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Patient's characteristics and outcomes in necrotising soft-tissue infections: results from a Scandinavian, multicentre, prospective cohort study

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Abstract

Purpose: Necrotising soft-tissue infections (NSTI) are characterised by necrosis, fast progression, and high rates of morbidity and mortality, but our knowledge is primarily derived from small prospective studies and retrospective studies.

Methods: We performed an international, multicentre, prospective cohort study of adults with NSTI describing patient's characteristics and associations between baseline variables and microbiological findings, amputation, and 90-day mortality.

Results: We included 409 patients with NSTI; 402 were admitted to the ICU. Cardiovascular disease [169 patients (41%)] and diabetes [98 (24%)] were the most common comorbidities; 122 patients (30%) had no comorbidity. Before surgery, bruising of the skin [210 patients (51%)] and pain requiring opioids [172 (42%)] were common. The sites most commonly affected were the abdomen/ano-genital area [140 patients (34%)] and lower extremities [126 (31%)]. Monomicrobial infection was seen in 179 patients (44%). NSTI of the upper or lower extremities was associated with monomicrobial group A streptococcus (GAS) infection, and NSTI located to the abdomen/ano-genital area was associated with polymicrobial infection. Septic shock [202 patients (50%)] and acute kidney injury [82 (20%)] were common. Amputation occurred in 22% of patients with NSTI of an extremity and was associated with higher lactate level. All-cause 90-day mortality was 18% (95% CI 14–22); age and higher lactate levels were associated with increased mortality and GAS aetiology with decreased mortality.

Conclusions: Patients with NSTI were heterogeneous regarding co-morbidities, initial symptoms, infectious localisation, and microbiological findings. Higher age and lactate levels were associated with increased mortality, and GAS infection with decreased mortality.

Keywords: Necrotising fasciitis, Fournier's gangrene, Group A streptococcus, Sepsis, Critical care

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Introduction

Necrotising soft-tissue infection (NSTI) is characterised by necrosis of the deep soft tissue, often with rapid progression along the subcutaneous fasciae [1]. There is great variety in NSTIs, including necrotising cellulitis, necrotising fasciitis type I, type II, and myositis. Regardless of infection category, prompt surgery, antibiotics, and organ support are the cornerstones of treatment [2], but despite multimodal management, morbidity and mortality remain high [3], and the survivor's quality of life is reduced [4]. The infection is often polymicrobial, but monomicrobial NSTI caused by *Streptococcus pyogenes* (group A streptococcus, GAS) is also frequent [1]. The incidence rate varies considerably between studies, but was estimated to 4.5 per 100,000 inhabitants per year in the United States in 2005 [5]. Awareness is critical as it is an important differential diagnosis to common and less severe skin infections [6]. A scoring system to aid clinical decision-making has been developed [7], but its performance remains questionable [8]. Few prospective studies have been performed, and current knowledge is primarily derived from retrospective single centre studies. We designed the 'Improving Outcome of Necrotising Fasciitis: Elucidation of Complex Host and Pathogen Signatures that Dictate Severity of Tissue Infection' (INFECT) observational study to provide detailed clinical information on patients with NSTI and to explore associations between clinical features and outcome [9]. The INFECT observational study is part of the INFECT project, which aims at advancing our understanding of the pathophysiological mechanisms in NSTI [10], and the clinical data in the present study will support the basic science findings, contributing to improve patient outcome in NSTI.

Take-home message

Patients with necrotising soft-tissue infections were heterogeneous regarding comorbidities, initial symptoms, infectious localisation, and microbiological findings. Higher age and higher lactate levels were associated with increased risk of death and group A streptococcus aetiology was associated with decreased risk. The heterogeneity of the patients regarding disease severity and microbes suggests that improved survival is accomplished through increased stratification and individualised targeted treatment.

Methods

Study design and patients

We did an international, multicentre, prospective, cohort study of adult patients with NSTI at five Scandinavian hospitals, all of which were referral centres for NSTI. Patients admitted at surrounding hospitals with confirmed or strong suspicion of NSTI were referred to these centres. All patients admitted or transferred to one of the study hospitals with confirmed or suspected NSTI were screened for eligibility; if the medical staff suspected NSTI, a dedicated team on call 24/7 to enrol patients was contacted. The diagnosis was determined by the surgeon doing either the primary operation or revision and was based on findings of necrotic or deliquescent soft tissue with undermining of the surrounding tissue. All patient files were subsequently reviewed by project personnel, and patients whose surgical description did not include findings of NSTI were excluded. Patients were also excluded if consent could not be obtained. All patients were treated according to the local protocols for management of NSTI at the respective hospitals, including repeated surgical revisions, broad-spectrum antibiotics, intravenous polyspecific immunoglobulin G (IVIG), hyperbaric oxygenation therapy (HBOT), and intensive care [Table S1 in the Electronic Supplementary Material (ESM)].

The study was approved by the national or regional ethics committees and data protections agencies in all countries. Written informed consent was obtained from every patient or their legal surrogate as soon as possible. In all cases, consent was obtained from the patient when possible. The protocol and statistical analysis plan have been published previously [9]. The INFECT project is registered at ClinicalTrials.gov, number NCT01790698. We report the study in accordance with the STROBE reporting guidelines [11]. All authors vouch for the adherence to the study protocol and the accuracy and completeness of the data and analyses. The INFECT project was supported by the European Union's Seventh Framework Program under the Grant agreement 305340.

Outcomes

The primary objective of the study was to describe the clinical characteristics of patients with NSTI. Secondary outcomes included identification of associations between affected body part and microbiological findings; identification of baseline characteristics associated with amputation of the extremities; associations between affected body part, acute kidney injury, Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) score [7], and LRINEC scored risk of NSTI and 90-day mortality; and associations between predefined baseline characteristics and 90-day mortality. Finally, an exploratory analysis included associations between all baseline characteristics and 90-day mortality.

Statistical analysis

We expected to enrol 400–500 patients based on previous rates of NSTI admissions to the participating hospitals and an enrolment period of approximately

54 months. We expressed continuous data as medians with interquartile ranges, categorical data as proportions, results from logistic regression analyses as odds ratios including 95% confidence intervals (CI), and results from Cox proportional hazards model as hazard ratios including 95% CI. We differed from our statistical analysis plan, as we did not report relative risks. Seven patients were not admitted to the intensive-care unit (ICU) after initial surgery; data for these patients were not included in descriptions of treatment and length of stay, as we did not have detailed data on these patients, but data were included in all analyses. Further details are given in the ESM and Ref. [9].

Role of the funding source

The funders and sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed the final manuscript and approved submission.

Results

From February 19, 2013 to June 30, 2017, we screened 525 patients and enrolled 409 of these (Fig. 1). We excluded 90 patients after they had been transferred to one of the study sites and assessed by a surgeon as not having NSTI. After a secondary review of the patient files, we omitted an additional 20 patients, because surgical findings were not consistent with NSTI. 402 (98%) of the patients were admitted to the ICU.

Clinical characteristics, blood values, and risk score

The patient's characteristics from the first 24 h in the ICU are presented in Table 1 and in Tables S2, S3 (ESM). All patients had undergone at least one operation before admittance to the ICU, and treatment (including antibiotics, fluids, and organ support) had been initiated. Half the patients (202) had septic shock and 20% (82) had acute kidney injury. Laboratory values from the first 24 h are presented in Table S4 (ESM). Among the patient symptoms and signs registered before initial surgery, skin bruising [210 patients (51%)] and severe pain requiring opioid analgesics [172 patients (42%)] were the most common. LRINEC scored risk of NSTI was available in 376 patients; 212 (56%) were categorised as having high risk of NSTI, 91 (24%) with moderate risk, and 73 (19%) with low risk (Table S5, ESM).

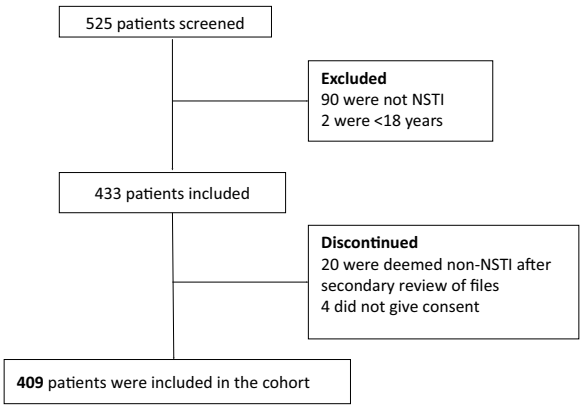

Fig. 1 Flow of patients. Patients with suspected necrotising soft-tissue infection (NSTI) were all screened for eligibility. Referred patients from other hospitals with confirmed NSTI were included. Patients were excluded if they did not meet the inclusion criteria of intraoperative findings of NSTI as judged by the surgeon or were below 18 years of age. After inclusion, patient's files were reviewed, and 20 patients were discontinued in the study, because no intraoperative signs of NSTI were noted. Four patients were discontinued as we could not obtain informed consent. In total, 409 patients were included; of these, 402 were admitted to the intensive-care unit

Microbiological findings

Polymicrobial infections were found in 204 (50%) patients, and 179 (44%) had a monomicrobial infection; GAS was found in 126 (31%) patients (Table S6, ESM). In the remaining 26 (6%) patients, no microbes were identified. Microbiological findings by affected body part are presented in Fig. 2, and a detailed list of microorganisms in Table S7 (ESM) and patients with positive cultures in Table S8 (ESM).

Interventions

The median time from hospital admission to surgery, including that of patients initially admitted for other reasons than NSTI, was 19 h (IQR 6–43), the median number of surgical procedures during ICU stay was 4 (IQR 3–5), and 54 of 402 (13%) patients underwent amputation of an extremity or penis (Table 2 and Table S9, ESM). Antibiotic treatment included a beta-lactam [386/402 (96%)] and clindamycin [394/402 (98%)] in most patients. In the ICU, a total of 376/402 (94%) patients were mechanically ventilated [median duration: 5 days (IQR 3–11)], 331/402 (82%) were given vasopressors or inotropes, and 78/402 (19%) underwent renal-replacement therapy [median duration: 6 days (IQR 3–15)]. Adjuvant therapy with IVIG was given to 232/402 (58%) patients and HBOT to 322/402 (80%).

Follow-up

Patients had a median ICU stay of 7 days (IQR 4–13), including patients subsequently transferred to ICUs in

Table 1 Patient characteristics at arrival at the referral hospital

	n = 409
Age (years)	61 (48–69)
Male	237 (58%)
Weight (kg)[a]	80 (70–98)
BMI (kg/m^2)[a]	26.1 (23.7–31.1)
Comorbidities[b]	
Chronic obstructive pulmonary disease	47 (11%)
Cardiovascular disease	169 (41%)
Diabetes, type I or II	98 (24%)
Chronic kidney disease	34 (8%)
Chronic liver disease	25 (6%)
Peripheral vascular disease	40 (10%)
Rheumatoid disease	27 (7%)
Chronic wound or other skin disease	42 (10%)
Varicella infection	1 (< 1%)
Active malignancy	33 (8%)
Metastatic carcinoma	8 (2%)
Haematologic cancer	12 (3%)
HIV positive	5 (1%)
Other immunodeficiency	12 (3%)
No comorbidities	122 (30%)
Pre-existing conditions	
Active smoking[c]	125 (31%)
Alcohol use[d]	58 (14%)
Use of steroids	54 (13%)
Use of immunosuppressing drugs given for rheumatoid disease or malignant disease	34 (8%)
Use of IV drugs (as drug addict or use of IV medication not given in hospital)	19 (5%)
Surgery up to 4 weeks before diagnosis of NSTI	77 (19%)
Penetrating trauma up to 4 weeks before diagnosis of NSTI	32 (8%)
Blunt trauma up to 4 weeks before diagnosis of NSTI	44 (11%)
Previously affected by NSTI	5 (1%)
Site of infection	
Head/neck including intrathoracic space	70 (17%)
Upper extremities including thoracic involvement	73 (18%)
Abdomen and ano-genital area	140 (34%)
Lower extremities	126 (31%)
SAPS II[e]	43 (34–53)
Mechanical ventilation	366 (89%)
Acute kidney injury[f]	82 (20%)
Septic shock[g]	202 (50%)
Norepinephrine infusion rate (µg/kg/min)[h]	0.18 (0.08–0.40)

Data are number of patients (%) or median (IQR). The values for mechanical ventilation (invasive or non-invasive), acute kidney injury, septic shock, SAPS II, and norepinephrine infusion rate pertain to the first 24 h in the intensive-care unit (ICU). Patients had undergone at least one surgical procedure before ICU admittance. For additional patient characteristics, see Table S2–S4 (ESM)

BMI body mass index, *IV* intravenous, *KDIGO* Kidney Disease: Improving Global Outcomes, *NSTI* necrotising soft-tissue infection, *SAPS* Simplified Acute Physiology Score

[a] Data on height and weight were missing for 7 (2%) and 2 (< 1%) patients

[b] Cardiovascular, chronic liver disease, and chronic kidney disease were defined as described in the patient files. Cardiovascular disease includes hypertension. Active malignancy was defined as malignancy other than haematological, and that had not been eradicated. One of the 5 HIV positive patients had AIDS. Other immunodeficiency included alfa-1-antitrypsin deficiency (1), autoimmune hepatitis (1), bullous pemphigoid (1), colitis ulcerosa (1), Crohn's disease (1), IgA deficiency (1), liver re-transplantation (1), MGUS (1), motor neuron disease (1), and sarcoidosis (3)

[c] Data were missing for 63 (15%) patients

Table 1 (continued)

[d] Defined as weekly intake of > 14 units of alcohol for women and > 21 for men. Data were missing for 97 (24%) patients

[e] SAPS II is calculated from 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease [30]. Data regarding one of the 17 variables were missing for 40 (10%) patients; the scores for these patients were not included here. If the missing variables were replaced by the worst possible and best possible values, respectively, the median SAPS II was 43 and 44

[f] Acute kidney injury was defined as KDIGO stage 3 (serum creatinine level 3 times above preadmission level, a serum creatinine of 354 µmol/l or higher, or initiation of renal-replacement therapy) [31]. Urine output was not evaluated, and preadmission creatinine was calculated from the Modification of Diet in Renal Diseases equation [32]

[g] Septic shock was defined as lactate > 2 mmol/l and use of vasopressor or inotrope [23]. Data were missing for 3 (1%) patients

[h] Highest rate recorded. Data were missing for 2 (< 1%) patients

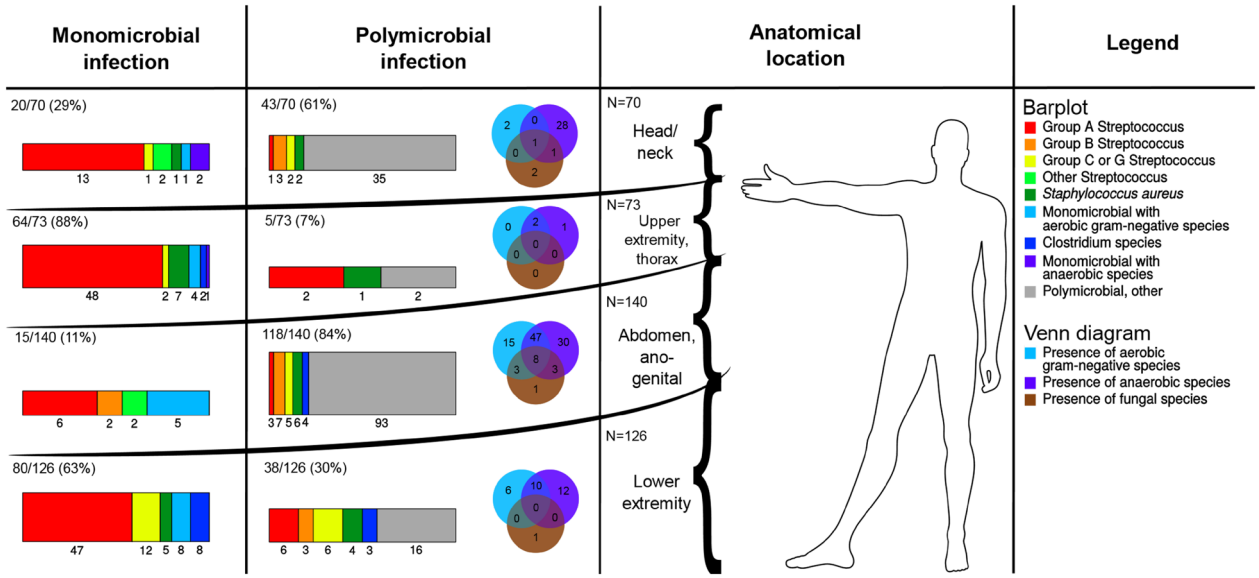

Fig. 2 Microbiological findings by affected body part. In 26 (6%) patients, no microbe was detected (7 patients with infection located to head/neck area, 4 in the upper extremities, 7 in the abdomen and ano-genital area, and 8 in the lower extremities). The square diagrams show the distribution of the microbiological agents found in monomicrobial and polymicrobial infections, separated by the body part affected. The size of the square represents the number of patients. The Venn diagrams show the distribution microbiological findings of aerobic Gram-negative species, anaerobic species, and fungal species in patients with polymicrobial infection

other hospitals, and the median percentage of days alive and out of hospital in the 90 days after inclusion was 51 (IQR 1–72) (Table S11, ESM). All-cause mortality was 14% at day 30 (95% CI 11–18) and 18% at day 90 (95% CI 14–22) (Fig. 3 and Table S11, ESM).

Variables associated with microbiological findings, amputation, and mortality

NSTI located to the upper extremities was associated with monomicrobial GAS and *Staphylococcus aureus* infection (OR 7.80, 95% CI 4.36–14.25; $p < 0.0001$; and OR 5.80, 95% CI 1.61–21.60; $p = 0.0184$, respectively) (Table S12, ESM and Fig. 2). Infection of the lower extremities was associated with monomicrobial GAS, group C and G streptococcus, and clostridial species (OR 1.91, 95% CI 1.18–3.09; $p = 0.0266$; OR 9.76, 95% CI 2.57–54.85; $p = 0.0008$; and OR 9.47, 95% CI 1.85–92.85; $p = 0.0102$). Finally, NSTI of the abdomen and ano-genital area was associated with polymicrobial infection (OR 8.01, 95% CI 4.95–13.15; $p < 0.0001$).

A total of 196 (48%) patients had NSTI located to either upper or lower extremities; 43 (22%) of these had an extremity amputated. Only higher lactate level was statistically significantly associated with amputation of an extremity (hazard ratio 1.07, 95% CI 1.01–1.13; $p = 0.0194$) (Table S13, ESM). Seventeen patients had missing data in one or more of the included variables. In an analysis including only complete cases, results were consistent with the primary analysis.

Higher age and higher baseline lactate level were associated with higher 90-day mortality (OR 1.07, 95% CI 1.04–1.10; $p < 0.0001$ and OR 1.26, 95% CI 1.15–1.37; $p < 0.0001$, respectively) (Table 3); the presence of GAS was associated with lower 90-day mortality (OR 0.17,

Table 2 Treatment characteristics from ICU day 1 to 7

	n = 402
Surgical management[a]	
Estimated maximum skin defect during surgery (percent body surface)[b]	5 (2–10)
Number of operations during ICU admission at specialised hospital	4 (3–5)
Time from admission to surgery (h)[c]	19 (6–43)
Amputation (any body part)[d]	54 (13%)
Upper arm	4 (1%)
Lower arm	3 (1%)
Hand	0
Finger	1 (< 1%)
Upper leg	39 (10%)
Lower leg	1 (< 1%)
Foot	0
Toe	1 (< 1%)
Penis	7 (2%)
Medical management[e]	
Antibiotics	
Penicillin G	74 (18%)
Dicloxacillin	10 (2%)
Piperacillin + tazobactam	19 (5%)
Meropenem	350 (87%)
Cefuroxime	6 (1%)
Ceftriaxone	6 (1%)
Cefotaxime	23 (6%)
Ciprofloxacin	248 (62%)
Moxifloxacin	2 (1%)
Gentamicin	23 (6%)
Clindamycin	394 (98%)
Vancomycin	35 (9%)
Linezolid	9 (2%)
Metronidazole	80 (20%)
Imipenem	23 (6%)
Antifungal[f]	24 (6%)
Other[g]	31 (8%)
IVIG	232 (58%)
Number of IVIG doses[h]	3 (1–3)
Use of blood products, including blood products given during operation (ml)	
Erythrocytes	245 (0–1150)
Fresh frozen plasma	0 (0–540)
Platelets	0 (0–0)
Supportive modalities	
Mechanical ventilation (invasive and non-invasive)	376 (94%)
Renal-replacement therapy	78 (19%)
Use of vasopressor/inotrope	354 (88%)
HBOT at any time	322 (80%)
Number of HBOT sessions[i]	3 (3–3)

Data are number of patients (%) or median (IQR). Data from inclusion up to day 7. Seven patients were not admitted to the ICU; their data were not included

HBOT hyperbaric oxygenation therapy, *ICU* intensive-care unit, *IVIG* intravenous polyspecific immunoglobulin G

[a] Surgical procedures were registered as long as the patient was admitted to the ICU, up to a maximum of 7 days. The primary surgical procedure(s) at referring hospital was included

Table 2 (continued)

[b] The largest skin defect observed during surgery. If a body part was amputated, we used a skin defect corresponding to the amputated body part according to the rule of nine [33]

[c] Including patients who were primarily admitted for other reasons. Data regarding exact time of initial hospital admission were missing for 6 (1%) patients

[d] One patient in Copenhagen had both lower arm and upper leg amputated, and one patient in Karlskrona had both upper leg and penis amputated

[e] Medications given at any time during ICU stay

[f] Antifungal included fluconazole, amphotericin B, posaconazole, and anidulafungin

[g] Other antibiotics included erythromycin, colimycin, rifampicin, tobramycin, and mecillinam/pivmecillinam

[h] In patients who received IVIG

[i] In patients who received HBOT

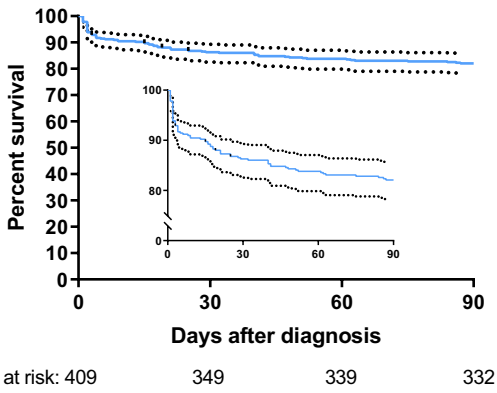

Fig. 3 Survival curve. The blue line denotes the survival curve, with data censored at 90 days. The doted black lines denote the 95% confidence intervals, and the black marks on the survival curve denote censored patients. The insert shows the same curve where the y-axis is broken

95% CI 0.06–0.45; $p=0.0004$). Alcohol consumption was omitted from the analysis due to the large amount of missing data [97 patients (24%)]. Complete cases analysis, analysis including alcohol consumption, and the exploratory analysis supported the primary analysis (Tables S14, S15 and S17, S18, ESM).

Post hoc, unadjusted analyses showed that 90-day mortality in patients with septic shock was higher than in patients without (26% vs 9%; OR 3.38, 95% CI 1.92–5.97; $p<0.001$) (Table S19, ESM), and that patients with NSTI caused by GAS had higher rate of septic shock (65% vs 45%; OR 2.25, 95% CI 1.45–3.50; $p=0.0003$) and lower 90-day mortality (10% vs 22%; OR 0.40, 95% CI 0.21–0.77; $p=0.0058$) (Table S20, ESM).

Discussion

In this international, prospective cohort study, we observed that patients with NSTI presented with bruising of the skin in 51% of cases and severe pain requiring analgesics in 42%. Necrotising soft-tissue infection was caused by a variety of different pathogens, affected every body part, and was associated with high rates of septic shock and acute kidney injury at arrival to the referral hospital. Necrotising soft-tissue infection located to the upper and lower extremities was associated with monomicrobial infection by GAS, whereas NSTI located to the abdomen and ano-genital area was associated with polymicrobial infection. Amputation of an extremity occurred in 22%, and higher lactate level was associated with amputation. All-cause mortality at day 90 was 18%; higher age and higher lactate level were associated with increased 90-day mortality, and the presence of GAS was associated with decreased mortality.

Only few and small prospective studies have included patients with NSTI. It is a paradox that this very sick group of patients is only poorly described, limiting advances in diagnostics and treatment. The overall aim of the international INFECT project was to explore the pathogenesis and host–microbe interactions of NSTIs [10], and with this study, we provide detailed clinical characteristics and microbe distribution that potentially can be used as targets for future diagnostics or therapy. To our knowledge, this is the largest prospective study of patients with NSTI.

The mortality rates observed in our study are lower than those reported in most previous, retrospective observational studies [3, 12], but higher than the 28-day mortality rate of 10% in a recent randomised trial [13]. In many retrospective studies, in-hospital mortality has been used, and in some studies, the time of assessing mortality was not specified [14]. In our study, patients were managed at referral hospitals for NSTI with the capacity and logistics to deliver multidisciplinary management; early surgery with many revisions, and broad-spectrum antibiotics, and a large proportion of patients received adjuvant HBOT and IVIG. This may have influenced mortality rates. Patients were included prospectively which may have resulted in the inclusion of less severe cases of NSTI. However, we may have missed patients that were considered too sick for transport or died before referral. We have no data on resistance to antibiotics in the microbiological cultures, but as all

Table 3 Patient characteristics at arrival at referral hospital and associations with 90-day mortality

	Odds ratio (95% CI)	*p* value
Factors associated with 90-day mortality[a]		
Age (per year increase)	1.07 (1.04–1.10)	< 0.0001
Acute kidney injury[b]	1.70 (0.69–4.19)	0.25
Alcohol consumption[c]	–	–
Body mass index		
Underweight vs normal weight	0.87 (0.04–18.73)	0.93
Pre-obesity vs normal weight	1.37 (0.63–2.96)	0.42
Obesity grade I vs normal weight	0.58 (0.18–1.88)	0.36
Obesity grade II vs normal weight	0.88 (0.19–4.01)	0.86
Obesity grade III vs normal weight	1.41 (0.37–5.41)	0.62
Diabetes mellitus, type I and II	1.23 (0.55–2.71)	0.62
Haematological or metastatic cancer	2.88 (0.78–10.60)	0.11
Fluid input (litres)[d]	1.00 (1.00–1.00)	0.13
Group A streptococcus	0.17 (0.06–0.45)	0.0004
Lactate (per mmol/l increase)	1.26 (1.15–1.37)	< 0.0001
Norepinephrine infusion rate (per µg/kg/min)	1.72 (0.93–3.18)	0.0858
Study centre		
Stockholm vs Copenhagen	0.88 (0.29–2.63)	0.81
Karlskrona vs Copenhagen	0.54 (0.08–3.59)	0.52
Gothenburg vs Copenhagen	0.95 (0.29–3.12)	0.94
Bergen vs Copenhagen	0.92 (0.26–3.29)	0.90
Affected body part[e]		
Head/neck vs mean	1.34 (0.71–2.52)	0.36
Lower extremity vs mean	1.26 (0.79–2.04)	0.32
Abdomen and ano-genital area vs mean	1.42 (0.88–2.28)	0.16
LRINEC score ≥ 6[f]	0.63 (0.30–1.35)	0.23
LRINEC score	1.07 (0.96–1.18)	0.21
Maximum skin defect (pct. body surface)[g]	1.03 (1.00–1.06)	0.0604

Data on 90-day mortality were missing in 4 patients. Data from 405 patients with 73 events were included in the analysis. Missing data were imputed based on the variables in the specific analysis, age, SOFA score at day 1, presence of haematological cancer, presence of diabetes, acute kidney injury at baseline, shock at baseline, and group A streptococcus as causative microbiological agent. For continuous variables, the odds ratio refers to an increase of one unit. The LRINEC score includes sub-scores ranging from 0 to a maximum of 4 for six different blood samples (C-reactive protein, white blood cells, blood haemoglobin, and plasma sodium, creatinine, and glucose). Aggregated scores range from 0 to 13, with higher scores indicating higher risk of necrotising soft-tissue infection [7]. The SOFA score includes sub-scores ranging from 0 to 4 for each of five components (circulation, lungs, liver, kidneys, and coagulation) [34]. Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure. The scoring was modified, because cerebral failure was not assessed

CI confidence interval, *LRINEC* Laboratory Risk Indicator for Necrotising Fasciitis, *SOFA* sequential organ failure assessment

[a] The 11 variables were included in a single step. Alcohol abuse was omitted due to the large amount of missing data (97 patients (24%))

[b] Acute kidney injury was defined as Kidney Disease: Improving Global Outcomes stage 3 (serum creatinine level 3 times above preadmission level, a serum creatinine of 354 µmol/l or higher, or initiation of renal-replacement therapy) [31]. Urine output was not evaluated, and preadmission creatinine was calculated from the Modification of Diet in Renal Diseases equation [32]

[c] Alcohol consumption was defined as weekly intake of > 14 units of alcohol for women and > 21 for men

[d] Fluid input was defined as total volume of all fluids given during the first 24 h. If observation period was below 24 h, the amount was calculated to estimate the number of litres given per 24 h. Fluids given during operations were included

[e] Analyses were adjusted for SOFA score day 1 and age. The association of a body part was tested against the average association of all body parts (sum-to-zero contrast) instead of testing the association of a body part against a body part taken arbitrarily as a reference. The model can only be fitted with a non-singular matrix, and therefore, only three of the four body parts were analysed

[f] Analyses were adjusted for SOFA score day 1 and age

[g] The 7 patients who were not admitted to the ICU were excluded from the analysis. No data were imputed as data were obtainable for 398 (97%) patients with 73 events

centres were in Scandinavia, the frequencies of antibiotic-resistant strains were likely low (Table S21, ESM). As most patients received a carbapenem and clindamycin, we expect that most patients were treated with antibiotics covering the infective organism.

Interestingly, we observed an association between the anatomical site infected and microbiological aetiology, rendering it possible to categorise NSTI patients at an anatomical level. Necrotising soft-tissue infections located to the upper and lower extremities was associated with monomicrobial infections, predominantly GAS, whereas NSTI located to the abdomen and anogenital area was associated with polymicrobial infection, where a mixture of anaerobic and intestinal microbes was commonly seen. Group A streptococcus was infrequently accompanied by other microbes and most often then with *Staphylococcus aureus*. We found GAS infection in 31% of patients. In other studies, rates of GAS infection varied considerably, ranging from 9 to 50% [15–18]. In our patients infected with GAS, the mortality rate of 10% was similar to rates previously observed [19–21], but lower than in patients with other microorganisms. This association has not been consistently observed in other observational studies [3, 15, 22]. Apparently, patients with NSTI caused by GAS have higher rates of septic shock, have less comorbidities, and do not differ in age as compared with non-GAS patients (Table S20 in the ESM). Possibly, the lower rate of comorbidities can be part of the explanation for the lower mortality rate observed in these patients.

Higher lactate level was associated with an increased risk of amputation of an extremity and 90-day mortality. As elevated lactate is part of the definition of septic shock [23], it is likely that patients with septic shock have higher mortality rates and levels of amputation. Elevated lactate could also be a sign of local ischemia.

Many patients had comorbidities, but worth noting, 122 (30%) patients had no comorbidities registered. We observed no association between diabetes or high body mass index and 90-day mortality. This was unexpected as both have previously been associated with increased mortality in patients with NSTI and in sepsis [24, 25], but it may be difficult to compare the results of previous retrospective studies with our result.

At Copenhagen and Stockholm, > 15% of the patients had undergone surgery in the 4 weeks preceding the NSTI. If the infection developed as a complication to this procedure, these patients might represent a subgroup of NSTI patients with a different course and bacterial aetiology. The larger proportion of postoperative patients could also be due to a larger quantity and more complex surgical operations being performed at these centres. More than half of the patients received IVIG as adjuvant treatment. Intravenous polyspecific immunoglobulin G is used for the treatment of NSTIs [26], and it was part of the protocolised treatment for NSTIs in Copenhagen, and given on specific indications—mainly GAS infection—at the other centres. One hundred of the patients included in Copenhagen were also included in a randomised placebo-controlled trial on IVIG for NSTI, where no difference in physical quality of life or other outcomes were observed between the groups [27]. Most patients also received adjuvant HBOT, as this was part of protocolised treatment at the study centres. There are no high-quality data to support or refute the use of HBOT, and suggestions based on the present literature vary [2, 6]. In retrospective studies, the time from diagnosis to surgery has been associated with increased in-hospital mortality [28]. However, it is difficult to pinpoint this time, especially when data are retrieved retrospectively, and we chose not to include time to surgery in our analysis. Given the observational design, we could not say whether the interventions observed in our study had any impact on 90-day mortality or other outcomes.

In our cohort, 73 (19%) patients were categorised as having a low risk of NSTI by the LRINEC score, and we observed no association between increased LRINEC score or moderate-to-high risk of NSTI by the LRINEC score and 90-day mortality. Although the LRINEC score was not developed as a tool to predict outcome in patients with NSTI, we a priori assumed an association between increased LRINEC score and death. The LRINEC score was developed in a population of patients with NSTI included retrospectively, with a high risk of selection bias, and was validated in another retrospective cohort [7]. A recent review of the LRINEC score including 846 patients found a receiving operating characteristic curve with an area under curve of 0.927 [29], and it was concluded that the LRINEC score was a useful clinical determinant in the diagnosis and surgical treatment in patients with NSTI. Despite the fact that our population was different, as we only included patients with confirmed NSTI, our findings do not support this statement, and are in line with the results of a recent meta-analysis [8].

Our study has certain limitations. For some data, we had to rely solely on source data, and some characteristics may be less precise, e.g., initial symptoms. In the definition of acute kidney injury, urine output was not assessed, and preadmission creatinine was estimated. We had to omit alcohol consumption from the logistic regression analysis due to missing data and we had limited power for some of the association analyses. As it was an observational study, we cannot make causative inferences. All including centres were in Scandinavia,

limiting generalisability. A greater proportion of patients were included in Copenhagen. In Denmark, patients with NSTI are referred to Copenhagen University Hospital, and this could in part explain the higher number of patients included at this site.

The strengths of our study include the prospective multicentre design, the inclusion of patients by a dedicated team, and the publication of our protocol and statistical analysis plan. Our sample size and event rate for death were close to predicted and we had a high rate of follow-up and data completeness.

In conclusion, our international study showed that NSTI patients at the five study centres were heterogeneous regarding co-morbidities, initial symptoms, infectious localisation, and microbiological findings, and we demonstrated unique, clinical endotypes. Patients received appropriate antibiotics and multiple surgical revisions, and many patients were treated with adjuvant IVIG and HBOT. We observed that age and higher lactate level were associated with increased risks of 90-day mortality, and the presence of GAS was associated with a decreased risk. The heterogeneity of the patients regarding comorbidities, disease severity, and microbes suggests that further improvement of outcome requires more individualised treatment, addressing both host vulnerability and pathogen-specific mechanisms.

Electronic supplementary material
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Author contributions
SS, AP, ECJ, TB, ANT, and OH contributed to the conception and the design of the study. MBM, SS, PA, MN, TB, MBH, PP, MH, AR, DB, NFB, GHF, LBM, RM, EMJP, FR, IFGSM, AMW, SW, SA, JT, TN, OO, and ER were involved in the acquisition of data. MBM, SS, AP, TB, ES, FB, VAPMS, ANT, and OH contributed to analysis or interpretation of data or both. MBM, AP, and OH were involved in drafting the manuscript. MBM, SS, AP, MN, TB, MBH, AR, ES, VAPMS, NFB, OO, ER, ANT, and OH critically revised the manuscript. All authors approved the final version for submission.

Compliance with ethical standards

Conflicts of interest
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