How to diagnose and treat haemorrhagic skin necrosis

Haemorrhagic skin necrosis is a common manifestation of a number of different pathological processes that can evolve dramatically and carry a grave prognosis. The divergent patho-physiological basis of the condition and the many specialities involved in the initial and subsequent care of the patient means that not all patients are seen by wound care professionals. Yet such patients do present to wound healing clinics and wounds invariably develop if the affected area is large. It is therefore important that wound care experts are familiar with the common causes of haemorrhagic skin necrosis and are able to instigate the appropriate investigations and treatment.

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KEY WORDS
Haemorrhagic skin necrosis
Thrombosis
Cutaneous necrosis
Vasculitis

The vast majority of wounds presenting to a wound healing clinic are either post-surgical wounds or chronic ulcers; in over 90% of cases the aetiology of the wound can be attributed to either venous disease with or without coexistent arterial disease, arterial disease, diabetes, pressure ulceration or trauma (including surgery) (Banerjee et al, 2001; Patel et al, 2006). Therefore a patient with rapidly evolving, painful black haemorrhagic skin necrosis is unusual and may be daunting for the clinician. This article describes the presentation, diagnosis and management of haemorrhagic skin necrosis.

Haemorrhagic skin necrosis: a diagnostic framework

Patients with haemorrhagic skin necrosis may present with one or more painful and extremely tender black eschars surrounded by dusky grey-red coloured skin. Diagnosing the cause of these symptoms may be a clinically intimidating prospect. But when considering the diagnostic possibilities, it is important first to establish the pathological sequence of events that have led to this presentation.

The process resulting in haemorrhagic skin necrosis begins with the sudden thrombotic occlusion of single or multiple blood vessels supplying the skin. The compromised blood vessels leak red cells into the surrounding tissues where they become trapped within the ensuing tissue necrosis. The subsequent deoxygenation of haemoglobin in the red blood cells results in the black colour of the necrotic tissue. In addition, many cytokines are synchronously released by dying cells and promote inflammation. At the boundary of the necrosis the blood vessels dilate, resulting in hyperaemia which gives rise to the dusky grey-red colour of the surrounding skin.

The necrotic tissue initially swells and later it will be sloughed off after the underlying tissue has healed with a scar. However, if the affected area is sufficiently large the fibrin molecules will solidify to form an eschar that will shrink as the underlying wound heals (Carlson and Chen, 2007).

Thus, the successful diagnosis of haemorrhagic skin necrosis depends upon the identification of a disease that causes vessel thrombosis.

Determining the cause of sudden thrombosis of the skin vessels

Rudolf Virchow worked extensively on the causes of thrombosis in the early 1900s and his findings still provide a useful framework. Virchow's triad consists of:

- Alterations to blood flow (haemostasis)
- Injury to the vascular endothelium
- Alteration in blood constituents (hypercoagulability) (Malone, 2005).

Diseases that cause thrombosis typically fit into one or more of these groups and each group in turn has a particular pattern of skin necrosis. By looking at the pattern and distribution of skin necrosis it should be possible, using Virchow's triad, to shorten the list of possible diagnoses.

Haemostasis leading to haemorrhagic skin necrosis

Probably the most common example of microcirculation haemostasis is skin necrosis resulting from pressure ulceration (Whitney et al, 2006). In this case the necrosis is extremely localised and is characteristically centred over a bony prominence.

The external pressure compresses the tissue against the underlying bone, so that blood no longer flows effectively through the tissue. There is a tendency

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Table 1
Factors associated with the development of pressure ulcers

Extrinsic factors	Intrinsic factors
Moisture	Systemic infection
Friction	Sensory neuropathy with or without motor neuropathy
Shear	Tissue oedema
	Malnutrition
	Hypotension
	Medications that interfere with healing, e.g. systemic corticosteroids
	Diabetes mellitus
	Atherosclerosis
	Reduced consciousness
	Incontinence
	Coexistent skin diseases

to think that pressure ulceration is limited to the sacral area or hip, but these same factors can result in ulcers over any bony prominence, including the scalp, thoracic vertebrae, elbows, knees and heels. Occasionally, pressure ulcers can also develop in the absence of a bony prominence when there are two solid surfaces that compress the tissues between them, as has been observed with nasogastric tubes, blood-pressure monitoring devices or plaster casts (Devbhandari et al, 2006).

The pathophysiology of pressure ulceration is relatively straightforward, but in addition to treating the wound, management of patients with pressure ulcers should address internal and external exacerbating factors (*Table 1*) (Reddy et al, 2006). These same factors can affect the extent of tissue death in all forms of haemorrhagic skin necrosis associated with haemostasis and, to a lesser extent, haemorrhagic skin necrosis from other causes.

When the larger vessels are affected or when there is severe hypotension, haemostasis and therefore haemorrhagic skin necrosis may affect multiple sites, often in a symmetrical distribution. The sites affected will be in the areas of lowest perfusion. Pressure-bearing areas will be affected as well as the most distal sites, the digits. Digital necrosis may be a prominent feature (*Figures 1 and 2*). The causes of this type of skin necrosis can be divided into those affecting a solitary vessel or those affecting multiple vessels (*Table 2*).

Injury to the vascular endothelium leading to haemorrhagic skin necrosis

Injury to the vascular endothelium can also lead to haemorrhagic necrosis. Diseases in this group can present either in a localised manner, such as in popliteal artery aneurysms that cause necrosis in the forefoot, or be more widespread such as in Henoch-Schonlein purpura. Occasionally the disease may be widespread as in atherosclerosis, but then sudden plaque rupture and thrombosis may result in a solitary localised area of skin necrosis.

Figure 1. A patient with systemic sclerosis and associated Raynaud's disease, complicated by painful skin necrosis and ulceration affecting the left distal middle finger.

Table 2
Factors associated with reduced blood flow that predispose to haemorrhagic skin necrosis

Reduced blood flow in a solitary vessel	Reduced blood flow in multiple vessels
Trauma	Trauma
Chilblains	Chilblains
	Severe hypotensive shock
	Drugs, e.g. sympathomimetics and ergot alkaloids
	Vibration white finger
	Raynaud's disease
	Berger's disease
	Blood hyperviscosity, e.g. multiple myeloma

Atherosclerosis is the most common cause of injury to the vascular endothelium and it results in blood vessel occlusion from thrombosis or from emboli (*Figure 3*). The majority of arterial ulcers arise from peripheral arterial disease caused by atherosclerosis (Weitz, 1996). Moreover atherosclerosis is also involved in the pathogenesis of arterial aneurysms which can rupture, thrombose and cause emboli that can present with haemorrhagic skin necrosis. While the pathogenesis of atheroma that gives rise to atherosclerosis is complex, reversible risk factors associated with atherosclerosis include hypertension, a history of smoking, hyperlipidaemia and diabetes mellitus (Grey et al, 2006). Thus, in addition to treating the area

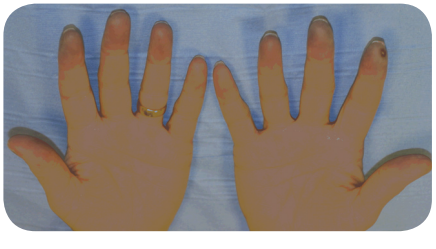

Figure 2. A patient with sudden onset Raynaud's disease. Skin necrosis can be a presentation of underlying malignancy. In this case, the patient had an adenocarcinoma which is the most common type of malignancy with this presentation.

Table 3
Vasculitides associated with different types of infiltrate

Haemorrhagic skin necrosis with a neutrophil rich vessel wall inflammation:
Leucocytoclastic vasculitis
Sweet's syndrome
Bowel associated dermatosis-arthritis syndrome
Rheumatoid neutrophilic dermatosis
Behcet's syndrome
Pyoderma gangrenosum
Erythema elevatum diutinum
Haemorrhagic skin necrosis with a lymphocyte rich vessel wall inflammation:
Pyoderma gangrenosum
Leukaemic vasculitis
Polymorphic light eruption
Pityriasis lichenoides
Haemorrhagic skin necrosis with a granulomatous vessel wall inflammation:
Wegener's granulomatosis
Lymphomatoid granulomatosis
Giant cell arteritis
Takayasu's arteritis

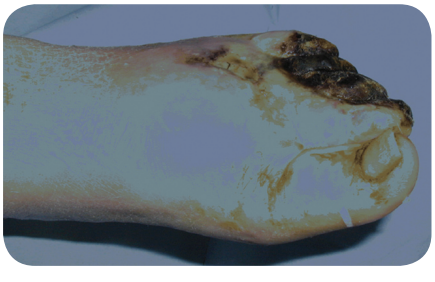

Figure 3. A diabetic female smoker presented with skin necrosis and a pulseless left foot. Subsequent arterial dupplex confirmed severe atherosclerosis and occlusion of the posterior tibial artery.

of haemorrhagic skin necrosis, such patients need to be counselled and given therapy for these preventable risk factors.

In contrast to the insidious nature of atherosclerosis, vascular endothelial inflammation can also have an acute onset. Vascular endothelial inflammation that results in vasculitis can present dramatically with widespread purpura and haemorrhagic skin necrosis (Carlson and Chen, 2006). In most

Figure 4. Sudden onset of palpable purpura of the lower legs can be a manifestation of small vessel vasculitis, as in this case. The leucocytoclastic vasculitis was restricted to the skin and the patient subsequently recovered with conservative treatment.

forms of vasculitis of the skin, lesions (usually purpura and haemorrhagic skin necrosis) tend to be widespread and symmetrically distributed, usually on weight-bearing (dependent) sites (*Figure 4*).

The skin lesions arising as a result of the various causes of vasculitis tend to be similar and so for further characterization of the disease it is necessary to do a skin biopsy for histological identification. Skin biopsies need to be taken from the edge of a new lesion to include unaffected skin and in some instances the biopsy needs to include deeper vessel (as in the case of giant cell arteritis, when the temporal artery needs to be biopsied). The pathologist is then able to confirm the presence of vessel wall inflammation and the type of inflammatory infiltrate, which in turn facilitates further classification of the causes (*Table 3*). Additional investigations may be necessary to confirm a particular form of vasculitis, such as antineutrophil cytoplasmic antibody (ANCA) studies for Wegner's granulomatosis or microscopic polyangitis (Lagford, 2007; Ozaki, 2007).

Thus, histology is fundamental when making a diagnosis of vasculitis. In addition, tissue can also be submitted for direct immunofluorescence to identify immune deposits, such as

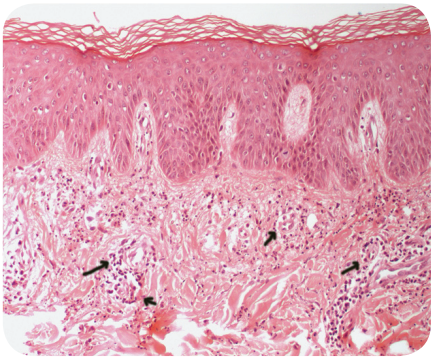

Figure 5. A histological feature of leucocytoclastic vasculitis, in keeping with the clinical features presented in figure 4, is based on the presence of transmural infiltration by neutrophils and fibrinoid vessel necrosis (highlighted by the arrows). Often as in this case there is fragmentation of neutrophils (leucocytoclasis) and extravasation of red cells.

immunoglobulin A in Henoch-Schonlein purpura or complement in systemic lupus erythematosus (Carlson et al, 2005). Once the type of vasculitis is diagnosed, a causal association may become evident such as drug usage, infection (as in necrotizing fasciitis), co-existent inflammatory disease (e.g. systemic lupus erythematosus or rheumatoid arthritis) and likelihood of malignancy. In addition to aiding a diagnosis, interpretation of clinical findings and investigations is necessary to determine the extent of the disease, in particular to establish if internal damage to vital organs has occurred (Crowson et al, 2003).

Leucocytoclastic vasculitis is the most common histological pattern and is characterised by transmural neutrophil-rich inflammation and associated fibrinod necrosis (*Figure 5*). Often extravasated red cells, neutrophilic debris (leucocytoclasis) and deposition of immunoreactants around the vessel wall are also evident. In keeping with other forms of vasculitis, while the disease may present with skin lesions, the same pathology can also involve vessels supplying vital internal organs such as the kidneys, lungs, heart or brain. Leucocytoclastic vasculitis can be further divided into two groups; those with and without a definable precipitating cause. About half of all cases are caused by infection,

inflammatory disease, drugs and malignancy (Carlson and Chen, 2006).

About 15–20% of all vasculitides result from underlying infection from viruses such as hepatitis B and C, bacteria such as group A beta-haemolytic streptococcus and *Staphylococcus aureus*, fungi or parasites (Carlson and Chen, 2006). Infection should be considered when there is an antecedent history of high fever associated with signs of purulence. Recognising infection as a cause of vasculitis is particularly important as the condition may resolve with antimicrobials alone, but also because underlying infection can be exacerbated by the immunosuppressants commonly used to treat severe vasculitis. Another 15–20% of individuals that develop vasculitis have an underlying inflammatory disease, typically systemic lupus erythematosus, Sjogren's syndrome or inflammatory bowel disease. In such patients the underlying autoimmune disease tends to be severe, with high antibody titres, and results in extensive vasculitis affecting both small and medium-sized vessels. Management strategies should aim to treat the underlying disease, vasculitis and provide support for affected organs.

Recurrent bouts of vasculitis occurring after taking certain drugs account for 10–15% of cases. Drug groups commonly associated with leucocytoclastic vasculitis include the penicillins, sulfonamides, thiazides and oral contraceptives.

Last, internal malignancies especially those involving expansion of B lymphocytes, such as lymphoproliferative disorders and paraproteinaemias, can also cause vasculitis. However, in 50% of cases an underlying cause cannot be identified and the vasculitis may be part of a primary vasculitic syndrome which has characteristic diagnostic features (Piette, 2001).

The primary vasculitides are classified according to the size of vessel affected (*Table 4*). Those causing haemorrhagic skin necrosis primarily affect small and medium-sized vessels (Jennette et al, 1994). The small vessel primary vasculitides are cutaneous small vessel vasculitis, urticarial vasculitis and Henoch-Schonlein purpura. Only polyarteritis nodosum, of the medium-sized vessels primary vasculitides causes haemorrhagic skin necrosis (Piette, 2001). In addition, there are vasculitides that cause disease of both small and medium-sized vessels that cause skin necrosis; cryoglobulinaemia, Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangitis. Each of the primary vasculitides have distinct clinical features and they differ in presentation, organs affected and treatment (Crowson et al, 2003). There are many review articles (Langford, 2007; Ozaki, 2007) describing these diseases, but a thorough description is beyond the scope of this review.

Table 4
Classification of vasculitis based on size of vessel affected

Small vessel	Medium vessel	Large vessel
Wegener's granulomatosis	Classical polyarteritis nodosum	Takayasu's arteritis
Churg-Strauss syndrome	Kawasaki disease	Giant cell (temporal) arteritis
Microscopic polyangitis		
Henoch-Schonlein purpura		
Essential cryoglobulinaemia		
Cutaneous leukocytoclastic angiitis		

In addition to internal causes of endothelial damage, extrinsic factors can also damage the microcirculation. These include injury from blunt trauma, burns, scalds, radiation and drug extravasation (Carlson et al, 2005).

Hypercoagulability leading to haemorrhagic skin necrosis

Haemorrhagic skin necrosis frequently results from an alteration in blood constituents, leading to a hypercoagulable or prothrombotic state (Bick, 2006). The resultant skin necrosis is often painful and potentially fatal. Typically skin histology reveals thrombosed vessels throughout the dermis (*Figure 6*) with relatively few associated inflammatory cells. The pattern of necrosis is often generalised, symmetrical and is dependent upon the size of vessels that are occluded. In conditions such as heparin necrosis, thrombosis begins by affecting small vessels but then progresses to involve much larger vessels which can result in fatal thrombosis. Hence, there is an urgency to establish the diagnosis and implement therapy.

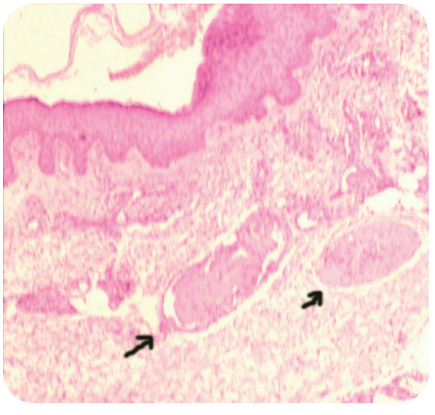

Figure 6. Thrombosis of vessels (highlighted by the arrows) in the dermis in the presence of limited or absent inflammation is a feature of skin necrosis caused by a prothrombotic state. Often, as in this case, the vessels appear dilated and filled with thrombus or undergoing re-canalisation as seen in the lower right vessel.

A working knowledge of the coagulation cascade (Schenone et al, 2004) and assistance from a haematologist are essential to establish the diagnosis and begin therapy. The coagulation cascade has two competing components: the prothrombotic arm

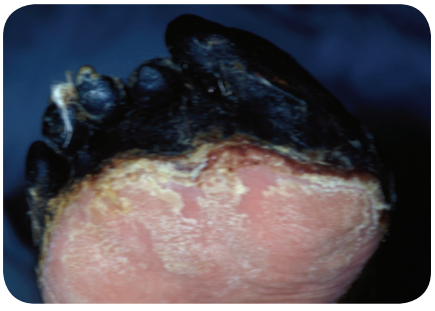

Figure 7. This patient presented with 3 day malaise, followed by widespread cutaneous necrosis affecting her face, arms and legs; with particular involvement of the digits. Histology showed widespread intravascular thrombosis and further investigations revealed a heterozygous factor V Leiden mutation and complicating sepsis. Antibiotics led to resolution of the initial infection, however her recovery was complicated by a further episode of septicaemia from wound infection leading to her death.

consisting of clotting factors that lead to the formation of thrombin and fibrin the major components of a thrombus, and the modulatory arm which is responsible for preventing clot propagation (Schenone et al, 2004). Either an excess of pro-coagulant factors or deficiencies in naturally-occurring anticoagulants can lead to a prothrombotic state, typically as a result of genetic abnormality. These conditions predispose to haemorrhagic skin necrosis (Simioni et al, 2006). To date mutations or deficiencies of the following anti-coagulant factors have been or may be associated with haemorrhagic skin necrosis: factor V (*Figure 7*) (Patel et al, 2000) and prothrombin of the pro-cogulant factors, as well as deficiencies in protein C, protein S, anti-thrombin III, heparin co-factor II and factor XII. Protein C and S deficiency can also present as purpura fulminans, in which skin necrosis favours the extremities, such as digital skin necrosis. In addition, homocystineuria is associated with a greater risk of thrombosis and possibly venous ulcer formation (Franchini, 2006). Usually, these genetic prothrombotic states only manifest with haemorrhagic skin necrosis when activated by either severe trauma or sepsis but can result in the condition in the absence of a clear precipitant in older people.

There are many acquired prothrombotic states, three of which require specific mention: antiphospholipid syndrome (*Figure 8*), warfarin-induced necrosis and thrombotic thrombocytopenia (which when caused by heparin, is also called heparin necrosis). In contrast, paroxysmal nocturnal haemoglobulinuria and myeloproliferative disorder, which are also acquired prothrombotic states, tend to predispose to deep vein thrombosis and therefore to venous leg ulceration.

Antiphospholipid syndrome is characterised by the presence of autoantibodies against various negatively charged cell membrane phospholipids, such as lupus anticoagulant and anticardiolipin antibodies. It remains to be established how these antibodies result in widespread thrombosis. Patients with these antibodies display abnormalities in one or more of the following coagulation tests: activated partial thromboplastin time, kaolin clotting time, dilute prothrombin time or dilute Russell viper venom test (Moll, 2006; Abo and Debari, 2007). Antiphospholipid syndrome mostly affects women and can be associated with systemic lupus erythematosus. Antiphospholipid syndrome may present as a cause of multiple arterial and venous thrombotic episodes, recurrent spontaneous abortions, and with livedo reticularis.

Antiphospholipid syndrome is a cause of livedoid vasculopathy, a disorder characterised by painful ulceration in association with livedo reticularis and atrophie blanche. Livedoid vasculopathy has also been described in association with factor V Leiden mutation (Patel et al, 2000). This progressive, painful, and debilitating disease requires anticoagulation and drugs to treat the underlying disease.

Warfarin necrosis is an uncommon transient phenomenon which occurs at the start of warfarin treatment in the absence of heparin. The condition mostly affects women usually in their 50s or 60s, and typically involves the breasts, hip, buttock, and thigh. The use of warfarin results in a transient decrease of vitamin K sensitive factors, including protein C, resulting in a temporary hypercoagulable state which then spontaneously corrects itself. Therefore in affected patients warfarin should be continued with advice and supervision by a haematologist.

Heparin necrosis is rare and may be caused by both unfractionated and low molecular weight heparin (*Figure 9*) (Patel and Knight, 2005). It is associated with the formation of antibodies against heparin that lead to platelet clumping. The continued use of heparin can lead to the formation of larger emboli that can occlude vessels supplying both the skin and internal organs. Initially, skin necrosis occurs at the injection site, but can later involve distant areas. Continuation of heparin therapy aggravates the condition, with potentially fatal consequences, so it should be stopped immediately.

Certain infections can also cause coagulopathy, which can arise from a systemic cause as in disseminated intravascular coagulopathy associated with septicaemia. This form of sudden thrombosis and resultant haemorrhagic skin necrosis is often widespread and develops rapidly, and it is known as purpura fulminans. A number of different bacterial infections that result in septicaemia have the potential to also cause purpura fulminans, such as septicaemia from: group A streptococci, meningococci, staphylococci, and pneumococci. Purpura fulminans is most common with menigococcal septicaemia, arising in up to 20% of cases (Betrosian et al, 2006). The development of purpura fulminans with these infections is thought to result from the consumption and eventual depletion of endogenous anti-coagulant factors, such as anti-thrombin III, protein C and S (Betrosian et al, 2006). Infection with these bacteria engenders a variety of inflammatory and procoagulant host responses that interact to result in vascular and tissue

Figure 8. Anti-phospholipid syndrome can present with explosive onset necrosis associated with internal organ damage, which in this case proved fatal.

Figure 9. This patient with a suspected deep vein thrombosis was given subcutaneous low molecular weight heparin for only 3 days, while awaiting a venogram that showed no venous thrombosis. After 10 days she developed widespread cutaneous necrosis associated with a mild reduction in platelet count. She eventually required surgical debridement followed by skin grafts.

injury, some of which are mediated by bacterial toxins. The host inflammatory cytokines associated with sepsis activate coagulation by stimulating the release of thromboplastin, from monocytes and the endothelium. This leads to the formation of thrombin and a fibrin clot. The thrombin in turn stimulates multiple inflammatory pathways and also activates the fibrinolysis cascade. This explosive activation of both pro-coagulant and anti-thrombotic cascades, called disseminated intravascular coagulopathy, perpetuates the consumption of factors in the coagulation cascade, including the endogenous anticoagulants. The preferential consumption of endogenous anticoagulants is responsible for the prothrombotic state that results in purpura fulminans. The end result of the host response is diffuse endovascular injury, microvascular thrombosis, organ ischemia, multiorgan dysfunction, and death in over 40% of cases (Gordon, 2001). Activated protein C and anti-thrombin III proteins can be efficacious when administered to patients with purpura fulminans to reverse the pathophysiology and facilitate recovery (Gordon, 2001).

There is evidence to suggest that a localised consumptive coagulopathy is responsible for the haemorrhagic skin necrosis in necrotizing faciitis and clostridium-associated gas gangrene (Bryant, 2003). However, while histology confirms the presence of intravascular thrombosis, it also demonstrates the presence of a sepsis-associated vasculitis; as such the precise mechanism remains to be determined (Wong and Wang, 2005).

Management of haemorrhagic skin necrosis

The most important aspect in the management of a patient with haemorrhagic skin necrosis is the establishment of a diagnosis. There are many clinical and investigational clues that can narrow down the hunt for the cause. Based upon the original works of Rudolf Virchow it has been possible to categorise the causes of haemorrhagic skin necrosis into three subgroups: haemostasis, vessel wall inflammation and coagulopathy. The clinical presentations also differ subtly between these categories (*Table 5*) so based on the clinical presentation alone it should be possible to narrow the focus of investigations.

Over and above investigations to find the cause, in many instances of haemorrhagic skin necrosis there is associated internal damage to vital organs, and so tests are needed to identify potential problems and monitor function. In some cases it will be apparent — based upon the natural history of the disease — which organs are likely to be affected, for example, Wegner's granulomatosis has a predilection to cause renal damage; while in the case of purpura fulminans there may be multiple organs affected. It is damage to the internal organs that will in the end determine the morbidity and mortality associated with the haemorrhagic skin necrosis episode. As such, multiple clinical sub-specialities may be involved to ensure the well-being of the patient; but it may fall upon the wound care specialist to coordinate and administer treatment.

Renal involvement may necessitate a renal biopsy and dialysis, while respiratory compromise may require ventilator support and potential transfer of the patient to the intensive care unit. Acute surgery may also be necessary, for example, in the management of sudden embolism and occlusion of an important vessel. Therefore, while a diagnosis is being formulated and thereafter, it will be necessary to support vital organs and determine:

- The best location for the patient (consider intensive care)
- Mattress requirement
- Pain management
- Fluid management and nutritional care
- Infection risk assessment and infection management
- Wound care strategy.

Consideration should be given as to how the areas of skin necrosis can be managed. Intuitively areas of extensive necrosis should be treated with surgical debridement, to promote healing of the wound and to reduce the risk of secondary infection. However, extensive debridement may cause release of cytokines that may further exacerbate any difficulties with vital organ function. Also surgical debridement in the absence of a diagnosis can be harmful, particularly in the case of vasculitis or coagulopathy where upon it may precipitate the development of further lesions. Once surgical debridement of the lesions has been planned, another consideration is whether to promote healing by secondary intention or skin grafting; often the two procedures are combined when the loss of tissue results in deep wounds.

The eventual treatment of the disease will vary based upon the diagnosis, in some instances such as severe hypotension the diagnosis will be reached quickly and the treatment option will be clear. Indeed many of the disease entities mentioned have specific treatment guidelines, take for example the management of purpura fulminans where in addition to treatment with antibiotics and anticoagulants, activated protein C and anti-thrombin III can be administered

Table 5

Haemorrhagic skin necrosis
(painful, tender, haemorrhagic skin necrosis with surrounding hyperaemia)

Causes of acute vessel thrombosis

	Haemostasis			Vessel wall inflammation		Hypercoagulability		
Clinical presentation of necrosis	Localised solitary lesions	Multiple, symmetrical peripheral lesions	Multiple, symmetrical peripheral lesions	Unilateral, regional, distal lesions	Symmetrically distributed multiple lesions often over weight-bearing area	Multiple lesions, often with a predilection for fatty areas	Multiple lesions, often with a predilection for distal sites	Multiple lesions, often with a predilection for sites of trauma
Common sites of involvement	Often over weight-bearing bony prominences, such as sacrum or hip	Typically affects distal digits tips	Typically affects distal digits tips	Lower limbs, either the area supplied by the dorsalis pedis or posterior tibial arteries or both	When ambulatory lesions predominate over the lower legs	Typically buttocks, abdomen and breasts (females).	Digits	Arms and legs
Typical pathophysiology	Pressure ulceration	Hypoperfusion	Blood hyperviscosity (e.g. polycythaemia rubra vera or multiple myeloma)	Atherosclerosis	Vasculitis	Warfarin necrosis	Factor V Leiden mutation	Purpura fulminans (Protein C deficiency)
Preceding features	Immobility	Severe hypotension/ shock, cool skin temperature, poor capillary return and peripheral cyanosis	Livedo reticularis, poor capillary return and peripheral cyanosis	Claudication, cool skin temperature distal to involved vessel, loss of hairs and poor capillary refill	Systemic symptoms such as malaise, lethargy and fever; abrupt onset with lesions appearing in waves	Initiation of warfarin therapy	Often there is a history of trauma or infection	Septicaemia
Investigations: Skin biopsy helpful	No	No	No	No	Yes	Yes	Yes	Yes
Initial investigations	Sensory assessment, assessment for infection, x-ray for underlying bone osteomyelitis, full blood count, renal and liver function tests, C-reactive protein, thyroid function test, albumin, transferrin, vitamin B12 and folate levels	Blood pressure, blood cultures, full blood count, renal and liver function tests, C-reactive protein, electrocardiograph and echocardiogram	Full blood count, renal and liver function tests, C-reactive protein, immunoglobulins, plasma and urine electrophoresis, hepatitis B and C antibody titres and bone marrow biopsy	Blood pressure, blood cultures, full blood count, renal and liver function tests, C-reactive protein, electrocardiograph, echocardiogram, arterial Doppler and possibly arteriogram	Skin histology, skin immunofluorescence, full blood count, renal and liver function tests, C-reactive protein, immunoglobulins, hepatitis B and C antibody titres, anti-nuclear antibody, extranuclear antibodies, complement levels, rheumatoid factor, anti-streptolysin O titre, blood cultures, convalescent viral titres, antineutrophilic cytoplasmic antibodies. Chest and sinus xrays, electrocardiogram and throat swab	Skin histology, full blood count, renal and liver function tests, C-reactive protein, immunoglobulins, protein electrophoresis, cryoglobulins, hepatitis B and C antibody titres, rheumatoid factor, kaolin clotting time, dilute pro-thrombin time, activated partial thromboplastin time, factor V mutational analysis, complement levels, protein C levels, Protein S levels, anti-thrombin III levels and dilute Russell viper venom test		

Key Points

- Haemorrhagic skin necrosis is painful and potentially fatal.
- Common causes of lower leg ulceration can present with haemorrhagic skin necrosis, although occasionally it can be a manifestation of a serious systemic disease.
- The management of haemorrhagic skin necrosis is dependent upon a rapid diagnosis.
- Haemorrhagic skin necrosis is associated with vessel thrombosis.
- Virchow's triad is a framework that is clinically useful to consider the causes of vessel thrombosis.

to prevent excessive tissue thrombosis. Occasionally these therapies may even be counter-intuitive, such as the continuation of warfarin therapy in warfarin-associated necrosis. It is beyond the scope of this article to outline all the treatment options for the diseases mentioned and these are clearly described elsewhere. Ultimately, it is not be necessary for the wound healing expert to be aware of all the therapeutic options, because often the care of such patients demands involvement from several different specialities.

Even after recovery, additional management may be necessary, for example, physiotherapy to prevent wound-associated contractures. Also, compromised internal organs may require long-term support, such as the need for renal dialysis. Some diseases can be associated with late complications, for example, Henoch-Schonlein purpura can result in renal failure up to a year or more after the acute episode of vasculitis and resoultion of haemorrhagic skin necrosis.

Conclusions

The diagnosis and management of patients that present with haemorrhagic skin necrosis can be challenging. This article has highlighted some of the more common, as well as some rarer, causative diseases. It is hoped that the strategy and approach outlined provides a useful framework for the diagnosis of haemorrhagic skin necrosis, and helps to direct the practitioner in initiating appropriate treatment. **WUK**

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