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RESEARCH ARTICLE

Characterization of patients with odontogenic necrotizing soft tissue infections in the head and neck area. A retrospective analysis

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ABSTRACT

Objective: Necrotizing soft-tissue infection (NSTI) in the head and neck area may develop from odontogenic infections. The aim of this study was to characterize patients with NSTI in the head and neck with odontogenic origin in a well-defined prospectively collected cohort.

Material and methods: Patients with NSTI in the head and neck, hospitalized between 2013 and 2017 at Copenhagen University Hospital and registered in the Scandinavian INFECT database were included. Medical records of identified patients and from the INFECT database were screened for a defined set of data including the primary focus of infection, comorbidities, predisposing factors, clinical and radiographic diagnostics, course of treatment, and treatment outcome.

Results: Thirty-five patients with NSTI in the head and neck area were included in the study. A total of 54% had odontogenic origin, primarily from mandibular molars, and 94% had radiographic signs of infectious oral conditions. Overall, comorbidities were reported in 51% with cardiovascular disease being the most prevalent. In 20%, no comorbidities or predisposing conditions could be identified. The overall 30-day mortality rate was 9%.

Conclusions: More than half of NSTI cases in the head and neck region had an odontogenic origin, and special attention should be paid to infections related to mandibular molars.

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Introduction

Necrotizing soft-tissue infection (NSTI) is a potentially life-threatening disease with an incidence of 0.3–5 cases per 100,000 people in Western countries [1,2] and a mortality rate of 11–18% [3,4]. NSTI in the head and neck region accounts for 5–17% of all NSTI cases [3,4]. The most frequent origins of infection for NSTI in the head and neck include odontogenic infections, peri-tonsillitis, pharyngitis and trauma [5,6]. It is presently unknown why some patients may develop cervical NSTI from otherwise inconspicuous oral infectious conditions, while others with similar odontogenic foci experience a harmless course of disease.

NSTI presents as a rapidly progressive soft-tissue infection, which spreads along the subcutaneous fasciae and results in widespread tissue destruction [1]. It is characterized by pain, erythema, swelling, and is often accompanied by systemic complications like fever, septic shock and multi-organ failure [3,7]. NSTI occurs more frequently in persons above the age of 50 years with comorbidities and alcoholism [5,8], and both age and high plasma lactate levels at hospital admission have been associated with increased mortality [3]. It can be difficult to distinguish early signs of NSTI in the head and neck area from other, less critical soft-tissue infections like cellulitis or abscess [6,9,10]. Therefore, diagnosis of cervical NSTI may be missed at an early stage, allowing the pathologic process to develop aggressively. In the absence of strict clinical and serologic deterministic criteria, the diagnosis of NSTI is definitively established intraoperatively, when recognizing the undermining of the soft tissue along the muscle fasciae of the neck [2,11]. The primary treatment of NSTI includes early, aggressive and repeated surgical excisions of necrotic tissue in addition to elimination of the focus of the infection, broad-spectrum antibiotics and intensive care support [6,12]. Although this aggressive treatment protocol has increased survival after NSTI significantly, the patients may suffer severe complications and morbidity and may require long-term ICU support, stay hospitalized for several months, and need reconstructive surgery after extensive excision of soft tissue [3]. Therefore, the identification of diagnostic and

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prognostic factors is of significant interest to avoid treatment delay, to eliminate eliciting factors, and to reduce morbidity and mortality. However, limited data have been reported on the characteristics, treatment course and long-term health status of patients surviving NSTI in the head and neck area [5].

The aim of the present study is to determine patient characteristics of a well-defined and prospectively documented cohort of patients with NSTI in the head and neck area. The focus will be on comparing NSTI patients with an odontogenic and non-odontogenic background of disease, with the goal of evaluating local as well as systemic risk factors and prognostic factors. In addition, socio-economic aspects of the treatment course and post-treatment rehabilitation will be discussed.

Methods

All patients hospitalized at the Copenhagen University Hospital, Rigshospitalet (RH), Denmark between February 2013 and June 2017 with confirmed NSTI located in the head and neck area were potentially eligible for the present study. Patients admitted to the hospital were identified through the prospective, observational INFECT study [3] that includes patients hospitalized with any kind of NSTI in Copenhagen (DK), Stockholm (SE), Karlskrona (SE), Gothenburg (SE) and Bergen (NO) between February 2013 and June 2017 [3]. The present cohort exclusively included patients from RH. A defined set of data were prospectively documented in the database from patients who were admitted to RH at 90-day and 365-day follow-up (Table 1). In addition, for the present study, medical records of identified patients were retrospectively screened to collect recordings of pathologic oral conditions, surgical removal of pathologic oral conditions and CT scans or panoramic radiographs (OP) from the day of hospitalization (Table 1).

Table 1. Data collected through the database and medical records.

Data from the INFECT database, prospectively	Data from medical records, retrospectively
Demographics • Gender, age, general diseases, working status, risk factors including smoking habits and alcohol consumption	
Diagnosis and clinical characteristics • Date of diagnosis	Diagnosis and clinical characteristics • Clinical recordings of pathological oral conditions
ICU treatment • Date of hospitalization, date of discharge • Clinical data and laboraytory values the first 7 d at ICU	
Surgical treatment • Number of surgical interventions	Surgical treatment • Surgical removal of pathologic oral conditions
Medical treatment • Antibiotics type, dose and duration during hospitalization • IVIG	Medical treatment • Antibiotics administered before hospitalization
Supportive treatment • Number of HBO treatments	
Microbiology • Samples obtained from the deep tissues before or within 48 h of diagnosis	
Serology CRP	
Treatment outcome • Duration of hospitalization • Need for plastic reconstructive surgery	
Mortality	
	Radiographic material • CT scans or OP from the day of hospitalization

ICU: Intensive care unit; IVIG: intravenous polyspecific immunoglobulin G; HBO: hyperbaric oxygen; CRP: C-reactive protein; OP: Panoramic radiograph.

When cervical NSTI was suspected and subsequently confirmed surgically, a standard protocol for treatment was followed at RH, including repeated surgical interventions (debridement of necrotic tissue and sampling for microscopy, cultivation and determination of antibiotic resistance), empiric antibiotic treatment (meropenem, ciprofloxacin, and clindamycin), administration of intravenous immunoglobulin G (IVIG) (except for patients participating in the INSTINCT study who were randomized to IVIG or placebo) [13] and hyperbaric oxygen (HBO) treatment.

Exclusion criteria were patients ≤18 years of age and missing medical records or radiographic material including both jaws (Figure 1).

The Regional Scientific Ethical Committee of the Capital Region of Denmark (H-20046532) approved the study, and a license to store and handle the data was granted by the institutional office for data protection of the University of Copenhagen (license no. 514-0547/20-3000).

Radiographic examination

Based on computed tomography (CT) scans of the head and neck from the day of hospitalization, the following variables were recorded: number of teeth and implants, periapical radiolucencies, pericoronal radiolucencies, marginal bone loss and fresh extraction sockets. An apical lesion was recorded if a tooth presented with a distinct apical bone destruction, exceeding the width of the periodontal ligament [14]. Marginal bone loss was recorded if the bone loss was more than 1/3 of the length of the roots. Extraction sockets were defined as distinct radiolucencies in the alveolar process, indicating the recent presence of a root complex.

The presence of root fillings and carious lesions could not consistently be identified due to variations in section thickness and quality of the CT scans. Therefore, these variables were excluded from the radiographic recordings. If panoramic radiographs (OP) were available, the same variables as noted above were recorded. All patients in this study had a digital CT or OP recorded at the primary hospital or RH. Two dentists (MM and SSJ) and two last year dental students (FB and SH) evaluated all CT scans and reached a consensus of all recordings.

Based on radiographic findings and medical records, the prospectively documented cohort was divided into two subgroups according to the origin of infection: odontogenic or non-odontogenic. The origin of infection was considered odontogenic if it fulfilled the following criteria: 1) clinical signs of active dental disease documented in medical records

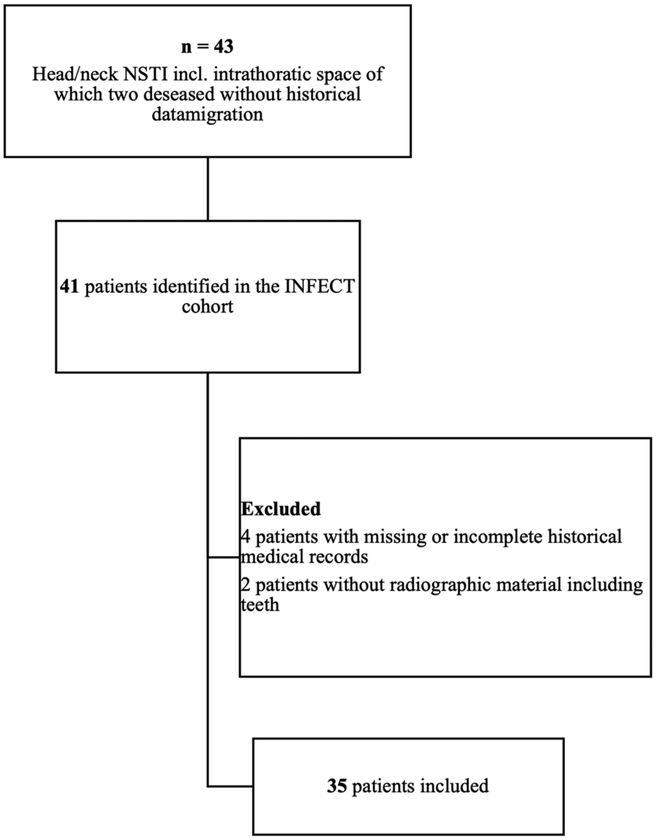

Figure 1. Flow of patients. Patients with cervical necrotizing soft tissue infection were all screened for eligibility. Patients were excluded if they did not meet the inclusion criteria. Data extracted from the INFECT database and otherwise extracted from historical medical records.

pre- or intraoperatively, and/or radiographic imaging with a verified radiolucency compatible with an infectious oral condition, and 2) no other obvious origin of infection. If only one of the abovementioned requirements was fulfilled, the origin was classified as non-odontogenic.

Statistics

Categorical variables were analyzed using Fisher Exact tests. Student's *t*-test was used comparing continuous variables. The level of significance was defined as $p < .05$. The statistical analyses were performed using SPSS Statistics version 28.0 (IBM Corporation, Armonk, NY, USA).

Results

Forty-one patients with NSTI in the head and neck area were identified. Six patients were excluded due to missing medical records or radiographs (Figure 1). The median number of NSTIs in the head and neck at RH was seven cases/year (range: 5–9 cases/year) in the study period. The median prevalence of NSTI in the head and neck with an odontogenic origin of infection was four cases/year (range: 2–5 cases/year).

The mean age was 58.4 years ±16.7 years and 57% were males. Comorbidities were present in 51% of the patients with cardiovascular disease (37%) and diabetes (20%) being the most prevalent. Five male patients suffered from cardiovascular disease as well as diabetes. Of those with diabetes, six out of seven (86%) were males. Tobacco use (40%) and alcohol over-consumption (exceeding the recommendations of the Danish Health Authorities) (37%) were the most common pre-existing conditions (Table 2). Fifty percent of the patients presenting with comorbidities were also either smokers, had an over-consumption of alcohol, or both.

The odontogenic group comprised 19 patients (54%) and the non-odontogenic group 16 patients (46%). Half of the non-odontogenic group consisted of patients with peritonsillar/parapharyngeal abscess as the suspected origin of infection (Figure 2).

The average time from initial hospitalization to definitive diagnosis at the surgical intervention was 53 h and 49 min (range: 2 h, 55 min–260 h and 45 min.). In the odontogenic group, the diagnosis was made within 24 h for 74% of the patients, while it was 44% in the non-odontogenic group. The median number of surgical interventions was seven (range: 1–11) including surgical procedures performed before admission at RH. No patients had a recurrence of previous NSTI. The infection had spread to the thoracic region in ten patients, of whom one had IVIG treatment prior to hospitalization at the intensive care unit (ICU). All patients needed ICU supportive treatment and the average duration of ICU treatment was 13.9 d ± 8.9 and of hospitalization at RH 33.3 d ± 23.9 (Table 3).

C-reactive protein (CRP) levels were elevated (>8 mg/L) for all patients and ranged from 25 mg/L to 646 mg/L pre-operatively. In the odontogenic group, the CRP levels declined from day one to day seven at ICU in 16 out of 19 cases and it dropped with 126 mg/L (range: 44–218 mg/L), on average. One of three patients with elevated CRP level from day one through day seven had septic shock and died. Six patients had elevated baseline lactate levels (>2 mmol/L), two in the odontogenic group and four in the non-odontogenic group. All patients received respiratory support the first three days at the ICU, and at day seven, 27 patients (77%) still needed respiratory support.

Eight patients received antibiotics before hospitalization at the primary hospital and subsequent transfer to the study hospital. Six of these eight patients had an odontogenic origin of NSTI, of which three had antibiotics prescribed by their general dental practitioner and the rest had antibiotics prescribed by their general physician. It is unknown, which antibiotics the patients received before hospitalization. For six patients, it was unclear from the medical records whether they got antibiotics before hospitalization or not. Before ICU admission, 26 patients (74%) received meropenem, clindamycin and ciprofloxacin, and three patients (9%) received one or two of the abovementioned antibiotics. One patient (3%) did not receive any antibiotics before ICU admission. All patients received meropenem and clindamycin at day one at ICU and 94% received ciprofloxacin as well. Eighty percent still got antibiotics at day 7 at the ICU.

In the odontogenic NSTI group, two patients died within the first day after hospitalization and one after 20 days versus none in the non-odontogenic NSTI group ($p = .234$). The overall 30-days mortality rate was 9% (odontogenic NSTI

Table 2. Patient demographics, comorbidities and pre-existing conditions.

	Total *n* (%)	NSTI with odontogenic origin *n* (%)	NSTI with non-odontogenic origin *n* (%)	*p* value
Patients	35 (100)	19 (100)	16 (100)	
Age in years, mean (± SD)	58.4 (±16.7)	56 (±16.8)	61 (±16.7)	.377
Gender, male	20 (57)	12 (63)	8 (50)	.506
Comorbidities				
Active malignancy	4 (11)	1 (5)	3 (19)	.312
Chronic obstructive pulmonary disease	2 (6)	1 (5)	1 (6)	1.000
Cardiovascular disease	13 (37)	6 (32)	7 (44)	.503
Peripheral vascular disease	3 (9)	1 (5)	2 (13)	.582
Diabetes	7 (20)	5 (26)	2 (13)	.415
Chronic Kidney Failure	1 (3)	1 (5)	0	1.000
Number of comorbidities				
0	17 (49)	10 (53)	7 (44)	.738
1	8 (23)	4 (21)	4 (25)	1.000
2–3	10 (29)	5 (26)	5 (31)	1.000
Pre-existing conditions				
Active smoking	14[a] (40)	10 (53)	4 (25)	.166
Alcohol consumption	13[b] (37)	10 (53)	3 (19)	.078
Active smoking and alcohol consumption	9 (26)	7 (37)	2 (13)	.135
Intravenous drug use	1 (3)	1 (5)	0	1.000
Use of steroids	1 (3)	0	1 (6)	1.000
Blunt trauma[d]	1 (3)	1 (5)	0	1.000
Surgery before NSTI diagnosis[d]	14 (40)	6 (32)	8 (50)	.317
Working before hospitalization	14[c] (40)	7 (37)	7 (44)	.739

Demographic data, comorbidities and risk factors.
NSTI: necrotizing soft tissue infection; SD: standard deviation. The blunt trauma is due to a fall 3 d prior to admittance. Alcohol consumption was defined as > 14 units/week for women and > 21 units/week for men. Data is collected prospectively through the INFECT databaseand otherwise extracted from medical records.
[a]7 is unknown.
[b]5 is unknown.
[c]7 is unknown.
[d]Within 4 weeks of NSTI.

group: 16%). The average age at death was 69 years and 66% were male. One out of the three deceased patients had an elevated baseline lactate level. The three deceased patients all had the diagnosis within 24 h and had their first surgery within 24 h. Two of the patients had skin bruising and discoloration preoperatively, and one had skin bullae. However, it is unknown how long these symptoms had been present before hospitalization. The suspected odontogenic foci of these three patients were (1) apical periodontitis of multiple teeth including mandibular molars in one patient, (2) pericoronitis around a lower right third molar in the second, and (3) apical periodontitis of multiple teeth as well as pericoronitis in the third patient.

All patients, except the three deceased, received HBO treatment (median: 3 HBO treatments).

On completion of treatment, nine patients (26%) could be discharged to their own home, whereas 20 patients (57%) needed additional rehabilitation (11%) or were discharged to a nursing home (46%). None of the patients have been re-hospitalized due to recurrence of NSTI. Prior to hospitalization, fourteen patients (40%) were documented to be active in the labor market. Of these, three (9%) had returned to their jobs one year after hospitalization.

Preoperatively, gas visualized on CT was the most common diagnostic sign (63%), followed by skin bruising (26%) and severe pain (26%) (Table 4). There were no significant differences between the two groups regarding diagnostic signs of NSTI.

Microbiological results from the intraoperative tissue sampling were available for 30 of the 35 patients. Ten were monomicrobial, and 20 were polymicrobial. Six out of ten patients with monomicrobial flora had group A *Streptococcus*. Patients with polymicrobial microbiota were often dominated by anaerobic species in combination with the *Streptococcus anginosus* group (11 out of 20 patients). Four patients with NSTI of odontogenic origin had a monomicrobial microbiota, 13 had a polymicrobial and for two patients the microbiota was unknown. Of the 13 polymicrobial cases, seven patients presented *Streptococcus anginosus* and nine presented *Prevotella* spp. (*Prevotella buccae, Prevotella baroniae, Prevotella nigrescens and Prevotella intermedia*). For the patients with monomicrobial microbiota, group A *Streptococcus* were found in two individuals, both of whom died within the first day after hospitalization.

For the entire cohort, 94% had radiographic signs of infectious oral conditions, and no patients had crestal bone loss as the sole pathologic condition. In the odontogenic group, 84% had periapical radiolucencies and 37% had pericoronal radiolucencies. In the non-odontogenic group, 81% had periapical and 25% had pericoronal radiolucencies (Table 5). Furthermore, all patients in the odontogenic group had either periapical radiolucencies, pericoronal radiolucencies, or both (21%), and all patients with crestal bone loss also had periapical radiolucencies. Sixteen out of 19 patients (84%) in the odontogenic group had received some kind of dental treatment in the period just prior to or at hospitalization. In the non-odontogenic group, one patient (6%) had dental treatment at hospitalization. The suspected foci of the odontogenic NSTI infections were located in the mandibular

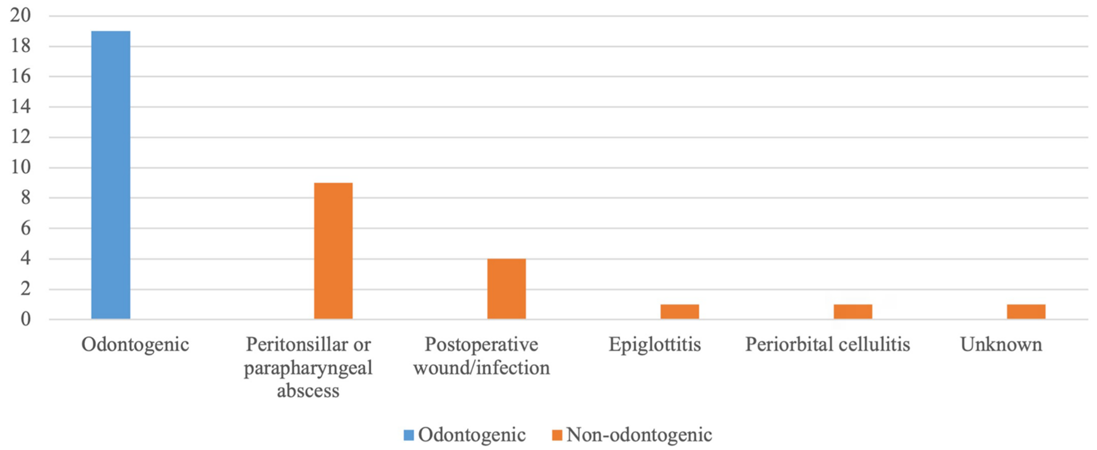

Figure 2. Grouping of the primary origin of infection, judged from medical records. The non-odontogenic group consists of all other subgroups than that with odontogenic NSTI. Total $n = 35$ patients.

molar regions in 79% of the cases. Of these, 53% had more than one potential odontogenic infectious focus.

Discussion

The main observation from the present retrospective study was that odontogenic NSTI often patients without known comorbidities and/or predisposing factors, and that mandibular molars were the most likely focus of infection in the vast majority of the patients.

There were no significant differences in age, gender or comorbidities when comparing patients having an odontogenic origin of infection with patients having non-odontogenic origin of infection. Fifty-three percent of the odontogenic group did not have any known comorbidities. This is comparable with a study by Juncar et al. [15] where 60% developed NSTI in the head and neck area with odontogenic origin without having any comorbidities. Comorbidities (e.g. diabetes), HIV-infection and alcoholism have previously been associated with a higher risk of developing any kind of NSTI [12,16] and there are several good reasons always to pay extra attention to oral health in patients with a compromised general status. However, since patients without known comorbidities may also develop NSTI, it supports the ambition of dentists always to maintain their patients free from oral infections throughout life. The large proportion (49%) of patients without comorbidities stood in contrast to the entire INFECT project, where only 30% were without comorbidities. In the INFECT cohort of 409 patients with any anatomic location of NSTI, cardiovascular disease was the most common comorbidity observed in NSTI patients, which is in agreement with the present sub-group [3].

The diagnosis of NSTI remains challenging because no strict clinical or radiographic deterministic criteria exist, and the definitive diagnosis can so far only be made intraoperatively [11]. Skin bruising and severe pain were the most prevalent symptoms in this study (Table 4), indicating the importance of recording such clinical signs even though they may also be present with other odontogenic infections and is not per se exclusively diagnostic or prognostic. The time from onset of the first symptoms to confirmation of diagnosis and early surgery are reported to be crucial for reducing mortality [6]. The non-odontogenic tended to get the diagnosis later than the odontogenic group, which indicates that odontogenic foci may be discovered earlier.

NSTI patients in the present cohort were characterized by higher CRP levels (262 mg/L) than usually observed with localized odontogenic infections (13–24 mg/L) [17] and even severe odontogenic infections leading to hospitalization [18]. However, due to large variations in CRP levels within the groups of localized infections, a high or a low CRP cannot be used to determine the diagnosis of NSTI nor to exclude NSTI as a sole deterministic criterion but should increase awareness and suspicion by the clinician.

Notably, among all patients in the entire cohort, oral pathologic conditions on radiographic imaging were observed in 94% of the patients, of which apical radiolucencies accounted for 83%. This is a high proportion of untreated odontogenic pathologic conditions. Though the proportion of teeth with apical radiolucencies in the Danish population seems to increase with age [19], the proportion in the present cohort is remarkably large, although the exact numbers should be interpreted with caution considering the limited number of included patients in both groups. Thirteen (68%) out of the 19 patients with suspected odontogenic NSTI, including two out of the three deceased patients, presented with multiple potential odontogenic infectious foci. It may be speculated that an increased bacterial load from multiple foci increase the risk of NSTI development and a severe course of disease.

Despite a comprehensive treatment protocol for patients suspected to suffer from NSTI including aggressive repeated surgical revisions, broad-spectrum antibiotics, HBO treatment, IVIG and ICU support, the 30-days mortality in the present cohort was 9% (16% among patients with odontogenic NSTI), which is comparable to previous studies [20,21]. A higher mortality has previously been seen with head and neck NSTI when the infection spreads to the thoracic region [22], but this was not the case in this study where only one patient out of ten with involvement of the thoracic region died. The mortality rate for NSTI in the head and neck area is lower than for NSTI in other parts of the body, where the mortality

Table 3. Course of treatment and outcome.

	Total *n* (%)	NSTI with odontogenic origin *n* (%)	NSTI with non-odontogenic origin *n* (%)	*p* value
Patients	35 (100)	19 (100)	16 (100)	
Time from primary hospitalization to diagnosis				
Within 24 h	21 (60)	14 (74)	7 (44)	.094
More than 24 h	10 (29)	5 (26)	9 (56)	.094
Antibiotics before hospitalization	6 (17)	4 (21)	2 (13)	.666
CRP (mg/L) highest preoperative				
<100	3 (9)	3 (16)	0	.234
>100	32 (91)	16 (84)	16 (100)	.234
Lactate (mmol/L) highest preoperative				
< 2	29 (83)	17 (89)	12 (75)	.379
> 2	6 (17)	2 (11)	4 (25)	.379
Transferral to ICU				
Within 1 d	19 (54)	11 (58)	8 (50)	.740
Within 2–3 d	7 (20)	3 (16)	4 (25)	.677
Within 4–5 d	4 (11)	2 (11)	2 (13)	1.000
More than 5 d	5 (14)	2 (11)	3 (19)	.642
Days at ICU, average (±SD)	13.9 (±8.9)	13.6 (±8.7)	14.25 (±9.5)	.842
Number of surgical procedures in relation to NSTI, median (range)	7 (1–11)	7 (1–10)	7 (3–11)	
HBO treatment				
HBO treatment	32 (91)	16 (84)	16 (100)	.234
Number of HBO treatments, median (range)	3 (0–6)	3 (0–4)	3 (1–6)	
Affection of thorax	10 (29)	4 (21)	6 (38)	.454
Need for reconstructive surgery (if not in hospital day 90)	2 (6)	1 (5)	1 (6)	1.000
Duration of hospitalization at RH, average (± SD)	33.3 (±23.9)	28.4 (±21.4)	39.2 (±26.7)	.192
Discharged from RH to[a]				
Nursing home	16 (46)	10 (53)	6 (38)	.500
Rehabilitation facilities	4 (11)	1 (5)	3 (19)	.312
Home	9 (26)	4 (21)	5 (31)	.700
Death within 30 d	3 (9)	3 (16)	0	.234

NSTI: Necrotizing soft tissue infection; CRP: C-reactive protein; ICU: Intensive care unit; HBO: hyperbaric oxygen; RH: Copenhagen University Hospital, Rigshospitalet Data is collected prospectively through the INFECT databaseand otherwise extracted from medical records.
[a]3 patients were still in hospital at day 90 and 3 patients died.

Table 4. Clinical characteristics before NSTI diagnosis.

	Total *n* (%)	NSTI with odontogenic origin *n* (%)	NSTI with non-odontogenic origin *n* (%)	*p* value
Severe pain, in need of opioids	9 (26)	6 (32)	3 (19)	.461
Skin bullae	1 (3)	1 (5)	0	1.000
Purple/black discoloration of skin	3 (9)	3 (16)	0	.234
Skin bruising	9 (26)	7 (37)	2 (13)	.135
Skin anesthesia	1 (3)	0	1 (6)	1.000
Palpable gas (crepitus)	6 (17)	2 (11)	4 (25)	.379
Gas visualized on radiology	22 (63)	11 (58)	11 (69)	.727

Clinical and radiographic characteristics recorded before diagnosis of necrotizing sotf-tissue infection. Total $n=35$ patients. One patient may have more than one clinical characteristic finding. *NSTI* Necrotizing soft tissue infection. Data is collected prospectively through the INFECT database and otherwise extracted from medical records.

is reported to range from 18 to 25% [2,3]. Due to the few deaths in this cohort, it was not possible to conclude on specific risk factors affecting mortality.

Although not universally accepted [23], HBO treatment, is used as adjuvant treatment in a multidisciplinary NSTI treatment protocol at RH. A recent randomized controlled trial on the effect of IVIG administration [13] showed a lack of effect on the primary outcome parameter quality-of-life scores (SF-36) at 12 months. However, a favorable trend was noted when NSTI involved the head and neck as well as the extremities. Therefore, IVIG may be considered in non-odontogenic NSTI cases in the head and neck that are known frequently to be associated with Group A *Streptococcus* [3,24,25].

Besides a considerable risk of dying from NSTI in the head and neck area, several findings from the present study underline the severity of the condition, expressed by an average duration of hospital stay of 33.3 days, need for intensive care for an average of 13.9 days, and a median of 7 surgical procedures in general anesthesia. In addition, NSTI is documented to encounter significant personal consequences in terms of morbidity and a long-term incapacity for work with 72% of the patients still being hospitalized, discharged to a nursing home or to a rehabilitation facility. In the Danish population in general, on average 68% of the population aged 55–64 years are still active on the labor market (Danish Ministry of Employment, 2018). In the present cohort, 40% were still working before hospitalization. However, only 9% were working one year later. Hence, NSTI in the head and neck area is accompanied by significant socio-economic costs related to the comprehensive course of treatment and personal lost earnings. This is an additional reason why every measure should be taken to identify patients and conditions with an increased risk of developing NSTI.

Gas formation in the subcutaneous soft tissues has been suggested to be a diagnostic sign of NSTI [20].

Table 5. Radiographic findings in the jaws.

	Total n (%)	NSTI with odontogenic origin n (%)	NSTI with non-odontogenic origin n (%)	p value
Average number of teeth, (range)	22 (0–32)	23 (6–32)	22 (0–31)	.795
Periapical radiolucency	29 (83)	16 (84)	13 (81)	1.000
Pericoronal radiolucency	11 (31)	7 (37)	4 (25)	.493
Marginal bone loss	16 (46)	8 (42)	8 (50)	.740
Extraction socket	9 (26)	6 (32)	3 (19)	.461

Number of patients with radiographic findings in the jaws at panoramic radiograph or computed tomography.
Total $n = 35$. One patient may have more than one radiographic finding. NSTI: Necrotizing soft tissue infection. Data is collected prospectively through the INFECT database and otherwise extracted from medical records.

Therefore, radiographic imaging with CT is an indispensable supplemental diagnostic tool in patients suspected for NSTI in the head and neck area [20,26]. In the present cohort, gas formation was observed preoperatively on radiographic imaging in 66% of all cases, underlining that the diagnostics cannot be based on radiographic findings alone [27].

Depending on the anatomical site of NSTI the microbiota varies. NSTI in the head and neck area is most often polymicrobial [1], which was also the case in the present study with 67% of the entire cohort identified with polymicrobial isolates. Group A *Streptococcus* were identified in 60% of isolates characterized as monomicrobial, which is in accordance with previous studies [3]. However, a monomicrobial culture in isolates from the oral cavity can be the result of a distortion of the environment. Antibiotics administered before and during hospitalization can modify the diversity and load of pathogens that can be identified. Odontogenic infections most often have a polymicrobial etiology [28], but the reason why otherwise harmless infections develop into life threating disease like NSTI is still unclear. Previously, it has been suggested that comorbidities and an impaired immune defense may contribute considerably to the development of NSTI [5]. However, since half of the NSTI patients in the present study presented without known comorbidities and 20% without known comorbidities and/or pre-existing conditions, it seems that NSTI can also affect patients that are otherwise considered healthy.

NSTI in the head and neck is frequently reported to have an odontogenic origin [7,15,29]. In a review by Gunaratne et al. [5] including 1235 patients, an odontogenic source of infection was reported in 47% of the cases, which is comparable with the 54% observed in the present study. The odontogenic origin was, in the majority of cases, related to mandibular molars, which underlines the importance of dentists paying specific attention to keeping these areas free from disease [30]. The anatomic position of mandibular molars with a close relationship to the submandibular space is a plausible explanation why microorganisms from pathologic conditions in and around these teeth easily can invade the many layers of fascia in the neck and contribute to the dissemination of the infection [31].

The main limitations of the present study were the retrospective access to recordings on clinical characteristics and the radiographic material as well as the limited number of patients with NSTI in the head and neck area. However, given the low incidence of NSTI in the head and neck area and the number of cases documented in previous publications, the present consecutive cohort can still be considered of a sufficient size to provide valuable information [15,30]. CT-scans were obtained with the purpose of identifying the localization and extent of the infectious process and were not indicated for detailed diagnostics of pathologic conditions in and around remaining teeth. In addition, the compromised general condition of the patients most often did not allow taking panoramic or intraoral radiographs for more focused radiographic dental examination. Therefore, the radiographic evaluation was limited to the recording of osseous lesions in the maxilla and mandible with an extent that allowed identification on a medical CT scan. Another limitation was the cultivation of all microbiological samples. DNA sequencing might have increased the accuracy and reliability of identifying all pathogens present. A strength is that all data obtained through the INFECT project were collected prospectively and systematically, although some of the socio-demographic recordings were incomplete.

Conclusion

NSTI in the head and neck area developed from infections in the oral cavity in 54% of all cases and frequently affected individuals without known comorbidities or predisposing factors. Characteristically, patients with odontogenic NSTI have the focus of infection located in the mandibular molar regions and present with exceptionally high pain intensity and CRP levels as well as subcutaneous gas formation visualized on CT, although these findings cannot be considered deterministic compared to non-odontogenic NSTI, cellulitis and cervical abscesses. It is documented that post-treatment complications and social consequences for patients surviving NSTI in the head and neck area are frequent and severe. Future studies should focus on an in-depth characterization of the immune response of NSTI patients to further understand and be able to identify patients at increased risk of developing this severe condition.

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