotizing fasciitis, was 24% among the entire necrotizing fasciitis population (Table 2). The overall in-hospital mortality of necrotizing fasciitis during the inclusion period of this study was 32% (n = 26). Subgroup analysis showed that patients classified as ASA I were less likely to die of necrotizing fasciitis compared to patients classified as ASA II – IV (2% vs. 30%, p = 0.004) with an odds ratio of 0.16 (95% CI 0.03 – 0.63) for mortality (Table 3).

Impact of GAS on outcome

There were no significant differences between the total number of surgeries, number of amputations, hospital length of stay or ICU admittance between GAS necrotizing fasciitis and non-GAS necrotizing fasciitis. Patients with GAS necrotizing fasciitis were statistically significant more likely to develop a pneumonia compared to patients with non-GAS necrotizing fasciitis (39% vs. 13%, p = 0.017; OR 4.42, 95% CI 1.24 – 15.79). The in-hospital mortality rate of patients with GAS necrotizing fasciitis was significantly lower compared to patients with non-GAS necrotizing fasciitis (18% vs. 44%, p = 0.013) (Table 2). No significant association was found in the subgroup analysis assessing ASA classification and mortality in GAS necrotizing fasciitis patients. A significant association between the presence of underlying comorbidities and in-hospital mortality rate was seen in non-GAS necrotizing fasciitis (0% ASA I vs. 44% ASA II-IV, p = 0.027) (Table 3). Patients with GAS necrotizing fasciitis received immunoglobulins in 40% of the cases (n = 14). Analyses showed no association between administration of immunoglobulins and the outcome variables.

Patients with pneumonia

No significant differences were found in baseline characteristics of necrotizing fasciitis patients developing pneumonia and those who did not. Patients who developed pneumonia were most often classified as ASA II (56%). Pneumonia was diagnosed at a median of 11 days (IQR 19) after start of treatment for necrotizing fasciitis, which was 10 days (IQR 9) in the GAS group and 33 days (IQR 43) in the non-GAS group. Most commonly isolated organism associated with pneumonia was the *Pseudomonas aeruginosa*, other frequent organisms isolated from sputum cultures were *Candida albicans* and *Klebsiella oxytoca* (Table 4). All patients with pneumonia were admitted to the ICU at some point during their treatment for the necrotizing fasciitis (100% vs. 75%, p = 0.027). The group with a pneumonia required more

Table 4 Pathogens associated with development of pneumonia in patients with necrotizing fasciitis

Case no.	Days until onset pneumonia (days)	Necrotizing fasciitis associated micro-organism found	Pneumonia associated isolated organism	Antibiotic treatment given for necrotizing fasciitis
1	2	GAS	Yeast	Benzylpenicillin, clindamycin
2	3	GAS	*Candida albicans*	Benzylpenicillin, clindamycin
3	6	GAS	No cultures, diagnosis based on chest x-ray	Meropenem
4	6	GAS	*Aspergillus fumigatus*	Benzylpenicillin, clindamycin, gentamicin
5	7	GAS	*Enterobacter cloaca*	Benzylpenicillin, clindamycin
6	10	GAS	*Enterobacter cloaca complex, Stenotrophomonas maltophilia*	Benzylpenicillin, clindamycin
7	10	GAS	*Klebsiella oxytoca, Escherichia coli*	Cefuroxime
8	11	GAS	*Candida albicans, Pseudomonas aeruginosa, Klebsiella oxytoca*	Benzylpenicillin, clindamycin
9	14	GAS	*Proteus mirabilis, Candida albicans*	Benzylpenicillin, clindamycin, gentamicin
10	15	GAS, *E. coli*	*Pseudomonas aeruginosa*	Cefuroxime, clindamycin, gentamicin, metronidazole
11	21	GAS	*Pseudomonas aeruginosa, Candida albicans*	Benzylpenicillin, clindamycin, gentamicin
12	26	GAS	*Klebsiella oxytoca, Serratia marcescens, Streptococci*	Benzylpenicillin, clindamycin, gentamicin
13	7	*S. pneumoniae, S. aureus*	*Pseudomonas aeruginosa*	Benzylpenicillin, clindamycin, gentamicin
14	26	GGS, *S. aureus*	No cultures, diagnosis based on chest x-ray	Benzylpenicillin, clindamycin, gentamicin
15	40	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Piperacilline, tazobactam
16	60	*Morganella morganii*	No cultures, diagnosis based on clinical presentation	Meropenem

GAS = Group A Streptococcus; GGS = Group G Streptococcus;

frequent amputations (50% vs. 15%, p = 0.014) and required more surgical debridements (5 (IQR 4) vs. 3 (IQR 3), p = 0.015). Patients who developed pneumonia had a longer length of hospital stay (62 days (IQR 44) vs. 23 days (IQR 22), p < 0.001) and ICU stay (24 days (IQR 24) vs. 5 days (IQR 7), p < 0.001).

Discussion

This study found that patients with GAS necrotizing fasciitis are more likely to develop pneumonia during hospitalization compared to patients with necrotizing fasciitis without involvement of GAS. Notably, pneumonia became clinically evident 10 days after the necrotizing fasciitis diagnosis in the GAS group, compared to 33 days in patients without involvement of GAS. Furthermore, patients with GAS necrotizing fasciitis were significantly younger and had less comorbidities. The clinical course of GAS necrotizing fasciitis was more prolonged, especially in patients developing a late secondary infection, with more surgical debridements and more frequent an indication for amputation.

This is, to our knowledge, the first study assessing the clinical course and occurrence of late secondary infections focusing on necrotizing fasciitis with involvement of GAS. Previous studies have assessed the differences between type I and type II necrotizing fasciitis, but no evident differences in clinical course or outcome were reported [21,22]. However, the microbiologic classification is still used since the specific pathophysiologic mechanisms of the disease often depends on the specific properties of the byproducts produced by the bacteria involved, resulting in significant differences in patient populations and clinical presentation [11,23,24]. Type I necrotizing fasciitis occurs more frequent in immunocompromised hosts and effects typically the perineum and trunk, whereas type II necrotizing fasciitis patients tend to have no comorbidities and typically have necrotizing fasciitis of the extremities or trunk [3,11,12,23,25]. All these studies assessed GAS necrotizing fasciitis as part of type II, combined with all other monomicrobial necrotizing fasciitis, which limits the ability to provide firm conclusions about the clinical course of solely GAS necrotizing fasciitis. The exact incidence of GAS as isolated organisms in necrotizing fasciitis is unknown, incidences varying from 9% up to 56% have been reported [3,21,26–28]. This study found a relatively high number (47%) of positive fascia biopsies with GAS. Such high incidences are mainly seen in Europe and the United States [28].

This study found that patients with GAS necrotizing fasciitis were significantly younger and were more often classified as ASA I, indicating a healthier patient population. These finding are in line with previously conducted studies [3,11,12]. Therefore, it seems contradictory that especially these patients are more susceptible for late secondary infections. The most plausible explanation for this finding can be

found in the pathophysiology of GAS infections. GAS produce a broad array of virulence factors, such as the M protein and pyrogenic exotoxins [23]. The M proteins permit tissue adherence, evasion of phagocytosis and bypass of the typical antigen presentation pathway. Pyrogenic exotoxins act as superantigens by binding directly to and activating a large number of T-helper-cells. Resulting in an amplified activation of the inflammatory cascade, including a massive release of pro-inflammatory cytokines, leading to systemic toxicity and the development of toxic shock syndrome [11,23,29–31]. Furthermore, the produced exotoxins are known to damage neutrophils, prevent phagocytosis and bacterial clearance by fluid secretion, and break down hyaluronic acid in connective tissues facilitating spread along deep tissue planes [11,23,32]. These virulence factors and exotoxins make GAS a highly potent micro-organism, which can effectively evade the immune system of even a previously healthy patient [23,31]. The same response is seen in severe trauma patients, in which a reduced responsiveness of polymorphonuclear neutrophils and a state of immune paralysis due to dysregulation of the pro- and anti-inflammatory response is seen. This contributes to an elevated incidence of infectious complications on day 7 to 14 after trauma [33,34]. This theory could be extrapolated to our cohort in which the GAS infection can be considered equal to severe trauma. Both result in a massive immune response with an amplified pro-inflammatory response and subsequent dysregulation, resulting in exhaustion of the immune system followed by severe infectious complications by opportunistic micro-organisms. Even the timeline for development of late secondary infections due to depletion of the immune system caused by GAS is in line with the theory of the dysregulated immune system seen in polytrauma patients, with pneumonia occurring a median of 10 days after diagnosis of necrotizing fasciitis [33,34].

A compromised immune system makes patients more susceptible to normally non-virulent bacterial and fungal infections [35]. Necrotizing fasciitis patients without involvement of GAS developed pneumonia 33 days after diagnosis, making it very unlikely that the pneumonia in this group was a direct consequence of a dysregulated immune system such as seen in GAS necrotizing fasciitis, but more likely the result of illness in patients with multiple comorbidities during a prolonged hospital stay.

Only Faraklas et al. have previously reported on the occurrence of pneumonia in a necrotizing fasciitis cohort, which occurred in 7% of all patients, thereby presenting a considerably lower incidence than the 25% in our cohort [13]. Faraklas et al. did not perform subgroup analysis based on microbiology, therefore the influence of GAS on their percentage is unknown, and thus, prevents direct comparison to our cohort.

Almost all patients, including patients eventually developing a pneumonia, received benzylpenicillin and clindamycin at presentation, with or without the addition of a single-dose of gentamicin, as initial treatment for necrotizing fasciitis. Benzylpenicillin and clindamycin are both effective against Gram-positive organisms [4,10,16]. Both antibiotics thus exert a selective pressure toward Gram-negative colonization and subsequent nosocomial pneumonia with Gram-negative pathogens. In healthy individuals the immune system is potent enough to clear these Gram-negative bacteria [36]. This appears not to be the case in necrotizing fasciitis patients developing pneumonia. The dysfunctional immune system caused by GAS results in an inability to clear Gram-negative organisms and fungi effectively with an opportunistic pneumonia as outcome.

In this cohort, the overall in-hospital mortality was 32%, which is in line with previously reported mortality rates of 14 – 33% [2,13,21,37]. Remarkably, the mortality rate of GAS necrotizing fasciitis was significantly lower compared to the group without involvement of GAS, even though patients with GAS necrotizing fasciitis are more at risk for late secondary infections. Two possible theories could explain this unexpected finding. First, patients with GAS necrotizing fasciitis tend to be younger and have less comorbidities making them more vigilant to severe disease, as ASA classification was the most important factor for mortality. This is in line with previous studies in which the presence of GAS did not influence the mortality, but the presence of pre-existent comorbidities did [21,24,37,38]. Patients classified ASA II or higher are more at risk to developing necrotizing fasciitis and, when they do, have a worse prognosis. Necrotizing fasciitis patients with comorbidities, especially patients with necrotizing fasciitis without involvement of GAS, were more likely to die compared to patients without comorbidities. The high frequency of comorbidities found in patients with necrotizing fasciitis without involvement of GAS could (partly) explain the relative high mortality rate in this group compared to patients with GAS necrotizing fasciitis [3,21,26,37]. The second theory is that due to the severity of GAS necrotizing fasciitis, it might be that diagnosis was made more promptly and debridement more aggressive. However, this study was unable to provide rigid data supporting this matter.

These results should be interpreted in the right context. The retrospective nature of this study unfortunately resulted in some degree of information bias due to certain missing variables. Not all variables were reported in the level of detail as desired, such as the exact time of presentation and diagnosis. When possible, time was categorized, which resulted in less missing values. Additionally, the relatively high in-hospital mortality rate within five days after diagnosis in necrotizing fasciitis patients without involvement of GAS could have caused selection bias in our risk assessment of the occurrence of pneumonia, since they might have developed a pneumonia if

they had lived longer. Furthermore, there was a difference in the selection process between both hospitals, due to the absence of a corresponding ICD-code for necrotizing fasciitis at the St. Antonius Hospital. This might have resulted in selection bias. However, the elaborated search of different databases and lists at this hospital limited the risk of missing eligible patients for inclusion. Furthermore, we consider the generalizability of this study to be high, as it is predominantly conceptual in nature and with underlying data obtained from an academic and a peripheral hospital and covering a substantial time period.

Conclusion

Patients with GAS necrotizing fasciitis have an increased risk to develop late secondary infections compared to patients with necrotizing fasciitis without involvement of GAS. This increased risk is likely due to the fulminant disease course of GAS necrotizing fasciitis with exhaustion of the immune system caused by the virulent factors of GAS, preventing adequate immunologic response against opportunistic bacteria and fungi.

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5

A five-year evaluation of the implementation of triple diagnostics for early detection of severe necrotizing soft tissue disease: a single-center cohort study

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Abstract

Background: The standardized approach with triple diagnostics (surgical exploration with visual inspection, microbiological and histological examination) has been proposed as golden standard for early diagnosis of sever necrotizing soft tissue disease (SNSTD, or necrotizing fasciitis) in ambivalent cases. This study's primary aim was to evaluate the protocolized approach after implementation for diagnosing (early) SNSTD and relate this to clinical outcome.

Methods: A cohort study analyzing a five-year period was performed. All patients undergoing surgical exploration (with triple diagnostics) for suspected SNSTD since implementation were prospectively identified. Demographics, laboratory results and clinical outcomes were collected and analyzed.

Result: Thirty-six patients underwent surgical exploration with eight (22%) negative explorations. The overall 30-day mortality rate was 25%, with an early, SNSTD related mortality rate of 11% (n = 3). Of these, one patient (4%) underwent primary amputation, but died during surgery. No significant differences between baseline characteristics were found between patients diagnosed with SNSTD in early/indistinctive or late/obvious stage. Patient diagnosed at an early stage had a significant shorter ICU stay (2 vs. 6 days, *p*-value = 0.031). Mortality did not differ between groups, patients who died were all ASA IV patients.

Conclusion: Diagnosing SNSTD using the approach with triple diagnostics resulted in a low mortality rate and only a single amputation in a pre-terminal patient in the first five years after implementation. All deceased patients had multiple pre-existing comorbidities consisting of severe systemic diseases, such as end stage heart failure. Early detection proved to facilitate faster recovery with shorter ICU stay.

Introduction

Severe necrotizing soft tissue disease (SNSTD, or necrotizing fasciitis), is a rapidly spreading and life-threating infection with subsequent necrosis of the fascia often extending into the skin, soft tissue and muscles [1,2]. If untreated, the development of septic shock is inevitable and the infection will have a mortality rate reaching 100% [1,3]. Early recognition, immediate aggressive surgical debridement, adequate antibiotic coverage and, if necessary in cases of sepsis, aggressive resuscitation should reduce mortality [2,4,5]. However, diagnosing SNSTD timely remains one of the greatest challenges in managing the disease [6,7]. There are no pathognomonic early signs of SNSTD available to differ between other less severe soft tissue infections such as cellulitis or erysipelas, resulting in a high rate of misdiagnoses [2,7,8]. Therefore the consensus is that the diagnosis can only be established surgically [1–4].

Since a direct correlation between delayed diagnosis and mortality has been demonstrated, the diagnostic process should improve [3,7,9]. Therefore, triple diagnostics (surgical exploration with visual inspection, microbiological and histological examination) has been advocated as golden standard for diagnosing SNSTD in ambivalent cases [3,5,10]. If fascial necrosis is macroscopically evident, the treating surgeon can immediately start debridement. If the exploration remains indecisive (i.e. fascial edema) further diagnostics with intra-operative fresh frozen section and Gram stain of fascial biopsies should be obtained. Histological signs of fascial necrosis or bacterial invasion warrant further exploration and debridement. In case of negative finding, the procedure can be discontinued with assumed little risk or morbidity for the patient [5]. Five years ago, the approach of diagnosing SNSTD using triple diagnostics was protocolized at our hospital. Therefore, this study's primary aim is to evaluate the diagnostic and clinical outcomes achieved after implementation of triple diagnostics for suspected SNTSD.

Material and Methods

The institutional review board provided a waiver (WAG/om/15/032329) for retrospective data collection.

Study Design

A single-center cohort study was performed of all patients with suspected SNSTD undergoing surgical exploration at an academic level I trauma center and tertiary referral center, as part of the standardized approach with triple diagnostics. All patients over 18 years and undergoing triple diagnostics for suspected diagnosis of SNSTD since its implementation at this hospital in January 2013 were prospectively

identified and included for quality evaluation. Patient not undergoing surgical exploration based on clinical symptoms evaluated by the surgeon were excluded.

The approach of triple diagnostics

The algorithm used for diagnosing SNSTD in our cohort, known as "triple diagnostics", is previously described in an article by Hietbrink et al. [5] and based on previous reports [3,10]. Patients presenting with clinical symptoms consisted with SNSTD were taken to the operation room if a fair suspicion for SNSTD remained after clinical evaluation of the presenting symptoms, vital parameters and laboratory values by the (attending) surgeon. The approach consists of surgical exploration with visual inspection of the infected soft tissues and when deemed necessary combined with histological and microbiological examination of a surgically obtained fascial sample in case of clinically suspected or indistinct SNSTD. The clinical diagnosis can be assured immediately based on intra-operative macroscopic findings of fascial necrosis or can remain indistinct. If the diagnosis remains ambivalent (i.e. perifascial edema), fascial biopsies should be examined intra-operatively as fresh frozen section and Gram stain. Criteria for positive histological examination were necrosis of the superficial fascia, fibrinous thrombi of arteries and veins passing through fascia, angiitis with fibrinoid necrosis of vessel walls, infiltration of fascia (and deep dermis) with abundant polymorphonuclear neutrophils or micro-organisms within the destroyed fascia and dermis [5,11]. Gram stain was conclusive for SNSTD if the fascial biopsy contained microbes with or without leukocytes [5]. To ensure reliable results from the fresh frozen section and Gram stain, the surgeon should be aware that the biopsy taken for fresh frozen section unequivocally consists of multiple tissue layers – from skin to muscle - of the affected area [5,11,12]. On the contrary, the biopsy sent for Gram stain should only consist of fascia and should be taken with sterile instruments with a no-touch technique to prevent contamination with colonizing skin flora [13]. Based on those results, the patient is allocated to one of three treatment strategies (Table 1) [5]. For this study, all included patients were divided into one of these three groups as well based on the findings during surgical exploration.

Data collection

Some of the patients in this cohort were previously published by Hietbrink et al. in 2016 as part of an evaluation of the triple diagnostics technique [5]. For all identified patients, demographic characteristics (age, American Society of Anesthesiologists (ASA) classification, medical history), disease characteristics (location, cultures, hours since onset symptoms), vital functions, laboratory results (leukocytes, C-reactive protein, hemoglobin, sodium, creatinine, glucose, creatine kinase) and arterial blood gas results at presentation, hours from suspicion to surgery, intra-

Table 1 Possible treatment strategies based on standardized approach with triple diagnostics for diagnosing severe necrotizing soft tissue disease

Group 1	Intra-operative findings of necrotic fascia and/or muscle resulting in immediate decision to perform debridement.
Group 2	Intra-operative findings of fascial edema combined with positive intra-operative results of the fascia frozen section OR Gram staining, requiring further exploration and debridement.
Group 3	Negative exploration with no macroscopic intra-operative abnormalities or macroscopic fascial edema, together with negative intra-operative results of the fascia frozen section AND Gram staining.

operative results of triple diagnostics, attempt at skin-sparing debridement, cultures results, length of hospitalization, length of Intensive Care Unit (ICU) stay, amputation rate and in-hospital mortality were collected from the hospital's electronic medical chart. The laboratory results were used to calculate the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score at presentation for each patient [9]. Definitive culture results were used to classify the SNSTD in type I (polymicrobial), type II (monomicrobial) or type III (e.g. *Clostridium* spp. or *Vibrio* spp.) [1]. Early diagnosis of SNSTD was defined as the patients with only histological or microbiological signs of SNSTD (group 2), late diagnosis of SNSTD was defined as the patients with already macroscopic signs of fascial necrosis (group 1).

The primary outcomes of this study were the amputation and 30-day mortality rate. The secondary outcomes were length of hospital stay and ICU stay, which were compared between patients with macroscopic fascial necrosis and diagnosis established by triple diagnostics.

Statistical analysis

Continuous data were presented as means with standard deviation (SD) or medians with interquartile ranges (IQR). Categorical data were presented as frequencies with percentages. The independent samples t-test was used to analyze normally distributed continuous variables and the two-tailed Mann-Whitney-U test for not normally distributed continuous variables and ordinal categorical variables. The Fisher exact test was used for nominal categorical variables. For all analyses, a two-sided p-value < 0.05 was considered statistically significant. Data were analyzed using STATA (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

Results

Patient demographics

After implementation, 36 patients underwent surgical exploration for suspicion of SNSTD. The average age of patients was 54 ± 16 years and most patients had multiple comorbidities (66% were ASA III or IV) (Table 2). Eight explorations with triple diagnostics (22%) were negative for SNSTD and 28 patients (78%) were diagnosed with SNSTD. Of these 16 (57%) patients had macroscopic findings of necrotic fascia and/or muscle and 12 (43%) patients were diagnosed based on macroscopic tissue edema combined with a positive fresh frozen section or Gram stain (Fig. 1). There were no false positive or false negative debridements. The median time from suspicion to surgical exploration was 1 hours and 15 minutes (Table 2). The longest time from suspicion to surgery being nine hours in one patient, while all other patients were brought to the OR within 2.5 hours after presentation. The treatment delay in this patient was caused by misjudgment of the severity of the symptoms during initial screening. The shortest time was 16 minutes between suspicion and surgery. Most SNSTDs were localized at the lower extremity (n = 21, 58%) and *Streptococcus pyogenes* (e.g. beta hemolytic group A Streptococcus; GAS) was most often the isolated causative micro-organism (n = 17, 61%). The mean LRINEC score at admission was 6 ± 3, which differed between groups (Group 1: 7 ± 2; Group 2: 5 ± 3; Group 3: 5 ± 3).

Clinical outcomes of positive exploration

The overall 30-day mortality rate of SNSTD was 25% (n = 7), with an early, direct SNSTD related, mortality rate of 11% (n = 3). The three patients who died as a direct consequence of SNSTD all died within two days after admission. The four additional patients with late mortality died as result of withdrawal of care due to severe comorbidities and poor preclinical condition, which occurred in all cases after two days of admission. All seven patients who died were classified as ASA IV patients. Only one patient (4%) underwent an amputation, which was performed within 30 minutes after presentation at the emergency room, however he died during this surgery (his comorbidities included end stage diastolic and systolic heart failure, cardiac output of <15%). Median length of hospitalization was 18 days (IQR 9 - 29) and median ICU stay was 3 days (IQR 1 - 8) (Table 3).

Factors associated with negative exploration

Most of the arterial blood gas results (pH, bicarbonate and base deficit) at admission deviated from their normal values in patients with SNSTD compared to patients with negative exploration. Furthermore, patients with a positive exploration for SNSTD had an elevated median creatinine (137 µmol/L (IQR 96 – 267) vs. 79 µmol/L (IQR

Table 2 Demographics of patients with clinical suspicion for severe necrotizing soft tissue disease divided by intra-operative findings

	Total n = 36	Group 1 n = 16 (44%)	Group 2 n = 12 (33%)	Group 3 n =8 (22%)
Age in years, mean ± SD	54 ± 16	55 ± 17	52 ± 16	54 ± 15
ASA classification, n (%)				
I	7 (20)	6 (37)	1 (8)	0 (0)
II	5 (14)	3 (19)	1 (8)	1 (12.5)
III	12 (33)	3 (19)	6 (50)	3 (37.5)
IV	12 (33)	4 (25)	4 (34)	4 (50)
Medical history, n (%)				
Diabetes mellitus	5 (14)	2 (13)	2 (17)	1 (12.5)
Cardiovascular disease	15 (42)	7 (44)	5 (42)	3 (37.5)
Pulmonary disease	11 (31)	4 (25)	5 (42)	2 (25)
Malignancy	5 (14)	3 (19)	1 (8)	1 (12.5)
Auto-immune disease	13 (36)	3 (19)	6 (50)	4 (50)
Morbid obesity (Body Mass Index ≥35 kg/m2)	3 (8)	1 (6)	2 (17)	0 (0)
Surgery within past 30 days	8 (22)	5 (31)	2 (17)	1 (12.5)
Locations with signs of SNSTD n (%)				
Head/neck	3 (8)	2 (12.5)	1 (8)	0 (0)
Upper extremity	3 (8)	2 (12.5)	1 (8)	0 (0)
Trunk	6 (17)	4 (25)	1 (8)	1 (12.5)
Perineum	2 (6)	2 (12.5)	0 (0)	0 (0)
Lower extremity	21 (58)	6 (37.5)	8 (66)	7 (87.5)
Whole body (>50% of total body surface area affected)	1 (3)	0 (0)	1 (8)	0 (0)
Vital functions at presentation, median (IQR)				
Systolic blood pressure in mmHg[a]	117 (90 - 139)	110 (80 - 120)	118 (87 - 148)	131 (115 - 140)
Pulse rate in beats per minute[b]	104 (87 - 114)	109 (84 - 114)	107 (84 - 119)	100 (91 - 112)
Breathing frequency per minute[c]	20 (18 - 28)	20 (18 - 29)	18 (16 - 40)	28
LRINEC score[b], mean ± SD	6 ± 3	7 ± 2	5 ± 3	5 ± 3
Laboratory results				
Leukocytes in 10*9/L (normal range: 4.0 – 10.0 10*9/L), median (IQR)	11.7 (6.8 - 18.3)	13.2 (5.5 – 21.6)	11.6 (8.7 - 13.2)	10.5 (5.1 – 16.5)

Continuation of table 2

CRP in mg/L[a] (normal range: <10 mg/L), mean ± SD	231 ± 144	278 ± 137	216 ± 157	168 ± 124
Hemoglobin in mmol/L (normal range: ♂ 8.6 – 10.7 mmol/L; ♀ 7.4 – 9.6 mmol/L), mean ± SD	7.6 ± 1.3	7.8 ± 1.2	7.4 ± 1.6	7.5 ± 1.4
Sodium in mmol/L (normal range: 136 – 146 mmol/L), median (IQR)	135 (133 - 137)	135 (133 - 136)	135 (133 - 137)	134 (132 - 139)
Creatinine in µmol/L (normal range: ♂ 64 – 104 µmol/L; ♀49 – 90 µmol/L)[a], median (IQR)	112 (78 - 196)	167 (107 - 338)	119 (58 - 216)	79 (65 - 97)
Glucose in mmol/L (normal range: 3.5 - 7.8 mmol/L), median (IQR)	6.6 (5.7 - 7.5)	7.1 (6.1 - 7.7)	6.3 (5.5 - 7.4)	6.3 (5.6 - 7.3)
Creatine Kinase in U/L (♂ <170 U/L; ♀< 145 U/L)[d], median (IQR)	156 (74 - 395)	231 (61 - 345)	110 (36 - 682)	124 (88 - 180)
Arterial blood gas results at presentation, mean ± SD				
pH (normal range: 7.37 - 7.45)[e]	7.38 ± 0.11	7.34 ± 0.09	7.39 ± 0.10	7.48 ± 0.06
pCO2 in mmHg (normal range: 35 - 45 mmHg)[f]	35 ± 9	34 ± 9	37 ± 10	34 ± 4
Bicarbonate in mmol/L (normal range: 22 - 29 mmol/L)[e]	20 ± 5	18 ± 4	22 ± 5	25 ± 2
Base deficit in mmol/L (normal range: -3 - +3 mmol/L)[e]	5 ± 6	8 ± 6	3 ± 6	-1 ± 2
Hours since onset symptoms, median (IQR)	24 (20 - 66)	24 (12 - 72)	24 (20 - 48)	42 (24 - 69)
Hours from suspicion to surgery, median (IQR)	1.5 (0.5 - 2)	1 (0.5 - 2)	2 (1.5 - 2.25)	1.75 (0.75 - 2.5)
Intra-operative macroscopic findings, n (%)				
Necrotic fascia and/or muscle	16 (44)	16 (100)	0 (0)	0 (0)
Edema of tissue and/or "dishwater" fluid	16 (44)	0 (0)	12 (100)	4 (50)
No abnormalities	4 (11)	0 (0)	0 (0)	4 (50)
Intra-operative fresh frozen section results, n (%)				
Necrosis of fascia	14 (39)	7 (44)	7 (58)	0 (0)

Continuation of table 2

Suggestive findings for SNSTD	8 (22)	2 (12)	5 (42)	1 (12.5)
Inflammation surrounding fascia	2 (6)	0 (0)	0 (0)	2 (25)
No abnormalities	8 (22)	4 (25)	0 (0)	4 (50)
Not performed	4 (11)	3 (19)	0 (0)	1 (12.5)
Intra-operative Gram stain results, n (%)				
Bacteria in fascia	28 (78)	15 (94)	12 (100)	1 (12.5)
No bacteria in fascia	7 (19)	0 (0)	0 (0)	7 (87.5)
Not performed	1 (3)	1 (6)	0 (0)	0 (0)
Type of SNSTD[b], n (%)				
Type I	7 (26)	4 (25)	3 (27)	NA
Type II	18 (67)	11 (69)	7 (64)	NA
Type III	2 (7)	1 (6)	1 (9)	NA
Final cultures, n (%)				
Streptococcus pyogenus	17 (61)	10 (62.5)	5 (42)	NA
Mixed flora	5 (18)	3 (19)	2 (17)	NA
Vibrio species or *Clostridium* species	1 (4)	1 (6)	0 (0)	NA
Isolated other bacteria	4 (14)	2 (12.5)	4 (33)	NA
No further differentiation	1 (4)	0 (0)	1 (8)	NA
Type of debridement, n (%)				
Skin sparing debridement	1 (4)	0 (0)	1 (8)	NA
Partial skin sparing debridement	8 (28)	5 (31)	3 (25)	NA
No attempt at skin sparing debridement	18 (64)	11 (69)	7 (59)	NA
No resection due to "to much"	1 (4)	0 (0)	1 (8)	NA

Abbreviations: ASA = American Society of Anesthesiologists; CRP = C-Reactive Protein; IQR = InterQuartile Range; LRINEC = Laboratory Risk Indicator for Necrotizing Fasciitis; NA = Not Applicable; SD = Standard Deviation; SNSTD = Severe Necrotizing Soft Tissue Disease. Missing cases: [a]1 missing; [b]2 missing; [c]18 missing; [d]16 missing; [e]4 missing; [f]5 missing.

Table 3 Clinical outcomes of patients with confirmed diagnosis of severe necrotizing soft tissue disease

	Total SNSTD patients n = 28 (100%)	Group 1 n = 16 (57%)	Group 2 n = 12 (43%)	*p* - value
Length of hospital stay in days, median (IQR)	18 (9 - 29)	23 (12 - 34)	167 (5 - 19)	0.285
Length of intensive care stay in days, median (IQR)	3 (1 - 8)	6 (3 - 10)	2 (0 - 3)	**0.031**
Amputation, n (%)	1 (4)	1 (6)	0 (0)	1.000
In-hospital mortality rate, n (%)	7 (25)	4 (25)	3 (25)	1.000
ASA classification of deceased patients, median (IQR)	4 (4 – 4)	4 (4 – 4)	4 (4 – 4)	NA
Death SNSTD related (e.g. MOF)	3 (11)	2 (12.5)	1 (8)	1.000
Withdrawal of treatment due to comorbidities	4 (14)	2 (12.5)	2 (17)	1.000
Days until death, median (IQR)	2 (1 - 7)	5 (1 - 19)	2 (1 - 3)	0.593
Days until SNSTD related death	1 (0 - 1)	1 (0 - 1)	1	1.000
Days until death due to withdrawal of treatment due to comorbidities	5 (3 - 19)	19 (7 - 30)	3 (2 - 3)	0.121

ASA = American Society of Anesthesiologists; IQR = Interquartile Range; MOF = Multi-organ failure; NA = Not Applicable; SNSTD = Severe Necrotizing Soft Tissue Disease. **Bold** font indicates significant result.

the highest predictive value for SNSTD (*p*-value = 0.001), pH (*p*-value = 0.032) and bicarbonate (*p*–value = 0.002) below reference values were as well associated with a positive diagnose.

Effect of early SNSTD recognition

No statistically significant difference between patient and disease characteristics was found between patients in group 1 and group 2. There appeared to be a small difference in LRINEC score (7 ± 2 for group 1 vs. 5 ± 3 for group 2), however not statistically significant. Both groups had similar vital functions, laboratory tests and arterial blood gas results (Table 2). A significant difference in outcome was found 65-97), *p*-value = 0.033). LRINEC score did not significantly differ between patients with positive and negative exploration (6 ± 3 vs. 5 ± 3, *p*-value = 0.253), as all patients were critically ill (Table 2). A base deficit greater than 3 mmol/L appeared to have between patients diagnosed in an earlier stage of SNSTD (group 2) and patients with

already more progressive SNSTD (group 1), being a significant shorter ICU stay (2 vs. 6 days, *p*-value = 0.031) for patients in group 2 (Table 3). No difference in direct SNSTD related mortality was found between both groups (n = 2, 12.5% in group 1 vs. n = 1, 8% in group 2) (Figure 1 and Table 3).

Discussion

Diagnosing SNSTD using the approach with triple diagnostics resulted in a low mortality rate and only a single amputation in a pre-terminal patient in the first five years after implementation. All deceased patients had multiple pre-existing comorbidities consisting of severe systemic diseases, such as end stage heart failure. Early detection also proved to facilitate faster recovery with shorter ICU stay. An arterial base deficit greater than 3 mmol/L was associated with a positive SNSTD diagnosis, whereas LRINEC scores could not differentiate between a positive and negative diagnosis in this cohort.

Over the past years, the literature described an average mortality rate of 34% with a range from 6% up to as high as 76% [1,4,9,14]. This study reports on the results of an overall 30-day mortality of 25%, with an early, direct SNSTD related mortality rate of 11%. Furthermore, the length of ICU stay was shorter compared to the eleven days or longer described in previous literature [3,4,15]. Patients who were diagnosed in an earlier stage had even a shorter ICU stay than patient with more progressive disease indicating less need for supportive care, while no differences in baseline laboratory or vital parameters could be identified. This further stresses the need for a timely diagnosis. Accurate diagnosis in the early stage of the disease prevents extensive involvement of limbs and other body regions, thereby reducing the risk of extensive debridement [12]. This current study shows that, with early diagnosis, no amputation was necessary in surviving patients, compared with previously described rates between 10% and 22% [15,16].

Triple diagnostics requires proper allocation of the patients with ambivalent SNSTD to hospitals with 24/7 available microbiologists and pathologists, however this is affected by the logistic possibilities of the institution or regional collaboration. In case of evident signs of SNSTD during clinical evaluation, triple diagnostics is less likely to be needed intraoperative and therefore the patient should undergo immediate surgical debridement regardless of the availability of a microbiologist or pathologist at that hospital. If needed the patient could be transferred after the debridement, or if the appropriate logistics are in place, even prior to exploration without causing treatment delay. In case of ambivalent signs of SNSTD, the patient needs to be at a hospital that is equipped with the resources necessary to perform surgical exploration with triple diagnostics to prevent unnecessary debridement due

to too much caution, or refrainment and/or delay of debridement due to unjust reassurance based on macroscopic findings.

Partly due to logistic reasons, the use of fresh frozen section for diagnosing SNSTD is still debated and in most hospitals not (fully) implemented, even though it has been associated with reduced mortality rates [10–12]. Solomon et al. previously argued that it is not reliable as an independent test and Anaya et al. stated that the use of fresh frozen section is not practical and too time-consuming [6,17]. However, this is if all cases are considered, including those with evidential macroscopic necrosis. We agree that in these cases, analysis should not lead to paralysis and prompt debridement is indicated. However, in ambivalent cases with perifascial edema, pathologists can often establish a diagnosis within 30 minutes after receiving the specimen, providing rapid and accurate results intra-operatively [10–12]. This requires an entire surgical team to wait for the results and thus logistics should be optimized. Nevertheless, when this half an hour adequately decreases the number of false negative explorations, this is worth the time and resource investments. This current study supports that theory, since twelve patients with suspicion for SNSTD had no macroscopic necrotic fascia or muscle, but their fascial biopsies showed on histological and microbiological examination signs consisting with SNSTD. As well as that four patients had fascial edema but did not have SNSTD based on histological and microbiological examination, preventing unnecessary debridement. Therefore, microscopic findings overrule macroscopic findings, since macroscopic findings are only visible if the infection has progressed far enough but might be preceded by histopathological change. Simultaneously, fascial biopsies should be sent for Gram staining. Results of Gram staining are known within approximately 30 minutes and can confirm diagnosis and guide the antibiotic regimen. This method is not able to completely rule out SNSTD, since culture results are needed to provide a definitive answer for ruling out SNSTD [5]. The sensitivity of diagnosing ambivalent SNSTD using the tests independently - macroscopic findings, fresh frozen sections or Gram stain - is not optimal, but combined led to no false negative explorations [5,17]. The current study shows that all patients with no abnormal macroscopic findings – no necrotic fascia/muscle and fascial edema – had negative diagnoses, this indicate that triple diagnostics in those cases might not be necessary to rule out SNSTD. It should be kept in mind that the patients presented in this study, and undergoing surgical exploration, are just a small selection of all patients presenting to our hospital with suspicion for SNSTD. This described strategy resulted in 22% negative explorations. Nevertheless, lowering this number should be weighed against the improved survival and amputation rates.

Survival remains the primary goal in treating SNSTD, however further reduction of mortality - even when triple diagnostics is used – appears to be challenging. After

optimization of the diagnostic process, further reduction of mortality seems to be mainly limited by patients' demographics, since all patients who died had (multiple) severe pre-existing comorbidities. Therefore, when this mortality rate proves to be persistent, future SNSTD research should aim their recourses to decreasing morbidity, such as reduced ICU length of stay. However, studies assessing (long-term) morbidity after surviving SNSTD are limited [18,19]. The results of this study provide practice base evidence but should be interpreted in the right context. Selection bias was limited due to the prospective identification of patients, however information bias remained in some degree due to the partial retrospective data collection. The retrospective data collection resulting in some missing vital parameters and laboratory test results at presentation, furthermore, the time from onset of symptoms to presentation was therefore estimated.

Concluding, the use of a standardized approach for diagnosing SNSTD using triple diagnostics for ambivalent cases has resulted in a reduced mortality and no amputations in the surviving patients. Early detection also proved to facilitate faster recovery with shorter ICU stay. Survival remains the primary goal, however further reduction of mortality might be limited by the severity of comorbidities prior to onset of disease.

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6

Getting it right the first time: frozen sections for diagnosing necrotizing soft tissue infections

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Abstract

Background: The aim of this study was to investigate which histopathologic findings are most indictive for necrotizing soft tissue infections (NSTIs) in ambivalent cases.

Methods: Patients undergoing surgical exploration for suspected NSTIs with obtainment of incisional biopsies for histopathological assessment were included from January 2013 until August 2019. The frozen sections and formalin-fixed paraffin-embedded (FFPE) samples were retrospectively re-assessed. The primary outcome was the discharge diagnosis.

Results: Twenty-seven (69%) biopsies of the 39 included samples were from patients with NSTIs. Microscopic bullae ($p = 0.043$), severe fascial inflammation ($p < 0.001$) and fascial necrosis ($p < 0.001$) were significantly more often present in the NSTI group compared to the non-NSTI group. Muscle edema (n = 5), severe muscle inflammation (n = 5), muscle necrosis (n = 8), thrombosis (n = 10) and vasculitis (n = 5) were most frequently only seen in the NSTI group. In thirteen tissues samples, there was some discrepancies between the severity of findings in the frozen section and the FFPE samples. None of these discrepancies resulted in a different diagnosis or treatment strategy.

Conclusion: Microscopic bullae, severe fascial or muscle inflammation, fascial or muscle necrosis, muscle edema, thrombosis and vasculitis upon histopathological evaluation all indicate a high probability of a NSTI. At our institution, diagnosing NSTIs is aided by using intra-operative frozen section as part of triple diagnostics in ambivalent cases. Based on the relation between histopathologic findings and final presence of NSTI, we recommend frozen section for diagnosing NSTIs in ambivalent cases.

Introduction

Early diagnosis and immediate radical surgical treatment are vital for reducing the mortality rate of necrotizing soft tissue infections (NSTIs) [1–3]. NSTIs are notorious for being difficult to diagnose based on clinical symptoms, resulting in high rates of misdiagnosis and treatment delay [4,5]. To resolve this problem, the approach using triple diagnostics (diagnosis based on macroscopic, histopathologic and microbiologic findings) has been proposed for ambivalent macroscopic cases [6]. The intra-operative evaluation of frozen sections and Gram stains enables identification of microscopic signs of NSTIs [6]. The use of triple diagnostics demonstrated a relatively low mortality rate and shorter intensive care stays, indicating a less severe disease course, likely due to identification of the NSTI in its earlier stages when only microscopically signs are visible [7]. However, there is still no clear consensus concerning the use of frozen sections for diagnosing NSTIs [8,9]. This is mainly caused by the lack of current literature on this topic [10–13]. Back in 1984, Stamenkovic et al. first reported that frozen sections might reduce the mortality rate of NSTIs resulting from the earlier recognition of the infection [11]. However, the first guideline recommendation for using frozen sections to diagnose NSTIs, as part of triple diagnostics, was not made until 2018 [8]. Nonetheless, this guideline also stated that frozen sections are not very practical and require availability and experience of the pathologists, while intra-operative assessment of frozen sections has already become routine practice in surgical oncology [8,14]. Therefore, the aim of this study was to investigate which histopathologic findings are most indicative for the diagnosis NSTI.

Methods

Study design

Patients undergoing surgical exploration for suspected NSTIs with obtainment of tissue biopsies for histopathological assessment during this initial exploration at an academic hospital were prospectively identified from January 2013 until August 2019 and included in this study. Biopsies taken secondarily from patients with an already confirmed and current NSTI were excluded. The clinical outcomes of patients included up to January 2019 were previously reported in an article by Nawijn et al. [7]. NSTIs were diagnosed based on macroscopic findings of necrosis of the subcutaneous tissue, fascia or muscle during surgical exploration. In case of ambivalent macroscopic findings such as fascial edema without clear necrosis, the triple diagnostics algorithm was used. Using this algorithm, the diagnosis NSTI was confirmed if either the intra-operative assessed frozen section or Gram stain was positive. If both were negative, the diagnosis NSTI was rejected [6]. Final diagnosis was made by clinical follow-up. When triple diagnostics were utilized, the following

histopathologic characteristics of NSTIs were often used for assessing tissue biopsies: necrosis of superficial fascia, polymorphonuclear infiltration of the deep dermis and fascia, fibrinous thrombi of arteries and veins passing through the fascia, angiitis with fibrinoid necrosis of vessels walls and micro-organisms within the destroyed fascia and dermis [6,11].

Data collection and outcome measures

Data collected from the medical charts included physical examination findings, intra-operative findings (based on surgical notes), histopathologic findings (both frozen sections and standard formalin-fixed paraffin-embedded (FFPE) samples) and discharge diagnosis. The sampling process for frozen sections is detailed in Figure 1 [6]. At our institute, all samples (frozen and FFPE) are archived for 35 years and all tissue blocks from which sections were sliced are archived for 110 years. A data-collection form was designed to retrospectively re-assess the frozen sections in a protocolized manure without knowing the conclusion given by the previous pathologist (Appendix 1). Notion was made of which tissue layers were available and if they showed any abnormalities. All samples were assessed by an experienced pathologist. The frozen section, if available, was examined prior to assessing the FFPE sample. For the assessment of the overall histopathological characteristics of NSTIs, the most atypical finding from either the frozen section or FFPE sample was recorded. The primary outcome of this study was the discharge diagnosis reported in the discharge papers.

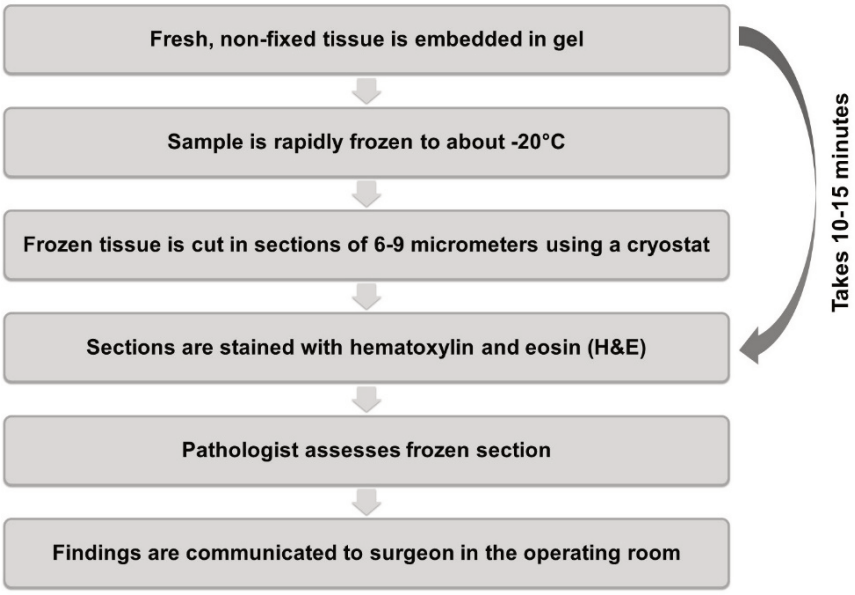


Figure 1 Flowchart of sampling process of frozen sections

Statistical analyses

Categorical variables are presented as fractions or frequencies. Missing data were handled using pairwise deletion. The Fisher exact test was used for dichotomous independent variables and the X^2 for trend for ordinal independent variables. For all analyses, a *p*-value <0.05 was considered statistically significant. Data were analyzed using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

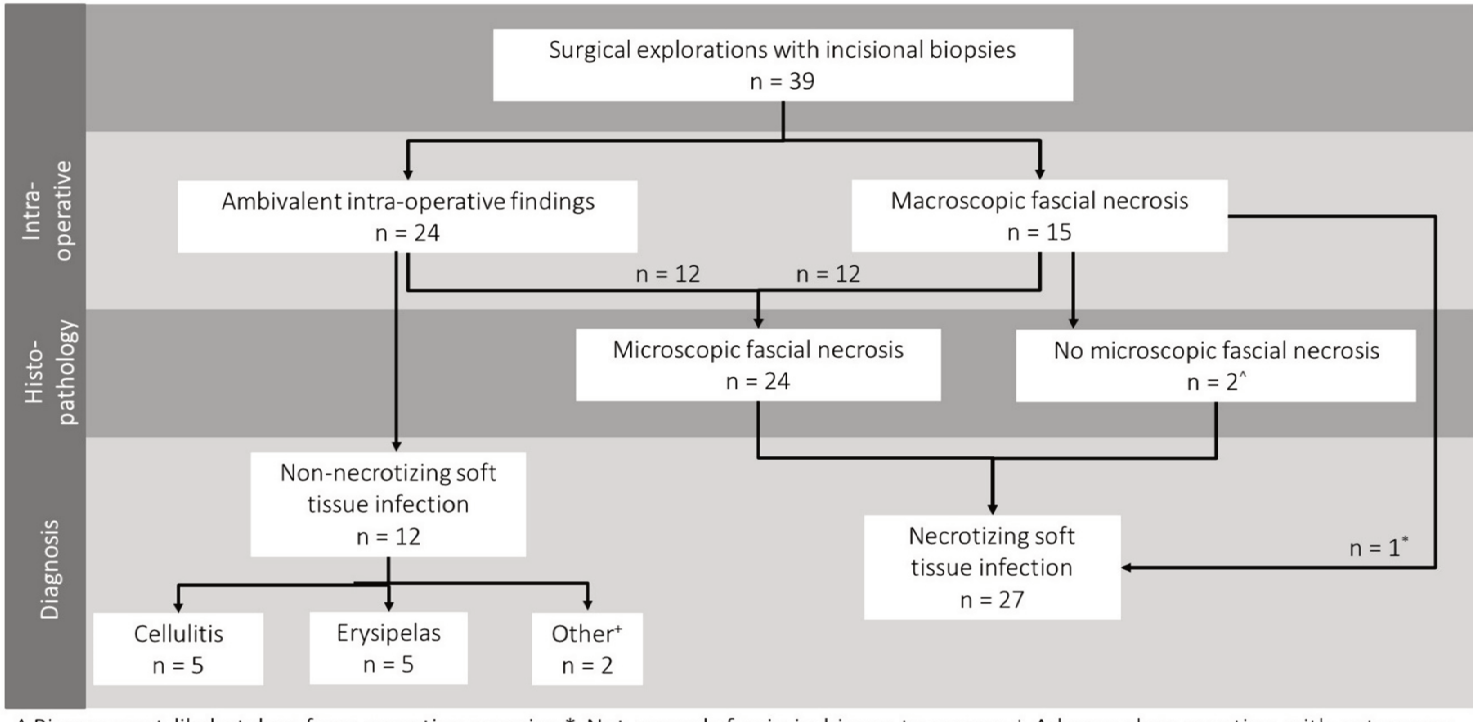
Thirty-seven patients underwent surgical explorations during which biopsies were taken for histopathologic evaluation. Twenty-six patients were diagnosed with NSTIs (70%), of which four patients eventually died (15%). One patient had initially a negative exploration; however, due to clinically deterioration triple diagnostics were repeated two days later and were positive for NSTI. Another patient underwent a new exploration three months after hospitalization for an earlier NSTI, which was eventually negative (diagnosis: erysipelas). From both patients, the histopathologic samples were included, resulting in a total of 39 biopsies from 37 patients (Figure 2). Eight biopsies were truly full-thickness biopsies (epidermis to muscle). The epidermis and dermis were both most commonly missing (both in 22 samples) (Figure 3).

Histopathologic characteristics of NSTIs

Bullae ($p = 0.043$), more severe fascial inflammation ($p < 0.001$), especially if rated as severe inflammation ($p < 0.001$), and fascial necrosis ($p < 0.001$) were significantly more often present in the NSTI group compared to the non-NSTI group (Table 1; Figure 4-6). There were two NSTI patients without microscopic fascial necrosis, however, both had reported macroscopic fascial necrosis. Microscopic muscle edema (n = 5), severe muscle inflammation (n = 5), muscle necrosis (n = 8), thrombosis (n = 10) or vasculitis (n = 5) were in a minority of the cases found, however if present, it was in all but two cases only found in NSTI patients (Figure 7a).

Histopathologic characteristics of non-NSTIs

Twelve biopsies were from patients with eventually a non-NSTI discharge diagnosis. Severe fascial inflammation (n = 12), vasculitis (n = 12), thrombosis (n = 11 and fascial necrosis (n = 10) were absent in all or a majority of the cases (Figure 7b). If histopathological abnormalities were found, this was most often either edema in the dermis (5/6), subcutaneous fat inflammation (7/11) or fascial edema (8/12) (Table 1, Appendix 2). These patients had as discharge diagnosis either cellulitis (n = 5), erysipelas (n = 5), bacteremia with septic embolisms caused by an endocarditis (n = 1) or an adverse drug reaction (ADR) with cutaneous eosinophilia (n = 1). One of the



^ Biopsy most likely taken from resection margin; * Not enough fascia in biopsy to assess; + Adverse drug reaction with cutaneous eosinophilia (n = 1) and bacteremia caused by endocarditis (n = 1)

Figure 2 Flowchart of patients undergoing surgical exploration for suspected necrotizing soft tissue infection with obtainment of biopsies for histopathological assessment

Table 1 Histopathological characteristics of incisional biopsies taken from patients with suspected necrotizing soft tissue infections

Tissue layer	NSTI (n = 27)	Non-NSTI (n = 12)	*p*-value
Epidermis (n = 17)			
No abnormalities	4/11	5/6	0.131[c]
Bullae	6/11	0/6	**0.043**[c]
Necrosis	1/11	1/6	1.000[c]
Dermis (n = 17)			
No abnormalities	2/11	1/6	1.000[c]
Edema	8/11	5/6	1.000[c]
Acute inflammation			1.000[d]
Mild	1/11	3/6	
Moderate	1/11	1/6	
Severe	3/11	0/6	
Necrosis	1/11	0/6	1.000[c]
Subcutaneous fat (n = 37)			
Inflammation (regardless of severity)	18/26	7/11	1.000[c]
Necrosis	20/26	5/11	0.122[c]
Fascia (n = 38)[a]			
No abnormalities	0/26	3/12	**0.026**[c]
Edema	13/26	8/12	0.486[c]
Acute inflammation			**<0.001**[d]
Mild	1/26	5/12	
Moderate	6/26	2/12	
Severe	16/26	0/12	
Necrosis	24/26	2/12[b]	**<0.001**[c]
Muscle (n = 19)			
No abnormalities	0/12	3/7	**0.036**[c]
Edema	5/12	0/7	0.106[c]
Acute inflammation			0.160[d]
Mild	1/12	3/7	
Moderate	1/12	0/7	
Severe	5/12	0/7	
Necrosis	7/12	1/7	0.147[c]
Vessels (n = 39)			
Thrombosis	9/27	1/12	0.131[c]
Vasculitis	5/27	0/12	0.299[c]

Most atypical findings found in either the frozen section or formalin-fixed paraffin-embedded sample is displayed in this table. NSTI = Necrotizing Soft Tissue Infection; [a] Not enough fascia to assess (n =1); [b] hypothesized to be caused due to systemic (micro)vascular disease in patient with adverse drug reaction with cutaneous eosinophilia and early abscess formation in patient with cellulitis; [c] Fisher exact test used; [d] X^2 for trend used. **Bold** font indicates significant result.

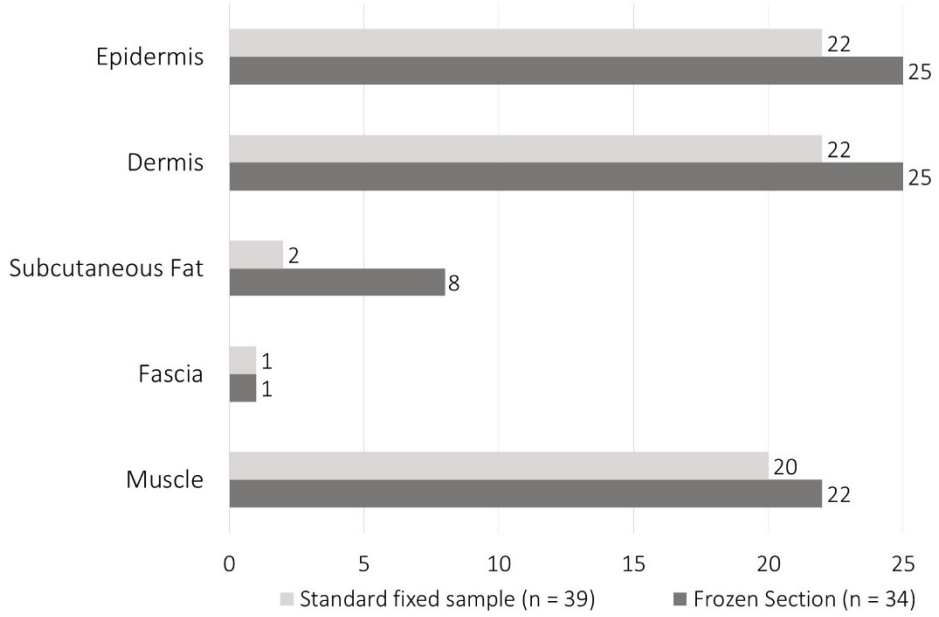


Figure 3 Tissue layers absent for histopathologic assessment in incisional biopsies obtained from patients with suspected necrotizing soft tissue infections.

two non-NSTI patients with fascial necrosis also had microscopic thrombi (diagnosis: ADR with cutaneous eosinophilia). The thrombi and fascial necrosis were most likely secondary to the patient's systemic (micro)vascular disease, which also explained the secondary influx of neutrophils. In the other patient with microscopic fascial necrosis (diagnosis: cellulitis), the necrosis was found during re-assessment of the biopsies for this study and was not reported by the pathologist that originally assessed the biopsy. This pathologist concluded ambivalent signs of a NSTI in the frozen section. Combined with a negative Gram stain and macroscopic vital fascia, the diagnosis NSTI was found unlikely and no debridement was performed. This patient did not clinically deteriorate after the exploration, however developed an abscess at the same location a week later. In retrospect it is hypothesized that early abscess formation might have caused the necrosis seen microscopically.

Discrepancies

Thirty-four biopsies were first processed as frozen section followed by processing as FFPE sample. The five other samples were only processed as FFPE samples. In eleven samples (out of 34), one or more tissue layers were missing in the frozen section compared to the FFPE sample. Most often, the subcutaneous fat tissue was missing in the frozen section but present in the FFPE sample (n = 6) (Figure 3). In thirteen

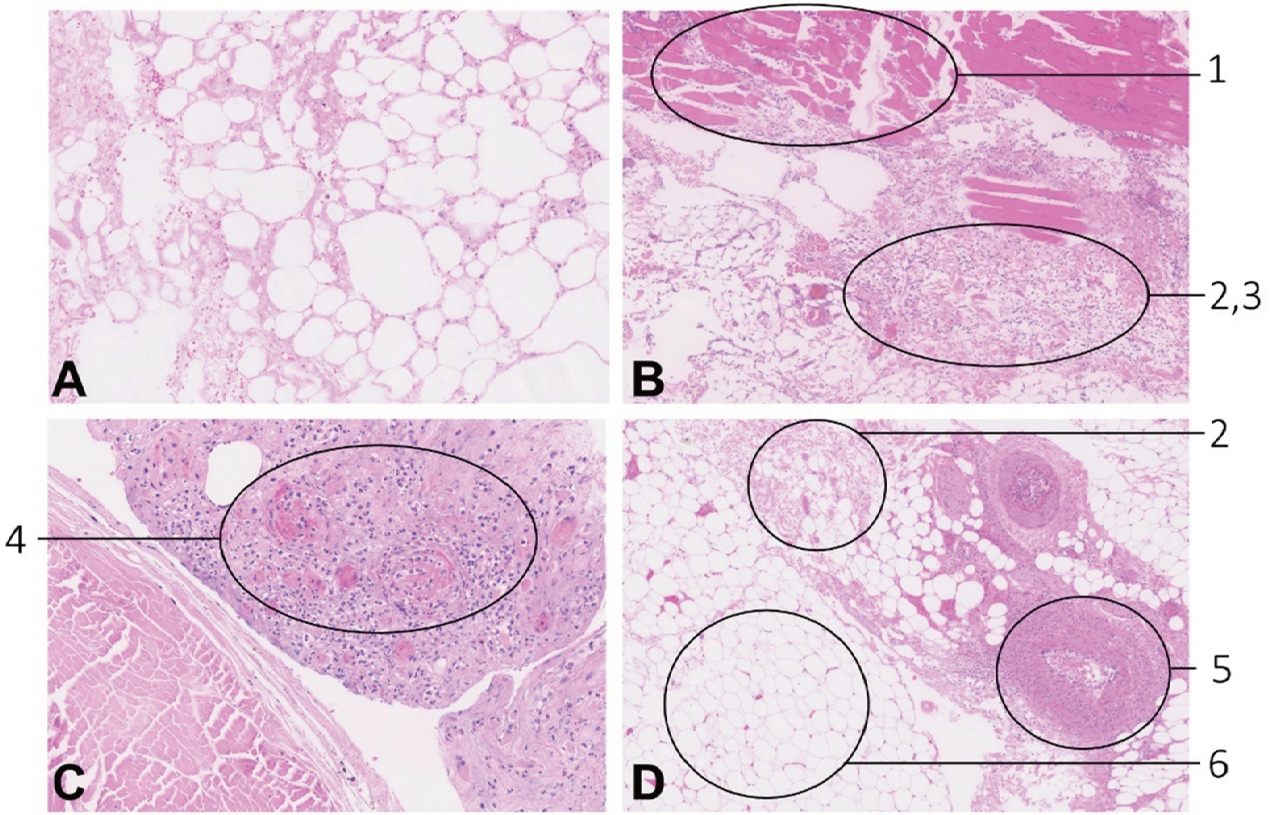


Figure 4 Microscopic views of different histopathologic findings in necrotizing soft tissue infections. A) Necrotic subcutaneous fat; B) Inflammation of subcutaneous fat and muscle tissue, combined with necrosis of the subcutaneous fat; C) Micro-thrombi; D) Necrotic and intact subcutaneous fat combined with vasculitis.
1) Inflammation of muscle tissue; 2) Inflammation of subcutaneous fat; 3) Necrosis of subcutaneous fat; 4) Micro-thrombus; 5) Vasculitis; 6) Intact subcutaneous fat

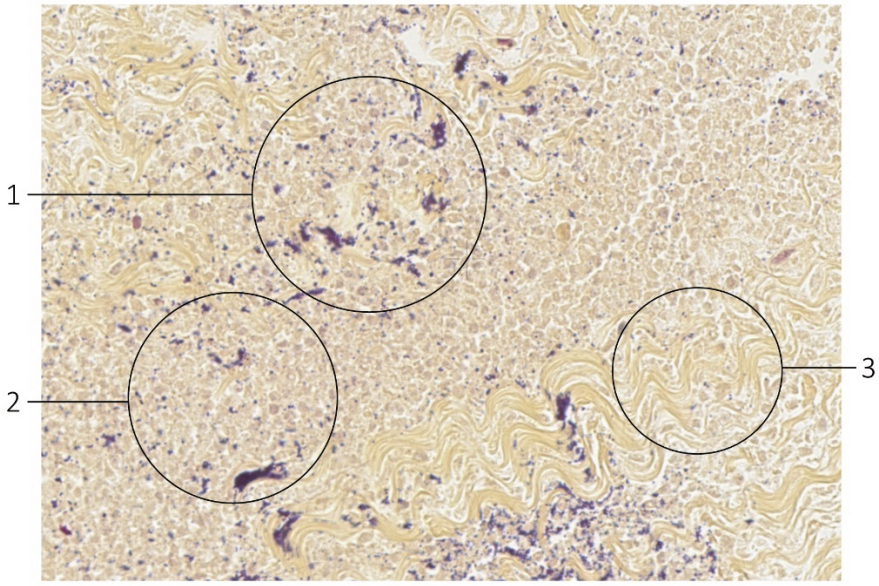


Figure 5 Microscopic view after Gram stain of biopsy from patient with necrotizing soft tissue infection showing multiple bacteria surrounded by intact and necrotic collagen

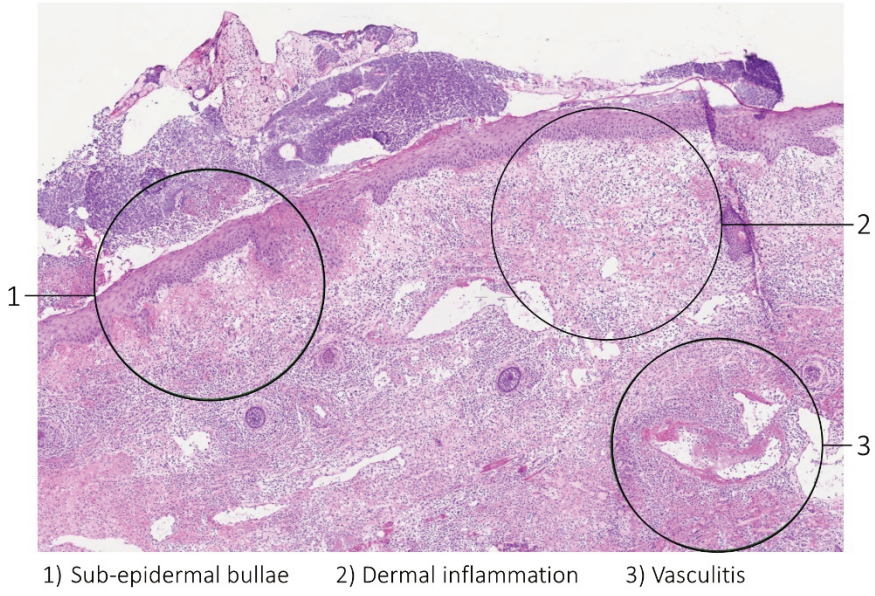


Figure 6 Microscopic view of frozen section from patient with necrotizing soft tissue infection showing sub-epidermal bullae, severe dermal inflammation and vasculitis

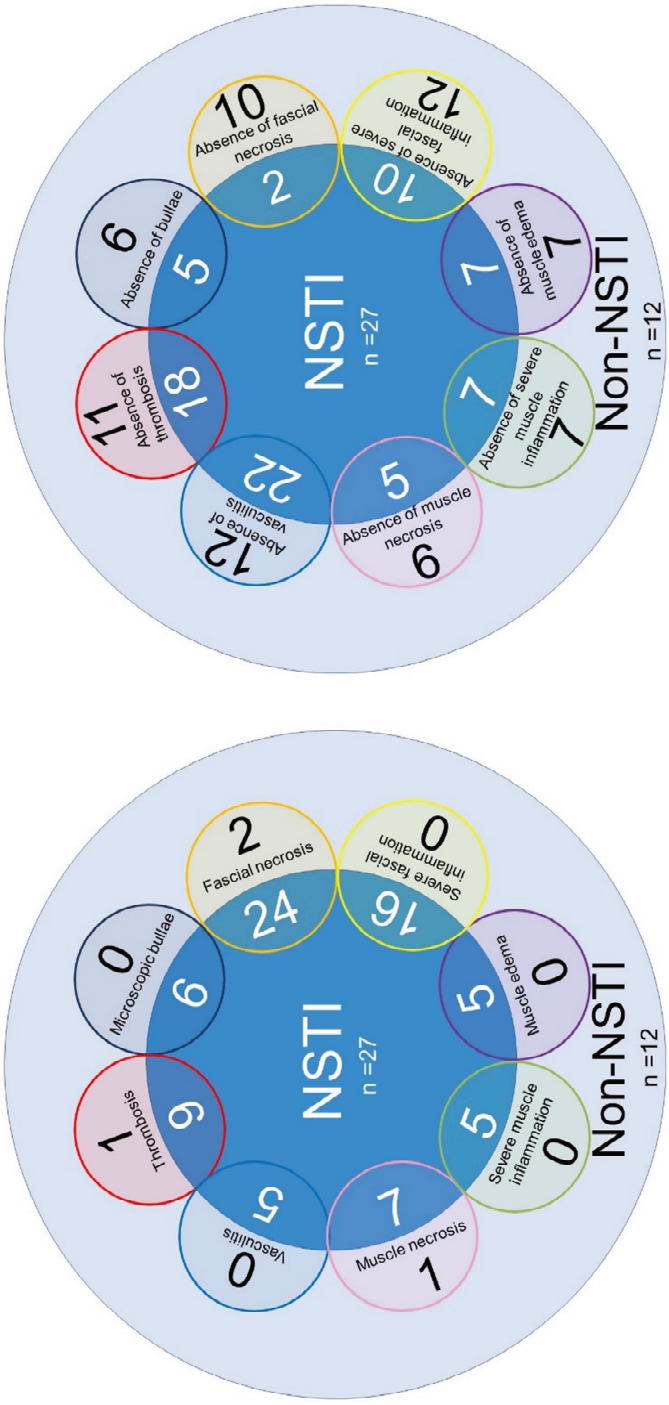


Figure 7 Histopathological findings of necrotizing soft tissue infection (NSTI) found in biopsies from patients undergoing surgical exploration for suspected NSTI. A) Positive histopathological findings B) Negative histopathological findings. Figure legend: Dark blue inner circle represents all 27 NSTI patients; White numbers report the number of NSTI patients with a certain (in case of figure 7b: absent) histopathological findings (written in black); Light blue outer circle represents all 12 non-NSTI patients; Black numbers report the number of non-NSTI patients with a certain (in case of figure 7b: absent) histopathological findings (written in black)

Table 2 Histopathological discrepancy between frozen sections and formalin-fixed paraffin-embedded samples from patients with suspected necrotizing soft tissue infections

Reason for discrepancy	n = 13
Inflammation less severe in frozen section	5
No thrombi in frozen section	4
Inflammation more severe in frozen section	1
Inflammation less severe in frozen section AND no muscle necrosis in frozen section	1
Inflammation less severe in frozen section AND no thrombi in frozen section	1
No fascial necrosis in frozen section AND no vasculitis in frozen section	1

samples (out of 34), there was a discrepancy between the severity of findings upon histopathological assessment of the frozen section and the FFPE samples (Table 2). However, none of these less severe findings in the frozen sections resulted in a different diagnosis or treatment strategy. In eleven of those thirteen samples, material of the FFPE sample was sliced from the same biopsy as the frozen section and in the two other sample, the material of the sample was sliced from additionally taken tissue biopsies from which no frozen section was made.

Physical examination

The findings upon physical examination prior to surgery were reported in 38 cases. Blue or purple skin discoloration was reported in nineteen cases (15 in NSTI group). All of these fifteen NSTI cases had either microscopic necrosis of the subcutis or fascia and in five cases microscopic thrombi were found. Macroscopic bullae were reported in eleven cases (9 in NSTI group). Microscopic bullae were as well seen upon histopathologic evaluation in five NSTI cases and only microscopically seen in one case (not reported upon physical examination). In the two non-NSTI cases with macroscopic bullae, the discharge diagnoses were a bacteremia caused by an endocarditis and an ADR with cutaneous eosinophilia.

Intra-operative findings

In 24 cases (out of 39), no macroscopic fascial necrosis was visible upon surgical exploration and triple diagnostics were necessary to make the diagnosis NSTI more or less likely. In twelve out of those 24 cases, microscopic necrosis of the fascia was found (Figure 2). In five out of the twelve NSTI cases without macroscopic necrosis, fascial edema was also not explicitly reported. In total, fascial edema was explicitly reported in fourteen out of the 39 cases, of which two cases were non-NSTIs (diagnosis: both erysipelas).

Discussion

The use of intra-operative frozen section as part of the triple diagnostics algorithm in less evident macroscopic cases of NSTI has been suggested. Based on our findings, we propose major and minor histopathologic criteria for patients with suspected NSTIs (Table 3) and provide key notes for using frozen section sections (Table 4). In case of using frozen sections, pathologist should especially look for bullae, muscle edema, severe fascial or muscle inflammation, fascial or muscle necrosis and vascular abnormalities (e.g. thrombosis or vasculitis). The major criteria are the significant findings from this study, the minor criteria are findings that were distinctly seen in patients with NSTIs. These findings are in our opinion beneficial for recognizing NSTIs in frozen sections and should be the focus of larger studies with sufficient power.

The histopathological criteria regarding the fascia found in this study are comparable with prior studies (Table 5) [10,13]. Although microscopic fascial necrosis was found to be a predictive finding for NSTIs in this current study and the study by Solomon et al., two patients in our study had no microscopic fascial necrosis [13]. In both cases macroscopic fascial necrosis was reported in the operative report, resulting in hypothesis that these biopsies might have been taken from the resection margin (not well documented) and therefore necrotic tissue was absent in the biopsy. Thus, it is important for surgeons to report the location from which area, in relation to the infection, the biopsy was taken. Furthermore, this shows that only looking for (microscopic) fascial necrosis does not result in 100% sensitivity and therefore biopsies should be assessed for other, additional, histopathologic findings. Considering that histopathological findings in the fascia as well as in the epidermis and muscle were predictive, obtaining full-thickness biopsies is strongly recommended. Unfortunately, only 21% of the biopsies in this study were full-

Table 3 Major and minor histopathological criteria for diagnosing necrotizing soft tissue infections in patients undergoing triple diagnostics

Major histopathological criteria
• Bullae • Severe fascia inflammation • Fascial necrosis
Minor histopathological criteria
• Muscle edema • Severe muscle inflammation • Muscle necrosis • Capillary thrombosis • Vasculitis

Table 4 Key points for using frozen sections for diagnosing necrotizing soft tissue infections

Key points
✓ Obtain full-thickness (epidermis to muscle) incisional biopsy; in contrast to the biopsy for microbiological evaluation, which must consist of only the fascia.
✓ Report from which location, in relation to the infection, the incisional biopsy was taken
✓ Only order frozen section assessment if results will have acute consequences for treatment strategy (e.g. not if evident macroscopic fascial necrosis is seen, patient will undergo amputation regardless of results, patient is deceased). Otherwise, order histopathologic assessment as standard formalin fixed paraffin embedded sample
✓ Be aware of possible loss of subcutaneous fat during processing of frozen section
✓ Use frozen sections as part of the triple diagnostic principle, not as independent test. Frozen sections make the diagnosis more or less likely, but do not diagnose the necrotizing soft tissue infection

Table 5 Literature overview of histopathological findings for diagnosing necrotizing soft tissue infections

Author	Most important histopathological finding
Stamenkovic et al. (1984)[11]	• Intact superficial dermis and epidermis • Within superficial fascia, deep dermis and surrounding adipose tissue: - Necrosis - Polymorphonuclear infiltration - Microorganisms - Vasculitis - Thrombosis
Stegeman et al. (2012)[10]	• Whole microscopic view filled with granulocytes in the subcutis and fascia
Solomon et al, (2018)[13]	• More severe inflammation • More extensive necrosis • Presence of bacteria • Presence of karyorrhexis • Presence of fibrine

thickness biopsies, so awareness among surgeons to obtain full-thickness biopsies (epidermis to muscle) should increase [6,10,11]. This is in contrast to samples for Gram-staining and culture, which preferable only contains clean handled fascia [7]. This is the first study differentiating the histopathological findings by tissue layer for NSTIs [10,13].

Even if multiple tissue layers are biopsied, there is still a risk of losing tissue layers during processing of frozen sections. In 32% of the biopsies, tissue layers were absent in the frozen section compared to the FFPE sample, which was most often the subcutaneous fat. This is commonly caused by sampling errors; fat needs lower temperature to freeze compared to most other tissues, but when fat is overfreezed, it shatters more easily. Furthermore, fatty tissues are known to be more difficult to cut which can cause artifacts [15,16]. Due to the instability of subcutaneous fat in frozen sections, subcutaneous fat findings were not included in our criteria.

In 38% of the biopsies, there were histopathological discrepancies between the frozen section and the FFPE sample. The signs of NSTIs appeared to be less outspoken in the frozen section (e.g. less severe inflammation, absent thrombi). The discrepancies in this study were most commonly due to the assessment of more superficial slices from the incisional biopsy for the frozen section and not due to sampling errors or artifacts. Even though, discrepancies between frozen sections and FFPE samples were common and could result in underestimation of certain histopathologic characteristics, the diagnosis made and corresponding treatment strategy based on the frozen sections did not change after assessment of the FFPE sample. This is in line with studies from other medical fields using frozen sections, which report low rates of discordance between the frozen section conclusion and final diagnosis [14,17,18].

Histopathologic assessment is beneficial for diagnosing NSTIs, since clinical symptoms are not seldom unreliable [4,5,19]. A prior study showed that macroscopic fascial necrosis during surgical exploration has a high positive predictive value, but a low negative predictive value and therefore cannot simply rule out NSTIs [7]. Especially patients without evident macroscopic fascial necrosis benefit from using frozen sections, since half of the patients with NSTIs in this study did not have any signs of macroscopic fascial necrosis, while microscopic necrosis was (already) present. Also, patients with a high clinical suspicion for NSTI but with eventually a non-NSTI benefited from the frozen section, since ruling out microscopic necrosis in case of per-operative fascial edema averted unnecessary debridement. However, there were two patients with non-NSTIs and microscopic fascial necrosis in this study. A NSTI was eventually very unlikely in both cases based on the macroscopic evaluation, a negative Gram stain and the whole histological image. In these patients it can be argued if a frozen section should have been taken in the first place, since the fascia was vital and no dishwater fluid or edema (which was present in all other ambivalent cases) was found upon macroscopic assessment. This stresses using frozen sections as part of the triple diagnostics algorithm and not as independent test. Using frozen sections in combination with other tests increases the reliability of the diagnosis made, especially in ambivalent cases.

Imaging, such as plain radiographs or computed tomography (CT), has also been proposed for diagnosing (ambivalent) NSTIs, however it is not part of the diagnostic work-up at our institute and remains controversial in the current literature [8]. The use of CT-scans might be beneficial for certain patients, such as patients with a suspected intra-abdominal source of the infection [20]. A few studies have evaluated the diagnostic value of CT scans, all reporting high specificity, but widely variable sensitivity results [21–23]. Martinez et al. proposed diagnosing NSTIs by assessing CT-scans using four criteria, resulting in a sensitivity of 100% and specificity of 98% [22]. On the other hand, McGillicuddy et al. reported a sensitivity of 43% for diagnosing NSTI based on fascial air (specificity 98%) and a sensitivity of 39% for diagnosing NSTIs based on fluid tracking on CT-scans (specificity 85%), both criteria (with low sensitivity in the literature) were used in the criteria by Martinez et al. [22,23]. Furthermore, CT scans cannot be performed in hemodynamically unstable patients (which is upon presentation frequent the case in NSTI patients) and could cause a significant delay in the surgical treatment of NSTIs [2,24].

This study is limited by its small sample size, which constrained us to a descriptive analysis. One of the biggest arguments made against using frozen sections for diagnosing NSTIs, is that it requires a pathologists with frozen section expertise [8]. Fortunately, we had the benefit of an experience pathologist who specializes in skin and soft tissues to re-assess all samples. With our protocolled assessment, we aimed to simplify the assessment, maintain generalizability and applicability of our results, provide some sort of quantitative assessment of the samples and thus recommendations. During the retrospective scoring and assessment of the samples by the pathologist, the conclusion made did not differ from the conclusion reported in the first pathology report. The retrospective assessment only resulted in more details. We acknowledge that the implementation of frozen sections for diagnosing NSTI is affected by a hospital resources and regional collaborations, which requires the appropriate logistics for assessing frozen sections in emergency setting.

Conclusion

The presence of bullae, severe fascial or muscle inflammation, fascial or muscle necrosis, muscle edema, thrombosis or vasculitis upon histopathological evaluation all indicate a high probability of a NSTI. In more than half of all surgical explorations for NSTIs, frozen sections aided in making the diagnosis NSTI more or less likely. Even though discrepancies between frozen and FFPE samples were common, none of the diagnoses made based on the frozen section had to be revised after examination of the FFPE samples. Therefore, we recommend frozen section for diagnosing NSTIs in ambivalent cases as part of the triple diagnostics algorithm.

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Appendix 1 Assessment form for assessing frozen sections and formalin-fixed paraffin-embedded samples for signs of necrotizing soft tissue infection

Type of coupe: Frozen section Formalin-fixed paraffin-embedded sample	
Epidermis: Absent Normal Bullae Necrosis	**Fascia:** Absent Normal Edema Acute inflammation/neutrophils Mild Moderate Severe Necrosis
Dermis: Absent Normal Edema Acute inflammation/neutrophils Mild Moderate Severe Necrosis	**Muscle:** Absent Normal Edema Acute inflammation/neutrophils Mild Moderate Severe Necrosis
Subcutaneous fat: Absent Necrosis Acute inflammation	**Vascular:** Thrombosis Vasculitis
Comments:	

Appendix 2 Histopathological characteristics of incisional biopsies from patient with eventually no necrotizing soft tissue infection

Tissue layer	Cellulitis (n = 5)	Erysipelas (n = 5)	Bacteremia (n = 1)	ADR with cutaneous eosinophilia (n = 1)
Epidermis (n = 6)				
No abnormalities	2/2	2/2	1/1	0/1
Bullae	0/2	0/2	0/1	0/1
Necrosis	0/2	0/2	0/1	1/1
Dermis (n = 6)				
No abnormalities	0/2	0/2	1/1	0/1
Edema	2/2	2/2	0/1	1/1
Acute inflammation				
Mild	1/2	2/2	0/1	0/1
Moderate	1/2	0/2	0/1	0/1
Severe	0/0	0/2	0/1	0/1
Necrosis	0/2	0/2	0/1	0/1
Subcutaneous fat (n = 11)				
Inflammation (regardless of severity)	3/4	3/5	1/1	0/1
Necrosis	2/4	2/5	1/1	0/1
Fascia (n = 12)				
No abnormalities	0/5	2/5	1/1	0/1
Edema	4/5	3/5	0/1	1/1
Acute inflammation				
Mild	3/5	2/5	0/1	0/1
Moderate	1/5	0/5	0/1	1/1
Severe	0/5	0/5	0/1	0/1
Necrosis	1/5	0/5	0/1	1/1
Muscle (n = 7)				
No abnormalities	0/2	2/4	1/1	NA
Edema	0/2	0/4	0/1	NA
Acute inflammation				
Mild	2/2	1/4	0/1	NA
Moderate	0/2	0/4	0/1	NA
Severe	0/2	0/4	0/1	NA
Necrosis	0/2	1/4	0/1	NA
Vessels (n = 12)				
Thrombosis	0/5	0/5	0/1	1/1
Vasculitis	0/5	0/5	0/1	0/1

ADR = Adverse Drug Reaction; NA = Not Available

7

Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis

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Abstract

Background: Although the phrase 'time is fascia' is well acknowledged in case of necrotizing soft tissue infections (NSTI), solid evidence is lacking. The aim of this study is to review the current literature concerning the timing of surgery in relation to mortality and amputation in patients with NSTIs.

Methods: A systematic search in PubMed/MEDLINE, Embase, Cumulative Index to Nursing & Allied Health Literature (CINAHL) and the Cochrane Controlled Register of Trials (CENTRAL) was performed. The primary outcomes were mortality and amputation. These outcomes were related to the following time related variables 1) time from onset symptoms to presentation; 2) time from onset symptoms to surgery; 3) time from presentation to surgery; 4) duration of the initial surgical procedure. For the meta-analysis, the effects were estimated using random-effects meta-analysis models.

Result: A total of 109 studies, with combined 6,051 NSTI patients, were included. Of these 6,051 NSTI patients, 1,277 patients died (21.1%). A total of 33 studies, with combined 2,123 NSTI patients, were included for quantitative analysis. Mortality was significantly lower for patients with surgery within 6 hours after presentation compared to when treatment was delayed more than 6 hours (OR 0.43; 95% CI 0.26 – 0.70; 10 studies included). Surgical treatment within 6 hours resulted in a 19% mortality rate compared to 32% when surgical treatment was delayed over 6 hours. Also, surgery within 12 hours reduced the mortality compared to surgery after 12 hours from presentation (OR 0.41; 95% CI 0.27 – 0.61; 16 studies included). Patient delay (time from onset of symptoms to presentation or surgery) did not significantly affect the mortality in this study. None of the time related variables assessed significantly reduced the amputation rate. Three studies reported on the duration of the first surgery. They reported a mean operating time of 78, 81 and 102 minutes with associated mortality rates of 4%, 11.4% and 60%, respectively.

Conclusion: Average mortality rates reported remained constant (around 20%) over the past 20 years. Early surgical debridement lowers the mortality rate for NSTI with almost 50%. Thus, a sense of urgency is essential in the treatment of NSTI.

Background

Necrotizing soft tissue infections (NSTIs) are notorious for their acute, aggressive and rapidly progressive character. Of all NSTIs, necrotizing fasciitis is the most well-known and most common NSTI, other NSTIs are myonecrosis and necrotizing cellulitis [1]. Mortality and amputation rates for NSTI are considered high, with described mortality rates varying between 6% and 33% [2–5]. Factors such as advanced age, female sex, multiple comorbidities and sepsis upon presentation have previously been linked to increased mortality rates [2,5,6]. The bacteria causing NSTI can spread rapidly along the fascial planes, therefore the saying "time is fascia" seems suitable. This resulted in the established belief that source control with early surgical resection of necrotic and infected tissue reduces progression of the infection and improves outcomes [1,7]. However, the achievability of early treatment is sometimes hindered by a prolonged interval between the onset of symptoms and the patient seeking medical care (patient delay), or between hospital presentation and the eventual diagnosis (doctor delay) [8]. Furthermore, logistical challenges within hospitals might cause unwanted delays in treatment (system delay). In these cases, it is interesting to know if the prognosis can be predicted by the time frame in which the initial surgery is performed. If such a "golden" time frame exists, it could also indicate that when the delay was already too great, a higher mortality or amputation rate can be expected after initial surgery. There is still no consensus on a potential cut off point for such a time frame [9]. Multiple cohort studies have previously assessed the relation between surgical timing and mortality and amputation, however a large number of studies are under-powered and were unable to reject the null hypothesis [10–14]. Therefore, the aim of this review was to analyze the current literature concerning the timing of surgery in relation to mortality and amputation in patients with necrotizing soft tissue infections.

Review methods

A study protocol was developed a priori and registered with PROSPERO. This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search and study selection

Published cohort studies and randomized controlled trials (RCT) reporting on mortality or amputation rates for NSTIs were included. These studies had to evaluate one of the following time related variables: 1) time from onset symptoms to presentation; 2) time from onset symptoms to surgery; 3) time from presentation to surgery and/or 4) duration of the initial surgical procedure. Studies written in English

or Dutch were included. Conference abstracts, studies including pediatric patients, study protocols, reviews, animal studies, case reports and studies reporting the results for the time variables for less than five patients were excluded.

Two reviewers (FN and DS) independently conducted a systematic search in PubMed/MEDLINE, Embase, Cumulative Index to Nursing & Allied Health Literature (CINAHL) and the Cochrane Controlled Register of Trails (CENTRAL) for articles published from inception of the databases up to October 29, 2019. The search syntax is available in Appendix 1. No filters were applied during the search. Titles and abstract were screened for potential eligible studies, after which duplicates were removed. The full texts of the potential eligible studies were screened by one reviewer (FN) for the reporting of one or more of the time related variables. If the full text article was not available online, attempts were made to request the article from the library or the authors. After screening the available full texts, the remaining articles were read in full to determine eligibility. In case of uncertainty, the eligibility of a study was discussed between both reviewers. Disagreement of eligibility between reviewers was solved by discussion with a third independent reviewer (FH).

Data extraction

The following data were extracted if available: first author, year of publication, country in which the study was conducted, study design, inclusion period, number of participating medical institutions, number of patients included, mean age of included patients, the anatomical regions affected by NSTI, in- and exclusion criteria, diagnostic criteria used for diagnosing NSTI (e.g. operative findings, histopathologic results, microbiology results, clinical signs during physical examination), time onset symptoms to presentation or surgery, time from presentation to surgery, duration of first surgery, mortality rate and amputation rate. Data was extracted including the available odds ratio's (OR), confidence intervals (CIs) and *p*-values.

Outcomes

The primary outcomes were mortality and amputation in NSTI patients. The previous mentioned time related variables were assessed in relation to these outcomes. Due to heterogeneity in the reporting of the time variables, we assumed that time of presentation would be equal to time of hospital admittance or diagnosis, since NSTI patients often present septic and require immediate treatment hence the immediate hospital admission. We assumed that mortality rates reported in studies were in-hospital mortality rates, unless reported otherwise.

Quality assessment

The methodological quality of the studies included in the meta-analysis was independently assessed by two reviewers (FN and DS). Since no suitable tool was available for this non-intervention-non-diagnostic study, a modified quality assessment tool based on the most applicable criteria from the Quality in Prognosis Studies (QUIPS) tool and Methodological Index for Non-Randomized Studies (MINORS) was used (Appendix 2) [15,16]. Disagreement between reviewers during the quality assessment was resolved by discussion with a third independent reviewer (FH).

Statistical analysis

Data management and statistical analysis were performed using Review Manager software (RevMan, version 5.3; Cochrane, Copenhagen, Denmark). Studies with data available for one or more of the time related variables as categorical or dichotomous data in relation to either mortality or amputation were identified and included in the meta-analysis. If there was insufficient quantitative data to perform a meta-analysis for one or more of the time related variables in relation to the outcomes, the time variable was assessed qualitatively. If required, data were manually categorized or calculated based on the available text or tables and was converted in the same units.

The stratification of time categories was data driven. If the same time category (e.g. 6h, 12h, 24h) was compared in relation to mortality or amputation by ≥ 2 studies, this time categories was evaluated in a meta-analysis. Therefore, the available data per time category determined the stratification of the analyses for mortality and amputation. For the meta-analysis with amputation as outcome, the sample size was corrected to only include the patients with NSTI of the extremity or NSTI affecting multiple body areas. This was done to prevent underestimating the amputation rate if also NSTIs involving the trunk or perineum were included in the calculation of the amputation rate. The effect estimate for all analyses was an OR with a 95% CI calculated using the Mantel-Haenszel method. A p-value <0.05 in the overall effect Z test was considered statistically significant. Heterogeneity was evaluated using the following statistical measures: τ^2, I^2 and χ^2. All analyses were performed using the random-effects model. Potential publication bias was assessed by eyeballing the funnel plots.

Subgroup analyses

A priori, the following subgroup analyses were planned for each time related variable if ≥ 2 studies were found for the subgroup analyses: 1) high quality studies (a quality assessment score of 6 or higher out of a possible score of 8); 2) studies published in the last decade; 3) studies assessing NSTI of the entire body without excluding

specific body regions; 4) studies that assessed all microbial NSTI entities without excluding specific micro-organism.

Review results

Search

After full text screening, 109 eligible studies were identified. The studies from Tsai et al. from 2004 [17] and 2009 [18] were excluded based on overlap in patient populations with a later published study from their group in 2010 [19]. The studies by Ahn et al., Holena et al. and Sugihara et al. were excluded, since they included patients from nationwide financial code based databases without evident review of the included patients medical charts on content for eligibility [13,20,21]. All 109 articles combined, 6,051 patients were included. Of these 6,051 NSTI patients, 1,277 patients died (21.1%) and 529 of the 2,781 patients with NSTI of the extremity underwent an amputation (19.0%). Comparing mortality rates before and after 2000, there was a significant reduction in mortality from 28.3% to 20.6% (p = 0.004). However, average mortality rates reported remained constant (around 20%) over the past 20 years (Figure 1). The baseline characteristics are summarized in table 1. The elaborate baseline characteristics, study in- and exclusion criteria, the time related variables assessed and outcomes can be found in Appendix 3. A total of 33 studies were included for quantitative analysis. The selection process and reasons for exclusion can be found in figure 2.

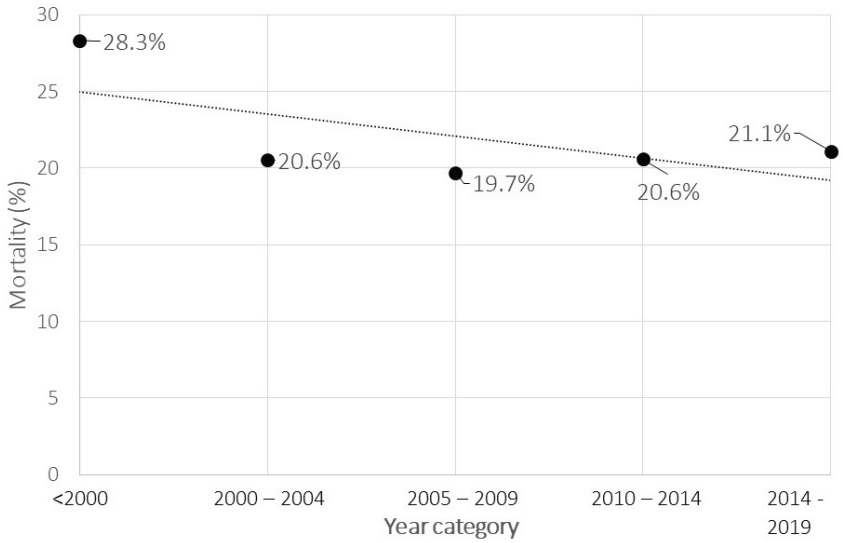

Figure 1 Historical cumulative mortality rates for necrotizing soft tissue infections based on included studies

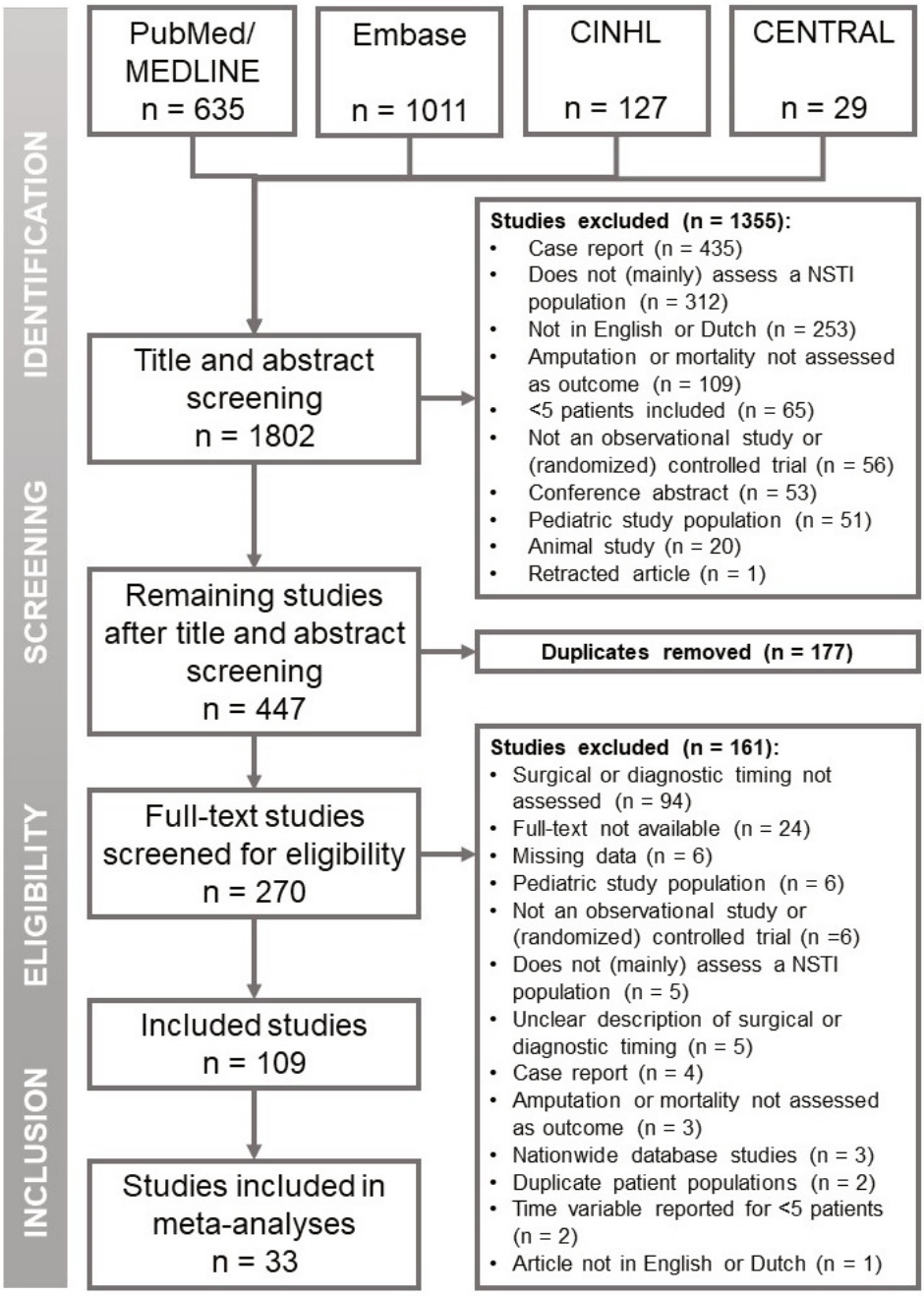

Figure 2 Flowchart of study inclusion process for meta-analysis of surgical timing of necrotizing soft tissue infections

Baseline characteristics of studies in quantitative analysis

The 33 studies available for quantitative and thorough analysis included a combined number of 2,123 NSTI patients with a mean age of 54 years. Of the 2,123 patients, 417 patients (19.6%) died due to the NSTI. The number of patients included per study ranged between 9 and 472 patients. The majority of the studies included NSTI patients without having exclusion criteria for specific body regions affected (n = 23, 70%) (Table 1).

Time from presentation at hospital to surgery

Surgery within 6 hours

Ten (30%) of the 33 included studies reported the number of patients operated on within and after 6 hours after presentation. The mortality was significantly lower for surgery within 6 hours after presentation compared to surgical treatment delayed more than 6 hours, with an OR of 0.43 (95% CI 0.26 – 0.70, $p < 0.01$) (Figure 3a). Surgical treatment within 6 hours resulted in a 19% mortality rate and surgical treatment after 6 hours in a mortality rate of 32%. Surgery within 6 hours did not result in a significant reduction in the amputation rate, with an OR of 0.68 (95% CI 0.34 – 1.39, $p = 0.30$) (Table 2 and Appendix 4).

Surgery within 12 hours

Sixteen (48%) of the 33 included studies reported the number of patients operated on within and after 12 hours after presentation. The mortality was significantly lower for surgery within 12 hours after presentation compared to surgical treatment delayed more than 12 hours, with an OR of 0.41 (95% CI 0.27 – 0.61, $p < 0.01$) (Figure 3b). Surgical treatment within 12 hours resulted in a 19% mortality rate and surgical treatment after 12 hours in a mortality rate of 34%. Surgery within 12 hours did not result in a significant lower amputation rate, with an OR of 0.71 (95% CI 0.28 – 1.82, $p = 0.48$) (Table 2 and Appendix 4).

Surgery within 24 hours

Eighteen (55%) of the 33 included studies reported the number of patients operated on within and after 24 hours after presentation. Analysis showed no significant reduction in the mortality or amputation rate between surgical treatment within or after 24 hours, with an OR of 0.79 (95% CI 0.52 – 1.20, $p = 0.26$) for mortality and an OR of 0.63 (95% CI 0.20 – 2.05, $p = 0.45$) for amputation (Table 2 and Appendix 4).

Table 1 Baseline study characteristics of necrotizing soft tissue infection studies assessing surgical timing

	Eligible studies (n = 109)	Studies in meta-analyses (n = 33)
Publication year, n (%)		
1989 and older	8 (7)	3 (9)
1990 – 1999	7 (6)	4 (12)
2000 – 2009	29 (27)	7 (21)
2010 – 2019	65 (60)	19 (58)
Continent where study was performed[a], n (%)		
Africa	8 (7)	0 (0)
Asia	42 (39)	14 (43)
Europe	23 (21)	7 (21)
North-America	32 (30)	12 (36)
Oceania	3 (3)	0 (0)
South-America	0 (0)	0 (0)
Type of study[b], n (%)		
Retrospective cohort study	89 (90)	27 (93)
Prospective cohort study	9 (9)	2 (7)
Randomized controlled trial	1 (1)	0 (0)
Study period in years, median (IQR; range)	7 (5 – 11; 2 -24)	6 (5 – 11; 2 -16)
Number of participating medical institutions[a], median (IQR; range)	1 (1 – 1; 1 - 6)	1 (1 – 1; 1 – 2)
Number of included patients per study, median (IQR; range)	35 (20 – 67; 5 – 472)	33 (20 – 84; 9 - 472)
Body regions affected by NSTI assessed per study, n (%)		
Head and/or neck	9 (8)	1 (3)
Extremities	8 (8)	3 (9)
Trunk	2 (2)	1 (3)
Fournier	32 (29)	4 (12)
Full body	58 (53)	24 (73)

IQR = Interquartile Range; NSTI = Necrotizing Soft Tissue Infection; Missing cases: [a]1 missing; [b] 10 missing.

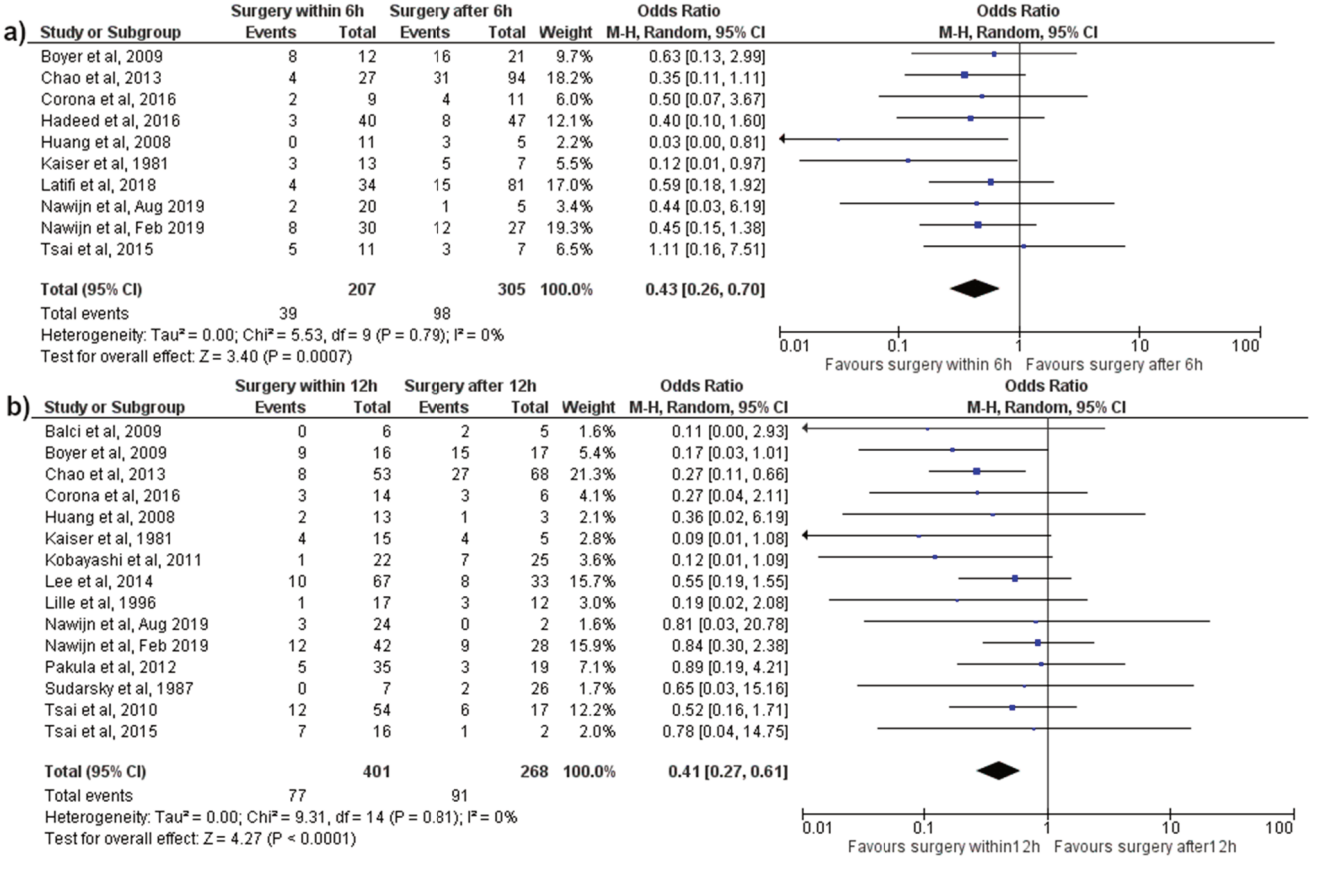

Figure 3 Mortality in a meta-analysis assessing time from presentation to surgery in necrotizing soft tissue patients. a) Mortality in a meta-analysis comparing surgery within and after 6 hours after presentation; b) Mortality in a meta-analysis comparing surgery within and after 12 hours after presentation

Table 2 Results of meta-analyses assessing influence of surgical timing on outcomes in necrotizing soft tissue infections

Mortality analysis						
			Subgroup Analysis			
Outcomes	Events/ total patients (n)	Results (OR, 95% CI)	High-quality studies[a] (OR, 95% CI)	Studies published ≥ 2009[b] (OR, 95% CI)	Studies without limitation on affected body region by NSTI[c] (OR, 95% CI)	Studies without limitation based on specific microbial types of NSTI[d] (OR, 95% CI)
Surgery within 6h after presentation	137 / 512	**0.43 (0.26 – 0.70)**	**0.46 (0.27 – 0.80)**	**0.49 (0.30 – 0.82)**	**0.44 (0.25 – 0.75)**	**0.45 (0.25 – 0.79)**
Surgery within 12h after presentation	168 / 669	**0.41 (0.27 – 0.61)**	**0.40 (0.23 – 0.69)**	**0.43 (0.28 – 0.67)**	**0.45 (0.29 – 0.70)**	**0.41 (0.22 – 0.74)**
Surgery within 24h after presentation	271 / 1372	0.79 (0.52 – 1.20)	0.63 (0.29 – 1.34)	0.84 (0.52 – 1.37)	0.85 (0.53 – 1.38)	1.11 (0.77 – 1.60)
Surgery within 3 days after onset symptoms	33 / 172	0.40 (0.15 – 1.08)	0.41 (0.13 – 1.29)	0.35 (0.12 – 1.02)	0.46 (0.16 – 2.42)	0.13 (0.01 – 2.42)
Hospital admission within 3 days after onset symptoms	98 / 326	0.49 (0.16 – 1.44)	0.66 (0.15 – 2.83)	0.61 (0.17 – 2.24)	0.41 (0.08 – 2.13)	1.01 (0.37 – 2.74)

Continuation of table 2

			Amputation analysis			
			Subgroup analysis			
Outcomes	Events/ total patients (n)	Results (OR, 95% CI)	High-quality studies[a] (OR, 95% CI)	Studies published ≥ 2009[b] (OR, 95% CI)	Studies without limitation on affected body region by NSTI[c] (OR, 95% CI)	Studies without limitation based on specific microbial types of NSTI[d] (OR, 95% CI)
Surgery within 6h after presentation	45 / 197	0.68 (0.34 – 1.39)	0.57 (0.23 – 1.42)	0.65 (0.31 – 1.38)	0.64 (0.30 – 1.38)	0.61 (0.28 – 1.32)
Surgery within 12h after presentation	26 / 138	0.71 (0.28 – 1.82)	0.54 (0.11 – 2.54)	0.71 (0.25 – 1.98)	0.71 (0.24 – 2.11)	0.55 (0.19 – 1.54)
Surgery within 24h after presentation	21 / 102	0.63 (0.20 – 2.05)	0.25 (0.04 – 1.60)	0.70 (0.19 – 2.58)	0.41 (0.08 – 2.26)	0.53 (0.14 – 2.06)

CI = Confidence Interval; NSTI = Necrotizing Soft Tissue Infection; OR = Odds Ratio. **Bold** font indicates significant result.

[a] Excluding: Bair, Balci, Catena, Corona, Ferretti, George, Huang 2008, Kaiser, Kalaivani, Knutson, Lille, Liu, Mittapalli, Ogilvie, Pakula, Palmer, Park, Stephenson, Sudarsky, Tsai 2010, Tsai 2015, Wang, Yu

[b] Excluding: Catena, Huang 2008, Kaiser, Knutson, Lille, Ogilvie, Palmer, Stephenson, Sudarsky, Wang, Yu

[c] Excluding: Balci, Boyer, Corona, Ferretti, Huang 2008, Liu, Palmer, Stephenson, Sugihara, Wang

[d] Excluding: Chao, Huang 2008, Knutson, Lee, Tsai 2010, Tsai 2015

Time from onset symptoms to presentation at hospital

Forty-three studies included in the qualitative analysis reported on time from onset symptoms to presentation. The average time weighted by study sample sizes was 4.5 days (range 1.0 – 13.3 days). Since continuous independent variables cannot be used in meta-analyses, only studies with similar dichotomous variables were included in this meta-analysis. Eight (24%) of the 33 studies included for meta-analysis reported the number of patients presenting to the hospital within and after three days after the onset of the symptoms. Presentation to the hospital within three days after onset of symptoms did not result in significant lower mortality than patients presenting after three days, with an OR of 0.49 (95% CI 0.16 – 1.44) (Table 2 and Appendix 4).

Time from onset symptoms to surgery

Thirteen studies included in the qualitative analysis reported on time from onset symptoms to surgery. The average time weighted by study sample sizes was 4.6 days (range 2.1 – 7.5 days). Only studies with similar dichotomous variables were included in this meta-analysis. Three (9%) of the 33 included studies reported the number of patients operated on within and after three days after onset of symptoms. Surgery within three days after onset of symptoms did not result in significant lower mortality than patients operated after three days, with an OR of 0.40 (95% CI 0.15 – 1.08) (Table 2 and Appendix 4).

Duration of first surgery

Only three studies reported on the duration of the first surgery. Corman et al. found a mortality rate of 4% (1 out of 26 patients) with associated mean duration of the initial surgery of 78 minutes, Elskaket et al. reported a mortality rate of 11.4% (5 out of 44 patients) associated with a mean duration of the initial surgery of 81 minutes, while Hong et al. reported a mortality rate of 60% (9 out of 15 patients) associated with a mean duration of the initial surgery of 102 minutes.

Quality assessment

The elaborate results of the quality assessment for each study can be found in Appendix 5. The mean quality score was 5 ± 2. Ten (30%) studies scored 6 or higher, indicating high quality.

Subgroup analyses

The subgroup analyses either using only studies published in the last decade, studies assessing NSTI of the entire body without excluding specific body regions, or studies that assessed all microbial NSTI entities without only including a specific micro-

organism did not result in new results. No outcomes changed direction or significance (Table 2 and Appendix 4).

Assessment of publication bias

The funnel plot for the analysis of time from presentation to surgery within and after 6 hours and 12 hours in relation to mortality are presented in figure 4. Upon eyeballing the funnel plots, both showed relative symmetry indicating a low risk of publication bias in these meta-analyses.

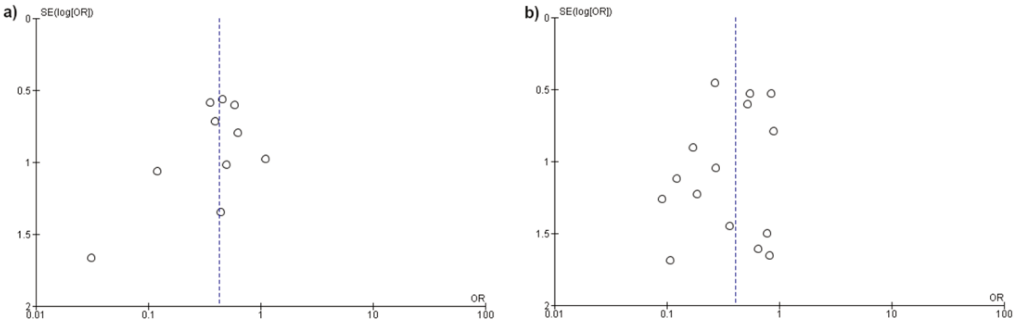

Figure 4 Funnel plot of meta-analysis assessing surgical timing and mortality in necrotizing soft tissue infections. a) Funnel plot for meta-analysis comparing mortality in necrotizing soft tissue infection patients operated within or after 6 hours after presentation; b) Funnel plot for meta-analysis comparing mortality in necrotizing soft tissue infection patients operated within or after 12 hours after presentation.

Discussion

This study clearly shows that the average mortality rate for NSTI did not improve over past 20 years. Timely initial surgery after presentation to the hospital for NSTI cuts mortality almost in half. This stresses the need for early surgical treatment of all NSTIs.

There is only one similar meta-analysis published that assesses the time to surgery for NSTIs. Gelbard et al. pooled the results from six studies and found an OR of 0.43 (95% CI 0.24 – 0.78) in favor of surgery within 12 hours (13% mortality) compared to surgery after 12 hours from presentation (26% mortality) [8]. Our study shows a similar reduction in mortality if the initial surgery is performed within 12 hours after presentation (19% vs. 34%), but even more, also found such an association for surgery within 6 hours (19% vs. 32%). Based our results, initial surgery within 12 hours should be regarded as the minimal “golden” time frame to operate patients with NSTIs, while surgery within 6 hours might be strongly preferred. However, based on these analyses it is difficult to give a prognosis for the patients operated on between 6 and 12 hours. Based on the analyses comparing surgery within and

after 12 hours, these patients were less likely to die (OR 0.41 for surgery within 12 hours; 95% CI 0.27 – 0.61), while in the analysis comparing surgery within and after 6 hours this group of patients had worse outcomes (OR 0.43 for surgery within 6 hours; 95% CI 0.26 – 0.70). Although surgery within 12 hours is essential, surgery within 6 hours might be beneficial. However, to determine a more exact cut off point for the "golden" time frame, more research is necessary.

Patient delay (time from onset of symptoms to surgery) did not seem to affect mortality, although availability and robustness of the data for this part of the question was limited. Nevertheless, based on the presented mortality data in this review, the time from presentation to surgery (which encompasses both doctor delay and part of the system delay) has significant effect on outcome. On the other hand, this study did not find an association between timing of surgery and the amputation rate, indicating that other factors, such as comorbidities, the local situation of the tissue (e.g. the presence of bullae) or the severity of disease (e.g. severe sepsis) are more predictive for amputation [22,23]. However, those factors were outside the scope of this review.

The goal of the initial surgical procedure for NSTIs is to gain control and prevent further (trans-fascial and hematogenous) spreading of the infection by complete debridement of all the infected and necrotic tissue [1,9]. Sarani et al. suggested that each hour delay of surgical treatment can lead to a local spread of the infection as fast as an inch per hour and results in higher chances of systematic spread [24]. Early surgical treatment does not only reduce the mortality rate, but several studies also found that it can reduce the risk of septic shock, number of surgical debridements and the length of hospital stay [14,25]. The exact pathophysiology behind the rapid spread of bacteria across the fascia is still poorly understood. However, it is thought that especially during NSTIs the microbial virulence caused by the toxins produced by the involved bacteria outweighs the host defense system providing the opportunity for rapid spreading of the infection [24,26]. Early resection of necrotic and infected tissue results in a lower microbial load. As a result, the immune system combined with broad spectrum antibiotics has better odds at controlling the infection [1,27]. Thus, time is of the essence.

However, clinical implementation of the desired urgent debridement is often hindered by multiple factors. First, patient delay is a problem not easily influenced by medical personnel. The time a patient waits before seeking medical care is dependent on a wide variety of clinical, economic and social factors. The physical and financial access to emergency care, the nature of the acute illness, underlying chronic comorbidities and understanding of the severity of symptoms all influence the likelihood of a patient seeking emergency care [28].

Next, doctor delay is a well-known problem for this disease. Before NSTI can be treated, the accurate diagnosis must be made. Awareness of NSTI is frequently described as low, due to its low incidence compared to non-necrotizing soft tissue infections with a higher a-priori chance such as cellulitis and erysipelas [3,29]. Furthermore, symptoms of NSTI mimic those of cellulitis and erysipelas and no pathognomic symptoms for NSTI are known [23,30,31]. Wong et al. developed the laboratory risk indicator for necrotizing fasciitis (LRINEC) score to help physicians with identifying NSTIs [32]. However, a meta-analysis performed by Fernando et al. showed that this is a suboptimal score for identifying patients with NSTI due to its low sensitivity [30]. The substantial problem of misdiagnosing is illustrated in a systematic review by Goh et al. They reported that 71.4% of the NSTIs were initially misdiagnosed and that the mortality rate increased with the percentage of initially missed diagnoses [23]. Interoperative diagnostic accuracy can be increased by using the method of triple diagnostics. In case of ambivalent signs of NSTI upon intra-operative macroscopic evaluation, samples should be taken for intra-operative assessment of fresh frozen sections and Gram stains. Based on those results, the NSTI diagnosis can be confirmed or waived [7,33]. A solution for improving pre-operative diagnostics is a strongly recommended focus for future studies.

Finally, the medical system should be organized with enough surgical capacity to prevent system delay. After the accurate diagnosis is made, the logistics needs to be in place to facilitate urgent surgical debridement. The initial debridement for NSTI holds the highest surgical priority. McIsaac et al. reported that 27% of the urgent or emergency surgeries at their hospital with the highest priority were delayed beyond the waiting time appointed to surgeries with the highest priority. The main reasons for the delays were unavailability of surgeons, followed by unavailability of resources such as operating rooms [34]. Improving the availability of the appropriate surgeons and resources at the presenting hospital is crucial, since transfer, even to a center specialized in NSTIs, increases the delay and therefore the risk at mortality [21].To improve immediate availability of the appropriate resources, the system using 24/7 in-house attending surgeon and the 24/7 readiness of an operating room could significantly decrease the time to surgery and mortality [35,36].

Not only the time to surgery influences the outcomes, but shorter operative times of emergency surgeries are also associated with less postoperative complications [37]. Matsuyama et al. reported that the mortality and morbidity are significantly lower if emergency surgeries in adults were completed within 120 minutes and Kaushal-Deep et al. reports better outcomes if operative times are less than 100 minutes for pediatric emergency surgeries [37,38]. In severely physiological compromised trauma patients, the damage control strategy is indicated if the operative time would be longer than 90 minutes [39]. Unfortunately, our study is

unable to comment on the ideal duration of the initial debridement for NSTI and remains therefore unknown. However, since most NSTI patients are severely physiological compromised, short and efficient debridements might be recommended, as a major difference in mortality rate was noted between the published results of patients with an operating time shorter and longer than 90 minutes. The risk at more postoperative complications associated with longer operative times should considered when skin-sparing debridement for NSTIs is contemplated [37,40]. Therefore, the clinical condition of the patient should determine the course of actions and surgical strategy.

The limitations of this study need to be kept in mind during interpretation of the results. For example, we were unable to vary between time from diagnosis to surgery and time from presentation to surgery. The time from presentation to diagnosis is often underreported and could not be assessed. Furthermore, even though we used a broad search, there is still a possibility of missing studies. Finally, for the interpretation of the cumulative mortality rates, it should be kept in mind that the included studies used different and sometimes very specific in- and exclusion criteria, limiting the generalizability of mortality rates to the entire NSTI population. For example, eight studies excluded patients that did not undergo surgery, which indicates that those patients were unsuitable for surgery (i.e. based on severity of illness or patients' wishes) [10,41–47]. Excluding these patients from the mortality rate could results in a seemingly better mortality rate than the reality, since these patients are likely to have died of NSTI. The strength of this meta-analysis is the relatively low heterogeneity in the meta-analysis and the risk at publication bias is estimated to be limited. Furthermore, this meta-analysis contributes to solving the problem of underpowered studies, which is especially relevant in the field of NSTI research. The incidence of NSTI has been estimated to be 3.64 per 100,000 person-years, this suggests that most single-center NSTI study would automatically be underpowered due to the limited incidence of NSTI to that hospital [3]. Therefore, meta-analyses remain an efficient way of increasing the body of evidence if only studies with limited sample sizes are available.

Conclusion

Average mortality rates reported remained constant (around 20%) over the past 20 years. Surgical debridement as soon as possible lowers the mortality rate for NSTI with almost 50%. However, early surgical treatment did not reduce the amputation rate. Nevertheless, this systematic review and meta-analysis shows that early surgical treatment of NSTIs within 12 hours is essential for reducing the mortality rate, while surgical treatment within 6 hours is might even further improve outcomes.

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Appendix 1 Search syntax for systematic review assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections

PubMed/MEDLINE syntax (n = 635) (fasciitis, necrotizing [MESH Terms] OR necrotizing fasciitis[Title/Abstract] OR necrotizing soft tissue infection[Title/Abstract] OR gas gangrene[Title/Abstract] OR Fournier's gangrene[Title/Abstract] OR severe necrotizing soft tissue disease[Title/Abstract]) **AND** ((Time-to-treatment [MESH Term] OR Operative Time [MESH Term] OR time[Title/Abstract] OR hours[Title/Abstract] OR days[Title/Abstract]) AND (Surgical Procedures, operative[MESH Terms] OR Surgery [MESH Terms] OR Debridement [MESH Terms] OR surgery[Title/Abstract] OR debridement[Title/Abstract] OR operation[Title/Abstract])) **NOT** case report[Title/Abstract]

Embase syntax (n = 1011) ('necrotizing fasciitis'/exp OR 'necrotizing fasciitis':ti,ab OR 'necrotizing soft tissue infection':ti,ab OR 'gas gangrene':ti,ab OR 'Fournier gangrene':ti,ab OR 'severe necrotizing soft tissue disease':ti,ab) **AND** (('time to treatment'/exp OR 'operation duration'/exp OR 'time':ti,ab OR 'hours':ti,ab OR 'days':ti,ab) AND ('debridement'/exp OR 'surgery'/exp OR 'surgery':ti,ab OR 'debridement':ti,ab OR 'operation':ti,ab)) **NOT** 'case report':ti,ab

CINAHL syntax (n=127) (MH fasciitis, necrotizing OR TI necrotizing fasciitis OR AB necrotizing fasciitis OR TI necrotizing soft tissue infection OR AB necrotizing soft tissue infection OR TI gas gangrene OR AB gas gangrene OR TI Fournier's gangrene OR AB Fournier's gangrene OR TI severe necrotizing soft tissue disease OR AB severe necrotizing soft tissue disease) **AND** (MH Time-to-treatment OR MH Operative Time OR TI time OR AB time OR TI hours OR AB hours OR TI days OR AB days) AND (MH Surgical Procedures, operative OR MH Surgery OR MH Debridement OR TI surgery OR AB surgery OR TI debridement OR AB debridement OR TI operation OR AB operation) **NOT** (TI case report OR AB case report)

CENTRAL syntax (n=29) (MH 'necrotizing fasciitis' OR necrotizing fasciitis:ti,ab OR necrotizing soft tissue infection:ti,ab OR gas gangrene:ti,ab OR Fournier gangrene:ti,ab OR severe necrotizing soft tissue disease:ti,ab) **AND** ((MH 'time to treatment' OR MH 'operation duration' OR time:ti,ab OR hours:ti,ab OR days:ti,ab) AND (MH 'debridement' OR MH 'surgery' OR surgery:ti,ab OR debridement:ti,ab OR operation:ti,ab))

Appendix 2 Quality assessment tool for systematic review assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections

Points	Prospective collection of data	Inclusion and exclusion criteria	Diagnostic criteria for necrotizing soft tissue infections used	Definition of the outcome
2	Prospective	Inclusion and exclusion criteria are adequately described	Macroscopic findings fascia, histopathology results and/or microbiology results	A clear definition of outcome is provided, including duration of follow-up period
1	Retrospective	Unclear or poor described inclusion and/or exclusion criteria	Only clinical signs	A definition of outcome is provided without reporting duration of follow-up period (including "in-hospital mortality" without reporting length of hospital stay)
0	Not reported	Not reported	Not reported	Not reported

Appendix 3 Extracted data from eligible studies assessing surgical timing related to mortality and amputation due to necrotizing soft tissue infection
Due to large file size, not included in thesis. Online available at: https://static-content.springer.com/esm/art%3A10.1186%2Fs13017-019-0286-6/MediaObjects/13017_2019_286_MOESM3_ESM.xlsx

Appendix 4 Forrest plots for all (subgroup) analyses assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections
Due to large file size, not included in thesis. Online available at: https://static-content.springer.com/esm/art%3A10.1186%2Fs13017-019-0286-6/MediaObjects/13017_2019_286_MOESM4_ESM.pdf

Appendix 5 Results from quality assessment of articles included in meta-analyses assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections
Due to large file size, not included in thesis. Online available at: https://static-content.springer.com/esm/art%3A10.1186%2Fs13017-019-0286-6/MediaObjects/13017_2019_286_MOESM5_ESM.pd

8

The impact of operative time on the outcomes of necrotizing soft tissue infections: a multicenter retrospective study

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Submitted

Abstract

Background: The primary aim of this study was to identify if there is an association between the operative time of the initial debridement for necrotizing soft tissue infections (NSTIs) and the mortality corrected for disease severity.

Methods: A retrospective multicenter study was conducted of all patients with NSTIs undergoing surgical debridement. The primary outcome was the 30-day mortality. The secondary outcomes were days until death, length of intensive care unit (ICU) stay, length of hospital stay, number of surgeries within first 30 days, amputations and days until definitive wound closure.

Results: A total of 160 patients underwent surgery for NSTIs and were eligible for inclusion. Twenty-two patients (14%) died within 30 days and 21 patients (13%) underwent an amputation. The median operative time of the initial debridement was 59 minutes (IQR 35 – 90). In a multivariable analysis, corrected for sepsis just prior to the initial surgery, estimated total body surface (TBSA) area affected and the American Society for Anesthesiologists (ASA) classification, a prolonged operative time (per 20 minutes) was associated with a prolonged ICU (β 1.43, 95% CI 0.46 – 2.40; $p = 0.004$) and hospital stay (β 3.25, 95% CI 0.23 – 6.27; $p = 0.035$), but not with 30-day mortality. Operative times were significantly prolonged in case of NSTIs of the trunk ($p = 0.044$), in case of greater estimated TBSA affected ($p = 0.006$) or if frozen sections and/or Gram stains were assessed intra-operatively ($p < 0.001$).

Conclusions: The principles of damage control surgery might be beneficial for NSTI patients, since a prolonged operative time of the initial debridement for NSTIs result in prolonged ICU and hospital stays, regardless of the estimated TBSA affected, presence of sepsis prior to surgery and the ASA classification.

Background

Necrotizing soft tissue infections (NSTIs) are potentially lethal infections that cause necrosis of the subcutaneous fat, fascia and/or muscles. NSTIs are notorious for their acute onset and progressive nature, requiring prompt treatment [1]. Bacteria involved in NSTIs can spread rapidly along the fascial planes causing rapid progression and systemic complications [2]. A recent meta-analyses showed that early surgical debridement is vital for lowering mortality rates, since surgery within six hours after presentation lowered the mortality rate for NSTIs with almost 50% [3]. In this review, it was also attempted to identify a relationship between the operative time of the initial surgery for the NSTI and the mortality, the results for this analysis were too scarce. Even though only three studies reported on operative times, these results revealed a possible association between the duration of the initial surgery and the outcome of the NSTI [3–6]. It is well established in trauma and emergency surgery that prolonged operating times potentially lead to higher complication rates [7–9]. Therefore, in critical ill patients with physiological derangement, the damage control surgery principles are more widely applied, specifically in trauma. Damage control procedures are in their initial stage not aimed at definitive repair, but rather aimed to perform limited interventions to control the situation and to recover the patient's physiology preferable within an operating time of 90-120 minutes [10,11]. In trauma patients, this commonly refers to hemorrhage control and prevention of contamination. In NSTI patients this would refer to adequate and rapid source control with temporary closure [10]. After initial surgical control and resuscitation, secondary surgical procedures are required to perform reconstructions a definitive wound closure. However, since information on the association between operative time of the initial debridement for NSTIs and its outcomes is scarce, the aim of this study was to identify if such an association exists and to determine if the principles of damage control surgery are beneficial to NSTI patients.

Methods

The institutional review board of the initiating hospital provided a waiver (WAG/mb/20/012110) for consent for retrospective data collection. The board of all participating studies approved data collection. A protocol was a priori written, however, not published.

Study design

A retrospective cohort study of all patients with confirmed NSTIs who underwent their initial surgical debridement at one of the four participating study hospitals (an academic medical center and three large peripheral hospitals) between January 1st, 2010, and December 31st, 2019, was performed. NSTI refers to the necrotizing forms

of fasciitis, myositis and cellulitis. The NSTI had to be confirmed by either operative findings and/or histopathologic tissue findings and/or microbiology results [12,13]. Patients younger than 18 years at time of onset of the NSTI were excluded, as well were patients who were lost to follow-up after their initial debridement (e.g. due to transfer of patient to another hospital) or if operative times were missing. Eligible patients were identified using different methods per hospital which are outlined in Appendix 1. The study size was based on the number of eligible patients presenting to the study hospitals in the aforementioned study period.

Data collection

The patient demographics extracted from the medical charts included age, sex, the American Society of Anesthesiologist (ASA) classification. The extracted disease-related characteristics were location of the infection, estimated total body surface area (TBSA) affected, cultured micro-organisms, and laboratory results and hemodynamic parameters just prior to the initial surgery. The TBSA affected was estimated using the rule of nines for burn injuries [14]. Operative time of the initial surgery (incision to end surgery and time in het operating room), (primary or secondary) amputation, if a skin sparing operating technique was used (as reported in the operative note), complications, days until wound closure and mortality (including cause of death and time from initial surgery to death) were among the treatment related variables extracted. If possible, based on the available hemodynamic parameter and laboratory results, the Laboratory Risk Indicator for Necrotizing fasciitis (LRINEC), the sequential organ failure assessment (SOFA) score, the quick sequential organ failure assessment (qSOFA) score and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score were calculated prior to the initial surgery. For the laboratory results and hemodynamic parameters prior to surgery, only values reported within twelve hours prior to the start of the surgery were analyzed. Patients were determined to be septic prior to surgery if either the qSOFA or the SOFA was scored two or higher [15]. The primary outcome of this study was the 30-day mortality. The secondary outcomes were days until death, length of ICU stay, length of hospital stay, number of surgeries within first 30 days, the need for an amputation during re-exploration and days until definitive wound closure.

Statistical analysis

Normally distributed continuous variables are presented with means and standard deviations (SD), and, if more appropriate based on normality, presented with medians and interquartile ranges (IQR). Categorical variables are presented with frequencies and percentages. Missing data were handled using pairwise deletion. Multivariable analyses (either logistic or linear) were used to determine the association between the operative time per 20 minutes and the primary and

secondary outcomes. For the assessment of factors influencing the operative time, the Mann-Whitney U test was used for dichotomous independent variables, the Kruskal Wallis test for nominal independent variables and the Chi-squared test for trend for ordinal independent variables. For all analyses, a two-sided *p*-value <0.05 was considered statistically significant. Data will be analyzed using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

A total of 187 patients with NSTIs were identified, of which 160 were eligible for this study (Figure 1). The mean age of the included patients was 56 ± 16 years. Most patients had no or minor comorbidities (ASA I or II: n = 98, 62%). The lower extremity was most commonly affected by the NSTI (n = 75, 45%). The estimated TBSA affected ranged between 1% and 30% with a median of 3% (IQR 2 – 6%). Most NSTIs were monomicrobial infection, with group A streptococcus being identified as causative pathogen in almost half of all NSTIs (n = 74, 46%) (Table 1).

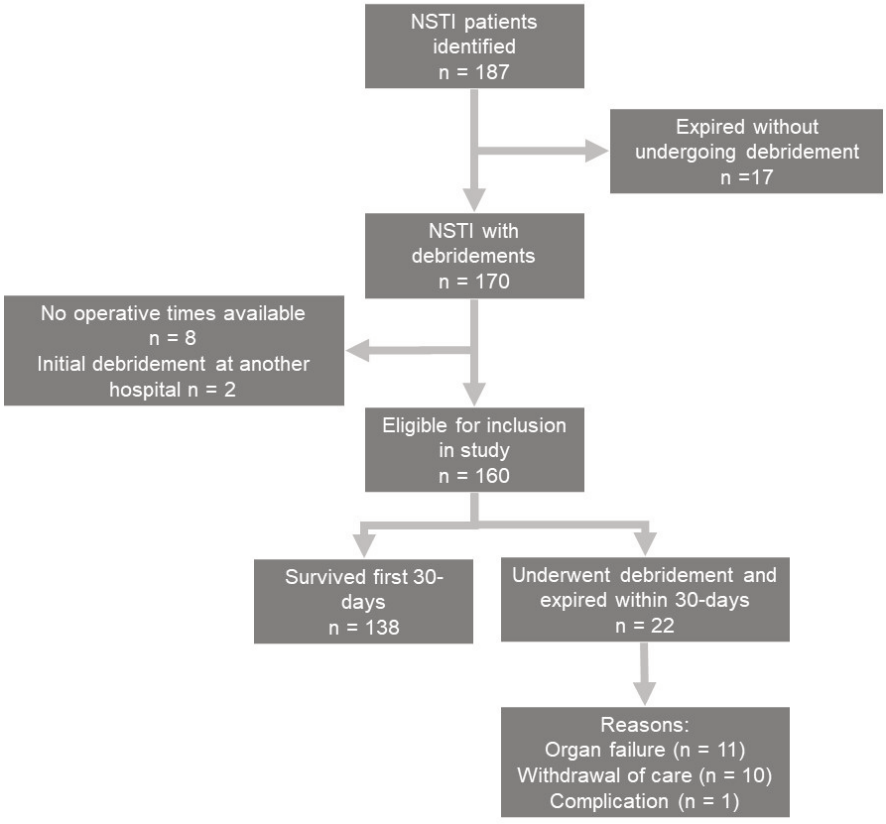

Figure 1 Inclusion flowchart of necrotizing soft tissue infections patients undergoing surgery

Table 1 Patient characteristics of necrotizing soft tissue infection patients undergoing surgery

	n = 160 (100%)
Age in years, mean ± SD	56 ± 16
Male sex, n (%)	108 (68)
ASA classification	
I	33 (21)
II	65 (41)
III	52 (32)
IV	10 (6)
Location of NSTI, n (%)	
Head/neck	8 (5)
Trunk	16 (10)
Perineum	44 (27)
Upper extremity	19 (12)
Lower extremity	72 (45)
Multiple body areas involved	1 (1)
Estimated TBSA affected in %[a], median (IQR)	3 (2 – 6)
0 – 5%	111 (70)
6 – 10%	36 (23)
11 – 15%	7 (4)
>15%	4 (3)
Cultured micro-organism from incisional biopsy, n (%)	
Monomicrobial	102 (64)
Group A *Streptococcus*	74 (72)
Other *Streptococcus spp.*	10 (10)
Staphylococcus aureus	7 (7)
Escherichia coli	3 (3)
Pseudomonas spp.	2 (2)
Clostridium spp.	1 (1)
Other[b]	5 (5)
Polymicrobial	55 (34)
Escherichia coli involved	18 (32)
Pseudomonas spp. involved	3 (5)
Clostridium spp. involved	7 (12)
Negative cultures	3 (19)

ASA = American Society of Anesthesiologists; IQR = Interquartile Range; NSTI = Necrotizing Soft Tissue Infection; SD = Standard Deviation; TBSA = Total Body Surface Area. [a] 2 cases missing. [b] *Acinetobacter baumanii, Enterobacter cloacae*, *Neisseria meningitidis, Proteus vulgaris* and *Vibrio parahaemolyticus*.

Hemodynamic parameters and clinical chemistry prior to surgery

Just prior to the initial surgery, 52 patients (34%) had a systolic blood pressure lower than 100 mmHg, 81 patients (52%) were tachycardic and 40 patients (40%) were tachypnoeic. The mean base excess for all patients was - 6.1 ± - 5.8. See table 2 for the mean values of the hemodynamic and laboratory parameters. The median LRINEC score was 7 (IQR 6 – 9, 22 patients (20%) had a score <6). Fifty patients (33%) were determined to be septic just prior to their initial surgery for the NSTI, of which 21 (42%) received continuous vasopressors to maintain an adequate mean arterial pressure (Table 2).

Impact of operative times on outcomes

The median operative time of the initial debridement for NSTIs was 59 minutes (IQR 35 – 90, range 10 – 400 minutes), while 35 initial surgeries (22%) took longer than 90 minutes (Figure 2). A total of 22 patients (14%) died within 30 days after presentation. The median duration of the initial surgery for deceased patients was 62 minutes (IQR 45 – 90) and 57 minutes for survivors (IQR 31 – 89, $p = 0.335$). Post-hoc power analysis of our primary objective, the association between the operative time and 30-day mortality, showed a medium effect size (d = 0.30) and a power of 0.28 (α = 0.05, β 0.72). Surgeries that took longer than 140 minutes had a two-fold higher mortality rate (4/15, 27%) compared to surgeries shorter than 140 minutes (18/126, 13%), however this difference was not significant with the current sample size ($p = 0.133$)

During 36 surgeries (23%), frozen sections and/or Gram stains were intra-operatively assessed for diagnostic purposes. The use of frozen section and/or gram stain resulted in a shorter time from presentation to diagnosis (4 hours (IQR 3 -15) vs. 7 hours (IQR 4- 26), $p = 0.035$), but resulted in significantly longer operative times ($p < 0.001$). In 36 cases (23%) skin sparing operative techniques were utilized, those surgeries had a median operative time of 46 minutes (IQR 30 – 90, range 15 – 400, $p = 0.715$), but was mostly used in cases with relatively low estimated TBSA affected (median 4%, IQR 2 – 6%). In case of a NSTI affecting the trunk, the initial surgery was significantly prolonged compared to other body locations ($p = 0.044$), this also applied to cases in which a greater estimated TBSA was affected ($p = 0.006$) (Table 3 and 4).

A multivariable logistic regression, which was corrected for the presence of sepsis just prior to the initial surgery, estimated TBSA and the ASA classification, found no significant association between the operative time and 30-day mortality (β 0.14, 95% CI -0.06 – 0.33; $p = 0.170$). There were also no significant associations between the

Table 2 Hemodynamic parameters and laboratory results prior to surgery in necrotizing soft tissue infection patients

	n	Mean ± SD or Median (IQR)	Reference values
Hemodynamic parameters			
Systolic blood pressure	155	114 ± 24	90 – 120 mmHg
Diastolic blood pressure	155	65 ± 17	60 – 80 mmHg
Mean arterial pressure	155	81 ± 18	70 – 100 mmHg
Heart rate	155	104 (88 – 120)	60 – 100 beats/minute
Respiratory rate	100	20 (15 – 25)	12 – 20 breaths/minute
Temperature	156	37.4 ± 1.1	36 – 38 °C
Blood test results			
Hemoglobin	94	♂ 8.0 ± 1.5	♂ 8.6 – 10.7 mmol/L
	46	♀ 7.2 ± 1.2	♀7.4 – 9.6 mmol/L
Hematocrit	134	37 ± 7	41 – 50%
Platelet count	118	183 (137 – 264)	150 – 450 $x10^9$/L
White blood cell count	146	15.4 (10.2 – 20.5)	0.8 – 4.0 $x10^9$/L
Sodium	130	135 ± 6	136 – 146 mmol/L
Potassium	130	4.0 ± 0.6	3.8 – 5.0 mmol/L
Creatinine	136	125 (78 – 184)	64 – 104 µmol/L
Total bilirubin	82	16 (9 – 28)	3 – 21 mmol/L
Lactate	65	3.5 (2.2 – 5.4)	0.0 – 2.2 mmol/L
Lactate dehydrogenase	85	235 (194 – 329)	0 – 250 U/L
Creatine kinase	61	389 (75 – 1333)	0 – 170 U/L
C-reactive protein	146	296 ± 142	0 – 10 mg/L
Glucose	114	7.0 (5.9 – 8.4)	3.6 – 5.6 mmol/L
Arterial blood gas results[a]			
pH	91	7.36 (7.28 – 7.44)	7.37 – 7.45
PaO_2	81	89 (80 – 132)	70 – 100 mmHg
$PaCO_2$	81	33 (27 – 40)	35 – 45 mmHg
Bicarbonate	91	19 ± 5	22.0 – 28.0 mmol/L
Base excess	91	-6.1 ± 5.8	-3.0 – 3.0 mmol/L
Risk scores			
LRINEC score	108	7 (6 – 9)	Range 0 – 13
SOFA score	54	5 ± 3	Range 0 – 24
APACHE II score	55	13 ± 6	Range 0 – 67
Septic, n (%)			
upon admission	152	47 (31)	qSOFA <2 and/or SOFA
prior to surgery	153	50 (33)	score <2

APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; IQR = Interquartile Range; LRINEC = Laboratory Risk Indicator for Necrotizing fasciitis; qSOFA = Quick Sequential Organ Failure Assessment. SD = Standard Deviation; SOFA = Sequential Organ Failure Assessment.

[a] If only a venous blood gas was available, only pH, bicarbonate and base deficit were extracted

Table 3 Treatment characteristics and outcomes of necrotizing soft tissue infection patients undergoing surgery

	n = 160 (100%)
Surgical treatment	
Time from surgical consult to surgery in hours[a], median (IQR)	7 (4 – 31)
Operative time of initial surgery in minutes[a], median (IQR)	59 (35 – 90)
Time in operating room for initial surgery in minutes[b], median (IQR)	90 (64 – 121)
Amputation performed, n (%)	21 (13)[c]
Amputation during initial surgery	13 (62)
Skin sparing operating technique utilized, n (%)	33 (21)
Intra-operative assessed frozen section and/or Gram stain, n (%)	36 (23)
Frozen section, n (%)	22 (14)
Gram stain, n (%)	24 (15)
Number of surgeries for NSTI within first 30 days[d], median (IQR)	3 (2 – 5)
Days from initial surgery to definitive wound closure in days[d], median (IQR)	25 (10 – 56)
Postoperative phase	
Admitted to ICU, n (%)	110 (67)
Length of ICU stay in days[e], median (IQR)	4 (2 – 10)
Length of hospital stay in days[d], median (IQR)	24 (15 – 42)
Major infectious complication during hospital course, n (%)	
Sepsis	88 (55)
Multiple organ dysfunction syndrome	14 (9)
Deceased within 30 days after presentation, n (%)	22 (14)
Days from initial surgery to death in days, median (IQR)	2 (1 – 6)
Cause of death, n (%)	
Sepsis	11 (50)
Withdrawal of care	10 (45)
Complication	1 (5)

ICU = Intensive Care Unit; IQR = Interquartile Range; NSTI = Necrotizing Soft Tissue Infection. [a] 1 case missing; [b] 36 cases missing; [c] Of which 11 were lower extremity amputation, 7 (hemi)scrotectomies, 2 orchidectomies, 1 bilateral mastectomy; [d] Only patients who survived hospital stay; [e] Only patients who survived ICU stay.

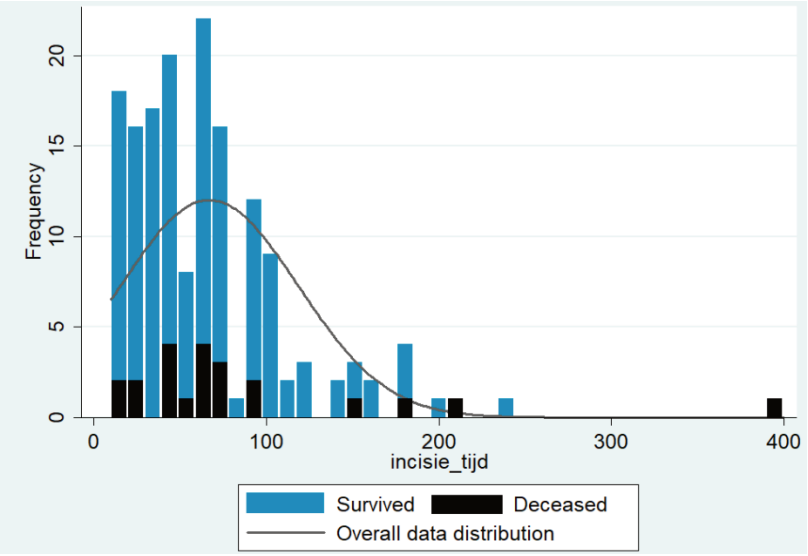

Figure 2 Histogram of distribution of operative times of initial surgery for necrotizing soft tissue infections

Table 4 Factors associated with prolonged operative time for patients with necrotizing soft tissue infections

	Operative time in minutes, if yes median (IQR)	Operative time in minutes, if no median (IQR)	*p* value
Location of NSTI			0.158[a]
Head/neck	76 (55 – 104)	57 (31 – 90)	0.147
Trunk	90 (59 – 110)	55 (31 – 76)	**0.044**
Perineum	49 (36 – 68)	60 (31 – 90)	0.474
Upper extremity	45 (19 – 90)	60 (37 – 90)	0.368
Lower extremity	59 (35 – 76)	59 (34 – 90)	0.650
Estimated TBSA affected			**0.006[b]**
0 – 5%	47 (29 – 75)	71 (43 – 100)	**<0.001**
6 – 10%	72 (45 – 98)	50 (29 – 75)	**0.006**
11 – 15%	70 (60 – 97)	57 (35 – 89)	0.246
>15%	111 (33 – 290)	59 (36 – 89)	0.416
Amputation during initial surgery	59 (43 – 93)	59 (35 – 89)	0.584
Skin sparing operating technique utilized	46 (30 – 90)	60 (36 – 89)	0.715
Intra-operative assessed frozen section and/or Gram stain	87 (63 – 106)	46 (29 – 73)	**<0.001**

IQR = Interquartile range; NSTI = Necrotizing Soft Tissue Infection; TBSA = Total Body Surface Area.
[a] Kruskal Wallis test; [b] Chi-squared for trend. **Bold** font indicates significant result.

operative time and the need for an amputation during re-exploration (β 0.11, 95% CI -0.12 – 0.35; p = 0.356), number of surgeries within first 30 days (β 0.01, 95% CI -0.14 – 0.16; p = 0.873) or days until definitive wound closure (β -2.77, 95% CI -7.64 – 2.09; p = 0.262). However, within the linear multivariable analysis, each 20 minutes increase in operative time resulted in an increase of the ICU stay with 1.4 days (β 1.43, 95% CI 0.46 – 2.40; p = 0.004) and an increase of the hospital stay with 3.3 days (β 3.25, 95% CI 0.23 – 6.27; p = 0.035) (Table 5). The same multivariate analyses, corrected for operative time of the initial surgery, sepsis prior to surgery and ASA classification, showed that an increased estimated TBSA resulted in higher mortality rates (β 0.16, 95% CI 0.04 – 0.27; p = 0.007), longer hospital length of stay (β 6.37, 95% CI 4.19 – 8.55; p < 0.001) and more surgeries within the first 30 days (β 0.25, 95% CI 0.13 – 0.37; p < 0.001). Also, sepsis prior to surgery was independently associated with adverse outcomes (corrected for operative time of the initial surgery, estimated TBSA and ASA classification), being an increase in ICU stay with 9 days (β 9.19, 95% CI 4.91 – 13.47; p < 0.001) and the hospital stay with 17 days (β 17.17, 95% CI 3.41 – 30.94; p = 0.015).

Discussion

This study found a median operative time of the initial debridement for NSTIs of 59 minutes, with most of the debridements (78%) lasting no longer than 90 minutes and an overall 30-day mortality rate of 14% in NSTI patients who underwent at least one debridement. Greater estimated TBSA affected and a higher ASA classification were independently associated with increased mortality, while the operative time did not demonstrate a direct relation with mortality, however the fifteen patients (9%) who underwent surgery for >140 minutes had a two-fold increase in mortality. Multivariate analysis showed that each 20 minutes of extra operative time during the initial debridement resulted in a 1.4-day increase in ICU stay and 3.3-days increase in hospital stay, even if corrected for the presence of sepsis prior to the surgery, estimated TBSA affected and ASA classification.

No other study has investigated the association between the operative time of the initial debridement for NSTIs and its outcomes. However, three prior studies have reported the mean operative time for their entire NSTI cohort. Hong et al. reported an mortality rate of 60% for fifteen septic *Vibrio* NSTI patient with all a NSTI affecting the extremities, which was associated with a mean duration of the initial debridement of 102 minutes [5]. Corman et al. found a mortality rate of 4% for Fournier gangrene with an associated mean duration of the initial surgery of 78 minutes and Elsaket et al. reported an mortality rate of 11.4% for Fournier gangrene associated with a mean duration of the initial debridement of 81 minutes [4,6]. Notable, all patients underwent a scrotectomy for source control in the study by Corman et al. and in the study by Elsaket et al. only 5% of the patients were septic

Table 5 Association of operative time per 20 minutes on various outcomes of necrotizing soft tissue infections

	β coefficient (95% CI)	Standard error	*p* - value
Mortality (n = 150)			
Operative time (per 20 minutes)	0.14 (-0.06 - 0.33)	0.10	0.170
Estimated total body surface area affected (in %)	***0.16 (0.04 – 0.27)***	***0.06***	***0.007***
Septic prior to surgery	*0.49 (-0.06 – 1.59)*	*0.56*	*0.391*
ASA classification	***1.01 (0.31 – 1.72)***	***0.36***	***0.005***
Amputation required after initial surgery (n = 150)			
Operative time (per 20 minutes)	0.11 (-0.012 – 0.35)	0.12	0.356
Estimated total body surface area affected (in %)	*0.03 (-0.13 – 0.20)*	*0.09*	*0.696*
Septic prior to surgery	*0.49 (-1.04 – 2.02)*	*0.78*	*0.528*
ASA classification	*0.26 (-0.62 – 1.14)*	*0.45*	*0.568*
Length of ICU stay (n = 104)			
Operative time (per 20 minutes)	**1.43 (0.46 – 2.40)**	**0.49**	**0.004**
Estimated total body surface area affected (in %)	*0.29 (-0.33 – 0.91)*	*0.31*	*0.352*
Septic prior to surgery	***9.19 (4.91 – 13.47)***	***2.16***	***<0.001***
ASA classification	*-1.31 (-3.67 – 1.06)*	*1.19*	*0.275*
Length of hospital stay (n = 129)			
Operative time (per 20 minutes)	**3.25 (0.23 – 6.27)**	**1.53**	**0.035**
Estimated total body surface area affected (in %)	***6.37 (4.19 – 8.55)***	***1.10***	***<0.001***
Septic prior to surgery	***17.17 (3.41 – 30.94)***	***6.96***	***0.015***
ASA classification	*6.84 (-0.69 – 14.37)*	*3.80*	*0.074*
Number of surgeries within first 30 days (n = 145)			
Operative time (per 20 minutes)	0.01 (-0.14 – 0.16)	0.08	0.873
Estimated total body surface area affected (in %)	***0.25 (0.13 – 0.37)***	***0.06***	***<0.001***
Septic prior to surgery	*-0.24 (-1.05 – 0.58)*	*0.41*	*0.565*
ASA classification	*-0.16 (-0.58 – 0.25)*	*0.21*	*0.438*
Days until definitive wound closure (n = 120)			
Operative time (per 20 minutes)	-2.77 (-7.64 – 2.09)	2.46	0.262
Estimated total body surface area affected (in %)	-2.52 (-6.01 – 0.96)	1.76	0.154
Septic prior to surgery	8.32 (-14.40 – 31.05)	11.47	0.470
ASA classification	11.41 (-1.27 – 24.09)	6.40	0.077

Bold font indicates significant result.

upon presentation. As a result, and combined with the fact that those studies only investigated specific NSTI subtypes, these studies cannot directly be compared to our study which consisted of a heterogeneous population with mainly GAS infections in non-Fournier regions. Nonetheless, there is a shorter median operative time in this current cohort, with only 22% of the patients undergoing initial debridements for over 90 minutes.

As seen in this study, NSTI patients often undergo surgery while they are physiologically compromised (e.g. metabolic acidosis, high sepsis scores), therefore it was postulated that these patients could also benefit from the damage control principles. The concept of damage control was first established to improve outcomes of severely injured trauma patients by obtaining rapid hemorrhage control and prevent contamination without definitive repairs during the first surgery, followed by resuscitation in attempt to prevent and/or reverse the pathophysiological triad of coagulopathy, metabolic acidosis and hypothermia ("lethal triad") [16]. Definitive surgical repair was reserved until after the goals of resuscitation were reached. In this study reduced operative times were not associated with a reduction in mortality, however, since this study is underpowered for this association, the hypothesis cannot yet be rejected nor confirmed. On the other hand, the reduced operative times were indeed associated with a significant shorter ICU and hospital stays, regardless of the presence of sepsis prior to surgery, the estimated TBSA affected and the ASA classification. The concept of reducing length of ICU and hospital stay by reducing operative times has not yet been described for NSTIs, but has been suggested for surgical procedures in trauma and general surgery [8,17]. Procter et al. studied general surgical procedures and found that the odds ratio for ICU admission, adjusted for operative and patient risk variables, increased with 0.32 each half-hour of extra operative time and the hospital length of stay increased with 6% with each half hour extra operative time [8]. Harvin et al. studied emergency trauma laparotomies and found that damage control principles when applied correctly significantly increased the probability of a shorter ICU and hospital stay compared to when a definitive laparotomies was performed [17]. Furthermore, this study showed that besides operative time, sepsis prior to surgery is also independently associated with prolonged ICU and hospital stay, however this variable is often non-modifiable.

The principle of damage control is based on the philosophy of doing only what is necessary in order not to exhaust the physiological reserves of the patient. Therefore, it can be questioned if performing debridement utilizing the skin sparing technique for NSTIs is doing something more than necessary [18]. In the current study, the skin sparing technique did not result in median prolonged operative times,

which might indicate that the technique was used in the proper cases. Nevertheless, a case of 400 minutes was documented with fatal outcome.

The use of intra-operative diagnostics such as frozen section or Gram stain have also been argued to cause treatment delay, since the time waiting on the results could also be used for debridement, however this statement was not yet investigated in a clinical study [19,20]. This study found indeed a prolonged operative time with a difference in medians of 41 minutes, which is to be expected since it can take up to 30 minutes to process and assess a frozen section [12,13]. However, the time to diagnosis was significantly shorter in cases that used intra-operative diagnostics (difference in medians of 3 hours), which enables timely debridement. However, these intra-operative diagnostic modalities should only be used if indicated: in ambivalent cases to prevent unnecessary debridements in non-NSTI cases or prevent delay and/or refrainment of debridement due to less evident macroscopic findings in NSTI cases [21].

The findings of this study need to be interpreted in context of its limitations. First, the retrospective nature of this study resulted in a substantial amount of missing dating for certain variables, especially limiting our ability to use blood gasses results to calculate SOFA and APACHE II scores and to determine the degree of sepsis. Especially for these variables, selection bias is likely present, because patient presenting without systemic toxicity will not always have a comprehensive laboratory work-up. Second, the TBSA was estimated based on operative notes and might be over- or underestimated in certain patients. Furthermore, this study is underpowered regarding the main objective, this warrants further research in bigger cohorts. However, the strengths of this study are the fairly large sample size compared to other NSTI cohorts and that it is the first study assessing the consequences of prolonged operative times of the initial debridement for NSTIs.

Conclusions

The principles of damage control can be beneficial for NSTI patients, since reduced operative times of the initial debridement of NSTIs result in shorter ICU and hospital stays. The goal remains to prevent treatment delay and to perform an efficient and adequate debridement to obtain source control followed by adequate resuscitation in the ICU. Treating physicians should aim to optimize prompt surgical debridement and start of adequate intravenous antibiotics upon presentation and minimize operative times, since reduced hospital stays will reduce health care costs and has a positive impact on the patient outcomes.

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Appendix 1 Methods of identifying patients with necrotizing soft tissue infections

University Medical Center Utrecht	Jan 2010 – Jan 2013	Patient sought using the International Code for Disease (ICD) 10 for necrotizing fasciitis (M72.6)
	Jan 2013 – Dec 2019	Prospective database of patients with necrotizing soft tissue infection
St. Antonius Hospital	Jan 2010 – Sept 2016	Patients identified using search terms necrotizing fasciitis, Fournier gangrene, myonecrosis in three databases: • Rare disease list kept by intensive care department • The consulting system of the microbiology department • The microbiology laboratory information management system for documented positive fascia cultures
	Oct 2016 – Dec 2019	Patient sought using the International Code for Disease (ICD) 10 for necrotizing fasciitis (M72.6) and Fournier gangrene (N49.3) and the Surgical Diagnosis Treatment Combination (DBC) codes for necrotizing fasciitis (164), soft tissue infections (160), large wounds (282) and Fournier gangrene (068 and 098)
Diakonessenhuis	Jan 2010 – Dec 2019	Patient sought using the International Code for Disease (ICD) 10 for necrotizing fasciitis (M72.6) and Fournier gangrene (N49.3) and the Surgical Diagnosis Treatment Combination (DBC) codes for necrotizing fasciitis (164), soft tissue infections (160), large wounds (282) and Fournier gangrene (068 and 098)
Meander Medical Center	Jan 2010 – Dec 2019	Patient sought using the Surgical Diagnosis Treatment Combination (DBC) codes for necrotizing fasciitis (164), soft tissue infections (160), large wounds (282) and Fournier gangrene (068 and 098)

9

Factors associated with mortality and amputation caused by necrotizing soft tissue infections of the upper extremity: a retrospective cohort study

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Abstract

Background: It is unclear what the exact short-term outcomes of necrotizing soft tissue infections (NSTIs), also known and necrotizing fasciitis, of the upper extremity are and if these are comparable to other anatomical regions. Therefore, the aim of this study is to assess factors associated with 30-day mortality and amputation of patients with upper extremity NSTIs.

Methods: A retrospective study over a 20-year time period of all patients treated for NSTIs of the upper extremity was performed. The primary outcomes were the 30-day mortality rate and the amputation rate in patients admitted to the hospital for upper extremity NSTIs.

Results: Within 20 years, 122 patients with NSTIs of the upper extremity were identified. Thirteen patients (11%) died and 17 patients (14%) underwent amputation. Independent risk factors for mortality were an American Society of Anesthesiologists (ASA) classification of 3 or higher (OR 9.26, 95% CI 1.64 – 52.31) and a base deficit of 3 meq/L or greater (OR 10.53, 95% CI 1.14 – 96.98). The independent risk factor for amputation was a NSTI of the non-dominant arm (OR 3.78, 95% CI 1.07 – 13.35). Length of hospital stay was 15 (IQR 9 – 21) days.

Conclusion: Upper extremity NSTIs have a relatively low mortality rate, but a relatively high amputation rate compared to studies assessing NSTIs of all anatomic regions. ASA classification and base deficit at admission predict the prognosis of patients with upper extremity NSTIs, while a NSTI of the non-dominant side is a risk factor for limb loss.

Introduction

Necrotizing soft tissue infections (NSTIs) are rapidly spreading and progressive infection of the soft tissues, most often affecting the fascia and subcutaneous layers [1–3]. The extremities have been described to be affected in 45% to 74% of all NSTI cases, of which the lower extremity are most commonly involved [2,4,5]. NSTIs of the upper extremity have reported frequencies varying between 7% to 27% [6–8]. Most of the studies assessing upper extremity NSTIs are limited to small case series or big national database studies with less detail about the presentation and admission itself [6–8]. Due to this low representation of upper extremity NSTIs in the literature, it is unknown what the exact short-term outcomes are and if they are comparable to NSTIs affecting other anatomical regions. Knowledge of risk factors for mortality and morbidity provides insight in the prognosis and possibilities to improve outcomes of NSTIs of the upper extremity. Therefore, this study aims to assess which factors are associated with mortality within 30 days and amputation in patients with necrotizing soft tissue infections of the upper extremity.

Methods

This study was approved by the hospitals' institutional review board. A retrospective study of patients treated for NSTIs of the upper extremity at two academic referral centers between January 1998 and January 2018 was performed. We identified eligible patients from the Institution's Research Patient Data Registry (RPDR) by using the International Classification of Diseases (ICD)-9 (928.86) and ICD-10 (M72.6) codes for necrotizing fasciitis. The search resulted in 1507 patients. All patients diagnosed with NSTIs of the upper extremity were eligible for inclusion and determined the sample size. Since no pathognomic clinical symptoms are known for NSTIs, the diagnosis needed to be established either by histopathology or microbiology (e.g. gram stain and/or definitive culture) [1,9,10]. Cases in which the disease started at another anatomical region but progressed to one or both upper extremities were included as well. Exclusion criteria were patients <18 years and pregnancy at time of the infection.

Outcome measures and explanatory variables

The primary goals of this study were to describe the 30-day mortality rate and the amputation rate in patients with upper extremity NSTIs. In addition, we described the microbiology, types of procedures performed and hospital course. The patient demographics extracted from medical charts include age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, comorbidities, medical history, smoking status, history of intravenous drug use and work status. The extracted disease related characteristics include time from symptoms to

diagnosis, affected side, dominant hand, causative event for the NSTI, date of causative event, location where symptoms started, affected body areas, parts of upper extremity affected by the NSTI, vital signs and laboratory results at presentation and causative micro-organism found. The extracted treatment related variables include the hospital of first debridement, amputation, mortality, date of death, intensive care unit (ICU) admittance, length of ICU and hospital stay, type and number of surgeries performed for the NSTI, date of last surgery for the NSTI, infectious complications during admission and discharge location. If the ASA classification was unknown, the researchers determined the ASA classification based on comorbidities known prior to the NSTI. We defined manual laborers as workers mainly doing physical work dominated by grasping and lifting [11]. The extent of the NSTI was approximated by calculating the percentage of total body surface area (TBSA) affected using the rule of nines commonly used in burns [12]. The Laboratory Risk Indicator for Necrotizing fasciitis (LRINEC) score was calculated if the necessary laboratory results were available. The LRINEC score is used to predicts the likelihood of NSTIs. A LRINEC score <6 represents a low suspicion for NSTI [13]. By using the definitive culture results, we classified the NSTIs in type I (polymicrobial), type II (monomicrobial) or type III (e.g. *Clostridium* spp., *Vibrio* spp. or gram-negative bacteria) [14].

Statistical analysis

Continuous parametric variables are presented as means with standard deviations (SD), continuous non-parametric variables as medians with interquartile ranges (IQR) and categorical variables as frequencies with percentages. Missing data were handled using pairwise deletion. Univariable logistic regressions were used to identify predictors for mortality and amputation. Variables with a *p*-value <0.10 were eligible for inclusion in the multivariable logistic regression with simultaneous entry. Only the most clinically relevant variables were selected to prevent overfitting the model and variables with small numbers of occurrence in our cohort (e.g. 6 patients with a specific variable) were not included due to their limited statistical power. For analyses related to surgical procedures, the Mann-Whitney U test was used. For all analyses, a *p*-value of <0.05 was considered statistically significant. Analyses were performed with STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

After exclusion, 122 eligible patients were identified with a mean age of 50 ± 17 years (Figure 1). Patients were predominately classified ASA classification 1 or 2 (n =74, 62%), which is indicative for no or minor comorbidities. The forearm was involved in most patients (n = 89, 74%). If a causative event was known, an injection

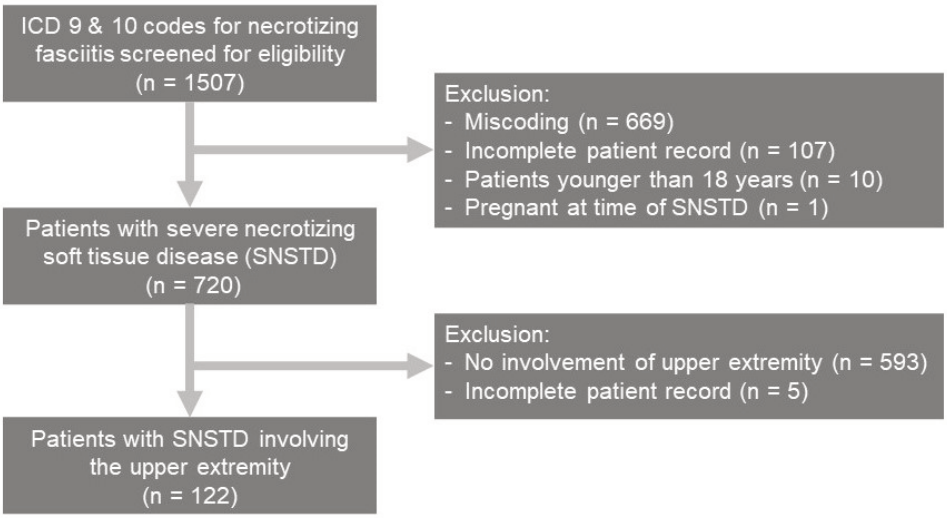

Figure 1 Flowchart of patient in- and exclusion of necrotizing soft tissue infections of the upper extremity

was most frequently described (n = 26, 35%), of which 21 cases were caused by self-administrated intravenous drugs (Table 1 and 2).

Mortality within 30 days

Thirteen patients (11%) died within 30 days after the NSTI diagnosis. Nine of these patients (83%) were classified as ASA 3 or 4, indicating severe and/or multiple comorbidities. Patients with fatal NSTIs died at a median of 3 days after hospital admission (IQR 1 – 8), with the most common cause of death being sepsis (n = 10, 77%) (Table 3). In three other patients (23%) further surgical treatment was averted due to patients' wishes combined with severe pre-existing comorbidities. Univariable analyses showed that higher age (OR 1.07, 95% CI 1.03 – 1.12), ASA classification 3 or 4 compared to ASA 1 or 2 (OR 9.00, 95% CI 1.85 – 43.85), history of intravenous drug use (OR 4.04, 95% CI 1.07 – 15.50), a higher respiratory rate (OR 1.10, 95% CI 1.00 – 1.21), a higher glucose (OR 1.00, 95% CI 1.00 – 1.02), a higher base deficit (OR 1.40, 95% CI 1.14 – 1.72) or a higher serum lactate at time of diagnosis (OR 1.65, 95% CI 1.17 – 2.32), NSTIs that started at another anatomical region than the upper extremity (OR 10.60, 95% BI 1.89 – 21.76), NSTIs at other anatomical regions (especially the trunk and lower extremity) besides the upper extremity (OR 6.33, 95% CI 1.84 – 21.76), NSTIs affecting a greater TBSA (OR 1.05, 95% CI 1.00 – 1.10) and NSTIs of the shoulder (OR 3.87, 95% CI 1.10 – 13.61) resulted in a significantly greater risk at dying of the NSTI (Table 1 - 3). Multivariable analysis showed that an ASA classification of 3 or higher (OR 9.26, 95% CI 1.64 – 52.31) and

Table 1 Patient characteristics associated with mortality and amputation in patients with necrotizing soft tissue infections of the upper extremity

	Total n = 122 (100%)	Died ≤ 30 days n = 13 (11%)	Survived n = 109 (89%)	OR (95% CI)	Amputation n = 17 (14%)	Limb salvage n = 105 (86%)	OR (95% CI)
Age in years, mean ± SD	50 ± 17	67 ± 14	48 ± 17	**1.07 (1.03 - 1.12)**	52 ± 20	50 ± 17	1.01 (0.98 - 1.04)
Sex, n (%)							
Female	53 (43)	3 (6)	50 (94)	0.35 (0.09 - 1.36)	7 (13)	46 (87)	0.90 (0.32 – 2.54)
Male	69 (57)	10 (14)	56 (86)	2.82 (0.74 - 10.83)	10 (14)	59 (86)	1.11 (0.39 - 3.15)
Body Mass Index in kg/m2[a], median (IQR)	25 (23 - 31)	26 (23 - 32)	25 (23 - 31)	1.03 (0.95 - 1.13)	27 (25 - 34)	25 (23 - 30)	1.01 (0.92 - 1.10)
ASA classification[b], n (%)							
1 and 2	74 (62)	2 (3)	72 (97)	RC	9 (12)	65 (88)	RC
3 and 4	45 (38)	9 (20)	36 (80)	**9.00 (1.85 - 43.85)**	7 (16)	38 (84)	1.33 (0.46 - 3.86)
Diabetes mellitus, n (%)	20 (16)	4 (20)	16 (80)	2.58 (0.71 - 9.40)	4 (20)	16 (80)	1.71 (0.49 - 5.92)
History of malignancy[c], n (%)	16 (13)	4 (25)	12 (75)	**4.04 (1.07 - 15.50)**	4 (25)	12 (75)	2.36 (0.66 - 8.42)
Current smoker[d], n (%)	42 (35)	3 (7)	39 (93)	0.66 (0.17 - 2.65)	6 (14)	36 (86)	1.11 (0.38 - 3.32)
History of intravenous drug use[c], n (%)	35 (29)	2 (6)	33 (94)	0.41 (0.08 - 1.97)	2 (6)	33 (94)	0.29 (0.06 - 1.33)
Occupation at time of onset NSTI[d], n (%)							
Manual laborer	19 (17)	0 (0)	19 (100)	NC	1 (5)	18 (95)	0.29 (0.04 - 2.36)
Occupation without manual labor	44 (39)	3 (7)	41 (93)	0.77 (0.18 - 3.24)	6 (14)	38 (86)	0.93 (0.31 - 2.77)
Retired or unemployed	50 (44)	6 (12)	44 (88)	2.73 (0.65 - 11.50)	9 (18)	41 (82)	1.76 (0.60 - 5.10)
Vital signs at presentation, median (IQR)							
Systolic blood pressure in mmHg[e]	116 (102 – 132)	110 (96 – 132)	117 (102 – 133)	0.99 (0.97 – 1.02)	118 (110 – 146)	116 (101 – 128)	1.01 (0.99 – 1.04)

Continuation of table 1

Diastolic blood pressure in mmHg[e]	65 (56 – 76)	65 (54 – 75)	65 (56 – 77)	0.98 (0.94 – 1.03)	74 (63 – 84)	65 (56 – 75)	**1.05 (1.00 – 1.09)**
Mean arterial pressure in mmHg[e]	82 (73 – 93)	83 (69 – 89)	82 (73 – 94)	0.99 (0.95 – 1.03)	92 (79 – 98)	81 (73 – 92)	1.03 (0.99 – 1.07)
Heart rate in beats per minute[e]	98 (87 – 116)	105 (99 – 125)	98 (86 – 111)	1.03 (0.99 – 1.06)	104 (97 – 120)	98 (87 – 115)	1.02 (0.99 – 1.05)
Respiratory rate in breaths per minute[f]	18 (16 – 20)	20 (20 – 30)	18 (16 – 20)	**1.10 (1.00 – 1.21)**	16 (16 – 20)	18 (16 – 20)	0.96 (0.84 – 1.09)
Laboratory results at presentation, median (IQR)							
C-reactive protein mg/L (reference: <10)[g]	145 (101 – 237)	140 (118 – 210)	146 (101 – 237)	1.00 (0.99 – 1.01)	155 (127 – 188)	144 (101 – 243)	0.99 (0.99 – 1.01)
White blood cell count x10,000/µL (reference: 4 – 10)[h]	15 (9 – 22)	9 (4 – 18)	15 (9 – 23)	0.94 (0.88 – 1.01)	19 (7 – 34)	15 (9 – 22)	1.02 (0.99 – 1.06)
Hemoglobin in g/dL (reference ♀ 7.4 – 9.6; ♂ 8.6 – 10.7)[i]	11.2 (9.9 – 12.6)	11.0 (9.1 – 13.1)	11.2 (9.9 – 12.5)	0.88 (0.66 – 1.18)	10.3 (9.1 – 12.9)	11.3 (10.0 – 12.6)	0.81 (0.62 – 1.05)
Sodium in mmol/L (reference 136 – 146)[j]	135 (132 – 138)	137 (135 – 141)	135 (132 – 138)	1.14 (0.99 – 1.32)	135 (131 – 136)	135 (132 – 138_	0.96 (0.85 – 1.08)
Creatinine in mg/dL (reference ♀ 58 – 103; ♂ 74 – 120)[k]	1.0 (0.8 – 1.5)	1.6 (1.1 – 2.3)	1.0 (0.8 – 1.4)	1.39 (0.90 – 2.15)	1.2 (0.8 – 2.1)	1.0 (0.8 – 1.5)	1.07 (0.67 – 1.74)
Glucose in mg/dL (reference 3.6 – 5.6)[l]	119 (95 – 147)	145 (102 – 226)	118 (95 – 145)	**1.00 (1.00 – 1.02)**	115 (92 – 193)	120 (98 – 147)	1.00 (0.99 – 1.01)
Base deficit in meq/L (reference: -3 - 3)[m]	4.3 (0.7 – 8)	11.0 (6.3 – 13.3)	3.2 (-0.1 – 7.0)	**1.40 (1.14 - 1.72)**	5.0 (-0.5 – 9.7)	4.0 (1.4 – 8.1)	1.00 (0.89 - 1.11)

Continuation of table 1

Serum lactate in mmol/L (reference: 0.5 - 1.0)[n]	1.7 (1.2 – 3.0)	4.5 (2.4 – 14.3)	1.7 (1.1 – 2.5)	**1.65 (1.17 – 2.32)**	2.7 (1.3 – 5.9)	1.7 (1.2 – 3.0)	1.12 (0.95 – 1.31)
LRINEC score at presentation[o], median (IQR)	4 (2 - 8)	4 (2 - 7)	5 (2 - 8)	0.91 (0.67 - 1.23)	7 (3 - 10)	4 (2 - 7)	1.22 (0.90 - 1.66)

Abbreviations: ASA = American Society of Anesthesiologists; CI = Confidence Interval; IQR = Interquartile Range; OR = Odds Ratio; NC = Not Calculable; NSTI = Necrotizing Soft Tissue Infection; RC = Reference; SD = Standard Deviation. Missing cases: [a]20 missing; [b]3 missing; [c]1 missing; [d]9 missing; [e]21 missing; [f]30 missing; [g]72 missing; [h]12 missing; [i]13 missing; [j]58 missing; [k]49 missing; [l]49 missing; [o]70 missing. Odds Ratios in **bold** are statistically significant.

Table 2 Disease characteristics associated with mortality and amputation in patients with necrotizing soft tissue infections of the upper extremity

	Total n = 122 (100%)	Died ≤ 30 days n = 13 (11%)	Survived n = 109 (89%)	OR (95% CI)	Amputation n = 17 (14%)	Limb salvage n = 105 (86%)	OR (95% CI)
Time from onset symptoms to diagnosis in days[a], median (IQR)	2 (1 - 4)	1 (1 - 2)	2 (1 - 4)	0.70 (0.47 - 1.03)	1 (0 - 3)	2 (1 - 4)	0.93 (0.77 - 1.11)
Transfer without first debridement at presenting hospital, n (%)	63 (52)	4 (6)	59 (94)	0.38 (0.11 – 1.30)	10 (16)	53 (84)	1.40 (0.50 – 3.96)
Affected side, n (%)							
Left	62 (51)	6 (10)	56 (90)	0.81 (0.26 - 2.57)	11 (18)	51 (82)	1.94 (0.66 - 5.64)
Right	56 (46)	7 (12.5)	49 (87.5)	1.43 (0.45 - 4.53)	5 (9)	51 (91)	0.44 (0.15 - 1.34)
Bilateral	4 (3)	0 (0)	4 (100)	NC	1 (25)	3 (75)	2.13 (0.21 - 21.70)
Dominant hand affected[b], n (%)	51 (55)	1 (2)	50 (98)	0.39 (0.03 - 4.46)	4 (8)	47 (92)	**0.26 (0.08 - 0.92)**
Causative event if known[c], n (%)							
Injection (IVDU, blood drawl)	26 (35)	1 (4)	25 (96)	0.28 (0.03 - 2.26)	2 (8)	24 (92)	0.45 (0.09 - 2.11)

Continuation of table 2

Trauma without open wound	14 (19)	3 (21)	11 (79)	0.37 (0.05 - 3.02)	4 (29)	10 (71)	2.32 (0.72 - 7.48)
Traumatic wound	21 (28)	1 (5)	20 (95)	2.43 (0.58 - 10.06)	5 (24)	16 (76)	2.63 (0.73 - 9.48)
Bite (bug/cat/human)	10 (13)	0 (0)	10 (100)	NC	1 (10)	9 (90)	0.76 (0.09 - 6.47)
Prior surgery	4 (5)	1 (25)	3 (75)	2.94 (0.28 - 30.58)	2 (50)	2 (50)	6.87 (0.90 - 52.46)
Days between causative moment and diagnosis[d], median (IQR)	4 (3 - 8)	5 (4 - 7)	4 (3 - 8)	0.97 (0.80 - 1.17)	6 (4 - 10)	4 (3 - 6)	1.04 (0.95 - 1.14)
Infection not starting at the upper extremity, n (%)	6 (5)	3 (50)	3 (50)	**10.60 (1.89 - 59.59)**	0 (0)	6 (100)	NC
Other body regions affected by NSTI, n (%)	19 (16)	6 (32)	13 (68)	**6.33 (1.84 - 21.76)**	1 (5)	18 (95)	0.30 (0.04 - 2.43)
Head/neck involved	2 (2)	0 (0)	2 (100)	NC	0 (0)	2 (100)	NC
Trunk involved	17 (14)	5 (29)	12 (71)	**5.05 (1.42 - 17.96)**	1 (6)	16 (94)	0.35 (0.04 - 2.81)
Perineum involved	1 (1)	1 (100)	0 (0)	NC	0 (0)	1 (100)	NC
Lower extremity involved	6 (5)	3 (50)	3 (50)	**10.50 (1.87 - 59.03)**	0 (0)	6 (100)	NC
Percentage of total body surface area (TBSA) affect by NSTI, median (IQR)	4 (3 - 6)	6 (3 - 15)	4 (3 - 6)	**1.05 (1.00 - 1.10)**	5 (3 - 6)	4 (3 - 6)	0.98 (0.92 - 1.06)
Type of NSTI based on definitive cultures[e], n (%)							
Type I	22 (20)	2 (9)	20 (91)	0.84 (0.17 - 4.22)	3 (14)	19 (86)	0.87 (0.23 - 3.38)
Type II	75 (70)	7 (9)	68 (91)	0.72 (0.20 - 2.66)	11 (15)	64 (85)	0.93 (0.29 - 2.93)
Type III	11 (10)	2 (18)	9 (82)	2.17 (0.41 - 11.64)	2 (18)	9 (82)	1.32 (0.26 - 6.75)
Levels of upper extremity involved[a], n (%)							
Hand	64 (53)	5 (8)	59 (92)	0.61 (0.18 - 2.03)	14 (22)	50 (78)	**5.04 (1.37 - 18.58)**
Forearm	89 (74)	6 (7)	83 (93)	0.31 (0.09 - 1.06)	15 (17)	74 (83)	3.04 (0.65 - 14.1)
Upper arm	63 (52)	7 (11)	56 (89)	1.33 (0.40 - 4.43)	8 (13)	55 (87)	0.79 (0.28 - 2.21)
Shoulder	23 (18)	5 (23)	17 (77)	**3.87 (1.10 - 13.61)**	2 (9)	20 (91)	0.56 (0.12 - 2.65)

Continuation of table 2

Abbreviations: CI = Confidence interval; IQR = interquartile range; IVDU = intravenous drug use; NC = not calculable; NSTI = necrotizing soft tissue infection; OR = odds ratio; RC = reference; TBSA = total body surface area. Odds ratios in **bold** are statistically significant
Missing cases: [a]1 missing; [b]30 missing; [c]47 missing; [d]11 missing; [e]13 missing

Table 3 Disease outcomes and hospital course of patients with necrotizing soft tissue infections of the upper extremity

	Total n = 122 (100%)	Died ≤ 30 days n = 13 (11%)	Survived n = 108 (89%)	OR (95% CI)	Amputation n = 17 (14%)	Limb salvage n = 105 (86%)	OR (95% CI)
Amputation, n (%)	17 (14)	3 (18)	14 (82)	2.04 (0.50 - 8.31)	17 (100)	NA	NA
Digit	7 (41)	1 (14)	6 (86)		7 (100)	NA	
Forearm	2 (12)	0 (0)	2 (100)		2 (100)	NA	
Transhumeral	6 (35)	1 (17)	5 (83)		6 (100)	NA	
Forequarter	2 (12)	1 (50)	1 (50)		2 (100)	NA	
Mortality rate within 30 days, n (%)	13 (11)	13 (100)	NA	NA	3 (23)	10 (77)	2.04 (0.50 - 8.31)
Time between admission and death in days, median (IQR)	3 (1 - 8)	2 (1 - 4)	NA	NA	1 (1 - 18)	3 (2 - 8)	0.99 (0.92 - 1.06)
Length of hospital stay in days, median (IQR)	15 (9 - 21)	NA	15 (10 - 24)	NA	10 (6 - 19)	15 (9 - 21)	0.99 (0.96 - 1.02)
ICU admittance, n (%)	86 (70)	12 (14)	74 (86)	5.68 (0.71 - 45.40)	13 (15)	73 (85)	1.42 (0.43 - 4.71)
Length of ICU stay[a], median (IQR)	3 (2 - 9)	3 (1 - 7)	4 (2 - 9)	0.95 (0.85 - 1.07)	5 (3 - 11)	3 (2 - 8)	1.00 (0.96 - 1.03)
Infectious complications during hospital course, n (%)	73 (60)	13 (18)	60 (82)	NC	11 (15)	62 (85)	1.27 (0.44 - 3.70)
Sepsis/Toxic shock syndrome	70 (57)	13 (19)	57 (81)	NC	10 (14)	60 (86)	1.07 (0.38 - 3.03)
Pneumonia	8 (7)	0 (0)	8 (100)	NC	2 (25)	6 (75)	2.20 (0.41 - 11.92)
Discharge location, n (%)				NA			
Home	68 (63)	NA	68 (100)		6 (9)	62 (91)	0.38 (0.13 - 1.10)
Rehabilitation facility	39 (36)	NA	39 (100)		8 (21)	31 (79)	2.12 (0.75 - 6.01)
Transfer to other hospital	1 (1)	NA	1 (100)		0 (0)	1 (100)	NC

Continuation of table 3

Discharge location, n (%)			NA			
Home	68 (63)	NA	68 (100)	6 (9)	62 (91)	0.38 (0.13 - 1.10)
Rehabilitation facility	39 (36)	NA	39 (100)	8 (21)	31 (79)	2.12 (0.75 - 6.01)
Transfer to other hospital	1 (1)	NA	1 (100)	0 (0)	1 (100)	NC

Abbreviations: CI = Confidence interval; ICU = intensive care unit; IQR = interquartile range; NA = not applicable; NC = not calculable; OR = odds ratio. Missing cases: [a]14 missing. Odds ratios in **bold** are statistically significant.

Table 4 Multivariable logistic regression of risk factors for mortality and amputation in patients with necrotizing soft tissue infections of the upper extremity

30-day mortality	OR (95% CI)	Standard Error	*p* - value
ASA classification ≥III	9.26 (1.64 - 52.31)	8.18	**0.012**
Base deficit ≥3 meq/L at time of diagnosis	10.53 (1.14 - 96.98)	11.93	**0.038**
Amputation	**OR (95% CI)**	**Standard Error**	***p* - value**
Non-dominant side affected	3.78 (1.07 - 13.35)	2.43	**0.039**
Hand affected by NSTI	2.97 (0.75 - 11.82)	1.55	0.122

Abbreviations: ASA = American Society of Anesthesiologists; CI = Confidence Interval; NSTI = Necrotizing Soft Tissue Infection; OR = Odds Ratio. **Bold** font indicates significant result. Variables utilized in multivariable logistic regression, but eliminated during backward regression: 30-day mortality analysis: Age, ASA classification, history of malignancy, respiratory rate at presentation, base deficit at presentation, total body surface affected, other body regions affected by NSTI // Amputation analysis: Diastolic blood pressure at presentation, dominant hand affected, hand involved.

a base deficit of 3 meq/L or greater (OR 10.53, 95% CI 1.14 – 96.98) are both independent risk factors for mortality (Table 4).

Amputation

Seventeen patients (14%) underwent amputation in attempt to gain control of the infection, which was either an amputation during the index surgery (n = 9) or performed secondarily (n = 8). Three patients underwent amputation but died eventually. Types of amputation were an amputation of digit(s) (n = 7, 41%), transradial (n = 2, 12%), transhumeral (n = 6, 35%) or forequarter amputation (n = 2, 12%). Univariable analyses assessing the risk at amputation showed that only NSTIs of the non-dominant side (OR 3.79, 95% CI 1.09 – 13.16), a higher diastolic blood pressure at presentation (OR 1.05, 95% CI 1.00 – 1.09) and NSTIs of the hand (OR 5.04; 95% CI 1.37 – 18.58) had a greater risk at undergoing amputation (Table 1 - 3). Multivariable analysis showed that NSTIs of the non-dominant side (OR 3.78, 95% CI 1.07 – 13.35) were an independent risk factor for amputation (Table 4).

Microbiology

NSTIs of the upper extremity were predominately classified as type II (n = 75, n = 70%), of which Group A beta-hemolytic Streptococci (GAS) was most commonly isolated (n = 48, 64%). Of these patients, 10 patients (21%) received intravenous immunoglobulins (IVIG). Administration of IVIG was not associated with reduced mortality or amputation rates. Furthermore, 22 patients (20%) had type I NSTIs and 11 patients (10%) had type III NSTIs. Subgroup analysis of the specific isolated micro-organisms found no relation between the isolated micro-organisms and 30-day mortality or risk at amputation (Table 2 and Appendix 1).

Hospital course

Eighty patients (66%) first presented to an outside hospital, 63 of these patients (79%) were transferred to one of the two academic centers before their first debridement was performed. Transferring patients before the initial debridement did not results in higher mortality or amputation rates (OR 0.38, 95% CI 0.11 – 1.30 and OR 1.40, 95% CI 0.50 – 3.96, respectively) (Table 2).

Median length of hospital stay was 15 days (IQR 9 – 21). Eighty-six patients were admitted to ICU (70%) for a median stay of 3 days (IQR 2 – 9). During the hospital stay, 71 patients (58%) developed infectious complications (e.g. toxic shock syndrome, sepsis, pneumoniae). After hospital discharge, patients were discharged home (n = 63, 68%), to a rehabilitation facility (n = 39, 36%) or transferred to another hospital for further care (n = 1, 1%) (Table 3).

Patients underwent a median of four operations (IQR 3 – 6, range 0 – 22). A median of three debridement procedures (IQR 2 – 4, range 0 – 10) and a median of one reconstructive procedure (IQR 1 – 2, range 0 - 9) were performed. The first attempt at wound closure was made a median of eight days (IQR 4 - 12) after diagnosis. Closure of debridement wounds in surviving patients without amputations was done by using skin grafts (n = 50, 54%), delayed primary closure with sutures (n = 25, 27%), flap surgery (n= 9, 10%) and flap surgery combined with skin grafts (n = 8, 9%). There was no difference in number of surgeries between patients requiring amputation for infection control and those with salvaged upper extremities (Appendix 2).

Discussion

The 30-day mortality rate of 11% found in this study is low compared to mortality rates previously described for NSTIs [2,3,15,16]. Over 20 years ago, a cumulative mortality rate of 34% was described [17]. Looking at studies from the past ten years, the mortality rate of NSTIs varies between 6% and 33% [2,3,15,16]. The mortality rate probably decreased due to improvement in awareness and treatment, both surgical and in critical care support [9]. The cumulative mortality rate described for upper extremity NSTIs was 18.3% (90 patients died out of 493 included patients in 8 studies), with rates as low as 9% and as high as 36% [6,18–24]. The low mortality rate in this study might be caused by the relatively large group of intravenous drug user and type II NSTIs. Both of these groups are known to consist of young patients with few comorbidities, which are two factors previously associated with lower mortality rates [25,26]. The mortality rate for NSTIs of the extremity have been suggested to be lower compared to NSTIs of other anatomical regions (e.g. head, neck, trunk), since NSTIs at these location is commonly more widespread upon presentation and tend to be more difficult to treat [27].

Only two previous studies have looked at factors associated with mortality in upper extremity NSTIs. Both studies found that patients with pre-existing comorbidities and patients presenting with septic symptoms had a greater risk of dying [20,22]. In this study, the ASA classification was used to assess the overall physical status of the patients and the severity of the comorbidities combined. A higher ASA classification has been linked to higher mortality after major trauma and a wide variety of surgical procedures [28,29]. Patients with upper extremity NSTIs and major or multiple comorbidities (ASA 3 or 4) had a nine times greater risk of dying compared to patients with no to minimal comorbidities (ASA 1 or 2). This association has not yet been described for upper extremity NSTIs, but has been described by two studies assessing NSTIs of all body regions [2,4,30].

Base deficit at admission was also found to predict mortality due to upper extremity NSTIs. Patients with a base deficit ≥ 3 meq/L at admission had an 11-time greater

risk to die compared to patients with a base deficit of <3 meq/L. Base deficit provides a fast estimate of the physiological disturbance of the patient, is a marker for shock and is usually part of the standard diagnostic armamentarium in the emergency department [31,32]. Base deficit is already used to predict complications and mortality in trauma and intensive care patients and has been described by Elliot et al. to also predict mortality in NSTI patients [31–34]. It has been suggested that the LRINEC score might also be predictive for mortality, since this score also looks at markers for sepsis severity in NSTI patients, however, in this study the LRINEC score was not predictive for mortality and was in most patients far below the cutoff point for NSTI suspicion [13,35].

Amputation was in 14% of the cases required for management of the infection. Previous described amputation rates for NSTIs range from 6% to 28%, while the amputation rate of studies assessing the upper extremity vary between 6% and 36% with a cumulative amputation rate of 9% [19,21–23,34,36–38]. This rate is lower than seen in our study, which might be related to the lower mortality rate. More patients survived, but the patients that survived might have required more extreme measures, such as amputation, to survive. Only diabetes mellitus and sepsis have previously been associated with amputation in patients with NSTIs of the upper extremity [22]. This study did not find a relation between those factors but did find that patients with NSTIs of the non-dominant arm were more likely to undergo amputation. This seemed not to be influenced by a more distal location of the infection or by an injection, most commonly done in the non-dominant arm, as causative event. Therefore, we hypothesize that this might represent surgical bias. Surgeons might possibly be more likely to resort to amputation if the non-dominant arm was affected, weighing infection control and the remaining functionality of the dominant arm. Fortunately, due to improved awareness and diagnostics, the amputation rate has declined during the last five years of the study.

This study is limited by its retrospective nature. First, during the inclusion process patients might have been missed for inclusion due to miscoding of ICD codes or underdiagnosing of NSTIs in deceased patients. Second, the accuracy of retrospective data is determined by the accuracy of reporting of findings in patients' chart. This may have led to non-differential misclassification or absent variables. This was the case for the exact time (in hours) to diagnosis and surgery. Third, we included patients who first presented to outside hospitals, which results in less detailed information about findings at initial presentation. Fourth, this study assesses a broad study period during which the management of critical ill patients changed as well. Our data is representative of actual practice including the management variations, however, these variations should be kept in mind. Finally, due to the rarity of NSTIs and the associated small sample sizes and limited

occurrence of the outcomes, sparse-data bias should be kept in mind during interpretation of the results. However, the strength of this study is that this is one of the biggest and most detailed studies of NSTIs of the upper extremity.

Conclusion

NSTIs of the upper extremity have a relatively low mortality rate, but a relatively high amputation rate comparted to studies assessing NSTIs of all anatomic regions. ASA classification and base deficit at admission can predict the prognosis of a patients with upper extremity NSTIs, while a NSTI of the non-dominant arm is a risk factor for limb loss.

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Appendix 1 Isolated organisms from cultures from necrotizing soft tissue infections of the upper extremity

	Total n = 122 (100 %)	Died ≤ 30 days n = 13 (11%)	*p* - value	Amputation n = 17 (14%)	*p* - value
Patients with specific isolated organisms from cultures, n (%)	109 (89)	11 (85)		16 (94)	
Group A beta-hemolytic Streptococcus	48 (44)	3 (6)	0.341	6 (12.5)	0.600
Other *Streptococcus* species[a]	28 (26)	3 (11)	1.000	4 (14)	1.000
Staphylococcus species					
Methicillin-resistant *Staphylococcus aureus* (MRSA)	17 (16)	2 (12)	0.681	2 (12)	1.000
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	5 (5)	0 (0)	1.000	1 (20)	0.555
Coagulase-Negative Staphylococci (CoNS)	10 (9)	1 (10)	1.000	2 (20)	0.639
Anaerobes other than *Clostridium*[b]	19 (17)	2 (11)	1.000	2 (11)	0.733
Clostridium spp.	6 (6)	1 (17)	0.480	1 (17)	1.000
Vibrio spp.	2 (2)	0 (0)	1.000	1 (50)	0.273
Enterococci spp.	5 (5)	2 (40)	0.079	2 (40)	0.155
Klebsiella spp.	3 (3)	1 (33)	0.276	0 (0)	1.000
Pseudomonas spp.	1 (1)	1 (100)	0.101	1 (100)	0.147
Other[c]	2 (2)	0 (0)	1.000	0 (0)	1.000
No growth or no cultures taken	13 (11)	2 (15)		1 (6)	

[a] Includes Group B/C/F/G Streptococcus, *Streptococcus milleri, Streptococcus pneumoniae*

[b] Includes *Fusobacterium spp., Lactobacillus spp., Peptostreptococus spp., Proteus spp., Veillonella spp., Haemophilus parainfluenzae, Actinomyces odontolyticus, Granulicatella adiacens, Pasteurella multocida, Eubacterium lentum*

[c] Include Nocardia asteroides and Neisseria meningitidis

Abbreviations: NA = Not Applicable

Appendix 2 Surgical procedures performed in patients with necrotizing soft tissue infections of the upper extremity

	Total n = 122 (100%)	Died ≤ 30 days n = 14 (11%)	Survived n = 108 (89%)	*p* - value	Amputation n = 17 (14%)	Limb salvage n = 105 (86%)	*p* - value
Number of total operative procedures for NSTI, median (IQR)	4 (3 - 6)	1 (1 - 1)	4 (3 - 6)	**<0.001**	4 (3 - 5)	4 (3 - 6)	0.745
Number of total operative procedures on the upper extremity for NSTI, median (IQR)	4 (3 - 6)	1 (0 - 1)	4 (3 - 6)	**<0.001**	4 (3 - 4)	4 (3 - 6)	0.822
Debridement and irrigation procedures, median (IQR)	3 (2 - 4)	1 (0 - 1)	3 (2 - 5)	**<0.001**	3 (2 - 4)	3 (2 - 4)	0.517
Reconstruction procedures, median (IQR)	1 (1 - 2)	0 (0 - 0)	1 (1 - 2)	**<0.001**	1 (0 - 1)	1 (1 - 2)	0.060
Time from onset symptoms to last surgery for NSTI in weeks[a], median (IQR)	2 (1 - 6)	0 (0 - 0)	2 (1 - 8)	**<0.001**	1 (0 - 15)	2 (1 - 6)	0.233

Abbreviations: IQR = Interquartile Range; NA= Not Applicable; NSTI = Necrotizing Soft Tissue Infection. Missing cases: [a]4 missing.

c

10

Survival and health-related quality of life after necrotizing soft tissue infections of the upper extremity: a long-term outcome study

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Abstract

Aim: To investigate the survival and health related quality of life (HRQoL) after hospitalization for necrotizing soft tissue infections (NSTIs) of the upper extremity.

Methods: A retrospective study with long-term follow-up of patients surviving NSTIs of the upper extremity was performed. Survival and HRQoL after hospital discharge were the primary outcomes. The HRQoL was measured using the 36-item Short Form (SF-36), EuroQol-5D-5L (EQ-5D), Quick Disability of Shoulder, Arm and Hand (QuickDASH) and numeric rating scales (NRS) for satisfaction with appearance and pain.

Results: A median of 6.5 years after hospitalization, 81% of the 108 patients survived. The response rate was 45% (n=38). The SF-36 score was 80 (IQR 58 – 91), the EQ-5D score 1.4 (IQR 1.2 – 2.2), the EQ-VAS score 77 (67 – 90), the Quick-DASH score 13.6 (2.3 – 30.7), the NRS for satisfaction with appearance 8 (IQR 7 – 9) and NRS for pain 1 (0 – 5).

Conclusions: Six-and-a-half years after the NSTI, 81% of the patients were still alive. General health prior to the NSTI mainly influenced the risk at secondary mortality. In surviving patients, the HRQoL varied widely, but was adversely affected by female sex, intravenous drug use, NSTI type I or III and longer length of hospital stay.

Introduction

Necrotizing soft tissue infections (NSTIs) are rare, rapidly progressive and often fatal infections of the fascia and subcutaneous tissues with an estimated incidence in the United States of 4 cases per 100,000 person-years [1–3]. Necrotizing fasciitis, myonecrosis and necrotizing cellulitis are all NSTI subtypes, of which necrotizing fasciitis is the best known entity and most commonly seen [1,4]. A broad range of micro-organisms can cause NSTIs, of which the monomicrobial infection with Group A Streptococcus is most notorious, but NSTIs can also be polymicrobial [1,5]. The exact etiology of NSTIs is not always known, but trauma, intravenous drugs use, animal bites or surgical complications have frequently been reported as causative events [1,6]. To obtain good clinical outcomes, patients with NSTIs require early recognition, immediate aggressive surgical debridement for source control and adequate intravenous antibiotics [7]. However, prompt treatment is commonly delayed as a consequence of misdiagnosis [8]. This is due to the diagnostic challenge caused by absence of early pathognomic symptoms for NSTIs [1,9]. Unfortunately, reported mortality rates for NSTIs have not improved over the last two decades and remained stable around 20% [7]. Therefore, the subject of the majority of the available NSTI studies remains the short-term outcomes, such as the mortality and amputation rates [2,10–12]. However, the mortality rate did improve tremendously compared to the rates reported prior to the year 2000 [7]. Therefore, the focus should also start to shift towards the quality of life of these patients since such a severe infection requiring highly invasive surgical procedures is likely to adversely affect the quality of life [13,14]. Especially NSTIs of the upper extremity could have even greater (permanent) consequences, since proper upper extremity function has been thought to be essential for maintaining good quality of life due to its major role in self-care and the appearance of the extremity has also been linked to patients' quality of life [15]. Unfortunately, studies specifically assessing the long-term outcomes of upper extremity NSTIs are uncommon, even though prior epidemiology studies have found upper extremity involvement in 7 to 27% of all NSTIs cases and found that especially NSTIs of the upper extremity seem to have a relatively low mortality rate [4,6,11,16,17]. Therefore, the aim of this study is to investigate the survival and health related quality of life (HRQoL) after hospitalization for necrotizing soft tissue infections of the upper extremity and to identify the factors associated with these outcomes.

Methods

A study protocol was a-priori written, however was not registered or published. The institutional review board granted permission for retrospective data collection and the long-term follow up of patients (IRB #1999P008705). This article was written in

adherence to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [18].

Study design

A retrospective multicenter study with long-term follow-up of patients surviving initial hospitalization for NSTIs of the upper extremity at two urban tertiary referral hospitals was performed from January 1998 to January 2018. Eligible patients were identified from the Institutions' Research Patient Data Registry (RPDR) by using the International Classification of Disease (ICD) 9 (928.86) and ICD 10 (M72.6) code for necrotizing fasciitis. Patients who survived initial hospitalization for NSTIs of the upper extremity were eligible for inclusion. The diagnosis NSTI had to be confirmed based on clinical symptoms and, especially in ambivalent cases, confirmed by pathology (e.g. histology) and/or microbiology (e.g. gram stain or definitive culture) results [19]. Exclusion criteria were age younger than 18 years, pregnancy at time of the NSTI and death during initial hospitalization for the NSTI. The sample size was determined by the number of eligible patients during the inclusion period and the number of patients willing to participate in the long-term outcome survey.

Explanatory variables and outcome measures

Demographic characteristic collected were age, sex, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) classification, comorbidities, medical history, smoking status, history of intravenous drug use, history of opioid abuse and type of occupation. The disease related characteristics extracted were time from onset symptoms to diagnosis, affected side, dominant hand, causative event associated with the NSTI, date of causative event, location where symptoms first started, affected body areas, total body surface area (TBSA) affected, the Laboratory Risk Indicator for Necrotizing fasciitis (LRINEC) score, upper extremity levels affected by the NSTI and the micro-organism(s) identified. Treatment related characteristics extracted were the hospital of first presentation, amputation, mortality, date of death, ICU admittance, length of ICU and hospital stay, type and number of surgeries performed, date of last surgery for the upper extremity NSTI, infectious complications during admission and discharge location.

In case of an unreported ASA classification, the ASA classification was determined based on the reported comorbidities at time of admission. Manual laborers were defined as workers mainly doing physical work dominated by grasping and lifting [20]. The TBSA affected was calculated using the rule of nines commonly used in burns [21]. The LRINEC score is a diagnostic score that evaluates sepsis severity and thereby predicts the likelihood of NSTI as diagnosis. The score is based on C-reactive protein (CRP), white blood cell count, hemoglobin, sodium, creatinine and glucose. A LRINEC score <6 represents a low suspicion for a NSTI [22]. The type of NSTI was

categorized using the microbiological classification for NSTIs: type I (polymicrobial), type II (monomicrobial) and type III (e.g. *Clostridium* spp. or *Vibrio* spp.) [23].

Survival and HRQoL after hospitalization for NSTIs were the primary outcomes. The survival after hospitalization for NSTIs was determined by the secondary mortality rate, which was defined as death due to any cause after the initial hospitalization for a NSTI. The follow-up period for secondary death was calculated from the date of discharge to October 1st, 2018, which was the date on which mortality data was retrieved from RPDR. HRQoL was measured using the 36-item Short Form (SF-36), EuroQol-5-Dimensional-5 Levels (EQ-5D-5L) survey, EuroQol-Visual Analog Scale (EQ-VAS), Quick Disability of Arm, Shoulder and Hand (QuickDASH), Numeric Rating Scale (NRS) for satisfaction with appearance and NRS for pain. The SF-36 assesses eight different domains: physical functioning, limitations due to physical function, bodily pain, global health perception, vitality, social function, limitations due to emotional health and general mental health. The higher the score on the SF-36 (ranging from 0 to 100), the better the self-assessed quality of life [24,25]. The eight domains can be split into two sub-scores ranging from 0 to 50: the Physical Components Summary (PCS) score and the Mental Components Summary (MCS) score [26]. The EQ-5D-5L is a survey with five five-point scale (no problem to unable) questions assessing patient-reported quality of life. The lower the score, the higher the quality of life. An extension of the EQ-5D-5L is the EQ-VAS, which asks patients to rate their health on a scale from 0 (the worst health imaginable) to 100 (the best health imaginable) [27,28]. The QuickDASH assesses the amount of difficulty and symptoms experienced by the patients during daily activities, each question is scored on a scale from 1 (no difficulty or no symptoms) to 5 (unable or severe symptoms). These scores are transformed to a score from 0 to 100, with a higher score indicating worse patient-reported physical arm function and symptoms [29]. The NRS for satisfaction with appearance measures patients' satisfaction with their appearance on a scale from 0 (very unsatisfied) to 10 (very satisfied). The NRS for pain measures a patients' current amount of pain on a scale from 0 (no pain) to 10 (worst pain imaginable) [30].

Patients were contacted by telephone to participate in the survey. To obtain a satisfactory response rate and to reduce non-responder selection bias, four rounds of phone calls were made at different times of the day.

Statistical analysis

Continuous parametric variables are presented as means with standard deviations (SD), continuous nonparametric variables as medians with interquartile ranges (IQR) and categorical variables as frequencies and percentages. Missing data were handled using pairwise deletion. Simple logistic regressions were used to identify

predictors for secondary mortality. Bivariate analyses, using the Mann-Whitney U test, Kruskall-Wallis test and Spearman's rank correlation coefficient, were performed to identify associations between the explanatory variables and the survey scores. Multivariable linear regression analyses with backward deletion were used to identify independent predictors for each survey outcome. Variables with a *p*-value <0.10 in bivariate analyses were imputed in the model. The definitive model consisted of no more than four predictors to prevent overfitting the model. Additional analyses were performed to test generalizability of the results of the responder group to the entire cohort of NSTI patients surviving initial hospitalization. A *p*-value of <0.05 was considered significant. All analyses were performed with STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

A total of 108 patients survived initial hospitalization for NSTIs and were included. The short-term, in-hospital outcomes of this cohort were previously published [6]. The mean age was 48 ± 16 years. Most of these patients were classified ASA classification I or II (n = 71, 66%) (Table 1). In most cases, the forearm was affected (n = 83, 77%) (Table 2). Fourteen patients (13%) ultimately underwent an amputation (Table 3).

Survival after hospitalization

Twenty-one patients (19%) died prior to the start of this study, which corresponds to an 81% survival rate during the median follow-up period of 6.5 years (IQR 3.7 – 10.3). The precise date of death was only known of eight patients (38%), those patients died at a median of 18 months (IQR 2 – 43) after hospital discharge. Bivariate logistic analyses show that older age at time of the NSTI (OR 1.07, 95% CI 1.03 – 1.11), ASA classification III or IV compared to I or II (OR 4.45, 95% CI 1.63 – 12.12), diabetes mellitus (OR 6.08, 95% CI 1.94 – 19.04), a history of malignancy (OR 5.40, 95% CI 1.53 – 19.01), patients who were retired or unemployed (OR 4.57, 95% CI 1.60 – 13.05), type III NSTIs (OR 10.43, 95% CI 2.33 – 46.70), amputation as management for the NSTI (OR 3.95, 95% CI 1.20 – 13.03) and discharged to a rehabilitation facility (OR 4.96, 95% CI 1.79 – 13.74) increased the risk at dying secondarily. Patients who were manual laborers prior to the infection or were discharged home had a lower risk of dying secondarily (OR 0.22, 95% CI 0.08 – 0.63 and OR 0.21, 95% CI 0.08 – 0.59, respectively).

HRQoL after hospitalization

Eighty-five patients were contacted, of which 38 patients (45%) were willing to participate in the survey (Figure 1). The median time between discharge and follow-

Table 1 Patient demographic of patient surviving initial hospitalization for necrotizing soft tissue infections of the upper extremity

	Patient surviving initial hospitalization n = 108 (100%)	Patients deceased during follow-up n = 21 (19%)	OR (95% CI)	Patients with long-term follow-up n = 38 (45%)
Age in years, mean ± SD	48 ± 16	62 ± 15	**1.07 (1.03 - 1.11)**	47 ± 14
Male, n (%)	59 (55)	13 (62)	1.45 (0.55 - 3.84)	20 (53)
BMI in kg/m² [a], median (IQR)	25 (23 - 31)	26 (21 - 32)	1.00 (0.93 - 1.07)	24 (22 - 28)
ASA classification, n (%)				
I - II	71 (66)	8 (38)	RC	28 (74)
III - IV	36 (34)	13 (62)	**4.45 (1.63 - 12.12)**	10 (26)
Diabetes mellitus, n (%)	16 (15)	8 (38)	**6.08 (1.94 - 19.04)**	1 (3)
History of malignancy, n (%)	12 (11)	6 (29)	**5.40 (1.53 - 19.01)**	3 (8)
Smoker at time of NSTI, n (%)	39 (36)	5 (24)	0.48 (0.16 - 1.43)	8 (21)
History of intravenous drug use, n (%)	33 (31)	3 (14)	0.31 (0.08 - 1.14)	7 (18)
History of opioid abuse[b], n (%)	24 (23)	1 (5)	0.13 (0.02 - 1.03)	5 (14)
Occupation at time of onset NSTI[b], n (%)				
Manual laborer	19 (18)	2 (10)	**0.22 (0.08 - 0.63)**	4 (11)
Occupation without manual labor	40 (39)	4 (19)	0.33 (0.10 - 1.07)	23 (62)
Retired or unemployed	44 (43)	15 (71)	**4.57 (1.60 - 13.05)**	10 (27)

Abbreviations: ASA = American Society of Anesthesiologists; BMI = Body Mass Index; CI = Confidence Interval; IQR = Interquartile Range; NSTI = Necrotizing Soft Tissue Infection; OR = Odds Ratio; SD = Standard Deviation; RC = Reference. Missing case: [a]14 missing; [b]5 missing. **Bold** font indicates significant result.

Table 2 Disease related characteristics of patient surviving initial hospitalization for necrotizing soft tissue infection of the upper extremity

	Patient surviving initial hospitalization n = 108 (100%)	Patients deceased during follow-up n = 21 (19%)	OR (95% CI)	Patients with long-term follow-up n = 38 (45%)
Affected side, n (%)				
Left	55 (51)	11 (52)	0.98 (0.37 - 2.54)	21 (55)
Right	49 (45)	10 (48)	1.03 (0.39 - 2.68)	16 (42)
Bilateral	4 (4)	0 (0)	NC	1 (3)
Dominant hand affected[a], n (%)	50 (56)	11 (61)	1.69 (0.99 - 2.88)	18 (47)
Causative event if known[b], n (%)				
Injection (e.g. intravenous drug use, blood drawl)	25 (36)	2 (17)	0.49 (0.13 - 1.83)	5 (24)
Trauma without open wound	11 (16)	1 (8)	0.35 (0.04 - 2.84)	3 (14)
Open traumatic wound	20 (29)	5 (42)	1.50 (0.48 - 4.73)	10 (48)
Bite (e.g. bug, cat, human)	10 (15)	3 (25)	1.20 (0.23 - 6.26)	3 (14)
Prior surgery	3 (4)	1 (8)	2.13 (0.18 - 24.61)	0 (0)
Days between causative moment and diagnosis[c], median (IQR)	4 (3 - 8)	6 (3 - 12)	1.03 (0.94 - 1.13)	3 (3 - 5)
Upper extremity not as origin of first symptoms, n (%)	2 (2)	0 (0)	NC	36 (95)
Other body regions affected by the NSTI, n (%)	12 (11)	4 (19)	0.43 (0.12 - 1.59)	4 (11)
Head/neck	2 (2)	0 (0)	NC	1 (3)
Trunk	11 (10)	3 (14)	1.65 (0.40 - 6.82)	4 (11)
Perineum	0 (0)	0 (0)	NC	0 (0)
Lower extremity	3 (3)	2 (10)	8.95 (0.77 - 103.83)	1 (3)
Percentage TBSA affected by the NSTI, median (IQR)	4 (3 - 6)	5 (3 - 7)	1.02 (0.97 - 1.09)	4 (3 - 6)
LRINEC score at presentation[d], mean ± SD	5 ± 3	4 ± 3	0.86 (0.59 - 1.25)	5 ± 3
Type of NSTI based on definitive culture[e], n (%)				
Type I	19 (20)	3 (15)	0.66 (0.17 - 2.54)	3 (9)
Type II	68 (71)	11 (55)	0.41 (0.15 - 1.13)	28 (85)

Continuation of table 2

Type III	9 (9)	6 (30)	**10.43 (2.33 - 46.70)**	2 (6)
Levels of upper extremity involved, n (%)				
Hand	59 (55)	14 (67)	1.87 (0.69 - 5.07)	22 (58)
Forearm	83 (77)	18 (86)	2.03 (0.55 - 7.56)	29 (76)
Upper arm	56 (52)	11 (52)	1.03 (0.40 - 2.67)	19 (50)
Shoulder	16 (15)	4 (19)	1.47 (0.42 - 5.12)	7 (18)
Number of upper extremity levels involved, median (IQR)	2 (1 - 2)	2 (2 - 3)	1.65 (0.91 - 2.99)	2 (2 - 2)
Highest level of upper extremity involved, n (%)				
Hand	10 (9)	2 (10)	RC	3 (8)
Forearm	40 (37)	8 (38)	1.00 (0.17 - 5.65)	15 (40)
Upper arm	42 (39)	7 (33)	0.80 (0.14 - 4.60)	13 (34)
Shoulder	16 (15)	4 (19)	1.33 (0.20 - 9.08)	7 (18)

Abbreviations: CI = Confidence Interval; IQR = Interquartile Range; LRINEC = Laboratory Risk Indicator for Necrotizing fasciitis; NC = Not Calculable; NSTI = Necrotizing Soft Tissue Infection; OR = Odds Ratio; SD = Standard Deviation; RC = Reference; TBSA = Total Body Surface Area. Missing cases: [a]19 missing; [b] 39 missing; [c] 49 missing; [d]63 missing; [e]12 missing. **Bold** font indicates significant result.

Table 3 Treatment related characteristics of patient surviving initial hospitalization for necrotizing soft tissue infections of the upper extremity

	Patient surviving initial hospitalization n = 108 (100%)	Patients deceased during follow-up n = 21 (19%)	OR (95% CI)	Patients with long-term follow-up n = 38 (45%)
First presentation to outside hospital, n (%)	75 (69)	18 (86)	3.16 (0.86 - 11.58)	23 (61)
Time from onset symptoms to diagnosis in days, median (IQR)	2 (1 - 4)	2 (0 - 7)	1.03 (0.94 - 1.14)	2 (1 - 3)
Number of total operative procedures for the NSTI, median (IQR)	4 (3 - 6)	4 (3 - 5)	0.97 (0.85 - 1.11)	6 (3 - 8)
Number of total operative procedures on the upper extremity for the NSTI, median (IQR)	4 (3 - 6)	4 (2 - 4)	0.88 (0.73 - 1.07)	5 (3 - 8)
Debridement and irrigation procedures, median (IQR)	3 (2 - 5)	3 (2 - 4)	0.96 (0.78 - 1.18)	4 (2 - 6)
Reconstructive procedures, median (IQR)	1 (1 – 2)	1 (1 – 2)	0.83 (0.58 – 1.17)	2 (1 – 3)
Type of definitive wound closure[a], n (%)				
Wound closure with sutures	30 (32)	3 (16)	0.33 (0.09 – 1.25)	13 (41)
Skin graft	48 (51)	12 (63)	1.86 (0.66 – 5.24)	14 (44)
Flap surgery	8 (8.5)	3 (16)	2.63 (0.57 – 12.13)	2 (6)
Flap surgery and skin graft	8 (8.5)	1 (5)	1.86 (0.66 – 5.24)	3 (9)
Time from diagnosis to wound closure in days, median (IQR)	7 (4 – 12)	5 (3 – 17)	1.01 (0.96 – 1.05)	7 (3 – 11)
Time from onset symptoms to last surgery for the NSTI in weeks, median (IQR)	2 (1 – 8)	2 (1 – 8)	1.00 (0.99 – 1.01)	4 (1 – 27)
Amputation, n (%)	14 (13)	6 (29)	**3.95 (1.20 – 13.03)**	5 (13)
Level of amputation, n (%)				
Digits	6 (43)	1 (17)	0.12 (0.01 – 1.58)	2 (40)
Forearm	2 (14)	1 (50)	1.40 (0.07 – 28.12)	1 (20)

Continuation of table 3

Transhumeral	5 (36)	3 (60)	3.00 (0.31 – 28.84)	2 (40)
Forequarter	1 (7)	1 (100)	NC	0 (0)
Length of hospital stay in days, median (IQR)	15 (10 – 23)	18 (13 – 27)	1.02 (1.00 – 1.05)	14 (9 – 24)
ICU admittance, n (%)	73 (68)	17 (81)	2.35 (0.73 – 7.61)	26 (68)
Length of ICU stay in days[b], median (IQR)	4 (2 – 9)	6 (3 – 11)	1.02 (0.99 – 1.06)	5 (1 – 8)
Infectious complications during hospital course, n (%)	59 (55)	14 (67)	1.87 (0.69 – 5.07)	25 (66)
Sepsis/Toxic shock syndrome	56 (52)	13 (62)	1.66 (0.63 – 4.41)	24 (63)
Pneumonia	8 (7)	2 (10)	1.42 (0.27 – 7.60)	2 (5)
Discharge location, n (%)				
Home	68 (63)	7 (33)	**0.21 (0.08 – 0.59)**	29 (76)
Rehabilitation facility	39 (36)	14 (67)	**4.96 (1.79 – 13.74)**	9 (24)
Transfer to other hospital	1 (1)	0 (0)	NC	0 (0)

Abbreviations: CI = Confidence Interval; ICU = Intensive Care Unit; IQR = Interquartile Range; NC = Not Calculable; NSTI = Necrotizing Soft Tissue Infection; OR = Odds Ratio. Missing cases: [a]14 missing; [b] 13 missing. **Bold** font indicates significant result.

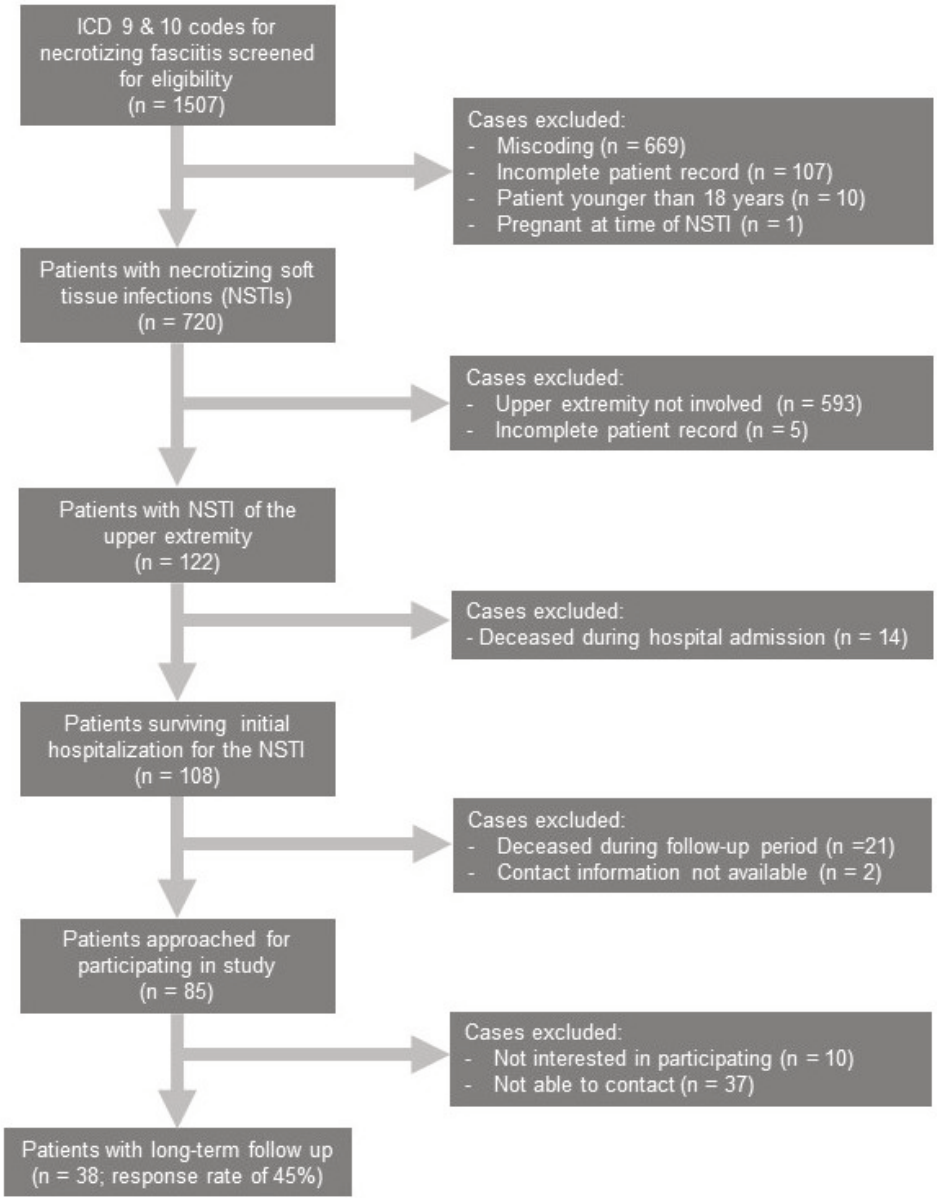

Figure 1 Flowchart of in- and exclusion of patients with necrotizing soft tissue infections of the upper extremity

up by survey was 4.7 years (IQR 3.1 – 9.4 years). Comparing the responders (n = 38) to the entire cohort of patients surviving initial hospitalization (n = 108), we found that the responders were more often diagnosed with diabetes mellitus (p = 0.009), smoked less often (p = 0.020), had less frequent a history of intravenous drug use (p

= 0.049), were more often employed (p = 0.002) and were more often discharged home than to a rehabilitation facility (p = 0.039).

The median overall SF-36 score was 80.0 (IQR 58.2 – 91.1) (Table 4). Patients scored lowest on vitality (median 65, IQR 50 – 75) (Appendix 1). Factors associated with a lower SF-36 score in bivariate analyses were a history of intravenous drug use (p = 0.009) and a longer length of hospital stay (p = 0.039). Multivariable analysis showed that a history of intravenous drug use (β = -32.78; p <0.001) and a longer length of hospital stay (β = -0.39; p = 0.036) were both independently associated with a lower overall SF-36 score (Table 5).

The overall median EQ-5D-5L score was 1.4 (IQR 1.2 – 2.2) (Table 4). Patients scored highest on questions about pain and discomfort (median 2 (IQR 1 – 3)) (Appendix 2). Factors associated with a higher EQ-5D-5L score (worse HRQoL) in bivariate analyses were a history of intravenous drug use (p = 0.015) and a higher LRINEC score (p = 0.028). Multivariable analysis showed that only a history of intravenous drug use (β = 1.51; p = 0.001) was independently associated with a higher score on the EQ-5D-5L and thus lower quality of life (Table 5).

Patients reported a median score of 77 (IQR 67 - 90) on the EQ-VAS (Table 4). Factors associated with a lower EQ-VAS (lower HRQoL) in bivariate analyses were a history of intravenous drug use (p = 0.048), a history of opioid abuse (p = 0.031), an open traumatic wound as causative event (p = 0.042), NSTIs not originating from the upper extremity (p = 0.032), NSTIs that spread to other body regions besides the upper

Table 4 Patient-reported long-term follow-up outcome measures of patients with previous necrotizing soft tissue infections of the upper extremity

	Median (IQR)
Years between hospitalization for NSTI and surveys (n = 38)	4.7 (3.1 – 9.4)
SF-36 score (n = 38)	80 (58.2 – 91.1)
Physical Components Summary (PCS) score	48.7 (42.2 – 55.3)
Mental Components Summary (MCS) score	55.3 (41.5 – 57.7)
EQ-5D-5L score (n = 38)	1.4 (1.2 - 2.2)
EQ-VAS (n = 36)	77 (67 - 90)
QuickDASH (n = 36)	13.6 (2.3 - 30.7)
NRS for satisfaction with appearance (n = 36)	8 (7 - 9)
NRS for pain (n = 36)	1 (0 - 5)

Abbreviations: EQ-5D-5L = EuroQol-5 Dimensional -5 Levels; EQ-VAS = EuroQol-Visual Analog Scale; IQR = Interquartile Range; NRS = Numeric Rating Scale; NSTI= Necrotizing Soft Tissue Infection; QuickDASH = Quick Disability of Arm, Shoulder and Hand; SF-36 = 36-Item Short Form.

Table 5 Multivariable linear regression for patient-reported long-term outcome measures in patients with previous necrotizing soft tissue infections of the upper extremity

SF-36	Coefficient β	Standard Error	95% CI	*p* - value
History of intravenous drug use	-32.78	8.23	-49.48 - -16.08	**<0.001**
Longer length of hospital stay	-0.39	0.18	-0.76 - -0.03	**0.036**
EQ-5D-5L				
History of intravenous drug use	1.51	0.35	0.76 - 2.26	**0.001**
Higher LRINEC score	0.04	0.04	-0.04 - 0.12	0.286
Longer length of hospital stay	-0.01	0.02	-0.05 - 0.02	0.431
EQ-VAS				
History of intravenous drug use	-18.18	8.83	-36.21 - -0.14	**0.048**
History of opioid abuse	-19.57	8.66	-37.26 - -1.88	**0.031**
Sepsis during admission	-10.03	5.67	-21.61 - 1.55	0.087
Longer length of hospital stay	-0.66	0.15	-0.97 - -0.34	**<0.001**
QuickDASH				
Female sex	6.85	4.46	-2.29 - 15.99	0.136
NSTI type I or III compared to type II	15.32	6.44	2.11 - 28.53	**0.025**
Higher number of reconstructive surgeries	1.68	1.06	-0.48 - 3.85	0.122
Longer length of hospital stay	0.48	0.15	0.18 - 0.78	**0.003**
NRS satisfaction with appearance				
Female sex	-1.89	0.78	-3.48 - -0.31	**0.021**
History of intravenous drug use	-4.78	1.86	-8.58 - -0.98	**0.015**
Smoker at time of onset NSTI	2.00	1.74	-1.56 - 5.56	0.261
ICU admittance	-1.89	0.86	-3.30 - 0.20	0.081
NRS for pain				
Female sex	1.55	0.70	0.12 - 2.98	**0.035**
NSTI type I or III compared to type II	3.06	0.96	1.09 - 5.03	**0.004**
Longer time between infection and survey	-0.10	0.08	-0.28 - 0.07	0.225

Abbreviations: CI = Confidence Interval; EQ-5D-5L = EuroQol-5 Dimensional-5 Levels; EQ-VAS = EuroQol-Visual Analog Scale; ICU = Intensive Care Unit; LRINEC = Laboratory Risk Indicator Necrotizing Fasciitis; NRS = Numeric Rating Scale; NSTI = Necrotizing Soft Tissue Infection; QuickDASH = Quick Disability of Arm, Shoulder and Hand; SF-36 = 36-Item Short Form. **Bold** font indicates significant result.

extremity (p = 0.039), NSTIs with involvement of the hand (p = 0.010) and sepsis during hospitalization for the NSTI (p = 0.027). Multivariable analysis showed that history of intravenous drug use (β = -18.18; p = 0.048), history of opioid abuse (β = -19.57; p = 0.031) and a longer length of hospital stay (β = -0.66; p <0.001) were independently associated with a lower score on the EQ-VAS (Table 5).

The median score on the QuickDASH was 13.6 (IQR 2.3 – 30.7) (Table 4). Factors associated with a higher QuickDASH score in bivariate analyses were the type of NSTI (p = 0.029), more NSTI related surgeries (p = 0.025), more reconstructive surgeries (p = 0.026), longer time between onset of the NSTI and the last surgery (p = 0.013), longer length of ICU stay (p = 0.028) and longer length of hospital stay (p = 0.034). Multivariable analysis showed that factors independently associated with higher DASH scores were type I or type III NSTIs compared to type II (β = 15.32; p = 0.025) and a longer length of hospital stay (β = 0.48; p = 0.003) (Table 5).

The mean score for satisfaction with appearance was 8 (IQR 7 – 9) (Table 4). Factors associated with less satisfaction with appearance in bivariate analyses were being a smoker at the time of onset of the NSTI (p = 0.039), history of intravenous drug use (p = 0.016) and ICU admittance (p = 0.030). Multivariable analysis showed that female sex (β = -1.89; p = 0.021) and a history of intravenous drug use (β = -4.78; p = 0.015) were independently associated with lower satisfaction with appearance (Table 5).

The median pain score at long-term follow-up was 1 (IQR 0 – 5) (Table 4). Factors associated with more pain in bivariate analyses were female sex (p = 0.033) and the type of NSTI (p = 0.041). Multivariable analysis showed that female sex (β = 1.55; p = 0.035) and type I or III NSTIs compared to type II (β = 3.06; p = 0.004) were independently associated with higher pain scores (Table 5).

Discussion

This study assessed the long-term outcomes of NSTIs of the upper extremity after successful discharge from the hospital. In surviving patients, the HRQoL, function, pain and satisfaction with appearance scores after NSTIs of the upper extremity were highly variable.

In total, 19% of the NSTI patients died during the follow-up interval of 6.5 years after hospital discharge, while the average age of this population was 48 years. Worse health at baseline (e.g. ASA III or IV, diabetes mellitus, history of malignancy) appears to not only predict the risk at short-term mortality, but also predicts an increased risk at early mortality after hospital discharge [5,6]. Light et al. reported an even higher rate of secondary mortality in a NSTI cohort without limitation on body region. They found a 25% mortality rate within the first 3.3 years after hospital discharge, which increased with the number of comorbidities and age [13]. They found that the cause of secondary death was more common infection-related compared to the cause of death in the general population (14% vs. 2.9%) [13]. The phenomenon of a high secondary mortality is also seen in other populations with

critical illnesses [31]. For example, a mortality rate of 50% was seen in ICU patients within the first 10 years after hospital discharge [32].

The HRQoL after NSTIs has only been assessed in four prior studies (one qualitative and three quantitative studies with respectively 4.2, 3.2, 4.1 and 5 years follow-up and similar sample sizes ranging from 19 to 56 participants) [14,33–35]. The biggest differences between these studies and ours are either the study design (qualitative vs. quantitative) or the study population (NSTI of all body regions vs. upper extremity NSTIs). Pikturnaite et al. reported an overall SF-36 score of 65.8, while Gawaziuk et al. reported a SF-36 PCS score of 36.7 and a SF-36 MCS score of 44.6 [14,35]. Suijker et al. found a PCS score of 43.8 and a MCS score of 53.3 [34]. The previously reported overall SF-36, PCS and MCS score for NSTIs affecting all body regions are lower than the scores found in our study specifically assessing NSTIs of the upper extremity, which were respectively 80.0, 48.7 and 55.3. Based on this comparison, it could be hypothesized that NSTIs of the upper extremity have less consequences for the eventual HRQoL compared to NSTIs affecting other body regions [14,35]. It is possible that NSTIs of the upper extremity have a more favorable anatomical location for aggressive debridement and reconstruction as needed. This theory is supported by the worse EQ-VAS score measured in this study in NSTI patients with involvement of other body regions besides the upper extremity. However, additional studies would be required to confirm this supposition.

The overall SF-36 score and MCS score in this study are both higher than the estimated scores of the overall United States population [25,26]. Mental HRQoL has been related to the level of confidence with appearance, which was scored relatively high in our study, possibly explaining this finding. Nonetheless, the PCS score was lower than the United States population score [25,26] Physical HRQoL is mainly related to the TBSA affected by the NSTIs, the remaining amount of pain and energy level [14,35]. Hakkarainen et al. performed qualitative interviews with survivors, who also reported that their quality of life was especially affected by ongoing pain and restricted physical function [33]. This is comparable to the results of our surveys, where limitations in physical function and relatively high pain and discomfort scores were frequently reported.

Our cohort consisted of a fairly large number of patients with a history of intravenous drug use, which is not uncommon since intravenous drug use is a known cause of (extremity) NSTIs [4]. Remarkable, patients with a history of intravenous drug use and NSTIs of the upper extremity report worse overall HRQoL. In theory, these patients should have a less complicated disease course since they are often younger, have less comorbidities, require fewer debridements and have a shorter hospital stay [36]. However, patients with a history of intravenous drug use are also known to have a preexistent lower HRQoL [37]. Unfortunately, we were unable to

measure changes in HRQoL, since we could not obtain HRQoL prior to the NSTI due to the acute setting of the infection requiring immediate treatment.

In this study, type I and III NSTIs result in worse functional outcomes and higher pain scores at long-term follow-up. Worse general health and social functioning for type I NSTIs compared to type II NSTIs has previously been reported [34]. Type II NSTIs seem to have a better long-term prognosis compared to type I and III, while it is theorized that the acute phase of type II NSTIs is often more fulminant [5]. A previous study found that involvement of anaerobic bacteria (e.g. *Bacteroides* spp. and *Clostridium* spp.), which is common in type I and III NSTIs, could be associated with an increase in number of surgical revisions [38]. However, the number of reconstructive surgeries and type I or type III NSTIs were both independent variables associated with worse physical function in this study. It is possible that this finding results from a greater difficulty in identifying the required debridement margin caused by a less evident margin between healthy and infected tissue in especially type I and III infection. The differences in microbial etiology has been suggested to cause a different clinical presentation, perhaps also different intra-operative findings [1]. The more favorable long-term functional and pain outcomes achieved in patients with type II NSTIs might also be explained by the fact that these patients are known to be younger and to have less comorbidities, what might contribute to the ability of these patients to rehabilitate better [1].

The results of this study should be interpreted in the context of its limitations. First, responder bias might be present. Responders with relatively good outcomes after hospitalization might have been more likely to participate. Assessment of the generalizability of the answers of the responders showed that the responders and non-responders had a comparable disease course, but the responders were overall healthier at baseline. Second, the exact date and cause of death was unknown for most patients, preventing us to draw conclusion about the exact relationship between the previous NSTI and the possible shorted life spam. To understand better which factors predispose secondary mortality after NSTIs and how to prevent it, a prospective study with monitoring of date and cause of death is necessary. Third, the number of patients deceased during the follow-up period might be even larger than presented in this study, since it had to be recorded in our electronic medical record system that the patient was deceased. Finally, this study is limited by the retrospective collection of data on the hospital course. The major strength of this study is that this study is to date the biggest and most detailed study assessing outcomes of NSTIs of the upper extremity after survival of the initial hospitalization and the only NSTI study reporting EQ-5D-5L scores.

Conclusion

We found that worse health at baseline, amputation as management for the NSTI and discharge to a rehabilitation facility were associated with an increased risk of secondary mortality. In surviving patients, the HRQoL, function, pain and satisfaction with appearance scores after upper extremity NSTIs varied widely, but were adversely affected by female sex, intravenous drug use, NSTI subtype I and III, and longer length of hospital stay.

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Appendix 1 Results of 36-Item Short Form Survey of patients with previous necrotizing soft tissue infections of the upper extremity

	Responders n = 38 Median (IQR)	US population-based Mean ± SD[a]
Overall SF-36 score	80.0 (58.2 – 91.1)	76.8 ± 22.9
Physical functioning	90 (75 – 100)	84.5 ± 22.9
Limitations due to physical function	100 (25 – 100)	81.2 ± 33.8
Bodily pain	85 (58 – 90)	75.5 ± 23.6
Global health perception	75 (45 – 90)	72.2 ± 20.2
PCS score	48.7 (42.2 – 55.3)	50 (95% CI 49.8 – 50.2)
Vitality	65 (50 – 75)	61.1 ± 20.9
Social function	100 (75 – 100)	83.6 ± 22.4
Limitations due to emotional health	100 (33 – 100)	81.3 ± 33.0
General mental health	84 (68 – 88)	74.8 ± 18.0
MCS score	55.3 (41.5 – 57.7)	50 (95% CI 49.8 – 50.2)

[a] The eight category mean scores of the US population are based on study by Grassi et al. (Dimensionality and summary measures of the SF-36 v1.6. Value Health. 2010;13(4)) and the PCS and MCS scores on study by Jenkinson (Comparison of UK and US methods for weighting and scoring the SF-36 summary measures. J Public Health Med. 1999;21(4)).

Abbreviations: IQR = InterQuartile Range; MCS = Mental Components Summary; PCS = Physical Components Summary; SD = Standard Deviation; SF-36 = 36-Item Short Form.

Appendix 2 Results of EQ-5D-5L survey for patients with previous necrotizing soft tissue infections of the upper extremity

		n (%)	Median (IQR)[a]	US population-based mean[b]
Overall EQ-5D-5L		36 (100)	1.4 (1.2 – 2.2)	0.853
Mobility	No problems	27 (71)	1 (1 – 2)	0.193
	Problems	11 (29)		
Self-care	No problems	26 (68)	1 (1 – 2)	0.037
	Problems	12 (32)		
Usual activity	No problems	20 (53)	1 (1 – 2)	0.183
	Problems	18 (47)		
Pain/Discomfort[c]	No problems	11 (30)	2 (1 – 3)	0.480
	Problems	25 (69)		
Anxiety/ Depression[c]	No problems	23 (62)	1 (1 – 2)	0.224
	Problems	14 (38)		
EQ-VAS		36 (100)	77 (67 – 90)	79.33

[a] The EuroQol-5D scores every topic on a scale of 1 to 5, with 1 being no problems and 2 to 5 being scores ascending in discomfort/ disability/complaints. The median provided here is the mean score on the 1 -5 scale; [b] Population norms from Szende A, Williams A. Measuring Self-Reported Population Health: An International Perspective based on EQ-5D. Eq-5D. 2004; [c] 1 missing case.
Abbreviations: EQ-5D-5L = EuroQol-5 Dimensional -5 Levels; EQ-VAS = EuroQol-Visual Analog Scale; IQR = Interquartile Range.

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Necrotizing soft tissue infections, the challenge remains

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Abstract

Background: Necrotizing Soft Tissue Infections (NSTIs) are uncommon and rapidly spreading infection of the soft tissues for which prompt surgical treatment is vital for survival. Currently, even with sufficient awareness and facilities available, ambiguous symptoms frequently result in treatment delay.

Objectives: To illustrate the heterogeneity in presentation of NSTIs and the pitfalls entailing from this heterogeneity.

Discussion: NSTI symptoms appear on a spectrum with on one side of the spectrum the typical critically ill patient with fast onset and progression of symptoms combined with severe systemic toxicity resulting in severe physical derangement and sepsis. In these cases, the suspicion of a NSTI rises quickly due to its typical and notorious presentation. On the other far side of the spectrum is the less evident type of presentation of the patient with gradual but slow progression of non-specific symptoms over the past couple of days without clear signs of sepsis initially. This side of the spectrum is underrepresented in current literature and some physicians involved in the care for NSTI patients are still unaware of this heterogeneity in presentation.

Conclusion: The presentation of a critically ill patient with evident pain out of proportion, erythema, necrotic skin and bullae is the classical presentation of NSTIs, which should be recognized by all care providers. On the other hand, nonspecific symptoms without systemic toxicity at presentation frequently result in a battery of diagnostics tests and imaging before the treatment strategy is determined. This may result in a delay in presentation (patient seeking medical aid), delay in diagnosis and delay in definitive treatment. This failure to perform an adequate exploration expeditiously can result in a preventable mortality.

Introduction

Necrotizing soft tissue infections (NSTIs) are an ancient challenge, considering that Hippocrates first described the infection in the 5th century BC. He reported the following clinical observation "many even while undergoing treatment suffered from severe inflammation, and the erysipelas would quickly spread widely in all directions. Flesh, sinews and bones fell away in large quantities … there were many dead" [1]. The disease Hippocrates described as "erysipelas all over the body" later became known by a broad range of names, such as "the flesh-eating infection", necrotizing fasciitis, Fournier gangrene and severe necrotizing soft tissue disease (SNSTD) [2–4]. All of those terms for this uncommon, rapidly spreading, progressive and potentially lethal infection of the soft tissues are currently represented in the internationally accepted term necrotizing soft tissue infection (NSTI) [5,6]. The incidence of NSTIs in the United States is estimated to be 4.0 to 10.3 per 100,000 person-years, while the incidence of the Dutch population, probably comparable to most European countries, is 1.1 – 1.4 per 100,000 person-years [7,8]. Unfortunately, the statement of Hippocrates that many died, remains current. Even though the mortality rates were decreased by half over the past decades, the last two decades the mortality rate for NSTIs remained unchanged, at approximately 20% [9,10]. Two recent meta-analyses reported that prompt surgical treatment is vital for further reduction of mortality [9,11]. However, even with sufficient awareness and facilities available, ambiguous symptoms may still result in delay, perhaps even more so when compared to a patient presenting critically ill [12,13]. In fact, NSTI are misdiagnosed initially more often than not due to pitfalls such as absence of fever, absence of cutaneous manifestations (table 1), intact skin in the area (no skin defect as entry), attributing pain to an injury or procedure, nondiagnostic/nonspecific imaging results, or ascribing the systemic signs to other causes [6,14]. Treatment delay is often preceded by a patient and/or diagnostic delay, which is thought to be even greater in case of first presentation with ambiguous symptoms [14]. As Hippocrates described, "Fever was sometimes present and sometimes absent"; patients with NSTI present with variable signs and symptoms, and only a limited number of patients present with the classic symptoms [1,4,5].

Clinical perspective

To illustrate the heterogeneity in presentation, three patients from a database previously published by our study group are presented [18].

First, a 69-year-old female patient with rheumatoid arthritis, presented with a painful and swollen leg since that morning. In the evening, she started vomiting and presented to the hospital with swelling, erythema and blue-purple discoloration of the entire lower leg and two large bullae, was hypotensive (mean arterial pressure

Table 1 Presence of cutaneous or systemic symptoms of necrotizing soft tissue infections [6, 15 – 17]

Cutaneous symptoms	Soft tissue edema ("woody induration")	79%
	Erythema	70%
	Severe pain or tenderness - out of proportion to signs - crescendo pain	77%
	Skin necrosis	24%
	Crepitus	5%
Systemic symptoms	Tachycardia	74%
	Fever	46%
	Hypotension	25%

of 59 mmHg), had tachycardia, elevated lactate levels (2.9 mmol/L) and base deficit of 7 mmol/L. Within six hours of first onset of symptoms, she was taken to the operating room and diagnosed with a NSTI caused by group A streptococcus (GAS).

Second, 53-year-old male patients with chronic obstructive pulmonary disease presented with acute and progressive dyspnea for two days. As the patient's history was obtained, it was discovered that he had a swollen leg for four days, which the general practitioner previously diagnosed as a bursitis. Upon presentation, the patient already had severe tachypnea and tachycardia, was his entire leg swollen, pale and warm, and had a severe metabolic acidosis (base deficit -19 mmol/L, lactate 13.7 mmol/L). At the emergency department, he further deteriorated and was intubated. Due to uncertainty about the focus of the infection, a computed tomography (CT) scan was obtained which showed gas formation in the soft tissues of the upper leg. Consequently, the patient was taken to the operating room and a NSTI caused by multiple anaerobic and aerobic micro-organism was diagnosed.

Third, 68-year-old male patients with diabetes mellitus, hypertension and a previous kidney transplant presented with a swollen upper leg with localized erythema without tachycardia, tachypnea or hypotension. The patient reported having malaise since last week and to have erythema of the leg for two days. The symptoms were diagnosed as cellulitis and the patient was admitted. Over the next 24 hours the erythema and pain gradually increased, the patient developed dyspnea and tachycardia and developed a metabolic acidosis (base deficit 6.9 mmol/L, 3.9 mmol/L at presentation). The patient was eventually taken to the operating room and a NSTI caused by an aerobic micro-organism was diagnosed.

Discussion

The outer ranges of the NSTI presentation spectrum

As described above, two sides of the NSTI presentation spectrum can be seen. On one side, the typical critically ill patient with fast onset and progression of symptoms (e.g. pain out of proportion, erythema, bullae) combined with severe systemic toxicity resulting in systemic inflammatory response syndrome (SIRS) and sepsis (patient 1). In these cases, the suspicion of a NSTI rises quickly due to its typical and notorious presentation. The response by care providers is all hands-on deck since the consequences, mortality and amputations, are well known. The sepsis protocol is immediately initiated and the patient is rapidly transported to the operating room without additional testing or imaging at the emergency department, since delay to the first debridement increases the need for subsequent debridements, as well as increases the risk at mortality [9,19–21]. On the other far side of the spectrum is the patient with gradual but slow progression of non-specific symptoms over the past couple of days without evident signs of sepsis initially. However, when these patients finally present, they can either deteriorate rapidly (patient 2) or may continue to deteriorate slowly (patient 3). This side of the spectrum is underrepresented in current literature and some physicians involved in the care for NSTI patients are still unaware of this heterogeneity in presentation. Both patient subtypes have the same severe infection, and both require immediate (surgical) treatment, but the challenge remains to treat them equally efficient.

Causes of variation in presentation

The precise cause of this misleading contrast in presentation remains unclear. Recent literature described differences in patient demographics between the different micro-organisms isolated from NSTIs [17,18,22]. This strengthens the hypothesis that the causative micro-organisms influences the different types of presentation, since the variance in early or late systemic toxicity was described to depend on the strain of bacteria and toxins produced [2]. Causative micro-organisms of NSTIs are generally categorized in three categories, based on the number of different micro-organisms found and less so the determination of the micro-organisms. Type I is polymicrobial and generally consists of various species of gram-positive cocci, gram-negative rods and anaerobes [2,10]. Type II is monomicrobial with GAS being the most common microbe found [18,23]. Recently an attempt was made to categorize specific strains of bacteria in their presentation, as Type III consists of more rare isolated microbes. Most commonly, this involves infections with the *Vibrio vulnificus or Clostridium* species. However, most authors still categorize them as type I due to it either being a gram-negative or anaerobic bacteria [2,10,17]. The frequency of presentation of each of these types differ across

geographical areas and populations, whereas *Vibrio* NSTIs are more often seen in Asia, GAS NSTIs more often in Europe and a relatively high frequency of methicillin-resistant *Staphylococcus aureus* NSTIs are seen in the United States [18,24,25].

Systemic toxicity of polymicrobial infections is most commonly dependent on the mechanism of microbial synergy and not necessarily on toxins. This process requires time and does not immediately cause a fulminant presentation of NSTIs as mainly seen in type II NSTIs. Micro-organisms causing monomicrobial infections do not require synergy. They frequently are able to produce (multiple) toxins on their own, causing rapid systemic toxicity [26]. Generally, physicians associate NSTIs with early systemic toxicity due to its rapidly progressive and destructive character. However, this is mostly exemplary for NSTI based on GAS, *Clostridium* spp. and *Vibrio* spp., while in most polymicrobial NSTIs signs of systemic toxicity commonly occur late [2,27]. Compared to type I NSTIs, patients with type II NSTIs tend to be younger, healthier and more commonly have a history of trauma, surgery or IV drug use as causative event [2,18]. Patients with type I NSTIs usually have more and severe comorbidities (such as diabetes mellitus, peripheral vascular disease, chronic renal failure) [2,6,18]. This could indicate that especially younger and healthier patients present with early systemic toxicity, while notable the older patients with severe and/or multiple comorbidities present with late systemic toxicity and have a higher risk of expiring [3,18,23,28]. Therefore, the absence of systemic toxicity can be misleading, but should be kept in mind as diagnostic pitfall.

Types of delay due to variation in presentation

Patient delay: Patients without signs of sepsis and indifferent symptoms will less urgently seek medical care, causing patient delay and therefore treatment delay. On the other hand, patients with high fever, low blood pressure and high heart rates are likely to rush to the emergency department.

Diagnostic delay: Furthermore, when critically ill patients present, they will receive priority for diagnostic tests and treatment. This is seen in a study comparing GAS NSTIs with non-GAS NSTIs. In the study, 77% of the GAS NSTI patients had surgical exploration within 24h compared to 66% of the non-NSTI patients [18]. This suggests that GAS NSTIs, or type II NSTIs, are diagnosed earlier and therefore treated faster. It can be considered common practice that the critically ill patients are rapidly seen by (senior) consults, while the more stable patients are commonly first seen by the (less experienced) residents. Another source of delay, caused by a nonspecific presentation of a NSTI, is the physician does not recognize the severity of the presentation and first starts with a myriad of diagnostic tests and in some cases imaging. The use of imaging for diagnosis of NSTIs is controversial. Some studies advocate the use of imaging modalities, such as plain radiographs or CT scan. A

recent meta-analysis showed limited added value of imaging. In addition, imaging can significantly delay treatment due to waiting times for the scan itself and due to the time required for interpretation of the scans by a radiologist [16]. However, this can take up to several hours, which could be a significant proportion of the recommended maximum time from presentation to surgery for NSTIs [9,29,30]. One of the few situations in which it can be contemplated to order a CT scan, is when an abdominal source (e.g. gastro-intestinal fistulas to the abdominal wall) of the NSTI is suspected, since this would require intra-peritoneal source control [31]. Nonetheless, logistics for an emergency CT-scan should be optimal since imaging should not delay surgical consultation or intervention [5]. Delay to first debridement or inadequate first debridement increases mortality [9,11].

Treatment delay: Besides diagnostic delay, treatment delay can occur in case of ambiguous presentation without evident signs of sepsis, when patients are first seen by non-surgical specialties, causing tendency towards a non-surgical course of treatment. A recent review showed that 71.4% of the NSTIs are misdiagnosed on initial evaluation [14]. This misdiagnosis frequently results in a wait-and-see course of treatment with intravenous antibiotics, without surgical involvement for the vital source control [4,5].

Surgical consequences of variation in presentation

When the decision is made to transport the patients to the operating room, there are still certain pitfalls to avoid during surgical exploration. First, skin, subcutaneous tissue, fascia and the muscle deep to the fascia must all be examined. In 57% of the NSTI cases, findings such as grey necrotic tissue, dishwater pus, and lack of bleeding or tissue resistance will be seen upon first evaluation of the soft tissues, which evidently confirms the diagnosis NSTI [3]. However, in the other 43%, only ambiguous findings are seen upon macroscopic evaluation. In these cases, the algorithm of triple diagnostics might be of added value. This algorithm indicates that in case of nondiagnostic macroscopic findings, a Gram stain and a fresh frozen section of a full-thickness incisional biopsy are intra-operatively assessed [10,32–35]. However, in case of a less strong indication for surgical exploration, based on an indifferent presentation and therefore only moderate suspicion for NSTI, the surgeon might be tempted to perform a less invasive exploration with a smaller and/or more superficial incision. This will result in only partial evaluation of the tissue layers and increases the odds that, based on this (limited) macroscopic evaluation, it is wrongfully discarded as a non-necrotizing infection without additional (microscopic) testing such as histopathological or Gram stain assessment [32]. While in case of a critically ill patients without evident macroscopic signs, it is more likely that the surgeon would want more reassurance intra-operatively.

Additionally, the skin sparing approach for debridement is increasing in popularity due to its reconstructive advantage. A recent cohort study showed no increase or reduction in mortality or in post-operative complications when skin spared debridement is performed. However, 85% of the patients in this study were transferred from outside hospitals indicating that these patients were stable enough to survive a significant delay caused by transfer [36]. Surgeons must be aware that, although results seem promising, this approach should not result in delay in source control or resuscitation.

Conclusion

NSTI have a heterogeneous presentation with a spectrum ranging from the classical presentation of a critically ill patient with evident pain out of proportion, erythema, necrotic skin and bullae, which should be recognized by all care providers. While on the other side of the spectrum are the nonspecific symptoms without systemic toxicity at presentation which frequently result in a battery of diagnostics tests and imaging before the treatment strategy is determined. This results in a delay in presentation (patient seeking medical aid) and delay in diagnosis and delay in definitive treatment. Confirmatory diagnosis of NTSI should occur in the operating room (not the radiology suite) with adequate exploration of all layers of areas of concern. Failure to perform an adequate exploration expeditiously can result in a preventable mortality.

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12

Summary, discussion and future perspectives

This thesis encompasses almost all facets of necrotizing soft tissue infections (NSTIs): from the current incidence and mortality within the Netherlands, the recommendation and validation of triple diagnostics to improve the diagnostic process, the confirmation that a NSTI is indeed a time-sensitive disease, to which factors (patient, disease and treatment related) predict mortality, loss of limb, quality of life and long-term satisfaction including aesthetics. It describes and demonstrates the essence of the treatment of NSTIs, which consist of early recognition, diagnosis without unnecessary delays, immediate administration of intravenous broad-spectrum antibiotics, prompt surgical treatment with adequate debridement of all infected and necrotic tissue and resuscitation in case of septic shock. These principles combined lead to lower mortality rates and shorter intensive care and hospital stays, giving NSTI patients an increased chance of satisfactory quality of life with good cognitive and physical function and the ability to focus more on the optimization of (objective and subjective) aesthetics.

NSTIs are known for their rarity, but mostly notorious for their rapidly progressive nature and the mutilating surgical treatment required for survival. As we demonstrated, the incidence of NSTIs with respectively 1.1 – 1.4 cases per 100,000 person-years (193 - 238 per year) in the Netherlands is relatively low compared to other countries such as the United States and Thailand with 4.0 – 10.3 cases per 100,000 person-years and 32.6 cases per 100,000 person-years respectively [5,6,29,30]. Furthermore, as seen in chapter 2, in the Netherlands NSTIs are still associated with a mortality rate of 23 to 29%, which is similar to the pooled mortality rate based on recent international literature of the past decade (18 – 21%) from chapter 7 [29,31,32].

Our study in chapter 3 showed that most patients (62%) died as a direct result of the infection (e.g. non-survivable dissemination of the infection or severe sepsis), but withdrawal of care is in our country also a common made decision (38%) after carefully weighing the proportionality of the treatment and prognosis with the patient and its family, especially in elderly patients with already severe pre-existing comorbidities [32]. Multiple patient characteristics have previously been linked to an increased risk at mortality in case of a NSTI, with the most common reported predictor being the patient's physical status. Specific comorbidities, such as a history of malignancy, kidney failure and liver cirrhosis, have been associated with higher mortality rates in NSTI patients, but also the American Association of Anesthesiologist (ASA) classification, commonly used to assess a patients overall pre-operative physical status, has been described as a predictor for mortality [6,32–37]. Although, younger patients previously considered healthy (no or only minor comorbidities) still have a mortality rate of 10% [32].

Knowing which patients are especially at risk for mortality aids patient-centered decision making by providing the patient with a realistic prognosis regarding how successful or futile the treatment is expected to be, which also weighs in a patient's desire to receive life supporting care. However, survival does not guarantee satisfying quality of life and it should be kept in mind that patients who do survive still sometimes have to learn to live with extensive scars and that they have a serious chance of having an amputated limb, which might be deemed necessary to achieve source control. Within the Netherlands, the amputation rate for all NSTI patients was 11-14% during the past decade [29]. From the review of 109 NSTI studies described in chapter 7, a pooled amputation rate of 9% was calculated for all NSTI patients, but more specifically, this rate is 19% for patients with a NSTI affecting an extremity [31]. Furthermore, patients with NSTIs often have a lengthy hospital stay and in a majority of the cases intensive care admission is required, which leads in combination with the necessity of multiple (reconstructive) surgeries to described mean health care costs of at least €42,000 per patient in the United States and Australia [5,38].

Adjuvant diagnostics: valuable tools or source of delay and false confidence

Before a NSTI can be adequately treated, the accurate diagnosis has to be made. Diagnosing NSTIs early on and based on clinical signs can be extremely tricky due to the absence of pathognomic symptoms [12,28,39]. The most common symptoms are soft tissue edema, erythema and pain, which are very nonspecific and are also common symptoms of less severe soft tissue infections not requiring surgery, such as cellulitis and erysipelas [2,12,28,39]. Cutaneous signs such as bullae, crepitus or skin necrosis are only seen in a minority of cases and are mostly late signs indicating progressed dissemination of the infection through multiple soft tissue layers and affecting vascular components of the skin and subcutaneous tissues [1,2,12]. Most physicians are aware of the notorious and typical presentation of a NSTI: the critically ill patients with fast onset and progression of cutaneous symptoms combined with pain out of proportion and severe systemic toxicity resulting in a septic patient. In case of these patients, NSTIs is likely to be quickly suspected, the surgeon immediately asked for consultation and treatment is promptly initiated [25]. However, on the other side of the presentation spectrum of NSTIs is the patient with gradual but slow progression of nonspecific symptoms over the past couple of days with initially no evident signs of sepsis, and therefore NSTIs is often not recognized in this patient. These patients can either deteriorate rapidly or continue to deteriorate slowly [15,40]. The heterogeneity in presentation is hypothesized to be caused by the difference in causative micro-organisms. For example monomicrobial infection (e.g. Group A Streptococcus) are known to cause rapid systemic toxicity by the production of toxins, while polymicrobial infections relay on microbial synergy,

a process that requires more time, resulting in a slower progression of the infection [3,40,41]. This lack of pathognomic symptoms combined with the heterogeneity in presentation complicates early recognition of NSTIs by resulting in high rates of missed and/or delayed diagnoses [14,15].

To improve the diagnostic process of NSTIs, three different diagnostic adjuncts are the main focus of current research papers on NSTIs, being diagnostic scores, imaging studies or intra-operative diagnostics.

First, the most well-known diagnostic score with as aim to differentiate NSTIs from non-NSTIs is the Laboratory Risk Indicator for NECrotizing fasciitis (LRINEC) score, which is widely advocated in literature. This score consists of 6 laboratory parameters: c-reactive protein (CRP), hemoglobin, leukocytes, sodium, creatinine and glucose. A score of ≥ 6 is considered intermediate risk of a NSTI and a score of ≥ 8 indicates a high risk. The initial study proposing the LRINEC score reported a great sensitivity (90%) and specificity (97%), but validating studies were unable to achieve such good results [17]. Fernando et al. performed a large meta-analysis and found a sensitivity of 68% and specificity of 85% [39]. Also within the studies in this thesis, patients with proven NSTIs regularly had a LRINEC score below the cut-off point for suspicion of a NSTIs [32,37,42]. Other study groups have proposed modified or new scores to replace the LRINEC score, but results are mediocre at best and often not externally validated [43–45].

Second, imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasounds, are increasingly proposed [18–21,25]. However, the extra confirmation physicians try to obtain by ordering imaging studies may give false confidence, or can have adverse consequences by significantly delaying treatment caused by the logistics surrounding ordering, executing and interpreting the imaging studies thus potentially increasing mortality rates [39,40,46]. However, in case of a suspected intra-abdominal source of the NSTIs, a pre-operative CT-scan can provide valuable information regarding the source of the infection enabling adequate source control [47].

Finally, intra-operative diagnostics have been proposed to facilitate early diagnosis of NSTIs [22]. Intra-operatively assessed frozen sections are one of those options [48]. Frozen sections are standard diagnostic tests within surgical oncology but are not yet widespread or routinely used during emergency surgeries. As described in chapter 6, frozen sections enable diagnosing NSTIs which are not yet macroscopically evident. Histopathological findings such as bullae, severe fascial inflammation and/or fascial necrosis can make a NSTIs more or less likely. Findings such as muscle edema, severe muscle inflammation and/or necrosis, capillary thrombosis and vasculitis are distinctly seen in NSTIs [48]. Due to the potentially

limited experience of pathologists with and the limited research upon the use of frozen sections for NSTIs, frozen sections cannot yet be used as independent test [23,24,48,49]. However, frozen sections as part of the triple diagnostics algorithm (figure 1) for ambivalent cases of NSTIs is investigated in this thesis (chapter 5). Implementation of the triple diagnostic algorithm resulted in a relatively low mortality (11% mortality directly related to NSTIs) and amputation rate (4%), but also showed that it resulted in earlier diagnosis and shorter intensive care unit stays when only microscopic necrosis was presence, while no differences were seen in baseline laboratory or vital parameters between patients with only microscopic necrosis or patients with already macroscopic necrosis [42,50]. These results stress the need for additional (microscopic) testing in cause of ambivalent symptoms to facilitate prompt and adequate treatment by preventing false-negative explorations.

Treatment: no time to lose!

NSTI is a time sensitive disease requiring early diagnosis and prompt surgical debridement of all infected tissues to prevent further dissemination of the infection and lower systemic toxicity by lowering the microbial load. Furthermore, other key pillars of the treatment of NSTI are broad-spectrum intravenous antibiotics and adequate resuscitation of septic patients (one third of the patients presents septic) [25,32]. We demonstrated in Chapter 7 that time from presentation to surgical treatment is vital for reducing mortality rates, as surgery within six hours after presentation is strongly recommended and surgery within twelve hours is mandatory to obtain favorable outcomes [31]. However, achieving surgical treatment within the “golden” time frame for this relatively rare disease might not always be achievable within daily clinical practice, partially since the problem of treatment delay is multifactorial. First, patient delay refers to the time frame between onset of symptoms to presentation. Not all patients immediately seek medical care, potentially due to unawareness of the severity of the situation or the nonspecific symptoms, especially in absence of signs of systemic toxicity [40]. Furthermore, the likelihood of a patient seeking medical care is also influenced by multiple other clinical, economic, and social factors, among which physical or financial access to medical care [51]. Second, the aforementioned diagnostic process needs to be optimal in order to prevent diagnostic delays. Diagnostic adjuncts should be used wisely and with caution, and physician’s suspicion for, and awareness of, NSTIs should be sufficient enough, even if a patients presents to a nonsurgical specialty [15,40]. Third, the appropriate logistics need to be in place to limit treatment delay, such as immediate availability of a surgeon, operating room staff and resources [52].

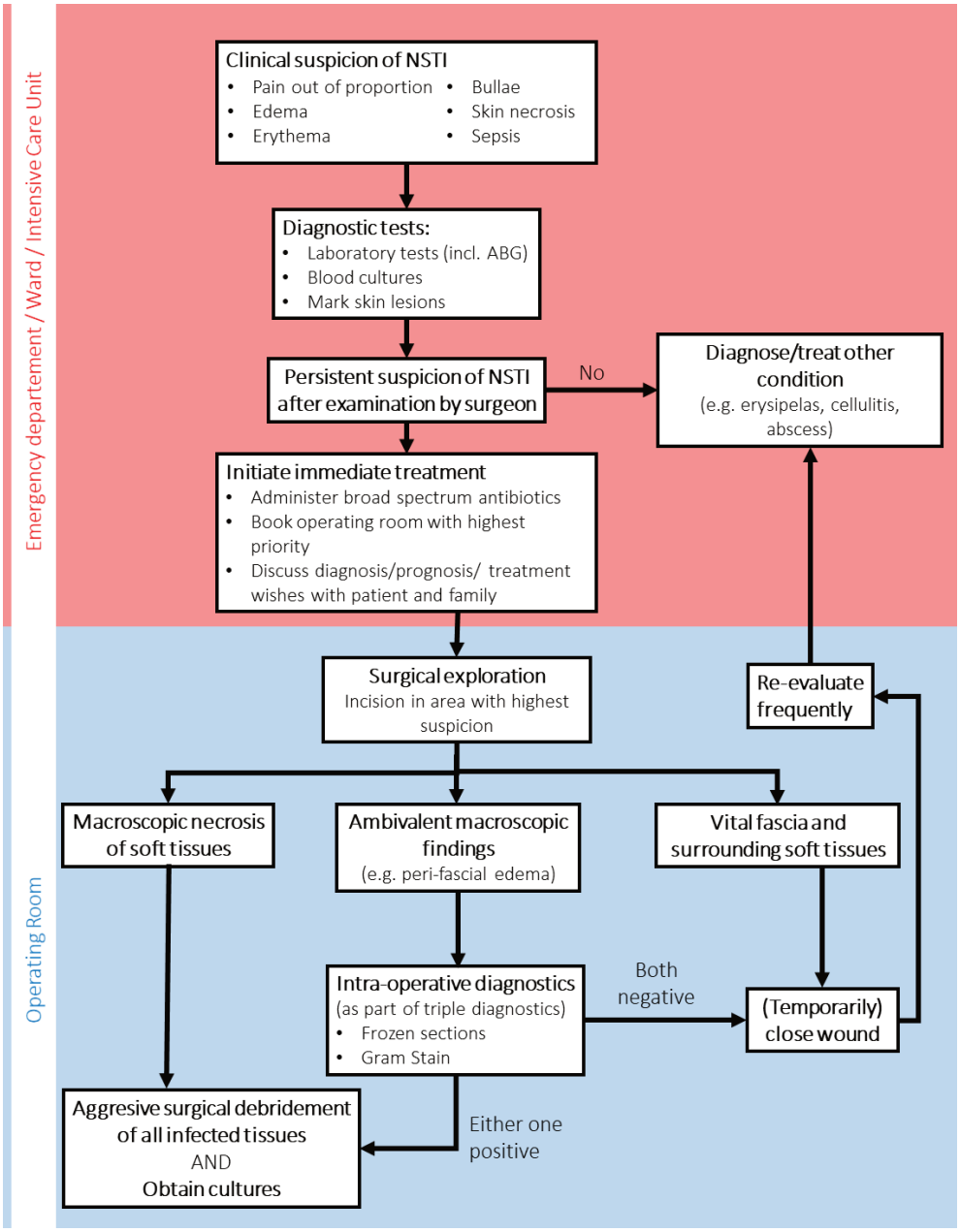

Figure 1 The triple diagnostics algorithm for necrotizing soft tissue infections

Besides time to treatment, the essence of time also applies to the length of the initial surgical debridement. This phenomenon is well established in trauma and emergency surgery: prolonged operating times lead to higher complication rates and longer ICU and hospital stays [53–55] . As seen in chapter 8, prolonged operative times lead in NSTI patients to prolonged intensive care and hospital stays, even corrected for the presence of sepsis prior to surgery, the total body surface area affected and the ASA classification [50]. Therefore, the goal for NSTIs remains adequate and rapid source control, but also to do no further harm by limiting further physiological derangement caused by prolonged operative times.

Giving a podium to a rare disease: the power of numbers and the lack thereof

Studying NSTIs entails certain challenges, mostly caused by the low incidence of the infections. With an annual incidence of 193-238 cases per year in the Netherlands as seen in chapter 2, not many patients are easily available for inclusion in studies resulting in limited sample sizes, causing underpowered studies [29]. Furthermore, currently NSTIs are often studies as one group of patients regardless of the heterogeneity in presentation and associated treatment of these infections, mostly as a result of the scarcity of patients. The diagnostic term “NSTI” composes a very heterogenous group of infections, for instance affecting different areas of the body and are caused by a broad range of different micro-organisms. For example, NSTIs affecting the genital area (also known as Fournier’s gangrene) are almost always caused by polymicrobial infections, while NSTIs of the neck (also known as Ludwig’s angina) are mainly monomicrobial infections caused by Group A Streptococci, NSTIs affecting the lower extremity are almost always caused by monomicrobial infections and affect relatively young patients, and NSTIs affecting the trunk are commonly seen in elderly patients [3,36,37,56,57]. Ideally, these subtypes of NSTIs would be investigated separately, as was done for the Group A Streptococcal NSTIs (chapter 4) and NSTIs affecting upper extremity (chapter 9 and 10) within this thesis. This showed that outcomes differ between pathogens and affected body regions; Group A Streptococcal NSTIs have lower mortality rates compared to NSTIs caused by other micro-organisms, and upper extremity NSTIs have lower mortality rates, are more often monomicrobial infections and seem to have a better quality of life after the infections compared NSTIs affecting other body regions [36,37,58].

A substantial part of the current body of NSTI knowledge is mainly based on case reports or cohort studies with very limited sample sizes or limited scientific quality, making it difficult to truly apply evidence-based decision making to the clinical practice when diagnosing or treating NSTIs. To improve the quality of NSTI studies, this thesis provides some strategies to enhance sample sizes to achieve sufficiently powered studies. In chapter 2, multiple nationwide data sources (financial database, notable diseases database and previous published studies) were combined to

establish the nationwide incidence of NSTIs in the Netherlands by obtaining the population size [29]. Vital for this strategy to work is unanimous and consistent registration of NSTI patients within diagnosis thesauri, procedural thesauri, hospital imbursement systems and notorious disease registries. Currently, there is no International Classification of Disease (ICD) code or Diagnosis Treatment Combination (DBC) code for NSTIs, only for fasciitis necroticans and Fournier's gangrene and therefore not including necrotizing cellulitis or necrotizing myositis [59]. Registration of procedures is even more challenging, as demonstrated by the more than 400 different terms formulated for the surgeries performed to threat NSTIs encountered within a time frame of five years in the Netherlands (chapter 2) [29]. In chapter 7, a different approach was taken to summarize recent internationally literature by including 6051 patients in an elaborate meta-analysis of NSTI studies, which is one of the few meta-analysis on NSTIs [26,31,39,60]. In chapter 3, 4 and 8, a closer look was taken to hospital data. Moderate sample effects could be achieved by performing a multicenter region-wide study of all patients during the past ten years presenting to hospitals within the same acute care region by using a very broad search strategy within the hospital registration systems [32,36,50]. Finally, a prospective multicenter study called "Identification of Necrotizing Soft Tissue Infections" (iNSTInct) study has started to identify all patients with suspected NSTIs to improve the diagnostic process of NSTIs, since this can only be done with limited reliability in a retrospective manner due to inconsistent registration of patients with suspected NSTIs.

Future perspectives for improving outcome

Based on the number of patients who die regardless of adequate source control, or in who care was withdrawn based on pre-existing comorbidities and/or age in combination with disease severity, it is hypothesized that the absolute minimum mortality rate of NSTIs achievable in well-equipped countries lies around 7-10% when logistics, diagnostics process and treatment are all fully optimized [32]. This latter 10% is partially caused by all factors causing delay. Nevertheless, if the mortality has been decreased to this hypothesized minimum percentage achievable with current standard of care, it will create the opportunity to increase the focus on the other outcomes, such as further reducing amputation rates, improving functional outcome and improving aesthetics for example by skin sparing surgical techniques when possible. Although there is an increasing interest within the field of NSTI research on skin sparing operating techniques, a recent systematic review pointed out that the current available evidence is insufficient to conclude whether the skin sparing technique is superior or noninferior to en bloc debridement [61].

However, as seen in this thesis reducing the worldwide mortality still holds a high priority, as in most studies twice the mortality rates are found to what might be

achievable. Further research should focus on three aspects, mainly with the aim to decrease treatment delays. First, the number of patients presenting with dissemination of a NSTI beyond repair, indicating significant delay in presentation, should be reduced. This could be done by increasing the public's and general practitioners' awareness of this infection by educating them on when to suspect a NSTI. Furthermore, worldwide equal access to good health care (geographically and financially) should be facilitated to prevent patients being delayed or hindered from seeking appropriate medical care. In addition, fundamental research can also contribute to the reduction of patients with dissemination beyond repair by understanding the pathophysiology of NSTIs. For example, why certain micro-organisms can cause NSTIs and the relationship between the involved micro-organism and why certain patients present with severe dissemination.

Second, the diagnostic process needs improvement. This thesis shows that the triple diagnostics approach improves outcomes, but is only for patients with macroscopic uncertainty during surgical exploration. Other less invasive tools, such as diagnostics scores, could aid in the decision making of which patients to take to the operating room for exploration. This would require a large, sufficiently powered, prospective study of all patients with suspected NSTIs, such as the iNSTInct study. However, due to the rarity of the infections and the time sensitive setting in which a patient presents, this requires the availability of enough research resources to include and collect data directly upon presentation of all patients suspected with a NSTI for a longer period of time.

Third, treating NSTIs requires teamwork, as it requires a multidisciplinary approach with involvement of surgical specialties (e.g. general surgery, plastic surgery, urology, ophthalmology), intensivists, anesthesiologists, microbiologists and pathologists. In addition, rehabilitation care (physical, mental, nutritional) is essential to optimize outcomes. Collaboration is not only key within the clinical setting, but also for research on NSTIs. Collaboration between different hospitals intra- and internationally is vital to obtain large enough sample sizes to differentiate between symptoms, predictors and outcomes of NSTI subtypes.

Concluding, outcome improvement of NSTIs still has a long way to go, but this thesis takes some essential steps onto the road to providing the most optimal care for NSTI patients. In short, this thesis showed that NSTIs remain a rare infection with to date still high mortality and morbidity rates even in a well-equipped country such as the Netherlands. NSTI is a time-sensitive disease, but mortality rate could potentially be lowered to around 10% if prompt diagnosis (within 6 hours) is achieved, aided by triple diagnostics in ambivalent cases, followed by brief and efficient surgical exploration and debridement. Physicians should be aware of the high risk of unfavorable outcomes in elderly, patients with poor pre-existing physical status and

in case of non-Group-A-Streptococci NSTIs. Future NSTI research should therefore continue on this road by assessing the exact effect of the implementation of these findings in daily practice and can, if possible based on the mortality reduction, start looking beyond mortality as outcome towards functional and cosmetic optimization.

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Samenvatting, discussie en toekomstperspectieven

Dit proefschrift beschrijft bijna alle facetten van necrotiserende weke delen infecties (NWDI's): van de huidige incidentie en mortaliteit in de Nederland, de aanbeveling en validatie van triple diagnostiek om het diagnostisch proces te verbeteren, de bevestiging dat NWDI's tijdgevoelige infecties zijn, tot welke (patiënt-, ziekte- en behandelings-) factoren de mortaliteit, noodzaak tot amputatie, kwaliteit van leven en lange-termijn tevredenheid met uiterlijk voorspellen. In dit proefschrift wordt de essentie van de behandeling van NWDI's, bestaand uit vroege herkenning, spoedige diagnostiek zonder onnodige vertraging, onmiddellijke toediening van intraveneuze breedspectrum antibiotica, chirurgische behandeling middels debridement van al het geïnfecteerd en necrotisch weefsel, en resuscitatie van de septische patiënt, zowel beschreven als gedemonstreerd. Het combineren van deze hoekstenen van de behandeling leidt tot een lagere mortaliteit en kortere intensive care en ziekenhuisopnames, waardoor de kans op een redelijk tot goede kwaliteit van leven met goede cognitieve en functionele uitkomsten vergroot wordt en de focus meer kan verschuiven naar het optimaliseren van het (objectieve en subjectieve) esthetisch resultaat.

NWDI's staan met name bekend als zeldzame infectie, maar zijn vooral berucht door de snelle verspreiding van de infectie en het mutilerende karakter van de benodigde chirurgische behandeling om de infectie onder controle te krijgen. Zoals gedemonstreerd in hoofdstuk 2 is de incidentie van NWDI's in Nederland relatief laag met 1,1 tot 1,4 casussen per 100.000 personenjaren (193 – 238 per jaar), helemaal in tegenstelling tot andere landen zoals de Verenigde Staten en Thailand waarbij de incidentie respectievelijk 4,0 – 10,3 casussen per 100.000 persoonsjaren en 32,6 casussen per 100.000 persoonsjaren is [5,6,29,30]. In hoofdstuk 2 wordt echter gezien dat de mortaliteit van NWDI's in Nederland nog steeds erg hoog is (23 – 29%), wel is dit percentage vergelijkbaar met de, op basis van recente internationale literatuur, gepoolde mortaliteit gedurende het afgelopen decennia (18 – 21%), zoals beschreven in hoofdstuk 7 [29,31,32].

De studie in hoofdstuk 3 laat zien dat de meeste patiënten (62%) overlijden aan een direct gevolg van de infectie (bijv. niet overleefbare vergevorderde verspreiding van de infectie of ernstige septische shock), maar abstineren is in Nederland ook een frequent gemaakte beslissing (38%) na het zorgvuldig afwegen van de proportionaliteit van de behandeling en de prognose samen met de patiënt en familie. De beslissing om een abstinerend beleid te voeren wordt met name gemaakt bij oudere patiënten met reeds bestaande ernstige comorbiditeiten [32]. Meerdere patiëntkarakteristieken zijn eerder al gelinkt aan een verhoogd risico op overlijden bij NWDI's, waarbij de meest genoemde predictor de gezondheidstoestand van de patiënt van voor de infectie is. Specifieke comorbiditeiten, zoals maligniteit in de voorgeschiedenis, nierfalen en levercirrose, zijn al vaker direct gelinkt aan een

hogere mortaliteit bij NWDI patiënten, maar ook de American Association of Anesthesiologist (ASA) classificatie, een score die met name gebruikt wordt om de fysieke toestand van een patiënt preoperatief te beoordelen, is beschreven als predictor voor mortaliteit [6,32–37]. Desalniettemin, hebben jonge patiënten, die voor de NWDI altijd gezond zijn geweest, nog steeds een mortaliteit van 10% [32].

Weten welke patiënten met name in gevaar zijn om te overlijden aan de NWDI's helpt bij het geven van een realistische prognose te aanzien hoe succesvol of zinloos de behandeling mogelijk zal zijn. Hierbij is het belangrijk dat de behandelwensen van de patiënt worden meegenomen zodat er een behandelbeleid geformuleerd kan worden waarbij de individuele patiënt centraal staat. Echter moet niet vergeten worden dat het overleven van de NWDI geen garantie is voor een goede kwaliteit van leven erna en dat patiënten die overleven soms moet leren leven met uitgebreide littekens en in sommige gevallen moeten leren omgaan met een geamputeerde ledemaat. In Nederland werd namelijk in het afgelopen decennia bij 11 tot 14% van de NWDI patiënten besloten dat het noodzakelijk was een amputatie uit te voeren van een ledemaat om de infectie onder controle te krijgen [29]. In een review van 109 internationale NWDI studies werd een gepoolde amputatiepercentage van 9% gevonden voor alle NWDI patiënten, echter ligt dit percentage rond de 19% bij patiënten met een NWDI van een van de ledematen [31]. Daarnaast hebben patiënten met NWDI's vaak langdurige ziekenhuisopnames en in de meerderheid van de gevallen is een intensive care opname nodig, dit leidt samen met de meerdere benodigde (reconstructie)operaties tot ziekenhuiskosten van gemiddeld €42.000,- per patiënt zoals beschreven in Amerikaanse en Australische literatuur [5,38].

Aanvullende diagnostiek: waardevolle hulpmiddelen of reden van vertraging en valse gevoel van zekerheid

Voordat een NWDI adequaat behandeld kan worden, moet eerst de juiste diagnose gesteld worden. Het vroeg diagnosticeren van NWDI's en het diagnosticeren van NWDI's gebaseerd op klinische symptomen is extreem moeilijk wegens de afwezigheid van pathognomische symptomen [12,28,39]. De meest voorkomende symptomen zijn oedeem, erytheem en pijn, echter zijn deze symptomen weinig specifiek en ook veel voorkomende symptomen bij minder ernstige weke delen infecties die geen chirurgische behandeling nodig hebben, zoals cellulitis en erysipelas [2,12,28,39]. Huidafwijkingen, zoals bullae, crepitaties of huidnecrose worden maar in de minderheid van de gevallen gezien en zijn late symptomen wijzend op gevorderde verspreiding van de infectie naar meerdere weke delen lagen en wijzend op aantasting van de vascularisatie van de huid, subcutis en/of spieren [1,2,12]. De meeste artsen zijn bewust van de beruchte en typische presentatie van NWDI's: de ernstig zieke patiënt met een acuut begin van klachten met daarbij snelle

uitbreiding van de huidafwijkingen gecombineerd met pijn buiten proporties en eventueel sepsis door de ernstige systemische toxiciteit als gevolg van de infectie. Bij deze presentatie wordt een NWDI snel vermoed als mogelijke oorzaak van de klachten waarop de chirurg met spoed in consult wordt gevraagd en de behandeling snel gestart wordt [25]. Echter, de andere kant van het presentatiespectrum van NWDI's is de patiënt met geleidelijke, maar langzaam toenemende aspecifieke klachten gedurende meerdere dagen zonder evidente aanwijzingen voor sepsis. Deze NWDI patiënten worden vaak niet of laat gediagnosticeerd, echter zullen deze patiënten of heel snel of langzaam progressief verder achteruitgaan als de infectie onbehandeld blijft [15,40]. Deze heterogeniteit in presentatie wordt gedacht veroorzaakt te worden door de verschillende micro-organismen die een NWDI kunnen veroorzaken; monomicrobiële NWDI infecties (bijv. Groep A Streptokokken) staan er om bekend om snelle systemische toxiciteit te kunnen veroorzaken door de productie van verschillende toxines, terwijl polymicrobiële NWDI infecties vaak afhankelijk zijn van microbiële synergie, een proces dat meer tijd nodig heeft waardoor er mogelijk een langzamere progressie van klachten optreedt [3,40,41]. Het gebrek aan pathognomische symptomen gecombineerd met deze heterogeniteit in presentatie maakt vroege herkenning van NWDI's moeilijk, met als gevolg het veel voorkomen van gemiste of vertraagde diagnoses [14,15].

Om het diagnostisch proces van NWDI's te verbeteren zijn met name drie vormen van aanvullend onderzoek de voornaamste focus van de huidige wetenschappelijke artikelen over NWDI's, namelijk diagnostische scores, beeldvormend onderzoek en intra-operatieve diagnostiek.

Ten eerste, de Laboratory Risk Indicator for NECrotizing fasciitis (LRINEC) score is de meest bekende en in de literatuur veelvoudig beschreven diagnostische score om NWDI's te differentiëren van niet-NWDI's. De score bestaat uit zes bloedwaarden: c-reactief proteïne (CRP), hemoglobine, leukocyten, natrium, kreatinine en glucose. Een score van ≥ 6 wordt beschouwd als een intermediair risico op een NWDI's en een score van ≥ 8 als een hoog risico. De originele studie die de LRINEC score introduceerde beschreef een erg hoge sensitiviteit (90%) en specificiteit (97%), echter zijn validerende studies niet in staat deze goede resultaten te reproduceren [17]. Fernando et al. vond in zijn meta-analyse slechts een sensitiviteit van 68% en specificiteit van 85% [39]. In de studies in dit proefschrift werd ook vaak een LRINEC score lager dan 6 gevonden bij patiënten met uiteindelijk bewezen NWDI's [32,37,42]. Andere studiegroepen stellen daarom ook aangepaste of nieuwe scores voor om de LRINEC score te vervangen, echter vallen de resultaten daarvan tot op heden tegen en zijn vaak niet extern gevalideerd [43–45].

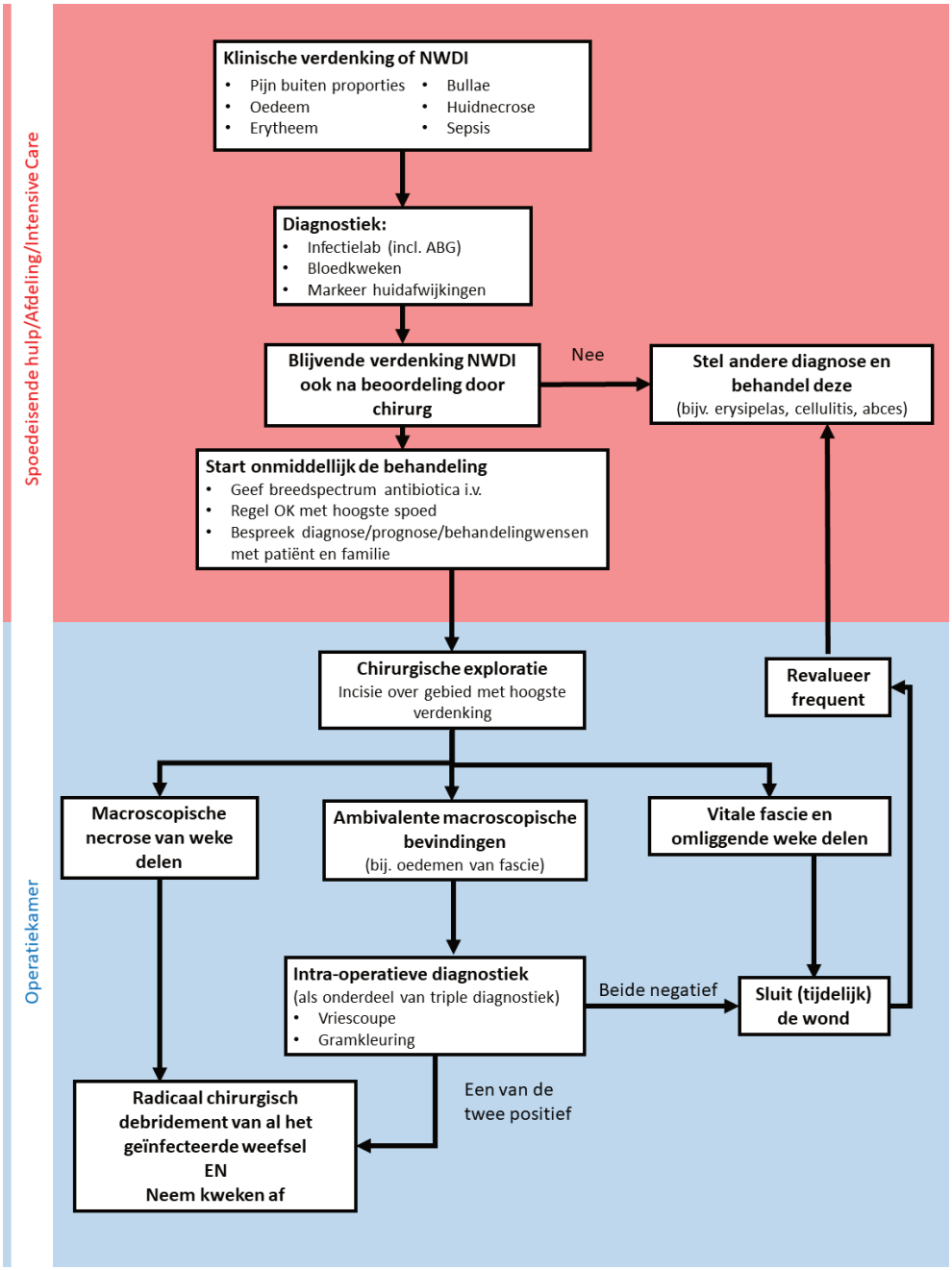
Ten tweede is er een toename van studies die beeldvorming, zoals computertomografie (CT), magnetic resonance imaging (MRI) en echo-onderzoek

voorstellen als aanvullende diagnostiek [18–21,25]. Echter kan de extra informatie die de arts probeert te verkrijgen middels het aanvragen van aanvullend beeldvorming leiden tot een onterecht gevoel van zekerheid wegens beperkte diagnostische waarden hiervan, of kan het mogelijk leiden tot ongewenste gevolgen, zoals een verhoogde mortaliteit door significante vertraging van de behandeling veroorzaakt door alle logistiek rondom het aanvragen, uitvoeren en interpreteren van deze beeldvorming [39,40,46]. Alleen bij de verdenking van een intra-abdominale focus van de NWDI kan een preoperatieve CT-scan mogelijk waardevolle aanvullende informatie opleveren ten aanzien van de oorsprong van de infectie en hoe dit het beste (chirurgisch) behandeld kan worden [47].

Ten slotte, intra-operatieve diagnostiek is reeds gesuggereerd als aanvullend onderzoek om al vroeg NWDI's te kunnen diagnosticeren of uit te sluiten [22]. Intra-operatieve beoordeling van vriescoupes is een van de intra-operatieve diagnostische opties [48]. Intra-operatieve vriescoupes worden al veelvoudig gebruikt bij oncologische chirurgie, echter worden ze nog niet standaard gebruikt bij spoedoperaties. Zoals beschreven in hoofdstuk 6 kunnen vriescoupes NWDI's diagnosticeren die macroscopisch nog niet evident zijn. Histopathologische bevindingen zoals bullae, ernstige ontsteking en/of necrose van de fascie, trombose van capillairen en vasculitis zijn kenmerkend voor NWDI's [48]. Door de mogelijk beperkte ervaring van pathologen met vriescoupes met de vraagstelling verdenking NWDI en de beperkte hoeveelheid wetenschappelijke studies naar het gebruik van vriescoupes voor het diagnosticeren van NWDI's, kunnen vriescoupes niet als alleenstaande diagnostische test gebruikt worden [23,24,48,49]. Daarom wordt in hoofdstuk 5 het gebruik van vriescoupes bij ambivalente NWDI's als onderdeel van het triple diagnostiek algoritme (figuur 1) onderzocht. Het implementeren van het triple diagnostiek algoritme leidde tot een relatief lage mortaliteit (11% mortaliteit direct gerelateerd aan de NWDI's) en amputatiepercentage (4%), maar ook leidde het vroeg diagnosticeren van NWDI's, waarbij alleen nog microscopische necrose aanwezig is, tot kortere intensive care opnames, terwijl er geen verschillen waren tussen de vitale parameters en bloedwaardes bij presentaties tussen patiënten met alleen microscopisch necrose en patiënten met reeds macroscopische necrose [42,50]. Deze resultaten benadrukken het belang van aanvullend (microscopisch) onderzoek bij ambivalente symptomen, zodat patiënten snel behandeld kunnen worden en vals-negatieve exploraties voorkomen worden.

Behandeling: geen tijd te verliezen!

Bij de behandeling van NWDI's is tijd van groot belang waarbij een snelle diagnose en chirurgisch debridement van al het geïnfecteerde weefsel voorop staat zodat



Figuur 1 Triple diagnostiek algoritme voor necrotiserende weke delen infecties

verdere verspreiding van de infectie voorkomen kan worden en de systemische toxiciteit verminderd wordt door het verlagen van de bacteriële lading. Andere hoekstenen van de behandeling van NWDI's zijn breedspectrum intraveneuze antibiotica en resuscitatie van septische patiënten (één op de drie patiënt presenteert septisch) [25,32]. Zoals beschreven in hoofdstuk 7 is de tijd tussen presentatie en chirurgische behandeling van groot belang om de mortaliteit te verlagen: chirurgie binnen zes uur na presentatie is sterk aanbevolen en chirurgie binnen twaalf uur is noodzakelijk om goede uitkomsten te behalen [31]. Echter is het faciliteren van chirurgie binnen dit "gouden" tijdframe bij deze relatief zeldzame ziekte niet altijd haalbaar in de dagelijkse praktijk. Dit komt met name doordat het probleem van een vertraagde behandeling multifactorieel is. Ten eerste, patiëntvertraging verwijst naar de tijd tussen de start van de symptomen en het moment waarop patiënt zich presenteert in het ziekenhuis. Niet alle patiënten zoeken direct medische hulp, mogelijk door zowel onwetendheid van de ernst van de situatie of door de aspecifieke symptomen, vooral in de afwezigheid van tekenen van sepsis [40]. Tevens is de waarschijnlijk waarmee een patiënt medische zorg zoekt ook sterk afhankelijk van andere klinische, economisch en sociale factoren, waaronder de fysieke en financiële toegang tot medische zorg [51]. Ten tweede, het eerdergenoemde diagnostische proces moet geoptimaliseerd zijn om diagnosevertraging te voorkomen. Aanvullend diagnostisch onderzoek moet weloverwogen gebruikt worden en artsen moeten alert zijn op een NWDI als mogelijke diagnose, ook al presenteert een patiënt zich bij een niet-chirurgisch specialisme [15,40]. Ten derde, de juiste logistiek, zoals onmiddellijke beschikbaarheid van een chirurg, operatiekamer en materiaal, moet aanwezig zijn in het ziekenhuis om vertraging van behandeling te voorkomen [52].

Naast de tijd tot behandeling, speelt tijd ook een essentiële rol bij de operatieduur van het initiële operatieve debridement. Het fenomeen, langere operatieduur leidt tot hogere complicatiepercentages en langere intensive care en ziekenhuisopnames, is wel bekend binnen de trauma- en spoedeisende chirurgie [53–55]. Zoals in hoofdstuk 8 wordt gezien, leidt een langere operatieduur ook bij NWDI's tot langere intensive care en ziekenhuisopnames, zelfs wanneer dit gecorrigeerd wordt voor de aanwezigheid van sepsis bij de start van de operatie, het totaal lichaamsoppervlakte aangedaan en de ASA classificatie [50]. Daarom blijft het hoofddoel bij de behandeling van NWDI's een adequaat en efficiënt debridement om de infectie onder controle te krijgen, maar ook om geen verder kwaad te doen door de fysiologische ontregeling veroorzaakt door een langdurige operatie te beperken.

Een podium geven aan een zeldzame ziekte: de kracht van getallen en het gebrek daarvan

Het onderzoeken van NWDI's gaat samen met een aantal uitdagingen met name veroorzaakt door de lage incidentie van de infectie. Met de jaarlijkse incidentie van 193 tot 238 gevallen per jaar in Nederland, zoals beschreven in hoofdstuk 2, zijn niet veel patiënten makkelijk beschikbaar voor inclusie in studies met als resultaat beperkte steekproefgroottes van de beschikbare studies en daardoor veel studies met te weinig power [29]. Daarnaast worden NWDI's wegens de schaarste van patiënten vaak bestudeerd als één groep ongeacht de heterogeniteit in presentatie en bijbehorende behandeling van deze infecties. De diagnostische term "NWDI's" omvat eigenlijk een erg heterogene groep van infecties die bijvoorbeeld vele verschillende lichaamsregio's omvat en door vele verschillende bacteriën wordt veroorzaakt. Ter illustratie: NWDI's van het genitale gebied (ook bekend als Fournier gangreen) zijn meestal polymicrobiële infecties, terwijl NWDI's van de nek (ook bekend als Ludwig angina) met name monomicrobiële infecties met Groep A Streptokokken zijn, NWDI's van de extremiteit zijn bijna altijd monomicrobiële infecties bij relatief jonge patiënten, en NWDI's van de romp komen juist met name voor bij relatief oude patiënten [3,36,37,56,57]. Idealiter zouden deze subtypes van NWDI's apart onderzocht worden, zoals in dit proefschrift gedaan is voor Groep A Streptokokken NWDI's (hoofdstuk 4) en NWDI's van de bovenste extremiteiten (hoofdstuk 9 en 10). Dit liet namelijk zien dat de uitkomsten verschillen tussen pathogenen en aangedane lichaamsregio's; Groep A Streptokokken NWDI's hebben een lagere mortaliteit ten opzichte van NWDI's veroorzaakt door andere pathogenen, en NWDI's van de bovenste extremiteit hebben juist een lagere mortaliteit, zijn vaker monomicrobiële infecties en patiënten lijken een betere kwaliteit van leven te behouden in vergelijking met NWDI's van andere lichaamsregio [36,37,58].

Een aanzienlijk deel van de huidig beschikbare kennis over NWDI's bestaat uit casusbeschrijvingen en cohortstudies met beperkte steekproefgroottes of beperkte wetenschappelijke kwaliteit. Dit maakt het moeilijk om op de wetenschap gebaseerde beslissingen te nemen ten aanzien van het diagnosticeren en behandelen van NWDI's in de dagelijkse praktijk. Om de kwaliteit van NWDI studies te vergroten worden in dit proefschrift enkele strategieën gedemonstreerd om de steekproefgroottes te vergroten om voldoende power te behalen. In hoofdstuk 2 zijn meerdere nationale data bronnen (financiële database, database van meldingsplichtige ziekten en eerdere gepubliceerde Nederlandse studies over NWDI's) gecombineerd om de nationale incidentie van NWDI's in Nederland te verkrijgen [29]. Unanieme en consistente registratie van NWDI patiënten in diagnose thesauri, procedure thesauri, financiële systemen van ziekenhuizen en databases

van meldingsplichtige ziekten is wel van vitaal belang om deze strategie zo betrouwbaar mogelijk toe te kunnen passen. Momenteel is er bijvoorbeeld geen International Classification of Diseases (ICD) code of diagnose-behandelcombinatie (DBC) code voor NWDI's, alleen voor fasciitis necroticans en Fournier gangreen [59]. Daardoor worden NWDI's, zoals necrotiserende cellulitis of necrotiserende myositis, onder vele andere diagnosecodes geregistreerd. Registratie van procedures is zelfs nog uitdagender, zoals af te leiden was uit de ruim 400 verschillende termen die in Nederland gedurende vijf jaar gebruikt werden om de operaties uitgevoerd voor NWDI's te declareren (hoofdstuk 2) [29]. In hoofdstuk 7 wordt juist een andere benadering genomen, namelijk het samenvatten van recente internationale literatuur waarbij 6051 patiënten geïncludeerd konden worden in een uitgebreide meta-analyse van NWDI studies. Dit is tot op heden nog een van de weinige meta-analyses op het gebied van NWDI's [26,31,39,60]. In hoofdstuk 3, 4 en 8 wordt gebruik gemaakt van ziekenhuis data. Door het uitvoeren van een multicenter studie van alle patiënten die de afgelopen tien jaar presenteerde in een van de ziekenhuizen die onderdeel zijn van ons regionale acute zorg netwerk en door hierbij gebruik te maken van een erg brede zoekstrategie binnen de ziekenhuisregistratiesystemen, kon een middelmatige effectgrootte behaald worden [32,36,50]. Ten slotte, een prospectieve multicenter study genaamd "Identification of Necrotizing Soft Tissue Infections" (iNSTInct) studie is gestart om alle patiënten met een verdenking op NWDI's te includeren met als doel om het diagnostisch proces te verbeteren. Dit moet prospectief gebeuren aangezien retrospectieve data bij deze onderzoeksvraag slechts beperkte betrouwbaar is wegens de inconsistente registratie van patiënten met een verdenking op NWDI's.

Toekomstperspectief voor het verder verbeteren van uitkomsten

Gebaseerd op het aantal patiënten die nog steeds overlijden ondanks volledig debridement om de infectie onder controle te krijgen en de patiënten bij wie een abstinerend beleid wordt afgesproken op basis van ernstige reeds bestaande ernstige comorbiditeiten en/of hogere leeftijd gecombineerd met de ziekte-ernst, is de hypothese geformuleerd dat de na te streven minimale mortaliteit van NWDI's in landen met een modern en ontwikkeld zorgsysteem rond de 7 tot 10% ligt wanneer de logistiek, diagnostisch proces en behandeling volledig geoptimaliseerd zijn [32]. De andere 10% van het huidige mortaliteitspercentage is voor een aanzienlijk deel het gevolg van allerlei factoren die vertraging veroorzaken. Desalniettemin, als de mortaliteit verlaagd is naar dit veronderstelde behaalbare minimum ontstaat er de mogelijkheid om meer te focussen op andere uitkomsten, zoals het verlagen van het amputatiepercentage en het verbeteren van functionele en esthetische uitkomsten door bijvoorbeeld huidsparend te opereren indien mogelijk. De afgelopen jaren is er namelijk een toenemende interesse binnen het veld van NWDI onderzoek naar

huidsparend opereren, echter liet een recente systematische review zien dat er op basis van de huidige literatuur te weinig resultaten beschikbaar zijn om te concluderen dat huidsparend opereren daadwerkelijk superieur of inferieur is aan de klassieke en-bloc debridement [61].

Zoals gezien wordt in dit proefschrift, heeft het verlagen van de mortaliteit tot op heden nog de hoogste prioriteit, aangezien de huidige mortaliteit het dubbelen is van wat waarschijnlijk mogelijk is. Toekomstig onderzoek zou zich met name moeten focussen op drie aspecten die als doel hebben de vertraging van behandeling te beperken. Ten eerste moet het aantal patiënten die zich presenteren met ver gevorderde verspreiding van de infectie waarvoor chirurgisch debridement niet meer mogelijk is, wijzend op significante vertraging in presentatie, verminderd worden. Dit kan door de bekendheid van NWDI's onder het algemene publiek te vergroten, maar ook door huisartsen extra te onderwijzen over wanneer een patiënt mogelijk een NWDI's kan hebben en doorgestuurd moet worden. Daarnaast is het van belang dat iedereen, wereldwijd, de toegang (zowel geografisch gezien, als financieel) heeft tot goede gezondheidszorg om te voorkomen dat patiënten belemmert of vertraagd worden in het zoeken van zorg. Tevens zou fundamenteel onderzoek bij kunnen dragen bij het verminderen van deze groep patiënten met vergevorderde infecties door beter begrip te krijgen van de pathofysiologie van NWDI's. Dit kan bijvoorbeeld door verder te onderzoek waarom sommige micro-organismen wel of niet NWDI's kunnen veroorzaken en door naar de relatie te kijken tussen de betrokken micro-organismen en waarom sommige patiënten zo snel vergevorderde verspreiding van de infectie hebben.

Ten tweede, het diagnostisch proces moet verbeterd worden. Dit proefschrift laat zien dat gebruik van het triple diagnostiek algoritme uitkomsten verbeterd, maar is alleen bestemd voor patiënten waarbij tijdens chirurgische exploratie macroscopisch gezien twijfel bestaat over de diagnose. Andere minder invasieve aanvullend onderzoeken, zoals diagnostische scores, zouden kunnen helpen bij de beslissing welke patiënten wel of niet naar operatiekamer moeten voor chirurgische exploratie. Hiervoor is echter wel een grote prospectieve studie van alle patiënten met een verdenking op een NWDI en met voldoende power nodig, zoals de iNSTInct studie. Echter zijn dit soort studies lastig op te zetten wegens de zeldzaamheid van de infectie en de spoedeisende setting waarin de patiënten presenteren. Om dit succesvol te doen moeten er beschikking zijn over genoeg onderzoekers om patiënten te includeren en om data te verzamelen van alle patiënten met een verdenking op NWDI's direct bij presentatie gedurende een lange tijdsperiode.

Ten derde, de behandeling van NWDI's vereist teamwork aangezien het een multidisciplinaire aanpak vereist met betrokkenheid van chirurgische specialismen (onder andere heelkunde, plastische chirurgie, urologie en oogheelkunde),

intensivisten, anesthesiologen, microbiologen en pathologen. Daarnaast speelt revalidatie (fysiek, mentaal en diëtiek) een belangrijke rol bij het optimaliseren van de uitkomsten. Samenwerking is niet alleen onmisbaar voor dagelijkse praktijk, maar ook voor onderzoek naar NWDI's. Samenwerking tussen ziekenhuizen intra- en internationaal is noodzakelijk om voldoende grote steekproevengrootte te verkrijgen om te differentiëren tussen verschillende symptomen, predictoren en uitkomsten van verschillende NWDI subtypes.

Concluderend, de uitkomstverbetering van NWDI's heeft nog een lange weg te gaan, maar dit proefschrift neemt een aantal essentiële stappen op de weg naar het optimaliseren van de zorg voor NWDI patiënten. In het kort, dit proefschrift laat zien dat NWDI's nog steeds een zeldzame infecties zijn met nog steeds een hoge mortaliteit en morbiditeit, zelfs in landen met moderne, goed ontwikkeld zorgsystemen zoals in Nederland. NWDI uitkomsten zijn erg tijdgevoelig, maar de mortaliteit zou mogelijk wel verlaagd kunnen worden naar 10% indien de diagnose snel (binnen zes uur) gesteld wordt, eventueel ondersteund door triple diagnostiek bij ambivalente casussen, gevolgd door kort en efficiënt chirurgische exploratie en debridement. Artsen moeten zich bewust zijn van het hoger risico op ongunstige uitkomsten bij oudere patiënten, patiënten met reeds een slechte fysieke toestand en bij NWDI's niet veroorzaakt door Groep A Streptokokken. Toekomstig NWDI onderzoek zou de volgende stappen op de weg naar optimale patiëntenzorg voor NWDI patiënten moeten zetten door het exacte effect van de implementatie van de bevindingen beschreven in dit proefschrift te evalueren en, indien mogelijk gebaseerd op de uiteindelijke mortaliteitreductie, verder gaan kijken dan mortaliteit als uitkomst en meer naar het optimaliseren van functionaliteit en esthetiek.

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Appendix

Review Committee

Appendix

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Prof. dr. I.M. Hoepelman
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Appendix

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Dankwoord

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Appendix

Curriculum Vitae

Appendix

Femke Nawijn was born on the 9th of August, 1996 in Amersfoort, the Netherlands. She grew up in Scherpenzeel and attended secondary school at the Johannes Fontanus College in Barneveld and graduated in 2014. The same year, she started medical school at the University of Utrecht. Within the first years of medical school, she grew a special interest in surgery and in September 2016 she started participating in clinical research at the Department of Trauma Surgery at the University Medical Center Utrecht under supervision of dr. F. Hietbrink to learn more about clinical research and trauma surgery. Starting from January 2018, she started focusing on necrotizing soft tissue infections as topic for her clinical research with this thesis as a result. In July 2018, she went to Massachusetts General Hospital (MGH) in Boston, the United States of America, for a scientific research internship at the Hand and Upper Extremity Service under supervision of dr. Neal Chen. She was giving the opportunity to also study necrotizing soft tissue infections at MGH. After returning from Boston, she continued studying necrotizing soft tissue infections in the Netherlands. In her final year of medical school, she was awarded the Frits de Waard award for original and outstanding epidemiologic research in medical research by a medical student for her article outlined in chapter 7. After graduating from medical school in January 2021, she finished the final projects for this thesis and started working as a surgical resident not in training (ANIOS) in April 2021 at the Elizabeth-TweeSteden Hospital in Tilburg. She hopes to be able to keep combining clinical work with clinical research and to keep learning and gaining more experience in both fields.

Appendix

List of Publications

F Nawijn, B de Gier, DAH Brandwagt, RHH Groenwold, J Keizer, F Hietbrink. Incidence and mortality of necrotizing fasciitis in the Netherlands: the impact of Group A Streptococcus. BMC Infectious Diseases. 2021. *In press*

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