BMJ Best Practice

Gangrene

The right clinical information, right where it's needed

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Summary

- A complication of necrosis characterised by the decay of body tissues. Results from ischaemia, infection, or trauma (or a combination of these processes).
- Two main categories: infectious gangrene (which includes necrotising fasciitis and gas gangrene) and ischaemic gangrene (which can arise from arterial or venous obstruction).
- Risk factors include diabetes, smoking, atherosclerosis, renal disease, drug and alcohol abuse, malignancy, trauma or abdominal surgery, contaminated wounds, malnutrition, hypercoagulable states, and prolonged use of tourniquets.
- Successful treatment of infectious gangrene requires early recognition and a combination of aggressive surgical debridement, appropriate IV antibiotics, and intensive supportive care.
- Ischaemic gangrene requires revascularisation for obstruction and thromboembolism, along with optimal treatment of any underlying disease. Measures to prevent superimposed infection must also be performed.
- Prognosis is highly variable, but can involve significant morbidity and mortality.

BASICS

Definition

Gangrene is a complication of necrosis characterised by the decay of body tissues. There are 2 major categories: infectious gangrene (wet gangrene) and ischaemic gangrene (dry gangrene). The condition may result from ischaemia, infection, or trauma (or a combination of these processes). Ischaemia may result from either arterial or venous compromise, and may be an acute or chronic process (or a combination of both). Critically insufficient blood supply is the most common cause of gangrene, and is often associated with diabetes and long-term smoking.[1]

Epidemiology

Gangrene occurs equally in men and women. Type I necrotising fasciitis occurs most commonly in patients with diabetes and patients with peripheral vascular disease. It is the most common form of necrotising fasciitis in the general population.[5] Type II necrotising fasciitis has an annual incidence of 5 to 10 cases per 100,000 in the US. Approximately, half of the cases of streptococcal necrotising fasciitis occur in young and previously healthy people.[13]

The incidence of gas gangrene in the US is nearly 3000 cases annually. Severe penetrating trauma or crush injuries associated with interruption of the blood supply are the usual predisposing factors.[14] Spontaneous gas gangrene caused by *Clostridium septicum* may be more common than trauma-associated gangrene, caused by other *Clostridium* species.[15] Among drug abusers *C perfringens* , *C sordellii* , and *C novyi* are most commonly involved.[5]

Among patients with atherosclerosis, the annual incidence of atheroembolism that leads to ischaemic gangrene ranges from 0.3% to 3.5% overall, although after a vascular procedure it can rise to 30%.[16] Patients with antiphospholipid syndrome can develop distal gangrene in up to 9% of cases.[17] [18] In malignancy affected by paraneoplastic acral vascular syndrome, the most common skin finding is acute digital gangrene, which occurs in 60% of cases. Most patients with Raynaud's phenomenon are women aged between 20 and 40 years, in whom lesions develop during the cold months.[17]

Aetiology

Infectious gangrene

- Necrotising fasciitis: the most common bacteria isolated are group A beta-haemolytic *Streptococcus* species, *Staphylococcus* species, non-group A *Streptococcus* species, Enterobacteriaceae, and anaerobes such as *Clostridium* and *Bacteroides* species.
- Gas gangrene: *Clostridium perfringens* is the most common aetiological agent, with other organisms in this species (*C histolyticum* , *C novyi* , *C sordellii* , *C bifermentans* , *C sporogenes* , and *C septicum*) also being reported.[8] These organisms are spore-bearing, gram-positive, anaerobic bacilli ubiquitous in soil and dust. Non-clostridial organisms have also been isolated in cases of gas gangrene, including *Bacteroides fragilis,* *Escherichia coli* , *Proteus* species, *Pseudomonas aeruginosa* , and *Klebsiella pneumoniae* .[8] [19]

Ischaemic gangrene

- Atherosclerosis underlies most peripheral arterial disease, but diabetes-associated microangiopathy is another important factor. Thrombosis associated with hypercoagulable states, IV drug abuse,

vasculitis, malignancy, or antiphospholipid syndrome and other autoimmune diseases are also important causes.[17] Vasospasm associated with Raynaud's phenomenon and cocaine abuse can also give rise to ischaemic gangrene.[9]

- Inadequate blood supply and gangrene can also result from venous obstruction. Phlegmasia cerulea dolens is a rare condition, usually associated with malignancy, in which there is total or near-total obstruction of venous drainage from a limb.

Pathophysiology

Infectious gangrene

- Bacterial multiplication and production of exotoxins require low oxygen tension. The precise role of exotoxins is not entirely clear, although it appears that alpha-toxin is the most important. Alpha-toxin is a metalloenzyme that causes cell destruction by hydrolysis of components of the cell membrane. By this mechanism, it can cause lysis of erythrocytes, leukocytes, platelets, fibroblasts, and muscle cells. It is also thought that this enzyme has C-protein activity.
- M proteins have been seen as an important virulence determinant for group A streptococci (GAS). Vimentin on the surface of cells increases binding to GAS at the site of a skeletal injury.
- Infection starts with tissue contamination of post-traumatic or post-operative wounds by *Clostridium* spores. Local wound conditions are more important than the level of clostridial contamination in determining the progression of the condition. Necrotic tissue provides the necessary environment for spore germination; the presence of tissue enzymes and a low oxidation/reduction potential have key roles in this step. Spreading local necrosis of muscle and subcutaneous fat, and thrombosis of blood vessels, create an environment ideal for continued bacterial multiplication. Tissue oedema may further compromise blood supply. Fermentation of glucose is probably the main mechanism of gas production.[20]

Ischaemic gangrene

- Atherosclerosis underlies most peripheral arterial disease. Narrowed blood vessels cannot supply sufficient blood flow to leg muscles and may cause claudication. Atheromatous plaques contain a necrotic core within the arterial intima, consisting of foam cells, cellular debris, and lipids (mainly cholesterol), covered over by a protective cap. Shear forces of the circulating blood or spontaneous rupture can disrupt this protective cap, causing embolisation of the cholesterol crystals and inducing thrombogenesis, further reducing blood flow.[17] Critical tissue ischaemia is characterised clinically by rest pain, chronic wounds, or tissue necrosis (typically found on the toes).[9] Hypercoagulable states can give rise to large thrombi, which can occlude prominent blood vessels and cause extensive gangrene. Drugs such as cocaine (a powerful sympathomimetic) can cause severe vasospasm sufficient to produce gangrene.[11]
- Phlegmasia cerulea dolens is a rare condition, in which there is total or near-total obstruction of venous drainage from a limb. Pain, oedema, cyanosis, and ischaemia from reduced blood flow ensue, and unless the obstruction is relieved the condition can progress to a form of gangrene known as venous gangrene.

Classification

Infectious gangrene (wet gangrene)

Necrotising fasciitis: infection of subcutaneous fat and fascia with sparing of skin and underlying muscle[2]

- Type I (polymicrobial): caused by Enterobacteriaceae and anaerobes and accounts for 80% of necrotising fasciitis.[3] It occurs most frequently after surgical procedures, and in patients with diabetes, alcoholism, immunosuppression, IV drug use, or peripheral vascular disease.
    - Fournier's gangrene is a type I necrotising fasciitis of the perineal and genital region, resulting from synergistic polymicrobic infection. These are usually from facultative organisms like *Escherichia coli* , *Klebsiella* , or enterococci along with anaerobes like *Bacteroides* , *Fusobacterium* , *Clostridium* , or microaerophilic streptococci.[4]
    [Fig-1]
    - Necrotising fasciitis of the head and neck is usually caused by mouth anaerobes.
- Type II (streptococcal): rare form of gangrene caused by group A (or C or G) streptococci, which usually develops at a site of trauma on an extremity.[1] Accounts for 20% of necrotising fasciitis.[3]
    - Ludwig's angina: in the head and neck region, bacterial penetration into the submandibular and sublingual fascial compartments can result in a syndrome known as Ludwig's angina, which may develop into necrotising fasciitis.[5]

Gas gangrene (clostridial myonecrosis) and anaerobic cellulitis (wet necrosis or wet gangrene)

- A necrotising soft-tissue infection with the specific clinical sign of gas formation; it may lead to death. The pathogens most frequently responsible are *Clostridium* species.[6] [7] [8] It may occur post-traumatically, post-operatively, or spontaneously.
[Fig-2]

Progressive bacterial (Meleney's) synergistic gangrene

- This usually occurs after infection at an abdominal operative wound, around an ileostomy or colostomy site, at the exit of a fistulous tract, or in proximity to chronic ulceration on an extremity. It results from a synergistic interaction between *Staphylococcus aureus* and microaerophilic streptococci.

Gangrenous cellulitis in an immunosuppressed patient[1]

- The aetiological considerations for cellulitis occurring in an immunocompromised host include agents that produce such infections in healthy people, as well as a variety of other organisms.

Ischaemic gangrene (dry gangrene)

Occurs due to chronic impairment of blood flow. In most patients, the affected part is not infected. This type of gangrene presents clinically as tissue that is cold, black, and dry. In most cases, self-amputation eventually occurs.[9] The pathological processes involved may include:

- Atherosclerosis: associated with peripheral artery disease, diabetes mellitus, smoking[10]
- Thrombosis: associated with vasculitis, IV drug abuse, trauma, antiphospholipid syndrome, malignancy
[Fig-3]
- Vasospasm: associated with Raynaud's phenomenon, cocaine abusers.[11]

Although the vast majority of ischaemic gangrene arises from arterial compromise, rarely it may also occur due to venous obstruction. This rare condition is known as phlegmasia cerulea dolens and involves total or near-total obstruction of venous drainage from a limb. Pain, oedema, cyanosis, and ischaemia from reduced blood flow ensue, and unless the obstruction is relieved the condition can progress to a form of gangrene known as venous gangrene.

Primary prevention

Aggressive debridement of devitalised tissue and repair of compromised vascular supply greatly reduce the frequency of gas gangrene in contaminated deep wounds. Intramuscular adrenaline (epinephrine), prolonged application of tourniquets, and surgical closure of traumatic wounds should be avoided. Patients who have open fractures are at particular risk of gas gangrene if the wound is surgically closed. Patients who have contaminated wounds should receive prophylactic antibiotics.[5]

For patients who have evidence of an aggressive localised soft-tissue infection, prompt surgical exploration of that site is of extreme importance to determine whether a necrotising process is present. The same is true for patients who have milder local features associated with severe systemic toxicity.[5]

The main modifiable factors in the primary prevention of ischaemic gangrene are avoidance and cessation of smoking, control of lipids and cholesterol, tight glycaemic control in diabetics, control of hypertension, regular exercise and avoidance of obesity, regular medical check-up, and timely and appropriate interventions if ischaemia starts to develop.

Case history

Case history #1

A 60-year-old man with a history of diabetes, hypercholesterolaemia, and heavy smoking for over 20 years presents giving a 3-week history of increasing pain in his left forefoot, which is affecting his ability to walk and is disrupting his sleep. On examination, his left foot is pale, cold, devoid of hair, and his lateral 2 toes are dusky and discoloured. No foot pulses are palpable and are only just detectable by Doppler probe.

Case history #2

A 56-year-old man with history of poorly controlled diabetes mellitus and alcoholism presents with severe scrotal pain and fever for 3 days. He denies perianal tenderness. His vital signs are blood pressure 125/60 mmHg, heart rate 120 beats per minute, respiratory rate 25 breaths per minute, and temperature is 38.6°C (101.5°F). His scrotum is extremely tender, black, and malodorous. The adjacent perineal and femoral skin is crepitant.

Other presentations

In patients with conditions such as post-surgical infection, gunshot or knife wounds, or diabetes, the early signs and symptoms of infection may not be apparent or may be misinterpreted. For example, in patients with diabetes, pain may be reduced or absent due to neuropathy at the site of infection. In surgical patients, people with traumatic injuries, and postnatal patients, pain may be assumed to be part of the normal convalescence rather than due to acute infection. Delay in diagnosis may allow the disease to progress to later stages before treatment is initiated.[5] In immunocompromised patients, atypical organisms may be involved in the formation of gangrene. For instance, mucormycotic gangrenous cellulitis may occur in patients with diabetes mellitus or patients receiving immunosuppressive therapy. Spores of *Rhizopus* species may contaminate occlusive dressings. *Apophysomyces elegans* may infect patients with *Pseudomonas* bacteraemia or with thermal burns.[1] Patients with chronic renal disease have extensive calcification of the small arteries of subcutaneous tissue and marked elevation of calcium-phosphate product (calciphylaxis), which can contribute to the development of gangrene by reducing blood supply to the tissues.[12]

Step-by-step diagnostic approach

When gangrene is suspected, the most important decision is to differentiate ischaemic gangrene from infectious gangrene and to recognise deep necrotising infections that require urgent surgical intervention.

This usually requires:

- Identification of any risk factors
- A careful history and comprehensive physical examination
- Appropriate laboratory investigations
- Imaging and other studies, in selected cases.

Rapid progression, spread, or clinical deterioration indicates a need for surgical exploration. In ambiguous cases, biopsy or surgical exploration is necessary to determine if the fascia is involved, because observation of the deeper soft tissue is the only definitive method to make the diagnosis.[32]

Identification of risk factors

Risk factors for ischaemic gangrene include diabetes mellitus, atherosclerosis, smoking, prolonged application of tourniquets, hypercoagulable states, drug abuse, malignancy, and renal disease.

Risk factors for infectious gangrene include trauma or abdominal surgery, contaminated wounds, diabetes mellitus, alcoholism, renal disease, drug abuse, malignancy, and malnutrition.

Clinical evaluation

Findings suggestive of arterial ischaemic gangrene include: cold extremity, history of previous thrombosis, chronic course, trophic skin changes, pain (classically described as a burning pain in the ball of the foot and toes that is worse at night), purpura, oedema, ulcers, and livedo reticularis.[17] An ankle systolic pressure of 50 mmHg or less, or a toe systolic pressure of 30 mmHg or less, supports diagnosis of ischaemic gangrene; however, these parameters may be less reliable in patients with diabetes because arterial wall calcification can impair compression of vessels by a blood pressure cuff and produce systolic pressure measurements that are greater than true levels.[9] Another useful measure is the ankle-brachial index (ABI), which is the ratio of the systolic pressure at the dorsalis pedis or posterior tibial artery divided by the systolic pressure at the brachial artery. Patients with critical limb ischaemia usually have an ABI of 0.4 or less.[9]

Clinically, features that may help categorise the viability of an acutely ischaemic limb include:

- Viable: not immediately threatened; no sensory loss or muscle weakness; audible arterial and venous Doppler signals
- Threatened marginally: salvageable if promptly treated; no or minimal (toes) sensory loss; no muscle weakness; often inaudible arterial Doppler signals; audible venous Doppler signals.
- Threatened immediately: salvageable with immediate revascularisation; sensory loss of more than toes accompanied by rest pain; mild to moderate muscle weakness; usually inaudible arterial Doppler signals; audible venous Doppler signals.
- Irreversible/non-viable: major tissue loss and/or permanent nerve damage; profound anaesthesia; profound paralysis (rigor); inaudible arterial and venous Doppler signals.

Phlegmasia cerulea dolens, usually associated with malignancy, causes total or near-total obstruction of venous drainage from a limb. Pain, marked oedema of the limb, and cyanosis of the skin ensue over a variable time course. In approximately one half of cases, the cyanosis may be preceded by a white appearance of the skin, caused by subcutaneous oedema without venous congestion.

Findings suggestive of infectious gangrene include: low-grade fever and chills, purple or red bullous lesions, severe pain on palpation over contiguous but seemingly unaffected areas, indistinct margins, crepitus, loss of sensation distal to the affected area, and rapid progression of the infection.[6]

Necrotising cellulitis (NC) presents with thin dark wound drainage and gas formation in the skin with sparing of fascia and deep muscles. Onset is gradual with no pain, swelling, and systemic toxicity.[33] [34]

Necrotising fasciitis (NF) is a deep infection of the subcutaneous tissue that results in progressive destruction of fascia and fat. It is usually erythematous without sharp margins, swollen, warm, shiny, and

exquisitely tender with rapid progression over days with changes in skin colour and bullae formation. Frank cutaneous gangrene can be observed in 3 to 5 days with a prodrome of anaesthesia before the appearance of skin necrosis. This helps to distinguish from NC above.[33] [34]

Necrotising myositis (spontaneous gangrenous myositis) is an aggressive infection with fever, exquisite pain, and muscle swelling. Overlying skin can transition to erythema, warmth, petechiae, bullae, and vesicles with progression over several hours to involve contiguous muscle groups and soft tissue. Septic shock in the form of streptococcal toxic shock syndrome can occur. Timeline of progression aids in differentiation from NF.[33] [34]
[Fig-4]

[Fig-5]

Laboratory testing

For ischaemic and infectious gangrene, initial laboratory assessment includes FBC with peripheral blood smear, liver function tests, renal function tests, C-reactive protein, serum LDH, and baseline coagulation studies.

Findings that would be supportive of diagnosis of gangrene and may warrant further investigation include:

- C-reactive protein >143 nanomol/L (>15 mg/L)
- White blood cell count >15 x 10^9/L (>15,000 cells/microlitre); note that despite serious infection, WBC may not be raised
- Haemoglobin <135g/L (<13.5 g/dL); haemolytic anaemia is a common finding in gas gangrene
- Sodium <135 mmol/L (<135 mEq/L)
- Elevated LDH levels
- Lab results suggesting acute renal failure, hepatic failure, or metabolic acidosis.

Blood cultures are recommended if infectious gangrene is suspected.

The LRINEC scoring system is a useful tool to utilise the initial laboratory test to predict the risk of necrotising fasciitis.[3] [35] It has a 92% positive predictive value and 96% negative predictive value. Scores are given for levels of C-reactive protein, WBC count, haemoglobin, sodium, creatinine, and glucose. Any score of 6 or greater is suspicious for NF, and a score of 8 or greater is highly predictive of necrotising fasciitis.

If routine tests are unrevealing, further tests may help diagnose conditions that may contribute to produce ischaemia and gangrene: antinuclear antibodies (Sjogren's syndrome, SLE, discoid lupus), antiphospholipid antibodies (antiphospholipid syndrome), cold agglutinins (primary or secondary cold agglutinin disease), cryofibrinogens (essential cryofibrinogenaemia or in association with infections, rheumatological disorders, or cancer), and cryoglobulin (associated with lymphoproliferative, inflammatory or infective disease) may all be indicated in patients with suspected ischaemic gangrene causing blue or purple toes.[17]

Gram stain of infected tissue may demonstrate gram-positive bacilli. Small chains of gram-positive cocci suggest a streptococcal infection; clumps of large cocci suggest *Staphylococcus aureus* .[1] Blood and tissue cultures can provide definitive bacteriological diagnosis and indicate whether infection is polymicrobial or monomicrobial.

Imaging

If a patient has suspected gas gangrene, plain x-rays may demonstrate gas in the soft tissues and/or indicate underlying osteomyelitis. MRI or CT scanning may reveal abscess formation or evidence of enhancement, oedema, or thickening in the fascia. However, a lack of demonstrable gas in the soft tissue does not exclude diagnosis of a necrotising infection. CT can reveal smaller collections of gas in the tissues than plain x-rays and so may be preferable in this regard. CT scans can also more readily demonstrate fluid collections. MRI, while offering greater soft-tissue details than CT, is generally less readily available and can also present logistical problems in patients who are often quite severely ill.

In a patient with suspected ischaemic gangrene a number of imaging techniques may be indicated, depending on the exact clinical situation:

- Duplex ultrasound can be useful to demonstrate location and severity of arterial narrowing or obstruction and can also detect venous thromboembolism.[17] It is the most widely used modality to assess location and degree of stenosis in peripheral vascular disease as well as patency of bypass grafts. The sensitivity and specificity of 50% or greater stenosis from the iliac artery to popliteal artery are 90% and 95%, respectively.
- Conventional angiography is frequently used to identify the site and extent of arterial or venous obstruction. Accuracy and interpretation is enhanced by using techniques such as digital subtraction techniques, which eliminate bony and dense body tissue artifacts. However, it is an invasive procedure requiring contrast.
- If available, CT angiography or magnetic resonance angiography (MRA) may be used to look for the presence of atheroemboli. CT angiography is increasingly used, but it still requires IV contrast, although there is less radiation than with traditional angiography. It can also reconstruct the images into 3D images. The new 64-slice CT images can have sensitivity from 89% to 100% and specificity from 92% to 100% for >50% stenosis. However, its spatial resolution is lower than digital subtraction angiography and venous opacification can obscure arterial filling. Less widely available, the sensitivity and specificity of MRA to detect a stenosis greater than 50% can be as high as 90% to 100% with the greatest accuracy when gadolinium is used. However, it does have several limitations. MRA tends to overestimate stenosis and occlusions; metal clips can mimic occlusions thus limiting its use in post-surgical patients. Also, patients with pacemakers, defibrillators, and some cerebral aneurysm clips cannot be scanned safely, and gadolinium has caused nephrogenic systemic fibrosis (NSF) in patients with chronic renal insufficiency.
- CT scans of the chest and abdomen are indicated in patients where it is suspected that there may be an occult malignancy causing a paraneoplastic thromboembolism syndrome as a cause of ischaemia.
- Echocardiography is indicated in cases where features of the history and clinical examination (e.g., hx of valvular disease, presence of cardiac murmurs) suggest possible suspected infective endocarditis, myxoma, and non-bacterial thrombotic endocarditis.

Risk factors

Strong

diabetes mellitus

- A particularly important risk factor because it is frequently associated with both ischaemic and infectious gangrene.[9]

[Fig-2]

Infectious gangrene subtypes in patients with diabetes include non-clostridial anaerobic cellulitis, synergistic necrotising cellulitis, and type I necrotising fasciitis. High blood glucose levels, inefficient immunological responses, peripheral neuropathy, and peripheral arterial disease are the most important features of diabetes that contribute to limb-threatening diabetic foot infections.[21] PAD in patients with diabetes tends to involve smaller arteries and affects younger age group compared with non-diabetics.[22] The Framingham study showed that more than 50% of patients with diabetes have absent pedal pulses.[23] Nearly 70% of patients with necrotising fasciitis have diabetes.[5]

atherosclerosis (ischaemic gangrene)

- Atheromatous plaques contain a necrotic core within the arterial intima, consisting of foam cells, cellular debris, and lipids, covered by fibrous cap of endothelial cells. Spontaneous plaque rupture or shear forces of the circulating blood can disrupt this plaque, causing an atheroembolism that leads to tissue ischaemia and necrosis.[17]

smoking (ischaemic gangrene)

- Tobacco smoking is directly related to vascular damage, contributing to chronic limb ischaemia. The presence of endothelial dysfunction is an early marker of vascular injury, predisposing to the development of atherosclerotic lesions.[24] Some studies have found a direct causal association between tobacco use and foot ulceration or amputation in patients with diabetes. A case-control study of people with diabetes in the UK found a lower risk of leg amputation in those of South Asian origin compared with those of European ancestry, which was partly attributed to lower rates of smoking.[25]

renal disease

- Gangrene is a common complication in patients with end-stage renal disease, including kidney transplant recipients and those undergoing chronic peritoneal dialysis or haemodialysis. Patients often have evidence of secondary or tertiary hyperparathyroidism with an elevated serum calcium-phosphate product. Calciphylaxis may be unilateral or bilateral, and lesions may occur on the extremities, trunk, and buttocks. Lesions on the distal lower extremities may begin as livedo reticularis or acral cyanosis, but typically progress rapidly to ulceration and gangrene. Extreme cutaneous pain is common.[12] [17]

drug and alcohol abuse

- Cocaine causes intense vasoconstriction and also enhances platelet aggregation, placing users at risk of ischaemic gangrene.[11] Severe soft-tissue infections caused by *Clostridium perfringens* , *C sordellii* , and *C novyi* have been described among intradermal ('skin popping') and IV drug users.[26] [27] Anaerobic infections occur at a much higher rate in drug users who inject. Accidental intra-arterial injection can cause arterial obstruction, leading to distal gangrene and amputation of fingers, toes, or even whole limbs.[28] These patients also often have impaired immunological response, due to habitual massive alcohol consumption and profound liver dysfunction.[29]

malignancy

- A risk factor for both infective and ischaemic gangrene. Colorectal carcinoma is a common factor in spontaneous gas gangrene caused by *Clostridium septicum* infection, which may progress to septicaemia.[15] [30] Haematological malignancy and neutropenia are also associated with increased risk of infective gangrene.[1] [20]

- Malignancy is also a risk factor for ischaemic gangrene. Its association with Raynaud's phenomenon, acrocyanosis, and gangrene is called paraneoplastic acral vascular syndrome. About 60% of reported underlying malignancies are carcinomas of various histologies, most commonly adenocarcinomas (lung, ovaries, and stomach), and 20% are haematological malignancies.[17] The abnormalities in the skin appear simultaneously with cancer detection in about 50% of patients, precede the diagnosis in about 45%, and develop after the discovery of malignancy in about 5% of patients.[17] The most common skin finding is acute digital gangrene (in about 60% of cases), with the fingers being the affected site in 95% of patients.[17]

trauma or abdominal surgery (infectious gangrene)

- Factors related to traumatic gas and infectious gangrene are bowel and biliary tract surgery, intramuscular injection of adrenaline (epinephrine), surgical closure of traumatic wounds, illegal or missed abortion, retained placenta, prolonged rupture of the membranes, and intrauterine fetal demise.

contaminated wounds (infectious gangrene)

- Can predispose to the development of infectious gangrene.

Weak

malnutrition (infectious gangrene)

- Contributes to immunosuppression, and so is a risk factor for infectious gangrene, such as Fournier's gangrene.[31]
[Fig-1]

hypercoagulable states (ischaemic gangrene)

- Can give rise to large thrombi, which can occlude prominent blood vessels and cause extensive ischaemic gangrene.[11]
[Fig-3]

prolonged application of tourniquets (ischaemic gangrene)

- Can predispose to the development of ischaemic gangrene.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Major risk factors include: diabetes mellitus, atherosclerosis, smoking, hypercoagulable states, drug abuse, malignancy, renal disease, trauma or abdominal surgery, alcoholism, and malnutrition.

pain (common)

- Pain is often a feature of gangrene, although its absence does not exclude the diagnosis. There may be a history of chronic claudication-type pain in patients with ischaemic gangrene. By contrast, a sudden onset of pain is usually the first symptom of infectious gangrene. In addition, 50% of patients report a feeling of heaviness in the affected extremity.[36]

oedema (ischaemic gangrene) (common)

- The affected region may become markedly oedematous, with overlying erythema.[36]

skin discoloration (uncommon)

- Ecchymoses, purpura, skin blebs, and haemorrhagic bullae may develop in gangrene.[36] [Fig-4]

[Fig-5]
- A black necrotic eschar may be evident at the borders of the affected areas. [Fig-6]

[Fig-2]

crepitus (gas gangrene) (uncommon)

- With gas gangrene, gentle palpation may demonstrate crepitus. It is found only in 14% of patients at presentation, but if present, some series have reported 99% specificity for gas gangrene.[36]

Other diagnostic factors

diminished pedal pulses and ankle-brachial index (ischaemic gangrene) (common)

- Suggests chronic arterial insufficiency. Erroneous ankle-brachial index readings can occur if there is calcification of arteries.

low-grade fever and chills (infectious gangrene) (uncommon)

- These may be early signs of infectious gangrene.

Diagnostic tests

1st test to order

Test	Result
FBC • On admission, a WBC count >15.4 x 10^9/L (>15,400/microL) is present in 90% of the patients with necrotising soft-tissue infections.[36] • Haemoglobin is usually <135 g/L (<13.5 g/dL).[5]	**leukocytosis, haemoconcentration, or anaemia**
comprehensive metabolic panel • Sodium <135 mmol/L (<135 mEq/mL) is present in nearly 100% of the patients with gangrene on admission.[36]	**may indicate metabolic acidosis, liver derangement, renal failure**
serum LDH • Rapidly developing haemolytic anaemia with an increased lactate dehydrogenase level is common in patients with gas gangrene.[17] [32] • Haemolytic anaemia may also be part of the presentation of underlying conditions such as cold agglutinin disease.	**elevated if haemolytic anaemia**

Test	Result
coagulation panel • Perform as baseline.	**normal**
blood cultures • Recommended if infectious gangrene is suspected.	**positive for infective organism**
serum C-reactive protein • C-reactive protein >143 nanomol/L (>15 mg/L) is highly suggestive of necrotising soft-tissue infections in an appropriate clinical scenario.	**elevated**
plain x-rays • Specificity of 95% for gas gangrene, but present in only 10% to 15% of the patients with the condition on admission.[36]	**may demonstrate gas in the soft tissues and/or indicate underlying osteomyelitis**
CT of affected site • CT scanning is helpful, especially in abdominal cases of gas gangrene.[5] The absence of abnormal findings in the fascia makes necrotising fasciitis less likely; its presence, however, may also occur with simple cellulitis.[32]	**may reveal abscess formation or evidence of enhancement, oedema, or thickening in the fascia**
MRI of affected site • A lack of demonstrable gas in the soft tissue does not exclude diagnosis of a necrotising infection.	**may reveal abscess formation or evidence of enhancement, oedema, or thickening in the fascia**
Doppler ultrasonography • A change in the Doppler waveform from triphasic to biphasic to monophasic and then stenotic waveforms can identify sites of arterial blockage.[9]	**may indicate presence and severity of arterial or venous obstruction**

Other tests to consider

Test	Result
surgical exploration and skin biopsy • Observation of the deeper soft tissue is the only definitive method to make the diagnosis.[32] It may be useful to culture the tissue.[17]	**may determine involvement of the fascia**
CT angiography • If available, CT angiography may be used to look for presence of atheroemboli. CT angiography is increasingly used, but it still requires IV contrast, although there is less radiation than with traditional angiography. It can also reconstruct the images into 3D images. The new 64-slice CT images can have sensitivity from 89% to 100% and specificity from 92% to 100% for a greater than 50% stenosis. However, its spatial resolution is lower than digital subtraction angiography and venous opacification can obscure arterial filling.	**may show source of atheromatous emboli or specific sites of obstruction**

Test	Result
magnetic resonance angiography (MRA) • Less widely available, the sensitivity and specificity of MRA to detect a stenosis greater than 50% can be as high as 90% to 100% with the greatest accuracy when gadolinium is used. However, it does have several limitations: MRA tends to overestimate stenosis and occlusions; metal clips can mimic occlusions thus limiting its use in post-surgical patients. Also, patients with pacemakers, defibrillators, and some cerebral aneurysm clips cannot be scanned safely, and gadolinium has caused nephrogenic systemic fibrosis (NSF) in patients with chronic renal insufficiency.	**may show source of atheromatous emboli or specific sites of obstruction**
CT chest and abdomen • May be useful in detecting a suspected malignancy.[36]	**useful in detecting suspected malignancy**
ANA, lupus anticoagulant, anticardiolipin, and anti beta2 glycoprotein-1 antibodies • May be indicated in a patient with suspected ischaemic gangrene.	**elevated if antiphospholipid syndrome**
serum cold agglutinins • May be indicated in a patient with suspected ischaemic gangrene.	**elevated if cold agglutinin disease**
serum cryofibrinogens • May be indicated in a patient with suspected ischaemic gangrene.	**elevated in cases of cryofibrinogenaemia**
plasma cryoglobulin • May be indicated in a patient with suspected ischaemic gangrene.	**positive if cryoglobulinaemia**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Staphylococcal skin lesions	• Distinct pustules, subcutaneous abscesses, purulent purpura often present in this condition.[1]	• Blood culture: positive for staphylococcal infection. • Aspiration and microscopy: reveals staphylococci and polymorphonuclear leukocytes.[1]
Erysipelas	• History of recent pharyngitis. Infants and older people are usually affected. Pruritus and burning are present before the dermatosis.[1] Sharply delineated, painful lesion with a bright red, oedematous, indurated (peau d'orange) appearance. Bullae only in 5% of cases.	• Antistreptococcal antibodies may be detectable.

Condition	Differentiating signs / symptoms	Differentiating tests
Cellulitis	• Absence of purple or red bullous lesions, absence of crepitus, intact sensation distal to the affected area, and comparatively slow spread. Systemic toxicity (e.g., renal failure, hypotension, and acidosis) usually absent with cellulitis.	• Serous discharge may be expressed on compression of the wound margins, and streptococci can be identified on a Gram-stained smear.[1] • Imaging studies (radiography, CT, and MRI): absence of the gas, fascial enhancement, and soft-tissue oedema characteristic of gangrene.
Insect bites	• History of insect or spider bite, or suitable clinical scenario. The bite of the brown recluse spider (*Loxosceles reclusa*) can produce a necrotising skin lesion that resembles infectious gangrenous cellulitis. Fever is not commonly present, but the occurrence of fever and chills 24 to 48 hours after the bite enhances the mimicry.[1]	• Clinical diagnosis.

Step-by-step treatment approach

Successful treatment of infectious gangrene requires a combination of surgical debridement, appropriate antibiotics, and intensive supportive care.[14] [20] [37]

Ischaemic gangrene requires revascularisation for obstruction and thromboembolism, along with treatment of any underlying disease. Measures to prevent superimposed infection must also be performed.

Limb amputation

In cases of severe limb sepsis, amputation is mandated: this is a two-stage procedure starting with guillotine amputation and later, when the infection has cleared, a definitive amputation and wound closure is advisable.[38]

Patients with non-viable extremities (i.e., large amounts of established necrosis, profound anaesthesia, profound paralysis, and inaudible pulse on Doppler), should undergo prompt amputation. The level of amputation is determined by clinical findings and by the viability of tissues at the time of surgery. Every effort should be made to preserve as many joints as possible, in order to decrease the work of ambulating with a prosthesis and to improve the chances for successful rehabilitation.[39]

Necrotising fasciitis

Type I (polymicrobial)

- Type I infections are mixed infections with anaerobes. Organisms can include, for example, *Bacteroides* or *Peptostreptococcus* with a facultative anaerobe such as the Enterobacteriaceae *Escherichia coli* , *Enterobacter* , *Klebsiella* , or *Proteus* ; or non-group A streptococci. It occurs most frequently after surgical procedures, and in patients with diabetes, alcoholism, immunosuppression, IV drug use, or peripheral vascular disease. Fournier's gangrene is a type I necrotising fasciitis of the perineal and genital region, resulting from synergistic polymicrobic infection.[4]
  [Fig-1]
- Surgical care: wide excision of all necrotic tissue, placement of drains, and appropriate surgical debridement are necessary for both diagnosis and treatment.[37] Following surgical debridement, many surgeons use local irrigation with bacitracin-infused normal saline. Amputation may be required.
- Antibiotic therapy: for empiric treatment of type I mixed infections, the Infectious Diseases Society of America (IDSA) recommends agents effective against both aerobes (including MRSA) and anaerobes.[14] Options include vancomycin or linezolid combined with either: piperacillin/tazobactam; a carbapenem; ceftriaxone plus metronidazole; or a fluoroquinolone plus metronidazole. For patients allergic to penicillin, clindamycin or metronidazole with an aminoglycoside or fluoroquinolone may be used. When further information is available and aetiological agent has been determined, antibiotic therapy should be amended to target the specific agent. As there are currently no definitive clinical trials, the IDSA recommends continuing antibiotics until no further surgical debridement is needed, the patient has improved clinically, and fever has been absent for 48 to 72 hours.[14]

Type II (streptococcal)

- Type II disease is a rare form of gangrene, caused by group A (or C or G) streptococci, that usually develops at a site of trauma on an extremity.[1]
- Surgical care: immediate surgical exploration is required using longitudinal incisions through the deep fascia and extending beyond the involved gangrenous and undermined areas. Areas of cutaneous necrosis are excised, and non-viable fascia is debrided. Re-exploration is commonly performed within 24 hours.[20] [37] Amputation may be required.
- Antibiotic therapy: in addition to urgent surgical debridement, penicillin plus clindamycin should be administered to treat group A streptococci and inhibit their ability to synthesise toxins.[14] Clindamycin is used as it has been shown to be superior to penicillin for treatment of experimentally induced necrotising fasciitis or myonecrosis caused by group A streptococci because:[20]
    - It reduces the in vitro release of streptococcal pyrogenic exotoxin A
    - It is not affected by inoculum size or stage of growth
    - It facilitates phagocytosis of *Streptococcus pyogenes* by inhibiting M-protein synthesis
    - It suppresses the production of regulatory elements that control cell wall synthesis
    - It has a long post-antibiotic effect.
- If there is any question regarding the aetiological agent (e.g., possibly *Staphylococcus aureus* rather than a group A *Streptococcus*), nafcillin should be used.[1]
- For patients with penicillin allergy, vancomycin, daptomycin, or linezolid (if co-existent vancomycin allergy) as a monotherapy can be substituted in place of the penicillin-clindamycin or nafcillin-clindamycin combination.[14]
- The addition of IV immunoglobulin (IVIG) should also be considered for treatment of streptococcal toxic shock syndrome, although data on efficacy are conflicting.[14]

Gas gangrene

Treatment of gas gangrene requires a combination of surgical debridement and antibiotic therapy. Hyperbaric oxygen (HBO) therapy is no longer recommended as it has no proven advantage to the patient and may delay resuscitation and treatment.[14]

- Surgical care: aggressive and thorough surgical debridement is mandatory to improve survival, preserve limbs, and prevent complications.[1] [6] [20] In patients with extremity involvement, fasciotomy may be necessary to treat compartment syndrome, and it should be done immediately after the diagnosis is made. Daily debridement is necessary, and it is extremely important to remove all necrotic and infected tissue. It is also important to consider amputation of the extremity when necessary, as this could be life-saving.
- Antibiotic therapy: currently, a combination of penicillin and clindamycin is widely used.[14] Some studies have shown that protein synthesis inhibitors (e.g., clindamycin, chloramphenicol, rifampicin, tetracycline) may be more effective than penicillin because they inhibit the synthesis of clostridial exotoxins and lessen the local and systemic toxic effects of these proteins.[40] For patients allergic to penicillin, a combination of clindamycin and metronidazole is a good choice.

Ischaemic gangrene

For acute limb ischaemia, unless contraindicated, all patients should immediately receive an IV heparin bolus, followed by a continuous heparin infusion.[41] [42] After the initiation of heparin, treatment then varies depending on the viability of the limb. The following features can help categorise the viability of an acutely ischaemic limb:

- Viable: not immediately threatened; no sensory loss or muscle weakness; audible arterial and venous Doppler signals.
- Threatened marginally: salvageable if promptly treated; no or minimal (toes) sensory loss; no muscle weakness; often inaudible arterial Doppler signals; audible venous Doppler signals.
- Threatened immediately: salvageable with immediate revascularisation; sensory loss of more than toes accompanied by rest pain; mild to moderate muscle weakness; usually inaudible arterial Doppler signals; audible venous Doppler signals.
- Irreversible/non-viable: major tissue loss and/or permanent nerve damage; profound anaesthesia; profound paralysis (rigor); inaudible arterial and venous Doppler signals.

Treatment options include surgery, percutaneous transluminal angioplasty (PTA), and thrombolytic therapy.

Surgery

- Patients with a threatened but viable extremity (i.e., demonstrating rest pain, sensory loss, or mild muscle weakness, but without substantial areas of necrosis) should undergo urgent surgical revascularisation after heparin anticoagulation. The majority of these patients will have had an embolic event, and irreversible changes can occur within as little as 4 to 6 hours of profound ischaemia. While pharmacological thrombolysis may successfully dissolve an embolus, the time required is usually too long to allow this to be an acceptable alternative to surgery.[42]
- In 2010, the bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial result was published based on first treatment received analysis.[43] The outcomes measured were amputation-free survival (AFS) and overall survival (OS). It also compared vein with prosthetic bypass surgery, and transluminal with subintimal balloon angioplasty, and examined outcomes from bypass surgery after failed balloon angioplasty. The author concluded that balloon angioplasty was associated with a significantly higher early failure rate than bypass surgery. Most balloon angioplasty patients ultimately required surgery. Furthermore, bypass surgery outcomes after failed balloon angioplasty are significantly worse than for bypass surgery performed as a first revascularisation attempt. Bypass surgery with vein offers the best long term AFS and OS and, overall, balloon angioplasty appears superior to prosthetic bypass surgery.

Percutaneous transluminal angioplasty (PTA)

- In the BASIL trial, 450 patients with severe limb ischaemia due to infra-inguinal disease were randomly assigned to PTA or bypass surgery.[44] At 30 days, there was no difference in mortality between the groups, but surgery was associated with a significantly higher rate of morbidity (57% versus 41%). On intention-to-treat analysis, there was no difference in the primary end point (survival without amputation) at 1 year and 3 years, and surgery was associated with a significantly lower rate of reintervention (18% versus 26%). Based on these findings, the authors recommend that PTA should be offered first to patients with significant comorbidities who are not expected to live more than 2 years. For patients expected to live longer than 2 years, the benefits of bypass surgery could outweigh the short-term increase in morbidity.

Thrombolytic therapy

- In highly selected patients, catheter-based intra-arterial thrombolytic therapy may be an alternative to surgery or percutaneous intervention in the management of critical limb ischaemia. The main indication is acute limb ischaemia of less than 14 days' duration in patients with a viable extremity.[39]

- Phlegmasia cerulea dolens, a rare condition in which there is total or near-total obstruction of venous drainage from a limb, may be treated by IV thrombolytic therapy to help prevent the onset and progression of venous gangrene.[45]

Intensive supportive care

In patients with infective types of gangrene, intractable hypotension and diffuse capillary leak are frequent, and massive amounts of IV fluids (10-20 L per day) are often required. In some patients, blood pressure improves with IV fluid alone. Pressors, such as dopamine, may be useful, but there is little information from controlled clinical or experimental studies in this specific condition. Although potent vasoconstrictors such as adrenaline (epinephrine) may improve blood pressure, symmetric gangrene may ensue, partly as a result of the drug and partly as a result of poor perfusion caused by the bacteria, toxins, and endogenous mediators.[14] [20]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Presumptive (summary)

Patient group	Tx line	Treatment
necrotising fasciitis awaiting confirmation of microbial culture and sensitivity results	**1st**	**surgical debridement + intensive supportive care**
	plus	**empiric broad-spectrum antibiotics**

Acute (summary)

Patient group	Tx line	Treatment
confirmed type I necrotising fasciitis (polymicrobial)	**1st**	**intensive supportive care + surgical debridement ± amputation**
	plus	**local irrigation with bacitracin-infused normal saline**
	plus	**broad-spectrum intravenous antibiotics**
confirmed type II necrotising fasciitis (streptococcal)	**1st**	**intensive supportive care + surgical debridement ± amputation**
	plus	**intravenous antibiotics**
streptococcal toxic shock	**adjunct**	**intravenous immunoglobulin (IVIG)**

Acute (summary)

gas gangrene	**1st**	**intensive supportive care+ surgical debridement ± amputation**
	plus	**intravenous antibiotics**
	adjunct	**hyperbaric oxygen therapy**
ischaemic gangrene	**1st**	**intravenous heparin**
with threatened or non-viable extremity: life expectancy >2 years	**plus**	**surgical revascularisation ± amputation**
with threatened or non-viable extremity: life expectancy ≤2 years	**plus**	**percutaneous transluminal angioplasty (PTA) ± amputation**
with viable extremity	**plus**	**thrombolytic therapy**
with phlegmasia cerulea dolens	**plus**	**thrombolytic therapy**

Treatment options

Presumptive

Patient group	Tx line	Treatment
necrotising fasciitis awaiting confirmation of microbial culture and sensitivity results	**1st**	**surgical debridement + intensive supportive care** » Surgical incisions should extend beyond the areas of visible necrosis and the entire necrotic area excised. Further surgical evaluation and debridement as necessary is essential and several procedures may be required.[14] Intensive haemodynamic support with IV infusion is an important aspect of surgical management.
	plus	**empiric broad-spectrum antibiotics** » For empiric treatment of type I mixed infections, the Infectious Diseases Society of America (IDSA) recommends agents effective against both aerobes (including MRSA) and anaerobes.[14] Options include vancomycin or linezolid combined with either: piperacillin/tazobactam; a carbapenem; ceftriaxone plus metronidazole; or a fluoroquinolone plus metronidazole. Penicillin plus clindamycin is recommended for treatment of suspected (or confirmed) group A streptococcal necrotising fasciitis. » For patients allergic to penicillin, clindamycin or metronidazole with an aminoglycoside or fluoroquinolone may be used. » When further information is available and aetiological agent has been determined, antibiotic therapy should be amended to target the specific agent. » As there are currently no definitive clinical trials, the IDSA recommends continuing antibiotics until no further surgical debridement is needed, the patient has improved clinically, and fever has been absent for 48 to 72 hours.[14]

Primary options

» vancomycin: 30 mg/kg/day intravenously given in divided doses every 12 hours
-or-
» linezolid: 600 mg intravenously every 12 hours

--AND--

TREATMENT

Presumptive

Patient group	Tx line	Treatment
		» piperacillin/tazobactam: 3.375 g intravenously every 6 hours Dose consists of 3 g piperacillin plus 0.375 g tazobactam. **-or-** » imipenem/cilastatin: 1 g intravenously every 6-8 hours **-or-** » meropenem: 1 g intravenously every 8 hours **-or-** » ertapenem: 1 g intravenously every 24 hours
		OR
		Primary options
		» vancomycin: 30 mg/kg/day intravenously given in divided doses every 12 hours **-or-** » linezolid: 600 mg intravenously every 12 hours
		--AND--
		» ceftriaxone: 1-2 g intravenously every 12-24 hours **-or-** » ciprofloxacin: 400 mg intravenously every 12 hours
		--AND--
		» metronidazole: 30 mg/kg/day intravenously given in divided doses every 6 hours
		OR
		Primary options
		» benzylpenicillin: 2.4 to 4.8 g/day intravenously given in divided doses every 4-6 hours **-and-** » clindamycin: 600-900 mg intravenously every 8 hours
		OR
		Secondary options
		» clindamycin: 600-900 mg intravenously every 8 hours **-or-** » metronidazole: 30 mg/kg/day intravenously given in divided doses every 6 hours
		--AND--

Presumptive

Patient group	Tx line	Treatment
		» gentamicin: 3-5 mg/kg/day intravenously given in divided doses every 8 hours **-or-** » ciprofloxacin: 400 mg intravenously every 12 hours

Acute

Patient group	Tx line	Treatment
confirmed type I necrotising fasciitis (polymicrobial)	**1st**	**intensive supportive care + surgical debridement ± amputation** » Necrotising fasciitis is a surgical emergency, and the patient should be urgently taken to the operating room for debridement of all infected devitalised tissues. Amputation may be required. » Wide excision of all necrotic tissue, placement of drains, and appropriate surgical debridement are necessary for both diagnosis and treatment.[37] Further surgical evaluation and debridement as necessary is essential, and several procedures may be required.[14] » Intensive haemodynamic support with IV infusion is an important aspect of surgical management.
	plus	**local irrigation with bacitracin-infused normal saline** » Following surgical debridement, many surgeons use local irrigation with bacitracin-infused normal saline.
	plus	**broad-spectrum intravenous antibiotics** » For empiric treatment of type I mixed infections, the Infectious Diseases Society of America (IDSA) recommends agents effective against both aerobes (including MRSA) and anaerobes.[14] Options include vancomycin or linezolid combined with either: piperacillin/tazobactam; a carbapenem; ceftriaxone plus metronidazole; or a fluoroquinolone plus metronidazole. » For patients allergic to penicillin, clindamycin or metronidazole with an aminoglycoside or fluoroquinolone may be used.

Acute

Patient group	Tx line	Treatment

» When further information is available and aetiological agent has been determined, antibiotic therapy should be amended to target the specific agent.

» As there are currently no definitive clinical trials, the IDSA recommends continuing antibiotics until no further surgical debridement is needed, the patient has improved clinically, and fever has been absent for 48 to 72 hours.[14]

Primary options

» vancomycin: 30 mg/kg/day intravenously given in divided doses every 12 hours
-or-
» linezolid: 600 mg intravenously every 12 hours
--AND--
» piperacillin/tazobactam: 3.375 g intravenously every 6 hours
Dose consists of 3 g piperacillin plus 0.375 g tazobactam.
-or-
» imipenem/cilastatin: 1 g intravenously every 6-8 hours
-or-
» meropenem: 1 g intravenously every 8 hours
-or-
» ertapenem: 1 g intravenously every 24 hours

OR

Primary options

» vancomycin: 30 mg/kg/day intravenously given in divided doses every 12 hours
-or-
» linezolid: 600 mg intravenously every 12 hours
--AND--
» ceftriaxone: 1-2 g intravenously every 12-24 hours
-or-
» ciprofloxacin: 400 mg intravenously every 12 hours
--AND--
» metronidazole: 30 mg/kg/day intravenously given in divided doses every 6 hours

OR

Acute

Patient group	Tx line	Treatment
		Secondary options » clindamycin: 600-900 mg intravenously every 8 hours **-or-** » metronidazole: 30 mg/kg/day intravenously given in divided doses every 6 hours **--AND--** » gentamicin: 3-5 mg/kg/day intravenously given in divided doses every 8 hours **-or-** » ciprofloxacin: 400 mg intravenously every 12 hours
confirmed type II necrotising fasciitis (streptococcal)	**1st**	**intensive supportive care + surgical debridement ± amputation** » Necrotising fasciitis is a surgical emergency, and the patient should be urgently taken to the operating room for debridement of all infected devitalised tissues. » Wide excision of all necrotic tissue, placement of drains, and appropriate surgical debridement are necessary for both diagnosis and treatment.[37] Further surgical evaluation and debridement as necessary is essential, and several procedures may be required.[14] » Intensive haemodynamic support with IV infusion is an important aspect of surgical management.
	plus	**intravenous antibiotics** » Type II infections are caused by Group A *Streptococcus* (i.e., *Streptococcus pyogenes*). In addition to urgent surgical debridement, penicillin plus clindamycin should be administered to treat group A streptococci and inhibit their ability to synthesise toxins.[14] » Clindamycin has been shown to be superior to penicillin for treatment of experimentally induced necrotising fasciitis or myonecrosis caused by group A streptococci.[20] It has been shown to reduce the in vitro release of streptococcal pyrogenic exotoxin A; is not affected by inoculum size or stage of growth; facilitates phagocytosis of *Streptococcus pyogenes* by inhibiting M-protein synthesis; suppresses the production of regulatory elements that control cell wall synthesis; and it has a long post-antibiotic effect.[20]

Acute

Patient group	Tx line	Treatment
		» If there is any question regarding the aetiological agent (e.g., possibly *Staphylococcus aureus* rather than a group A *Streptococcus*), nafcillin should be used in place of penicillin.[1] » For patients with penicillin allergy, vancomycin, daptomycin, or linezolid (if co-existent vancomycin allergy) as a monotherapy should be substituted in place of the penicillin-clindamycin or nafcillin-clindamycin combination.[14] **Primary options** » benzylpenicillin: 2.4 to 4.8 g/day intravenously given in divided doses every 4-6 hours **-and-** » clindamycin: 600-900 mg intravenously every 8 hours **OR** **Secondary options** » nafcillin: 1.5 to 2 g intravenously every 4-6 hours **-and-** » clindamycin: 600-900 mg intravenously every 8 hours **OR** **Secondary options** » vancomycin: 30 mg/kg/day intravenously given in divided doses every 12 hours **OR** **Secondary options** » daptomycin: 4 mg/kg intravenously once daily **OR** **Secondary options** » linezolid: 600 mg intravenously every 12 hours
streptococcal toxic shock	**adjunct**	**intravenous immunoglobulin (IVIG)** » The addition of IVIG should also be considered for treatment of streptococcal toxic shock syndrome, although data on efficacy are conflicting.[14]

Acute

Patient group	Tx line	Treatment
		Primary options » immunoglobulin (human): 1 g/kg intravenously on day 1, followed by 0.5 g/kg on days 2 and 3; or 2 g/kg intravenously as a single dose Dose regimens vary; consult specialist for further guidance on dose.
gas gangrene	**1st**	**intensive supportive care+ surgical debridement ± amputation** » Aggressive and thorough surgical debridement is mandatory to improve survival, preserve limbs, and prevent complications.[1] [6] [20] In patients with extremity involvement, fasciotomy could be necessary to treat compartment syndrome, and it should be done immediately after the diagnosis is made. Daily debridement is necessary, and it is extremely important to remove all necrotic and infected tissue. It is also extremely important to consider amputation of the extremity when necessary, as this could be life-saving. » Intensive haemodynamic support with IV infusion is also an important aspect of surgical management.
	plus	**intravenous antibiotics** » Currently, a combination of penicillin and clindamycin is widely used.[14] Protein synthesis inhibitors (e.g., clindamycin, chloramphenicol, rifampicin, tetracycline) are effective because they inhibit the synthesis of clostridial exotoxins and lessen the local and systemic toxic effects of these proteins.[40] » For patients allergic to penicillin, a combination of clindamycin and metronidazole is a good choice. **Primary options** » benzylpenicillin: 2.4 to 4.8 g/day intravenously given in divided doses every 4-6 hours **-and-** » clindamycin: 600-900 mg intravenously every 8 hours **OR** **Secondary options**

Acute

Patient group	Tx line	Treatment
		» clindamycin: 600-900 mg intravenously every 8 hours **-and-** » metronidazole: 30 mg/kg/day intravenously given in divided doses every 6 hours
	adjunct	**hyperbaric oxygen therapy** » Some retrospective studies have reported longer survival when surgery and antibiotics are combined with hyperbaric oxygen (HBO) therapy.[46] [47] [48] However, other reviews have found that HBO therapy did not have an impact on the mortality of truncal necrotising infections.[49] HBO therapy has a direct bactericidal effect on clostridial species, inhibits toxin production, and improves polymorphonuclear function and bacterial clearance; it may also facilitate antibiotic penetration or action, and enhances the presence of non-viable tissue before surgical treatment. The recommended regimen for HBO therapy involves administration of 100% oxygen at 2.5 to 3 absolute atmospheres for 90 to 120 minutes 3 times a day for 48 hours, then twice a day as needed.[14]
ischaemic gangrene	**1st**	**intravenous heparin** » Unless contraindicated, all patients should immediately receive an intravenous heparin bolus, followed by a continuous heparin infusion.[41] [42] After the initiation of heparin, treatment then varies depending upon the viability of the limb. **Primary options** » heparin: 80 units/kg intravenous bolus, followed by 18 units/kg/hour infusion
with threatened or non-viable extremity: life expectancy >2 years	**plus**	**surgical revascularisation ± amputation** » Patients with a threatened extremity should undergo emergency surgical revascularisation after heparin anticoagulation. The majority of these patients will have had an embolic event, and irreversible changes can occur within as little as 4 to 6 hours of profound ischaemia. While pharmacological thrombolysis may successfully dissolve an embolus, the time required is usually too long to allow this to be an acceptable alternative to surgery.[42]

Acute

Patient group	Tx line	Treatment
		» Patients with a non-viable extremity should undergo prompt amputation. The level of amputation is determined by clinical findings and by the viability of tissues at the time of surgery. Every effort should be made to preserve as many joints as possible, in order to decrease the work of ambulating with a prosthesis and to improve the chances for successful rehabilitation.[39] Revascularisation of the non-viable extremity may be required to allow healing of the amputation or to permit amputation at a lower level.
with threatened or non-viable extremity: life expectancy ≤2 years	**plus**	**percutaneous transluminal angioplasty (PTA) ± amputation** » In the bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial, 450 patients with severe limb ischaemia due to infra-inguinal arterial disease were randomly assigned to PTA or bypass surgery.[44] At 30 days, there was no difference in mortality between the groups, but surgery was associated with a significantly higher morbidity (57% versus 41%). On intention-to-treat analysis, there was no difference in the primary end point (survival without amputation) at 1 year and 3 years, and surgery was associated with a significantly lower rate of reintervention (18% versus 26%). » Based on these findings, the authors recommend that PTA should be offered first to patients with significant comorbidities who are not expected to live more than 2 years. » For patients expected to live longer than 2 years, the benefits of bypass surgery could outweigh the short-term increase in morbidity.
with viable extremity	**plus**	**thrombolytic therapy** » The absence of rest pain, sensory loss, and muscle weakness helps differentiate a viable limb from a threatened limb.[50] In highly selected patients, catheter-based intra-arterial thrombolytic therapy may be an alternative to surgery or percutaneous intervention in the management of critical limb ischaemia. The main indication is acute limb ischaemia of less than 14 days' duration in patients with a viable extremity and only limited gangrenous change.[39]
with phlegmasia cerulea dolens	**plus**	**thrombolytic therapy** » Phlegmasia cerulea dolens, a rare condition in which there is total or near-total obstruction of

Acute

Patient group	Tx line	Treatment
		venous drainage from a limb, may be treated by IV thrombolytic therapy to help prevent the onset and progression of venous gangrene.[45]

Emerging

Prostaglandin E1

The 2007 TASC II consensus document on the management of peripheral arterial disease (PAD) does not recommend prostaglandin E1 or any other prostanoids for the management of limb-threatening ischaemia.[41] However, in patients with advanced PAD not suitable for any other form of intervention, prostanoids have been shown to relieve rest pain.[51]

Stimulation of angiogenesis

This treatment involves the administration of angiogenic growth factors, as recombinant protein or naked DNA, to augment the collateral circulation and enhance blood flow to ischaemic tissues. Another approach is the autologous implantation of bone marrow mononuclear cells to stimulate angiogenesis, or multiple intramuscular injections of autologous granulocyte colony-stimulating factor.[52]

Recommendations

Monitoring

Patients with gangrene can be severely ill. Close monitoring and frequent review, often in a high dependency or intensive care environment, are necessary to optimise treatment and monitor for lack of response to therapy, which can occur from antibiotic resistance of the bacteria or be due to the need for more extensive debridement. Furthermore, monitoring for decline in respiratory and/or haemodynamic function is essential, with consideration of possible toxic shock in patients with group A streptococcal infection.

Patient instructions

Patients (and relatives) should be made aware of the potential life- and limb-threatening nature of the condition and the necessity for surgery and antibiotic therapy. Recurrence of necrotising fasciitis is rare. However, significant functional and cosmetic morbidity may remain following initial surgical therapies, which may require subsequent reconstruction, and patients should be made aware of this possibility. Patients with ischaemic gangrene should be strongly advised to stop smoking.

Complications

Complications	Timeframe	Likelihood
sepsis	**short term**	**high**
Sepsis is defined as systemic inflammatory response syndrome (SIRS) resulting from a documented or presumed infection. Criteria for SIRS is the presence of 2 or more of the following vital signs or laboratory results: temperature >38.4°C (>100.4°F) or <36°C (<96.8°F); heart rate >90 beats per minute; respiratory rate >20 breaths per minute, or PaCO2 <32 mmHg; WBC>12 x 10^9/L (>12,000/microL) or < 4 x 10^9/L (<4000/microL) or >10% immature neutrophils. This has fallen out of favour in consensus guidelines, due to it being a poor predictor of mortality, and the non-specific nature of these criteria in both infectious and non-infectious causes.[57] Septic shock includes: meeting the definition for sepsis (Sequential Organ Failure Assessment [SOFA] score >2 points from baseline scores, with organ dysfunction), elevated lactate >2 mmol/L (>18 mg/dL), persistent mean arterial pressure <65 mmHg, despite adequate volume resuscitation, or the use of vasopressors in the absence of hypovolaemia.[32] [57] A quick SOFA score (qSOFA): respiratory rate of 22 breaths per minute, altered mental status, and systolic blood pressure <100 mmHg, could be used in non-critical situations. However, it lacks prospective evaluation for mortality prediction, and as such has not been part of the consensus definition for sepsis.[57] These findings (previous sepsis definition using SIRS), plus skin infection accompanied with pain out of proportion, rapid progression, bullae formation, subcutaneous crepitus, and visible gas on imaging studies show an 85% sensitivity in detecting necrotising skin infections.[19]		
shock	**short term**	**high**

FOLLOW UP

Complications	Timeframe	Likelihood
Septic shock is a persistent hypotension (previous definition: systolic blood pressure <90 mmHg or <40 mmHg from baseline; current consensus: mean arterial pressure <65 mmHg) despite adequate fluid resuscitation, elevated lactate >2 mmol/L, and meets sepsis definitions (SOFA score >2 points from baseline with organ dysfunction).[19] [57] The mechanism of shock in gangrene is poorly understood. Unconcentrated filtrate from *Clostridium perfringens* , purified alpha-toxin, and purified phi-toxins cause hypotension, bradycardia, and decreased cardiac output when injected into laboratory animals. Because alpha-toxins and phi-toxins are lipophilic and may remain locally bound to tissue plasma membranes, the toxins may stimulate synthesis of secondary mediators that cause cardiovascular abnormalities.[6] Shock is present in 50% of patients with gangrene at the time they present to the hospital.[5]		
acute renal failure	**short term**	**high**
Exotoxins may cause severe haemolysis. When this occurs in combination with hypotension, haemoglobinuria, and myoglobinuria, it may cause acute tubular necrosis and renal failure.[1] [16] There may also be a direct effect of toxins on renal tubular cells, contributing to renal failure.[5]		
haemolysis	**variable**	**high**
Alpha-toxin, a metalloenzyme that has phospholipase-C activity and causes cell destruction by hydrolysis of key cell membrane components, is produced in gas gangrene. It acts to cause lysis of erythrocytes, leukocytes, platelets, fibroblasts, and muscle cells.[5]		
loss of limb	**variable**	**high**
A substantial number of cases of gangrene result in partial or complete loss of a limb. Careful observation is required to ensure that there is adequate healing.		
disseminated intravascular coagulation (DIC)	**variable**	**medium**
A clinical manifestation of inappropriate thrombin activation. The activation of thrombin leads to fibrinogen conversion to fibrin, platelet activation and consumption, activation of factors V and VIII, protein C activation, endothelial cell activation, and fibrinolysis. The leading causes are malignancy and infection that leads to gangrene. Sometimes DIC may be the presenting sign of the infection, and prompt recognition and appropriate management may be life-saving. It can occur at any age, and the reported mortality for this complication is near 35%, with a morbidity because of amputation as high as 85%.[58]		

Prognosis

The prognosis for gangrene is highly variable, reflecting the spectrum of types and severity that may be encountered clinically. Even though outcomes have improved generally, it remains a potentially life- and limb-threatening condition. The 2 key factors in improving outcomes are early recognition and aggressive antibiotic and surgical management.

Before the availability of antibiotics, gas gangrene was usually fatal. However, with aggressive antibiotic therapy and aggressive surgical therapy this is no longer the case.

Mortality from necrotising fasciitis properly treated with surgery plus antibiotics has been estimated to be between 10% and 40%.[5] Mortality is higher in patients who develop shock and end-organ damage, approaching 30% to 70%.[14] Recurrence of necrotising fasciitis is rare.[53] However, significant functional and cosmetic morbidity may remain following initial surgical therapies, which may require subsequent reconstruction. Predictors of mortality include WBC >30 x 10^9/L (>30,000/microlitre), serum creatinine >177 micromol/L (>2.0 mg/dL), clostridial infection, presence of heart disease on admission, cirrhosis of the liver, soft-tissue air, *Aeromonas* infection, age >60 years, band neutrophils >10%, activated PTT >60 seconds, and bacteraemia. Length of time from admission to surgery has had mixed results in terms of impact on mortality.[54] [55]

In patients with critical leg ischaemia, 50% to 60% will undergo some form of surgical or endovascular procedure (although in some specialist units the figure may be nearer 90%). Primary amputation rates range from 10% to 40%. Mortality rate in these patients with standard therapy is around 20% at 1 year, and between 40% and 70% at 5 years. However, 95% of patients who present with ischaemic gangrene, and 80% of those presenting with rest pain, are dead within 10 years.[56]

Diagnostic guidelines

Europe

Diabetic foot problems: prevention and management

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Summary: Makes recommendations concerning foot examination in all patients with diabetes.

Treatment guidelines

Europe

Diabetic foot problems: prevention and management

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Summary: Provides evidence-based recommendations concerning care of people with footcare emergencies and foot ulcers.

North America

Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America

Published by: Infectious Diseases Society of America **Last published:** 2014

Summary: Comprehensive evidence- and opinion-based guidance on the management of a range of soft-tissue infections, including necrotising infections and gas gangrene.

Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations)

Published by: American College of Cardiology; American Heart Association **Last published:** 2013

Summary: Provides evidence- and opinion-based guidance and recommendations on the management of peripheral arterial disease. The guidelines are a compilation of the recommendations from the 2005 ACC/AHA Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic), and the 2011 ACCF/AHA Focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline).

Quality improvement guidelines for percutaneous management of acute lower-extremity ischemia

Published by: Society of Interventional Radiology **Last published:** 2013

Summary: Covers acute limb ischaemia, options for thrombolysis and its complications, indications and patient selection, laboratory monitoring, thromboembolectomy devices, and success rates.

North America

Diabetic foot disorders (2006 revision)

Published by: American College of Foot and Ankle Surgeons **Last published:** 2006

Summary: Clinical consensus statement for diabetic foot disorders based on currently available evidence, committee consensus, and current clinical practice. The pathophysiology and treatment of diabetic foot ulcers, infections, and the diabetic Charcot's foot are reviewed. Provides evidence-based guidance for general patterns of practice. This document should be considered as a clinical consensus statement document and not a clinical practice guideline document as it no longer meets the clinical practice guideline development standards of the Institute of Medicine.

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Images

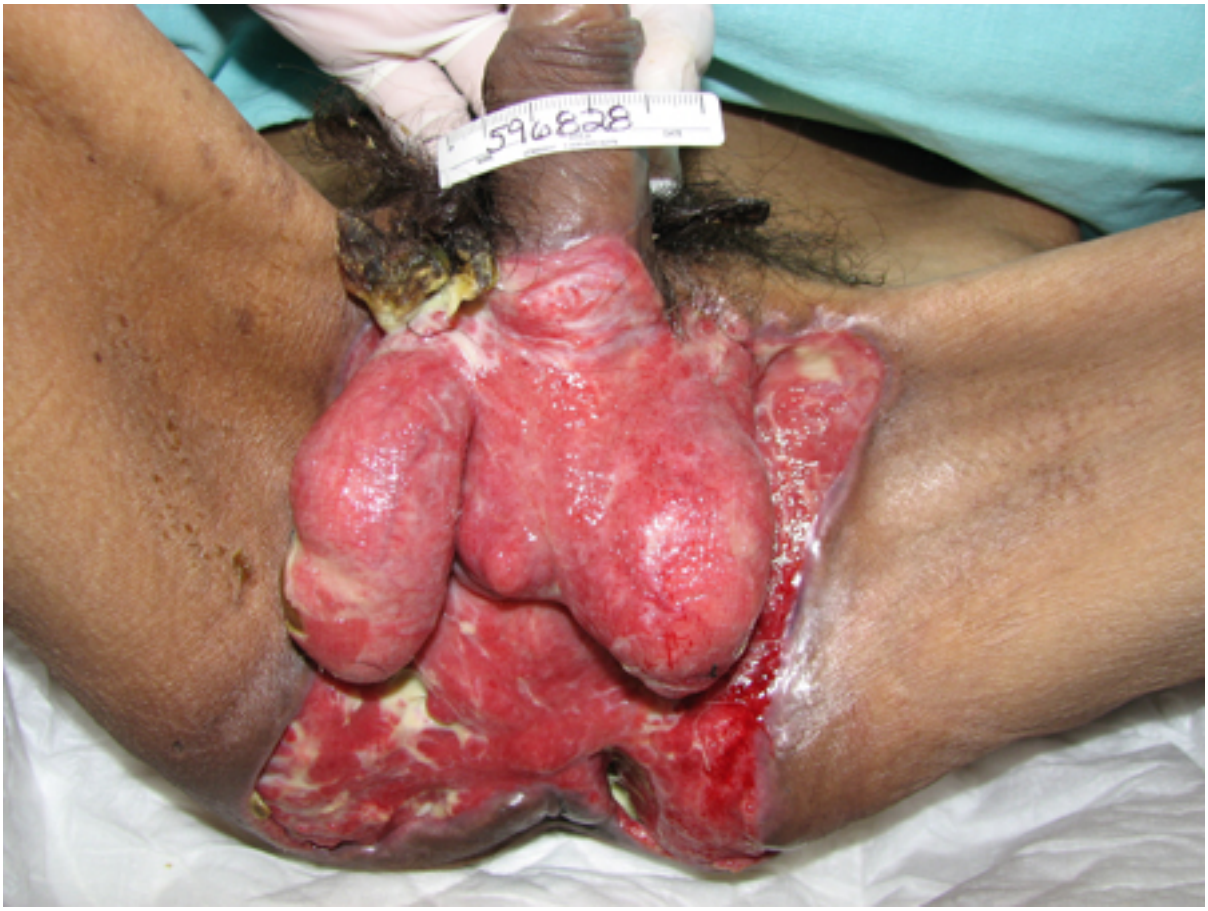

Figure 1: Necrotising fasciitis I subtype involving genital and perineal region; image taken after extensive surgical debridement

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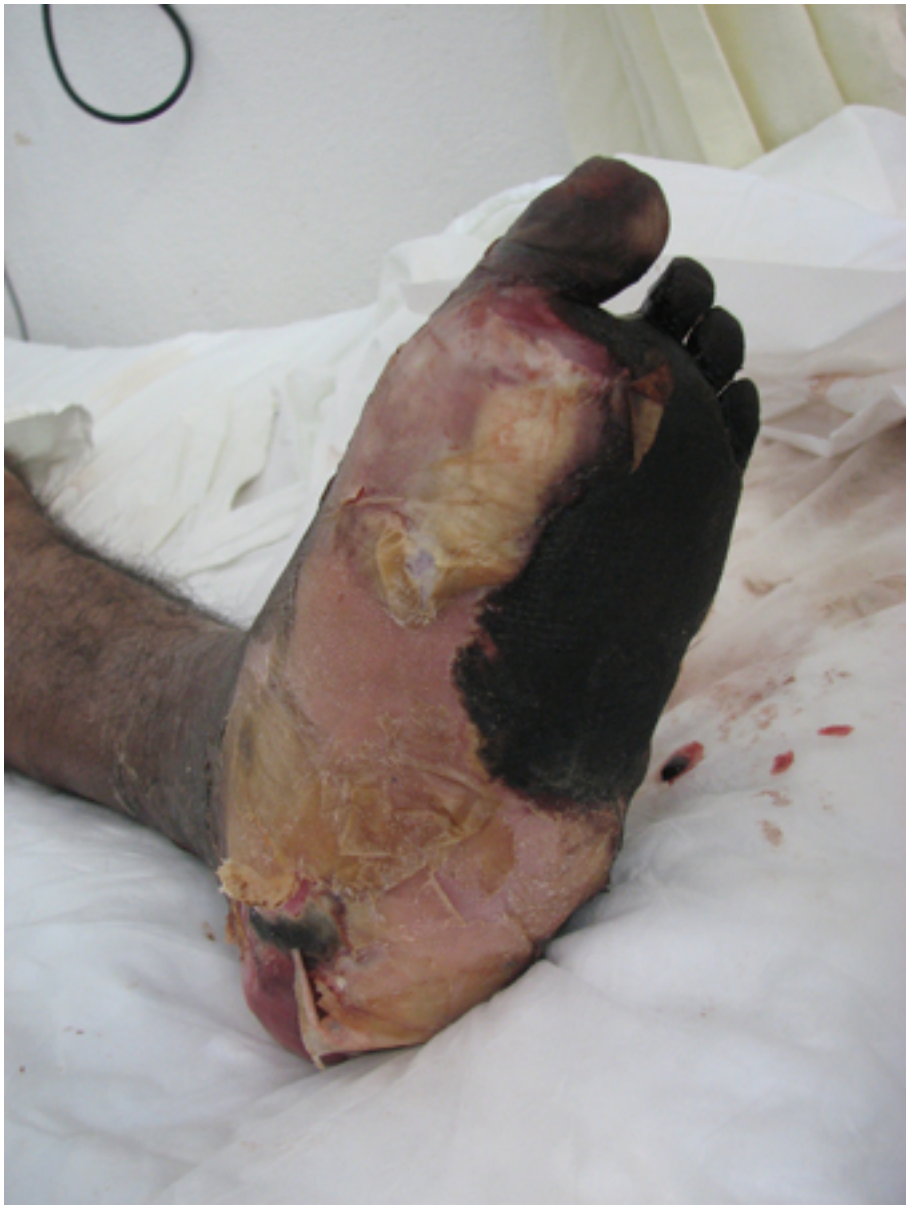

Figure 2: Eschar and blister formation with notable oedema in diabetic patient who developed gas gangrene after a lower limb trauma

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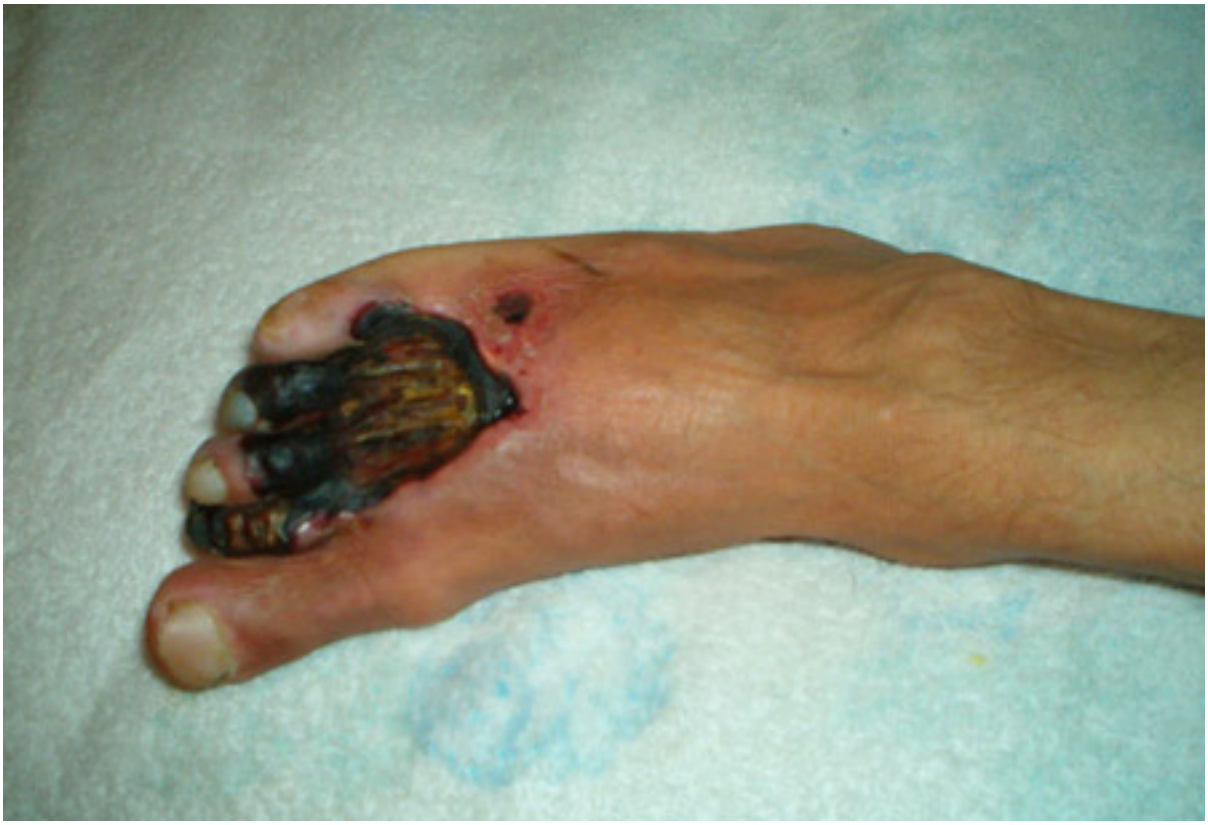

Figure 3: Ischaemic gangrene secondary to antiphospholipid syndrome

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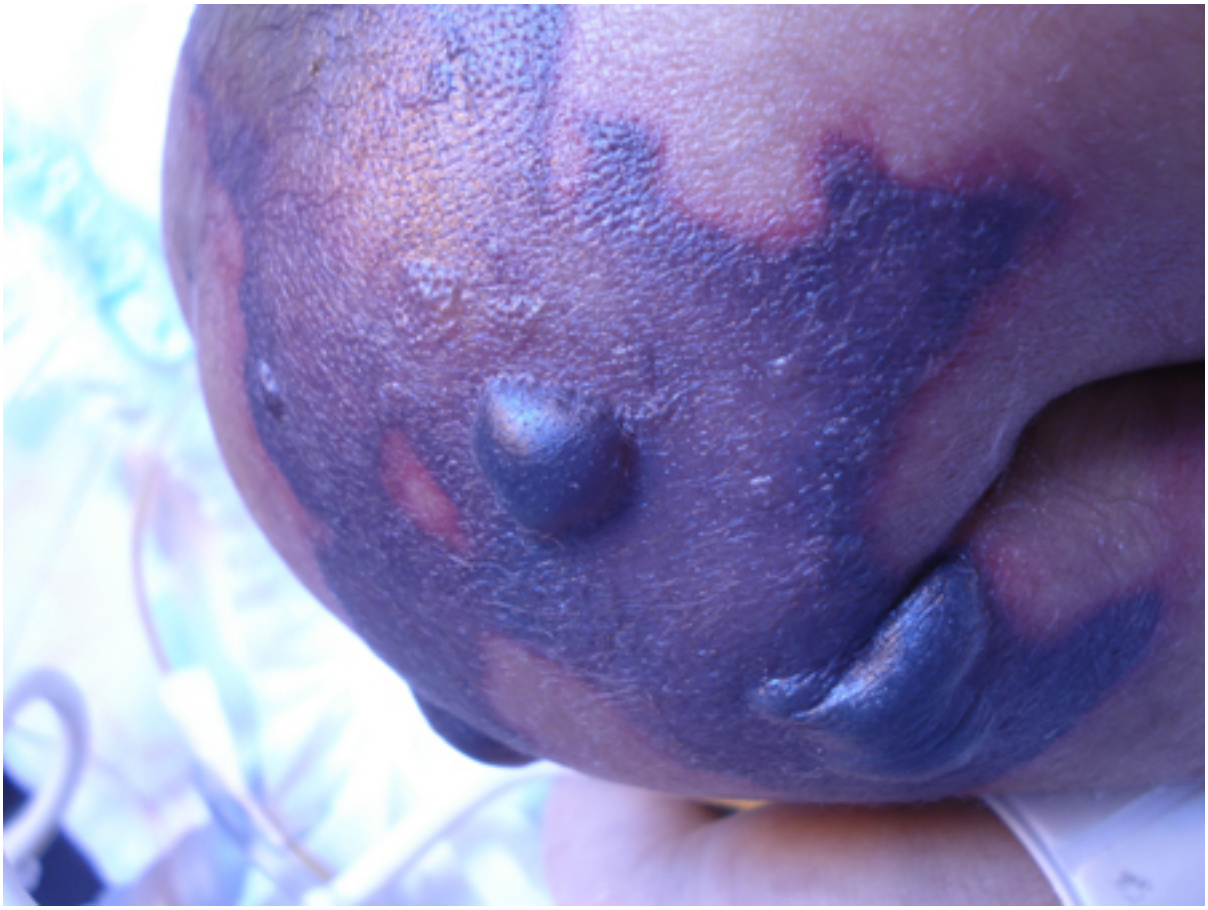

Figure 4: Haemorrhagic blister formation secondary to ischaemic gangrene

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Figure 5: Newborn with purpura fulminans due to Streptococcus B haemolyticus

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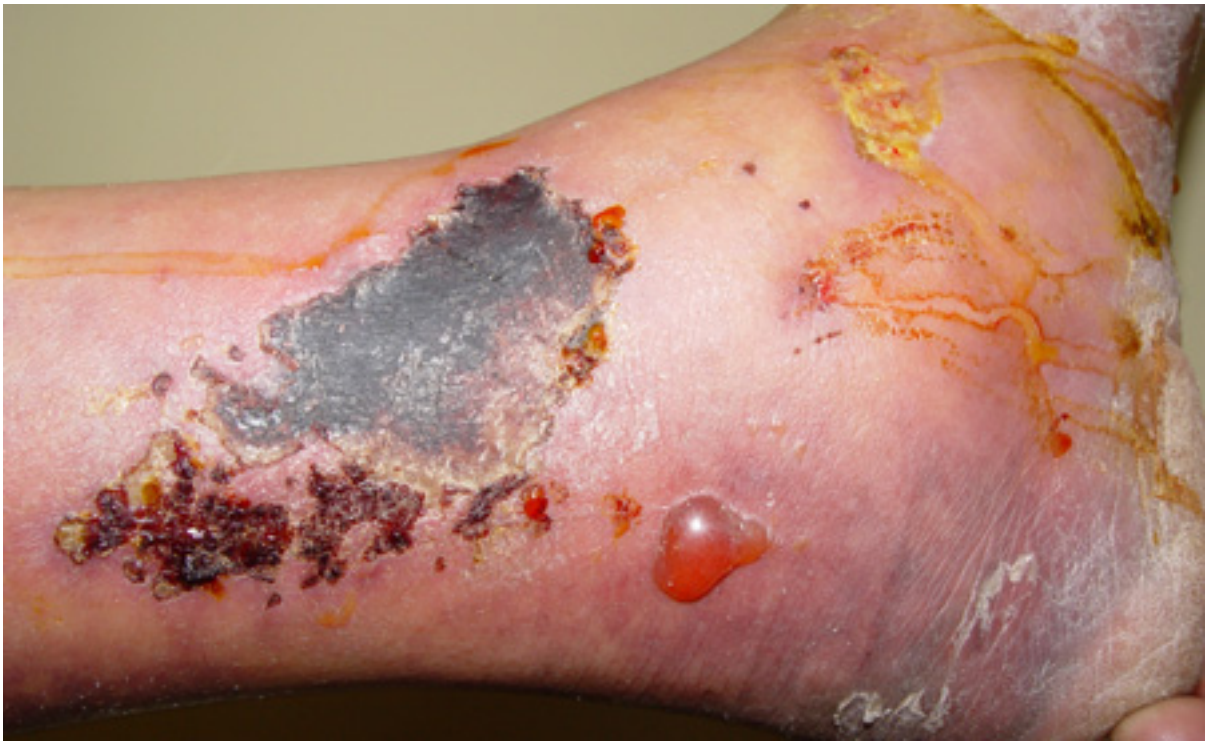

Figure 6: Eschar surrounded by erythema, oedema, and haemorrhagic blisters

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