Classic diseases revisited

Necrotizing soft tissue infections

John D Urschel

Summary

Necrotizing soft tissue infections are a group of highly lethal infections that typically occur after trauma or surgery. Many individual infectious entities have been described, but they all have similar pathophysiologies, clinical features, and treatment approaches. The essentials of successful treatment include early diagnosis, aggressive surgical debridement, antibiotics, and supportive intensive treatment unit care. The two commonest pitfalls in management are failure of early diagnosis and inadequate surgical debridement. These life-threatening infections are often mistaken for cellulitis or innocent wound infections, and this is responsible for diagnostic delay. Tissue gas is not a universal finding in necrotizing soft tissue infections. This misconception also contributes to diagnostic errors. Incision and drainage is an inappropriate surgical strategy for necrotizing soft tissue infections; excisional debridement is needed. Hyperbaric oxygen therapy may be useful, but it is not as important as aggressive surgical therapy. Despite advances in antibiotic therapy and intensive treatment unit medicine, the mortality of necrotizing soft tissue infections is still high. This article emphasizes common treatment principles for all of these infections, and reviews some of the more important individual necrotizing soft tissue infectious entities.

Keywords: fasciitis; gas gangrene; clostridium infections; streptococcal infections; necrosis; debridement; surgical infections; soft tissue infections

Department of Surgery, McMaster University, Hamilton, Ontario, Canada
J D Urschel

Correspondence to John Urschel, MD, Chief of Surgery, St Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario, Canada L8N 4A6

Accepted 3 June 1999

Necrotizing soft tissue infections are a highly lethal group of infections that require early and aggressive surgical debridement.¹⁻³ These infections may occur in almost any anatomic area, but they most frequently involve the abdomen, perineum, and lower extremities. Surgery and trauma are common aetiologies, but in some cases the aetiology remains uncertain.^{4,5} Immunocompromised patients, especially those with diabetes, are more likely to develop necrotizing infections. A great deal of attention has been directed toward classifying these infections by bacteriological features or layers of tissue involved, but it is useful to view necrotizing infections as a spectrum of clinical conditions with similar pathophysiological features and common treatment principles.^{3,6,7} In this review, the common treatment concepts applicable to all necrotizing soft tissue infections will be emphasized, and the more important specific disease entities will be described.

Clinical features of necrotizing soft tissue infections include wound pain, crepitus, foul watery wound discharge, skin blistering, and rapid progression to septic shock.^{1,8} The external appearance of the skin wound may initially betray the seriousness of the necrotizing infection beneath it (figure 1); this contributes to diagnostic delay. Soft tissue gas, detected clinically or radiologically, is a classic sign, but its absence does not exclude the presence of a necrotizing infection.⁹ This common misconception is also responsible for delayed diagnosis in some cases. The infection spreads rapidly through the soft tissue planes, and produces severe systemic sepsis. Progression to septic shock, multiple organ failure, and death ensues if aggressive treatment is not instituted immediately. Even with timely and skilled treatment, death from necrotizing soft tissue infections is all too frequent.^{1,2,9}

Some necrotizing infections are caused by single organisms. Myonecrosis (gas gangrene) from *Clostridium* infection and necrotizing fasciitis from group A *Streptococcus* are two classic examples of monomicrobial necrotizing infection. However, most necrotizing soft tissue infections are caused by a mixture of aerobic and anaerobic bacteria, that act synergistically to cause fulminant infection.^{10,11} Organisms commonly identified include aerobic and anaerobic streptococci, coagulase-negative and coagulase-positive staphylococci, facultative and aerobic Gram-negative rods, *Bacteroides* species,^{9,10} and *Clostridium* species.^{9,10} Facultative organisms lower the oxidation-reduction potential of the wound microenvironment, and promote favourable conditions for the growth of anaerobes. Anaerobes interfere with host phagocyte function, and thereby facilitate the proliferation of aerobic bacteria.¹² Several bacteria, such as *Bacteroides fragilis*, produce β -lactamase enzymes that interfere with antibiotic activity.

Bacterial necrotoxins, such as those produced by *Clostridium perfringens* and *Streptococcus pyogenes*, cause tissue necrosis.¹ In addition, the infectious process activates the coagulation system that in turn produces local vascular thrombosis and infarction. Bacterial heparinase production contributes to this process. As the infection progresses, pressure increases within the soft tissues causing further impairment of blood supply.¹¹

The diagnosis of necrotizing soft tissue infections is usually made at the time of surgical exploration. Securing a diagnosis non-invasively is very difficult; this contributes to diagnostic delay, and the ultimate demise of many patients.^{2,13} The clinical presentation is often mistaken for simple cellulitis. However, pain in the affected region and systemic toxicity are more pronounced than would be expected in simple cellulitis.¹⁴ Despite recommendations for the diagnostic use of computed tomography and magnetic resonance imaging studies in these infections,^{15,16} the best diagnostic strategy is to perform surgical exploration when clinical features raise the possibility of necrotizing soft tissue infection.¹⁷⁻¹⁹ Initially, diagnostic surgical exploration can be very limited in scope; small incisions under local anaesthesia serve to establish the presence or absence of fascial and muscle necrosis. Frozen section examination of tissue specimens will establish the diagnosis if the gross findings at surgical exploration leave any doubt

Figure 1 External appearances often betray the seriousness of underlying infection. This woman was in septic shock at the time this photograph was taken. Despite amputation, fulminant sepsis led to death within 24 hours of amputation

Figure 2 Histology shows necrotic connective tissue and acute inflammatory cells (haematoxylin and eosin, × 200). The patient suffered from polymicrobial necrotizing fasciitis involving the abdominal wall

(figure 2).^{18 19} Although limited surgical interventions are appropriate for diagnostic purposes, there is no role for conservative surgical treatment strategies.³

Treatment of necrotizing soft tissue infections entails early surgical debridement, fluid resuscitation, antibiotics, and general cardiorespiratory supportive care to maintain vital organ function (box).^{20 21} After diagnostic delay, the most common pitfall in treatment is inadequacy of surgical debridement. Debridement should be early and aggressive; all necrotic tissue must be excised (figure 3).^{17 22} 'Incision and drainage' approaches are not appropriate. These infections are characterized by necrotic tissue and watery drainage, as opposed to the viable tissue and pus that characterize localized bacterial abscesses. Repeat debridement, sometimes on a daily basis, should be done until the local infectious process has been arrested.^{23 24} After sepsis is controlled, coverage of the wound is usually obtained by skin grafting.

Intravenous fluid resuscitation, mechanical ventilation, and inotropic support are instituted according to established principles for managing septic shock. These principles are reviewed elsewhere.^{25–27} Nutritional support is started after urgent resuscitation and debridement are carried out. Antibiotic coverage should be broad-spectrum, and anaerobic coverage is essential. Many antibiotic combinations are acceptable. Usually penicillin (or a cephalosporin), anaerobic coverage (clindamycin or metronidazole), and Gram-negative coverage (aminoglycoside, third-generation cephalosporin, or ciprofloxacin) are used together.¹ Antimicrobial therapy of life-threatening surgical infections has recently been reviewed in detail elsewhere.^{11 28 29} Antibiotics are modified after Gram stains and culture reports become available. Blood cultures and wound cultures are both useful, but simple wound swabs are often inadequate for proper culturing. Wound tissue samples should be sent in both aerobic and anaerobic containers. Finally, antibiotic treatment is also guided by the information gained during surgical exploration. Operative findings may be indicative of one of several distinct clinical–bacteriologic infectious entities (reviewed below).

Hyperbaric oxygen therapy has an uncertain role in the management of necrotizing soft tissue infections. Some studies suggest a survival benefit,^{21 30 31} but others do not.^{24 32} Survival from clostridial myonecrosis is probably improved by hyperbaric oxygen therapy.^{32 33} For other types of necrotizing soft tissue infection, hyperbaric oxygen therapy may hasten local wound healing and closure.^{9 30} Most investigators agree on one point: hyperbaric oxygen therapy is not as important as urgent surgical intervention. Debridement should take priority over patient transfer to a hyperbaric oxygen facility.

Despite aggressive therapy, and modern intensive treatment unit care, the mortality of necrotizing soft tissue infections remains high (15–50%).^{1–5 13} Factors associated with increased mortality include extent of soft tissue involvement, delay in diagnosis, inadequate debridement, advanced age, and truncal involvement.^{20 23 24} Chest wall involvement is particularly ominous, and survival is rare.^{3 34} Considering the seriousness of necrotizing soft tissue infections, and the complexity of treatment, a multidisciplinary team approach is needed. Surgeons, anaesthetists, intensive care physicians, and infectious disease consultants must work together.

Specific syndromes

Many authors have stressed the importance of a unified approach to necrotizing soft tissue infections,^{3 6 7} and the initial diagnostic and management approach is similar for all of the entities within the spectrum. Previous complex classification schemes were not relevant for the initial care of patients; confused clinicians were left without practical management algorithms.² Nevertheless, there are several distinct clinical–bacteriological entities that should be recognised (table). After initial treatment has been instituted, subtle differences in management for the various specific syndromes become important.^{10 13} However, it is worth reiterating that the broad general principles of diagnosis and treatment outlined above are undoubtedly more important than the specifics discussed below. Three of the major necrotizing soft tissue infections will be reviewed: necrotizing fasciitis type I (polymicrobial), necrotizing fasciitis type II (group A streptococcal), and *Clostridial myonecrosis* (gas gangrene). Finally, several other necrotizing soft tissue infectious entities will be briefly described.

NECROTIZING FASCIITIS TYPE I (POLYMICROBIAL)

Necrotizing fasciitis usually occurs after trauma or surgery (figure 4).^{8 35} The subcutaneous fat and fascia overlying muscle are prominently involved, but in the late stages extension occurs into the muscle tissue itself. Anaerobes and facultative bacteria act synergistically to cause tissue destruction. The clinical pace

Treatment principles for necrotizing soft tissue infections

- clinical suspicion
- early surgical exploration
- aggressive and repetitive debridement
- antibiotics
- intensive treatment unit care
- nutritional support
- hyperbaric oxygen (if available)

Figure 3 Appearances of the chest wall after aggressive debridement for a necrotizing soft tissue infection. Despite control of infection, the patient died of respiratory failure several weeks later

Figure 4 Minor trauma was the initiating cause of necrotizing infection in this lower extremity. Amputation was done and the patient survived

of disease is usually somewhat slower than that seen with type II (streptococcal) necrotizing fasciitis and clostridial myonecrosis, but its overall severity and lethality should not be underestimated. Clinicians often mistake it for simple wound cellulitis, but severe pain and systemic toxicity point to a more sinister underlying infection. The diagnosis is easily established by making a small skin incision and passing a haemostat or probe through the subcutaneous tissues.³⁵ In necrotizing fasciitis the subcutaneous and fascial layers lack resistance to this manoeuvre, a feature that indicates widespread tissue necrosis underneath seemingly viable skin. Gas may or may not be present in the soft tissues. Histology of affected tissues shows widespread necrosis of subcutaneous fat and fascia, with relative sparing of muscle. An acute inflammatory reaction, with many polymorphonuclear cells, is seen. Thrombosis of blood vessels and abundant bacteria are other typical histologic findings. Aggressive surgical debridement is the key to successful treatment.

Necrotizing fasciitis may occur in the perineum. This type of infection is usually secondary to urogenital or anorectal infections. It is termed Fournier's gangrene.³⁶ Patients usually have a predisposing systemic illness, such as diabetes mellitus. Another distinct form of necrotizing fasciitis is that caused by salt-water contamination of an otherwise minor skin wound. *Vibrio* species are responsible. The affected patients usually suffer from a predisposing condition, such as chronic liver disease. This form of necrotizing fasciitis is highly lethal.³⁷

NECROTIZING FASCIITIS TYPE II (GROUP A STREPTOCOCCAL)

Type II necrotizing fasciitis is caused by virulent subtypes of *Streptococcus pyogenes*.^{13 14} It has gained considerable recent attention in the lay press where the bacteria is often referred to as a flesh-eating bacteria. The incidence of this infection seems to have increased in the last two decades, but this could simply reflect improvements in diagnosis and reporting.¹ Alternatively, there is some evidence to suggest a true increase in incidence.³⁸ It could be the result of an evolutionary trend towards greater organism virulence in the setting of a more immunologically naïve population.^{13 38} The presence of the M1 and M3 proteins is associated with virulent infection. The occurrence of outbreaks of streptococcal necrotizing fasciitis has set it apart from related infections, and captured the public's attention. Most of the general features of necrotizing soft tissue infections apply to this particular entity, but the presence of gas in tissues is unusual. There are some other unique aspects of this condition that warrant further discussion.

Two specific predisposing factors are varicella infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs). Although necrotizing fasciitis is rare in children, almost half of cases occur in the setting of varicella.³⁹ NSAIDs may attenuate host immune responses and therefore they may predispose to, and adversely effect the outcome of, streptococcal necrotizing fasciitis.^{14 40} However, some investigators have failed to find an increased incidence or severity of streptococcal necrotizing fasciitis in patients using NSAIDs.^{39 41} Another distinct feature of this form of necrotizing fasciitis is its frequent association with streptococcal toxic shock syndrome.⁴² This syndrome is similar to that originally described for staphylococcal infections. Its features include a high fever, early onset of shock, multiple organ failure, and a very high mortality rate. Approximately 50% of patients with streptococcal toxic shock syndrome have streptococcal necrotizing fasciitis as the initiating infection.

Treatment of type II necrotizing fasciitis is generally in keeping with the principles outlined above. Once the diagnosis has been established, penicillin combined with clindamycin replaces the previous broad-spectrum empiric antimicrobial therapy. The combination of clindamycin and penicillin appears to be superior to the traditional treatment with penicillin alone.¹⁴ Finally, there is

Table Necrotizing soft tissue infections — major clinical entities

	Predisposing factors	Microbiology	Dominant features	Management
Necrotizing fasciitis type I (polymicrobial)	Surgery, trauma, diabetes mellitus	Anaerobes, Gram-negative aerobic bacilli	Necrosis of fat and fascia, may have gas	Debridement, broad-spectrum antibiotics, ITU support
Necrotizing fasciitis type II (group A streptococcal)	Surgery, minor trauma, varicella	<i>Streptococcus pyogenes</i>	Rapidly progressing necrosis of multiple tissue layers, no gas, shock	Debridement, penicillin & clindamycin, ITU support
Clostridial myonecrosis (gas gangrene)	Trauma, surgery, spontaneous (cancer)	Clostridial species	Fulminant myonecrosis, prominent gas formation	Debridement, penicillin & clindamycin, ITU support, hyperbaric oxygen

ITU support = intensive treatment unit support (ie, fluids, ventilation, inotropic drugs, nutrition)

some evidence to support the use of intravenous immunoglobulin as an immunomodulator in this condition.^{13 39}

CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)

Clostridial myonecrosis is a distinct necrotizing infection of skeletal muscle.^{43 44} As the older term gas gangrene suggests, muscle necrosis and gas production are prominent features of this illness. Most cases arise in the setting of recent surgery or trauma, but some arise spontaneously. *Clostridium perfringens* (formerly *C. welchii*) is the most common causative organism. This anaerobic Gram-positive spore-forming bacillus is widely distributed in soil, and it can be found within the gastrointestinal tract of animals and humans. The organism produces over 10 different exotoxins of which the α -toxin is the most important.⁴⁵ The α -toxin hydrolyses cell membranes. It causes tissue necrosis, inactivates leukocytes, and haemolyses red blood cells. In addition, the α -toxin has direct cardiodepressive effects.

The pathologic features of clostridial myonecrosis are very dramatic. Grossly, there is obvious release of gas upon surgically entering the involved muscle compartment. The muscle is oedematous, pale or grey, and it does not bleed or contract when cut. Unlike the other necrotizing infections described above, clostridial myonecrosis shows very little inflammation on histologic examination. This lack of inflammatory host response goes along with the classic fulminant clinical course of clostridial myonecrosis. The infection rapidly advances, often over a matter of hours.

Surgical debridement and antibiotics are the mainstays of treatment. As for necrotizing infections caused by group A *Streptococci*, clindamycin combined with penicillin is preferable to penicillin alone.¹ Hyperbaric oxygen is of greater benefit for clostridial myonecrosis than it is for other necrotizing infections.^{46 47} This is logical, since clostridial myonecrosis is a monomicrobial anaerobic infection. After aggressive debridement and stabilisation, hyperbaric oxygen therapy should be instituted if available. It inhibits clostridial growth and arrests α -toxin production.⁴⁸

Spontaneously occurring clostridial myonecrosis is usually caused by *Clostridium septicum*.⁴⁹ The organism spreads to muscle haematogenously from a small break in the normal gastrointestinal mucosal barrier. It usually occurs in patients suffering from either colon cancer or leukaemia. Patients surviving *Clostridium septicum* infection should undergo colonoscopy to check for an occult colon cancer.

OTHER NECROTIZING SOFT TISSUE INFECTIOUS ENTITIES

Anaerobic streptococcal myonecrosis is a necrotizing infection of skeletal muscle that clinically resembles clostridial myonecrosis.^{50 51} Compared to clostridial myonecrosis, the pace of this infectious process is slower and gas production is not as marked. Anaerobic streptococcal myonecrosis is a polymicrobial infection. General treatment principles of necrotizing soft tissue infections are applicable.

Group A streptococci can occasionally cause myonecrosis, although these organisms more commonly cause necrotizing fasciitis (type II).^{42 52} The clinical features and treatment are similar to clostridial myonecrosis, but gas production is not typically present.

Aeromonas hydrophilia is a facultatively anaerobic, Gram-negative bacillus, which causes a fulminant myonecrosis.^{53 54} The rapidity of the infectious process is similar to that of clostridial myonecrosis, but gas production is not a consistent feature. The infection usually occurs in the setting of penetrating freshwater trauma. Aggressive surgical debridement and antibiotic coverage for Gram-negative rods are the essential features of treatment.

Clostridial cellulitis is a necrotizing soft tissue infection that clinically resembles necrotizing fasciitis, but the infection is more superficial.^{14 55-57} It usually occurs in the setting of surgery or trauma (*Clostridium perfringens*), but it can occur spontaneously in association with malignancy (*Clostridium septicum*). The skin and subcutaneous fat are involved. Gas production is a prominent feature. Since the infection is more superficial than clostridial myonecrosis, the associated toxicity is usually not as severe. Surgical exploration reveals viable fascia and muscle; this distinguishes clostridial cellulitis from necrotizing fasciitis and gas gangrene. The differentiation is obviously important. Clostridial cellulitis requires debridement of skin and subcutaneous fat, but more aggressive and extensive surgical therapy is not needed. A very similar superficial necrotizing infection can also be caused by a variety of anaerobic bacteria, either alone or as a mixed infection. This is termed nonclostridial anaerobic cellulitis, or synergistic necrotizing cellulitis.^{14 56 57} Diabetes mellitus is often a predisposing factor. The treatment approach is the same as for clostridial cellulitis.

- 1 Chapnick EK, Abter EI. Necrotizing soft-tissue infections. *Infect Dis Clin North Am* 1996;10: 835-55.
- 2 Sutherland ME, Meyer AA. Necrotizing soft-tissue infections. *Surg Clin North Am* 1994;74: 591-607.
- 3 Urschel JD, Takita H, Antkowiak JG. Necrotizing soft tissue infections of the chest wall. *Ann Thorac Surg* 1997;64:276-9.
- 4 Freischlag JA, Ajalat G, Busuttill RW. Treatment of necrotizing soft tissue infections: the need for a new approach. *Am J Surg* 1985;149:751-5.
- 5 Janevicius RV, Hann SE, Batt MD. Necrotizing fasciitis. *Surg Gynecol Obstet* 1982;154:97-102.
- 6 Dellinger EP. Severe necrotizing soft-tissue infections: multiple disease entities requiring a common approach. *JAMA* 1981;246:1717-21.
- 7 Kaiser RE, Cerra FB. Progressive necrotizing surgical infections: a unified approach. *J Trauma* 1981;21:349-55.
- 8 Green RJ, Dafeo DC, Raffin TA. Necrotizing fasciitis. *Chest* 1996;110:219-29.
- 9 Elliott DC, Kufera JA, Myers RAM. Necrotizing soft tissue infections: risk factors for mortality and strategies for management. *Ann Surg* 1996;224:672-83.
- 10 Giuliano A, Lewis F, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. *Am J Surg* 1977;134:52-7.
- 11 File TM Jr, Tan JS. Treatment of skin and soft-tissue infections. *Am J Surg* 1995;169(suppl): 27-33S.
- 12 Rotstein OD, Pruett TL, Simmons RL. Mechanisms of microbial synergy in polymicrobial surgical infections. *Rev Infect Dis* 1985;7:151-70.
- 13 Low DE, McGeer A. Skin and soft tissue infection: necrotizing fasciitis. *Curr Opin Infect Dis* 1998;11:119-23.
- 14 Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med* 1996;334: 240-5.
- 15 Wysoki MG, Santora TA, Shah RM, et al. Necrotizing fasciitis: CT characteristics. *Radiology* 1997;203:859-63.
- 16 Loh NN, Ch'en IY, Cheung LP, et al. Deep fascial hyperintensity in soft-tissue abnormalities as revealed by T-2 weighted MR imaging. *AJR* 1997;168:1301-4.
- 17 McHenry CR, Piotrowski JJ, Petrinic D, et al. Determinants of mortality for necrotizing soft-tissue infections. *Ann Surg* 1995;221:558-65.
- 18 Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen section biopsy. *N Engl J Med* 1984;310: 1689-93.
- 19 Majeski J, Majeski E. Necrotizing fasciitis: improved survival with early recognition by tissue biopsy and aggressive surgical treatment. *South Med J* 1997;90:1065-8.
- 20 Bosshardt TL, Henderson VJ, Organ CH Jr. Necrotizing soft-tissue infections. *Arch Surg* 1996;131:846-52.
- 21 Gozal D, Ziser A, Shupak A, et al. Necrotizing fasciitis. *Arch Surg* 1986;121:233-5.
- 22 Urschel JD, Horan TA, Unruh HW. Necrotizing chest wall infection. *Comp Surg* 1993;12:37-43.
- 23 Rea WJ, Wyrick WJ. Necrotizing fasciitis. *Ann Surg* 1970;172:957-64.
- 24 Pessa ME, Howard RJ. Necrotizing fasciitis. *Surg Gynecol Obstet* 1985;161:357-61.
- 25 Edwards JD. Management of septic shock. *BMJ* 1993;306:1661-4.
- 26 Demling RH, Lalonde C, Ikegami K. Physiologic support of the septic patient. *Surg Clin North Am* 1994;74:637-58.
- 27 Dunn DL. Gram-negative bacterial sepsis and sepsis syndrome. *Surg Clin North Am* 1994;74: 621-35.
- 28 Solomkin JS, Miyagawa CI. Principles of antibiotic therapy. *Surg Clin North Am* 1994;74: 497-517.
- 29 Shands JW Jr. Empiric antibiotic therapy of abdominal sepsis and serious perioperative infections. *Surg Clin North Am* 1993;73:291-306.
- 30 Riseman JA, Zamboni WA, Curtis A, et al. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. *Surgery* 1990;108:847-50.
- 31 Brown DR, Davis NL, Lepawsky M, et al. A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. *Am J Surg* 1994;167: 485-9.
- 32 Darke SG, King AM, Slack WK. Gas gangrene and related infection: classification, clinical features and aetiology, management and mortality. A report of 88 cases. *Br J Surg* 1977;64:104-12.
- 33 Jackson RW, Waddell JP. Hyperbaric oxygen in the management of clostridial myonecrosis (gas gangrene). *Clin Orthop* 1973;96:271-6.
- 34 Hammainen P, Kostianen S. Postoperative necrotizing chest-wall infection. *Scand Cardiovasc J* 1998;32:243-5.
- 35 Wilson B. Necrotizing fasciitis. *Am Surg* 1952; 18:416-31.
- 36 Clayton MD, Fowler JE Jr, Sharifi R, et al. Causes, presentation and survival of 57 patients with necrotizing fasciitis of the male genitalia. *Surg Gynecol Obstet* 1990;170:49-55.
- 37 Howard RJ, Bennett NT. Infections caused by halophilic marine *Vibrio* bacteria. *Ann Surg* 1993;217:525-31.
- 38 Cleary PP, Kaplan EL, Handley JP, et al. Clonal basis for resurgence of serious *Streptococcus pyogenes* disease in the 1980s. *Lancet* 1992;339: 518-21.
- 39 Kaul R, McGeer 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.
- 40 Brun-Buisson CJ, Saada M, Trunet P, et al. Haemolytic streptococcal gangrene and non-streptococcal anti-inflammatory drugs. *BMJ* 1985; 290:1786.
- 41 Choo PW, Donahue JG, Platt R. Ibuprofen and skin and soft tissue superinfections in children with varicella. *Ann Epidemiol* 1997;7:440-5.
- 42 Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. *N Engl J Med* 1989;321:1-7.
- 43 Altmeier WA, Fullen WD. Prevention and treatment of gas gangrene. *JAMA* 1971;217: 806-13.
- 44 Hart GB, Lamb RC, Strauss MB. Gas gangrene. *J Trauma* 1983;23:991-1000.
- 45 McDonel JL. *Clostridium perfringens* toxins (type A, B, C, D, E). *Pharmacol Ther* 1980;10:617-55.
- 46 Rudge FW. The role of hyperbaric oxygenation in the treatment of clostridial myonecrosis. *Military Med* 1993;158:80-3.
- 47 Shupak A, Halpern P, Ziser A, et al. Hyperbaric oxygen therapy for gas gangrene casualties in the Lebanon War, 1982. *Isr J Med Sci* 1984;20: 323-6.
- 48 Kindwall EP. Uses of hyperbaric oxygen therapy in the 1990s. *Cleveland Clin J Med* 1992;59:517-28.
- 49 Kornbluth AA, Danzig JB, Bernstein LH. *Clostridium septicum* infection and associated malignancy. *Medicine* 1989;68:30-7.
- 50 Chambers CH, Bond GF, Morris JH. Synergistic necrotizing myositis complicating vascular injury. *J Trauma* 1974;14:980-4.
- 51 Swartz MN. Myositis. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*, 4th edn. New York: Churchill Livingstone, 1995; pp 929-36.
- 52 Jahnson L, Berggren L, Bjorsell-Ostling E, et al. Streptococcal myositis. *Scand J Infect Dis* 1992; 24:661-5.
- 53 Heckerling PS, Stine TM, Pottage JC Jr, et al. *Aeromonas hydrophila* myonecrosis and gas gangrene in a nonimmunocompromised host. *Arch Intern Med* 1983;143:2005-7.
- 54 Hennessy MJ, Ballon-Landa GR, Jones JW, et al. *Aeromonas hydrophila* gas gangrene: a case report of management with surgery and hyperbaric oxygenation. *Orthopedics* 1988;11:289-93.
- 55 MacLennan JD. The histotoxic clostridial infections of man. *Bacteriol Rev* 1962;26:177-274.
- 56 Swartz MN. Cellulitis and subcutaneous tissue infections. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*, 4th edn. New York: Churchill Livingstone, 1995; pp 909-29.
- 57 Finegold SM. *Anaerobic bacteria in human disease*. New York: Academic Press, 1977.