



Diagnosis and treatment of necrotizing fasciitis in the head and neck region

Mark McGurk, MD, FRCS, DLO, FDSRCS

Department of Oral and Maxillofacial Surgery, Guy's, King's, and St. Thomas' Dental Institute, Floor 23 Guy's Tower, Guy's Hospital, London Bridge, London SE1 9RT, UK

A rare event encountered in current medical practice is necrotizing fasciitis. Its presence is occasionally brought to public attention by the press through headlines such as “Killer or Flesh-Eating Bug” [1], when the impression is conveyed of the advent of a newly discovered disease. Nothing could be further from the truth because the condition was well known to the military surgeons of past centuries. In his book “Lectures on Inflammation,” J. Thomson, the Regius Professor of Military Surgery at Edinburgh [2], attributed the first description of the disease to L. Gillespie, who was a surgeon in the Royal Navy [3]. The condition was known to Amboise Pare and can be found in the writings of most army surgeons who kept careful records of their experiences. Knowledge of the disease can be traced back to Hippocrates, who gave a classic description of the disease process:

“Sometimes a very small wound broke out and if such an accident was neglected great inflammation took place. In most of them the abscess ended in suppurations and there was great falling off of the flesh, tendons and bones; and the defluxion which seated in the parts was not like pus, but a sort of putrefaction and the running was large and of various characters. About the head these things were accompanied by falling off of the hairs of the head and chin, the bones were laid bare and separated and there were excessive runnings; and these symptoms happened in fevers and without fevers.” [4]

In modern practice, necrotizing fasciitis occurs sporadically, which makes a true estimate of its prevalence difficult to ascertain. Invasive streptococ-

cal infections are monitored nationally, and in the 5-year period from 1989 to 1994, 160 cases of necrotizing fasciitis were reported in England and Wales. Most were attributed to group A streptococci [1]. Because many cases are caused by polymicrobial infection, however, this was almost certainly an underestimate. In the United States, an estimated 10,000 to 15,000 cases of invasive group A streptococcal infections occur annually, of which 5% to 10% are necrotizing fasciitis, with a case fatality of 28% [5]. A prospective population-based study of group A streptococcal necrotizing fasciitis conducted in Ontario between November 1991 and May 1995 showed that the incidence increased from 0.085 per 100,000 population in the first 12 months to 0.4 per 100,000 population in the last year of the study [6]. This pattern mirrors a world trend increase in group A streptococcal infections since 1980 [7].

Typically, necrotizing fasciitis occurs on the abdomen/perineum or lower limbs after trauma or surgery. In a few cases (1%–10%), however, it occurs in the head and neck region, particularly when the patient's health is already compromised. Delayed diagnosis is a common event because the condition can arise unexpectedly out of a seemingly trivial infection or injury. The defining characteristic is rapid, progressive tissue destruction that is disproportionate to the initial clinical signs and symptoms.

Despite modern advances in medicine, this disease presents similar problems currently just as it did 200 years ago. Necrotizing fasciitis is a clinical syndrome rather than a pathologic entity. Mortality rates have been reported in the region of 40%. Success depends on prompt diagnosis and treatment without delay for microbiologic confirmation.

E-mail address: mark.mcgurk@kcl.ac.uk

An historical perspective

The identification of disease entities from historical texts can be difficult because of changing nomenclature and vague clinical descriptions that lack diagnostic detail; however, necrotizing fasciitis was described clearly in the late eighteenth century by Claude Pouteau, chief surgeon to the Hotel Dieu in Lyon in 1783 [8]. At that time the disease complex was given many names, such as “malignant ulcer,” “gangrenous ulcer,” “putrid ulcer,” “phagedenis ulcer,” “phagedena gangraenosa,” and “hospital gangrene.” In the late eighteenth century, a series of outbreaks affected the British Home Fleet. In confined quarters the disease could spread quickly. On HMS San Josef the surgeon observed “. . .an ulcer that had devoured the one side of a sailor’s face, which had followed a blow on the ear, that was attended by a very slight wound” [9]. In the early nineteenth century, the disease was reported from military hospitals by the name of “hospital gangrene” or “phagedena gangraenosa.” In one case, “half the cranium was denuded, the bones having become as black as charcoal; in another the neck was denuded to expose the trachea.” The characteristic features of the disease were as follows:

- extreme rapidity with which the disease progressed (measured in hours), which distinguishes it from standard gangrene;
- a tendency to turn soft parts into a putrid, pulpy substance;
- severe pain together with a smell, which was peculiar and extremely offensive;
- starting at the site of a wound or following a trivial scratch and attacking young and healthy persons and debilitated soldiers.

The disease was recorded in the Gendarmerie Hospital at Brussels after Waterloo [10], and Miss Nightingale noted 80 cases in 1 month at Scutari [11]. The disease was well known to the surgeons in the American Civil War (Fig. 1), and Joseph Jones (Confederate Army surgeon) is credited with the first clear investigation and characterization of hospital gangrene [12]. It is not possible to discriminate between the different types, but 2642 cases were reported, of which 1142 were fatal (Table 1). A serious outbreak occurred in September 1862 in the hospitals at Fredrick and West Philadelphia after the battles of South Mountain and Antietam. In January 1863, because of the poor prisoner of war sanitation in Richmond, three outbreaks occurred as the sick were transferred to Annapolis. The dis-



Fig. 1. Private Milton Warren, aged 41 years, of the 1st Kentucky Cavalry was captured in August 1863 at the Cumberland River. While in captivity at Richmond he was shot in the right elbow. An amputation was required on June 1, 1864. On June 20, the stump looked inflamed, and by June 24, the whole stump and bone were exposed. He was treated with charcoal and yeast poultices, a generous diet, and ale. By August the sloughing process had stopped and he survived to claim his pension in 1873.

ease was also present at the Douglas hospital in Fredricksburg [13].

In civilian life it was much less common and occurred sporadically in clusters, being much less contagious. The hospital surgeon of London knew a form of it as a genital disease that was said to be confined to prostitutes and the destitute, and a few cases were admitted to St. Bartholomew’s Hospital London [14], where the disease was aggressive and if unchecked “. . .involves in its ravages the vagina, perineum and anus and sometimes even the bladder and uterus.” Fournier’s classical description of the condition was of phagedena of the penis and scrotum [15], but case histories demonstrated that it was the same disease process as reported by the military surgeons [16].

Sporadic cases continued to be reported into the early twentieth century. An American surgeon reported a hospital outbreak in Peking, where it was more common than in the West [17]. Melaney isolated a hemolytic *Streptococcus* from the wounds, and his name subsequently was associated with the disease (Melaney’s gangrene). In 1952, Wilson coined the name “necrotizing fasciitis,” which described the main feature of the disease and emphasized the polymicrobial nature of some of the infections. Currently, it occurs as unexpected isolated attacks so that few oral and maxillofacial surgeons have any experience with it. The effects remain as devastating as ever if not checked, however. This fact is illustrated by the aftermath of the Nevado del Ruiz volcano eruption in Colombia, where 38 patients

Table 1
Cases of gangrene by site and mortality recorded in the War of Rebellion

Site	No. of cases of gangrene (<i>n</i>)	Fatal cases of gangrene (<i>n</i>)
Head and neck	60	23 (38%)
Trunk	216	129 (60%)
Upper extremity	844	295 (35%)
Lower extremity	1522	695 (46%)

From Barnes J. Gangrene. In: Medical and surgical history of the War of Rebellion. 1867; Part III, Vol II Surgical History. Government Printing Office. Washington, DC. p. 823–51.

developed necrotizing fasciitis, and the disease proved fatal in 47.7% of those people.

Microbiology

Melaney was the first to associate group A streptococcal infections with severe necrotizing conditions, and this organism should be the principal suspect in any rapidly progressive necrotizing infection. Because culture techniques have improved, however, it has become clear that most necrotizing wounds sustain a mixture of bacteria working synergistically. Various bacterial strains may dominate different wounds, but essentially necrotizing fasciitis may be categorized into three types according to the causative organism. (1) In cool and temperate climates it tends to be associated with group A β -hemolytic streptococci (*Streptococcus pyogenes*) [6] alone or with *Staphylococcus aureus*. They are the only bacteria that seem to be able to generate solely this clinical picture. Serotypes M1 and M3 are the most common *S. pyogenes* serotypes associated with invasive disease [7], but multilocus sequence typing has confirmed that a genetically diverse range of strains is associated with these infections [18]. (2) In many cases (up to 60%) the necrotizing fasciitis may be polymicrobial, including one or more obligate anaerobes [19,20]. Brook and Frazier [21] reviewed 87 cases of necrotizing fasciitis over a 17-year period. Of these cases, only 4 were mono-infections with *S. pyogenes*. In the remaining cases, anaerobic bacteria were predominant, with *Peptostreptococcus*, *Prevotella*, *Porphyromonas*, *Bacteroides*, and *Clostridium* the commonest genera isolated. Facultative anaerobic bacteria, such as *Enterobacteriaceae*, are also important. Up to 11 bacterial species have been cultured with various streptococci (groups B and F) in attendance, not just group A [21]. (3) In tropical climates, the condition can be caused by members of the family *Vibrionaceae*, which are of seawater origin [22]. In Colombia, the dominant genus was a

mycosis that was particularly virulent and proved lethal in 70% of cases [23].

Streptococcus pyogenes produce several virulence factors that are likely to be involved in necrotizing fasciitis, including the extracellular pyrogenic exotoxins A, B, and C together with other exotoxins and superantigens [24]. Given this powerful virulence armory, it is perhaps surprising that invasive *S. pyogenes* infections are relatively rare. One reason for this might be the demonstration that mutations in the two-component CsrS/CsrR 2-component regulatory system led to increased virulence in a mouse model [25]. It could be hypothesized that exotoxin production by *S. pyogenes* is normally tightly regulated but that when that control is lost through mutation in the regulatory gene, a hypervirulent phenotype results. The pathogenesis of the polymicrobial form of the infection is unclear, although it is well known that consortia of bacteria work together to evade the host defenses and cause tissue damage. Host factors may predispose to the rapid spread of some infections.

Classification, pathogenesis, and clinical features of necrotizing fasciitis

The history of necrotizing fasciitis has been dominated by bacteriology. Pruitt [26] and Gorbach et al [27] produced a bacterial classification, each of which comprised five entities, and Simmons [28] produced a third classification, which incorporated seven. Even a simplified clinical classification based on necrotizing cellulitis, necrotizing fasciitis, and myonecrosis [23] is difficult to adopt because these entities are rare and clinical experience is unavailable to distinguish between them. In practice this is not important because the initial treatment for all rapidly progressive necrotizing infections is the same: wide surgical débridement. Attempts to subclassify the disorder are unnecessary [29] and may be a disadvantage if it leads to delay in surgery (even 24–48 hours) to obtain culture results. This principle greatly simplifies the approach to clinical management. Ultimately, success depends on rapid diagnosis of the early lesion and prompt treatment.

Pathogenesis

The overarching feature of necrotizing fasciitis is a rapid, progressive liquefaction of the subcutaneous fat and connective tissue below a relatively normal looking skin surface. The fascial planes disintegrate, and with the ensuing necrosis come edema and the

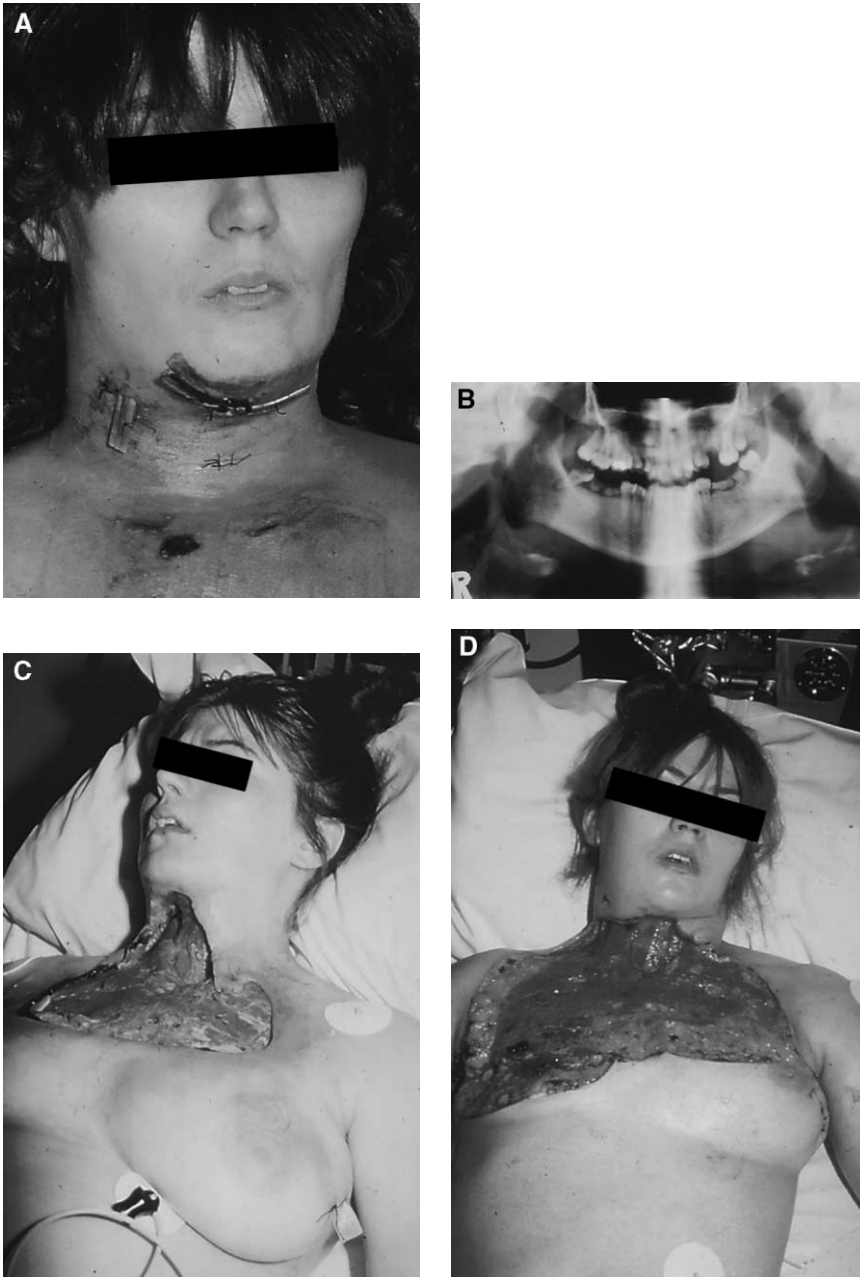


Fig. 2. (A,B) Necrotizing fasciitis arising from an infected tooth. The infection spread relentlessly, first into the neck and then the chest wall. (C) The patient became systemically unwell. (D,E) After wide débridement the patient made a full recovery and is married, with her own family. (Courtesy of Mr. P. McAndrew.)

release of tissue fluid. Early in the development of the disease the veins that traverse the liquefying subdermal fat become inflamed and start to thrombose, which gives the skin first a red and then a mottled color. Later the arterial supply is also jeop-

ardized and the skin becomes pale, which leads to necrosis and wet (coliquative) gangrene. The bacteria initiate an acute local inflammatory response within the dermis that is characterized by an intense polymorphonuclear infiltrate, focal necrosis, and micro-



Fig. 2 (continued).

abscess formation. The histologic picture is one of arteriolar and venous thrombosis of the subcutaneous fat, whereas the adjoining muscle shows comparatively little inflammation.

Clinical features

The rate of necrosis is disproportionate to the signs and symptoms of infection. A small wound can be painful. Early systemic symptoms may be subtle and amount to little more than a feeling of malaise or tachycardia. If there are systemic symptoms in the presence of an apparently innocuous wound, however, necrotizing fasciitis should be considered early. The incidence of this disease increases with age (median age, 57 years) and most adult cases (70%) occur in patients with at least one underlying chronic illness (immunosuppression, diabetes, alcohol/drug abuse, malignancy, or chronic systemic disease). Children by contrast tend not to have chronic illness, but necrotizing fasciitis may complicate chickenpox. Occasionally the disease afflicts apparently healthy individuals. It has been suggested (unconvincingly) that antiinflammatory medication might predispose to these spreading infections by interfering with granulocyte function [30], but Kauls et al [6] could find no such association. In two thirds of cases, the necrosis followed either a skin lesion or trauma. In an otherwise normal Western population, more than 50% of episodes occurred in the limbs,

whereas a few cases involved the trunk and perineum. The head and neck were involved in 1% to 10% of cases. The condition even has been reported after routine dental surgery or dental sepsis (Fig. 2).

The variable clinical picture means that delay in diagnosis is common, because the prodromal period in which the synergistic consortia of bacteria are evolving may be only 3 or 4 days before the phase of rapid acceleration. Diagnosis depends on being alert to the possibility of the disease and recognizing the pattern of clinical events, the main feature of which is a rapidly progressive necrotizing infection. The area is acutely painful, and the surrounding tissues are red (the signs depend on the specific mix of bacteria), but on close inspection a central portion of skin is pale and toxic (Fig. 3). The skin subsequently develops a slightly mottled appearance as it becomes congested through venous stasis. As the perfusion is further reduced through arterial failure, the skin starts to blister. Sensory perception is lost as nerves are destroyed and the wound weeps fluid from the underlying liquefaction. Gross edema is a feature of the disease, and gas may be present in up to 40% of cases [21]. The presence of gas is neither a reliable nor discriminatory sign for clostridial infections because it can be absent in gas gangrene and present in various nonclostridial infections [20]. Gas simply denotes the presence of anaerobic bacteria [29]. A marked leukocytosis (median 16,000 leucocytes/mm) is common, but 20% of patients have a normal white cell count, and in some cases the count even may be low. Fever is not always present, especially in the early stages of the disease.

With advancing disease the patient becomes progressively unwell, with a general malaise and tachycardia. More than 50% of patients develop significant hypotension. In 10% to 30% of cases the disease is complicated by one or more of the following conditions: acute renal failure, coagulopathy, abnormal liver function, acute respiratory distress syndrome, or hemolytic anemia. The rapid progression of the disease is a distinguishing feature.

Diagnosis

If the clinical features are suggestive of necrotizing fasciitis, the diagnosis should not wait for the results of bacterial culture. Clinical inspection of the wound demonstrates that the subcutaneous fat has no structural integrity and offers little resistance to the exploring finger. The skin is widely undermined by the progressing infection. Histologic criteria have been described for the early diagnosis of necrotizing fasciitis by frozen section [31], and the typical pattern

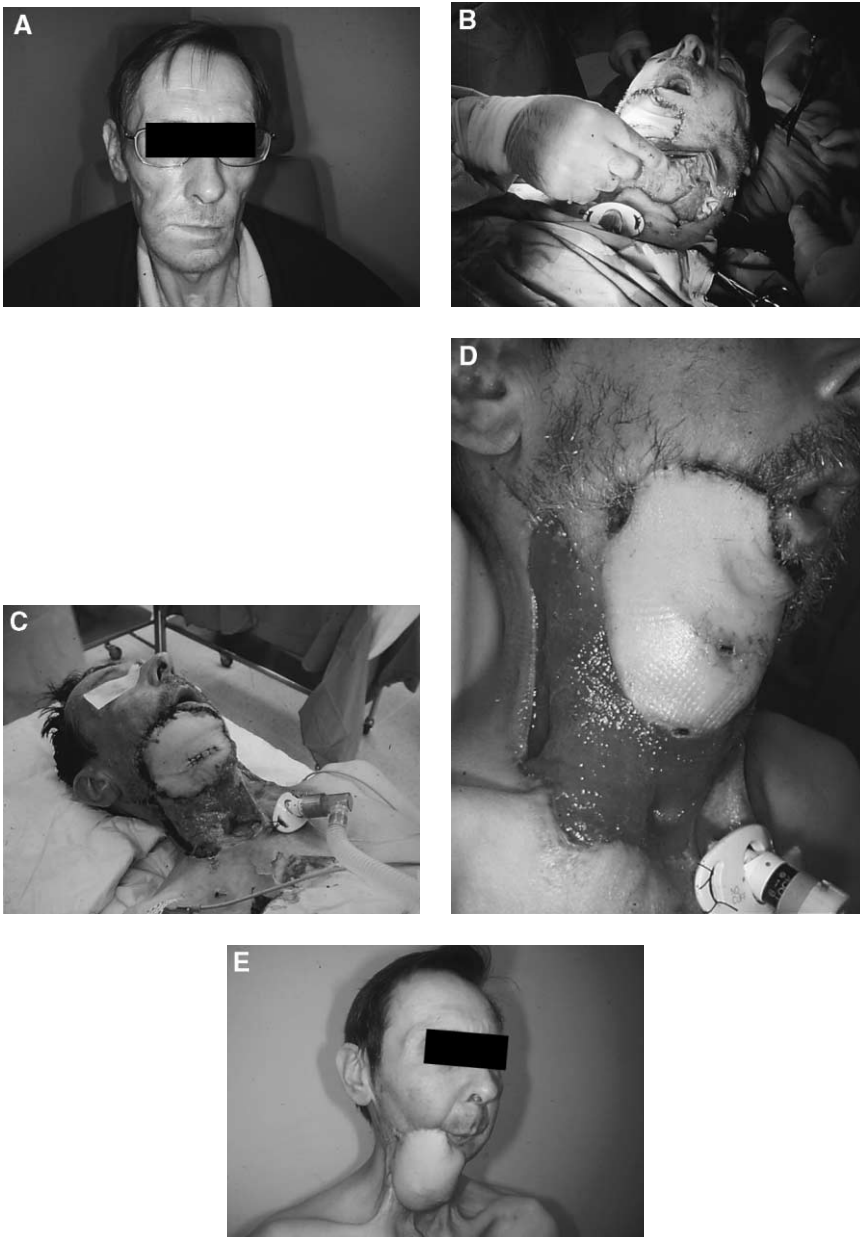


Fig. 3. An emaciated patient presented with a large oral carcinoma (A) and a history of alcoholism with associated liver failure, pancreatitis, and diabetes. Necrosis of the skin flaps occurred abruptly 72 hours after surgery (mixed flora) despite antibiotic prophylaxis (B). Surgical débridement was followed by a regimen of dressing changes every 4 hours (C). Healthy granulating tissue developed eventually (D) and the skin flaps reattached. The patient remains disease free 2 years after surgery (E).

of a dense polymorphonuclear infiltrate in the dermal layers of the skin clinches the diagnosis. Samples of necrotic tissue are uninformative; a biopsy should be taken from normal-looking adjacent tissue. A Gram's stain may be helpful in selecting first-line antibiotics, and blood cultures typically produce positive results.

Management

Shock and multiorgan failure are relatively common, so resuscitation and general supportive measures are vital in the established case. Two treatments are recommended: (1) surgery and (2) antibiotics, to

which hyperbaric oxygen might be added. Of these treatments, the single most important modality is surgery. There is no controversy regarding the initial management of spreading necrosis, the extent of débridement being determined clinically [29]. Underlying muscle can be preserved, but all necrotic tissue and overlying skin must be removed. Resected tissue (skin, muscle, connective tissue) should be sent for culture and antibiotic sensitivity (aerobic and anaerobic), and Gram's stain results should be obtained. Time is of the essence at this stage, because mortality is associated with delayed intervention. Even if recognized promptly, significant necrosis usually has taken place before resection is undertaken. More than one débridement may be necessary and it is considered prudent to make a second operative inspection of the wound after 24 to 36 hours.

Management is similar to that of an extensive burn. The wounds should be washed (hydrogen peroxide is useful for débridement) and packed regularly (every 4 hours) (Fig. 4), a procedure best done personally by the attending surgeon. Slowly the slough clears and shiny granulation tissue emerges

from beneath the yellow slime. The undermined skin at the edge of the wound reattaches to the underlying granulation tissue and the packing can be withdrawn slowly day by day. Regular dressing still should be maintained at 8-hour intervals, which demands a heavy nursing commitment.

Ultimately, antibiotic therapy is dictated by the cultures, but intravenous penicillin is the initial drug of choice. If the Gram's stain shows a mixed flora, a broad-spectrum antibiotic also should be used (gentamycin), and it can be supplemented as appropriate information is obtained. Finally, hyperbaric oxygen has been suggested as a supportive measure, but there is no definitive evidence of efficacy and there are obvious logistic problems if this technology is contemplated.

Results

Despite proper management of necrotizing fasciitis, mortality remains high. A collective review [32] [Janevicius, Han & Batt 1982] of 146 cases reported

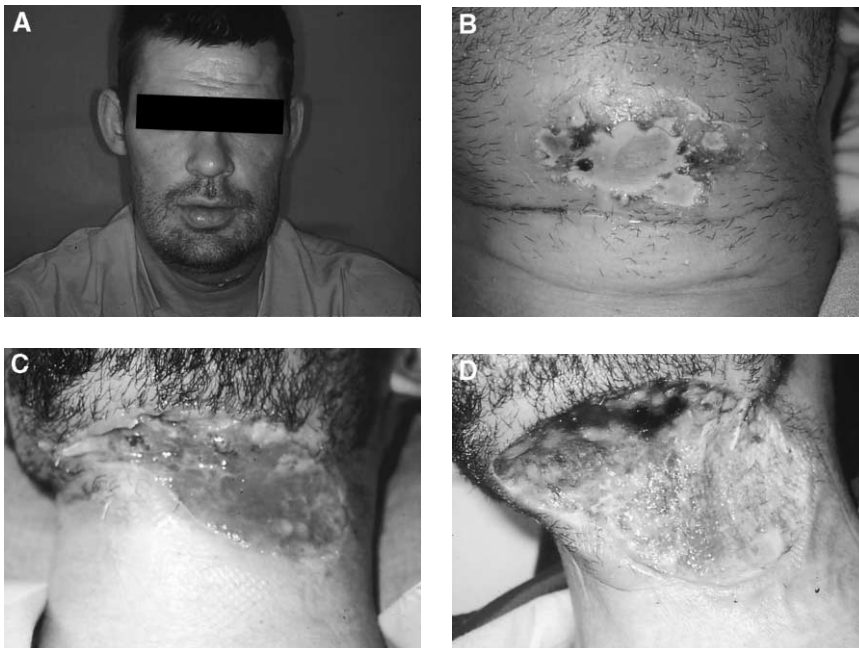


Fig. 4. During the preparation of this article a 27-year-old man presented with a recent history of third molar infection (A). He was otherwise healthy. The tooth was removed manually by the patient himself on a Sunday, he was admitted with low-grade cervical infection the following Thursday, and submental necrosis developed overnight (B). Note the ring of ischemia around the ulcer and the congestion in the surrounding tissue. Fluid can be seen leaking from the ulcer. The infection (mixed flora) settled quickly after débridement (C) and standard antibiotic therapy. The wound was allowed to granulate before repair with a split skin graft (D).

a 38% mortality rate. In a prospective study, Kaul [6] recorded a case fatality rate of 34%. Pessa and Howard [33] applied severity of illness scoring systems to predict outcome. They found that the scores continued to rise after débridement in patients who were to die, and accurate prediction of survival could be made as early as the third postoperative day. Mortality rates increase with age (> 50 years of age), concomitant illness (diabetes), delay in diagnosis or treatment [20], inadequate débridement, lesions of the abdomen, and mucormycosis [23,32]. In a multivariate analysis, age, hypotension, and bacteremia were independent variables that predicted mortality. Patients can die from systemic problems some days or weeks after the infection, and in historical texts there are reports of fatal arterial bleeds occurring approximately 10 days after surgery, just as the infective process is settling.

Summary

Necrotizing fasciitis is a dramatic but rare disease. In the head and neck it often strikes unexpectedly. Early diagnosis and radical treatment are important to maximize the chances of a good outcome. The outcome depends on the clinician having a high threshold of suspicion when rapidly progressive local and systemic symptoms appear in the presence of what was initially an apparently innocuous wound. Diagnosis is achieved principally by inspection and manual examination during explorative surgery but can be supported by frozen section examination. Treatment is mainly surgical, helped by general measures of support to combat the systemic effects of circulating toxins. The key to success is captured in a line by Shakespeare in *Macbeth*: “Be bloody, bold and resolute.”

References

- [1] Deans M. Flesh-eating bugs scare. *Lancet* 1994; 343:1418.
- [2] Thomson J. Hospital gangrene or malignant ulcers. In: *Lectures on inflammation*. Edin: James Ballantyne and Co.; 1813. p. 456–500.
- [3] Gillespie L. Observations on the putrid ulcer. *London Medical Journal* 1785;6:373–400.
- [4] Adams F. *The genuine works of Hippocrates*. London: Sydenham Society; 1771. p. 400–1.
- [5] Anonymous. Invasive group A streptococcal infections. *JAMA* 1994;272:16.
- [6] Kauls R, McGeer A, Low DE, Green K, Schwartz AE, Simor AE. Population based surveillance for group A streptococcal necrotizing fasciitis: clinical features, prognostic indications and microbiological analysis of seventy seven cases. *Am J Med* 1977; 103:18–24.
- [7] Schlievert PM, Aris P, Assimakopoulos Cleary PP. Severe invasive group A streptococcal disease: clinical description and mechanism of pathogenesis. *J Lab Clin Med* 1996;127:13–22.
- [8] Blackadder HH. *Observations on phagedena gangraenosa*. Edinburgh: David Brown; 1818.
- [9] Trotter T. *Medicina nautical*. London: Longman, Hurst, Rees and Orme; 1797. p. 1–111.
- [10] Henne J. *Principles of military surgery*. Edinburgh: Constable; 1820.
- [11] Nightingale F. *Notes on hospitals*, 3rd edition. London: Longman, Green; 1863.
- [12] Jones J. Investigation upon the nature, causes and treatment of hospital gangrene as it prevailed in the Confederate armies 1861–1865. In: Hamilton FH, editor. *United States Sanitary Commission memoirs: surgical II*. New York: Riverside Press; 1871. p. 146–70.
- [13] Barnes J. Gangrene. In: Barnes J, editor. *Medical and surgical history of the War of Rebellion*. 1867. p. 823–51.
- [14] Welbank R. *On sloughing phagedaena*. London: Longmans Brown and Green; 1844.
- [15] Fournier JA. *Gangrene fourdroyant de la verge*. *Semaine Medicale* 1883;3:345–7.
- [16] Travers T. Two cases of slough ulceration. *London Medical and Physical Journal* 1824;122–34.
- [17] Melaney F. Hemolytic Streptococcus gangrene. *Arch Surg* 1924;9:317–64.
- [18] Enright MC, Spratt BG, Kalia A, Cross JH, Bessen DE. Multilocus sequence typing of *Streptococcus pyogenes* and the relationships between emm type and clone. *Infect Immunol* 2001;69:2416–27.
- [19] Giuliano A, Lewis F, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. *Am J Surg* 1977; 134:52–7.
- [20] Freischlag JA, Ajalat G, Busuttill RW. Treatment of necrotizing soft tissue infections. *Am J Surg* 1985; 149:751–5.
- [21] Brook I, Frazier EH. Clinical and microbiological features of necrotizing fasciitis. *J Clin Microbiol* 1995; 33:2382–7.
- [22] Joynt GM, Gommersall CD, Lyon DJ. Severe necrotizing fasciitis of the extremities caused by *Vibrionaceae*: experience of a Hong Kong Territory referral hospital. *Hong Kong Med J* 1999;5:63–8.
- [23] Patino J, Castro D, Valencia A, Morales P. Necrotizing soft tissue lesions after a volcanic cataclysm. *World J Surg* 1991;15:240–7.
- [24] Cunningham MW. Pathogenesis of group A streptococcal infections. *Clin Microbiol Rev* 2000;13:470–511.
- [25] Engleberg NC, Heath A, Miller A, Rivera C, Di Rita VJ. Spontaneous mutations in the CsRS two component regulatory system of *Streptococcus pyogenes* resulting in enhanced virulence in a murine model of

- skin and soft tissue infection. *J Infect Dis* 2001;183:1043–54.
- [26] Pruitt BA. Burns and soft tissues. In: Polk Jr HC, editor. *Infection and the surgical patient: clinical surgery international*. London: Churchill-Livingstone; 1982. p. 113–31.
- [27] Gorbach SL, Bartlett JG, Nichols RL. *Manual of surgical infections: skin and soft tissue infections*. Boston: Little Brown and Co.; 1984.
- [28] Simmons RL, Ahrenholz DH. Infections of the skin and soft tissues. In: Howard RJ, Simmons RL, editors. *Surgical infections diseases*. 2nd edition. Norwalk: Appleton and Lange; 1988. p. 404–8.
- [29] Dellinger EP. Severe necrotizing soft-tissue infections: multiple disease entities requiring a common approach. *JAMA* 1981;246:1717–21.
- [30] Brun-Buisson CJL, Saada M, Trunet P, Rapin M, Roujeau J, Revuz J. Haemolytic streptococcal gangrene and non-steroidal anti-inflammatory drugs. *BMJ* 1985;290:1786.
- [31] Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen section biopsy. *N Engl J Med* 1984;310:1689.
- [32] Janevicius RV, Hann SE, Batt MD. Necrotizing fasciitis. *Surg Gynecol Obstet* 1982;154:97–102.
- [33] Pessa ME, Howard RJ. Necrotizing fasciitis. *Surg Gynecol Obstet* 1985;161:357.