Bromine, Bear-Claw Scratch Fasciotomies, and the Eagle Effect: The Management of Group A Streptococcal Necrotising Fasciitis and its association with trauma

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Abstract

Necrotising fasciitis (NF) is a rare, but potentially fatal, soft tissue infection. Described since classical times, historical depictions of the disease can mainly be found from wartime reports following battle injuries. Although a number of different species of bacteria have been implicated in the aetiology, perhaps the most well known is group A *Streptococcus* (GAS). Infection control, early surgical debridement and antibiotic therapy are now the central tenets of the clinical management of necrotising fasciitis; these treatment modalities all have their roots in wars occurring during the last 150 years. We review reports from the 19th century, early 20th century and mid-20th century onwards, to show how the management of necrotising fasciitis has evolved in parallel with prevailing scientific thought and medical practice. Historically, NF has often, but not exclusively, been associated with penetrating trauma, however, more recently along with a global increase in invasive GAS disease, reports have cited cases following non-combat related injuries or in the absence of antecedent events. We also examine the specific association between GAS necrotising fasciitis and trauma. In the 21st century, molecular biology has improved our understanding of GAS pathogenesis, but has not yet impacted on attributable mortality.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for the following words “necrotising fasciitis”, “hospital gangrene”, “group A streptococcus”, “*Streptococcus pyogenes*”, “Goldsmith”, “bromine”, “Eagle effect”, “bear claw” and “trauma”. Articles not obtained through Pubmed were identified through searches in Google Scholar, Imperial College or British Library. Articles resulting from those searches and relevant references cited in those articles were reviewed. Articles were published in English, French or German.

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Introduction

Phagedena, hospital gangrene, haemolytic streptococcal gangrene and, more recently, the “flesh-eating” disease form a collection of terms used to describe what we now call necrotising fasciitis (NF).¹ Although the aetiology of NF is often polymicrobial, the Gram-positive bacterium *Streptococcus pyogenes*, also known as group A *Streptococcus* (GAS), is historically most associated with NF, in part due to it being implicated in the first large NF case series described.² The original term “necrotising fasciitis” was suggested by Wilson in 1952, based on the pathology observed; a rapidly progressing infection that consistently resulted in fascial necrosis.³ Despite its varied nomenclature, this potentially life threatening soft tissue infection is easily recognised in historical reports.

Hippocrates described the association between a necrotising soft tissue infection and injury in the 5th century BC: “Many were attacked by the erysipelas... when the exciting cause was a trivial accident or a very small wound... the erysipelas would quickly spread wisely in all directions... Flesh, sinews, and bones fell away in large quantities...”⁴ Subsequently, there are numerous conditions consistent with NF in the literature (Figure 1A), with particular reference to traumatic wounds acquired during wartime.⁵⁻⁷ The American Civil War in the late 19th century influenced the epidemiology and management of NF (Figure 1B), with detailed descriptions of hospital gangrene⁸ and a trial of bromine antiseptics for this condition.⁹ Around the same time, the field of Microbiology was developing and, in 1874, the name *Streptococcus* was proposed for the organisms isolated from wound infections.¹⁰ The two World Wars and the intervening period improved our understanding of streptococci and NF, and emphasised the importance of surgery.^{2,11,12} Meanwhile, the Second World War stimulated large scale antibiotic production, representing a major transition in management of combat-related wounds.^{13,14}

At the end of the 20th century, increased NF incidence was reported in some countries.¹⁵ In particular, there was a worldwide increase in reporting of severe NF due to GAS.¹⁶⁻²⁰ Although GAS NF is rare (UK incidence 2.1 per 1000,000), recent case fatality rates vary from 13 to 31%,²¹⁻²⁴ and may rise to over 40% when associated with streptococcal toxic shock syndrome (STSS).²⁵ This morbidity prompted the introduction of antibiotics targeted at toxin production and also the use of adjunctive intravenous immunoglobulin. Notable in the modern literature are reports of the NF following non-

penetrating, minor injury such as muscle contusion,²⁶⁻³³ in contrast to historical reports, which were ostensibly linked to penetrating injury typified by combat wounds.^{4,8,11,34,35}

In this report, we predominantly focus on GAS NF and use historical data to review how the management of NF has evolved during three distinct periods: the late 19th century; the early 20th century and after the Second World War, leading to the multi-faceted approach used today. We also examine the association between blunt or penetrating trauma and GAS NF. Whilst reporting bias during wartime may in part account for the association between trauma and NF, there is also evidence from the peacetime literature supporting this association. As the term NF was only conceived in 1952, we will focus on conditions that have descriptive similarities with NF in the literature. In the 21st century, there is hope that modern scientific techniques to understand underlying pathophysiology will further refine management of this devastating disease process.

Late 19th century - hospital gangrene, infection control and the *Streptococcus*

Miasmas and laudable pus

Hippocrates (5th century BC) and Galen (2nd century CE) greatly influenced medical practice in Europe up to the 19th century. Prior to the 19th century, infectious disease was assumed to be from miasmas, poisonous vapours emanating from decomposing organic matter that contaminated the air. Furthermore, Hippocrates believed that disease susceptibility was related to an imbalance of four bodily fluids or “humours”. Galen proposed that pus expelled from wounds rebalanced the humours, “*pus bonum et laudabile*”, and was beneficial to the patient.³⁶ Unfortunately, this was interpreted as pus being necessary for wound healing, and pus formation was actively encouraged. Thick, creamy “laudable” pus, (most probably *Staphylococcus* infection), was encouraged and distinguished from thin, watery pus, (most likely *Streptococcus* or Gram-negative infection), associated with mortality. The erroneous concept of “laudable” pus was not refuted until the second half of the 19th century with the introduction of antisepsis by Joseph Lister.³⁷

The American Civil War and hospital gangrene

An estimated 700,000 soldiers died during the American Civil War from 1861 to 1865,⁸ the bloodiest war in US history.³⁸ However, only one third of deaths were directly related to battlefield trauma,

whilst the remainder were due to infectious diseases such as typhoid, dysentery and yellow fever.³⁹ Of 253,142 wounds reported in the permanent registers of the US Surgeon General's office, 59,376 (23%) were flesh wounds which included hospital gangrene.³⁸ Whilst hospital gangrene has been attributed to *S.pyogenes*, the aetiology is difficult to prove without historical specimens and, certainly, other organisms could also have been involved.

Jones and infection control

Joseph Jones, a Confederate Army surgeon, described vividly the rapid progression of hospital gangrene⁸ and the effect on the underlying tissues; *".....a purple or blue spot is first perceived...I have seen the skin in the affected spot melt away in twenty-four hours into a greyish and greenish slough, whilst a deep blue and purple, almost black areola, surrounding the dead mass, spread rapidly in ever increasing circles...Hospital gangrene destroys the cellular and adipose tissues most rapidly; the muscles, nerves, large blood-vessels, and the bones resist its action for a greater length of time."* Although French and British naval surgeons recognised hospital gangrene before the American Civil War,¹ Jones' depiction has been credited as the first modern description of NF.⁴⁰ Whilst skin discolouration is a late feature of GAS NF, this description is compatible with cutaneous anthrax and clostridial necrosis and thus, whether Jones is describing GAS NF remains inconclusive.

Jones believed in miasma theory and attributed the spread of hospital gangrene to *"crowding together of sick and wounded soldiers in imperfectly ventilated and filthy hospitals..."* which he felt led to favourable conditions for the *"...development of hospital gangrene upon reception of wounds."*⁸ Jones recommended infection control measures to tackle hospital gangrene and observed that *"the wounded should never be placed in wards with patients suffering from anyone of the contagious or infectious diseases... erysipelas, pyaemia, or hospital gangrene; and these various diseases should not be indiscriminately mixed together."*

Goldsmith and bromine

Middleton Goldsmith was a Union surgeon in Louisville, Kentucky during the American Civil War. He was struck by the high mortality associated with hospital gangrene and rapid spread on wards. He believed the condition occurred spontaneously *"where the wounded are crowded together – where the wards are filled with the stench of traumatic profluvia, and receive the air of sewers and cellars"*.⁹ He

postulated that epidemics were linked, and that controlling them should reduce mortality. He reviewed various treatments including corrosive acids and caustic alkalis, which prevented tissue spread of gangrene, but destroyed remaining viable tissue and were only applicable to open wounds.⁹ He became interested in halogens like chlorine, fluorine and bromine after noticing better recovery of patients on wards where bromine deodorants were being used as disinfectants.³⁹

Goldsmith recommended surgical debridement for hospital gangrene followed by bromine injections into muscle layers and exposed surfaces. He followed disease progression through the wound's odour. He undertook a trial of bromine therapy in 334 cases of hospital gangrene, 304 of which received bromine either alone or after other treatments (Figure 2). Eight patients who received bromine died (2.65% mortality) in comparison to patients treated with nitric acid (61.5% mortality) or other remedies (38.5% mortality).⁹ In comparison, previous treatments which included lead salts, caustic potash or nitric or carbolic acid yielded mortality rates of around 25 per cent,^{35,41} whilst cumulative mortality from hospital gangrene was 45.6%.³⁸ His work acknowledged the importance of infection control through antisepsis in wound infection management.

Germ theory and rise of the *Streptococcus*

In the late 19th century, whilst America was being reconstructed after the Civil War, the field of Microbiology was developing in Europe. It was during this time that the *Streptococcus* was recognised as a cause of disease. The scientific community was attempting to determine the cause of suppurative infections. Research often involved inoculating samples from affected individuals (animal or human) into other animals to observe disease progression. One proponent was Robert Koch, who in 1876, whilst investigating the aetiology of traumatic infective diseases, isolated the anthrax bacillus, thus proving the germ theory of disease and beginning the “golden age” of bacteriology.^{42,43}

In 1868, German surgeon Theodor Billroth isolated chain-forming bacteria from wound pus and named them *Streptococcus* (Greek: *strepto* – chain, and *kokkus* – berry).¹⁰ Eleven years later, Louis Pasteur in France isolated a chain-forming coccus from the blood and uterus of a woman with puerperal fever, attributing the disease to microorganisms invading the wounded uterine surface following childbirth.⁴⁴ In 1882, another German surgeon, Friedrich Fehleisen, cultured streptococci from the skin of patients

with erysipelas and reproduced signs of erysipelas following inoculation into humans, thus confirming an association between streptococcus and erysipelas.^{45,46} Two years later, the German physician, Friedrich Julius Rosenbach isolated streptococci from pus of an infected wound and named it *Streptococcus pyogenes* (Greek: *pyon* – pus, *genein* – to produce).⁴⁷ He believed this was separate from erysipelas-associated streptococci, a controversy only resolved with improved identification techniques,⁴⁸ and publication by Rebecca Lancefield in 1933, of a streptococcal classification system based on carbohydrate composition of bacterial cell wall antigens: *S.pyogenes* was classified as group A *Streptococcus*.⁴⁹

The 19th century ended with the miasma theory being superseded by the germ theory, and a better understanding of gangrene associated with penetrating wounds. With this paradigm shift, the management of infectious diseases evolved. Whilst limiting the spread to others through infection control had been the focus of Middleton's trial of bromine,⁹ there was now a microbiological rationale for these measures. However, it was not until the 20th century that the management of hospital gangrene became directed at infection eradication, through surgical advances and antibiotic discovery.

Early 20th century – the surgeon's scalpel and the antibiotic chemists

“Prior to the war, the surgeon gave most of his attention to aseptic methods, his great object being to exclude microbes from the wound. The question of how to deal with the bacteria after they were in possession was a problem of much less interest to him.”³⁴

Although the term NF was not coined until after the Second World War, several NF-like clinical syndromes were described in the early 20th century in association with traumatic processes including childbirth, burns and penetrating war-wounds (Table 1). Barrier nursing and infection control, antimicrobial treatment and effective debridement of necrotic tissue are consistent themes in the literature from this period (Table 1). Whilst infection control was rooted in the hospital gangrene pioneers of the 19th century, much of modern NF management has its basis in work that occurred during the World Wars.

Streptococci and wounds during the First World War

The Scottish physician-scientist, Alexander Fleming, eloquently described the predominance of streptococci in war wounds in 1915.¹¹ Whilst stationed in France with the Royal Army Medical Corps, he studied the bacterial flora of over 200 wounds and described a transition between early stage infections, which contained anaerobic organisms, to late stage infections containing mainly pyogenic cocci (Figure 3A and 3B). Penetrating traumatic wounds contained streptococci and he implicated short-chained streptococci in the development of gangrene. Additionally, blood cultures from febrile wounded soldiers isolated *Streptococcus*. Fleming thus observed, “*streptococcus is without doubt the most important member of this group as regards infection of wounds.*” His management was to not rely on antiseptics alone, as they did not penetrate into deep tissues. He encouraged irrigation with hypertonic saline³⁴ and emphasised surgical debridement; “*...if it were possible for the surgeon to remove completely the dead tissue I am quite sure the infections would sink into insignificance.*”¹¹

Dakin, Depage, debridement and delayed primary closure

During the First World War, surgical techniques were refined to manage infected wounds. The pioneering French military vascular surgeon, Alexis Carrel, and biochemist Henry Dakin devised a wound care technique utilising a chlorine-based disinfectant, “Dakin’s solution”, and rubber “Carrel” tubes for wound irrigation.⁵⁶ Belgian surgeon Antoine DePage proposed that Dakin’s solution was introduced following tissue debridement, excision of contaminated tissue, and epluchage, “peeling” of wounds before dressing.⁵⁷ Depage then advocated delayed primary wound closure depending on the bacteriology and observed that “*for streptococci infection never to suture but to submit the wound to adequate treatment...to wait until the streptococci had disappeared, or had become attenuated sufficiently to permit primary union.*”⁵⁷ He has been credited with making the most important contribution to wartime surgery of any war.⁵⁸

Meleney, gangrene and bear claw fasciotomy

In 1924, Frank Meleney, an American missionary surgeon working in China, reported an outbreak of 20 cases of haemolytic streptococcal gangrene in a Peking hospital, with a mortality of 20%, and illustrated that surgery is vital to reduce mortality.^{2,12} Meleney observed that gangrene was caused either by anaerobic bacteria or haemolytic streptococci. He noted that the “*infection usually starts from*

a superficial break in the skin, a scratch, a hypodermic injection, a cut, a pimple or a boil but occasionally develops without any point of origin,” implying that penetrating trauma is not a prerequisite for NF. Meleney successfully treated cases with “bear-claw scratch” debridement,^{2,12} building on the work of the First World War surgeons. In this method, single, long, incisions were made to the deep fascia on either side of the affected limb (similar to the appearance of a scratch from a “bear claw”), to just beyond the necrotic area. Extending incisions too far would spread infection but, if done correctly, would negate the need for amputation.¹² This technique was subsequently superseded in favour of more extensive fascial exposure and debridement.⁵⁹

Prontosil rubrum and the sulphonamides - the antibiotic era begins

In 1932, the German histopathologist and bacteriologist Gerhard Domagk observed that mice and rabbits treated with the red dye, *prontosil rubrum*, derived from sulphanilamide, survived lethal infections with haemolytic streptococci and staphylococci.⁶⁰ He received the Nobel Prize for Medicine in 1939 for his work on the sulphonamides, which revolutionised the treatment of infected war wounds. Animal research highlighted the benefit of sulphonamides in preventing wound infections when sprinkled in the wound.⁵¹ Whilst deaths of the wounded in the US army was 8.26% in the First World War, this decreased to 4.5% in the Second World War during which American soldiers were issued sulphonamide powder in first aid packs, along with improved surgical techniques.^{52,61} Sulphonamide usage on wounds escalated from 1942, but rather than sprinkling, the drug was dumped in lumps on wounds, thereby reducing drug absorption. Meanwhile, the importance of adequate wound debridement was neglected. Wounds became infected, and thus it was misinterpreted that sulphonamide powder was detrimental to wounds.⁵⁸ Leonard Colebrook, a contemporary of Fleming, also investigated the use of sulphonamides to treat puerperal sepsis,^{50,62} which is usually attributed to GAS and follows maternal tissue injury during childbirth.⁶³ Colebrook successfully treated 38 patients with haemolytic streptococcal puerperal fever with sulphonamides, reducing mortality from 24.4% in 1935 to 4.7% in 1936.^{50,64}

***Penicillium rubrum* and the push for penicillin**

After the First World War, Alexander Fleming had returned to work at St. Marys’ hospital in London and in 1929, he published a description of the antibacterial properties of penicillin, produced by the *Penicillium rubrum* mould.³⁴ However, it was not until a decade later, at the start of the Second World

War, that biochemist Ernst Chain and pathologist Howard Florey, along with colleagues Edward Abraham and Norman Heatley, working at the Dunn School of Pathology in Oxford were able to produce sufficient penicillin to undertake clinical trials.¹³ Florey, Chain and Fleming were awarded the 1945 Nobel Prize for Medicine for their discovery.⁶⁵

Limited research funding led Florey and Heatley to the USA in June 1941, to gain the support of the American pharmaceutical industry. Through improved deep fermentation techniques and isolation of *Penicillium* strains with higher penicillin yields, further clinical trials in military and civilian populations occurred and sufficient penicillin was produced to accompany troops for the D-Day landings.⁶⁶ Penicillin use during the Second World War was clearly documented.^{67,68} British Army surgeons in Italy prevented wound infections by inoculating penicillin-sulphathiazole powder into wounds following debridement in field hospitals, however, there was “...*no tendency on the part of surgeons to neglect surgery and rely too much on penicillin.*” Clearly, for traumatic battle wounds, surgery was the main priority, although a combination of surgery and penicillin was emphasised, “...*for the knife alone cannot get rid of infection*”.^{67,68}

Infection control revisited – nosocomial GAS during the Second World War

About a hundred years before the Second World War, Ignaz Semmelweis demonstrated the importance of hand-washing in preventing puerperal sepsis.⁶⁹ During the Second World War, nosocomial transmission of GAS was a recognised problem.⁵ Thus, the role of infection control was revisited. Wards were reorganised to prevent patient-to-patient transmission and environmental sampling and cleaning practised. Healthcare-workers were advised to clean hands and use masks and sterile instruments. A wound dressing technique was developed that included “clean” and “dirty” nurses.^{5,70} This was responsible for reducing GAS wound infection from 15.4% to 1.1% in one wartime neurosurgical unit.⁷⁰ Many practices advocated during this time are still recommended for prevention of nosocomial transmission of GAS today.⁷¹

Wilson and necrotising fasciitis

In 1952, Dr Ben Wilson, a surgeon in Parkland Hospital, Dallas, coined the phrase “necrotising fasciitis”, which was adopted into widespread use. He observed that fascial necrosis was a consistent

manifestation in 22 cases admitted at the hospital from 1948 to 1951 and earlier cases in the literature.³ He also observed that NF “...may start in an operative wound, in a trivial injury...or may appear spontaneously.” Of note, whilst haemolytic streptococci were cultured from all of Meleney’s cases,¹² haemolytic bacteria were cultured in about half of Wilson’s cases, of which 88% were identified as *Staphylococci*.³ Furthermore, mortality in Wilson’s cohort was only 8.7% compared to 20% observed by Meleney. Wilson stressed the importance of early recognition, prompt surgery, penicillin and support for abnormal physiology.³

By the mid-20th century, infection control advocated by American Civil War surgeons, had been joined by antibiotics targeted at *Streptococcus pyogenes* and effective surgical debridement, as emphasised by Fleming, Meleney and Wilson in the battle against streptococcal gangrene. Indeed, after the Second World War, there is a relative paucity of literature on GAS NF in conflicts in Korea, Vietnam and the Falklands, perhaps due to the measures described, leading to a decline in infections. However, the effectiveness of penicillin was questioned, and the last two decades of the 20th century saw a global re-emergence of invasive GAS infections.

Late 20th century – the Eagle effect, immunoglobulins and hyperbaric oxygen

The Eagle effect and antibiotics inhibiting toxin synthesis

Penicillin represented a major transition point in the management of NF. However, in 1948, Harry Eagle described the “Eagle effect”, the paradoxical reduced antibacterial effect of penicillin against a variety of *Staphylococcus* and *Streptococcus* species when administered at high doses *in vitro*.⁷² GAS were not subject to this, and there have been no GAS isolates resistant to penicillin.⁷³ However, treatment failure in spite of penicillin sensitivity and high mortality associated with severe disease, led to the hypothesis that when GAS reaches the stationary growth phase, as may occur rapidly with high inocula, there is reduced expression of penicillin-binding proteins and diminished susceptibility to beta-lactams.^{20,74} Eagle also demonstrated that delayed initiation of treatment with penicillin after infection with GAS, in a mouse model of myositis, led to an apparent reduction in bactericidal effect (Figure 4A).⁷⁴ In the 1980s this latter “Eagle effect” was revisited comparing penicillin, erythromycin and clindamycin in an animal model of GAS myositis and, unlike penicillin, the efficacy of clindamycin was not adversely affected (Figure 4B).⁷⁵ This supported clindamycin use for NF

treatment (in combination with a penicillin), particularly when associated with toxic shock syndrome, as clindamycin inhibits toxin production.⁷⁶ Retrospective clinical studies have been generally supportive of adjunctive clindamycin therapy in severe disease,⁷⁷⁻⁷⁹ however, recent outbreaks by clindamycin resistant GAS⁸⁰ may limit the utility of this drug.

Intravenous immunoglobulin and hyperbaric oxygen

STSS has a high mortality and is associated with almost half of NF cases.¹⁷ Patients require supportive measures in a high dependency or intensive care setting. Additionally, intravenous pooled human immunoglobulin (IVIG) has been advocated. Bacterial toxins, acting as superantigens, lead to massive inflammatory cytokine release, tissue destruction and shock.⁸¹ Augmenting the humoral immune response with IVIG neutralises superantigens,⁸² enhances GAS clearance, and is anti-inflammatory.⁸³ IVIG is prepared from pooling immunoglobulin from blood donors, and due to variant CJD in the 1990s,⁸⁴ its use is strictly controlled in the UK and elsewhere. Studies assessing IVIG in severe invasive GAS disease are limited. One randomised, double-blind, placebo-controlled trial was underpowered to reach statistical significance due to the small numbers of patients recruited.⁸⁵ Retrospective reports are complicated by multiple confounding factors, including use of historical controls with higher mortality rates⁸⁶ or children with less severe disease.⁸⁷ A recent retrospective cohort analysis appeared to favour IVIG in severe invasive GAS, but was again underpowered.⁷⁷ The sample size for clarifying the role of IVIG in this rare disease⁸⁸ means that the definitive answer is not forthcoming.

Another treatment modality tried in the late 20th century was hyperbaric oxygen therapy. This adjunctive therapy is thought to increase tissue partial pressure of oxygen, increasing bacterial killing and facilitating wound healing.⁸⁹ However, the few studies of hyperbaric oxygen therapy in GAS NF show little outcome benefit⁹⁰⁻⁹² and transferring patients to a centre with hyperbaric oxygen therapy may delay effective surgical debridement.^{90,93}

Diagnostic delays

Undoubtedly one of the most challenging aspects of GAS NF management remains diagnosis. Diagnostic delay is a common in historical and current literature^{2,32} and may result in adverse

outcomes.³² The innocuous appearance of the infection, relationship to muscle contusion or attribution of pain to an injury may delay presentation or mislead clinicians.^{30,32} Skin discolouration, blistering, and visible necrosis described in the literature are late features of NF and are ominous signs. Today, imaging and frozen sections with good histological examination may aid diagnosis, but intra-operative assessment and exploration is preferable when diagnostic uncertainty is present (reviewed in ⁹⁴).

Global GAS resurgence and non-penetrating trauma associated NF

Since the 1980s, there has been a global resurgence of invasive GAS diseases, such as NF and STSS.⁹⁵ GAS is known to infect wounds where skin integrity has been broken,⁹⁶ however, blunt trauma leading to muscle contusion preceding GAS NF have been reported worldwide.^{26-32,97-99} Amongst larger studies of GAS NF from North America and the UK, non-penetrating trauma or injury was present in approximately 25% of NF,^{17,100-102} with a significant association between non-penetrating trauma and GAS NF, but not cellulitis, observed.¹⁰³ Other predisposing factors include burns, surgery and varicella infection (Table 2). Varicella infections are commonly complicated by secondary bacterial infections, including NF^{104,105} and in countries with the varicella vaccine in children, there has been a reduction in paediatric cases of invasive GAS.¹⁰⁶

Generally, GAS NF affects more males than females, although whether this represents reporting bias is unclear. There have also been cases of GAS NF with no obvious portal of entry. For example, from a cluster of six NF cases in the UK, two had no predisposing history.¹⁰⁷ Other case series have also noted a similar lack of antecedent history, with no portal of entry in eight of 20 patients with invasive GAS infection in the USA,¹⁹ and five of 14 consecutive NF cases over five-years in Northern Australia.⁹⁰ Occasionally, patients reported mild upper respiratory tract infection.¹⁰⁸ Diabetes, obesity and chronic alcohol use also predispose to NF.^{21,109,110}

The management of patients in these reports are similar; initial broad-spectrum antibiotics, rationalised to benzyl-penicillin and clindamycin, once GAS is identified. Surgical debridement is always performed, with repeated intervention often necessary. Mortality is high, in spite of intensive care support, and patients have long hospital stays and require long-term rehabilitation (Table 2).

Invasive GAS and the modern military

The global resurgence of GAS has also been documented specifically in military personnel. Training facilities have seen outbreaks of the whole spectrum of GAS disease including pyoderma, ecthyma, NF and STSS, and post-infectious sequelae including rheumatic fever and glomerulonephritis.¹¹³⁻¹¹⁶ This morbidity amongst military cohorts has been attributed to crowded conditions, reduced hygiene and a lack of type specific immunity. Consequently, the US military has used prophylactic penicillin, or macrolides in penicillin allergy, in basic military trainees since 1953.¹¹⁷⁻¹¹⁹

Necrotising fasciitis due to other pathogens

Historically, GAS was the predominant organism recognised in NF, however, widespread antibiotic therapy and better bacterial identification, has meant that penetrating traumatic wound infections are frequently polymicrobial or contain resistant organisms. A recent review updated an earlier classification¹²⁰ and divided NF into four aetiological types: polymicrobial NF (type I) being distinguished from monomicrobial NF caused by Gram positive (type II) or Gram negative bacteria (type III) or fungi (type IV).¹²¹ Whilst some recent case series report polymicrobial aetiology being more common,^{109,122,123} others report single pathogens more commonly isolated,¹²⁴⁻¹²⁶ although limitations in culture methods may influence this.¹²⁴ Methicillin resistant *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus* and *Actinobacter baumannii* have all been isolated, with the predominant organism depending on geography.^{35,124-128}

One form of polymicrobial NF is Fournier's gangrene, a necrotising perineal and genital infection first described in healthy young men by venereologist Jean-Alfred Fournier in 1883. He also noted the association of gangrene with diabetes, alcoholism and urological trauma.¹²⁹ Organisms in Fournier's gangrene are usually commensals, with aerobic and anaerobic bacteria acting synergistically, through mutually beneficial nutrient and toxin production.¹³⁰ Widespread antibiotic use has led to bacterial resistance, necessitating the use of broad spectrum antibiotics at the outset.¹³¹

Gas gangrene not caused by GAS

No historical review of NF would be complete without mentioning the ubiquitous Gram-positive anaerobic bacteria, the *Clostridium* species. Gas gangrene also known as "clostridial myonecrosis" has

been associated with soil containing *Clostridium* which contaminate battlefield wounds from penetrating injury. Estimates of gas gangrene during the First World War are approximately 10% but less than 1% in the Second World War.¹³² Although advances in weaponry led to tissue destruction favouring anaerobic growth, improved surgical techniques including debridement and delayed primary closure led to a decrease in mortality from this condition.¹³³ Historically, *C. perfringens* is most associated with necrotising infections due to penetrating trauma, however, recently *C. septicum* and *C. sordellii* have also been implicated in infection at sites of minor injury.¹³⁴

Into the 21st century – molecular pathogenesis of GAS NF

The development of molecular biology over the last 40 years has enabled a better understanding of the mechanisms by which GAS cause disease. GAS is a human specific pathogen and must first colonise the host, usually the nasopharynx or skin. Following colonisation, immune evasion is a prerequisite for bacterial invasion and establishment of deep tissue infection. It is here that molecular biology has improved our understanding of GAS NF pathogenesis, with some mechanisms described below (Figure 5). Whilst not exhaustive, it illustrates our current understanding of the intricacies of host-pathogen interactions leading to NF.

Bacterial virulence factors in NF

GAS expresses several virulence factors to evade humoral immune effectors.^{136,139-141,144} The best-studied GAS virulence determinant is the M protein and although there are over 100 M-serotypes, M1 and M3 isolates predominate in invasive disease.^{145,146} This predominance is likely related to virulence genes carried by these M-types, coupled with serotype-specific ability to evade the immune response. Through its interaction with host immune proteins, the M protein itself may help invading bacteria. Additionally, some NF pathophysiology may be explicable by M protein binding fibrinogen, initiating a cascade resulting in vascular leakage and toxic shock.¹⁴⁷

GAS has several mechanisms to evade neutrophils, a key player in host innate immunity, such as the hyaluronic acid capsule, streptolysins and DNases.^{140,148,149} GAS expresses the protease SpyCEP, which cleaves the chemokine Interleukin-8 that is involved in recruitment and activation of neutrophils,¹⁴² perhaps explaining the paucity of neutrophil infiltrates in histopathological sections from severe NF.

SpyCEP enables survival and dissemination of GAS,¹⁵⁰ while high levels of SpyCEP activity correlated with increased disease severity and poor clinical outcome.¹⁴² Other GAS proteases are implicated in immune evasion and the pathology seen in NF.^{136,138,141} Notably, the cysteine protease, SpeB, may be involved in tissue necrosis¹³⁸ and also in phenotypic switching of bacteria during invasive infection.¹³⁷ Genetic reasons behind the aggressive phenotype of NF-causing GAS isolates are also being determined. For example, mutations in the CovR/S regulatory system, which enables the bacterium to respond to its environment, occur readily in M1 isolates. CovR/S mutations are associated with invasive bacterial phenotypes with reduced SpeB production and increased SpyCEP expression.^{142,143} Furthermore, a single nucleotide polymorphism in the *mtsR* gene of certain M3 isolates, which encodes a transcriptional regulator, is associated with a reduced propensity to cause NF.¹⁵¹ Other virulence determinants have been implicated in NF pathogenesis, as well as unique mechanisms by which GAS is exquisitely adapted to its host.¹⁵²

Animal models of muscle injury and GAS

To replicate the observation that GAS NF may occur with minor injury, mice inoculated with GAS were bruised at a site distant to the original inoculation. The investigators observed increased mortality compared to unbruised controls, implying that distant muscle sites may harbour bacteria.¹⁵³ Furthermore, M1 and M3 GAS adhere to damaged skeletal muscle cells, possibly via cytoskeletal vimentin,¹⁵⁴ and in a murine model, GAS seeded moderately damaged muscle, in association with vimentin upregulation, following non-penetrating injury.¹⁵⁵ Although the studies were limited, the collective literature hints at a possible mechanism for the association of GAS NF and non-penetrating trauma.

Vaccine development

Our understanding of GAS molecular pathogenesis has sadly not yet had a profound effect on NF management. Ultimately, molecular biology may lead to a GAS vaccine, which would prevent the whole GAS disease spectrum. GAS vaccine development has a long, varied history and was discussed by Fleming in 1915.¹¹ Inactivated whole cell vaccines were unsuccessful in the 1940s,¹⁵⁶ whilst the M protein containing vaccines have only slowly advanced to clinical trials.^{157,158} Other vaccine targets

include SpyCEP¹⁵⁹ and C5a peptidase.¹⁶⁰ As NF is rare, the success of vaccines at preventing GAS NF will be difficult to quantify and a surrogate of protection is needed.

Conclusion

The condition we now call necrotising fasciitis has existed since antiquity, and although its name has changed, it has consistently been associated with trauma. The modern management of NF has evolved over the last 150 years as our understanding of the aetiology of this condition has changed, with many advances resulting from the management of war wounds. Goldsmith's bromine trials arose from the stench of the hospital wards of the American Civil War, even before bacteria causing NF had been isolated. Surgical intervention was emphasised by Alexander Fleming from war-torn France during the Great War, and reiterated by Frank Meleney during the interwar years. The Second World War saw the use of sulphonamides to treat wound infections, and was the stimulus for mass production of penicillin. Infection control, effective debridement and broad-spectrum antibiotics remain the mainstay of the modern management of GAS NF.

And yet despite postoperative supportive care on technologically-advanced intensive care wards, and adjunctive therapy such as IVIG and hyperbaric oxygen, the outcome from GAS NF remains depressingly high. Mortality rates as high as 40%²⁵ are almost twenty times worse than Goldsmith's patients with hospital gangrene treated with bromine in 1863.⁹ It is the authors' experience that a failure to recognise NF contributes to this ongoing high mortality. Why the mortality remains so high is unclear; although historical reporting bias may contribute, an alternative view is that GAS has become more virulent.^{19,20} Hopefully, developments in molecular biology will allow us to answer this question and also lead to improved disease prevention through an effective GAS vaccine, which would be the ultimate successor to bromine, bear-claw scratch fasciotomies and the Eagle effect.

Authors' contributions

LEML conceived the manuscript and did the initial literature search. LKKT and LEML prepared the figures. All authors contributed to the writing of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of interest statements

We declare that we have no conflicts of interest.

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A **B**

Figure 1. (A) Hospital gangrene affecting the hand following a lancet puncture of an abscess. Watercolour by William Alfred Delamotte, 1847. (B) Hospital gangrene of an arm stump, reproduced from plate XV in *The medical and surgical history of the war of the rebellion, 1861-65*³⁸. Images are courtesy of Wellcome images, the Wellcome Trust.

CONDENSED TABULAR STATEMENT OF CASES OF HOSPITAL GANGRENE.

	Whole Number.	Recovered.	Died.	Amputations.	Average duration of treatment.	Percentage of deaths.
Treated with Bromine, in any way, - - -	152	148	4	0	5 days and 14 hours.	2.65
Treated with Bromine, pure, exclusively, - -	27	25	2	0	2 do. " 23½ do.	
Treated with Bromine, in solution, exclusively, -	86	84	2	0	6 do. " 11½ do.	
Treated with Bromine, pure, after the solution failed,	8	8	0	0	12 do. " 18 do.	
Treated with Bromine, after Nitric Acid had failed,	23	22	0	1	3 do. " 16½ do.	
Treated with Bromine after other remedies failed, -	8	8	0	0	3 do. " 4 do.	61.54 } 50 38.47 }
Treated with Nitric Acid exclusively, - - -	13	5	8	0	3 do. " 14½ do.	
Treated with other remedies exclusively, - - .	13	7	5	1	7 do. " 13½ do.	
Treated with other remedies after Bromine had failed,	4	4	0	0		

Figure 2 Results of the trial of bromine for the treatment of hospital gangrene undertaken by Middleton Goldsmith in Louisville, Kentucky during the American Civil War. Table reproduced from *A report on hospital gangrene, erysipelas and pyaemia: as observed in the departments of the Ohio and the Cumberland with cases appended.* ⁹

A

TABLE II.—Analysis of Bacteriological Examinations of a Series of Wounds.

Time after infection.	Total No. of cases.	<i>B. aerogenes capsulatus.</i>	<i>B. tetani.</i>	<i>Bac. X.</i> } Putre- factive <i>Bac. Y.</i> } bacilli.	<i>Streptococci.</i>	<i>Coliform bacilli.</i>	<i>Staphylococci.</i>	"Wisp" bacillus.	<i>Diptheroid</i> bacilli.	Large Gram + bacilli.	
Stage 1. 1-7 days.	127	103	22	14	5	102	37	40	9	—	2
Stage 2. 8-20 days.	66	19	5	4	1	51	13	16	17	4	4
Stage 3. Over 20 days.	27	5	—	—	—	24	19	19	16	—	6

B

Figure 3. Analysis of bacteriological examination of a series of wounds undertaken by Alexander Fleming of the Royal Army Medical Corps whilst stationed in Boulogne, France during the First World War. (A) The different bacteria observed in wounds during three different stages, based on the days after infection. Streptococci are present in all stages of infection. (B) Drawing from films of pus taken from wounds showing the late stage of infection with pyogenic cocci, "wisp" bacilli and many pus cells. Reproduced from *On the bacteriology of septic wounds*.¹¹

Figure 4. The “Eagle effect” in an *in vivo* model of myositis

(A) Eagle demonstrated *in vivo* the reduced bactericidal effect of delaying penicillin treatment. Mice were infected intramuscularly with 5×10^7 *Streptococcus pyogenes*, divided into groups (0, 1.5, 3, 6, 9 hours) and treated with procaine penicillin (0.15cc of suspension at 10,000units/cc). Each point represents the median number of organisms recovered from infected muscle tissue. The mortality of the animals increases as treatment is delayed. He suggested that the reduced activity of penicillin in older infections is not due solely to the large number of organisms, but due to the likely physiological state of the bacteria and the host tissue environment. Reproduced from *Experimental approach to the problem of treatment failure with penicillin. I. Group A streptococcal infection in mice.* ⁷⁴

(B) The “Eagle effect” was later revisited by comparing penicillin, erythromycin and clindamycin in another mouse model of myositis. When treatment was delayed to six hours post infection, mice treated with penicillin had a similar mortality to untreated control animals, whilst 80% of the clindamycin group survived. Reproduced from *The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis.* ⁷⁵

Figure 5. Bacterial virulence factors associated with invasive streptococcal disease.

Streptococcus pyogenes possesses a number of virulence factors, which enable the bacteria to evade the host innate and adaptive immune defences and establish a deep tissue infection. Surface expressed proteins such as the M protein and C5a peptidase are involved in complement evasion,^{135,136} whilst SpyCEP influences neutrophil activation and migration. The secreted protein SpeB is involved in the tissue necrosis in NF and phenotypic switching of bacteria in invasive infection.^{137,138} Other secreted proteins include; SIC that aids complement evasion,¹³⁹ the DNAase Sda1 that acts on neutrophil-derived extracellular traps,¹⁴⁰ and the immunoglobulin degrading protein, IdeS.¹⁴¹ The two component regulatory system, CovR/S is involved in the regulation of some of these virulence factors and may be associated with more invasive bacterial phenotypes.^{142,143}

Trauma or injury	Geographical Location	Presentation (number) and Aetiology	Management	Reference
Penetrating wounds due to explosives	Boulogne, France	Infected wounds (210) from penetrating trauma 177/210 isolated streptococci	Avoid antiseptics Irrigate wounds with hypertonic saline. Debridement of dead infected tissue	11,34
Haemolytic Streptococcal gangrene	Peking Union Medical College, China	Haemolytic streptococcal gangrene (20). Additionally 7/17 blood cultures positive for haemolytic streptococcus	Surgical debridement Hygiene and infection control measures. Wounds irrigated using Dakin solution	2,12
Puerperal Sepsis	Queen Charlotte's Hospital, London, UK	Haemolytic streptococcal puerperal fever (38 and 26 cases) 36/38 and 25/26 group A <i>Streptococcus</i>	Treatment with sulphonamides, (Prontosil) Effective Infection Control	50,51
Infected open wounds during Second World War	France	Haemolytic <i>Streptococcus</i> isolated from wound infections	Dusting of wounds with sterile sulphonamide powder (American soldiers in a first aid kit) or given systemically	52-54
Patients with burns	Glasgow Royal Infirmary, UK	Infection contaminating burns (516) 69/516 haemolytic <i>Streptococcus</i>	Treatment in specialised burn units Cubicle isolation to minimise contamination Strict barrier nursing Chloroxylenol disinfectant	55

Table 1. Different patterns of injury or trauma leading to *S. pyogenes* gangrene and recommended management of these cases during the early 20th century

Cases	Age	Sex	Country	Site	Risk factors	Aetiology	Trauma	Mortality	Management	Reference
2	58, 40	Male, Female	USA	Limb	Nil	<i>S.pyogenes</i>	Skin injury	100%	Surgical debridement, intravenous penicillin and ITU support.	²⁶
4	38, 29, 43, 41	1 Male, 3 Female	South Africa	Arm	Obesity	75% isolated <i>S.pyogenes</i>	Contusion of arm	50% of <i>S.pyogenes</i> cases	Debridement, iv penicillin, tobramycin, metronidazole	⁹⁹
1	17	Male	USA	Thigh	Nil	<i>S.pyogenes</i>	Bruise from sport	100% Mortality	High dose benzylpenicillin, fasciotomy and debridement of thigh, ITU support	²⁹
8	46	6 Male , 2 Female	USA	Limb	5/8 history of chronic illness	<i>S.pyogenes</i>	Blunt trauma, bee sting and ulcer	25%	Surgical debridement, 6/8 started on combination of clindamycin, penicillin or cephalosportin.	⁹⁸
1	19	Male	Germany	Thigh	Nil	<i>S.pyogenes</i>	Fall on side	0%	Debridement, ITU support, antibiotic regimen not described	²⁷

									except for Candida sepsis with Diflucan	
1	36	Female	Japan	Right hip	Nil	<i>S.pyogenes</i>	Injury to right hip	100%	Supportive care as arrived at hospital <i>in extremis</i>	¹¹¹
2	61, 32	Male	USA	Hand	Rheumatoid arthritis (61 year old)	<i>S.pyogenes</i>	Blunt trauma to the hand	50%	Debridement, ITU support, clindamycin, penicillin and IVIG	¹¹²
1	42	Male	UK	Anterior chest Wall	Epilepsy and heavy alcohol intake	<i>S.pyogenes</i>	Collapse following convulsion	0%	Ceftriaxone, flucloxacillin and metronidazole then changed to benzylpenicillin, ciprofloxacin and clindamycin (culture results) surgery and ITU support	²⁸
1	46	Female	France	Hand/arm	Nil	<i>S.pyogenes</i>	Contusion	0%	Surgery and antibiotics not specified.	³¹
1	47	Male	Germany	Leg	Likely NSAID injection	<i>S.pyogenes</i>	Minor trauma to left leg during tennis	100%	Surgical exploration and debridement, antibiotic treatment not mentioned	³⁰

2	48, 57	Female Male	Serbia	Chest wall, upper limb and trunk	NSAIDs - naproxen, aspirin and diclofenac	<i>S.pyogenes</i>	Injury, Fall	100%	Died on admission	⁹⁷
1	33	Male	UK	Hamstring	Nil	<i>S.pyogenes</i>	Muscle strain	100%	Surgical exploration and amputation no antibiotics	³²

Table 2. Summary of case reports illustrating the potential association between blunt trauma or non-penetrating muscular injury and the development of *S.pyogenes* NF

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