

Necrotising Soft Tissue Infections

Camille Hua, Tomas Urbina, Romain Bosc, Tom Parks, Shiranee Sriskandan, Nicolas de Prost[#], Olivier Chosidow[#]

[#] Equal contribution as last author

Service de Dermatologie, Hôpitaux universitaires Henri Mondor, Assistance Publique-Hôpitaux de Paris, , Créteil, F-94010, France (C Hua, MD, Prof O Chosidow, MD) ; Epidemiology in Dermatology and Evaluation of Therapeutics (EpiDermE) - EA 7379, Université Paris Est Créteil (UPEC), Créteil, France, (C Hua, MD) GrIDIST, Groupe Infectiologie Dermatologique – Infections Sexuellement Transmissibles, Société Française de Dermatologie, France (C Hua, MD, Prof O Chosidow, MD); Service de Médecine Intensive Réanimation, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, Paris, France (T Urbina, MD) ; Service de Chirurgie Plastique, Hôpitaux universitaires Henri Mondor, Assistance Publique-Hôpitaux de Paris, Créteil, F-94010, France (R Bosc, MD) ; Department of Infectious Diseases, Imperial College London, London, UK (T Parks, MD, Prof S Sriskandan, PhD); MRC Centre for Molecular Bacteriology & Infection, Imperial College London, London, UK (Prof S Sriskandan, PhD); CARMAS Research Group, UPEC- Université Paris-Est Créteil Val de Marne, Faculté de médecine de Créteil, F-94010, France (Prof N de Prost, MD) ; Service de Médecine Intensive Réanimation, Hôpitaux universitaires Henri Mondor, Assistance Publique-Hôpitaux de Paris, F-94010, Créteil, France (Prof N de Prost, MD) ; Research group Dynamyc, EA7380, Faculté de Santé de Créteil, Ecole nationale vétérinaire d'Alfort, USC ANSES, Université Paris-Est Créteil, F-94010, Créteil, France (Prof O Chosidow, MD)

1 Correspondence to: Prof Olivier Chosidow,
2 Service de Dermatologie
3 Hôpital Henri Mondor, AP-HP, Université UPEC - Paris-est Créteil Val de Marne
4 51 av du Maréchal de Lattre de Tassigny
5 94010 Créteil, France
6 Tel/fax: + 33 1 49 81 25 01 /25 08
7 E mail: olivier.chosidow@aphp.fr

8

9 **Words count: 4532**

10

11

12

13

14

15

1
2
3 **Summary (150 words)**
4

5 The incidence of necrotising soft tissue infections (NSTI) has increased during recent decades
6 such that most physicians might see at least one case of these potentially life-threatening
7 infections in their career. Despite advances in care, NSTI are still associated with high
8 morbidity and mortality, underlining a need for continued education of the medical community.
9 In particular, failure to suspect NSTI fueled by poor awareness of the disease promotes delays
10 to first surgical debridement, amplifying disease severity and adverse outcomes. This review
11 will focus on practical approaches to management of NSTI including prompt recognition,
12 initiation of specific management, exploratory surgery, and aftercare. Increased alertness and
13 awareness for NSTI should improve time to diagnosis and early referral to specialised centers,
14 with consequent improvement in NSTI prognosis.
15

1 Introduction

2 Necrotising soft tissue infections (NSTI) are life-threatening infections characterised by
3 subcutaneous tissue, fascia or muscle necrosis, associated with high morbidity and mortality.¹
4 Early diagnosis is a challenge, with more than half of patients initially misdiagnosed.^{2,3} Despite
5 their relative low incidence, most physicians might see one NSTI throughout their career and
6 should be aware of this condition. Indeed, initial misdiagnosis, prolonging time to first surgical
7 debridement, is associated with increased morbidity and mortality.⁴ Unlike previously
8 published reviews, this article focuses on a pragmatic approach to non cervico-facial NSTI
9 recognition and management in adults.

10 Classification

11 NSTI encompass all infections with a necrotising component involving any or all layers of the
12 soft tissue compartment, from the dermis and subcutaneous tissue to the deeper fascia and
13 muscle.^{2,5} Multiple terms have been used to describe NSTI (*i.e.*, *necrotising fasciitis*, *hospital*
14 *gangrene*, *Fournier's gangrene*, *Meleney's gangrene: haemolytic streptococcal gangrene*),
15 including classifications based on microbiological findings (*i.e.*, *type I, II or III infections*,
16 *synergistic gangrene*, *clostridial cellulitis*), anatomical location (*e.g.*, *Fournier's gangrene*) or
17 depth of infection (*e.g.*, *necrotising cellulitis*, *necrotising fasciitis*, *myonecrosis*) (Figure 1).
18 Regardless of these classifications, the most important step in clinical practice is to differentiate
19 non-necrotising soft tissue infections (NNSTI) from necrotising ones, the latter being surgical
20 emergencies. NSTI share common pathophysiological features and therefore require a broadly
21 similar approach to diagnosis and management, foremost broad-spectrum antimicrobial therapy
22 and early surgical debridement, with intensive supportive care.⁶

23 Incidence

24 NSTI incidence estimates may be inaccurate due to the wide range of terms describing the
25 condition, its rarity, and the absence of a systematic nation-wide reporting policy. The few
26 population-based studies have a risk of bias by misdiagnosis when hospital electronic databases
27 are used.⁷⁻⁹ The estimated incidence of NSTI varies between geographic areas from 0.2 to 6.9
28 per 100 000 person-years, with peak incidence reported in Thailand reaching 15.5 per 100 000
29 person-years^{7,10-19} (Figure S1A, supplementary appendix). An increased incidence of NSTI,
30 group A *Streptococcus* (GAS) associated or not, has been reported in the last decades
31 worldwide.^{7,11,14,18,20,21}
32 Data are best established for NSTI caused by GAS, as active surveillance of invasive GAS
33 infection (iGAS) exists in several countries.²⁰⁻³¹ Prospective population-based studies report

iGAS incidence to be 3 to 4 per 100 000 person-years, although incidence may be 5 to 10 fold higher among indigenous populations or in tropical countries.²³ iGAS including NSTI closely follow poverty with increased incidence in low and medium-income countries (LMIC)^{32,33}. Although soft tissue infection is the commonest presentation of iGAS, NSTI comprise only ~10% of iGAS^{20-29,31} (Figure S1B, supplementary appendix). Rates of GAS NSTI are highest in the seasons when GAS throat infections increase, -winter and spring in the northern hemisphere-, coinciding with influenza and scarlet fever seasons respectively.³⁴ Geographic differences in patient risk factors, microbiology and portal of entry, have been observed regionally and internationally.³⁵⁻³⁷ Many specific variations of NSTI have been described depending on the anatomical location of the infection, (*e.g.*, cervico-facial NSTI, abdominoperineal NSTI), the population involved (*e.g.*, children, neutropenic patients) or the microbiology (*e.g.*, *Vibrio spp* or *Aeromonas spp* NSTI). These specificities are summarised in Table S1.

Pathogenesis

The factors that trigger NSTI are those that allow exposure to the causative pathogen(s), provide a portal of entry to permit virulent bacteria to enter the subcutaneous fascia or muscles, and the characteristics of the causative bacteria. Patient factors also play a key part in pathogenesis, both inherited and acquired. Approximately 60% of patients with iGAS or NSTI more generally have some other underlying medical illness such as immunosuppression, obesity, cardiac disease, chronic renal failure, cirrhosis, cancer, alcoholism, injecting drug use, and diabetes³⁸⁻⁴⁰ (Table S1). Some of these may relate to a predisposition to skin lesions, impaired immune response, impaired tissue vitality or higher exposure to causative pathogens.⁴¹ Genetic traits that affect skin integrity, respiratory tract mucosal integrity, and antibody-mediated opsonophagocytosis of GAS may all predispose to severe NSTI.⁴² For instance, a specific DQA1 allele of the human leucocyte antigen has been linked to iGAS with or without NSTI.⁴³

Polymicrobial NSTI

For polymicrobial NSTI, causative bacteria are usually the resident microbiota of the patient's own skin, the endogenous enteric microbiota, or the pharyngeal microbiota, all of which may include bacteria that were originally nosocomially-acquired. Bacteria are introduced to the subcutaneous tissues due to lesions in the skin or following spread from the oro-pharyngeal or gastro-urinary tract via instrumentation, surgery, abscess rupture, or fistulation from non-sterile sites, sometimes associated with carcinoma (Table S1). Devitalised tissue, coupled with patient

comorbidity such as diabetes, steroid or non-steroidal anti-inflammatory drugs (NSAIDs) use, and immunosuppression, impair host neutrophil defenses, allowing otherwise non-virulent bacteria to synergise and lead to a NSTI.

GAS NSTI

GAS monomicrobial NSTI by contrast is usually presumed to have spread from another person by airborne, droplet, or contact transmission; 5-12% of all iGAS are linked to exposure in a healthcare setting.⁴⁴ Roughly one half of cases of monomicrobial GAS NSTI are associated with reported breaks in the skin, either due to trauma (including trivial cuts, injecting drug use, war wounds, and both major and minor surgery) or due to pre-existing skin lesions (including varicella, scabies, pressure sores, eczema and psoriasis)^{39,45,46} (Table S1). The other half of cases show no clear portal of entry but about one quarter report recent blunt trauma without any apparent skin penetration.^{5,39} Several patients anecdotally report antecedent upper respiratory tract infections, and it is hypothesised that GAS causing sore throat enter the bloodstream to seed distant tissues,⁴⁷ however the mechanism is poorly understood. Recent experimental evidence points to the specific ability of GAS to enter and survive within the lymphatic system reaching the bloodstream by metastasis, augmented by the hyaluronan capsule and other virulence factors.⁴⁸ (Figure 2) Furthermore, blunt trauma increases the production of vimentin, a GAS-binding protein, on the surface of injured skeletal muscles, facilitating the initiation of GAS infection in the deep tissue following transient bacteremia from the oropharynx in susceptible hosts.^{5,49,50} Virulence of GAS leads to its ability to cause NSTI without need for synergy with other bacteria.^{51,52} (Figure 2).

Role of non-steroidal anti-inflammatory drugs

Several studies reported an association between NSAIDs and NSTI, particularly GAS NSTI.^{53–55} In experimentally injured muscle, NSAIDs exposure after blunt trauma enhanced binding of GAS⁵⁶ and impaired the immune responses in a model of GAS myonecrosis.^{56,57} A case-control study identified a strong association between NSAIDs use and NSTI in children with varicella.⁵⁴ However, observational studies may lack power or be biased as NSAIDs are taken because of disease severity. One randomised controlled trial (RCT) comparing ibuprofen to placebo in patients with cellulitis did not find an excess risk of NSTI, although the study was probably underpowered to detect an effect.⁵⁸ Nevertheless, these data warrant caution in NSAIDs use in the setting of skin infections,⁵⁹ as these drugs could at least mask signs and symptoms of NSTI, thereby delaying diagnosis and management with associated prognostic

consequences. In April 2019, The French National Agency for the Safety of Medicines and Health Products (ANSM) published a warning on the use of NSAIDs in patients with infectious diseases, including NSTI⁶⁰ while, in the United Kingdom, the National Institute for Health and Care Excellence (NICE) published advice cautioning against the use of NSAIDs in children with varicella.⁶¹

Management

Clinical diagnosis and surgical assessment

NSTI remains a challenging clinical diagnosis with features ranging from subacute insidious progression to sudden fulminating disease; around 50% of patients are initially misdiagnosed.^{2,3}

NSTI may occur in any area of the body but limbs followed by perineal locations are the most commonly involved areas, as opposed to the trunk and cervico-facial region.^{1,5,62} Early signs may be similar to those seen in NNSTI, including the triad of pain, swelling and erythema.³ Pain out of proportion to the physical findings -difficult to evaluate in patients with neurologic dysfunction-, systemic toxicity and rapid progression despite antimicrobials should strongly raise the suspicion of NSTI.^{3,5} Later in the course of disease, severe local signs more typical of NSTI can be observed, including purple/cyanotic skin discoloration, necrosis, hemorrhagic bullae (Figure 3), crepitus and hypoesthesia, but crucially their absence never excludes the diagnosis.⁵ Even in patients with systemic toxicity, *i.e.*, sepsis/ shock, severe local signs may be absent, particularly when infection initiates in deep tissues such as muscle.

Similarly, fever is present in only 40% of patients.^{3,5} Due to the low incidence and the poor sensitivity of early clinical signs, with diagnostic pitfalls,⁶³ we suggest that senior NSTI-experienced decision-makers should be involved early to estimate the likelihood of NSTI and therefore need for surgical exploration. Limited bedside incision under local anaesthesia of suspicious area with fascial inspection has been reported to help diagnosis.^{3,64} However, the “gold standard” to confirm NSTI is surgical exploration that reveals specific intraoperative findings, including dull grey necrotic tissue and fascia, dishwater pus, non-contracting muscle, lack of bleeding and/or a positive finger test, *i.e.*, when tissues can be readily dissected with a gloved finger. The evaluation of infection extension can include electrical muscle stimulation to assess viability (Video 1, supplementary appendix). In some situations, including during the early stages of NSTI or immunosuppressed patients, these macroscopic signs may be absent and only edema may be observed in the tissues.^{65,66} To improve early diagnosis, a triad of diagnostic approaches, incorporating intraoperative macroscopic findings; a fresh frozen section for histopathology; and an urgent Gram stain has been advocated.⁶⁶ However, it may be

challenging for practical reasons, and at minimum samples of debrided deep tissue should be sent for detailed examination in histopathology and microbiology laboratories.¹ Post-operative multidisciplinary reassessment at the bedside is warranted, particularly for patients without macroscopic tissue necrosis during first surgery, as 14% of NSTI progress to “visible” obvious necrotising infection.⁶⁵ As such, performing “second-look” surgery routinely is therefore recommended.¹

Diagnostic tools

Imaging

Imaging should not delay urgent surgical exploration, particularly for patients in shock, as it has not shown satisfactory sensitivity to distinguish NSTI from NNSTI. In stable and equivocal cases, Magnetic Resonance Imaging (MRI) is the most effective method to diagnose limbs NSTI and might provide useful diagnostic clues if thickened fascia (>3 mm) with hypersignal on fat-suppressed T2 weighted sequences are seen (Figure S2)^{67,68}. Standard x-rays have poor sensitivity and can only detect NSTI at advanced stages with gas in the soft tissue. CT scan is of little diagnostic value for limb NSTI but should be performed for abdominoperineal (or cervico-facial) infections to detect the portal of entry and guide surgical management (Figure S2). CT scan findings associated with NSTI include presence of gas, fluid collections and involvement of fascia with asymmetrical fascial thickening and lack of enhancement after contrast injection -which is the most specific findings-.⁶⁹

Laboratory investigations

Several biomarkers and scores such as the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC, a score derived from blood CRP, leukocyte count, haemoglobin, sodium, creatinine, and glucose values) have been studied to distinguish NSTI from NNSTI and/or predict patient outcome.⁷⁰⁻⁷² LRINEC, which was developed retrospectively, has still debated diagnostic performance.⁷³⁻⁷⁵ Whether it could be of use for inexperienced or junior doctors by providing a standardised, objective tool for clinical assessment warrants further research. Hyperlactatemia is an independent predictor of need for amputation and mortality, while admission procalcitonin is associated with progression to septic shock.^{71,72} Creatinine kinase levels are often elevated, mostly in GAS NSTI,⁷⁶ suggesting myonecrosis. Importantly, no biomarker or score has been demonstrated to be sensitive enough to rule out NSTI and surgical exploration must always be conducted when clinical suspicion is high.

Microbiological diagnosis

1 NSTI are mostly polymicrobial infections (50% to 85%).^{38,77} In a recent metaanalysis (8718
2 total patients from 105 studies included), pooled prevalence of polymicrobial and
3 monomicrobial infections were 53% and 37.9%, respectively.⁷⁸ NSTI have been classified
4 microbiologically as type I (polymicrobial infection caused by Gram-positive cocci, fermenting
5 and non-fermenting bacilli and anaerobic bacteria), type II (monomicrobial infection caused by
6 *Streptococcus* spp or *Staphylococcus aureus*) or type III (caused by *Vibrio* species or
7 *Aeromonas* species).¹ A type IV category was recently proposed for fungal infections, mainly
8 involving *Candida* sp. and Zygomycetes in immunocompromised hosts.⁷⁹ Although Gram-
9 positive organisms are more typically associated with NSTI, a variety of Gram negative
10 organisms may also be responsible depending on local epidemiological and host factors (*Vibrio*
11 species in subtropical areas)⁸⁰(Table S1). Recent reports of Enterobacteriales limb NSTI,
12 occurring mostly in immunocompromised patients, with higher mortality than in type I and II
13 NSTI, suggested rethinking this classification.⁸¹ Beyond these specificities, with the exception
14 of *Vibrio* spp NSTI, which are associated with a more fulminant course of disease, the clinical
15 presentation are very close whatever the pathogen involved, even if the pathogenesis of GAS
16 NSTI has been much more studied.

17 Nevertheless, as the microbiological diagnosis is unknown at the time of admission, it cannot
18 influence early management. Furthermore, new microbiological techniques such as next
19 generation sequencing recently highlighted the complexity of the pathobiome often found in
20 NSTI.^{82,83}

21 Blood cultures, fine-needle aspiration in an area of skin necrosis (see below), and intraoperative
22 deep tissue biopsy have been recommended by the Infectious Diseases Society of America
23 (IDSA) for microbiological diagnosis, rather than superficial wound swabs,¹ which are
24 unreliable due to high contamination risk. Blood and intraoperative tissue biopsy cultures are
25 positive in 11-60% and 80% of cases respectively.^{79,84,85} Fine-needle aspiration of an area of
26 necrotic skin is simple and quick, and culture-positive in up to 73% of cases⁸⁶ (see Video 2,
27 supplementary appendix). Ultrasound-guided infectious fluid along the fascia aspiration might
28 be useful as well.⁸⁷ In immunocompromised patients, fungal cultures should be performed, in
29 addition to the bacteriological cultures performed in all patients. Performing polymerase chain
30 reactions (PCR) for specific bacterial species (e.g. GAS) may aid their identification, even after
31 initiation of anti-microbials, while shotgun metagenomics is promising for more exhaustive
32 identification of the wider pathobiome involved in NSTI, notably anaerobes.⁸³

33 Treatment

Noting the rarity of NSTI, a 2018 Cochrane systematic review found only three RCT that assessed the impact of therapeutic interventions on NSTI mortality. No conclusions could be drawn from these small disparate studies.⁸⁸ To date, current guidelines are mostly based on observational retrospective cohort studies.¹ However, some prospective registries of NSTI published^{40,84} or ongoing (worldwide-based “Skin-ICU” study) (NCT05116956) may provide better level of evidence. All available data suggest that a high index of diagnostic suspicion is required, optimising interventions most likely to impact outcome, mainly early surgical debridement of necrotic tissues –within 6-12 hours after admission with significantly lower mortality rates⁸⁹⁻⁹¹–, prompt initiation of broad-spectrum antibiotics and management of associated organ failures (Figure 4).

Triage, recognition, and multidisciplinary management

The main factors contributing to surgical delay are misdiagnosis, a delayed surgical decision, and logistical issues regarding operating room access.⁹² Implementing multidisciplinary bundles at the hospital scale has shown promising results.^{93,94} Using a triage algorithm including a 24/7 on-call NSTI-experienced specialist, identifying senior experienced practitioners in each specialty involved (*e.g.*, surgeons, intensivist, infectious disease physician, dermatologist, microbiologist) and implementing a bundle of measures may improve global management and patient prognosis. Ideally, centres with an expert multidisciplinary team should be available in each region, as several studies found an improved outcome for NSTI in high case volume centers.^{13,18,95} (Table S2).

Surgery

Urgent extensive surgical removal of necrotic tissues until healthy tissues (contractile muscle, glistening fat and bleeding tissues) is the cornerstone of management. In addition to controlling the source of infection, it allows for confirming the diagnosis of NSTI, obtaining microbiological/histological samples, and determining the extent of tissue necrosis^{96,97} (Video 1, supplementary appendix). According to Holena et al., performing the first surgical debridement “*is not considered to be a technically challenging operation*”.⁹⁸ Because the consequences of the surgical debridement can be devastating (*i.e.*, aggressive and extensive debridement with large tissue defect, risk of amputation) this procedure should ideally be performed by a senior surgeon. Anyhow, patient transfer should be considered if early surgery cannot be performed locally.^{8,98,99} (Table S2). Post-operative reassessment, ideally including a second-look surgery, is warranted for all patients, either to make the diagnosis in case of

initially reassuring surgical findings but no subsequent clinical improvement, or to perform further tissue debridement (a median of 2-3 debridements are required per patient).^{1,65}

Antibiotics

Physicians face several challenges regarding antibiotic therapy for NSTI. First, the frequency of polymicrobial infections and rapid progression of NSTI mandates broad-spectrum agents with bactericidal action. Second, the central role of toxins in GAS infections suggests use of agents that reduce toxin production. Finally, impairment in pharmacokinetics and pharmacodynamics in the NSTI context warrant optimized antibiotic choice and administration modalities to achieve satisfactory tissue diffusion. Data on antibiotic treatment specifically for NSTIs are scarce, with guidelines mainly based on expert consensus. Initial intravenous antibiotic therapy should cover Gram positive, Gram negative, and anaerobic bacteria. Anatomical NSTI location is strongly associated with microbiological diagnosis, but is insufficient to alter initial antibiotic therapy.^{38,100–102} As a minimum, an intravenous broad-spectrum β -lactam should be used (e.g., piperacillin-tazobactam, 4 g q6h or cefotaxime 2g q6h), informed by local ecology and individual patient factors (recent exposure to antibiotics, nursing-home residency, nosocomial infection, known carriage or previous infection due to resistant bacterial strains). Suspected MRSA can be covered by inclusion of vancomycin (30 mg/kg loading dose before 30 mg/kg/24h continuous infusion), or daptomycin (8-12 mg/kg q24h) or linezolid (600 mg q12h), depending on level of suspicion, while resistant Gram-negative strains can be covered by use of carbapenems (e.g., meropenem, 1-2 g q8h). Aminoglycosides (gentamicin, 5-8 mg/kg over 30 min q24h or amikacin, 25-30 mg/kg over 30 min q24h) should be considered to further broaden spectrum only in case of septic shock.^{1,103} (Figure 5). The only pharmaceuticals prospectively evaluated for NSTI are not routinely used: Tigecycline, which was not evaluated comparatively¹⁰⁴, and moxifloxacin, which did not show superiority to amoxicillin-clavulanate¹⁰⁵. Clindamycin has gained interest in NSTI management due to the high prevalence of GAS infection, ranging from 30% to 50%.^{14,38} *In vitro* and *in vivo* models of GAS infection have shown clindamycin-related reduction in exotoxin production and disease severity, with improved bacterial clearance.^{106–109} The impact of subinhibitory clindamycin concentrations is debated, prompting high dose use.¹⁰⁶ Although there are no data focusing on NSTI, several retrospective studies on streptococcal toxic shock syndrome (STSS) cohorts, that include 40-60% NSTI, suggested a survival benefit for GAS infections specifically.^{110–112} Empiric clindamycin (600-1200 mg q6 h-q8h IV) for documented GAS NSTI is currently recommended by IDSA guidelines¹ and may be started empirically once

suspicion of GAS is high. Robust data regarding other antibiotics with protein synthesis-inhibiting activity such as linezolid are lacking. However, although the antitoxin effects of clindamycin are independent of strain susceptibility,¹⁰⁹ linezolid could be considered in settings where clindamycin resistance is more prevalent.¹¹³ In NSTI patients, altered perfusion hinders antibiotic delivery to the infection site, favored by increased distribution volume (in septic shock) and local tissue necrosis.¹¹⁴ Beyond urgent source control by aggressive surgical debridement, optimisation of antibiotic delivery is of paramount importance. Appropriately high loading doses, prolonged infusion times, and therapeutic drug monitoring for hydrophilic and time-dependent drugs such as beta-lactams, as demonstrated in patients with sepsis/septic shock, are recommended.¹¹⁵ Data from diabetic foot infection, acute limb ischemia, or necrotising pancreatitis suggest lipophilic molecules are useful. Carbapenem diffusion might be reduced in ischemic tissues, limiting their use to cases with a high risk of resistance to other beta-lactams.¹¹⁶

There are no trials focusing on antibiotic treatment duration for NSTI, which varies widely between centers, typically between 7 to 14 days, without robust data on relapse or other outcomes to guide management.¹¹⁷ Guidelines based on expert opinion recommend treatment for 48-72 hours after the last surgical debridement, provided there is clinical improvement including afebrile.¹ This delay seems suited to assess treatment response and guide antibiotic stewardship.¹¹⁸ De-escalation to oral therapy has not been specifically studied in NSTI, but seems reasonable for patients whose clinical condition is improving and can be monitored, as peri-operative samples and blood cultures allow for a microbiological diagnosis to be obtained in most cases.^{38,104}

Adjuvant therapies

Polyvalent intravenous immunoglobulins (IVIG) were proposed for NSTI based on toxin neutralizing activity in STSS patient sera,¹¹⁹ with increased GAS clearance and decreased disease severity in experimental models.¹²⁰ Rates in IVIG use for NSTI vary widely, from 58% in a recent Scandinavian study³⁸ to 0.3% in the USA.¹²¹ The only RCT focusing on NSTI patients did not show improved outcomes.¹²² However, only 18% of patients included had confirmed GAS infection, limiting generalisability to GAS-related NSTI. Moreover, a meta-analysis assessing IVIG use in clindamycin-treated patients with STSS or GAS NSTI with shock did show a survival benefit,¹²³ including in the subset of a more recent US-based cohort with GAS NSTI. Although based mainly on observational studies, the currently available data supports using adjuvant IVIG for GAS NSTI but not for other pathogens.

Although a pathophysiological rationale was developed for hyperbaric oxygen (HBO) therapy in clostridial infections, data are conflicting on its benefits,^{124–127} and HBO is not consistently recommended in NSTI guidelines. HBO should not delay initiation of other treatments and not be the sole motive of inter-hospital transfer.

Building on the concept of toxin neutralization, immunomodulation has also been evaluated using reltecimod, an inhibitor of T-cell activation by bacterial superantigens. Although a RCT failed to show significant benefit in NSTI,¹²⁸ orphan drug designation for NSTI paves the way for future trials of immunomodulation in that setting.

Post-operative care and patient-centered management

There is no consensus on post-operative wound care in patients who undergo surgical debridement for NSTI. These large soft tissue defects can be a challenge and requires specially trained wound care nurses. Accumulating retrospective data supports a benefit of vacuum-assisted therapy on rates and timing of wound closure, workload, length of hospital stay, and possibly survival.¹²⁹ Negative pressure devices can promote granulation and tissue formation in a closed wound environment with removal of excess exsudate. Nevertheless, data are largely uncontrolled,¹³⁰ this therapy might be associated with higher pain scores and costs, and larger scale RCT are awaited (NCT05071443). Data are also lacking regarding the best timing of skin grafting, which is typically performed within 3 to 6 weeks of initial debridement (Figure S3). Physical and psychological support should be offered to all patients, as up to 30% of patients have major physical sequelae,¹³¹ with prolonged quality-of-life alterations in mental health.¹³² Indeed, Hospital Anxiety and Depression (HAD-D) and the Impact of Event Scale-Revised (IES-R) scores in NSTI survivors were higher than in matched controls with non NSTI septic shock.¹³² Patient support groups can provide peer support to patients and families and obtain useful patient-centred feedback. Indeed, a majority of NSTI survivors and their families reported a lack of information and general lack of knowledge about NSTI within the healthcare setting, while over half reported a lack of mental health and physical therapy support after NSTI (personal communication, Lee Spark Foundation).

Household contacts and transmission of GAS

The risk of iGAS among their household contacts, including GAS NSTI, is 20 to 200 times higher than in the general population.¹³³ Indeed, several cases of infections or pharyngeal carriage acquisition of identical strains have been described among households contacts of iGAS patients.^{134,135} No study has evaluated the impact of antibiotic chemoprophylaxis for contacts of NSTI. Nevertheless, in the USA, chemoprophylaxis is recommended in those with > 20 hours of close contact with GAS NSTI in the previous 7 days.¹³⁶ In England,

chemoprophylaxis is recommended for high-risk contacts of iGAS (neonates, women > 37 weeks pregnant or < 4 weeks after puerperium, persons $\geq$ 75 years old and individuals with chickenpox within 14 days).¹³⁷

Mortality

The sustained high mortality associated with NSTI is challenging. A pooled analysis of 67 studies between 1980 and 2008 including 3302 patients estimated mortality to be 23.5% (range 6-64%).² However, patient populations were heterogeneous with varying sample sizes (n=7 to 198).² Population-based data from the USA reported lower hospital mortality rates (9 %-12%)^{7,9,98,121} but should be interpreted with caution because International Classification of Diseases (ICD) codes were used, increasing the risk of mis-classification.

A metaanalysis showed that mortality rates decreased comparing before and after the year 2000 (28.8% to 20.6%, respectively) but remained stable over the past 20 years.⁴ In the USA, NSTI accounted for 4.8 deaths per 1 000 000-person years with no change in the incidence between 2002 and 2013.¹³⁸ Several risk factors for mortality have been published, including host-related risk factors (advanced age, underlying diseases, immunocompromised status), variables reflecting clinical presentation and severity of illness (disseminated NSTI, shock, number of organs failure), biological variables at hospital admission, microorganisms identified (*Aeromonas* spp, *Vibrio* spp, *Clostridial* spp, STSS) and therapeutic interventions (Figure S4). However, most studies had limitations, including heterogeneity of the studied populations and small sample sizes, with numerous studies being single-institution^{90,139,140} rather than population-based.^{13,39} Only a few predictors of mortality are consistent across studies, with variations according to geographic area location.³⁵ The most important and modifiable one is time to initial surgery^{4,18,64,89-91,122,141-147} (Table S3). A recent meta-analysis showed a reduction in hospital mortality associated with surgical debridement performed within 12 hours of hospital admission (OR 0.41; 95% CI 0.27–0.61; 16 studies included).⁴ Some studies suggest that interhospital transfer, when leading to delayed surgical treatment, might be associated with increased mortality.^{8,98} The benefit-to-risk ratio of interhospital transfers should be assessed on a case-by-case basis and postponed if the first surgery can be performed locally without delay.^{1,141,148}

Perspectives

Improving NSTI recognition

Lack of experience may lead to failure in distinguishing NSTI from NNSTI, resulting in higher mortality and disabilities. Ensuring medical education includes NSTI, as planned in the UK¹⁴⁹ and France¹⁵⁰, cellulitis clinics, 24/7 available expert centers, multidisciplinary and telemedicine could contribute to improved diagnosis, management and public health and therefore better prognosis.

Research priorities

See supplementary Table S4

Disabilities

In order to develop future treatment modalities, research should consider NSTI as an orphan disease, and note that disease heterogeneity may warrant microbe or host specific strategies.

Conclusion

NSTI are life-threatening and have major impacts on function and quality of life in survivors. Although recent years suggest an improvement in mortality and morbidity, early diagnosis and medical/surgical management of patients remain far from optimal. A clinically-approved vaccine against GAS, as recommended by WHO, could have a significant impact on NSTI incidence.¹⁵¹ We believe that NSTI should be considered as a major “Neglected Worldwide Diseases” (NWD). Public-health policies that promote education among both healthcare practitioners as well as patients, and expert centers, coupled with systematic data collection and translational world-wide research programs, including LMIC, could lead to better outcomes for NSTI in the future.

Search strategy and selection criteria

We searched PubMed for articles published up to March 2021 with the terms « necrotizing or necrotising fasciitis », « necrotizing or necrotising soft tissue infection », « synergistic necrotizing cellulitis », « progressive synergistic bacterial gangrene » and « suppurative fasciitis » and combined with the terms « case control studies », « cohort studies », « cross sectional studies », « observational studies », « randomized controlled trial », « clinical trials ». Articles resulting from these searches and relevant references cited in those articles were reviewed. We selected articles about necrotizing soft tissue infection of the limb and abdominoperineal location in adults aged 18 years and over. Articles published in English were included. We excluded articles about pediatric or cervico-facial forms of necrotizing infections.

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8

Author's contribution

CH wrote the first draft of the manuscript

TU, CH, NDP and OC contributed equally to the literature search and analysis, manuscript writing and critical revision of this Seminar.

TP and SS wrote the pathophysiology section of the manuscript

All authors contributed equally in revising the manuscript and approved the final version.

Declaration of interests

CH, TU, NDP, RB, SS, OC, TP declared no conflicts of interest

Acknowledgments

The authors acknowledge both patients, particularly the Lee Spark Foundation for Necrotising Fasciitis and Severe Strep A infections, and all caregivers involved in NSTI care.

TU, CH, OC and NDP acknowledge the Henri-Mondor Hospital Necrotising Fasciitis Group*, Prof Christian Brun-Buisson, Dr Saskia Oro, Prof Alain Rahmouni (deceased) and Prof Jean-Claude Roujeau (deceased).

SS and TP acknowledge the NIHR Imperial BRC.

SS acknowledges the support of the NIHR Biomedical Research Centre at Imperial College London and NIHR Health Protection Research Unit in Healthcare-associated infections and AMR

TP acknowledges funding from the National Institute for Health Research (CL-2020-21-001) and the Wellcome Trust (222098/Z/20/Z). The views expressed are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

***Henri-Mondor Hospital Necrotising Fasciitis Working Group, France,** Nicola de Angelis Lina El Bejjani, Olivier Chosidow, Barbara Hersant, Camille Hua, , , Raphael Lepeule, Alain Luciani, Lionel Nakad, Tiphaine Pelegrin, Claire Pressiat, Nicolas de Prost, Quentin de Roux Paul-Louis Woerther,

References

- 1 Stevens DL, Bisno AL, Chambers HF, *et al.* Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2014; **59**: e10-52.
- 2 May AK. Skin and soft tissue infections. *Surg Clin North Am* 2009; **89**: 403–20, viii.
- 3 Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. *Br J Surg* 2014; **101**: e119-125.
- 4 Nawijn F, Smeeing DPJ, Houwert RM, Leenen LPH, Hietbrink F. Time is of the essence when treating necrotizing soft tissue infections: a systematic review and meta-analysis. *World J Emerg Surg WJES* 2020; **15**: 4.
- 5 Stevens DL, Bryant AE. Necrotizing Soft-Tissue Infections. *N Engl J Med* 2017; **377**: 2253–65.
- 6 Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2007; **44**: 705–10.
- 7 Oud L, Watkins P. Contemporary Trends of the Epidemiology, Clinical Characteristics, and Resource Utilization of Necrotizing Fasciitis in Texas: A Population-Based Cohort Study. *Crit Care Res Pract* 2015; **2015**. DOI:10.1155/2015/618067.
- 8 Endorf FW, Klein MB, Mack CD, Jurkovich GJ, Rivara FP. Necrotizing soft-tissue infections: differences in patients treated at burn centers and non-burn centers. *J Burn Care Res Off Publ Am Burn Assoc* 2008; **29**: 933–8.
- 9 Mulla ZD, Gibbs SG, Aronoff DM. Correlates of length of stay, cost of care, and mortality among patients hospitalized for necrotizing fasciitis. *Epidemiol Infect* 2007; **135**: 868–76.
- 10 Khamnuan P, Chongruksut W, Jearwattananok K, Patumanond J, Tantraworasin A. Necrotizing fasciitis: epidemiology and clinical predictors for amputation. *Int J Gen Med* 2015; **8**: 195–202.
- 11 Das DK, Baker MG, Venugopal K. Increasing incidence of necrotizing fasciitis in New Zealand: a nationwide study over the period 1990 to 2006. *J Infect* 2011; **63**: 429–33.
- 12 Mulla ZD, Leaverton PE, Wiersma ST. Invasive Group A Streptococcal Infections in Florida: *South Med J* 2003; **96**: 968–73.
- 13 Audureau E, Hua C, de Prost N, *et al.* Mortality of necrotizing fasciitis: relative influence of individual and hospital-level factors, a nationwide multilevel study, France, 2007-12. *Br J Dermatol* 2017; **177**: 1575–82.
- 14 Bodansky DMS, Begaj I, Evison F, Webber M, Woodman CB, Tucker ON. A 16-year Longitudinal Cohort Study of Incidence and Bacteriology of Necrotising Fasciitis in England. *World J Surg* 2020; **44**: 2580–91.
- 15 Ellis Simonsen SM, van Orman ER, Hatch BE, *et al.* Cellulitis incidence in a defined population. *Epidemiol Infect* 2006; **134**: 293–9.
- 16 Soltani AM, Best MJ, Francis CS, Allan BJ, Askari M, Panthaki ZJ. Trends in the incidence and treatment of necrotizing soft tissue infections: an analysis of the National Hospital Discharge Survey. *J Burn Care Res Off Publ Am Burn Assoc* 2014; **35**: 449–54.
- 17 Liu TJ, Tai H-C, Chien K-L, Cheng N-C. Predisposing factors of necrotizing fasciitis with comparison to cellulitis in Taiwan: A nationwide population-based case-control study. *J Formos Med Assoc Taiwan Yi Zhi* 2020; **119**: 18–25.
- 18 Hedetoft M, Madsen MB, Madsen LB, Hyldegaard O. Incidence, comorbidity and mortality in patients with necrotising soft-tissue infections, 2005-2018: a Danish nationwide register-based cohort study. *BMJ Open* 2020; **10**: e041302.
- 19 Choi HK, Seo GH, Han E. The incidence and seasonal variation of necrotizing

fasciitis in Korea: a nationwide cross-sectional study. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2020; **26**: 1090.e1-1090.e6.

20 Nelson GE, Pondo T, Toews K-A, *et al.* Epidemiology of Invasive Group A Streptococcal Infections in the United States, 2005-2012. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2016; **63**: 478–86.

21 Plainvert C, Doloy A, Loubinoux J, *et al.* Invasive group A streptococcal infections in adults, France (2006-2010). *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2012; **18**: 702–10.

22 Vlamincx B, van Pelt W, Schouls L, *et al.* Epidemiological features of invasive and noninvasive group A streptococcal disease in the Netherlands, 1992-1996. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2004; **23**: 434–44.

23 Steer AC, Jenney A, Kado J, *et al.* Prospective surveillance of invasive group a streptococcal disease, Fiji, 2005-2007. *Emerg Infect Dis* 2009; **15**: 216–22.

24 O’Grady K-AF, Kelpie L, Andrews RM, *et al.* The epidemiology of invasive group A streptococcal disease in Victoria, Australia. *Med J Aust* 2007; **186**: 565–9.

25 Darenberg J, Luca-Harari B, Jasir A, *et al.* Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2007; **45**: 450–8.

26 Lamagni TL, Darenberg J, Luca-Harari B, *et al.* Epidemiology of Severe Streptococcus pyogenes Disease in Europe. *J Clin Microbiol* 2008; **46**: 2359–67.

27 Imöhl M, Fitzner C, Perniciaro S, van der Linden M. Epidemiology and distribution of 10 superantigens among invasive Streptococcus pyogenes disease in Germany from 2009 to 2014. *PloS One* 2017; **12**: e0180757.

28 Laupland KB, Ross T, Church DL, Gregson DB. Population-based surveillance of invasive pyogenic streptococcal infection in a large Canadian region. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2006; **12**: 224–30.

29 Meehan M, Murchan S, Gavin PJ, Drew RJ, Cunney R. Epidemiology of an upsurge of invasive group A streptococcal infections in Ireland, 2012-2015. *J Infect* 2018; **77**: 183–90.

30 Naseer U, Steinbakk M, Blystad H, Caugant DA. Epidemiology of invasive group A streptococcal infections in Norway 2010-2014: A retrospective cohort study. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2016; published online June 16. DOI:10.1007/s10096-016-2704-y.

31 Williamson DA, Morgan J, Hope V, *et al.* Increasing incidence of invasive group A streptococcus disease in New Zealand, 2002-2012: a national population-based study. *J Infect* 2015; **70**: 127–34.

32 Steer AC, Lamagni T, Curtis N, Carapetis JR. Invasive group a streptococcal disease: epidemiology, pathogenesis and management. *Drugs* 2012; **72**: 1213–27.

33 Streptococcus: An organism causing diseases beyond neglect - PubMed. <https://pubmed.ncbi.nlm.nih.gov/32437344/> (accessed May 23, 2022).

34 Lamagni TL, Efstratiou A, Dennis J, *et al.* Increase in invasive group A streptococcal infections in England, Wales and Northern Ireland, 2008-9. *Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull* 2009; **14**: 19110.

35 Kao LS, Lew DF, Arab SN, *et al.* Local variations in the epidemiology, microbiology, and outcome of necrotizing soft-tissue infections: a multicenter study. *Am J Surg* 2011; **202**: 139–45.

36 Lee Y-C, Hor L-I, Chiu H-Y, Lee J-W, Shieh S-J. Prognostic factor of mortality and its clinical implications in patients with necrotizing fasciitis caused by *Vibrio vulnificus*. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1011–8.

37 Lee TC, Carrick MM, Scott BG, Hodges JC, Pham HQ. Incidence and clinical characteristics of methicillin-resistant *Staphylococcus aureus* necrotizing fasciitis in a large

urban hospital. *Am J Surg* 2007; **194**: 809–12; discussion 812–813.

38 Madsen MB, Skrede S, Perner A, *et al.* Patient's characteristics and outcomes in necrotising soft-tissue infections: results from a Scandinavian, multicentre, prospective cohort study. *Intensive Care Med* 2019; **45**: 1241–51.

39 Kaul R, McGeer A, Low DE, Green K, Schwartz B. Population-based surveillance for group A streptococcal necrotizing fasciitis: Clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario Group A Streptococcal Study. *Am J Med* 1997; **103**: 18–24.

40 Bruun T, Rath E, Bruun Madsen M, *et al.* Risk factors and Predictors of Mortality in Streptococcal Necrotizing Soft-Tissue Infections: A Multicenter Prospective Study. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2020; published online Jan 10. DOI:10.1093/cid/ciaa027.

41 Valenciano SJ, Onukwube J, Spiller MW, *et al.* Invasive Group A Streptococcal Infections Among People Who Inject Drugs and People Experiencing Homelessness in the United States, 2010–2017. *Clin Infect Dis* 2020; : ciaa787.

42 Bisno AL, Brito MO, Collins CM. Molecular basis of group A streptococcal virulence. *Lancet Infect Dis* 2003; **3**: 191–200.

43 Parks T, Elliott K, Lamagni T, *et al.* Elevated risk of invasive group A streptococcal disease and host genetic variation in the human leucocyte antigen locus. *Genes Immun* 2020; **21**: 63–70.

44 Steer JA, Lamagni T, Healy B, *et al.* Guidelines for prevention and control of group A streptococcal infection in acute healthcare and maternity settings in the UK. *J Infect* 2012; **64**: 1–18.

45 Monnickendam MA, McEvoy MB, Blake WA, *et al.* Necrotising fasciitis associated with invasive group A streptococcal infections in England and Wales. *Adv Exp Med Biol* 1997; **418**: 87–9.

46 Thean LJ, Jenney A, Engelman D, *et al.* Hospital admissions for skin and soft tissue infections in a population with endemic scabies: A prospective study in Fiji, 2018–2019. *PLoS Negl Trop Dis* 2020; **14**: e0008887.

47 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 21–1995. A 33-year-old man with a sore throat followed by swelling and pain in the leg. *N Engl J Med* 1995; **333**: 113–9.

48 Siggins MK, Lynskey NN, Lamb LE, *et al.* Extracellular bacterial lymphatic metastasis drives *Streptococcus pyogenes* systemic infection. *Nat Commun* 2020; **11**: 4697.

49 Bryant AE, Bayer CR, Huntington JD, Stevens DL. Group A streptococcal myonecrosis: increased vimentin expression after skeletal-muscle injury mediates the binding of *Streptococcus pyogenes*. *J Infect Dis* 2006; **193**: 1685–92.

50 Charpentier C, Kouby F, Hua C, *et al.* Group B streptococcal necrotizing soft-tissue infection: role of pharyngeal and perineal carriage. *J Eur Acad Dermatol Venereol JEADV* 2020; published online Sept 15. DOI:10.1111/jdv.16943.

51 Edwards RJ, Taylor GW, Ferguson M, *et al.* Specific C-terminal cleavage and inactivation of interleukin-8 by invasive disease isolates of *Streptococcus pyogenes*. *J Infect Dis* 2005; **192**: 783–90.

52 Walker MJ, Barnett TC, McArthur JD, *et al.* Disease manifestations and pathogenic mechanisms of Group A *Streptococcus*. *Clin Microbiol Rev* 2014; **27**: 264–301.

53 Nuwayhid ZB, Aronoff DM, Mulla ZD. Blunt trauma as a risk factor for group A streptococcal necrotizing fasciitis. *Ann Epidemiol* 2007; **17**: 878–81.

54 Souyri C, , Olivier P, *et al.* Severe necrotizing soft-tissue infections and nonsteroidal anti-inflammatory drugs. *Clin Exp Dermatol* 2008; **33**: 249–55.

55 Chosidow O, Saiag P, Piquier L, Bastuji-Garin S, Revuz J, Roujeau JC. Nonsteroidal

anti-inflammatory drugs in cellulitis: a cautionary note. *Arch Dermatol* 1991; **127**: 1845–6.

56 Hamilton SM, Bayer CR, Stevens DL, Lieber RL, Bryant AE. Muscle injury, vimentin expression, and nonsteroidal anti-inflammatory drugs predispose to cryptic group A streptococcal necrotizing infection. *J Infect Dis* 2008; **198**: 1692–8.

57 Weng T-C, Chen C-C, Toh H-S, Tang H-J. Ibuprofen worsens *Streptococcus pyogenes* soft tissue infections in mice. *J Microbiol Immunol Infect Wei Mian Yu Gan Ran Za Zhi* 2011; **44**: 418–23.

58 Davis JS, Mackrow C, Binks P, *et al.* A double-blind randomized controlled trial of ibuprofen compared to placebo for uncomplicated cellulitis of the upper or lower limb. *Clin Microbiol Infect* 2017; **23**: 242–6.

59 Aronoff DM, Bloch KC. Assessing the relationship between the use of nonsteroidal antiinflammatory drugs and necrotizing fasciitis caused by group A streptococcus. *Medicine (Baltimore)* 2003; **82**: 225–35.

60 Anti-inflammatoires non stéroïdiens (AINS) et complications infectieuses graves - Point d'Information actualisé le 20/05/2020 - ANSM : Agence nationale de sécurité du médicament et des produits de santé. <https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Anti-inflammatoires-non-steroidiens-AINS-et-complications-infectieuses-graves-Point-d-Information-actualise-le-20-05-2020> (accessed Oct 27, 2020).

61 National Institute For Health and Care Management. <https://cks.nice.org.uk/topics/chickenpox/management/child-or-adult/>. <https://cks.nice.org.uk/topics/chickenpox/management/child-or-adult/>.

62 Hasham S, Matteucci P, Stanley PRW, Hart NB. Necrotising fasciitis. *BMJ* 2005; **330**: 830–3.

63 Stevens DL, Bryant AE. Necrotizing Soft-Tissue Infections. *N Engl J Med* 2018; **378**: 971.

64 Sudarsky LA, Laschinger JC, Coppa GF, Spencer FC. Improved Results from a Standardized Approach in Treating Patients with Necrotizing Fasciitis: *Ann Surg* 1987; **208**: 661–5.

65 Howell EC, Keeley JA, Kaji AH, *et al.* Chance to cut: defining a negative exploration rate in patients with suspected necrotizing soft tissue infection. *Trauma Surg Acute Care Open* 2019; **4**: e000264.

66 Nawijn F, Houwert RM, van Wessem KPJ, *et al.* A 5-Year Evaluation of the Implementation of Triple Diagnostics for Early Detection of Severe Necrotizing Soft Tissue Disease: A Single-Center Cohort Study. *World J Surg* 2019; **43**: 1898–905.

67 Kim K-T, Kim YJ, Won Lee J, *et al.* Can necrotizing infectious fasciitis be differentiated from nonnecrotizing infectious fasciitis with MR imaging? *Radiology* 2011; **259**: 816–24.

68 Rahmouni A, Chosidow O, Mathieu D, *et al.* MR imaging in acute infectious cellulitis. *Radiology* 1994; **192**: 493–6.

69 Carbonetti F, Cremona A, Carusi V, *et al.* The role of contrast enhanced computed tomography in the diagnosis of necrotizing fasciitis and comparison with the laboratory risk indicator for necrotizing fasciitis (LRINEC). *Radiol Med (Torino)* 2016; **121**: 106–21.

70 Wong C-H, Khin L-W, Heng K-S, Tan K-C, Low C-O. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 2004; **32**: 1535–41.

71 Chang C-P, Fann W-C, Wu S-R, Lin C-N, Hsiao C-T. Lactate on emergency department arrival as a predictor of in-hospital mortality in necrotizing fasciitis: a retrospective study. *J Orthop Surg* 2019; **14**: 73.

72 Al-Thani H, El-Menyar A, Shaikh N, *et al.* Risk Stratification of Necrotizing Fasciitis

Based on the Initial Procalcitonin Concentration: A Single Center Observational Study. *Surg Infect* 2015; **16**: 806–12.

73 Hsiao C-T, Chang C-P, Huang T-Y, Chen Y-C, Fann W-C. Prospective Validation of the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score for Necrotizing Fasciitis of the Extremities. *PloS One* 2020; **15**: e0227748.

74 Fernando SM, Tran A, Cheng W, *et al*. Necrotizing Soft Tissue Infection: Diagnostic Accuracy of Physical Examination, Imaging, and LRINEC Score. *Ann Surg* 2019; **269**: 58–65.

75 Bechar J, Sepehripour S, Hardwicke J, Filobos G. Laboratory risk indicator for necrotising fasciitis (LRINEC) score for the assessment of early necrotising fasciitis: a systematic review of the literature. *Ann R Coll Surg Engl* 2017; **99**: 341–6.

76 Simonart T, Nakafusa J, Narisawa Y. The importance of serum creatine phosphokinase level in the early diagnosis and microbiological evaluation of necrotizing fasciitis. *J Eur Acad Dermatol Venereol JEADV* 2004; **18**: 687–90.

77 Chen I-C, Li W-C, Hong Y-C, Shie S-S, Fann W-C, Hsiao C-T. The microbiological profile and presence of bloodstream infection influence mortality rates in necrotizing fasciitis. *Crit Care Lond Engl* 2011; **15**: R152.

78 Dhanasekara CS, Marschke B, Morris E, Kahathuduwa CN, Dissanaik S. Global patterns of necrotizing soft tissue infections: A systematic review and meta-analysis. *Surgery* 2021; **170**: 1718–26.

79 Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. *J Hosp Infect* 2010; **75**: 249–57.

80 Chen S-C, Chan K-S, Chao W-N, *et al*. Clinical outcomes and prognostic factors for patients with *Vibrio vulnificus* infections requiring intensive care: a 10-yr retrospective study. *Crit Care Med* 2010; **38**: 1984–90.

81 Kuehl R, Tschudin-Sutter S, Siegemund M, *et al*. High Mortality of Non-Fournier Necrotizing Fasciitis With Enterobacteriales: Time to Rethink Classification? *Clin Infect Dis Off Publ Infect Dis Soc Am* 2019; **69**: 147–50.

82 Thänert R, Itzek A, Hoßmann J, *et al*. Molecular profiling of tissue biopsies reveals unique signatures associated with streptococcal necrotizing soft tissue infections. *Nat Commun* 2019; **10**: 3846.

83 Rodriguez C, Jary A, Hua C, *et al*. Pathogen identification by shotgun metagenomics of patients with necrotizing soft-tissue infections. *Br J Dermatol* 2020; **183**: 105–13.

84 Kim T, Park SY, Kwak YG, *et al*. Etiology, characteristics, and outcomes of community-onset necrotizing fasciitis in Korea: A multicenter study. *PloS One* 2019; **14**: e0218668.

85 Bakleh M, Wold LE, Mandrekar JN, Harmsen WS, Dimashkieh HH, Baddour LM. Correlation of histopathologic findings with clinical outcome in necrotizing fasciitis. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2005; **40**: 410–4.

86 Lebre C, Girard-Pipau F, Roujeau JC, Revuz J, Saiag P, Chosidow O. Value of fine-needle aspiration in infectious cellulitis. *Arch Dermatol* 1996; **132**: 842–3.

87 Wu K-H, Wu P-H, Chang C-Y, *et al*. Differentiating necrotizing soft tissue infections from cellulitis by soft tissue infectious fluid analysis: a pilot study. *World J Emerg Surg WJES* 2022; **17**: 1.

88 Hua C, Bosc R, Sbidian E, *et al*. Interventions for necrotizing soft tissue infections in adults. *Cochrane Database Syst Rev* 2018; published online May 31. DOI:10.1002/14651858.CD011680.pub2.

89 Hadeed GJ, Smith J, O’Keeffe T, *et al*. Early surgical intervention and its impact on patients presenting with necrotizing soft tissue infections: A single academic center experience. *J Emerg Trauma Shock* 2016; **9**: 22–7.

- 90 Boyer A, Vargas F, Coste F, *et al.* Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. *Intensive Care Med* 2009; **35**: 847–53.
- 91 Chao W-N, Tsai C-F, Chang H-R, *et al.* Impact of timing of surgery on outcome of *Vibrio vulnificus*–related necrotizing fasciitis. *Am J Surg* 2013; **206**: 32–9.
- 92 Henri Mondor Hospital Necrotizing Fasciitis Group, de Prost N, Sbidian E, Chosidow O, Brun-Buisson C, Amathieu R. Management of necrotizing soft tissue infections in the intensive care unit: results of an international survey. *Intensive Care Med* 2015; **41**: 1506–8.
- 93 Urbina T, Hua C, Sbidian E, *et al.* Impact of a multidisciplinary care bundle for necrotizing skin and soft tissue infections: a retrospective cohort study. *Ann Intensive Care* 2019; **9**: 123.
- 94 Gatti M, Gasparini LE, Laratta M, *et al.* Intensive multidisciplinary management in critical care patients affected by severe necrotizing soft tissue infections: a cooperative method to improve the efficacy of treatment. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2019; **38**: 1153–62.
- 95 Sorensen MD, Krieger JN. Fournier’s Gangrene: Epidemiology and Outcomes in the General US Population. *Urol Int* 2016; **97**: 249–59.
- 96 Wong C-H, Yam AK-T, Tan AB-H, Song C. Approach to debridement in necrotizing fasciitis. *Am J Surg* 2008; **196**: e19–24.
- 97 Hsiao G-H, Chang C-H, Hsiao C-W, Fanchiang J-H, Jee S-H. Necrotizing Soft Tissue Infections: Surgical or Conservative Treatment? *Dermatol Surg* 1998; **24**: 243–8.
- 98 Holena DN, Mills AM, Carr BG, *et al.* Transfer status: a risk factor for mortality in patients with necrotizing fasciitis. *Surgery* 2011; **150**: 363–70.
- 99 Khoury MK, Pickett ML, Cripps MW, *et al.* Transfer Is Associated with a Higher Mortality Rate in Necrotizing Soft Tissue Infections. *Surg Infect* 2020; **21**: 136–42.
- 100 Urbina T, Madsen MB, de Prost N. Understanding necrotizing soft tissue infections in the intensive care unit. *Intensive Care Med* 2020; **46**: 1739–42.
- 101 Willis RN, Guidry CA, Horn CB, *et al.* Predictors of Monomicrobial Necrotizing Soft Tissue Infections. *Surg Infect* 2015; **16**: 533–7.
- 102 Wattel F, Mathieu D, Neut C, Dubreuil L, Cesari J-F, Favory R. [Necrotizing soft tissue infections: role of the localization for the antibiotic management]. *Bull Acad Natl Med* 2004; **188**: 473–86; discussion 486–490.
- 103 Sartelli M, Guirao X, Hardcastle TC, *et al.* 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. *World J Emerg Surg WJES* 2018; **13**. DOI:10.1186/s13017-018-0219-9.
- 104 Eckmann C, Heizmann W, Bodmann K-F, von Eiff C, Petrik C, Loeschmann P-A. Tigecycline in the Treatment of Patients with Necrotizing Skin and Soft Tissue Infections Due to Multiresistant Bacteria. *Surg Infect* 2015; **16**: 618–25.
- 105 The STIC Study Group, Vick-Fragoso R, Hernández-Oliva G, *et al.* Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. *Infection* 2009; **37**: 407–17.
- 106 Sriskandan S, McKee A, Hall L, Cohen J. Comparative effects of clindamycin and ampicillin on superantigenic activity of *Streptococcus pyogenes*. *J Antimicrob Chemother* 1997; **40**: 275–7.
- 107 Stevens DL, Gibbons AE, Bergstrom R, Winn V. The Eagle Effect Revisited: Efficacy of Clindamycin, Erythromycin, and Penicillin in the Treatment of Streptococcal Myositis. *J Infect Dis* 1988; **158**: 23–8.
- 108 Mascini EM, Jansze M, Schouls LM, Verhoef J, Van Dijk H. Penicillin and clindamycin differentially inhibit the production of pyrogenic exotoxins A and B by group A streptococci. *Int J Antimicrob Agents* 2001; **18**: 395–8.

109 Andreoni F, Zürcher C, Tarnutzer A, *et al.* Clindamycin Affects Group A
Streptococcus Virulence Factors and Improves Clinical Outcome. *J Infect Dis* 2016; : jiw229.

110 Carapetis JR, Jacoby P, Carville K, Ang S-JJ, Curtis N, Andrews R. Effectiveness of
 clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive
 group a streptococcal infections. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2014; **59**: 358–
 65.

111 Linner A, Darenberg J, Sjölin J, Henriques-Normark B, Norrby-Teglund A. Clinical
 efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal
 toxic shock syndrome: a comparative observational study. *Clin Infect Dis Off Publ Infect Dis
 Soc Am* 2014; **59**: 851–7.

112 Babiker A, Li X, Lai YL, *et al.* Effectiveness of adjunctive clindamycin in β -lactam
 antibiotic-treated patients with invasive β -haemolytic streptococcal infections in US hospitals:
 a retrospective multicentre cohort study. *Lancet Infect Dis* 2021; **21**: 697–710.

113 Horn DL, Roberts EA, Shen J, *et al.* Outcomes of β -Hemolytic Streptococcal
 Necrotizing Skin and Soft-tissue Infections and the Impact of Clindamycin Resistance. *Clin
 Infect Dis Off Publ Infect Dis Soc Am* 2020; : ciaa976.

114 Urbina T, Razazi K, Ourghanlian C, *et al.* Antibiotics in Necrotizing Soft Tissue
 Infections. *Antibiot Basel Switz* 2021; **10**: 1104.

115 Roberts JA, Paul SK, Akova M, *et al.* DALI: defining antibiotic levels in intensive
 care unit patients: are current β -lactam antibiotic doses sufficient for critically ill patients?
Clin Infect Dis Off Publ Infect Dis Soc Am 2014; **58**: 1072–83.

116 Maguire C, Agrawal D, Daley MJ, Douglass E, Rose DT. Rethinking Carbapenems: A
 Pharmacokinetic Approach for Antimicrobial Selection in Infected Necrotizing Pancreatitis.
Ann Pharmacother 2021; **55**: 902–13.

117 Faraklas I, Yang D, Eggerstedt M, *et al.* A Multi-Center Review of Care Patterns and
 Outcomes in Necrotizing Soft Tissue Infections. *Surg Infect* 2016; **17**: 773–8.

118 on behalf of the REACH study group, Garau J, Blasi F, Medina J, McBride K,
 Ostermann H. Early response to antibiotic treatment in European patients hospitalized with
 complicated skin and soft tissue infections: analysis of the REACH study. *BMC Infect Dis*
 2015; **15**: 78.

119 Norrby-Teglund A, Kaul R, Low DE, *et al.* Plasma from patients with severe invasive
 group A streptococcal infections treated with normal polyspecific IgG inhibits streptococcal
 superantigen-induced T cell proliferation and cytokine production. *J Immunol Baltim Md
 1950* 1996; **156**: 3057–64.

120 Sriskandan S, Ferguson M, Elliot V, Faulkner L, Cohen J. Human intravenous
 immunoglobulin for experimental streptococcal toxic shock: bacterial clearance and
 modulation of inflammation. *J Antimicrob Chemother* 2006; **58**: 117–24.

121 Al-Qurayshi Z, Nichols RL, Killackey MT, Kandil E. Mortality Risk in Necrotizing
 Fasciitis: National Prevalence, Trend, and Burden. *Surg Infect* 2020; published online March
 20. DOI:10.1089/sur.2019.277.

122 Madsen MB, Hjortrup PB, Hansen MB, *et al.* Immunoglobulin G for patients with
 necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial.
Intensive Care Med 2017; published online April 18. DOI:10.1007/s00134-017-4786-0.

123 Parks T, Wilson C, Curtis N, Norrby-Teglund A, Sriskandan S. Polyspecific
 intravenous immunoglobulin in clindamycin-treated patients with streptococcal toxic shock
 syndrome: a systematic review and meta-analysis. *Clin Infect Dis Off Publ Infect Dis Soc Am*
 2018; published online May 17. DOI:10.1093/cid/ciy401.

124 Soh CR, Pietrobon R, Freiburger JJ, *et al.* Hyperbaric oxygen therapy in necrotising
 soft tissue infections: a study of patients in the United States Nationwide Inpatient Sample.
Intensive Care Med 2012; **38**: 1143–51.

- 125 Hedetoft M, Bennett MH, Hyldegaard O. Adjunctive hyperbaric oxygen treatment for necrotising soft-tissue infections: A systematic review and meta-analysis. *Diving Hyperb Med* 2021; **51**: 34–43.
- 126 Massey PR, Sakran JV, Mills AM, *et al.* Hyperbaric oxygen therapy in necrotizing soft tissue infections. *J Surg Res* 2012; **177**: 146–51.
- 127 Levett DZ, Bennett MH, Millar I. Adjunctive hyperbaric oxygen for necrotizing fasciitis. *Cochrane Database Syst Rev* 2015; published online Jan 15. DOI:10.1002/14651858.CD007937.pub2.
- 128 Bulger EM, May AK, Robinson BRH, *et al.* A Novel Immune Modulator for Patients With Necrotizing Soft Tissue Infections (NSTI): Results of a Multicenter, Phase 3 Randomized Controlled Trial of Reltecimod (AB 103). *Ann Surg* 2020; **272**: 469–78.
- 129 Huang W-S, Hsieh S-C, Hsieh C-S, Schoung J-Y, Huang T. Use of Vacuum-assisted Wound Closure to Manage Limb Wounds in Patients Suffering from Acute Necrotizing Fasciitis. *Asian J Surg* 2006; **29**: 135–9.
- 130 Bronchard R, de Vaumas C, Lasocki S, *et al.* Vacuum-assisted closure in the treatment of perineal necrotizing skin and soft tissue infections. *Intensive Care Med* 2008; **34**: 1345–7.
- 131 Pham TN, Moore ML, Costa BA, Cuschieri J, Klein MB. Assessment of functional limitation after necrotizing soft tissue infection. *J Burn Care Res Off Publ Am Burn Assoc* 2009; **30**: 301–6.
- 132 Urbina T, Canoui-Poitaine F, Hua C, *et al.* Long-term quality of life in necrotizing soft-tissue infection survivors: a monocentric prospective cohort study. *Ann Intensive Care* 2021; **11**: 102.
- 133 Cartwright K, Logan M, McNulty C, *et al.* A cluster of cases of streptococcal necrotizing fasciitis in Gloucestershire. *Epidemiol Infect* 1995; **115**: 387–97.
- 134 Robinson KA, Rothrock G, Phan Q, *et al.* Risk for severe group A streptococcal disease among patients' household contacts. *Emerg Infect Dis* 2003; **9**: 443–7.
- 135 Lacy MD, Horn K. Nosocomial transmission of invasive group a streptococcus from patient to health care worker. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2009; **49**: 354–7.
- 136 de Almeida Torres RSL, dos Santos TZ, Torres RA de A, *et al.* Management of Contacts of Patients With Severe Invasive Group A Streptococcal Infection. *J Pediatr Infect Dis Soc* 2016; **5**: 47–52.
- 137 Mearkale R, Saavedra-Campos M, Lamagni T, *et al.* Household transmission of invasive group A Streptococcus infections in England: a population-based study, 2009, 2011 to 2013. *Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull* 2017; **22**: 30532.
- 138 Arif N, Yousfi S, Vinnard C. Deaths from necrotizing fasciitis in the United States, 2003-2013. *Epidemiol Infect* 2016; **144**: 1338–44.
- 139 Hua C, Sbidian E, Hemery F, *et al.* Prognostic factors in necrotizing soft-tissue infections (NSTI): A cohort study. *J Am Acad Dermatol* 2015; **73**: 1006-1012.e8.
- 140 Golger A, Ching S, Goldsmith CH, Pennie RA, Bain JR. Mortality in patients with necrotizing fasciitis. *Plast Reconstr Surg* 2007; **119**: 1803–7.
- 141 Gelbard RB, Ferrada P, Yeh DD, *et al.* Optimal timing of initial debridement for necrotizing soft tissue infection: A Practice Management Guideline from the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg* 2018; **85**: 208–14.
- 142 Latifi R, Patel AS, Samson DJ, *et al.* The roles of early surgery and comorbid conditions on outcomes of severe necrotizing soft-tissue infections. *Eur J Trauma Emerg Surg* 2018; published online May 22. DOI:10.1007/s00068-018-0958-z.
- 143 Kongkaewpaisan N, Hwabejire J, Lee JM, *et al.* Necrotizing Soft Tissue Infection: Time is Crucial, and the Admitting Service Matters. *Surg Infect* 2020; published online April 2. DOI:10.1089/sur.2019.262.
- 144 Gangopadhyay A, Sharma S, Kumar V, Gopal S, Gupta D, Pandey A. Surgical

1 considerations in pediatric necrotizing fasciitis. *J Indian Assoc Pediatr Surg* 2009; **14**: 19.
 2 145 Rieger UM, Gugger CY, Farhadi J, *et al.* Prognostic Factors in Necrotizing Fasciitis
 3 and Myositis: Analysis of 16 Consecutive Cases at a Single Institution in Switzerland. *Ann*
 4 *Plast Surg* 2007; **58**: 523–30.
 5 146 Kobayashi L, Konstantinidis A, Shackelford S, *et al.* Necrotizing Soft Tissue
 6 Infections: Delayed Surgical Treatment Is Associated With Increased Number of Surgical
 7 Debridements and Morbidity. *J Trauma Inj Infect Crit Care* 2011; **71**: 1400–5.
 8 147 Pakula AM, Kapadia R, Freeman B, Skinner RA. A 3-year experience with
 9 necrotizing fasciitis: favorable outcomes despite operative delays in a busy acute care
 10 hospital. *Am Surg* 2012; **78**: 1059–62.
 11 148 Osbun N, Hampson LA, Holt SK, Gore JL, Wessells H, Voelzke BB. Low-Volume vs
 12 High-Volume Centers and Management of Fournier’s Gangrene in Washington State. *J Am*
 13 *Coll Surg* 2017; **224**: 270-275.e1.
 14 149 Medical Licensing Assessment in UK. [https://www.gmc-uk.org/-](https://www.gmc-uk.org/-/media/documents/mla-content-map-_pdf-85707770.pdf)
 15 [/media/documents/mla-content-map-_pdf-85707770.pdf](https://www.gmc-uk.org/-/media/documents/mla-content-map-_pdf-85707770.pdf).
 16 150 Collège des Enseignants en Dermatologie de France.
 17 [https://document.cedef.org/enseignement/2021_R2C/lisa/item-155_infections-](https://document.cedef.org/enseignement/2021_R2C/lisa/item-155_infections-cutan%C3%A9es.pdf)
 18 [cutan%C3%A9es.pdf](https://document.cedef.org/enseignement/2021_R2C/lisa/item-155_infections-cutan%C3%A9es.pdf).
 19 151 Vekemans J, Gouvea-Reis F, Kim JH, *et al.* The Path to Group A Streptococcus
 20 Vaccines: World Health Organization Research and Development Technology Roadmap and
 21 Preferred Product Characteristics. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2019; **69**: 877–
 22 83.
 23
 24

Figures

Figure 1: Towards a more pragmatical approach of necrotising soft tissue infections (schema adapted from Professor Edouard Grosshans (1937-2020))

Figure 2: Pathogenetic steps leading to NSTI caused by *S. pyogenes*.

GAS has ability to enter and survive within the lymphatic system reaching the bloodstream by metastasis, augmented by the hyaluronan capsule and other virulence factors. Bacteria are more likely to leave the bloodstream in tissues where the endothelium is disrupted, for example, where bruising has occurred, providing a plausible explanation for the association of GAS NSTI with blunt trauma; with upregulation of skeletal vimentin in muscular cells. GAS virulence factors swiftly negate the body's normal immune defenses. GAS has a specific ability to prevent recruitment of white blood cells to the site of infection, and to withstand killing by white blood cells. GAS virulence factors are subject to repression by bacterial regulators that can undergo a 'switch' through either homeostatic phosphorylation or mutation that enables the bacterium to increase production of the factors that combat the immune response and become hyper-virulent. The consequent 'thwarted' inflammation leads to tissue damage as a result of both bacterial and neutrophil enzymes, while coagulation activation may result in microthrombi and tissue infarction. Perfusion is further reduced by increasing tissue oedema that can result in a compartment syndrome with consequent necrosis of muscle due to hypoxia. Progressive infection and necrosis of tissue in turn contribute toxic mediators that combined with bacterial virulence factors mean that many patients with GAS NF will present in septic shock and require intensive care support due to low blood pressure and low pH.

Figure 3: Clinical pictures of necrotising soft tissue infections (NSTI). Pictures show the same patients

before (left panels) and after (right panels) surgical debridements.

A, B: NSTI at early stages: upper limb NSTI in a 42-year-old intravenous drug user. Left panel shows erythema of the arm.

C, D: NSTI with local signs of gravity: polymicrobial NSTI of the lower limb in a 65-year-old man with. Left panel shows areas of necrosis.

E, F: NSTI with local signs of gravity: 81-year-old woman, kidney transplanted, with monomicrobial Gram-negative limb NSTI. Left panel shows hemorrhagic bullae with poorly delineated areas of necrosis

Figure 4: Proposed algorithm for multidisciplinary and multimodal management of necrotising soft-tissue infections.

Figure 5: Microbiological characteristics of necrotising soft tissue infections and suggested antibiotic regimens.

The non-exhaustive list of host-factors, clinical presentation or local epidemiology related factors presented here to guide antibiotic regimen are based on data from the recent literature and international guidelines. The presence of one or more of this risk factors should prompt clinicians to consider use of other antibiotics than solely the recommended broad-spectrum beta-lactam such as the piperacillin-tazobactam combination. Gram-positive cocci include *Streptococcus* (mainly group A but also B, C, G and *anginosus*), *Staphylococcus aureus*, *Enterococcus* and *Pneumococcus*, while coagulase-negative *Staphylococcus* are often identified in polymicrobial infections without a clear pathogenic role. Anaerobic bacteria most frequently isolated include *Clostridium perfringens*, *Bacteroides*, *Prevotella*, *fusobacterium*, while *Corynebacterium*, *Micrococcus* and *Bacillus*’ pathogenicity remains uncertain despite identification. Gram-negative bacilli include *Enterobacteriaceae*, non-fermenting species, *Haemophilus influenzae* and specific waterborne species such as *Vibrio vulnificus*.

Supplementary appendix

Supplemental Figure Legends

Figure S1. Epidemiology of necrotising soft tissue infections

A: Yearly incidence per 100 000 people of necrotising soft tissue infections; B: Yearly incidence per 100 000 people of invasive group A streptococcal infection (% of NSTI)

Figure S2: Imaging panels of necrotising soft tissue infections

A, B: Axial MR images in 25-year-old woman with surgically confirmed NSTI in the lower limb (A) T2 fat saturation: thick areas (>3mm) of high signal intensity in deep fascia, (B) T1 fat saturation areas of necrosis in the soleus muscle with fluid signal (arrows) C: Axial MR image in 55-year-old woman with confirmed NSTI of the leg. T1 fat saturation. Fluid collections with enhancement after IV contrast injections in muscle. D: Transversal computed tomography scan slice in 75-year-old man with chest NSTI confirmed surgically. Gas in soft tissue of the chest. E: Transversal computed tomography scan slice in 52-year-old woman with Fournier's gangrene as a manifestation of undiagnosed colorectal cancer. Gas in soft tissue and rectal mass (arrows). F

Figure S3: Evolution of necrotising soft tissue infection before, after surgical debridement and after skin graft.

Figure S4: Reported risk factors of mortality identified in epidemiological studies.

Table Supplementary Legends

Table S1: Predisposing factors for necrotising soft tissue infections and specificities of some variants

Table S2: Studies evaluating outcome according to transfer status or management in a referral or high-case volume center

Table S3: Studies evaluating outcome according to time to first surgical debridement

Table S4: Research priorities

Video

Video 1: Initial surgical exploration and debridement in necrotising soft tissue infection

Video 2: Fine-needle aspiration in necrotising soft tissue infection for microbiological diagnosis

Figure 1 to 5

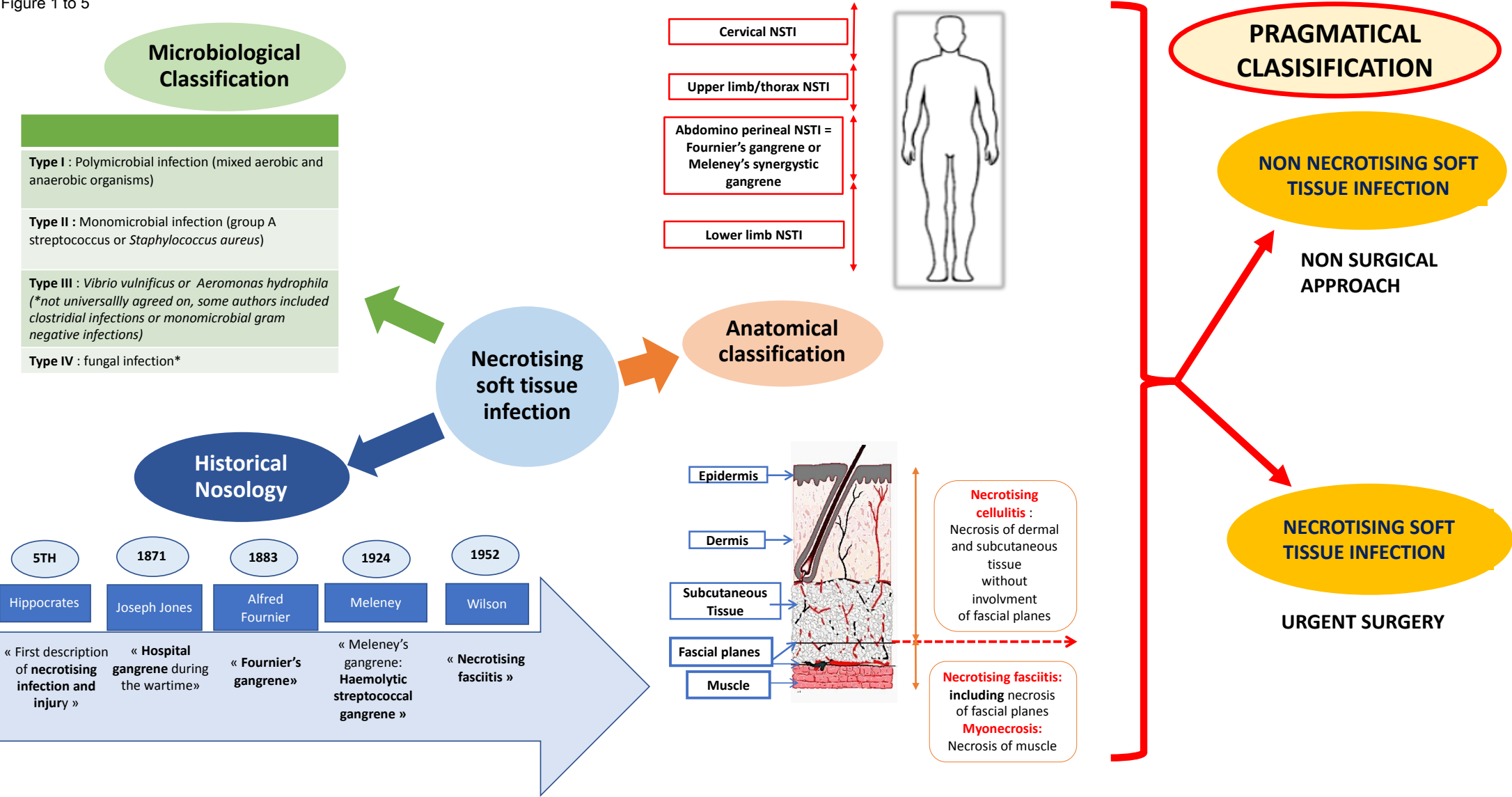


Figure 1: Towards a more pragmatical approach of necrotising soft tissue infections (schema adapted from Professor Edouard Grosshans (1937-2020))

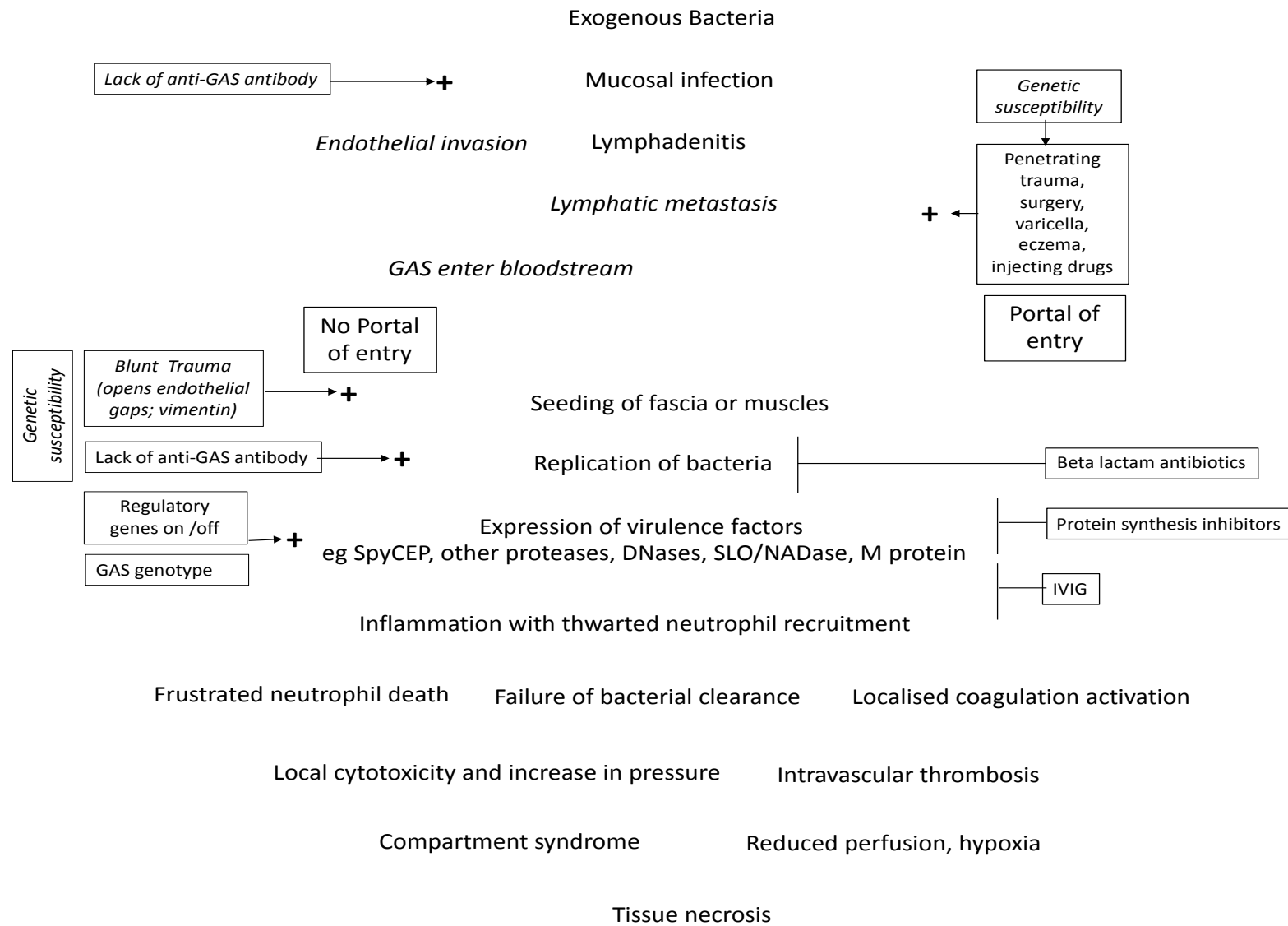


Figure 2: Pathogenetic steps leading to NSTI caused by *S. pyogenes*



Figure 3: Clinical pictures of necrotising soft tissue infections (NSTI). Pictures show the same patients before (left panels) and after (right panels) surgical debridements.

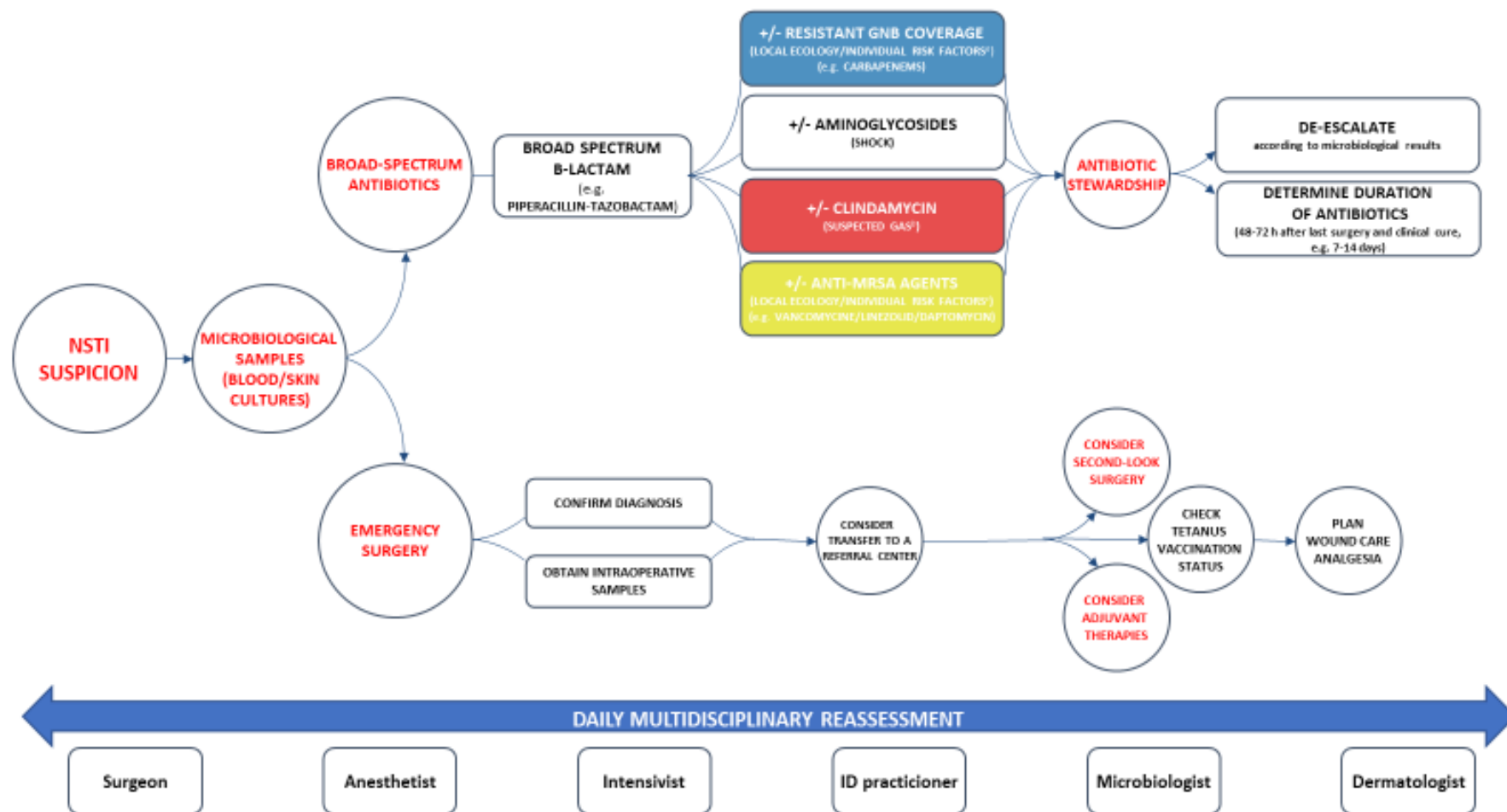


Figure 4: Proposed algorithm for multidisciplinary and multimodal management of necrotising soft-tissue infections.

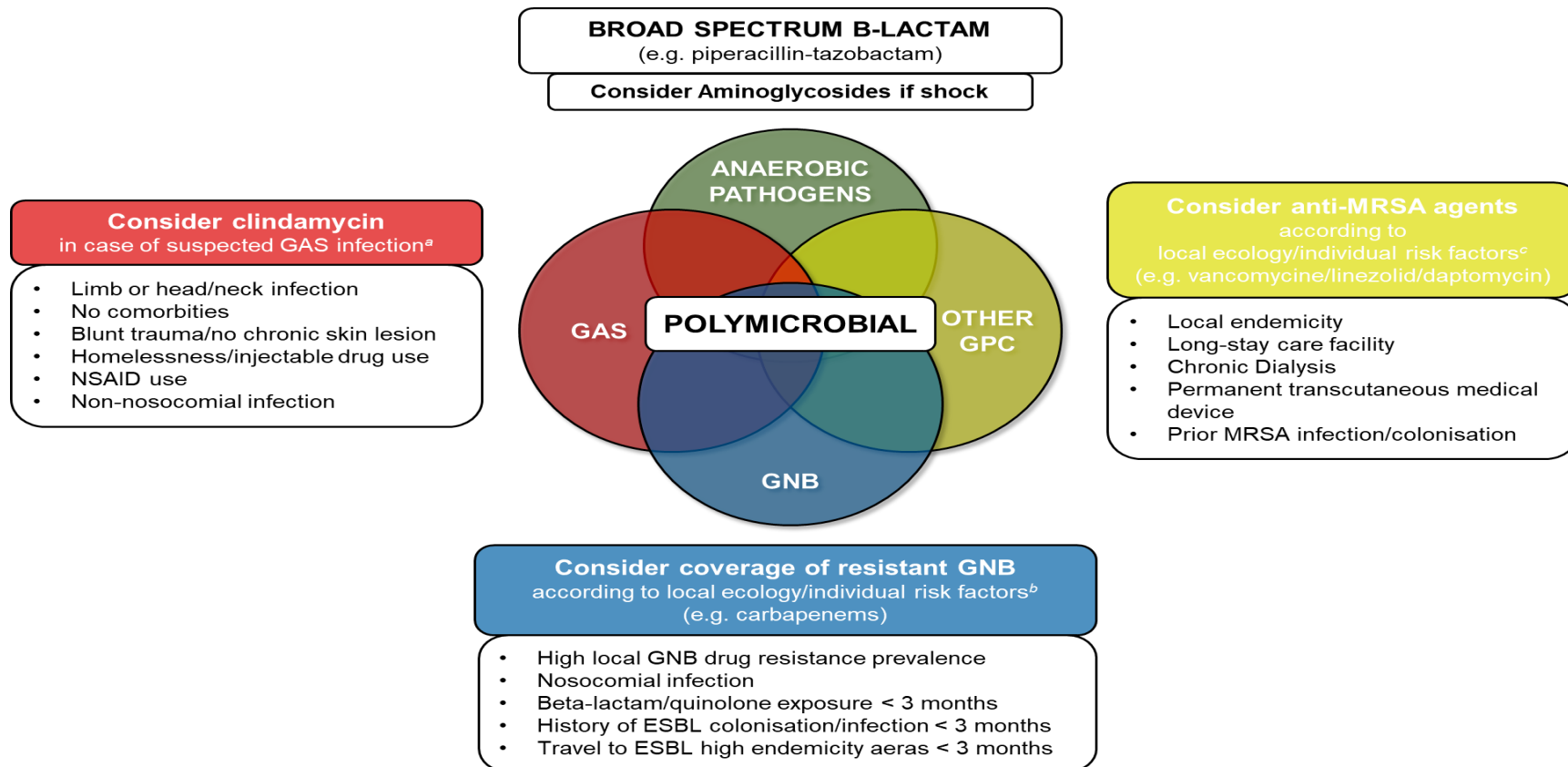


Figure 5: Microbiological characteristics of necrotising soft tissue infections and suggested antibiotic regimens.

Figures Supplementary appendix

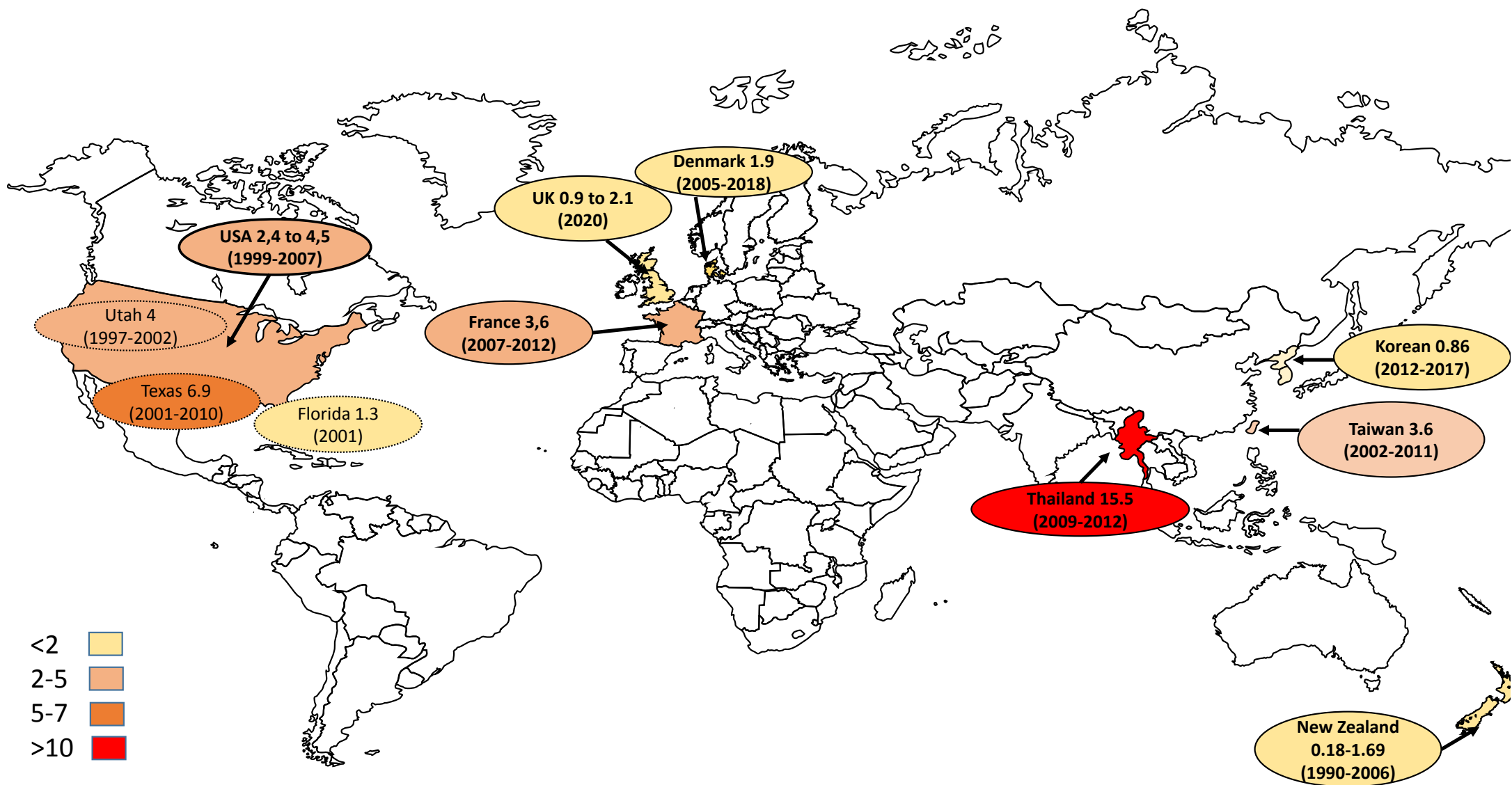
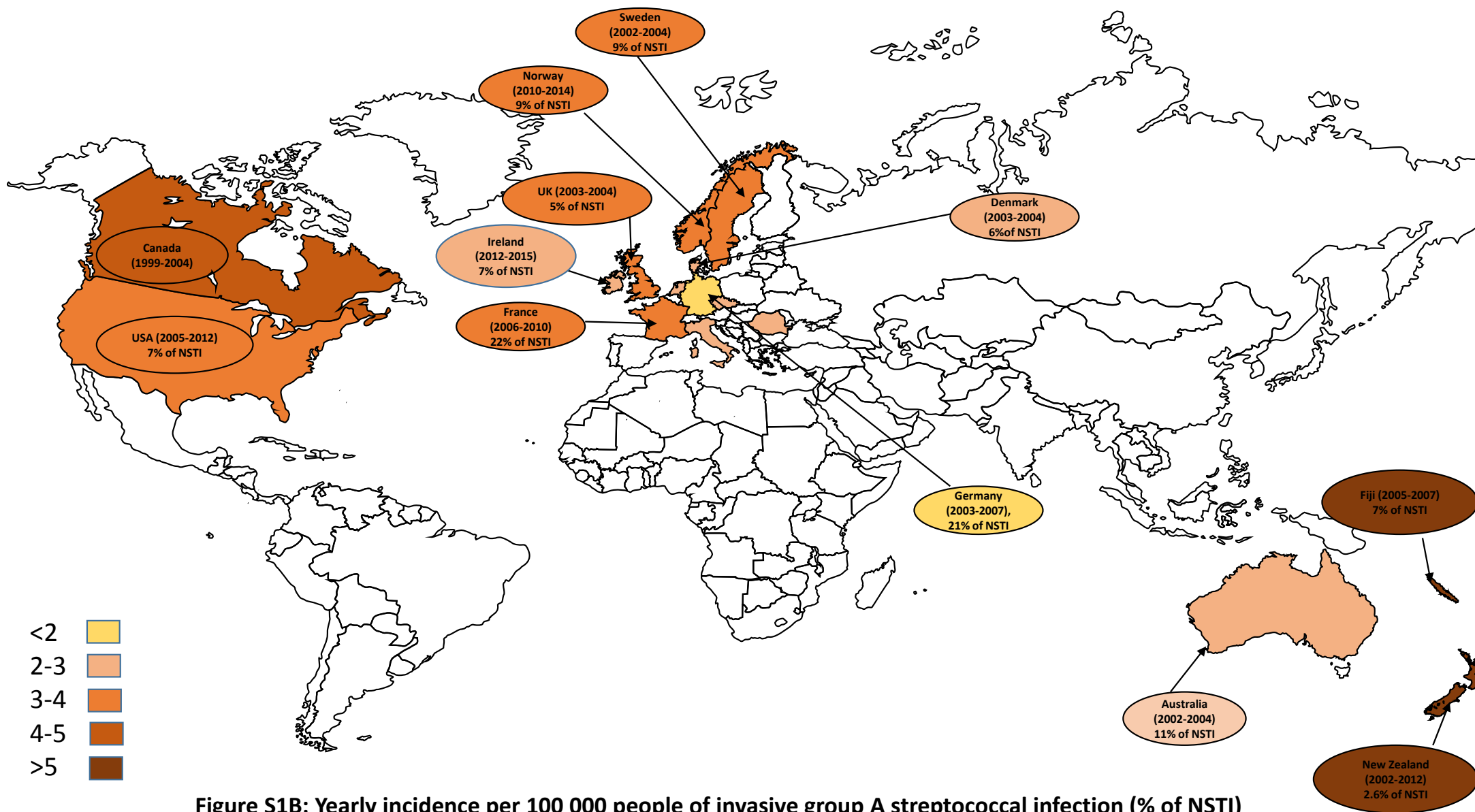


Figure S1A: Yearly incidence per 100 000 people of necrotising soft tissue infections



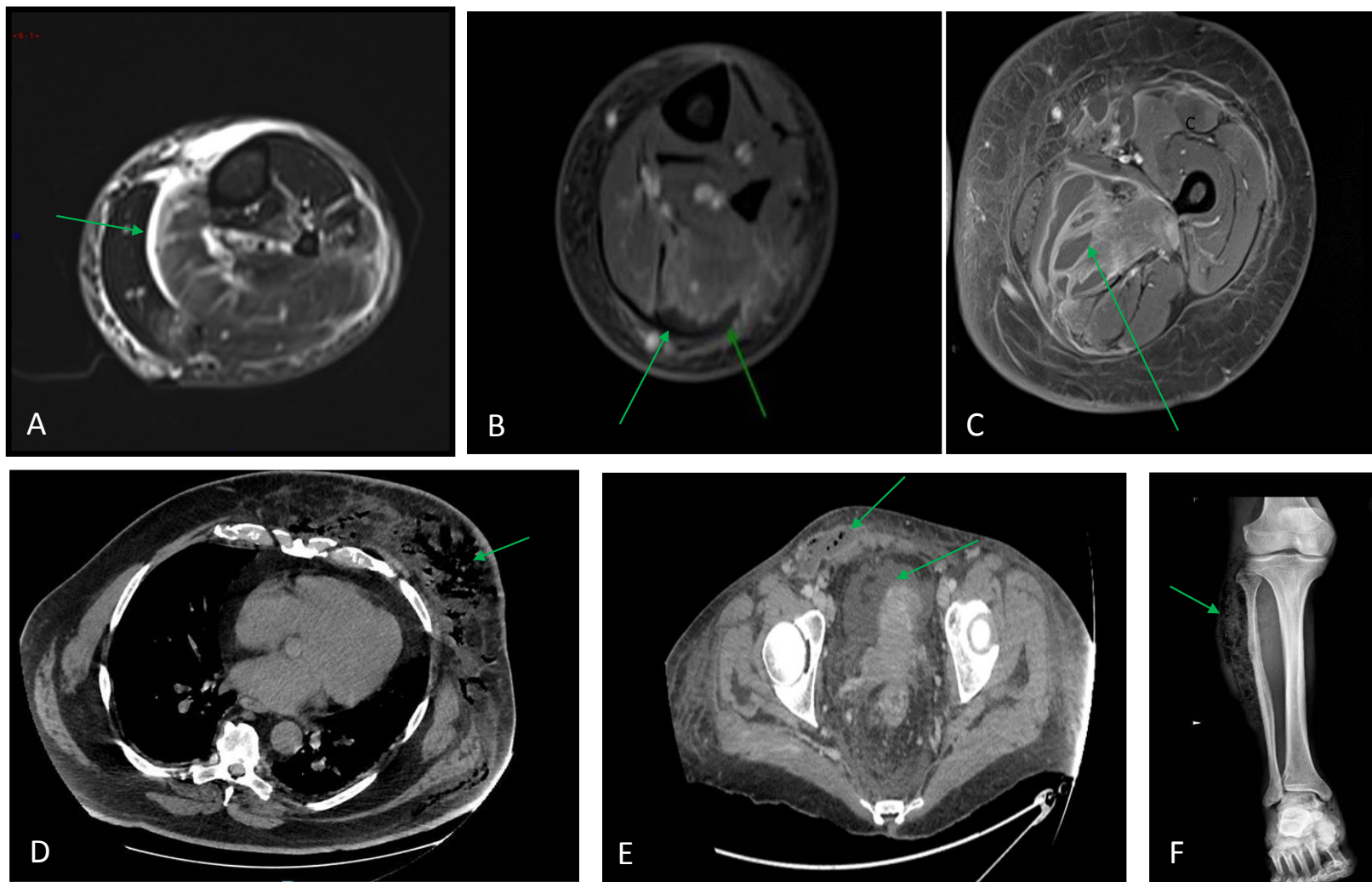


Figure S2: Imaging panels of necrotising soft tissue infections

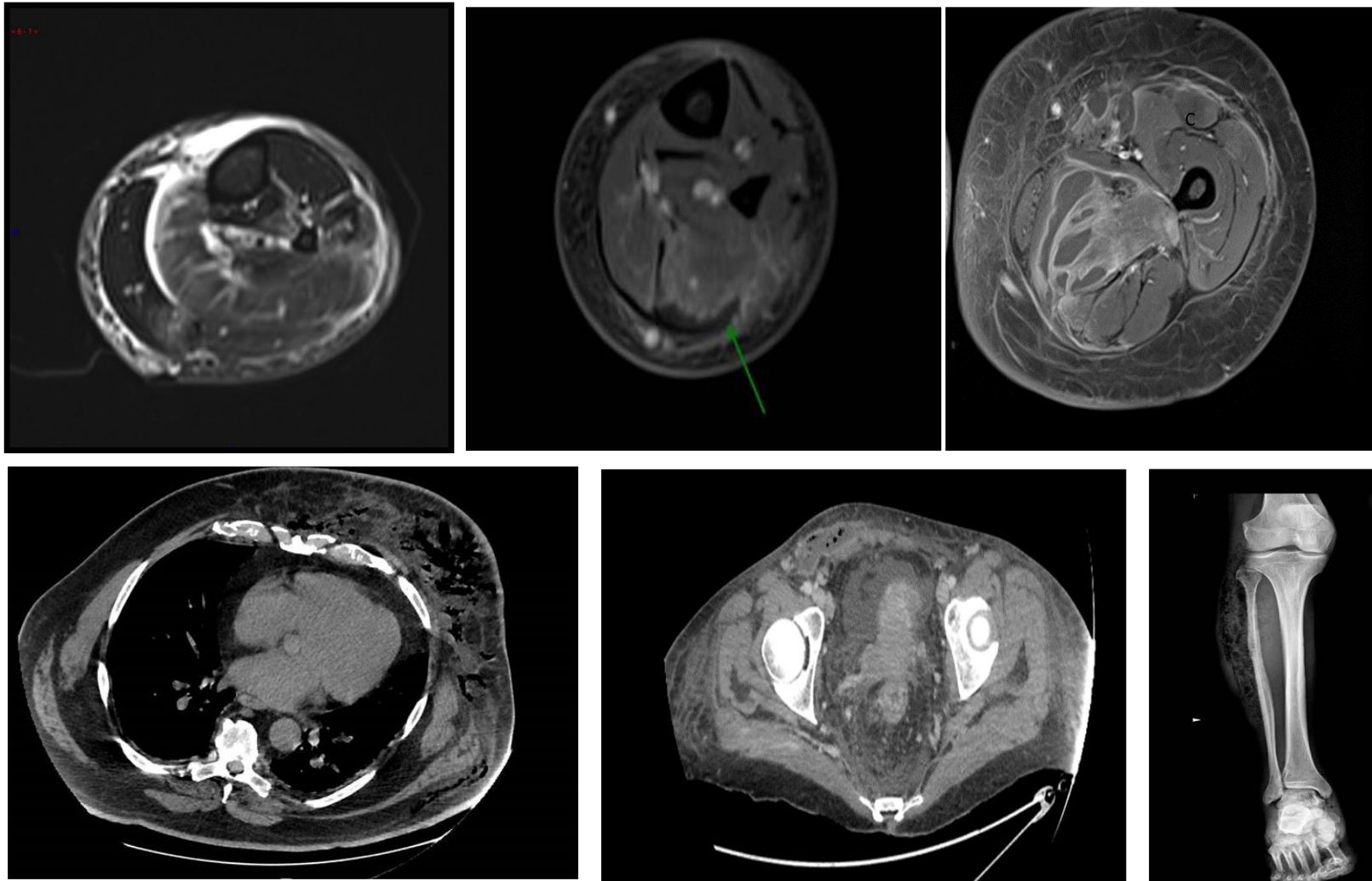


Figure S2: Imaging panels of necrotising soft tissue infections



Figure S3: Evolution of necrotising soft tissue infection before, after surgical debridement and after skin graft.

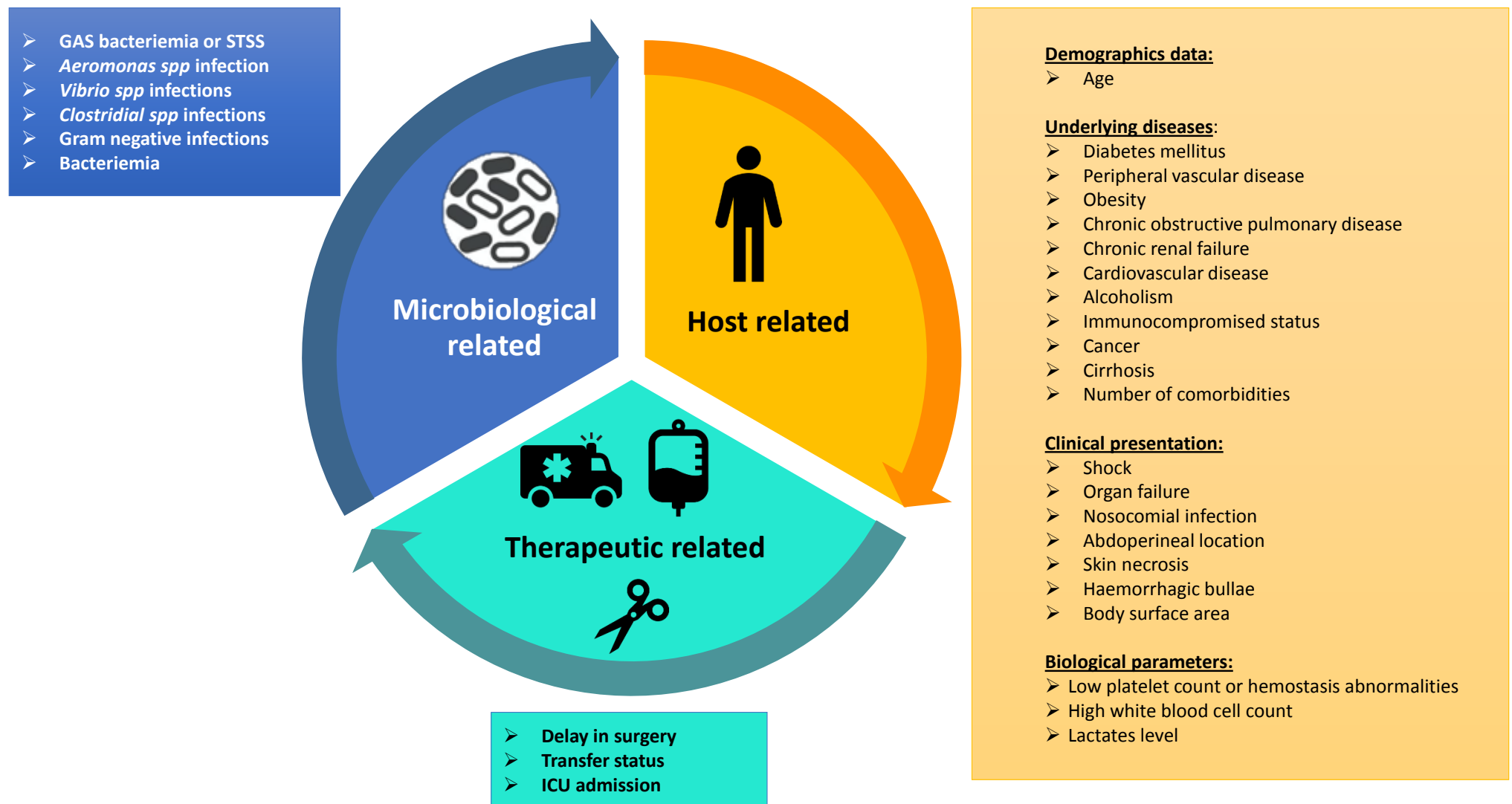


Figure S4: Reported risk factors of mortality identified in epidemiological studies^{1-3,3-6,6-28} .

Supplementary appendix references

Figure S4^{1–3,3–6,6–29}

- 1 Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. *Ann Surg* 1996; **224**: 672–83.
- 2 Kaul R, McGeer A, Low DE, Green K, Schwartz B. Population-based surveillance for group A streptococcal necrotizing fasciitis: Clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario Group A Streptococcal Study. *Am J Med* 1997; **103**: 18–24.
- 3 Golger A, Ching S, Goldsmith CH, Pennie RA, Bain JR. Mortality in patients with necrotizing fasciitis. *Plast Reconstr Surg* 2007; **119**: 1803–7.
- 4 Kao LS, Lew DF, Arab SN, *et al*. Local variations in the epidemiology, microbiology, and outcome of necrotizing soft-tissue infections: a multicenter study. *Am J Surg* 2011; **202**: 139–45.
- 5 Jabbour G, El-Menyar A, Peralta R, *et al*. Pattern and predictors of mortality in necrotizing fasciitis patients in a single tertiary hospital. *World J Emerg Surg WJES* 2016; **11**: 40.
- 6 Huang K-F, Hung M-H, Lin Y-S, *et al*. Independent predictors of mortality for necrotizing fasciitis: a retrospective analysis in a single institution. *J Trauma* 2011; **71**: 467–73; discussion 473.
- 7 Audureau E, Hua C, de Prost N, *et al*. Mortality of necrotizing fasciitis: relative influence of individual and hospital-level factors, a nationwide multilevel study, France, 2007–12. *Br J Dermatol* 2017; **177**: 1575–82.
- 8 Madsen MB, Skrede S, Perner A, *et al*. Patient's characteristics and outcomes in necrotising soft-tissue infections: results from a Scandinavian, multicentre, prospective cohort study. *Intensive Care Med* 2019; **45**: 1241–51.
- 9 Urbina T, Hua C, Sbidian E, *et al*. Impact of a multidisciplinary care bundle for necrotizing skin and soft tissue infections: a retrospective cohort study. *Ann Intensive Care* 2019; **9**: 123.
- 10 Dworkin MS, Westercamp MD, Park L, McIntyre A. The epidemiology of necrotizing fasciitis including factors associated with death and amputation. *Epidemiol Infect* 2009; **137**: 1609–14.
- 11 Mills MK, Faraklas I, Davis C, Stoddard GJ, Saffle J. Outcomes from treatment of necrotizing soft-tissue infections: results from the National Surgical Quality Improvement Program database. *Am J Surg* 2010; **200**: 790–6; discussion 796–797.
- 12 Mulla ZD, Gibbs SG, Aronoff DM. Correlates of length of stay, cost of care, and mortality among patients hospitalized for necrotizing fasciitis. *Epidemiol Infect* 2007; **135**: 868–76.
- 13 Oud L, Watkins P. Contemporary Trends of the Epidemiology, Clinical Characteristics, and Resource Utilization of Necrotizing Fasciitis in Texas: A Population-Based Cohort Study. *Crit Care Res Pract* 2015; **2015**. DOI:10.1155/2015/618067.
- 14 Faraklas I, Yang D, Eggerstedt M, *et al*. A Multi-Center Review of Care Patterns and Outcomes in Necrotizing Soft Tissue Infections. *Surg Infect* 2016; **17**: 773–8.
- 15 Holena DN, Mills AM, Carr BG, *et al*. Transfer status: a risk factor for mortality in patients with necrotizing fasciitis. *Surgery* 2011; **150**: 363–70.
- 16 Endorf FW, Klein MB, Mack CD, Jurkovich GJ, Rivara FP. Necrotizing soft-tissue infections: differences in patients treated at burn centers and non-burn centers. *J Burn Care Res Off Publ Am Burn Assoc* 2008; **29**: 933–8.
- 17 Boyer A, Vargas F, Coste F, *et al*. Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. *Intensive Care Med* 2009; **35**: 847–53.
- 18 Latifi R, Patel AS, Samson DJ, *et al*. The roles of early surgery and comorbid conditions on outcomes of severe necrotizing soft-tissue infections. *Eur J Trauma Emerg Surg* 2018; published online May 22. DOI:10.1007/s00068-018-0958-z.
- 19 Al-Qurayshi Z, Nichols RL, Killackey MT, Kandil E. Mortality Risk in Necrotizing Fasciitis: National Prevalence, Trend, and Burden. *Surg Infect* 2020; published online March 20. DOI:10.1089/sur.2019.277.
- 20 Hua C, Sbidian E, Hemery F, *et al*. Prognostic factors in necrotizing soft-tissue infections (NSTI): A cohort study. *J Am Acad Dermatol* 2015; **73**: 1006–1012.e8.
- 21 Chen S-C, Chan K-S, Chao W-N, *et al*. Clinical outcomes and prognostic factors for patients with *Vibrio vulnificus* infections requiring intensive care: a 10-yr retrospective study. *Crit Care Med* 2010; **38**: 1984–90.
- 22 Nisbet M, Ansell G, Lang S, Taylor S, Dzendrowskyj P, Holland D. Necrotizing fasciitis: review of 82 cases in South Auckland. *Intern Med J* 2011; **41**: 543–8.
- 23 Anaya DA, McMahon K, Nathens AB, Sullivan SR, Foy H, Bulger E. Predictors of mortality and limb loss in necrotizing soft tissue infections. *Arch Surg Chic Ill* 1960 2005; **140**: 151–7; discussion 158.
- 24 Liu TJ, Tai H-C, Chien K-L, Cheng N-C. Predisposing factors of necrotizing fasciitis with comparison to

cellulitis in Taiwan: A nationwide population-based case-control study. *J Formos Med Assoc Taiwan Yi Zhi* 2020; **119**: 18–25.

25 Krieg A, Dizdar L, Verde PE, Knoefel WT. Predictors of mortality for necrotizing soft-tissue infections: a retrospective analysis of 64 cases. *Langenbecks Arch Surg Dtsch Ges Chir* 2014; **399**: 333–41.

26 Schwartz S, Kightlinger E, de Virgilio C, *et al.* Predictors of mortality and limb loss in necrotizing soft tissue infections. *Am Surg* 2013; **79**: 1102–5.

27 Hadeed GJ, Smith J, O’Keeffe T, *et al.* Early surgical intervention and its impact on patients presenting with necrotizing soft tissue infections: A single academic center experience. *J Emerg Trauma Shock* 2016; **9**: 22–7.

28 Hsiao C-T, Weng H-H, Yuan Y-D, Chen C-T, Chen I-C. Predictors of mortality in patients with necrotizing fasciitis. *Am J Emerg Med* 2008; **26**: 170–5.

29 Lee Y-C, Hor L-I, Chiu H-Y, Lee J-W, Shieh S-J. Prognostic factor of mortality and its clinical implications in patients with necrotizing fasciitis caused by *Vibrio vulnificus*. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1011–8.

Supplemental Table S1: Predisposing factors for necrotising soft tissue infections and specificities of some variants

Type of NSTI	Comorbidities	Portal of entry	Specificities
NSTI in general	Immunosuppression Diabetes mellitus Cirrhosis Chronic kidney failure Age>60 years Obesity Malignancy Peripheral vascular disease Malnutrition Alcoholism NSAIDs use	Blunt trauma Penetrating trauma Post operative Intravenous drug use or other subcutaneous injection Chronic wounds Insect bites Skin lesions (eczema, scabies, varicella) Idiopathic	
Topography Cervicofacial NSTI	NSAIDs use Diabetes mellitus Alcoholism	Odontogenic infection Pharyngolaryngeal infection Peritonsillar abscesses Iatrogenic Cutaneous	Polymicrobial infection: hemolytic streptococci, staphylococci, and anaerobes
Abdomino-perineal NSTI (Fournier's gangrene)	Diabetes mellitus Alcoholism Immunosuppression Chronic kidney failure Obesity	Anorectal source Gastrointestinal source Genitourinary source Post operative Cutaneous lesions	Polymicrobial infection: mixed of anaerobes and aerobes (<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Bacteroides</i> , <i>Enterobacter</i> , <i>Proteus</i> , <i>Klebsiella</i>) Multidisciplinary surgery/preventive colostomy
Microbiological classification			
Type I	Diabetes mellitus Immunocompromised patients Peripheral vascular disease	Mucosal tear Post operative	Polymicrobial: mixed aerobic and anaerobic Mostly trunk and perineum
Type II	Healthy and young individuals NSAIDs use	Blunt or penetrating trauma	Monomicrobial: <i>Streptococcus pyogenes</i> , Methicillin resistant <i>Staphylococcus aureus</i> Limbs
Type III <i>Aeromonas hydrophila</i>		Freshwater exposure	
<i>Vibrio vulnificus</i>	Diabetes mellitus Cirrhosis Immunocompromised Cirrhosis		Common in Southeastern United States, Central and South America, and Asia
<i>Clostridial</i> (Gas gangrene)		Saltwater exposure Ingestion of raw oysters Trauma wounds Post operative Gastrointestinal tract lesion or malignancy	<i>Clostridium perfringens</i> , <i>Clostridium histolyticum</i> <i>Clostridium septicum</i> <i>Mucormycosis</i> in immunocompetent patients
Type IV (fungal)	Immunocompromised status Diabetes mellitus	Trauma wounds Burns	

Neutropenia

Candida in immunocompromised patients

GAS=Group A streptococcal. NSTI=necrotising soft tissue infections. NSAID=non-steroidal anti-inflammatory drugs. *Monkeypox virus infection as a risk factor for NSTI should be further evaluated

Supplemental Table 2: Studies evaluating outcome according to transfer status or management in a referral or high case-volume center in necrotising soft-tissue infections

First Author	Year of publication	Country	n	Methodology	Intervention evaluated	Result
Transfer status						
Proud	2013	Australia	219	Monocentric retrospective cohort	Impact of transfer timing (early: <24 h vs late >24 h) on survival in patients transferred to a referral center	ns, data not available
Eggerstedt	2015	USA	81	Monocentric retrospective cohort	Survival between patients directly admitted vs transferred to a referral center	20% vs 21%, p=0.75, CI ..
Osburn	2016	USA	165	Retrospective state administrative database	Impact of transfer timing (<1 day vs > 1 day after admission) to high volume case centers of Fournier's gangrene patients on rates of septic shock and renal failure	septic shock (21% vs 45%, p=0.05, CI ..) renal failure (18% vs 41%, p=0.04, CI ..) (unadjusted)
Ingraham	2017	USA	1801	Retrospective data base of the American college of surgeons	Impact of interhospital transfer on mortality	14.5% vs 13%, aOR 0.87 [0.62-1.22], p=0.42
Endorf	2008	USA	10940	Retrospective national administrative database	Impact of interhospital transfer on mortality	aOR 1.28 [1.07-1.54], p=0.007
Holena	2011	USA	9958	Retrospective national administrative database	Impact of interhospital transfer on mortality	aOR 2.04 [1.60-2.59], p<0.001
Audureau	2017	France	1537	Retrospective national administrative database	Impact of interhospital transfer on mortality	ns, aHR 1.04 [0.71-1.52], p=0.84
Khoury	2019	USA	138	Bicentric Retrospective cohort	Survival between directly admitted or patients transferred to two referral centers	aOR 5.33 [1.02-28.3], p=0.04
Referral/High case-volume centers						
Endorf	2008	USA	10940	Retrospective national administrative database	Impact of management in burn centers vs non-burn centers on health-care resources utilization	Burn centers more surgical procedures (p<0.01), higher hospital charges (p<0.01), and longer LOS (p<0.01) (unadjusted)
Osburn	2016	USA	165	Retrospective national administrative database	Impact of high case-volume (3 or more/year) on 28-day mortality of Fournier's gangrene patients	Similar mortality (6.4% vs 7%, p=0.87, CI ..) despite higher rate of septic shock (18% vs 37%, p<0.01, CI ..) and respiratory failure (20% vs 38%, p=0.01, CI ..)
Audureau	2017	France	1537	Retrospective national administrative database	Impact of High case-volume (> 2/year) on 28-day mortality	aOR 0.68 [0.46-0.99], p=0.045

aHR= adjusted hazard ratio. aOR=adjusted odds ratio. CI=confidence interval. h=hours. HR=hazard ratio. ICU=intensive care unit. LOS=length of stay. ns=non-significant. OR=odds ratio. vs= versus. ··data not available

Supplemental Table 3: Studies evaluating outcome according to time to first surgical debridement in necrotising soft-tissue infections.

First Author	Year of publication	Country	n	Population	Delay measured	Outcome	Result
Retrospective cohorts							
Sudarsky	1987	USA	33	All NSTI	Admission-surgery (<12 h vs 12-28 h vs >48 h)	LOS	36 vs 62 vs 38 days, p<0.05, CI ··
Lille	1996	USA	29	All NSTI	Admission-surgery (cut-off 24 h)	Overall mortality	6% vs 25%, p ··
Rieger	2007	Switzerland	16	All NSTI	Admission-surgery (<1 day vs 1-2 days vs >2 days)	Overall mortality	16.5% vs 33% vs 0%, p ··
Boyer	2009	France	106 (43)	ICU admitted NSTI (shock)	Diagnosis-surgery (cut-off 14 h) (available for 54 patients, 33 with septic shock)	Hospital mortality	In septic shock patients, 37% vs 89%, p=0.025, CI ··
Pandey	2009	India		Pediatric NSTI	Diagnosis-surgery, Immediate after diagnosis vs 3-5 days later	LOS	20.4% vs 23.81%, p>0.5, CI ··
Kobayashi	2011	USA	47	All NSTI	Admission-surgery (cut-off 12 h)	Overall mortality	4.5% vs 28%, p=0.033, CI ··
Pakula	2012	USA	54	All NSTI	Admission-surgery (cut-off 12h)	Overall mortality	15 vs 18%, p>0.99, CI ··
Chao	2013	Taiwan	121	<i>Vibrio</i> NSTI	Admission-surgery (cut-off 12h)	Hospital mortality	HR 0.64 (<0.001-0.25), p=0.037
Lee	2014	Taiwan	100	<i>Vibrio</i> NSTI	Mixed injury/symptom-surgery (cut-off 12 h)	Overall mortality	OR 10.75 (1.02-113.39), p=0.048
Hadeed	2016	Qatar	87	All NSTI	Diagnosis-surgery, (cut-off 6 h)	Overall mortality (LOS)	ns, 7.5% vs 17%, p ·· (13.5 [4.33] vs 18 [1.82] days, p=0.035)
Latifi	2019	USA	115	All NSTI	Admission-surgery (cut-off 6 h)	LOS (Overall mortality)	22.88 (SD 14.38) vs 38.14 (SD 45.82), p<0.008 (ns, OR 1.004 (0.989-1.018))
Kongkaewpaisan	2020	USA	91	All NSTI	Admission-surgery (early group 3.9 (2.6-7) h, delayed group 24.8 (9.0-33.7) h)	Hospital mortality	ns, (7% vs 20%, p=0.086, CI ··)
Meta-analyses							
Gelbardl	2018	Worldwide	341	6 studies	Diagnosis-surgery (cut-off 12 h)	Overall mortality	14% vs 25.8%, OR 0.38 (0.22-0.66)

Nawijn	2020	Worldwide	2123	33 studies	Admission-surgery (cut-off 6 h)	Overall mortality	19% vs 32%, OR 0·41 (0·27-0·61)
CI=confidence interval. h=hours. HR=hazard ratio. ICU=intensive care unit. LOS=length of stay. ns=non-significant. NSTI=necrotising soft-tissue infection. OR=odds ratio. vs=versus. ··data not available							

Table S4: Research priorities

Domains	Research priority	Justification
Pathophysiology	Studying host-pathogen interaction and polymorphism of immune innate responses	New therapeutics as adjuvant to antibiotics
Epidemiology	- Population-based studies with active surveillance or registries to better determine incidence and characteristics of NSTI - Evaluation of NSTI mortality and morbidity around the world (ongoing SKIN-ICU study, NCT05116956)	Better health provision
Treatment	- World-based database/ RCTs for NSTI treatment strategies - Ultra-rapid microbiologic evaluation of NSTI - Define role for immunomodulation therapies - Further assessment of IVIG in GAS NSTI - Impact of education healthcare workers campaigns on NSTI mortality - Stem cell graft in large losses of skin and muscle tissue	Improvement of NSTI management, bundle rational
NSTI=necrotizing soft tissue infections. RCTs=randomised controlled trials. IVIG=Intravenous immunoglobulin. GAS= Group A streptococcal		