fortune Journals

Research Article

ARCHIVES OF CLINICAL AND MEDICAL CASE REPORTS

ISSN: 2575-9655

Synchronous Necrotising Soft Tissue Infection: A Narrative Review of Presentation, Treatment and Outcomes

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Abstract

Background: Synchronous necrotising soft tissue infections (SNSTIs) are a rare and complex clinical phenomenon. Despite certain risk factors predisposing individuals to localized or single site NSTIs, the specific characteristics related to SNSTIs are not well-understood due to the lack of comprehensive epidemiological and clinical data.

Methods: A thorough search of databases such as PubMed, Google Scholar, and Cochrane CENTRAL was performed up to April 2023. Interventional or observational studies focused on SNSTI were included. Information regarding epidemiology, causative agents, clinical signs, diagnostic methods, management, and patient outcomes were extracted and qualitatively synthesized.

Results: SNSTIs present diagnostic challenges due to their varying and nonspecific symptoms, which contribute to increased morbidity and mortality rates. Our findings indicate that SNSTIs are typically caused by a single, gram-positive organism, differentiating them from localized NSTIs. There is a recognized need for the creation of new diagnostic tools, biomarkers, and treatments to enhance early identification and treatment of SNSTIs.

Conclusion: SNSTIs present substantial diagnostic and treatment challenges, carrying higher mortality rates compared to localized NSTIs. More research is crucial to deepen our understanding of the pathophysiology, risk factors, and epidemiology linked to these infections. This will pave the way for improved management approaches and better patient outcomes.

Keywords: Necrotising soft tissue infections; Fasciitis; Multifocal; Synchronous

Introduction

Necrotising soft tissue infections (NSTIs) represent a group of severe, rapidly progressive bacterial infections that cause extensive destruction of the skin, subcutaneous fat, and fascial layers [1]. NSTIs owe their severity to a combination of microbial virulence, host factors, and, occasionally, delayed medical interventions [2]. The infective agents often include a synergistic mix of aerobic and anaerobic organisms, with the potential of releasing a plethora of exotoxins and enzymes. These microbial products, in turn, facilitate rapid tissue destruction, systemic toxicity, and sepsis. SNSTI, although less commonly encountered, poses a unique clinical challenge. The presence of infection in multiple, often non-contiguous sites requires clinicians to not only identify and treat the primary site of infection but also anticipate

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Citation: Yi Xie, Ishith Seth, David J Hunter-Smith, Warren M Rozen. Synchronous Necrotising Soft Tissue Infection: A Narrative Review of Presentation, Treatment and Outcomes. Archives of Clinical and Medical Case Reports. 8 (2024): 101-111.

Received: January 02, 2024
Accepted: January 16, 2024
Published: May 07, 2024

Yi Xie, et al., Arch Clin Med Case Rep 2024
DOI:10.26502/acmcr.96550670

potential complications that arise from widespread systemic bacterial dissemination [3,4]. Furthermore, the synchronous presentation implies a potential hematogenous spread or a predisposing condition that makes the host susceptible to multiple-site infections.

This narrative review explores the available literature and discusses the nature of SNSTIs by examining their epidemiology, aetiology, pathophysiology, clinical presentation, diagnostic approaches, and management strategies. Additionally, this review will discuss the challenges faced in the diagnosis and treatment of SNSTIs and identify potential areas for future research. By synthesizing current evidence and highlighting knowledge gaps, this review seeks to enhance understanding of SNSTIs and contribute to improved patient outcomes.

Methods

PubMed, Google Scholar and Cochrane CENTRAL were searched for relevant studies published from January 1st, 1901 to April, 2023 by two independent authors (YX and IS). The search terms included (synchronous AND necrotising AND "soft tissue infections" [MeSH]), (multifocal AND necrotising AND "soft tissue infections" [MeSH]), (bilateral AND necrotising AND "soft tissue infections" [MeSH]), (synchronous AND necrotising AND "fasciitis" [MeSH]), (multifocal AND necrotising AND "fasciitis" [MeSH]), and (bilateral AND necrotising AND "fasciitis" [MeSH]). Furthermore, the references of selected studies were manually searched for relevant articles.

The inclusion criteria:

- Randomized control trials, observation studies, and case-control studies.
- Studies investigating presentation, diagnosis and management of necrotising fasciitis or NSTIs in two distinct, non-contiguous anatomical locations, excluding the orbit, face or neck.

The exclusion criteria:

- Animal studies, conference abstracts, and letters or editorial options
- Studies not published or translatable to English language
- Cases of cervicofacial or facial necrotising fasciitis

Titles and abstracts of studies were screened for inclusion. Full texts of potentially relevant papers were further screened using the eligibility criteria. These were done by independent reviewers (YX and IS). Any disparity was resolved through discussion with the other authors.

Due to the heterogeneity of the included studies and the narrative nature of the review, a meta-analysis was not feasible. Instead, we performed a qualitative synthesis of the extracted data to provide an overview of the current knowledge on SNSTIs. The findings were organized into distinct sections, covering the epidemiology, aetiology, pathophysiology, clinical presentation, diagnostic approaches, management strategies, and outcomes of SNSTIs. Additionally, we highlighted the challenges encountered in the diagnosis and treatment of these infections and identified potential avenues for future research.

Results

A total of 42 case reports describing 45 individual patients, and two separate case series involving 19 and 101 patients respectively. Given the more limited information provided in the case series, we discussed these separately to the case reported patients. Of the 45 patients described in the case reports, there were 17 females and 28 males. The mean age was 45 years (range 0.1 - 91 years), with the average female age being 44.2 years, and the average male age being 45.6 years.

Diabetes was the most common comorbidity, with 10 out of 45 patients (22.3%) reporting a history of diabetes mellitus. Five patients had Type 2 diabetes, one patient had Type 1 diabetes, the remaining four cases did not distinguish the type of diabetes the patients had. A total of six patients (13.3%) were immunosuppressed, due to varying causes including post-transplant immunosuppression, HIV, rectal cancer, chronic lymphocytic leukaemia, aplastic anaemia and hepatitis.

A total of 19 patients (42.2%) had a recorded or identifiable inoculating injury. 10 of these cases reported time from the injury to development of symptoms. Of these 10 cases, the average time to the development of symptoms in days was 2.3. Of the 45 cases, 31 cases (68.9%) reported involvement of two non-contiguous areas, five patients (11.1%) had involvement of three non-contiguous areas, while eight patients (17.8%) had involvement of four non-contiguous areas. The right lower limb was the most involved (80%), followed by the left lower limb (73.3%).

An identifiable culprit organism was isolated in 39 of the 45 cases. Type II or monomicrobial NSTI was the most common subtype, with 26 out of 39 (66.7%) cases involving a single identified organism on cultures. There were 10 cases (25.6%) of polymicrobial (Type I) NSTI. Gram positive bacteria was implicated in 26 cases (66.7%). Staph Aureus was the most common organism found, present in 10 (25.6%) of cases, followed by Group A streptococci and E. Coli, which were involved in eight (20.5%) and seven (17.9%) of cases respectively. Two cases (4%) involved the isolation of yeast and candida species respectively. Empirical antibiotic treatment was initiated in all cases and was later appropriately changed in response to cultures and sensitivity.

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DOI:10.26502/acmcr.96550670

Survival data was reported in 44 out of 45 cases. Overall mortality rate was 17 out of 44 (38.6%) cases. 40 (89.9%) cases underwent surgical debridement. Of the remaining five cases that did not receive surgery, three cases did not specify intervention, while two cases elected for palliative treatment after extensive discussions with the family. Of the 17 patients that did not survive, five patients were palliated, one patient died of cardiac arrest during a surgical debridement, and 11 patients died of septic shock. Six patients died despite receiving amputations. Of the 27 patients that survived, four patients had amputations, three patients underwent hyperbaric oxygen therapy, and two patients received intravenous immunoglobulin therapy. 17 patients required reconstruction via split skin grafts.

The Park et al case series [1] reviewed a total of 217 cases of necrotising fasciitis. Of these, 101 patients (44%) had the involvement of multiple sites, although it was not possible from the data presented to determine whether these were genuine non-contiguous sites. The series found that Gram-negative marine bacteria was significantly more likely to be associated with multiple site involvement compared with other organisms.

In the Lee et al case series [2], 144 patients with necrotising fasciitis were reviewed. 19 patients had multifocal involvement. The presence of shock at the initial presentation was significantly more frequent in patients with multiple site involvement compared with single site (74% vs 36%, p = 0.002). End-stage renal disease and liver cirrhosis were also significantly more frequent in patients with multifocal NSTI (p = 0.03 and p = 0.01 respectively). The total postoperative mortality rate was also significantly higher in patients with multiple site involvement (68% v 14%, p = 0.001). A multivariate analysis found that independent risk factors for multifocal NSTI were liver cirrhosis (p = 0.001) and end stage renal disease (p = 0.035). A single bacterial organism was isolated in 95% of patients with multifocal disease, and gram-negative bacteria were significantly more frequently isolated from patients with multiple site involvement (83% v 47%, p = 0.005).

Epidemiology

NSTIs are a rare clinical entity, making the estimation of their exact incidence and prevalence difficult. While NSTIs are generally estimated to have an incidence of 0.2 to 0.4 cases per 100,000, [3,4] NSTIs that simultaneously involve more than one non-contiguous anatomical site account for only a small fraction of these cases. The limited number of published case reports and case series on SNSTIs further restricts the availability of robust epidemiological data. Nevertheless, these infections have been reported across various age groups and in both genders. While certain risk factors have been described as predisposing individuals to NSTIs, such as diabetes mellitus, immunosuppression, intravenous drug use, and peripheral vascular disease [5,6], the specific risk factors and demographics associated with SNSTIs remain underexplored. Diabetes mellitus is one of the most common comorbidities in localised NSTIs [7], in one retrospective review, diabetes mellitus was present in 70.8% of patients with single site necrotising fasciitis [8]. In the Lee et al case series, 4 of 19 (21.1%) of patients with synchronous multifocal necrotising fasciitis had diabetes mellitus. This was more in line with our review of 45 cases, where 10 patients (22.3%) had a history of diabetes mellitus. Given the rarity of SNSTIs and the paucity of large-scale epidemiological studies, further research is warranted to better characterize the population at risk, and the comorbidities associated with these infections. One area which has not been explored and could form the basis for future research is the potential seasonal or geographic variations in the incidence of NSTIs and SNSTIs.

Pathophysiology

The pathophysiology of SNSTIs is complex and not yet fully understood, but it shares several key features with the more common, localised NSTIs. Microbiologically, NSTIs can be classified as either type 1 (polymicrobial) or type 2 (monomicrobial) [9]. Most studies find that NSTIs are typically caused by a polymicrobial mixture of aerobic and anaerobic bacteria, with Streptococcus being the most common causative organism overall [10-12]. Other organisms implicated include Staphylococcus aureus, Escherichia Coli, and Clostridium species, among others10. Our findings on SNSTIs lie in contrast to the literature, with 66.7% of our cases being classified as type 2 due to isolation of a single organism. This is reflected in the Lee et al case series, where 18 out of 19 (94.7%) cases of SNSTIs were monomicrobial. Similarly, an earlier systematic review of 33 cases of SNSTIs found that 52% of them could be classified as type 2. It is posited that in SNSTIs, these infections occur simultaneously in multiple anatomical locations, potentially due to haematogenous spread or direct inoculation by an aggressive, toxic shock causing organism, or a systemic immunologic predisposition.

The pathogenesis of NSTIs involves rapid bacterial multiplication and the production of various virulence factors, including exotoxins, proteases, and enzymes that destroy the surrounding tissue and impair local host defenses [13]. This process leads to the development of extensive tissue necrosis, thrombosis of blood vessels, and ultimately, gangrene. The systemic release of bacterial toxins and inflammatory mediators can also result in sepsis, and if treatment is delayed, multiorgan dysfunction and death. The exact mechanisms behind the development of SNSTIs, however, remains unknown. Further research is needed to uncover the factors contributing to the simultaneous emergence of infections in

distinct anatomical sites and to determine whether unique pathophysiological processes are at play in SNSTIs compared to their single site counterparts.

Clinical Manifestations

The clinical manifestations of SNSTIs can be diverse and challenging. In its initial presentation, SNSTIs may be difficult to distinguish from cellulitis, particularly as there is involvement of multiple anatomical sites. Presenting symptoms may vary depending on the location and severity of the infection, but common features include severe pain, erythema, oedema, warmth, and rapidly spreading areas of tissue necrosis7. Patients may initially present with seemingly innocuous skin changes, such as cellulitis or blisters, which can rapidly progress to extensive skin discoloration, bullae, skin sloughing, and gangrene. Pain out of proportion to the signs of soft tissue infection has also been reported as a sign of localised NSTIs [14]. Systemic symptoms such as fever, tachycardia, hypotension, and altered mental status may also be present, indicating the development of sepsis or septic shock.

Patients may not have an inoculating event, only 19 (42.2%) of our cases had a recorded prior injury. Erythema, oedema and warmth was present in all of our cases, consistent with the literature [15]. We found the lower limbs to be the most commonly involved anatomical sites for SNSTIs, with 30 out of 45 cases (66.7%) involving one or both of the lower limbs. The speed at which symptoms evolve should alert clinicians to the possibility of SNSTIs. While not a reliable indicator of disease progression, we found that patients presented an average of 3.8 days after the development of symptoms. Clinicians should maintain a high index of suspicion for SNSTIs in patients with relevant risk factors, rapidly evolving skin changes, and symptoms disproportionate to the apparent severity of the infection.

Diagnostic Methods

Diagnosing SNSTIs involves clinical assessment, laboratory investigations, and imaging. Early diagnosis is crucial for effective management, as delayed intervention can lead to increased morbidity and mortality. Due to its relatively non-specific presentation, assessment by an experienced clinician plays a vital role in the initial evaluation. The focus should be on identifying the characteristic signs and symptoms of NSTIs, as well as any risk factors that may predispose the patient to the infection. A thorough physical examination of all involved anatomical sites is essential for detecting skin changes and signs of rapidly progressing tissue necrosis.

Laboratory markers, such as elevated white blood cell count and C-reactive protein may indicate infection but are nonspecific. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score has been proposed as a screening test to distinguish NSTI from other soft tissue infections [16], with conflicting reports of its accuracy in subsequent studies [17,18]. Its sensitivity and specificity for SNSTIs remains unvalidated.

While imaging studies such as X-rays, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can provide valuable information about the extent of the infection and help differentiate NSTIs from other conditions, they should not delay surgical intervention if the clinical suspicion is high. In our review, 27 of 45 cases reported imaging findings. Nine out of 12 (75%) reported CT scans demonstrated subcutaneous gas. Six out of six (100%) MRIs demonstrated fascial thickening, fascial inflammation and subcutaneous gas highly demonstrative of NSTIs. From this limited series, CT and MRI offer important confirmatory value in the diagnosis of NSTIs, however the time delay in obtaining imaging should be taken into consideration.

Definitive diagnosis of NSTIs typically requires surgical exploration and tissue biopsy. Samples from the affected sites should be sent for Gram staining, histopathological examination, and microbiological cultures to identify the causative organisms and guide antibiotic therapy. As discussed earlier in this article, Staphylococcus Aureus was the most common organism found in our review, present in 10 (25.6%) of cases, followed by Group A streptococci which was involved eight (20.5%) cases. Gram-positive and gram-negative bacteria were isolated in 26 (57.8%) and 18 (40%) cases respectively. This differs from the Lee et al case series, which found gram-negative bacteria to be present in the overwhelming majority of SNSTI cases (83.3% v 16.6%). As the Lee et al case series was undertaken in a single hospital in Taiwan, and our review was not limited to any geographic location, it remains unclear whether demographic or environmental differences contribute to the variations in NSTI causing organisms.

The diagnostic approach for synchronous NSTIs should be swift and comprehensive, with a strong emphasis on clinical suspicion and a low threshold for surgical intervention. Early recognition and diagnosis are vital for initiating prompt treatment and improving outcomes.

Management Strategies

The management of SNSTIs requires a multidisciplinary approach. This encompasses prompt surgical intervention, the initiation of broad-spectrum antibiotic therapy, and supportive care. Such immediacy is imperative to reduce the morbidity and mortality associated with these rapidly progressing infections.

Broad-spectrum antibiotics should cover both aerobic and anaerobic bacteria. Empiric therapy typically includes a combination of vancomycin, piperacillin-tazobactam, or meropenem to address prevalent causative organisms [19]. On

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DOI:10.26502/acmcr.96550670

receipt of microbiological culture results, antibiotic regimens should be refined based on the identified organisms and their antibiotic sensitivities. All the cases reviewed adopted this antibiotic approach. Surgical debridement is the cornerstone of NSTI management and should be expedited once the diagnosis is suspected. The aim is to remove all necrotic tissue to halt the spread of infection. In SNSTIs, all affected anatomical sites must be addressed simultaneously or in rapid succession. Multiple debridements may be necessary, depending on the extent of the infection, and patients may require subsequent reconstructive procedures as a result.

Some evidence supports the supplemental benefits of hyperbaric oxygen therapy (HBOT) in oxygenating infected tissues, augmenting wound healing, and inhibiting bacterial proliferation [20,21]. Its application in SNSTIs remains a matter of debate and requires case-specific consideration. A Cochrane Review published in 2015 found no high-quality trials endorsing HBOT's adjunctive use in NSTIs, with HBOT rarely resulting in serious adverse effects [22].

The management of synchronous NSTIs demands a rapid, aggressive, and coordinated approach to optimize patient outcomes. Early recognition, timely surgical intervention, appropriate antibiotic therapy, and comprehensive supportive care are essentials components in the management strategy. Despite this, mortality of NSTI remains high, and even higher in SNSTIs. Single site NSTI is estimated to have a mortality of approximately 25% [23,24]. In our review of SNSTIs, overall mortality was 38.6%. This is in line with an earlier systematic review which found an overall mortality of 39.9% [25]. The Park et al case series found an overall 30-day mortality of 45.6%, while the Lee et al case series found a much higher overall mortality of 69.2% (nine of 19 cases) in SNSTIs, while single site NSTI had a mortality of 14.4%.

Challenges and future directions

SNSTIs pose challenges in diagnosis and management. Their rarity means less extensive epidemiological data, leading to gaps in knowledge and practice. Variable presentations of SNSTIs often hinder early diagnosis, resulting in potential treatment delays and higher morbidity.

Research should delve into the causes of multi-site NSTIs. Our review indicates that SNSTIs primarily stem from a single gram-positive organism, differing from localized NSTIs. Multicenter studies could shed light on the epidemiology and best practices for these infrequent infections. Novel diagnostic tools and biomarkers with greater accuracy could aid early NSTI detection. Investigating emerging treatments, like specific antimicrobials, immunotherapies, and advanced wound care, might benefit SNSTI management. Continued research and cooperation are essential for addressing SNSTI challenges and enhancing patient outcomes.

Table 1: Patient history and presentation

Author, year	Age and gender	Medical history	Injury / source	Site
Alexander et al. [26]	36F	Nil	Suction assisted lipectomy	LUL, LLL, RLL, back
Andreasen et al. [27]	41M	NS	Unknown	RUL, LUL, RLL
Bender et al. [28]	65M	T2DM Heart and renal transplant Abdominal hernia	Post abdominal hernia repair	RLL, LLL
Chaudhary et al. [29]	53M	Hypertension, T2DM, HIV	Unknown	RLL, LLL
Cheng et al. [30]	68M	Hepatitis C, liver cirrhosis, DM, pulmonary TB	Unknown	RLL, LLL
Cheng et al. [31]	44M	Marfan syndrome, ascending aortic aneurysm, prosthetic heart valve, endocarditis, previous stroke	Right ankle abrasion	RLL, LLL
Clark et al. [32]	4M	NS	Varicella	RUL, LUL, LLL, RLL
El-Khani et al. [25]	58M	Inguinal hernia repair, temporary hypocalcaemia and jaundice	Unknown	RUL, LUL, RLL
Fukuda et al. [33]	43M	T1DM	Unknown	RLL, LLL
Fustes-Morales et al. [34]	11F	NS	Unknown	RUL, LUL, RLL, LLL
	4F	Malnutrition	Unknown	RUL, LUL, RLL, LLL
Gallagher et al. [35]	29F	IV drug use, recurrent MRSA abscesses	Heroin injection	RUL, LUL
Gardam et al. [36]	67F	CLL	Unknown	RLL, LLL
Greer-Bayramoglu et al. [37]	39M	Cardiomyopathy, juvenile haemochromatosis	Post-heart transplant	RLL, LLL

Herrod et al. [38]	81M	Nil	Unknown	LUL, RLL
Kwak et al. [39]	51F	T2DM	Unknown	RUL, LUL
	83M	Ischaemic heart disease	Unknown	RLL, RUL
Lee et al. [40]	56M	Nil	Unknown	RUL, LUL, LLL, RLL
Li et al. [41]	29M	Nephritic syndrome	Unknown	RLL, LLL
Liu et al. [42]	56M	Rectal cancer, alcoholic cirrhosis, DM, chronic renal failure	Rectal biopsy	RUL, LUL, RLL, LLL
Lu et al. [43]	46F	NS	Unknown	RLL, LLL
MacDonald et al. [44]	71M	Parkinson's disease appendectomy	Unknown	LLL, LUL
Mifsud et al. [45]	35F	Nil	Chickenpox	Abdomen, LLL
Morrison et al. [46]	40F	Nil	Unknown	RLL, RUL, LUL, LLL
Musialkowska et al. [47]	25M	Nil	Unknown	LLL, LUL
Naseem et al. [48]	45F	Nil	Unknown	RLL, LLL
Park et al. [1]	22F	NS	Bilateral calf liposuction	RLL, LLL
Paynter et al. [49]	56M	Nil	Unknown	RLL, LLL, LUL
Perbet et al. [50]	16F	Nil	Hepatitis B vaccine	RUL, RLL
Phitsamai et al. [51]	64M	Hypertension	Pinched by mud crab	RUL, LUL
Porter et al. [52]	45M	NS	Tattooing	RLL, LLL
	29M	NS	Tattooing	RLL, LLL
Saliba et al. [53]	54F	Schizophrenia, DM	Insulin injection into thigh	RLL, LLL
Schwarz et al. [54]	2M	Varicella	Varicella	LUL, RLL, LLL
Spock et al. [55]	65F	DM, Hypertension, previous strokes, carotid disease, foot ulcers	Foot ulcers	RLL, LLL, LUL, back
Tocco et al. [56]	44M	T2DM Hypertension	Unknown	RLL, LLL
Toledo et al. [57]	1.5month M	Nil	Upper respiratory tract infection	RLL, LUL, oral
Tong et al. [14]	46M	IV drug use	Dog bite or IV drug use	RUL, LUL
Ugarte-Torres et al. [58]	37M	Aplastic anaemia, IV drug use	Unknown	RLL, LLL
Umemra et al. [59]	63M	Hypertension	Unknown	LUL, RUL, RLL, LLL
Wade et al. [60]	43M	Nil	Unknown	RUL, LUL
Xu et al. [61]	70F	T2DM Traumatic splenectomy Prev laparotomies for bowel obstruction	Unknown	LLL, RLL
Yamashiro et al. [62]	69F	Liver cirrhosis, previous leg phlegmon	Unknown	RLL, LLL
Yang et al. [63]	91F	Hypertension, dementia	Unknown	RLL, LLL
Yoshii et al. [64]	31M	Nil	IV drug use	RUL, LUL

Abbreviation: NS – Not specified; T2DM – Type 2 Diabetes Mellitus; DM – Diabetes Mellitus; T1DM – Type 1 Diabetes Mellitus; CLL – Chronic Lymphocytic Leukaemia; RUL – right upper limb; RLL – right lower limb; LUL – left upper limb; LLL – left lower limb

Citation: Yi Xie, Ishith Seth, David J Hunter-Smith, Warren M Rozen. Synchronous Necrotising Soft Tissue Infection: A Narrative Review of Presentation, Treatment and Outcomes. Archives of Clinical and Medical Case Reports. 8 (2024): 101-111.

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DOI:10.26502/acmcr.96550670

Table 2: Investigations and management

Author, year	Imaging	Organisms isolated	Antibiotics	Management	Outcome
Alexander et al. [26]	USS	Group A streptococcus, E Coli	Ampicillin, Gentamicin, Clindamycin, Metronidazole, Penicillin, Cefazolin, Amphotericin	Debridement, HBOT	Died
Andreasen et al. [27]	NS	Group A beta haemolytic strep	NS	Debridement, HBOT, SSG	Survived
Bender et al. [28]	CT	E. Coli	Meropenem, Linezolid	Debridement	Died
Chaudhary et al. [29]	CT	MRSA	Vancomycin, Piperacillin-tazobactam, Clindamycin	Debridement, SSG	Survived
Cheng et al. [30]	NS	Vibro cholerae	Imipenem, Clindamycin, Ciprofloxacin	Debridement	Died
Cheng et al. [31]	NS	Aeromonas hydrophila	Ceftriaxone, Clindamycin, Ciprofloxacin	Debridement	Died
Clark et al. [32]	MRI	Group A beta haemolytic strep	NS	Debridement	Survived
El-Khani et al. [25]	NS	Group A beta haemolytic strep	Tazocin, Clindamycin	Debridement, SSG, IVIG	Survived
Fukuda et al. [33]	CT	Group B streptococcus, Group G streptococcus, Morganella morganii, Staph aureus, Pseudomonas species	Meropenem	Debridement	Survived
Fustes-Morales et al. [34]	NS	Morganella morganii	NS	NS	Survived
	NS	Staph aureus	NS	NS	Died
Gallagher et al. [35]	CT	NS	Piperacillin-tazobactam, vancomycin	Debridement, SSG	Survived
Gardam et al. [36]	USS	Group B streptococci	Penicillin, Clindamycin, Ceftriaxone	Debridement, SSG	Died
Greer-Bayramoglu et al. [37]	USS	Klebsiella oxytoca	Vancomycin, Imipenem, Ciprofloxacin	Debridement	Survived
Herrod et al. [38]	CT	Gram -ve bacilli	Clindamycin, Flucloxacillin	NS	Died
Kwak et al. [39]	NS	Strep pneumoniae	Vancomycin, Levofloxacin, Clindamycin	Debridement	Survived
	NS	Strep pneumoniae	Ceftriaxone, Gentamicin, Penicillin G, Clindamycin	Debridement	Died
Lee et al. [40]	NS	Staph aureus	Oxacillin, Cefepime	Debridement, SSG	Survived
Li et al. [41]	NS	E. Coli	Penicillin, Meropenem	Debridement, SSG	Survived
Liu et al. [42]	USS	Group G streptococcus	Augmentin, Penicillin, Clindamycin, Metronidazole	Debridement	Died
Lu et al. [43]	CT, USS	Gram +ve bacilli	Penicillin, Metronidazole, Clindamycin	Debridement	Died
MacDonald et al. [44]	USS	Group G beta haemolytic strep	Cefotaxime, Ciprofloxacin, Imipenem	Debridement	Survived
Mifsud et al. [45]	USS	Strep pyogenes, MRSA	Piperacillin-tazobactam, Vancomycin, Rifampicin, Benzylpencillin, Clindamycin	Debridement, SSG	Survived
Morrison et al. [46]	NS	Group A streptococcus	Ceftriaxone, Flucloxacillin	Debridement	Died
Musialkowska et al. [47]	NS	Gram +ve cocci – no organism isolated	Ciprofloxacin, Metronidazole, Benzylpenicillin, Clindamycin, Piperacillin-tazobactam	Debridement, HBOT	Survived
Naseem et al. [48]	NS	E Coli	Piperacillin-tazobactam	Debridement, SSG	Survived
Park et al. [1]	MRI	Aeromonas caviae	Meropenem	Debridement, SSG	Survived
Paynter et al. [49]	NS	Strep intermedius, E Coli, Klebsiella Oxytoca, Staph Aureus	Benzylpenicillin, Flucloxacillin,, Clindamycin, Meropenem, Vancomycin	Debridement, SSG	Survived

Perbet et al. [50]	CT	MSSA	Augmentin, Piperacillin-tazobactam, Gentamicin, Metronidazole, Oxacillin, Clindamycin	Debridement, SSG	Survived
Phitsamai et al. [51]	USS	Vibrio-vulnificus	Ceftriaxone, Clindamycin, Ciprofloxacin	Debridement, SSG	Survived
			Doxycycline		
Porter et al. [52]	NS	Staph aureus, Strep pyogenes, Pseudomonas aeruginosa	Flucloxacillin, Penicillin, Clindamycin, Cefepime	Debridement	Survived
	NS	Strep pyogenes, Staph aureus, Corynebacterium, Klebsiella Oxytoca	NS	Debridement	Died
Saliba et al. [53]	CT	MSSA	Oxacillin, Vancomycin, Meropenem	Debridement	Survived
Schwarz et al. [54]	NS	Gram +ve cocci	Vancomycin, Cefotaxime	Debridement, SSG	Survived
Spock et al. [55]	CT	Staph aureus, E. Coli	NS	Debridement	Died
Tocco et al. [56]	CT	Group A beta-haemolytic strep	3rd generation Cephalosporin, Penicillin G, Clindamycin	Debridement	Died
Toledo et al. [57]	USS	Group A beta-haemolytic strep	NS	NS	NS
Tong et al. [14]	USS	Strep pyogenes, Staph aureus, Candida	Clindamycin, Meropenem, Vancomycin	Debridement, SSG, IVIG	Survived
Ugarte-Torres et al. [58]	MRI	Aeromonas hydrophila	Piperacillin-tazobactam, Meropenem, Clindamycin	Debridement	Died
Umemura et al. [59]	CT	Strep agalactiae	Meropenem, Vancomycin, Ampicillin, Clindamycin	Debridement, SSG	Survived
Wade et al. [60]	USS	Group A streptococcus	Piperacillin-tazobactam, Vancomycin, Ampicillin-sulbactam	Debridement, HBOT, SSG	Survived
Xu et al. [61]	CT	No organisms cultured	Piperacillin-tazobactam, Vancomycin, Fluconazole, Meropenem, Lincomycin	NS	Died
Yamashiro et al. [62]	MRI	Strep pneumoniae	Cefmetazole	Debridement	Died
Yang et al. [63]	MRI	E Coli	Ceftriaxone, Clindamycin, Ciprofloxacin	Debridement	Survived
Yoshii et al. [64]	MRI	Strep constellatus, Prevotella intermedia, Peptostreptococcus micros	Clindamycin, Meropenem, Sultamicillin	Debridement	Survived

Abbreviation: HBOT – Hyperbaric Oxygen Therapy; SSG – Split skin grafting; IVIG – intravenous immunoglobulin

Conclusion

SNSTIs are a rare and complex clinical entity that pose significant diagnostic and therapeutic challenges. Mortality rates for SNSTIs are higher than localised or single site NSTIs, and this review suggests they are more likely to result from a single causative organism. The limited data available on SNSTIs highlights the need for further research to better understand the underlying pathophysiology, risk factors, and epidemiology associated with these infections. Continued research and collaboration are warranted to improve our management of SNSTIs and optimise patient outcomes.

Acknowledgements: None

Conflict of Interest: The authors declare no conflict of interest

Financial Disclosure: No authors have received any funding or support.

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