Necrotising soft-tissue infections

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

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See Online for appendix

Introduction

Necrotising soft-tissue infections are life-threatening infections characterised by subcutaneous tissue, fascia, or muscle necrosis, associated with high morbidity and mortality.[1] Early diagnosis is a challenge, with more than half of patients initially misdiagnosed.[2,3] Despite their relative low incidence, most physicians might see one case of necrotising soft-tissue infection throughout their career and should be aware of this condition. Indeed, initial misdiagnosis, prolonging time to first surgical debridement, is associated with increased morbidity and mortality.[4] Unlike previously published reviews, our Review focuses on a pragmatic approach to non-cervicofacial necrotising soft-tissue infection recognition and management in adults.

Classification

Necrotising soft-tissue infections encompass all infections with a necrotising component involving any or all layers of the soft-tissue compartment, from the dermis and subcutaneous tissue to the deeper fascia and muscle.[2,5] Multiple terms have been used to describe necrotising soft-tissue infections (ie, necrotising fasciitis, hospital gangrene, Fournier's gangrene, Meleney's gangrene [haemolytic streptococcal gangrene]), including classifications based on microbiological findings (ie, type 1, 2, or 3 infections, synergistic gangrene, clostridial cellulitis), anatomical location (eg, Fournier's gangrene) or depth of infection (eg, necrotising cellulitis, necrotising fasciitis, myonecrosis; figure 1). Regardless of these classifications, the most important step in clinical practice is to differentiate non-necrotising soft-tissue infections from necrotising soft-tissue infections, the latter being surgical emergencies. Necrotising soft-tissue infections share common pathophysiological features and therefore require a broadly similar approach to diagnosis and management, foremost broad-spectrum antimicrobial therapy and early surgical debridement, with intensive supportive care.[6]

Incidence

Incidence estimates of necrotising soft-tissue infections might be inaccurate because of the wide range of terms describing the condition, its rarity, and the absence of national systematic reporting policies. The few population-based studies that exist have a risk of bias due to misdiagnosis when hospital electronic databases are used.[7–9] The estimated incidence of necrotising soft-tissue infections varies between geographical areas worldwide from 0·2 to 6·9 per 100 000 person-years, with peak incidence reported in Thailand reaching 15·5 per 100 000 person-years (appendix p 2).[7,10–19] An increased incidence of necrotising soft-tissue infections, group A streptococcus-associated or not, has been reported in the last decades worldwide.[7,11,14,18,20,21]

Data are best established for necrotising soft-tissue infections caused by group A streptococcus, as active surveillance of invasive group A streptococcus infection exists in several countries.[20–31] Prospective population-based studies report invasive group A streptococcus infection incidence to be 3–4 per 100 000 person-years, although incidence might be five-to-ten-times higher among indigenous populations or in tropical countries.[23] Invasive group A streptococcus infections including necrotising soft-tissue infections closely follow poverty with increased incidence in low-income and middle-income countries.[32,33] Although soft-tissue infection is the most common presentation of invasive group A streptococcus infection, necrotising soft-tissue infections comprise only about 10% of invasive group A streptococcus infections (appendix p 3).[20–29,31] Rates of group A streptococcus necrotising soft-tissue infections are highest in the seasons when group A streptococcus throat infections increase, coinciding with influenza season in winter and scarlet fever season in spring in the northern hemisphere.[34] Geographical differences in patient risk factors, microbiology, and portal of entry have been observed regionally and internationally.[35–37] Many specific variations of necrotising soft-tissue infections have been described depending on the anatomical location of the infection (eg, cervicofacial necrotising soft-tissue infection, abdominoperineal necrotising soft-tissue infection), the population involved (eg, children, patients with neutropenia), or the microbiology (eg, *Vibrio* spp or *Aeromonas* spp necrotising soft-tissue infections). These specificities are summarised in appendix (pp 8–9).

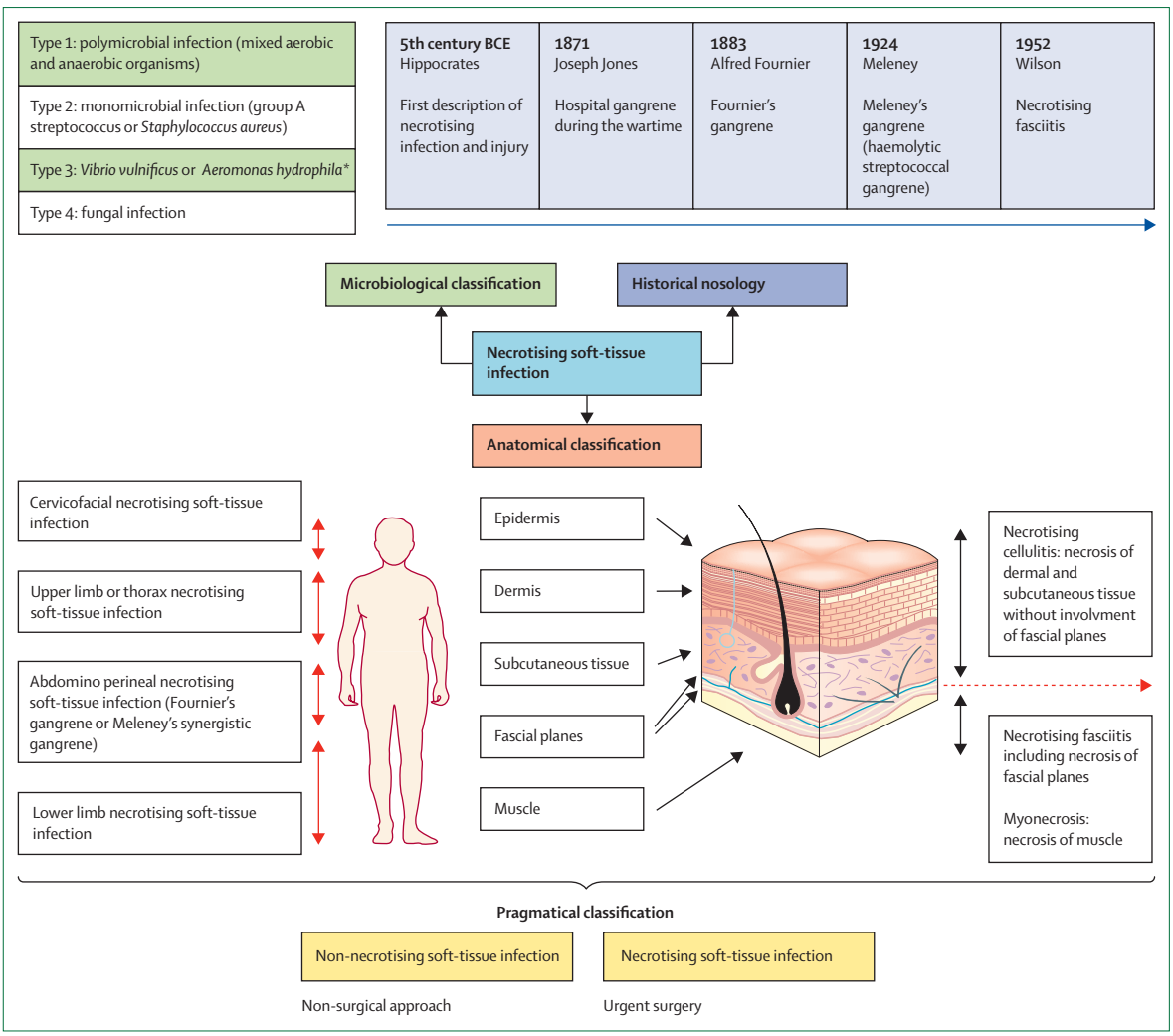

Figure 1: **A pragmatic approach of categorising necrotising soft-tissue infections**
Schema adapted from Prof Edouard Grosshans. *Not universally agreed on, some authors included clostridial infections or monomicrobial Gram-negative infections.

Pathogenesis

The factors that trigger necrotising soft-tissue infections are those that allow exposure to the causative pathogens, 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 have a key part in pathogenesis, both inherited and acquired. Approximately 60% of patients with invasive group A streptococcus or necrotising soft-tissue infections more generally have some other underlying medical illness such as immunosuppression, obesity, cardiac disease, chronic renal failure, cirrhosis, cancer, alcoholism, injecting drug use, and diabetes (appendix pp 8–9).[38–40] Some of these associations might 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 group A streptococcus might all predispose to severe necrotising soft-tissue infections.[42] For instance, a specific *DQA1* allele of the human leucocyte antigen has been linked to invasive group A streptococcus with or without necrotising soft-tissue infection.[43]

Polymicrobial necrotising soft-tissue infections

For polymicrobial necrotising soft-tissue infections, causative bacteria are usually the resident microbiota of the patient's own skin, the endogenous enteric microbiota, or the pharyngeal microbiota, all of which might 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 oropharyngeal or gastro-urinary tract via instrumentation, surgery, abscess rupture, or fistulation from non-sterile sites, sometimes associated with carcinoma (appendix pp 8–9). Devitalised tissue, coupled with patient comorbidity such as diabetes, use of steroids or non-steroidal

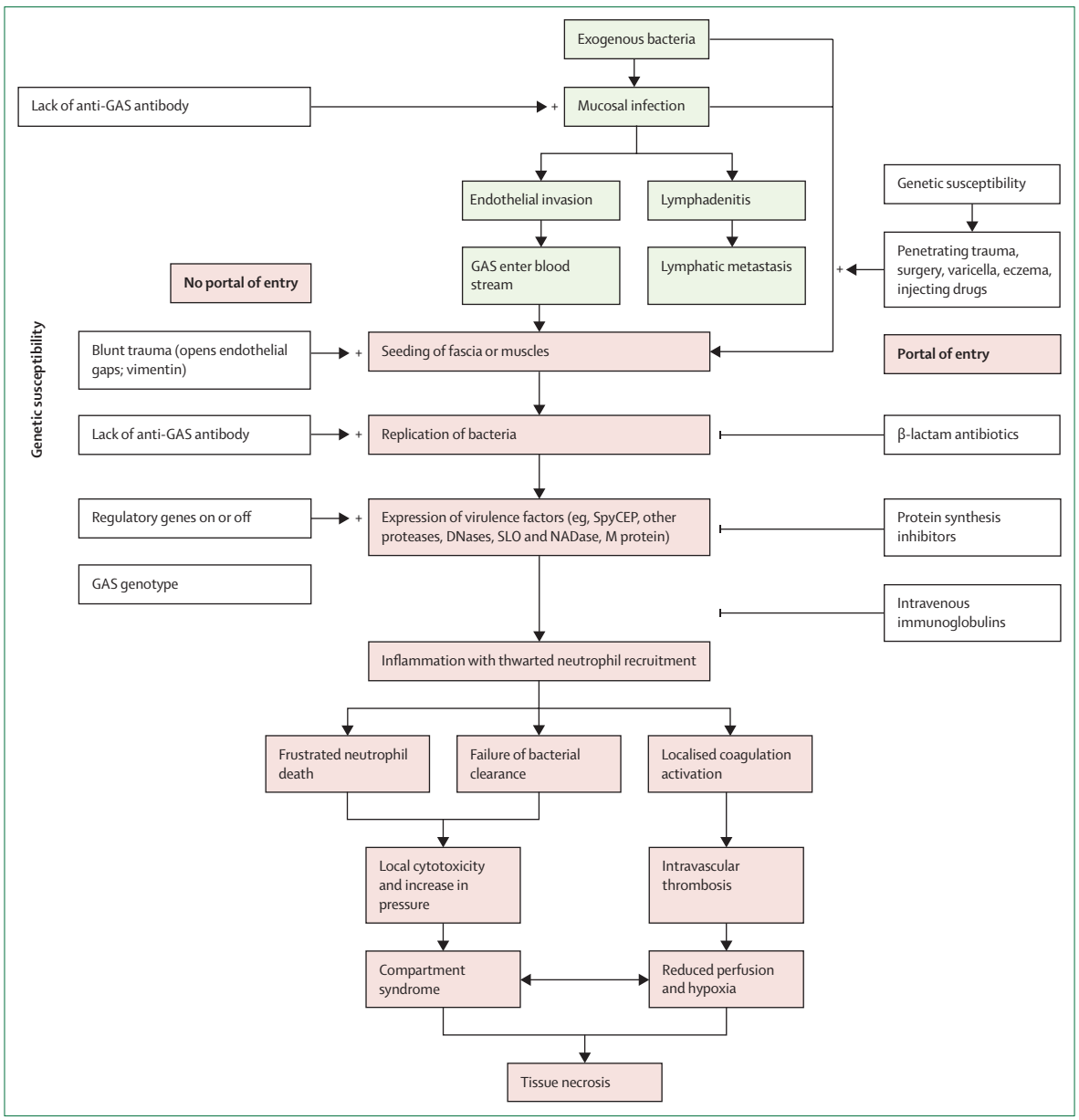

Figure 2: **Pathogenetic steps leading to necrotising soft-tissue infections caused by *Streptococcus pyogenes***
Streptococcus pyogenes or group A streptococcus has the ability to enter and survive within the lymphatic system reaching the bloodstream by metastasis, augmented by the hyaluronan capsule and other virulence factors. Bacteria are more likely to leave the bloodstream in tissues where the endothelium is disrupted—eg, where bruising has occurred—providing a plausible explanation for the association of *S pyogenes* necrotising soft-tissue infections with blunt trauma; with upregulation of skeletal vimentin in muscular cells. GAS virulence factors swiftly negate the body's normal immune defences. *S pyogenes* has a specific ability to prevent recruitment of white blood cells to the site of infection, and to withstand killing by white blood cells. Virulence factors of *S pyogenes* 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 hypervirulent. The consequent thwarted inflammation leads to tissue damage as a result of both bacterial and neutrophil enzymes, while coagulation activation might result in microthrombi and tissue infarction. Perfusion is further reduced by increasing tissue oedema that can result in compartment syndrome with consequent necrosis of muscle because of hypoxia. Progressive infection and necrosis of tissue in turn contribute toxic mediators that combined with bacterial virulence factors suggest that many patients with *S pyogenes* necrotising fasciitis will present in septic shock and require intensive care support because of low blood pressure and low pH. GAS=group A streptococcus. SLO=streptolysin O.

anti-inflammatory drugs (NSAIDs), and immunosuppression, impair host neutrophil defences, allowing otherwise non-virulent bacteria to synergise and lead to a necrotising soft-tissue infection.

Group A streptococcus necrotising soft-tissue infections

Group A streptococcus monomicrobial necrotising soft-tissue infections by contrast are usually presumed to

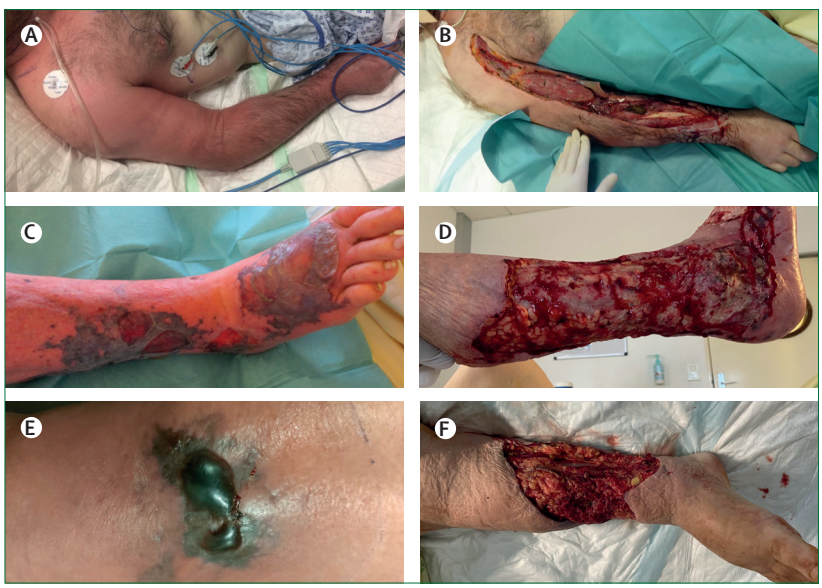

Figure 3: **Clinical pictures of necrotising soft-tissue infections**
Pictures show the same patients before (A, C, E) and after (B, D, F) surgical debridements. (A, B) Upper limb necrotising soft-tissue infection at early stages in a 42-year-old intravenous drug user, showing erythema of the arm. (C, D) Polymicrobial necrotising soft-tissue infection of the lower limb in a 65-year-old man with local signs of disease severity and areas of necrosis. (E, F) Monomicrobial Gram-negative limb necrotising soft-tissue infection in an 81-year-old woman, who had a kidney transplantation, showing local signs of disease severity and haemorrhagic bullae with poorly delineated areas of necrosis.

have spread from another person by airborne, droplet, or contact transmission; 5–12% of all invasive group A streptococcus infections are linked to exposure in a health-care setting.[44] About 50% of cases of monomicrobial group A streptococcus necrotising soft-tissue infections 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; (appendix pp 8–9).[39,45,46] The other 50% of cases show no clear portal of entry but about a quarter report recent blunt trauma without any apparent skin penetration.[5,39] Several patients anecdotally report antecedent upper respiratory tract infections, and group A streptococcus causing sore throat is hypothesised to enter the bloodstream to seed distant tissues,[47] however the mechanism is poorly understood. Recent experimental evidence points to the specific ability of group A streptococcus to enter and survive within the lymphatic system reaching the bloodstream by metastasis, augmented by the hyaluronan capsule and other virulence factors (figure 2).[48] Furthermore, blunt trauma increases the production of vimentin, a group A streptococcus-binding protein, on the surface of injured skeletal muscles, facilitating the initiation of group A streptococcus infection in the deep tissue following transient bacteraemia from the oropharynx in susceptible hosts.[5,49,50] Virulence of group A streptococcus leads to its ability to cause necrotising soft-tissue infections without need for synergy with other bacteria (figure 2).[51,52]

Role of NSAIDs

Several studies reported an association between NSAIDs and necrotising soft-tissue infections, particularly group A streptococcus necrotising soft-tissue infections.[53–55] In experimentally injured muscle, exposure to NSAIDs after blunt trauma enhanced binding of group A streptococcus[56] and impaired the immune responses in a model of group A streptococcus myonecrosis.[56,57] A case-control study identified a strong association between use of NSAIDs and necrotising soft-tissue infections in children with varicella.[54] However, observational studies might lack power or be biased as NSAIDs are taken because of disease severity. One randomised controlled trial (RCT) comparing ibuprofen with placebo in patients with cellulitis did not find an excess risk of necrotising soft-tissue infection, although the study was probably underpowered to detect an effect.[58] Nevertheless, these data warrant caution in the use of NSAIDs in the setting of skin infections, as these drugs could at least mask signs and symptoms of necrotising soft-tissue infections, thereby delaying diagnosis and management with associated prognostic consequences.[59] In April 2019, the French National Agency for the Safety of Medicines and Health Products published a warning on the use of NSAIDs in patients with infectious diseases, including necrotising soft-tissue infections[60] while, in the UK, the National Institute for Health and Care Excellence published advice cautioning against the use of NSAIDs in children with varicella.[61]

Management

Clinical diagnosis and surgical assessment

Necrotising soft-tissue infection remains a challenging clinical diagnosis with features ranging from subacute insidious progression to sudden fulminant disease; about 50% of patients are initially misdiagnosed.[2,3] Necrotising soft-tissue infections might 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 cervicofacial region.[1,5,62] Early signs might be similar to those seen in non-necrotising soft-tissue infections, 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 necrotising soft-tissue infections.[3,5] Later in the course of disease, severe local signs more typical of necrotising soft-tissue infection can be observed, including purple or cyanotic skin discoloration, necrosis, haemorrhagic bullae (figure 3), crepitus, and hypo-esthesia, but crucially their absence never excludes the diagnosis.[5] Even in patients with systemic toxicity (ie, sepsis or shock) severe local signs might be absent,

particularly when infection initiates in deep tissues such as muscle.

Similarly, fever is present in only 40% of patients.[3,5] Because of the low incidence and the poor sensitivity of early clinical signs, with diagnostic pitfalls,[63] we suggest that senior decision makers should be involved early to estimate the likelihood of necrotising soft-tissue infections and therefore the need for surgical exploration. Limited bedside incision under local anaesthesia of suspicious areas with fascial inspection has been reported to help diagnosis.[3,64] However, the gold standard to confirm necrotising soft-tissue infections is surgical exploration that reveals specific intraoperative findings, including dull grey necrotic tissue and fascia, dishwater pus, non-contracting muscle, lack of bleeding, or a positive finger test—ie, 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). In some situations, including during the early stages of necrotising soft-tissue infection or immunosuppressed patients, these macroscopic signs might be absent and only oedema might 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 might 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 necrotising soft-tissue infections 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 necrotising soft-tissue infections from non-necrotising soft-tissue infections. In stable and equivocal cases, MRI is the most effective method to diagnose necrotising soft-tissue infections in the limbs and might provide useful diagnostic clues if thickened fascia (>3 mm) with hypersignal on fat-suppressed T2-weighted sequences are seen (appendix pp 4–5).[67,68] Standard x-rays have poor sensitivity and can only detect necrotising soft-tissue infections at advanced stages with gas in the soft-tissue. CT scan is of little diagnostic value for limb necrotising soft-tissue infections but should be done for abdominoperineal or cervicofacial infections to detect the portal of entry and guide surgical management (appendix pp 4–5). CT scan findings associated with necrotising soft-tissue infections 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 finding.[69]

Laboratory investigations

Several biomarkers and scores such as the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC; a score derived from serum C-reactive protein, leukocyte count, haemoglobin, sodium, creatinine, and glucose values) have been studied to distinguish necrotising soft-tissue infections from non-necrotising soft-tissue infections and 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. Hyperlactataemia is an independent predictor of need for amputation and mortality, while increased procalcitonin on admission is associated with progression to septic shock.[71,72] Creatinine kinase concentrations are often elevated, mostly in group A streptococcus necrotising soft-tissue infection,[76] suggesting myonecrosis. Importantly, no biomarker or score has been demonstrated to be sensitive enough to rule out necrotising soft-tissue infection and surgical exploration must always be done when clinical suspicion is high.

See Online for video 1

Microbiological diagnosis

Necrotising soft-tissue infections are mostly polymicrobial infections (50–85%).[38,77] In a recent meta-analysis (a total of 8718 patients from 105 studies included), pooled prevalence of polymicrobial infections was 53% and monomicrobial infections was 37·9%.[78] Necrotising soft-tissue infections have been classified microbiologically as type 1 (polymicrobial infection caused by Gram-positive cocci, fermenting and non-fermenting bacilli, and anaerobic bacteria), type 2 (monomicrobial infection caused by *Streptococcus* spp or *Staphylococcus aureus*), or type 3 (caused by *Vibrio* spp or *Aeromonas* species).[1] A type 4 category was recently proposed for fungal infections, mainly involving *Candida* sp and Zygomycetes in immunocompromised hosts.[79] Although Gram-positive organisms are more typically associated with necrotising soft-tissue infections, a variety of Gram-negative organisms might also be responsible depending on local epidemiological and host factors (*Vibrio* spp in subtropical areas; appendix pp 8–9).[80] Recent reports of Enterobacteriales necrotising soft-tissue infections, occurring mostly in immunocompromised patients, with higher mortality than in type 1 and 2 necrotising soft-tissue infections, suggested rethinking this classification.[81] Beyond these specificities, with the exception of *Vibrio* spp necrotising soft-tissue infections, which are associated with a more fulminant course of disease, the clinical presentation is very similar whatever the pathogen involved, even if the pathogenesis

of group A streptococcus necrotising soft-tissue infection has been studied more extensively.

Nevertheless, as the microbiological diagnosis is unknown at the time of admission, early management cannot be influenced. Furthermore, new microbiological techniques such as next-generation sequencing recently highlighted the complexity of the pathobiome often found in necrotising soft-tissue infections.[82,83]

Blood cultures, fine-needle aspiration in an area of skin necrosis, and intraoperative deep tissue biopsy have been recommended by the Infectious Diseases Society of America (IDSA) for microbiological diagnosis, rather than superficial wound swabs,[1] which are unreliable due to high contamination risk. Blood cultures are positive in 11–60% of cases and intraoperative tissue biopsy are positive in 80% of cases.[79,84,85] Fine-needle aspiration of an area of necrotic skin is simple and quick, and culture-positive in up to 73% of cases[86] (video 2). Ultrasound-guided aspiration of fluid along the fascia might be useful as well.[87] In immunocompromised patients, fungal cultures should be done, in addition to the bacteriological cultures done in all patients. PCR for specific bacterial species (eg, group A streptococcus) might aid their identification, even after initiation of antimicrobials, whereas shotgun metagenomics is promising for more exhaustive identification of the wider pathobiome involved in necrotising soft-tissue infections, notably anaerobes.[83]

See Online for video 2

Treatment

Noting the rarity of necrotising soft-tissue infections, a 2018 Cochrane systematic review found only three RCTs that assessed the effect of therapeutic interventions on mortality from necrotising soft-tissue infections. No conclusions could be made from these small disparate studies.[88] To date, current guidelines are mostly based on observational retrospective cohort studies.[1] However, some prospective registries of necrotising soft-tissue infections published[40,84] or ongoing (worldwide-based Skin-ICU study; NCT05116956) might provide a better level of evidence. All available data suggest that a high index of diagnostic suspicion is required, optimising interventions most likely to affect outcome, mainly early surgical debridement of necrotic tissues—within 6–12 h after admission with significantly lower mortality rates[89–91]—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 h, 7 days a week on-call specialist experienced in necrotising soft-tissue infections, identifying senior experienced practitioners in each specialty involved (eg, surgeons, intensivist, infectious disease physician, dermatologist, microbiologist), and implementing a bundle of measures might 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 necrotising soft-tissue infections in high-case volume centres (appendix pp 10–11).[13,18,95]

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 necrotising soft-tissue infections, obtaining microbiological or histological samples, and determining the extent of tissue necrosis (video 1).[96,97] According to Holena and colleagues,[98] performing the first surgical debridement "is not considered to be a technically challenging operation". Because the consequences of the surgical debridement can be devastating (ie, 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 (appendix pp 10–11).[8,98,99] 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 necrotising soft-tissue infections. First, the frequency of polymicrobial infections and rapid progression of necrotising soft-tissue infections mandates broad-spectrum agents with bactericidal action. Second, the central role of toxins in group A streptococcus infections suggests use of agents that reduce toxin production. Finally, impairment in pharmacokinetics and pharmacodynamics in the context of necrotising soft-tissue infections warrants optimised antibiotic choice and administration modalities to achieve satisfactory tissue diffusion. Data for antibiotic treatment specifically for necrotising soft-tissue infections are scarce, with guidelines mainly based on expert consensus. Initial intravenous antibiotic therapy should cover Gram-positive, Gram-negative, and anaerobic bacteria. Anatomical location of necrotising soft-tissue infection 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

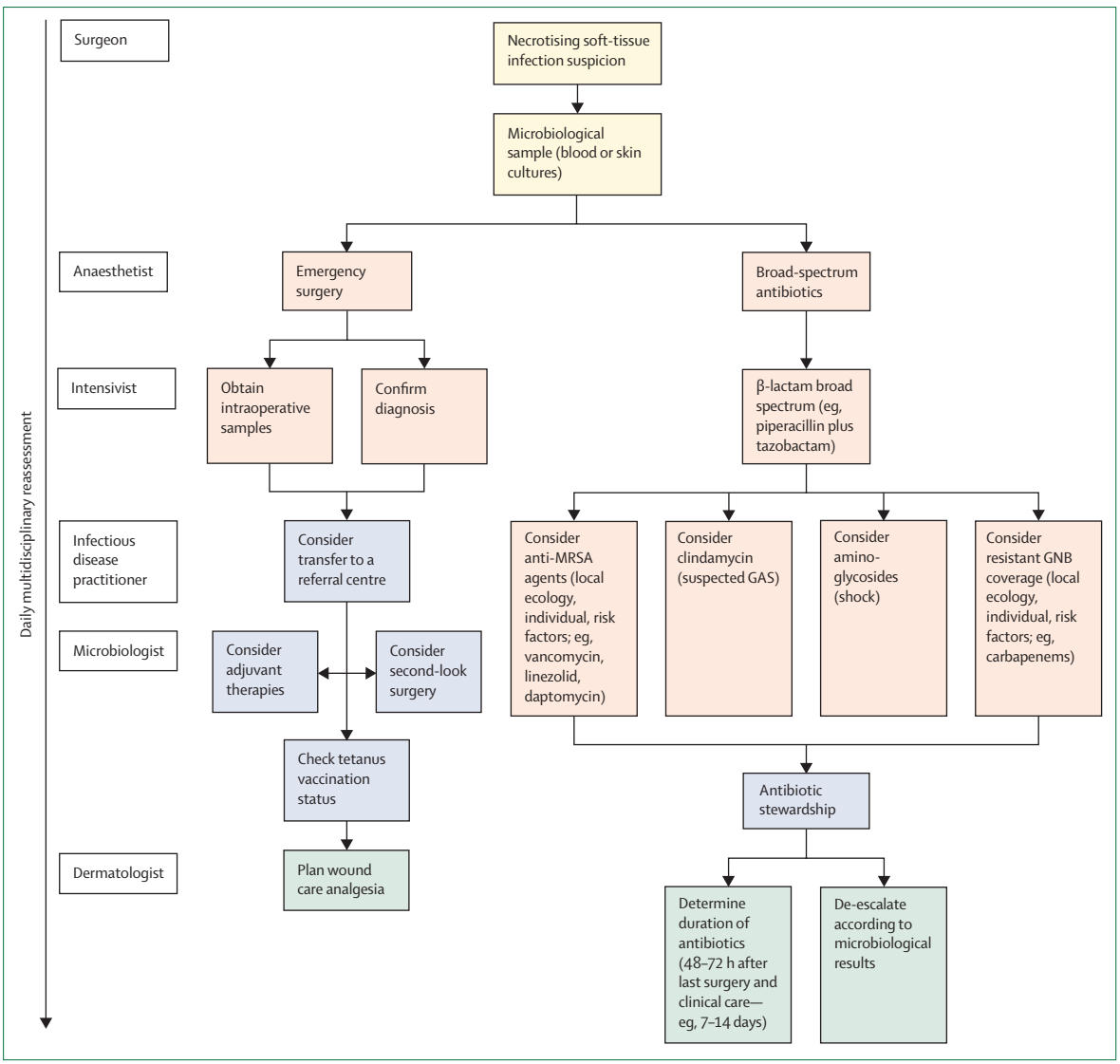

Figure 4: **Proposed algorithm for multidisciplinary and multimodal management of necrotising soft-tissue infections**
GAS=group A streptococcus. GNB=Gram-negative bacteria. MRSA=meticillin-resistant *Staphylococcus aureus*.

should be used (eg, piperacillin [4 g every 6 h] plus tazobactam [0·5 g every 6 h] or cefotaxime [2 g every 6 h]), informed by local ecology and individual patient factors (recent exposure to antibiotics, nursing-home residency, nosocomial infection, known carrier, or previous infection due to resistant bacterial strains). Suspected meticillin-resistant *S aureus* can be covered by inclusion of vancomycin (30 mg/kg loading dose before 30 mg/kg per 24 h continuous infusion), or daptomycin (8–12 mg/kg every 24 h) or linezolid (600 mg every 12 h), depending on level of suspicion, whereas resistant Gram-negative strains can be covered by use of carbapenems (eg, meropenem [1–2 g every 8 h]). Aminoglycosides (gentamicin [5–8 mg/kg over 30 min every 24 h] or amikacin [25–30 mg/kg over 30 min every 24 h]) should be considered to further broaden spectrum only in cases of septic shock (figure 5).[1,103] The only pharmaceuticals prospectively evaluated for necrotising soft-tissue infections are not routinely used: tigecycline, which was not evaluated comparatively,[104] and moxifloxacin, which did not show superiority to amoxicillin plus clavulanate.[105] Clindamycin has gained interest in necrotising soft-tissue infection management because of the high prevalence of group A streptococcus infection, ranging from 30% to 50%.[14,38] In-vitro and in-vivo models of group A streptococcus infection have shown clindamycin-related reduction in exotoxin production and disease severity, with improved bacterial clearance.[106–109] The effect of subinhibitory clindamycin concentrations is debated, prompting high-dose use.[106] Although no data focusing on necrotising soft-tissue infections exist, several retrospective studies on streptococcal toxic shock

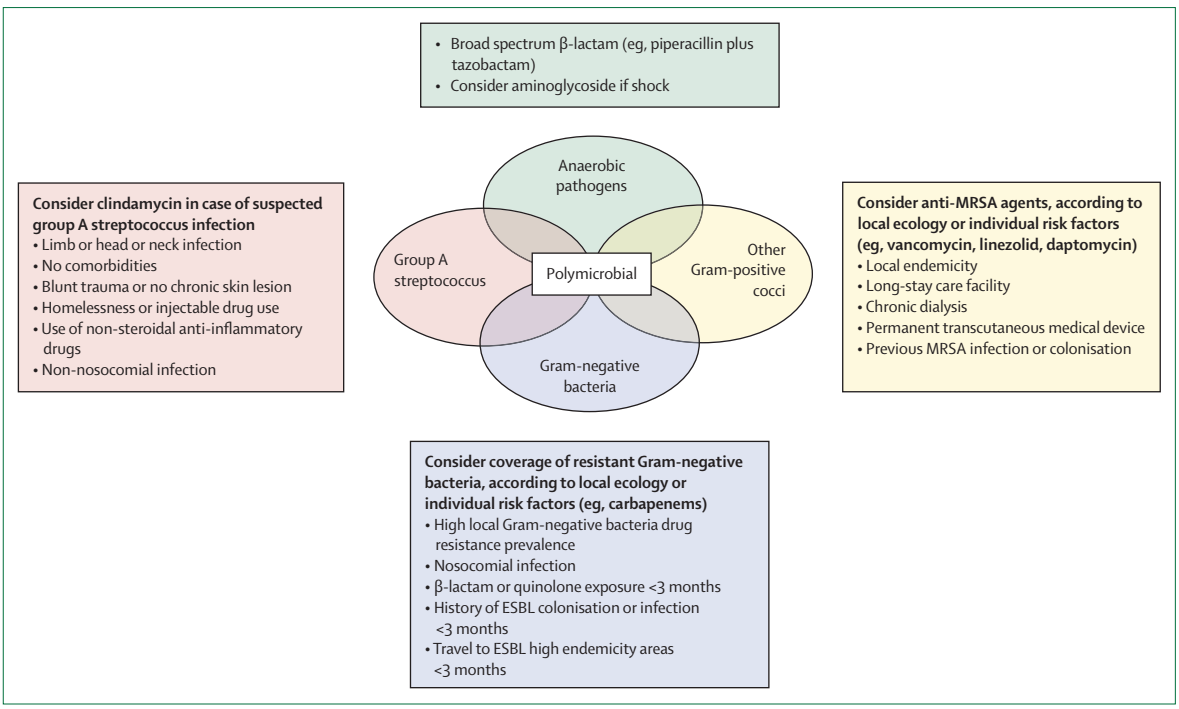

Figure 5: **Microbiological characteristics of necrotising soft-tissue infections and suggested antibiotic regimens**
The non-exhaustive list of host-factors, clinical presentation, or local epidemiology related factors presented here to guide antibiotic regimen are based on data from the recent literature and international guidelines. The presence of one or more of these risk factors should prompt clinicians to consider use of other antibiotics than solely the recommended broad-spectrum β-lactam such as the piperacillin plus tazobactam combination. Gram-positive cocci include *Streptococcus* (mainly group A but also B, C, G, and *Streptococcus 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*, and *Fusobacterium*, whereas *Corynebacterium*, *Micrococcus*, and *Bacillus*' pathogenicity remains uncertain despite identification. Gram-negative bacilli include *Enterobacteriacae*, non-fermenting species, *Haemophilus influenzae*, and specific waterborne species such as *Vibrio vulnificus*. ESBL=extended-spectrum β-lactamases. MRSA=meticillin-resistant *Staphylococcus aureus*.

syndrome cohorts, which include 40–60% necrotising soft-tissue infections, suggested a survival benefit for group A streptococcus infections specifically.[110–112] Empiric clindamycin (600–1200 mg every 6 h or every 8 h intravenously) for documented group A streptococcus necrotising soft-tissue infection is currently recommended by IDSA guidelines[1] and might be started empirically once suspicion of group A streptococcus is high. Robust data regarding other antibiotics with protein synthesis-inhibiting activity such as linezolid are scarce. 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 patients with necrotising soft-tissue infections, altered perfusion hinder antibiotic delivery to the infection site, favoured 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 β-lactams, as shown in patients with sepsis or septic shock, are recommended.[115] Data from diabetic foot infection, acute limb ischaemia, or necrotising pancreatitis suggest lipophilic molecules are useful. Carbapenem diffusion might be reduced into ischaemic tissues, limiting their use to cases with a high risk of resistance to other β-lactams.[116]

No trials focusing on antibiotic treatment duration for necrotising soft-tissue infections exist, which varies widely between centres, typically between 7 and 14 days, without robust data for relapse or other outcomes to guide management.[117] Guidelines based on expert opinion recommend treatment for 48–72 h after the last surgical debridement, provided clinical improvement including apyrexia.[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 necrotising soft-tissue infections, but seems reasonable for patients whose clinical condition is improving and can be monitored, as perioperative samples and blood cultures allow for a microbiological diagnosis to be obtained in most cases.[38,104]

Adjuvant therapies

Polyvalent intravenous immunoglobulins were proposed for necrotising soft-tissue infections based on toxin

neutralising activity in the sera of patients with streptococcal toxic shock syndrome,[119] with increased group A streptococcus clearance and decreased disease severity in experimental models.[120] Rates in the use of intravenous immunoglobulins for necrotising soft-tissue infections vary widely, from 58% in a recent Scandinavian study[38] to 0·3% in the USA.[121] The only RCT focusing on patients with necrotising soft-tissue infections did not show improved outcomes.[122] However, only 18% of patients included had confirmed group A streptococcus infection, limiting generalisability to group A streptococcus-related necrotising soft-tissue infections. Moreover, a meta-analysis assessing the use of intravenous immunoglobulins in clindamycin-treated patients with streptococcal toxic shock syndrome or group A streptococcus necrotising soft-tissue infections with shock did show a survival benefit,[123] including in the subset of a more recent US-based cohort with group A streptococcus necrotising soft-tissue infections. Although based mainly on observational studies, the currently available data support using adjuvant intravenous immunoglobulins for group A streptococcus necrotising soft-tissue infections but not for other pathogens.

Although a pathophysiological rationale was developed for hyperbaric oxygen therapy in clostridial infections, data are conflicting on its benefits,[124–127] and hyperbaric oxygen is not consistently recommended in the guidelines for necrotising soft-tissue infections. Hyperbaric oxygen should not delay initiation of other treatments and not be the sole motive of inter-hospital transfer.

Building on the concept of toxin neutralisation, immunomodulation has also been evaluated using reltecimod, an inhibitor of T-cell activation by bacterial superantigens. Although a RCT did not show significant benefit for patients with necrotising soft-tissue infections,[128] orphan drug designation for necrotising soft-tissue infections paves the way for future trials of immunomodulation in that setting.

Post-operative care and patient-centred management

No consensus exists for post-operative wound care in patients who undergo surgical debridement for necrotising soft-tissue infections. These large soft-tissue defects can be a challenge and require 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 exudate. Nevertheless, data are largely uncontrolled,[130] this therapy might be associated with higher pain scores and costs, and larger scale RCTs are awaited (NCT05071443). Data are also scarce for the best timing of skin grafting, which is typically performed within 3–6 weeks of initial debridement (appendix p 6). 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 and the Impact of Event Scale-Revised scores in survivors of necrotising soft-tissue infections were higher than in matched controls with non-necrotising soft-tissue infection septic shock.[132] Patient support groups can provide peer support to patients and families and obtain useful patient-centred feedback. Indeed, a majority of survivors and their families reported a lack of information and general lack of knowledge about necrotising soft-tissue infections within the health-care setting, while over half reported a lack of mental health and physiotherapy support after necrotising soft-tissue infections (Lee Spark Necrotising Fasciitis Foundation, personal communication).

Household contacts and transmission of group A streptococcus

The risk of secondary invasive infection, including necrotising soft-tissue infection, among household contacts of those with invasive group A streptococcus is increased up to 2000 folds.[133] Indeed, several cases of infections or pharyngeal carriage acquisition of identical strains have been described among households contacts of patients with invasive group A streptococcus.[134,135] No study has evaluated the impact of antibiotic chemoprophylaxis for contacts of necrotising soft-tissue infections. Nevertheless, in the USA, chemoprophylaxis is recommended in those with more than 20 h of close contact with a person with group A streptococcus necrotising soft-tissue infection in the previous 7 days.[136] In England, chemoprophylaxis is recommended for high-risk contacts of people with invasive group A streptococcus (neonates, women >37 weeks pregnant or <4 weeks after puerperium, individuals ≥75 years, and those with Varicella within 14 days).[133]

Mortality

The sustained high mortality associated with necrotising soft-tissue infections 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 codes were used, increasing the risk of misclassification.

A meta-analysis showed that mortality rates decreased, comparing before with after the year 2000 (28·8% *vs* 20·6%), but remained stable over the past 20 years.[4] In the USA, necrotising soft-tissue infections accounted for 4·8 deaths per 1 000 000 person-years with no change in

Search strategy and selection criteria

We searched PubMed for articles published from its inception to March 1, 2021, with the following search terms: "necrotizing OR necrotising fasciitis", "necrotizing OR necrotising soft-tissue infection", "synergistic necrotizing cellulitis", "progressive synergistic bacterial gangrene", and "suppurative fasciitis" combined with the terms "case control studies", "cohort studies", "cross sectional studies", "observational studies", "randomized controlled trial", "clinical trials". Articles from these searches and relevant references cited in those were reviewed. We selected articles about necrotising soft-tissue infection of the limb and abdominoperineal location in adults 18 years or older. Articles published only in English were included. We excluded articles about paediatric or cervicofacial forms of necrotising infections.

the incidence between 2002 and 2013.[137] 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 necrotising soft-tissue infection, shock, number of organs failure), biological variables at hospital admission, microorganisms identified (*Aeromonas* spp, *Vibrio* spp, *Clostridial* spp, streptococcal toxic shock syndrome) and therapeutic interventions (appendix p 7). However, most studies had limitations, including heterogeneity of the studied populations and small sample sizes, with numerous studies being single-centre[90,138,139] rather than population-based.[13,39] Only a few predictors of mortality are consistent across studies, with variations according to geographical locations.[35] The most important and modifiable predictor is time to initial surgery (appendix pp 12–13).[4,18,64,89–91,122,140–146] A recent meta-analysis showed a reduction in hospital mortality associated with surgical debridement performed within 12 h of hospital admission (odds ratio 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.[1,141,147]

Perspectives

Improving recognition of necrotising soft-tissue infections

A paucity of experience might lead to failure in distinguishing necrotising soft-tissue infection from non-necrotising soft-tissue infection, resulting in higher mortality and disabilities. Ensuring medical education includes necrotising soft-tissue infection, as planned in the UK[148] and France,[149] cellulitis clinics, expert centres available 24 h 7 days a week, multidisciplinarity, and telemedicine could contribute to improved diagnosis, management, and public health and therefore better prognosis.

Research priorities

In order to develop future treatment modalities, research should consider necrotising soft-tissue infection as an orphan disease, and note that disease heterogeneity might warrant microbe or host-specific strategies. Additional information about research priorities can be found in appendix (p 14).

Conclusion

Necrotising soft-tissue infections are life-threatening and have major impacts on the survivors' function and quality of life. Although recent years suggest an improvement in mortality and morbidity, early diagnosis and medical and surgical management of patients remain far from optimal. A clinically approved vaccine against group A streptococcus, as recommended by WHO, could have a substantial impact on the incidence of necrotising soft-tissue infections.[150] We believe that necrotising soft-tissue infections should be considered as a major neglected worldwide disease. Public-health policies that promote education among both health-care practitioners as well as patients, and expert centres, coupled with systematic data collection and translational worldwide research programmes, including low-income and middle-income countries, could lead to better outcomes for necrotising soft-tissue infections in the future.

Contributors

CH wrote the first draft of the manuscript. CH, TU, NdP, and OC contributed equally to the literature search and analysis, manuscript writing, and critical revision of this manuscript. 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

We declare no competing interests.

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