Review of management of purpura fulminans and two case reports

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Purpura fulminans (PF) is a haemorrhagic condition usually associated with sepsis or previous infection. Features include tissue necrosis, small vessel thrombosis and disseminated intravascular coagulation. Gram-negative organisms are the commonest cause of the acute infectious type, which is often associated with multi-organ failure. An idiopathic variety, however, is often confined to the skin. The mortality rate has decreased with better treatment of secondary infections, supportive care and new treatments, but it remains a disabling condition often requiring major amputations. We describe two cases and review the various treatments for this condition.


Keywords: infection, purpura fulminans; pharmacology, epoprostenol; pharmacology, ketanserin; pharmacology, protein C; pharmacology, antithrombin III; pharmacology, recombinant tissue plasminogen activator

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Purpura fulminans (PF), first described by Guelliot in 1884, is a haemorrhagic condition usually associated with either benign infection or severe sepsis. Features include hypotension, disseminated intravascular coagulation (DIC) and purpura leading to tissue necrosis with small vessel thrombosis. We describe two cases and review the treatment of this condition.

Case report 1

A previously fit 5-yr-old girl was admitted to hospital with a 10-day history of a chesty cough treated with erythromycin. The evening before admission she became generally unwell. On the morning of admission she was drowsy. A rash developed on her abdomen, and spread rapidly across her trunk and thighs.

At home and during transfer to hospital she had several seizures, which were treated with rectal diazepam.

On arrival at hospital she was drowsy and irritable and had an obvious purpuric rash. She weighed 22 kg. Her heart rate was 160 min\(^{-1}\) and arterial pressure 60/35 mm Hg. A provisional diagnosis of meningococcal septicaemia was made. After taking blood for culture, she was given benzylpenicillin (200 mg kg\(^{-1}\) 24 h\(^{-1}\)) and cefotaxime (200 mg kg\(^{-1}\) 24 h\(^{-1}\)) i.v. and gelofusin 20 ml kg\(^{-1}\). Tracheal intubation was carried out before transfer for intensive care.

After admission her rectal temperature was 38.4°C, heart rate 160 min\(^{-1}\), arterial pressure 70/30 mm Hg and central venous pressure 14 mm Hg. She received mechanical ventilation in pressure control mode, 16 cm H\(_2\)O, PEEP 4 cm H\(_2\)O and an \(F_{\text{IO}}\)\(_2\) 0.6.

The following results were obtained:

- Hb 12.2 g dl\(^{-1}\), white cell count 6.92\(\times\)10\(^9\) litre\(^{-1}\), platelets 162\(\times\)10\(^9\) litre\(^{-1}\), INR 2.5, APTT ratio 2.06;
- fibrin degradation products 64 ng ml\(^{-1}\) (ref. <300 ng ml\(^{-1}\));
- antithrombin III function 68% (ref. 80–120);
- protein C (free) 51% (ref. 70–150);
- protein S (free) 89% (ref. 70–150);
- protein S (total) 70% (ref. 70–130);
- urea 9.7 mmol litre\(^{-1}\), creatinine 140 μmol litre\(^{-1}\);
- CSF: clear and colourless, WBCs 5 mm\(^{-3}\), RBCs 3 mm\(^{-3}\), no organisms;
- blood cultures: *Neisseria meningitidis*.

Meningococcal septicaemia was diagnosed. Treatment with benzylpenicillin and cefotaxime was continued. She
was sedated with an infusion of i.v. morphine, intermittent diazemuls and trimeprazine via nasogastric tube, and given dextrose 4% saline 0.18% at 62 ml h⁻¹ i.v.

Her cardiovascular state became worse and an infusion of dobutamine and noradrenaline was started, along with i.v. hydrocortisone (20 mg kg⁻¹ 24 h⁻¹). Two days later her platelet count decreased to 54×10⁹ litre⁻¹. The white cell count was 49×10⁹ litre⁻¹ and the prothrombin ratio increased to 3. Platelets, cryoprecipitate and fresh frozen plasma were given.

The chest x-ray showed consolidation, considered to be caused by aspiration of vomit during a fit before admission to hospital. This was treated with i.v. metronidazole (10 mg kg⁻¹ 8 h⁻¹) for 5 days.

Over the following 2 days a number of ischaemic lesions developed on her toes and the tip of her left thumb. I.v. heparin (200 units h⁻¹ increasing to 500 units h⁻¹) and epoprostenol (increasing to 20 ng kg⁻¹ min⁻¹) were given with some improvement in her skin condition.

Four days after admission dobutamine and noradrenaline were stopped and she was extubated 4 days after that. The platelet count continued to decrease and the white cell count increased with a lymphocytosis, despite no evidence of infection. She was treated with daily fresh frozen plasma. The epoprostenol and heparin were decreased and stopped by day 10 and she was discharged to the ward the following day. Cefotaxime was discontinued after 10 days and the benzylpenicillin was changed to an oral preparation.

Four weeks after her admission she required amputation of all five toes through the proximal phalanx on her left foot, and three toes on her right.

She was discharged from hospital 6 weeks after admission, still with widespread areas of skin necrosis, mainly over the lower limbs and dorsum of the right hand. Later, de-sloughing, and grafting and excision of further necrotic areas were done, with good healing. She was later fitted with artificial toes (Figs 1 and 2).

**Case report 2**

A previously fit 18-yr-old girl was admitted to hospital 10 days after developing chickenpox. The day before admission she developed dusky discolouration of both legs. Her only medication was the oral contraceptive pill.

On examination she had good circulation to the hands and feet, she was conscious and afebrile with a heart rate of 80 min⁻¹ and arterial pressure of 116/80 mm Hg. She had tender bruises on both legs and thighs and knee movement was limited by pain. Examination found oral and vaginal thrush, but was otherwise unremarkable.

The following results were obtained:

- Hb 13.2 g dl⁻¹, white cell count 12.4×10⁹ litre⁻¹, platelets 65×10⁹ litre⁻¹, INR 1.4, APTT ratio 1.2, PT ratio 2.0, fibrinogen 0.3 g litre⁻¹ (ref. 2–4.5 g litre⁻¹), fibrin degradation products 2000–5000 ng ml⁻¹, urea 13.3 mmol litre⁻¹, creatinine 329 μmol litre⁻¹; anti-thrombin III (f) 60% (ref. 80–120); protein C (f) 37% (ref. 70–150); protein S (free) 41% (ref. 70–150); protein S total 79% (ref. 70–130); blood film: large platelets with haemangiopathic changes.

Chickenpox with PF was diagnosed. Treatment was started with fresh frozen plasma, i.v. azlocillin (100 mg kg⁻¹ 24 h⁻¹), i.v. acyclovir (10 mg kg⁻¹ 24 h⁻¹), oral nystatin (1 ml suspension qds), topical nystatin (one vaginal pessary daily) and topical acyclovir (vaginal cream qds).

Systemically she remained stable but she developed painful ischaemic lesions on her thighs, calves and upper limbs over the following 48 h and she was transferred to the intensive care unit for emergency plasma exchange. I.v. epoprostenol (prostacyclin) was started, increasing from 1 to 4 ng kg⁻¹ min⁻¹. I.v. fluids were increased to achieve a urinary output of 1 ml kg⁻¹ h⁻¹. Pain was treated with i.v. morphine using a patient controlled device.

The skin lesions spread to involve her flanks and hands, her white cell count increased to 28×10⁹ litre⁻¹, and coagulation measurements and renal function deteriorated.

Plasma exchange was continued, and fresh frozen plasma given to treat ‘thrombotic thrombocytopenic purpura’ and...
replace proteins C and S. Antithrombin III concentration was reduced and treatment with antithrombin III started.

Several digits became necrotic and an i.v. infusion of tissue plasminogen activator (t-PA) was started (0.5 mg kg⁻¹ over 4 h) followed by 100 units h⁻¹ of heparin. Blood analysis suggested haemolysis and blood transfusions and careful fluid monitoring were required.

By the seventh day of her intensive care unit admission she was started on i.v. ketanserin (10 mg bolus followed by 2 mg h⁻¹ for 24 h) in addition to treatment with i.v. epoprostenol (10 ng kg⁻¹ min⁻¹), i.v. heparin (100 units h⁻¹) and plasma exchange three to four times a week.

On day eight oral ketanserin was started (20 mg bd) and the epoprostenol reduced. On day 14 her epoprostenol was stopped and she left the intensive care unit receiving oral ketanserin, i.v. heparin, and regular plasma exchange.

Four days after discharge to the ward she had a pulmonary embolus (APTT 39 despite heparin) confirmed by radionuclide scan and treated with warfarin. Four weeks after admission she had plastic surgery and amputation of several digits.

**Discussion**

PF is a life-threatening disorder of acute onset characterized by cutaneous haemorrhage and necrosis caused by DIC and dermal vascular thrombosis.

Three distinct categories can be identified: inherited or acquired abnormalities of the protein C or other coagulation systems, ‘acute infectious’ PF and ‘idiopathic’.¹

We have described two cases of PF, one of the acute infectious variety and the other idiopathic. The idiopathic type was first recognized as an entity in 1964² and described as a disorder of childhood, which is preceded by a benign illness. It does, however, also occur in adults.

Inherited and acquired abnormalities of the protein C and protein S anticoagulant pathway are thought to be responsible for the majority of cases of PF, while Gram-negative organisms are the commonest cause of the acute infectious variety.³ The idiopathic variety is uncommon and differs from the acute infectious type in that microthrombi mainly occur in skin blood vessels rather than vessels of other organs.

The most common acute infection with which PF is associated is meningococcal sepsis, and in this condition the development of PF indicates a poor prognosis.³ Varicella is also a common association and, less commonly, pneumococcal sepsis and measles. In the neonatal period group B streptococcus appears to be the major cause but Staphylococcus, *Escherichia coli*, Enterobacter and others have been described.

**Clinical features**

The lesions of PF have a characteristic appearance, which distinguishes them from other purpuric lesions. Erythema is rapidly followed by irregular central areas of blue-black haemorrhagic necrosis with a surrounding erythematous border.⁴ Vesicles and bullae may form. Affected areas are painful and indurated. Although initially sterile, secondary infection of gangrenous tissue may occur, contributing to late mortality and morbidity. Necrosis may extend to muscle and bone. Healing leads to scarring, and auto-amputation of digits and extremities may occur.

The idiopathic variety is largely confined to the skin and mainly involves the lower half of the body. A similar distribution is seen in those with protein C or protein S deficiency, whereas infectious necrosis often begins distally with proximal progression or diffusely over the body.

Differential diagnosis includes thrombotic thrombocytopenic purpura, Henoch–Schönlein purpura and post-infectious thrombocytopenic purpura, but in none of these is this the skin necrosis so severe.

**Laboratory findings**

Typical haematological findings occur early and include low concentrations of fibrinogen, clotting factors and platelets as a result of their consumption, and prolonged prothrombin and partial thromboplastin times. Fibrinogen degradation products tend to be raised and concentrations of proteins C, S and antithrombin III reduced. Fever and leucocytosis with a left shift are common despite the absence of acute infection. The development of intravascular coagulation distinguishes PF from other forms of skin necrosis.

**Pathogenesis**

The pathogenesis is described as a ‘Shwartzman-like’ reaction, which is a necrotizing inflammatory lesion provoked by endotoxin from Gram-negative bacteria. The general picture in PF is of widespread microvascular thrombosis, the thrombi being made of fibrin with a mild inflammatory component. This differentiates it from other vasculitic skin disorders such as Henoch–Schönlein purpura and drug-induced purpura where the inflammatory component is more marked.

**Management**

The mortality rate of idiopathic PF has decreased considerably, mainly as a result of treatment of secondary infections but also from better supportive care and the use of other therapies. Management must be tailored to the individual and involve supportive therapy and replacement of blood products and clotting factors as appropriate.

In meningococcal septicaemia aggressive resuscitation, antibiotics and volume expansion are important for a good outcome. Correction of acid–base and electrolyte abnormalities and early use of oxygen and mechanical ventilation are helpful.⁵
Laboratory investigations that should be performed include a full blood count, PT, PTT, fibrinogen and fibrin degradation products. Whole blood and plasma supply both procoagulant and anticoagulant factors (protein C and S and antithrombin III) and rapid improvement in skin necrosis has been reported after their use.\(^4\) Massive quantities may be needed to replace losses into infarcted skin.\(^6\)

Prompt excision of necrotic tissue and wound closure is recommended. Patients who survive are often left with difficult wounds involving underlying muscle and bone, and a significant number of patients who survive multiple organ failure may need major amputations.\(^7\) Escharotomies and/or fasciotomies may be indicated.\(^2\)\(^8\) Fasciotomies should be considered early in patients with tense limbs and distal ischaemia, and should be performed on a clinical basis rather than on the basis of raised compartment pressures.\(^8\)

Many therapies, described below, have been used to arrest the progression of the disease.

**Heparin**

Heparin bonds with antithrombin III to inhibit thrombus formation and consumption of coagulation factors and may reverse the development of skin necrosis.\(^4\) Concurrent administration of fresh frozen plasma or antithrombin III may be necessary, particularly if antithrombin III concentrations are low. Difficulties arise in the clinical and laboratory monitoring of heparin where laboratory values are abnormal. Arbitrary schemes have been used such as a bolus of 4–10 000 units i.v. followed by an infusion,\(^9\) but heparin resistance may occur. Relapse can occur if heparin is reduced or discontinued within several days of initial response.\(^10\) There are arguments in favour of giving heparin before clotting factors are replaced, to as to avoid further thrombosis.\(^11\) Concerns about thrombocytopaenia and bleeding, however, continue to limit its use.

Idiopathic PF often responds well to heparin and tends not to recur, while that associated with protein C deficiency or inhibition is more responsive to protein C replacement.\(^4\)

**Protein C**

Protein C is a vitamin K-dependent glycoprotein with anticoagulant properties. It also has anti-inflammatory properties, which may contribute to improved survival.\(^5\)

In meningococcaemia there is a strong correlation between the severity of acquired protein C deficiency and mortality. Early protein C infusion corrects the deficiency and restores skin perfusion.

Daily protein C concentrations can be measured and the blood level and clinical condition should determine its use. It may be given as an i.v. infusion or intermittently,\(^12\)\(^13\) and the infusion should be reduced over several days when parameters have stabilized. The optimal duration of therapy and the target plasma level of protein C, however, are unknown.

In homozygous protein C deficiency, fresh frozen plasma (8–12 ml kg\(^{-1}\)) can give effective replacement therapy.

**Antithrombin III**

Antithrombin III may be reduced in PF and replacement has been shown to normalize levels and reverse DIC.\(^14\)\(^15\) High doses of antithrombin III may also compensate for decreases in levels of protein C in meningococcal PF.\(^14\) A loading dose is generally given, followed by an infusion.

**Recombinant tissue plasminogen activator (rtPA)**

Concentrations of plasminogen activator inhibitor tend to be increased in PF and correlate with mortality in the acute infectious type.\(^16\) Fibrin deposition results leading to microvascular thrombosis and multiple organ failure. PAI concentrations may decrease after treatment with antibiotics and fresh frozen plasma.\(^16\)

rtPA induces clot specific fibrinolysis without any direct haemodynamic effect and with supposedly few bleeding complications. Its half-life is about 5 min and doses in the range of 0.25–0.5 mg kg\(^{-1}\) h\(^{-1}\) can improve peripheral perfusion.\(^17\)\(^18\) Because the procoagulant state may continue beyond the first few hours, particularly in meningococcal sepsis, repeated infusions of rtPA may be beneficial. Concerns about haemorrhagic complications, however, tend to reserve its use for PF which has not responded to more conventional treatment.

**Epoprostenol (prostacyclin)**

I.v. epoprostenol is a powerful vasodilator and potent inhibitor of platelet aggregation. It has been used to treat PF from sepsis in infants and neonates at doses of 5–20 ng kg\(^{-1}\) min\(^{-1}\) without hypotensive side effects.\(^19\) The beneficial effects of the infusion can be maintained with oral dipyridamole. Hypotension is a complication.

**Topical nitroglycerin (TNG)**

Severe pain can accompany PF. This may be secondary to prostaglandin release from poor tissue perfusion, with consequent sensitization of A delta and C nerve fibres.\(^20\) TNG is metabolized to nitric oxide (NO) which produces vasodilatation. There are several reports of improved skin blood flow with topical nitroglycerin.\(^20\)\(^21\) It is applied as a 2% paste and can be repeated every 4–6 h. Pain relief occurs within 10–30 min.\(^20\) Reperfusion is probably by a combination of arteriolar and venous dilatation and opening collateral channels.\(^21\)

**I.v. dextran**

This coats vessel walls, red cells and platelets, inhibiting cell aggregation, and can reduce sludging and spread of
vascular damage. Low molecular weight dextran (mol. wt 40 000) is superior at counteracting red cell aggregation. Most of the reported responses have occurred when it has been given in combination with other treatments and it may be of use in those who fail to respond to plasma and heparin therapy.4

**Plasmapheresis**

Plasmapheresis removes circulating endotoxin, cytokines and inflammatory cell mediators and can assist in control of fluid balance, when excessive volumes of blood products may be needed. Fresh frozen plasma and cryoprecipitate as replacement fluid will increase fibrinogen concentrations and shorten PT and PTT.

Anticoagulation in fulminant PF remains controversial because of the tendency for both thrombosis and haemorrhage. Severe coagulopathy, placement of large catheters and heparinization all contribute to the risk of bleeding and demand experienced personnel in an intensive care setting.

**Regional anaesthesia**

Epidural sympathetic block with local anaesthetic (liognocaine 0.5%) has been reported to improve skin perfusion and reverse the development of PF. It avoids the haemodynamic instability associated with systemic vasodilators,22 of particular benefit in those with circulatory compromise, while also providing analgesia. However, the presence of a coagulopathy and the risk of vertebral canal haematoma may contraindicate its use.

**Other therapies**

Epsilon aminocaproic acid inhibits fibrinolysis but has been reported to arrest skin necrosis when given alone in idiopathic PF. The mechanism is unclear and it may potentiate vascular thrombosis.

Vitamin K will normalize levels of proteins C and S in those with vitamin K deficiency but there is no clear evidence of benefit.

Ketanserin is a serotonin (S2) antagonist and a weak alpha blocker. It has been used for the treatment of intermittent claudication and Raynaud’s disease,23 24 but there is no evidence to date for its benefit in PF.

Gangrenous areas have a peripheral margin of hypoxia because of partial arteriolar occlusion and these zones may benefit from hyperbaric oxygen,25 although there is insufficient evidence to suggest a consistent benefit in PF. Its use is restricted by the development of convulsions and bronchopulmonary dysplasia.4

Leech saliva contains an anticoagulant called hirudin, which is the most potent inhibitor of thrombin known and can promote local bleeding for hours. It can reverse thrombus formation in PF.26 The high affinity and specificity of hirudin for thrombin enable it to penetrate thrombi and neutralize fibrin-bound thrombin, and to enter the extravascular space to further quench thrombin at its site of origin.20 It may also enter the systemic circulation to reverse organ damage. Leeches may, however, introduce infection.

Glucocorticoids have often been used in idiopathic PF without evidence of benefit. Their role may be defined in the setting of PF after an allergic illness as a result of their anti-inflammatory effect, or as immunosuppressive therapy if an antibody inhibitor of protein C is present.3

Warfarin can reduce levels of active forms of protein C and S when given during the acute phase of PF and can, therefore, exacerbate thrombosis. It probably does not induce relapses but, as the risk of late relapse is low, there is probably no indication for long-term prophylactic therapy.

**Conclusion**

We have described two cases of PF, one associated with acute infection and the other of the idiopathic variety. Supportive treatment and replacement of deficient blood components, fresh frozen plasma and clotting factors is the mainstay of therapy.

Protein C and antithrombin III should be given if deficient. Heparin should be considered early on because of the risk of thrombosis with factor replacement. Dextran may have a role in complementing these treatments.

Other treatment modalities should be used depending on the progress of the disease, but there is no strong evidence in favour of one particular therapy.

Prostacyclin may cause hypotension and nitroglycerin can have unpredictable effects. Plasmapheresis may be helpful when fluid overload is a problem. There is no evidence to date regarding the benefit of ketanserin but it is a treatment option. Combination therapy is usually used.

We advise rigorous resuscitation with fluids, ventilation and inotropes, and early consideration of lower limb fasciotomies.

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**References**

Intra-operative and post-operative hypercapnia leading to delayed ventilatory failure. The hypercapnia and surgical emphysema were secondary to rectal insufflation with carbon dioxide used to facilitate visualization and resection of a rectal tumour. Despite a return to wakefulness after surgery, the patient's level of consciousness deteriorated in the recovery area as a result of surgical emphysema and increased respiratory failure. On close examination, surgical emphysema was identified in unusual areas, and surgical emphysema was secondary to rectal insufflation with carbon dioxide used to facilitate visualization and resection of a rectal tumour. The hypercapnia and surgical emphysema are well described in the literature, but this case highlights the unusual presentation.