Journal of Hospital Infection 75 (2010) 249–257

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Review

Diagnosis and management of necrotising fasciitis: a multiparametric approach

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ARTICLE INFO

Article history:
Received 7 September 2009
Accepted 13 January 2010
Available online 9 June 2010

Keywords:
Hyperbaric oxygen
Intravenous immunoglobulin
Necrotising fasciitis
Skin and soft tissue infections

SUMMARY

Necrotising fasciitis (NF) is situated with myositis and myonecrosis at the severe end of a spectrum of skin and soft tissue infections but is far removed from erisepelas, impetigo and cellulitis. Inexperienced clinicians are easily misled by the protean manifestations of infection, especially exotoxin or superantigen mediated consequences from streptococcal NF. Early clinical suspicion and surgery are key to improving survival, and patients with NF need integrated multidisciplinary management, adjusted to the infecting organism(s), the site of infection, and the effects from any toxins produced. A multiparametric approach, incorporating various clinical and laboratory parameters, can aid aggressive management. This review describes the diagnosis and management of the major types of NF, emphasising important aetiological clues from the history and the appropriate usage of diagnostic investigations. The potential benefits of controversial therapeutic approaches, including hyperbaric oxygen and intravenous immunoglobulin, are discussed.

Introduction

According to Martin *et al.*, necrotising fasciitis (NF) is essentially a 'severe inflammation of the muscle sheath that leads to necrosis of the subcutaneous tissue and adjacent fascia', that is difficult to diagnose early and even more difficult to manage effectively.[1,2] Early clinical suspicion, appropriate antimicrobials and surgery are key to improving survival.[3] In one survey of invasive group A β-haemolytic streptococcal (GAS) infection, including NF, the correct diagnosis was initially suspected in only 2% of admissions.[4]

History and terminology

The description of NF by Hippocrates in the fifth century BCE, and that of a Confederate physician in the American civil war, are no different from the presentation of today[5,6]: 'A purple or blue spot is first perceived … the skin in the affected spot melts away in 24 h … whilst a deep blue and purple, almost black, areola surrounding the dead mass, spreads rapidly in ever increasing circles.'[6] In Peking, a missionary surgeon reported similar presentations among opium addicts in 1924: 'A chill may usher in the general symptoms …. Irregular patches, dusky hue, blisters or large bullae develop, may break and discharge a dark serous fluid.'[7] In the days before the advent of antimicrobials, NF was treated successfully with 'bear-claw scratch debridement' and Carrel's tubes irrigating the tissues with Dakin's solution of chlorinated soda.[7]

'Meleney's gangrene' is commonly used to refer to abdominal wall fasciitis, but strictly should be streptococcal dermal gangrene anywhere on the body.[7] A confusing plethora of terms in the older literature refer to similar entities: necrotising erysipelas, acute non-clostridial crepitant cellulitis, synergistic necrotising cellulitis, haemolytic streptococcal gangrene, phagedena (literally 'eating away') and putrid ulcer. Fournier's gangrene refers to necrotising infection of the perineum and may be due to a variety of organisms, including GAS.[8,9]

Epidemiology and microbiology of NF

NF is not a notifiable disease in the UK, where the overall incidence of NF has been estimated as 0.24–0.4 per 100 000 adults.[10–12] In a large survey in Canadian children, the incidence of GASNF was 0.21 per 100 000, and non-GAS NF 0.08 per 100 000.[13] In older reports, inadequate culture techniques together with reviews and meta-analyses that fail to differentiate between synergistic and non-synergistic fasciitis make it difficult to attribute causation accurately. However, there are few organisms that have not, alone or in combination, caused NF. Essentially there are four types of NF, as outlined below (cf. Table I).

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0195-6701/$ – see front matter
doi:10.1016/j.jhin.2010.01.028

Table I
Micro-organisms causing necrotising fasciitis (NF)

Types of NF	Aetiology	Organism(s)	Clinical progress	Mortality
Type I (70–80% cases)[14]	Polymicrobial/synergistic, often bowel flora-derived	Mixed anaerobes and aerobes	More indolent, better prognosis, easier to recognise clinically	Variable; depends on underlying comorbidities
Type II (20–30% cases)[14]	Often monomicrobial, skin- or throat-derived	Usually group A β-haemolytic streptococcus (GAS), occasionally ± *S. aureus*	Aggressive, protean presentations easily missed	>32%.[23,25] Depends if associated myositis or toxic shock
Type III (commoner in Asia)[36–45]	Gram-negative, often marine-related organisms	*Vibrio* spp. mainly	Seafood ingestion or water contamination wounds	30–40%[37]
Type IV (fungal)[46,47]	Usually trauma associated, immunocompetent patients[47]	*Candida* spp. immunocompromised patients.[46] Zygomycetes immunocompetent patients[47]	Aggressive with rapid extension especially if immunocompromised	>47%[47] (higher if immunocompromised)

Based upon Giuliano *et al.*'s typing scheme involving two types of NF, two more can now be added.[10,14,46,47]

Type I NF (polymicrobial/synergistic)

Type I synergistic NF causes 80% of NF seen in practice.[14–16] Resulting from a synergistic mixture of anaerobic, aerobic and facultatively anaerobic bacteria (e.g. *E. coli*, *Pseudomonas* spp. and *Bacteroides* spp.), type I NF particularly affects the immunocompromised[14] or those with underlying abdominal pathology.[14–21] Synergistic NF in children usually affects the immunocompromised.[22]

Type II NF

Causing fewer than 20% of cases, usually monomicrobial and due to Gram-positive organisms, the commonest type II NF is caused most frequently by GAS alone or occasionally with *Staphylococcus aureus*.[14]

A significant increase in the incidence of GASNF has occurred since the 1990s, with a reported mortality of 43–58%.[23] In Ontario, from 1991 to 1995, the rate of GASNF increased from 0.085–0.4 per 100 000 population.[12] Between 1996 and 2000 in Florida, 18% of invasive GAS infection (iGAS) was associated with NF, far higher than during 1994–1995 in Atlanta, where only 3% of iGAS was associated with NF.[4,24] Active surveillance for GASNF in Canadian children in 2001–2003 found an incidence of 0.21 per 100 000, 15/26 associated with varicella infection.[13] A recent European study reported the mortality of GASNF as 32%, rising to 56% among those aged 70–79 years.[25]

Historically, monomicrobial *S. aureus* NF is uncommon, but occurs in neonates.[26–31] However, new 'epidemic' strains of community-associated MRSA (CA-MRSA) are causing alarming numbers of cases of NF in the USA, accounting for 16.7% of total NF cases and associated with purpura fulminans reminiscent of meningococcal septicaemia.[32–35]

Type III NF: Gram-negative monomicrobial NF, including marine-related organisms

The commonest Gram-negative causes of NF remain *Vibrio* spp., such as *V. damselae* and *V. vulnificus*, which were responsible for 0.53 cases per 100 000 in Hong Kong in the late 1990s.[36–38] *V. vulnificus*, associated with raw oyster ingestion, is the commonest cause of seafood-related deaths in the USA, particularly affecting patients with liver disease and iron overload.[37] Wound contamination with seawater accounts for 25% of cases.[37] Virulence factors and digestive enzymes contribute to the high mortality of 30–40% despite prompt diagnosis and aggressive therapy.[36,37,39,40] Monomicrobial Gram-negative, non-vibrio NF is uncommon, but does occur with *Pasteurella multocida, Haemophilus influenzae*, *Klebsiella* spp. and *Aeromonas* spp.[41–45]

Type IV NF: fungal

Cases of candida NF are very rare, mainly affecting the immunocompromised.[46] In contrast, zygomyotic necrotising infections (*Mucor* and *Rhizopus* spp.) affect immunocompetent patients after severe trauma and are responsible for nearly 32% of NF cases in some countries.[47] Fungal invasion most commonly follows traumatic wounds or burns, and isolation of aspergillus or zygomycetes should not be dismissed lightly.[47]

Risk factors for NF

Although occurring in all age groups, NF is slightly commoner in those >50 years of age.[4,10,15,48,49] General risk factors include diabetes mellitus, peripheral vascular disease, intravenous drug use, alcoholism, immunosuppression, obesity and old age.[15,48] Synergistic NF frequently occurs in people with some form of immune deficiency or more than one chronic underlying illness, including malignancy where impaired leucocyte function may be a contributing factor.[22,25,50]

Development of protective immunity during childhood or a genetic component may explain why only some within a family or community suffer streptococcal NF.[51] Occasionally, inexplicable clusters of streptococcal NF occur.[52,53] There may be some relationship between the prevailing strains and the nature of superantigens expressed.[53] Streptococcal NF in children is most commonly associated with varicella zoster infection, although perineal infection and omphalitis accounted for a third of cases in one series in which 19/20 children were previously healthy, and all four who died had delayed initial management.[53–55]

Pathophysiology of NF

The underlying pathophysiology is common to all types of NF, but the speed of development and associated clinical features differ markedly depending on the causative organism(s). Synergistic NF is a comparatively slow process, evolving over days. Often, following complicated abdominal surgery, ischiorectal or perineal abscesses, synergistic NF develops particularly where gut flora breaches the mucosa, entering tissue planes. A slowly evolving bruise on the abdominal wall or perineal infection may reflect underlying malignancy.[19] Culture of *Clostridium septicum* or *C. tertium* points to an intrabdominal focus, whereas *C. sordellii* is more associated with gynaecological pathology or black tar heroin skin-popping, where several tissue planes are included directly.[20,56]

Gas-forming organisms and anaerobic infection may produce crepitus. Surgically, classical 'dishwater fluid' due to lysis of polymorphs and serous discharge, together with macroscopic fascial necrosis, myositis or myonecrosis may be demonstrated.[11,40]

'Crescendo' pain, necessitating progressively stronger analgesia, is typical as occlusion of perforating nutrient vessels and infarction of the nerves produces progressive skin ischaemia and pain.[57] Muscle hypoxia and swelling alter oxygen tension, increasing intra-compartmental pressures, sometimes resulting in compartment syndrome.[58]

GASNF is initially more insidious than type I, but progresses far more rapidly. The disease may appear to have arisen spontaneously with no obvious focus.[16] In such cases, haematogenous infection from many foci, including the throat, ascending vaginitis, primary peritonitis or necrotising proctitis reaches the fascial layer, or seeds vimentin exposed by muscle damage.[56,59–62] Hence, initial symptoms are ascribed to influenza, gastroenteritis or muscle strain.[63] This mechanism may explain the association of GASNF with seemingly minor sporting injuries in athletes. Direct inoculation of GAS though wounds or associated with surgery is less common: examples include injection sites, caesarean section, plastic surgery, and even minor cosmetic procedures such as bikini waxing.[63–70] Where nosocomial GASNF is suspected, or if there is a cluster of cases, the source may prove to be a member of staff.[71–73]

The M protein of GAS confers resistance to phagocytosis, with mucoid strains being more pathogenic.[74] Exotoxins acting as superantigens produce massive T-cell proliferation and a concomitant release of inflammatory agents and cytokines, culminating in the systemic inflammatory response syndrome and multiple organ dysfunction. Streptococci embedded in tissue release massive amounts of enzymes, haemolysins, DNAase, protease and collagenases, allowing spreading streptococci to undermine normal skin with progressive coagulative necrosis. Streptokinase produces clotting abnormalities. In one patient, the area of visible cutaneous necrosis extended from 10 to 400 cm^2 in 3 h and visible spread during surgery is not uncommon.[75–77]

Hence the earliest clinical feature common to all types of NF is exquisite, agonising pain, quite out of proportion to any external signs.[74] The degree of pain may be lessened in diabetic neuropathy or following powerful analgesia.[78] It is common to find patients prescribed oral morphine for 'severe cellulitis' before the true diagnosis is suspected. As nerves supplying the necrotising areas of skin die, the central areas become anaesthetic, while laterally, the tissues overlying the deep spreading fascial infection remain tender.[38,74]

Infection in the deeper layers finally ascends, producing oedema of the epidermal and dermal layers (peau d'orange) and a 'woody' firmness of the tissues. Haemorrhagic bullae progress to cutaneous gangrene, with sensory and motor deficits resulting from fascial and nerve destruction.[3,16,50,79]

GASNF and GAS toxic shock syndrome (STSS)

Some 50% of type II NF cases are associated with STSS.[11,80] STSS is an exotoxin-driven disease that significantly increases the mortality of streptococcal NF alone from <40% to 67% with up to half of patients needing amputation.[11,81]

GAS with M-protein types 1, 3, 12 and 28 are responsible for most STSS including those associated with GASNF.[25,77] GAS superantigens bypass normal stimulatory mechanisms, causing massive activation of T-cells, cytokine release, tissue damage and the 'toxic shock-like syndrome'.[82] Shock is due to capillary leak syndrome causing hypotension and disseminated intravascular coagulation due to superantigen production. Hypoalbuminaemia ensues, with oedema, hypotension and respiratory distress syndrome.[82] Production of the prototypic Th_1 cytokine results in production of tumour necrosis factor-α, which mediates TSS symptoms by affecting myocardium and striated muscles causing myonecrosis.[82,83]

Increased mortality is in part due to the delay in identifying and excising the primary site of infection.[84] In one series including six patients with STSS and NF, where only one was correctly diagnosed on admission, two died, and the mean time taken for diagnosis was 72 h.[77]

Clinical diagnosis of NF

By the time the diagnosis is suspected, appearances are usually those of late NF, with visible bruising, bullae and cutaneous necrosis due to ascension of the necrotising process from the deeper fascial horizontal spread.

A thorough history should suggest the causative organisms in most cases. Specific enquiries should be made about minor trauma, soft tissue injury penetrating lesions including insect or human bites, recent surgery, skin infection or ulcers, injection sites and illicit intravenous drug usage. Many cases, however, remain idiopathic.[7,16,17,49,58,85–88]

Any history of foreign travel should prompt consideration of resistant or unusual organisms, and trauma involving soil contamination should prompt fungal culture.[47] Raw seafood ingestion or wound exposure to seawater justifies culture for *Vibrio* spp.[37]

A history of tonsillitis, close contacts with impetigo, or recent non-steroidal anti-inflammatory agent (NSAID) usage suggests streptococcal infection.[90] Since GAS vaginitis is associated with a serous discharge and easily overlooked, a search for the infective focus should include a vaginal examination and cultures. With puerperal GASNF, the baby should undergo a septic screen and prophylactic antimicrobials.[56,59,91]

Clinical evaluation of early GASNF is difficult as many patients appear well, with minor non-specific symptoms, and the cutaneous manifestations of disease may seem to appear spontaneously.[16] Patients with GASNF may have higher temperatures than patients with synergistic fasciitis.[92] One-fifth of patients have influenza-like symptoms characterised by fever and myalgia, while others present with severe pain, nausea, vomiting and diarrhoea.[63]

Diagnosis in general practice is particularly difficult, since patients are seen earlier in the infection and more easily misdiagnosed as muscle strains or viral illnesses. Other common misdiagnoses include gastroenteritis (exotoxins acting as enterotoxins), sunburn or an 'allergic rash' (exotoxin-mediated erythema), thrombosis, sprain or exacerbation of gout.[23,63,93] A widespread macular 'toxic erythema' is present in a minority of patients with associated STSS.

Misdiagnosis of NF is particularly common in children as it is rare, and then usually associated with recent varicella zoster.[55,92,94] Anaesthesia due to dead nerves in late fasciitis, or in peripheral neuropathy, may be falsely reassuring; self-administration of NSAIDs mask the temperature and degree of pain.[89,90] Since severe pain precedes skin changes by 24–48 h and is present in >97.8% of patients, a simple arbitrary pain 'score' – e.g. 'How bad is the pain on a scale of 10?' – is essential for monitoring the evolution of the disease.[74]

Despite severe pain and appearing quite unwell, some patients initially have only a mild erythema, cellulitis or swelling overlying the affected area. Since lymphatic channels are obstructed early in GAS infection, lymphangiitis and lymphadenitis are rare.[95,96] Overall, an exquisitely tender area evolves into a smooth, swollen area of skin with distinct margins progressing to dusky blue/purple, 'bruising' violaceous plaques, and finally full thickness necrosis with haemorrhagic bullae.[80,95] Patients in late stages of NF appear apathetic, indifferent to their surroundings.[96]

Radiological investigations

Ultrasound findings correlate reasonably well with histological fat changes in NF but correlation with fascial and muscle

abnormalities is poor.[97,98] Magnetic resonance imaging (MRI) with gadolinium can differentiate necrotic and inflamed or oedematous tissue.[98,99] T2-weighted images on MRI are probably the best radiological adjunctive investigation, but are more sensitive than specific.[100]

Laboratory diagnostic parameters

Microbiology

Blood cultures are positive in 11–60% of patients with GASNF, but the yield in synergistic fasciitis is lower.[17,23,101] *C. septicum* or *C. tertium* bacteraemia are associated with intrabdominal malignancy, whilst *Klebsiella* spp. are associated with liver abscess and endophthalmitis.[44]

Haemoglobinuria is common in GASNF, and routine culture of throat and vaginal swabs may be useful to establish a primary focus.[77,93] Blister fluid is often sterile.[3] Percutaneous needle aspiration of the advancing edge is painful, hence a tissue biopsy is the investigation of choice.[49] Tissues and aspirates should be Gram-stained, and cultured aerobically and anaerobically.[57] Few reports mention the sensitivity of Gram staining of tissues, but when seen in only 6/14 tissue specimens, 10 yielded streptococci on culture.[102,103] Fungal cultures, especially in immunosuppressed or trauma patients and enrichment cultures are useful, especially where patients have had recent antibiotic treatment.[47,101] Routine histological examination of tissue is important since intra-laboratory contamination of fungal culture plates can be excluded if the histological fungal stains are negative.[47]

Haematology

Disseminated intravascular coagulation and thrombocytopenia are common in any severe sepsis, and other haematological parameters should be interpreted with caution.[104] A rapidly falling haemoglobin in the presence of a stable haematocrit may suggest intravascular haemolysis. The dilutional effect of any fluids used in resuscitation should be borne in mind when interpreting blood results. With a wide range of values reported in NF, the leucocyte count is less helpful for diagnosis. Although leucocytosis is common in GASNF, leucopenia is commoner in association with STSS.[105] Infection with leucotoxin-producing organisms, e.g. Panton–Valentine leucocidin (PVL)-producing *S. aureus* or GAS, often leads to lymphopenia.[51] Eleven of 14 patients with NF and normal or elevated white blood cell (WBC) counts were lymphopenic ($<$1000 cells/mm^3), possibly representing endothelial recruitment and pooling of WBCs at sites of infection.[106]

Biochemistry

Acute renal failure is the norm in severe sepsis, and dosaging of renally excreted antimicrobials should be adjusted accordingly. Bacterial infection, inflammation, thrombosis and necrosis all increase serum C-reactive protein (CRP). A very high CRP level is common, particularly in GASNF; CRP levels of $>$16 mg/dL, with a sensitivity of 89% and specificity of 90%, have been reported in GASNF.[107] GASNF produces a higher CRP compared with other iGAS infections in children.[53]

Raised serum creatinine kinase (CK) indicates myositis or myonecrosis, as well as the effects of circulating toxins or ischaemia.[51,63] Involvement of adjacent muscle raises CK and is not present in all cases of NF, but CK levels of 600 U/L gave a sensitivity of 58% and a specificity of 95% for cases of NF.[107]

One-third of patients with GASNF are hypocalcaemic on admission, due to calcium precipitation with fat necrosis.[63,81] Hypocalcaemia may also be a sign of severity in synergistic NF.[108] Hypoalbuminaemia and hyponatraemia are common: in a series of 21 matched, consecutive cases, a serum sodium level of $<$135 mmol/L was found to be significantly associated with NF ($P = 0.0001$).[104]

Severe metabolic acidosis is the norm in GASNF.[77] A high serum lactate combined with low sodium levels may be predictive of mortality.[109] With serum lactate levels $\geq$6 mmol/L the mortality was 32% (8/25), whereas a lactate of $<$6 mmol/L and a serum sodium of $<$135 mg/L was associated with a mortality of 19% (13/70).[109]

Laboratory scoring systems for prediction of NF

The LRINEC (Laboratory Risk Indicator for Necrotising Fasciitis) scoring system has been useful in the diagnosis of NF when severe soft tissue infection was already suspected.[109] The LRINEC score was derived from routine blood tests on 89 consecutive patients with classical NF compared with 225 controls. Of the 13 variables studied (including age, sex, serum potassium and platelet count), the most reliable indicators of underlying NF were found to be CRP, creatinine, haemoglobin, leucocyte count, sodium and serum glucose.[109]

A score of 6 using the LRINEC system 'raises the suspicion', with a score $\geq$8 being 'strongly predictive' of NF (Table II).[109] For patients scoring $>$6, the positive predictive value for NF was 92% and the negative predictive value was 96%. The LRINEC score may also indicate outcome: mortality of those patients with LRINEC score of $<$6 was 11%, compared with 21% for those scoring $>$6.[110]

Application and clinical evaluation of the LRINEC scoring system to NF patients has not been performed in the UK. The original study was performed in the Far East and included unusually virulent Gram-negative organisms such as *Vibrio* spp. but few haemolytic streptococcal infections. Additionally, there was no attempt to correlate the LRINEC score with the causative organisms.

Histology

Deep incisional biopsies are more useful in the diagnosis of NF than punch biopsies and should include the advancing edge and central necrotic areas.[34,57] Histological examination reveals underlying thrombi, necrosis, polymorphonuclear infiltrate, micro-organisms, and vasculitis.[15,57,97] In a retrospective uncontrolled

Table II
Laboratory risk indicator for necrotising fasciitis scoring system[104,109]

Variable	Score
C-reactive protein (mg/dL)	
$<$150	0
$>$150	4
Total white blood cell count (/mm^3)	
$<$15	0
15–25	1
$>$25	2
Haemoglobin (g/dL)	
$>$13.5	0
11–13.5	1
$<$11	2
Sodium (mmol/L)	
$\geq$135	0
$<$135	2
Creatinine (μmol/L)	
$<$141	0
$>$141	2
Glucose (mmol/L)	
$<$10	0
$>$10	1

study of bedside frozen sections, 12/43 were confirmed as NF and all survived.[79] Frozen sections are not readily available out of hours, and the time taken to undertake and process biopsies could be used for definitive surgery following a 'finger test'.[15] This involves infiltrating the area with local anaesthetic, and making a 2 cm incision down to the deep fascia. On gross inspection the fascia will be swollen and grey. Lack of bleeding and contractile muscle suggests dead tissue which should be removed. If 'dishwater' fluid is found and the index finger dissects the subcutaneous tissue off the deep fascia while moving easily along the tissue plane, the finger test is considered positive.[15]

Non-bleeding, non-contractile muscle suggests myonecrosis, and myositis in combination with GASNF increases the mortality to 80–100%.[111] All patients should have tissue specimens sent for confirmatory histology in addition to culture.[109]

Gram staining in addition to histological staining of tissues is important, since a paucity of leucocytes in the presence of Gram-positive cocci may be seen in GASNF or CA-MRSA due to leucocidin-mediated destruction of WBCs.[112] Non-suppurative necrosis of the subcutaneous fat with minimal inflammatory reaction should raise the suspicion of zygomycosis.[47]

Infection control and NF

Synergistic NF pathogens in UK hospitals rarely cause cross-infection, but those with probable GASNF should be isolated and barrier-nursed. Strict infection control procedures must be enforced for intubating or handling patients with GASNF since nosocomial outbreaks have been reported. One ventilated patient following surgery for breast GASNF managed to infect 16 healthcare workers and colonise a further five with the same strain of organism.[113] A recent case of transmission of GAS from a patient to a physiotherapist after 48 h of therapy and contact isolation suggests that perhaps recommendations for duration of isolation need revising.[114] Since GASNF has been acquired after a needlestick injury during a postmortem, on transfer of a body with suspected GASNF, morticians should be alerted, and post-exposure penicillin prophylaxis given in the event of inoculation injury.[115]

Clinical management of NF

Immediate surgical referral improves survival, and early liaison between surgeons (preferably plastic surgeons), intensivists, microbiologists or infectious disease physicians is essential. In a series of childhood NF, all five patients with delayed initial management died.[3,55,102,116–118]

Resuscitation with intravenous fluids and colloids, and inotropic agents, is usually necessary. The pain score should be documented regularly, allowing for the effects of analgesia. The practice at the Royal Devon & Exeter Hospital is to stop non-steroidal analgesia on admission of patients with any soft tissue infections. Blood cultures, baseline full blood count, urea and electrolytes, liver function tests, clotting studies, CRP and CK levels should be performed. Serum lactate and CRP are markers of severity of the infection and help guide therapy. A history of previous MRSA colonisation or clindamycin-resistant streptococcal infection should be noted, as empirical antimicrobial choices may be affected. Baseline immunoglobulin levels may be measured in cases of STSS if contemplating adding intravenous immunoglobulin (IVIG) therapeutically.

Chest X-ray may reveal early changes of fluid overload or changes of adult respiratory distress syndrome. Radiology of the affected areas is generally unhelpful, although occasionally more complex radiology such as MRI of the suspected area of fasciitis may be helpful, but should not delay surgery.[100]

Role of NSAIDs in GASNF

The contribution of NSAIDS to the development of GASNF is controversial: some authors recommend stopping NSAIDs in cases of soft tissue infection, others such as Brun Buisson recommend using NSAIDs 'with caution'.[119–123]

Whether the apparent association between NF and the use of NSAIDs is due to masking of early NF symptoms or whether usage for specific musculoskeletal symptoms contributes to the pathogenesis of NF remains unclear. There are many reports where presentation was delayed due to usage of NSAIDs.[90,124] The majority of patients with NF have used NSAIDs prior to admission.[124] NSAIDs inhibit renal prostaglandin synthesis, potentiate the development of renal failure and prevent the respiratory burst necessary for phagocytes to kill intracellular organisms.[90]

Surgery for NF

A senior surgical opinion, preferably from a plastic surgeon if available, is vital since inexperienced juniors can be misled by the lack of the necrosis and blistering in early cases of NF. In cases of doubt, the tissue oxygen tension can be measured with a probe using transcutaneous soft tissue oximetry. The oxygen tension was significantly lower in NF than cellulitis (52% in NF, cf. 84% in patients with simple cellulitis) with a sensitivity of 100% and a specificity of 97%.[58]

Anaesthesia for patients with NF is often difficult. The incision is often larger than expected and the patient is cardiovascularly unstable with multi-organ failure, coagulopathy and blood loss.[12] Massive third space fluid loss necessitates aggressive fluid replacement which may have a dilutional effect on the doses of antimicrobials administered. The amount of fluid protein and electrolyte losses may be similar to those of severe burn victims. In 1924, Meleney raised the dilemma of today's surgeons, namely, how much tissue to debride and when: 'the surgeon who sees one of these cases for the first time is often at a loss to know what to do and either delays operation or in haste performs an amputation.'[7]

Nowadays surgeons must 'be bloody, bold and resolute.'[74,125] Aggressive surgery removes the source of infection and toxins, and removal of infarcted tissue improves the penetration of antibiotics.[4] Early thorough debridement is essential.[16,117] In a series of 20 patients, all 15 survivors underwent aggressive surgical debridement within 3 h of admission and required a mean of 3.8 operations: fascial excision of up to 35% of total body surface area was required, one patient required amputation, two had colostomies, and six required extensive skin grafting for reconstruction.[55]

Inadequate or delayed surgery was associated with a mortality of 38% (8/21), compared with a mortality of only 4.2% (2/48) in those who underwent aggressive surgery at recognition ($P = 0.0007$).[102] Delaying surgery by 24 h increased the mortality associated with *Vibrio* spp. NF from 35% to 53%, with 100% mortality if surgery was not performed within 3 days.[126] Eleven of 12 patients where surgery was delayed more than 12 h died, whereas a 24 h delay resulted in a quadrupling of mortality in another study.[117,118]

The rate of spread of GASNF may outpace the rate of debridement.[77] Most patients need intensive care initially, the mean stay being 18 days.[77] Whereas some surgeons believe that all infected material should be removed in one operation, a 'second look' procedure is usually advisable.[102,127,128] Repeat debridements are often necessary with a mean of 3–4 such procedures during admission.[48,55]

Extensive debridement produces large areas that need covering.[129] Negative pressure therapy [vacuum-assisted closure or (VAC) dressing] with a continuous pressure of 40–100 mmHg is useful for wound coverage and encourages granulation before and

after skin grafting.[4] Porcine-derived skin substitute has also been used successfully.[130]

Role of hyperbaric oxygen (HBO)

For synergistic infections, particularly involving *Clostridium* spp., HBO switches off α-toxin production. HBO is also believed to increase the bactericidal action of neutrophils since at low oxygen tensions peroxide-dependent killing mechanisms are less efficient.[131] However, the overall evidence of benefit in non-clostridial NF is weak. Despite reports of rapid amelioration of clinical and mental status after only one HBO session, there are few published data to support the use of HBO in GASNF.[132] When used as adjunctive therapy in 12 patients, HBO produced subjective benefit in six.[133] An American study that examined the effect of HBO in 42 cases of NF found that the mortality rate was comparatively low at 11.9%, although 36 had polymicrobial necrotising infections and only two had GASNF.[131] There are few hospitals in the UK with easy access to HBO units, appropriate staffing and chambers large enough for patients needing intensive care facilities.

Antimicrobial prescribing in NF

With no evidence-based guidelines regarding the optimal management of NF, a pragmatic approach must be adopted.[134] Sporadic cases and difficulty in early recognition of NF make randomised double-blind controlled trials impossible. Whereas antibiotic therapy may be guided by the Gram stain of aspirates or biopsies, the poor sensitivity and the fulminant nature of the infection make broad-spectrum empirical therapy covering most types of NF seem sensible.[55,96] Subsequent rationalisation of antibiotic prescribing may be based on culture data.

Although almost always penicillin sensitive, the high tissue concentrations of GAS in GASNF result in most organisms being in stationary phase, rendering cell-wall-active antimicrobials ineffective (the 'Eagle' effect).[135,136] Clindamycin has the benefit of switching off exotoxin production even in stationary phase organisms, and GASNF patients treated with clindamycin have a significantly lower mortality than those not receiving clindamycin: 14% vs 60% (odds ratio: 0.13; 95% confidence interval: 0.02–0.08; $P = 0.03$).[101,136–139] Clindamycin usage strongly protects against mortality.[4] A 'D-test' to exclude inducible clindamycin resistance must be performed if erythromycin resistance is demonstrated.[140,141]

Intravenous benzyl penicillin and clindamycin are recommended by many authors for the treatment of GASNF. However, in order to provide adequate cover for synergistic and exotoxin-producing Gram-positive NF, this establishment's empirical protocol is intravenous clindamycin 1.2–1.8 g six-hourly together with intravenous imipenem 0.5–1 g six-hourly. When MRSA is suspected, intravenous linezolid 600 mg twice daily or daptomycin 6 mg/kg may be added in preference to vancomycin, as the latter has no effect on exotoxin production.

For suspected *Vibrio* spp. NF, therapy with doxycycline 100 mg twice daily plus intravenous ceftazidime 2 g eight-hourly is recommended.[38] Ciprofloxacin may be an alternative.[106]

Other agents

Drotrecogin α (activated protein C) has not been used effectively in NF and its use is limited to those patients not actively bleeding or within 24 h of surgery.[142]

After resuscitation, potent antibiotics and surgical debridement, some patients are 'irretrievably sucked down the vortex of the cytokine cascade', suggesting that there may be a role for antitoxin or immunomodulatory agents. Gram-positive (exotoxin-producing type 2) NF in particular may justify consideration of IVIG.[4,143]

It must be emphasised that there is very little evidence of any benefit from using IVIG in Gram-negative sepsis, about which there remains considerable debate regarding its mode of action. IVIG may promote clearance of GAS by the immune system, neutralise streptococcal superantigens and act as an immunomodulatory agent.[143,144] Since a suitably powered study is unlikely ever to be performed, small case series and anecdotal evidence predominate.[145,146] Department of Health guidelines state that IVIG 'may be added to adequate toxin-neutralising antimicrobials, source control and sepsis management when these approaches have failed to elicit a response.'[147]

In GASNF with additional myositis and myonecrosis, where superantigens abound, usage of IVIG can have a dramatic effect on outcome.[124,143,148–152] Despite the one report of GASNF in which a profoundly immunosuppressed patient was on haemodialysis, deemed too ill for surgery, and was cured with IVIG and clindamycin alone, surgery is still essential for survival.[150]

There are very few instances of side-effects attributable to IVIG infusion, the major contraindication to usage of IVIG being selective IgA deficiency or a history of anaphylaxis with immunoglobulins.

Suggested IVIG dosages vary but most authors now recommend 2 g/kg.[143,145,147–151] Our practice is to use 2 g/kg, with the option of a second dose if necessary after 24 h. Infusion is started initially at a rate of 20 mL/h, increasing incrementally after 10 min to a maximum of 160 mL/h.

Outcome

Generally, synergistic NF has a better immediate prognosis, although underlying malignancy or other comorbidities account for later demise. The absence of myonecrosis or myositis in GASNF is associated with a better prognosis as myositis and STSS increase mortality from 9% to 63%.[97,120,125]

High serum lactate combined with low sodium levels may be predictive of mortality.[153] Overall, major determinants of mortality included the time until operation, percentage of body area involved, acidosis, peripheral vascular disease and the number of comorbidities and age.[16,102]

Although one early study found no relationship between the mortality of GASNF with the M type, a recent European survey found that *emm*3, *emm*1 and *emm*87 caused most cases of NF, with *emm*3 and *emm*87 having the highest case fatality rates.[23,154]

Another factor in GASNF survival may be the production of differing exotoxins and presence of STSS.

Recurrent NF

There are only a few case reports of recurrent NF, including MRSA and a case of complement C4 deficiency where GASNF was succeeded by *Streptococcus pneumoniae* NF.[33,155]

Antimicrobial prophylaxis for contacts of GASNF

This is a controversial issue, despite the recognition that sporadic secondary cases of iGAS infection occur following close contact with an index case of GASNF.[112,156–158] Some 27% of household contacts may be GAS carriers.[159] The Ontario experience suggested that secondary iGAS cases within the household of an index case were 200 times more likely to occur (294 per 100 000 contacts), but international guidelines on prophylaxis vary widely in their recommendations.[11] The Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) do not recommend routine testing for GAS colonisation or administration of chemoprophylaxis to household contacts.[160] However, where prophylaxis is

prescribed to an elderly or at-risk patient, then the rest of the household should receive chemoprophylaxis as the source of GAS may not necessarily be the person with iGAS infection. Household contacts should be informed about the clinical manifestations of pharyngeal and iGAS infection and advised to seek immediate medical attention if symptomatic.[160]

In 2004 the Ontario Group A Streptococcal Study Group consensus recommended that prophylaxis was offered to all household contacts having regular contact for more than 4 h per day in the week prior to the patient becoming ill.[161]

Following a limited survey by the UK Health Protection Agency in 2004 which found several clusters of infection, recommendations for antimicrobial prophylaxis were limited to mothers and babies if either was infected during the neonatal period.[91] The recommendations included warning close contacts to seek early medical advice in the event of signs and symptoms of streptococcal infection developing.[91]

Patient information and support

It is vital that the family are informed at all stages about the illness. The Lee Spark Foundation is a valuable patient support group that also provides educational material including a free educational DVD for interested clinicians (Moor Hey Farm, Knowle Green, Ribchester, Preston PR3 2XE, UK).

Discussion

Since delay in recognition and effective treatment increases the mortality of NF, early diagnosis and management of NF is essential. In cases where the diagnosis is uncertain, repeated clinical assessment and a multiparametric approach integrating a range of diagnostic modalities and multidisciplinary involvement will optimise the diagnosis. Antimicrobial management should be tailored to the nature of the infecting organism, and infection control aspects considered as soon as the diagnosis is entertained. Early surgical referral is essential, both for diagnostic confirmation and therapeutic removal of as much infected tissue as possible, although a 'second look' is advisable.

References

1. Martin A. Necrotising fasciitis – early recognition and treatment can minimise risk of fatalities. *N Z Publ Health Rep* 1994;**1**:9–10.
2. Wong CH, Song C, Ong YS. Abdominal wall necrotizing fasciitis: it is still "Meleney's minefield". *Plast Reconstr Surg* 2006;**117**:147e–150e.
3. Cunningham JD, Silver L, Rudikoff D. Necrotizing fasciitis: a plea for early diagnosis and treatment. *Mt Sinai J Med* 2001;**68**:253–261.
4. Mulla ZD. Streptococcal mysositis. *Br J Plast Surg* 2003;**56**:424.
5. Descamps V, Aitken J, Lee MG. Hippocrates on necrotising fasciitis. *Lancet* 1994;**344**:556.
6. Jones J. Investigation upon the nature, causes and treatment of hospital gangrene as prevailed in the confederate armies 1861–65. Cambridge: Riverside Press. In: Hamilton FH, editor. *Surgical memoirs of the war of the rebellion*. New York: Hurd & Houghton for the U.S. Sanitary Commission; 1871. p. 257.
7. Meleney FL. Haemolytic streptococcal gangrene. Importance of early diagnosis and early operation. *J Am Med Assoc* 1929;**92**:2009–2012.
8. Fournier J-A. Gangrène foudroyante de la verge. *La Semaine Medicale* 1883;**3**: 345–348.
9. Ekelius L, Bjorkman H, Kalin M, *et al*. Fournier's gangrene after genital piercing. *Scand J Infect Dis* 2004;**36**:610–622.
10. O'Brien KL, Beall B, Barrett NL. Epidemiology of invasive group A streptococcal necrotizing fasciitis. *Clin Infect Dis* 2002;**35**:268–276.
11. Kaul R, McGreer A, Low DE, *et al*. Population based surveillance for group A streptococcal necrotizing fasciitis: clinical features, prognostic indicators, and microbiologic analysis of 77 cases. *Am J Med* 1997;**103**:18–24.
12. Baxter F, McChesney J. Severe group A streptococcal infection and streptococcal toxic shock syndrome. *Can J Anaesth* 2000;**47**:1129–1140.
13. Eneli I, Davies HD. Epidemiology and outcome of necrotising fasciitis in children: an active surveillance study of the Canadian paediatric surveillance program. *J Pediatr* 2007;**151**:79–84.
14. Giuliano A, Lewis Jr F, Hadley K, *et al*. Bacteriology of necrotizing fasciitis. *Am J Surg* 1977;**134**:52–57.
15. Childers BJ, Potyndy LD, Nachreiner R, *et al*. Necrotizing fasciitis: a fourteen-year retrospective study of 163 consecutive patients. *Am J Surg* 2002;**68**:109–116.
16. McHenry CR, Piotrowski JJ, Peterinic D, Malangoni MA. Determinants of mortality for necrotising soft tissue infections. *Ann Surg* 1995;**221**:558–565.
17. Ward RG, Walsh MS. Necrotising fasciitis: 10 years experience in a district general hospital. *Br J Surg* 1991;**78**:488–489.
18. Gozal D, Ziser A, Shupak A, *et al*. Necrotizing fasciitis. *Arch Surg* 1986;**121**: 233–235.
19. Marron CD, McArdle GT, Rao M, Sinclair S, Moorehead J. Perforated carcinoma of the caecum presenting as necrotising fasciitis of the anterior abdominal wall. The key to early diagnosis and management. *BMC Surg* 2006;**6**:11–17.
20. Kimura A, Higa J, Levin R, Simpson G, Vargas Y, Vugia D. Outbreak of *Clostridium sordellii* necrotising fasciitis among black tar heroin users. *Clin Infect Dis* 2004;**38**:e87–e91.
21. Chen JL, Fullerton KE, Flynn NM. Necrotising fasciitis associated with injection drug use. *Clin Infect Dis* 2001;**33**:6–15.
22. Murphy JJ, Granger R, Blair GK, Miller GG, Fraser GC, Magee JF. Necrotizing fasciitis in childhood. *J Pediatr Surg* 1995;**8**:1131–1134.
23. Haywood CT, McGeer A, Low DE. Clinical experience with 20 cases of group A streptococcus necrotizing fasciitis and myonecrosis: 1995 to 1997. *Plast Reconstr Surg* 1999;**103**:1567–1573.
24. Zurawaski CA, Bardsley M, Beall B, *et al*. Invasive group A streptococcal disease in metropolitan Atlanta: a population based assessment. *Clin Infect Dis* 1998;**27**:150–157.
25. Lamagni TL, Darenberg J, Luca-Harari B, *et al*. Epidemiology of severe *Streptococcus pyogenes* disease in Europe. *J Clin Microbiol* 2008;**46**: 2359–2367.
26. Lee YT, Chou TD, Peng MY, *et al*. Rapidly progressive necrotizing fasciitis caused by *Staphylococcus aureus*. *J Microbiol Immunol Infect* 2005;**38**:361–364.
27. Regev A, Weinberger M, Fishman M, *et al*. Necrotizing fasciitis caused by *Staphylococcus aureus*. *Eur J Clin Microbiol Infect Dis* 1998;**17**:101–103.
28. Romano R, Lu D, Holtom P. Outbreak of community-acquired methicillin-resistant *Staphylococcus aureus* skin infections among a collegiate football team. *J Athl Train* 2006;**41**:141–145.
29. Alvarez CA, Barientes OJ, Leal AL, *et al*. Community-associated Methicillin-resistant *Staphylococcus aureus*, Colombia. *Emerg Infect Dis* 2006;**12**:2001–2002.
30. Ohlsen RJ, Burns KM, Chen L, *et al*. Severe necrotizing fasciitis in a human immunodeficiency virus-positive patient caused by methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol* 2008;**46**:1144–1147.
31. Bodemer C, Panhans A, Chretien-Marquet B, *et al*. Staphylococcal necrotizing fasciitis in the mammary region in childhood: a report of five cases. *J Pediatr* 1997;**131**:466–469.
32. Young LM, Price CS. Community-acquired methicillin-resistant *Staphylococcus aureus* emerging as an important cause of necrotizing fasciitis. *Surg Infect (Larchmt)* 2008;**9**:469–474.
33. Wong CH, Tan SH, Kurup A, *et al*. Recurrent necrotizing fasciitis caused by methicillin-resistant *Staphylococcus aureus*. *Eur J Clin Microbiol Infect Dis* 2004;**23**:909–911.
34. Dehority W, Wang E, Vernon PS, *et al*. Community-associated methicillin-resistant *Staphylococcus aureus* necrotizing fasciitis in a neonate. *Pediatr Infect Dis J* 2006;**25**:1080–1081.
35. Miller LG, Perdreau-Remington F, Rieg G, *et al*. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med* 2005;**352**:1445–1453.
36. Goodell KH, Jordan MR, Graham R, *et al*. Rapidly advancing necrotizing fasciitis caused by *Photobacterium (Vibrio) damsela*: a hyperaggressive variant. *Crit Care Med* 2004;**32**:278–281.
37. Bross MH, Soch K, Morales R, Mitchell RB. *Vibrio vulnificus* infection: diagnosis and treatment. *Am Fam Physician* 2007;**76**:539–544.
38. Tang HJ, Chang MC, Ko WC, *et al*. *In vitro* and *in vivo* activities of newer fluoroquinolones against *Vibrio vulnificus*. *Antimicrob Agents Chemother* 2002;**46**:3580–3584.
39. Moreno ML, Landgraf M. Virulence factors and pathogenicity of *Vibrio vulnificus* strains isolated from seafood. *J Appl Microbiol* 1998;**84**:747–751.
40. Chang AK, Kim HY, Park JE, *et al*. *Vibrio vulnificus* secretes a broad-specificity metalloproteinase capable of interfering with blood homeostasis through prothombin activation and fibrinolysis. *J Bacteriol* 2005;**187**:6909–6916.
41. Hamamoto Y, Soejima Y, Pgasawara M. Necrotizing fasciitis due to *Pasteurella multocida* infection. *Dermatology* 1995;**190**:145–149.
42. McLellan E, Suvarna K, Townsend R. Fatal necrotising fasciitis caused by *Haemophilus influenzae* serotype f. *J Med Microbiol* 2008;**57**:249–251.
43. Saito T, Matsunaga H, Matsumura Y, *et al*. Necrotising fasciitis caused by *Haemophilus influenzae* type b in an elderly patient. *J Clin Microbiol* 2009;**47**: 852–854.
44. Wong CH, Kurup A, Wang YS, *et al*. Four cases of necrotizing fasciitis caused by *Klebsiella* species. *Eur J Clin Microbiol Infect Dis* 2004;**23**:403–407.
45. Monahan SF, Anjaria D, Mohr A, *et al*. Necrotizing fasciitis and sepsis caused by *Aeromonas hydrophila* after crush injury of the lower extremity. *Surg Infect (Larchmt)* 2008;**9**:459–467.
46. Cook DA, Heiner JP, Rao VK. Necrotizing candidal fasciitis following hip surgery. *Orthopedics* 1990;**13**:768–770.

47. Jain D, Kumar Y, Vasishta RK, *et al*. Zygomycotic necrotizing fasciitis in immunocompetent patients: a series of 18 cases. *Mod Pathol* 2006;**19**:1221–1226.
48. Elliott DC, Kufera JA, Myers RA. Necrotising soft tissue infections. Risk factors for mortality and strategies for management. *Ann Surg* 1996;**224**:672–683.
49. Francis KR, Lamaute HR, Davis JM, Pizzi WE. Implications of risk factors in necrotising fasciitis. *Am Surg* 1993;**59**:304–308.
50. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. *Chest* 1996;**110**:219–229.
51. Barnham MR, Weightman NC, Anderson AW, *et al*. Streptococcal toxic shock syndrome: a description of 14 cases from North Yorkshire, UK. *Clin Microbiol Infect* 2002;**8**:174–181.
52. Cartwright K, Logan M, McNulty C, *et al*. A cluster of streptococcal necrotising fasciitis in Gloucestershire. *Epidemiol Infect* 1995;**115**:387–397.
53. Minodier P, Bidet P, Rallu F, Tapiero B, Bingen E, Ovetchkine P. Clinical and microbiologic characteristics of group A streptococcal necrotising fasciitis in children. *Pediatr Infect Dis J* 2009;**28**:541–543.
54. Meza A, Gil H. Severe streptococcal infections and toxic shock in children. *Int Pediatr* 2000;**15**:232–235.
55. Moss RL, Musemeche CA, Kosloske AM. Necrotizing fasciitis in children: prompt recognition and aggressive therapy improve survival. *J Pediatr Surg* 1996;**8**:1142–1146.
56. Golde A, Leger WJ. Necrotising fasciitis in post partum patients: a report of 4 cases. *Obstet Gynecol* 1977;**50**:670–673.
57. Stamkenovicz I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen section biopsy. *N Engl J Med* 1984;**310**:1689–1693.
58. Wang TL, Hung CR. Role of tissue oxygen saturation monitoring in diagnosis in necrotizing fasciitis of the lower limbs. *Ann Emerg Med* 2004;**44**:222–228.
59. Stegmayr B, Bjorck A, Holm S, Nisell J, Rydvall A, Settergren B. Septic shock induced by group A streptococci infection: clinical and therapeutic aspects. *Scand J Infect Dis* 1992;**24**:589–597.
60. Barnham M, Holm SE. Serious streptococcal disease. *Clin Microbiol Infect* 1997;**3**:251–260.
61. Barnham M, Al-Dabbagh AK, Gray C, *et al*. Necrotizing proctitis caused by *Streptococcus pyogenes*. *J Infect* 2000;**40**:285–286.
62. Bryant AE, Bayer CR, Huntington JD, *et al*. Group A streptococcal myonecrosis: increased vimentin expression after skeletal-muscle injury mediates the binding of *Streptococcus pyogenes*. *J Infect Dis* 2006;**193**:1685–1692.
63. Bisno AL. The initial outpatient-physician encounter in group A streptococcal necrotising fasciitis. *Clin Infect Dis* 2000;**31**:607–608.
64. Campion J, Allum R. Necrotising fasciitis following anterior cruciate reconstruction. A case report. *Knee* 2006;**13**:51–53.
65. Nseir S, Pronnier P, Soubrier S, *et al*. Fatal streptococcal necrotising fasciitis as a complication of axillary brachial plexus block. *Br J Anaesth* 2004;**92**:427–429.
66. Hofmeister E, Engelhardt S. Necrotising fasciitis as complication of injection into greater trochanteric bursa. *Am J Orthop* 2001;**30**:426–427.
67. Saw A, Kwan M, Sengupta S. Necrotising fasciitis: a life threatening complication of acupuncture in a patient with diabetes mellitus. *Singapore Med J* 2004;**45**:180–182.
68. Goepert AR, Guinn DA, Andrews WW, *et al*. Necrotizing fasciitis after caesarian delivery. *Obstet Gynecol* 1997;**89**:409–412.
69. Heitmann C, Czermak C, Germann G. Rapidly fatal necrotising fasciitis after aesthetic liposuction. *Aesthetic Plast Surg* 2000;**24**:344–347.
70. Dendle C, Milvey S, Pyrlis F, Grayson L, Johnson PDR. Severe complications of a Brazilian bikini wax. *Clin Infect Dis* 2007;**45**:e29–e31.
71. Aragon T, Katz M, Mintz L. Nosocomial GAS associated with asymptomatic HCWs. *Morb Mortal Wkly Rep* 1999;**48**:163–166.
72. Chan H-T, Low J, Wilson L, Harris OC, Cheng AC, Athan E. Case cluster of necrotising fasciitis and cellulitis associated with vein schlerotherapy. *Emerg Infect Dis* 2008;**14**:180–181.
73. Ejlertsen T, Prag J, Holmskov A, Pettersson E. A 7 month outbreak of relapsing postpartum GAS infections linked to a nurse with atopic dermatitis. *Scand J Infect Dis* 2001;**33**:734–737.
74. Chelsom J, Halstensen A, Haga T, *et al*. Necrotising fasciitis due to group A streptococci in western Norway: incidence and clinical features. *Lancet* 1994; **344**:1111–1115.
75. Talkington DF, Schwartz B, Black CM, *et al*. Association of phenotypic and genotypic characteristics of invasive *Streptococcus pyogenes* isolates with clinical components of streptococcal toxic shock syndrome. *Infect Immun* 1993;**61**:3369–3374.
76. Smeets L, Bous A, Heymans O. Necrotising fasciitis: case report and review of literature. *Acta Chir Belg* 2007;**107**:29–36.
77. Sellers BJ, Woods ML, Morris ASE, *et al*. Necrotizing group A streptococcal infection associated with streptococcal toxic shock syndrome. *Am J Surg* 1996;**172**:523–528.
78. Quirk WF, Sternbach G. Joseph Jones: infection with flesh eating bacteria. *J Emerg Med* 1996;**14**:747–753.
79. Majeski J, Majeski E. Necrotizing fasciitis: improved early survival with early recognition by tissue biopsy and aggressive surgical treatment. *South Med J* 1997;**90**:1065–1068.
80. Stevens DL, Bisno AL, Chambers HF, *et al*. Practice guidelines for the management of skin and soft tissue infections. *Clin Infect Dis* 2005;**41**:1373–1406.
81. Simonart T. Group A beta-haemolytic streptococcal necrotising fasciitis: early diagnosis and clinical features. *Dermatology* 2004;**208**:5–9.
82. Tarkowski A, Collins LV, Jonsson IM, *et al*. Microbial superantigens as virulence factors and ways to counteract their actions. *Scand J Infect Dis* 2003;**35**: 642–646.
83. Roggiani M, Schlievert PM. Streptococcal toxic shock syndrome, including necrotising fasciitis and myositis. *Curr Opin Infect Dis* 1994;**7**:423–426.
84. Baracco GJ, Bisno AL. Therapeutic approaches to streptococcal toxic shock syndrome. *Curr Infect Dis Rep* 1999;**1**:230–237.
85. Sudarsky L, Laschinger JC, Coppa GF, *et al*. Improved results from a standardised approach in treating patients with necrotizing fasciitis. *Ann Surg* 1987;**206**:661–665.
86. Poitelea C, Wearne MJ. Pericocular necrotising fasciitis – a case report. *Orbit* 2005;**24**:215–217.
87. Sikora CA, Spielman J, MacDonald K, Tyrrell GJ, Embil HJM. Necrotising fasciitis resulting from human bites: a report of two cases of disease caused by group A streptococcus. *Can J Infect Dis* 2005;**16**:221–224.
88. Freischlag AJ, Ajalat G, Busuttil RW. Treatment of necrotising fasciitis, the need for a new approach. *Am J Surg* 1985;**149**:741–755.
89. Zerr DM, Alexander ER, Duchin JS, Koutsky LA, Rubens CE. A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999;**103**: 783–790.
90. Aronoff DM, Bloch KC. Assessing the relationship between the use of NSAIDS and necrotising fasciitis caused by group A streptococcus. *Medicine* 2003;**82**: 225–235.
91. Interim UK guidelines for management of close community contacts of invasive group A streptococcal disease. *Commun Dis Public Health* 2004;**7**:364–371.
92. Fustes-Morales A, Gutierrez-Castrellon P, Duran-Mckinster C, *et al*. Necrotizing fasciitis: report of 39 pediatric cases. *Arch Dermatol* 2002;**38**:893–899.
93. Sakata S, DasGupta R, Leditschke JF, Kimble RM. Extensive necrotising fasciitis in a 4 day old neonate: a successful outcome from a modern dressings, intensive care and early surgical intervention. *Pediatr Surg Int* 2008;**25**:117–120.
94. Wong CH, Wang YS. The diagnosis of necrotizing fasciitis. *Curr Opin Infect Dis* 2005;**18**:101–106.
95. Buchanan CS, Haserlick JR. Necrotizing fasciitis due to group A beta-haemolytic streptococci. *Arch Dermatol* 1970;**101**:664–668.
96. Janecicius RV, Hann SE, Batt MD. Necrotising fasciitis. *Surg Gynecol Obstet* 1982;**154**:97–102.
97. Barker FG, Leppard BJ, Seal DV. Streptococcal necrotising fasciitis: comparison between histological and clinical features. *J Clin Pathol* 1987;**40**:4335–4341.
98. Brothers TE, Tagge DU, Stutley JRE, Conway WF, Del Schutte H, Byrne TK. Magnetic resonance imaging differentiates between necrotizing and non-necrotizing fasciitis of the lower extremity. *J Am Coll Surg* 1998;**187**:417–421.
99. Schmid MR, Kossmann T, Duewell S. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. *Am J Roentgenol* 1998;**170**:615–620.
100. Parenti GC, Marri C, Calandra G, *et al*. Necrotizing fasciitis of the soft tissues: role of diagnostic imaging and review of the literature. *Radiol Med* 2000;**99**:334–339.
101. Bakleh M, Wold LE, Mandrekar JN, *et al*. Correlation of histopathological findings with clinical outcome in necrotizing fasciitis. *Clin Infect Dis* 2005;**40**: 410–414.
102. Bilton BB, Zibarui GB, McMillan RW, *et al*. Aggressive surgical management of necrotising fasciitis serves to decrease mortality: a retrospective study. *Am Surg* 1998;**64**:397–401.
103. Jarrett P, Rademaker M, Duffill M. The clinical spectrum of necrotising fasciitis: a review of 15 cases. *Aust N Z Med J* 1997;**27**:29–34.
104. Wall DB, de Virgilio C, Black S, *et al*. Objective criteria may assist in distinguishing necrotizing fasciitis from non-necrotizing soft tissue infection. *Am J Surg* 2000;**179**:17–21.
105. Rantala S, Vuopio-Varkila J, Vuento R, *et al*. Predictors of mortality in beta hemolytic streptococcal bacteraemia: a population based study. *J Infect* 2009;**58**:266–272.
106. Demers B, Simor AE, Vellend H, *et al*. Severe invasive group A streptococcal infections in Ontario Canada: 1987–1991. *Clin Infect Dis* 1993;**16**:792–800.
107. Simonart T, Simonart JM, Derdelinckx I, *et al*. Value of standard laboratory tests for the early recognition of group A streptococcal necrotizing fasciitis. *Clin Infect Dis* 2001;**32**:E9–12.
108. Nakamura S, Hashimoto Y, Ishida-Yamamoto A, *et al*. Hypocalcaemia: a sign of severity of necrotizing fasciitis. *Dermatology* 2004;**209**:64–65.
109. Wong CH, Khin LW, Heng KS. The laboratory risk indicator for necrotising fasciitis score: a tool for distinguishing necrotising fasciitis form other soft tissue infection. *Crit Care Med* 2004;**32**:135–141.
110. Su Y-C, Chen H-W, Hong Y-C, *et al*. Laboratory risk indicator for necrotizing fasciitis and the outcomes. *Aust N Z J Surg* 2008;**78**:968–972.
111. Stevens DL. Streptococcal toxic shock syndrome associated with necrotizing fasciitis. *Annu Rev Med* 2000;**51**:271–288.
112. Theis JC, Rietweld J, Danesh-Clough T. Severe necrotising soft tissue infections in orthopaedics surgery. *J Orthop Surg* 2002;**10**:108–113.
113. Kakis A, Gibbs L, Equia J, *et al*. An outbreak of group A streptococcal infection among health care workers. *Clin Infect Dis* 2002;**35**:1353–1359.
114. Lacy MD, Horn K. Nosocomial transmission of group A streptococcal infections from patient to health care worker. *Clin Infect Dis* 2009;**49**:354–357.
115. Hagberg C, Radulescu A, Rex JH. Necrotizing fasciitis due to group A streptococcus after an accidental needlestick injury. *N Engl J Med* 1997;**337** (23):1699.
116. Ward RG. Necrotising fasciitis: immediate surgical opinion is essential. *Br Med J* 1994;**309**:341.

117. Rouse TM, Malangoni MA, Schulte WJ. Necrotising fasciitis: a preventable disaster. *Surgery* 1982;**92**:765–770.
118. Lille ST, Saito TT, Engrav LH. Necrotizing soft tissue infections: obstacles in diagnosis. *J Am Coll Surg* 1996;**182**:7–11.
119. Myslinski W, Mosieovicz J, Kazubek M, *et al*. Non steroidal anti-inflammatory drugs over dosage – the cause or the consequence of necrotising fasciitis? *J Eur Acad Dermatol Venereol* 2003;**17**:227.
120. Stevens DL. Could nonsteroidal anti-inflammatory drugs (NSAIDs) enhance the progression of bacterial infections to toxic shock syndrome. *Clin Infect Dis* 1995;**21**:977–990.
121. Van Ammers PM, Moore PJ, Sacho H. Necrotising fasciitis after caesarian section – association with non-steroidal anti-inflammatory drugs. A report of 3 cases. *S Afr Med J* 1991;**80**:203–204.
122. Barnham M. Nonsteroidal anti-inflammatory drugs: concurrent or causative drugs in serious infection? *Clin Infect Dis* 1997;**25**:1272–1273.
123. Brun Buisson CJL, Saada M, Trunet P, Rapin M, Roujeau J-C, Revuz J. Haemolytic streptococcal gangrene and non-steroidal anti-inflammatory drugs. *Br Med J* 1985;**290**:1786.
124. Rietweld JA, Pilmore HL, Jones PG, *et al*. Necrotizing fasciitis: a single centre's experience. *N Z Med J* 1995;**108**:72–74.
125. Donaldson PM, Naylor B, Lowe JW, Goldesborough DR. Rapidly fatal necrotising fasciitis caused by *Streptococcus pyogenes*. *J Clin Pathol* 1993;**43**: 617–620.
126. Klontz KC, Lieb S, Schreibver M, *et al*. Syndromes of *Vibrio vulnificus* infections. Clinical and epidemiological features in Florida cases, 1981–1987. *Ann Intern Med* 1988;**109**:318–323.
127. Stephenson H, Dotters DJ, Katz V, *et al*. Necrotising fasciitis of the vulva. *Am J Obstet Gynecol* 1991;**36**:818–822.
128. Sudarsky L, Laschinger JC, Coppa GF, Spencer FC. Improved results from a standardized approach in treating patients with necrotizing fasciitis. *Ann Surg* 1987;**206**:661–665.
129. Steinstraesser L, Sand M, Steinay H-U. Giant VAC in a patient with extensive necrotizing fasciitis. *Int J Low Extrem Wounds* 2009;**8**:28–30.
130. Akita S, Tanaka K, Hirano A. Lower extremity reconstruction after necrotising fasciitis and necrotic skin lesions using a porcine-derived skin substitute. *J Plast Reconstr Aesthet Surg* 2006;**59**:759–763.
131. Escobar SJ, Slade HJB, Hunt TK, Cianci P. Adjuvant hyperbaric oxygen (HBO_2) for necrotising fasciitis reduces mortality and amputation rate. *Undersea Hyperb Med Soc* 2005;**32**:437–443.
132. Aitken DR, Mackett MC, Smith LL. The changing pattern of hemolytic streptococcal gangrene. *Arch Surg* 1982;**117**:561–567.
133. Brogan TV, Nizet V, Waldhausen JH, Rubens CE, Clarke WR. Group A streptococcal necrotizing fasciitis complicating primary varicella: a series of fourteen patients. *Pediatr Infect Dis J* 1995;**14**:588–594.
134. Thompson CD, Brekken AL, Kutteh WH. Necrotizing fasciitis: a review of management guidelines in a large obstetrics and gynaecology teaching hospital. *Infect Dis Obstet Gynecol* 1993;**1**:16–22.
135. Eagle H. Experimental approach to the problem of treatment failures with penicillin. I. Group A streptococcal infection in mice. *Am J Med* 1952;**13**: 389–399.
136. Stevens DL, Gibbons AE, Bergstrom R, *et al*. The eagle effect revisited: efficacy of clindamycin, erythromycin and penicillin in the treatment of streptococcal myositis. *J Infect Dis* 1988;**158**:23–28.
137. Schlievert PM, Kelly JA. Clindamycin induced suppression of toxic shock syndrome associated exotoxin production. *J Infect Dis* 1984;**149**:471.
138. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotics treatment for invasive *Streptococcus pyogenes* infection. *Pediatr Infect Dis J* 1999;**12**:1096–1110.
139. Brook I, Gober AE, Leyra F. *In vitro* and *in vivo* effects of penicillin and clindamycin on expression of group A beta-haemolytic streptococcal capsule. *Antimicrob Agents Chemother* 1995;**39**:1565–1568.
140. Panagaea S, Perry JD, Gould JK. Should clindamycin be used as treatment of patients with infections caused by erythromycin-resistant streptococci? *J Antimicrob Chemother* 1999;**44**:581–582.
141. Siberry GK, Tekle T, Carroll K, *et al*. Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible resistance *in vitro*. *Clin Infect Dis* 2003;**7**:1257–1260.
142. Cone LA, Stone RA, Schlievert PM, *et al*. An early favourable outcome of streptococcal toxic shock syndrome may require a combination of antimicrobial and intravenous gamma globulin therapy together with activated protein C. *Scand J Infect Dis* 2000;**38**:960–963.
143. Barry W. Intravenous immunoglobulin therapy for toxic shock syndrome. *J Am Med Assoc* 1992;**267**:3315–3316.
144. Norrby-Teglund A, Haul R, Low DE, *et al*. Evidence for the presence of streptococcal-superantigen neutralising antibodies in normal polyspecific immunoglobulin O. *Infect Immun* 1996;**64**:5395–5398.
145. Darenberg J, Ihendyane N, Sjölin J, *et al*. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2003;**37**:333–340.
146. Kaul R, McGeer A, Norrby-Teglund A, *et al*. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome – a comparative observational study. *Clin Infect Dis* 1999;**28**:800–807.
147. Provan D, Nokes TJC, Agrawal S, Winer J, Wood P. *Clinical guidelines for immunoglobulin use*. 2nd edn. London: Department of Health; 2008. p. 62.
148. Cawley MJ, Briggs M, Haith LR, *et al*. Intravenous immunoglobulin as adjunctive treatment for streptococcal toxic shock syndrome associated with necrotizing fasciitis: case report and review. *Pharmacotherapy* 1999;**19**: 1094–1098.
149. Chiu CH, Lin TY. Successful treatment of severe streptococcal toxic shock syndrome with a combination of intravenous immunoglobulin, dexamethasone and antibiotics. *Infection* 1997;**25**:47–48.
150. Lamothe F, D'Amico P, Ghosn P, *et al*. Clinical usefulness of intravenous human immunoglobulins in invasive group A streptococcus infections. *Clin Infect Dis* 1995;**21**:1469–1470.
151. Korzets A, Ori Y, Zevin D, *et al*. Streptococcal bacteraemia and necrotizing fasciitis in a renal transplant patient; a case for intravenous immunoglobulin therapy. *Nephrol Dial Transplant* 2002;**17**:150–152.
152. Chapman SJR, Opdam H, Donato R, *et al*. Successful management of severe group A streptococcal soft tissue infection using an aggressive medical regimen including intravenous immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis* 2006;**38**:742–743.
153. Yaghoubian A, de Virgilio C, Dauphine C, *et al*. Use of admission serum lactate and sodium levels to predict mortality in necrotizing soft tissue infection. *Arch Surg* 2007;**142**:840–846.
154. Luca-Harari B, Darenberg J, Neal S, *et al*. Clinical and microbiological characteristics of severe *Streptococcus pyogenes* disease in Europe. *J Clin Microbiol* 2009;**47**:1155–1165.
155. Kumar DP. Recurrent necrotising fasciitis in complement C4 deficiency. *Ann Intern Med* 2001;**8**:635–636.
156. Gamba M-A, Martinelli M, Schaad HJ, *et al*. Familial transmission of a serious disease-producing group A streptococcus clone case reports and review. *Clin Infect Dis* 1997;**24**:1118–1121.
157. Valenzuela TD, Hooton TM, Kaplan EL, Schlievert P. Transmission of 'toxic strep' syndrome from an infected child to a fire-fighter during CPR. *Ann Emerg Med* 1991;**20**:90–92.
158. Chandler RE, Lee LE, Townes JM, Taplit RA. Transmission of GAS limited to healthcare workers with exposure in the operating room. *Infect Control Hosp Epidemiol* 2006;**27**:1159–1163.
159. Weiss K, Laverdiere M, Lovgren M, *et al*. Group A streptococcus carriage among close contacts of patients with invasive infections. *Am J Epidemiol* 1999;**149**:83–88.
160. Prevention of Invasive Group A Streptococcal Infections Workshop Participants. Prevention of invasive group A streptococcal disease among household contacts of cases patients and among postpartum and post surgical patients: recommendations from the Centres for Disease Control and Prevention. *Clin Infect Dis* 2002;**35**:950–959.
161. Guidelines for the prevention and control of infection with invasive group A streptococcal disease. *Can Commun Dis Rep* 2006;**3252**:1–25.