

# Purpura fulminans: recognition, diagnosis and management

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## ABSTRACT

Purpura fulminans (PF) is a haematological emergency in which there is skin necrosis and disseminated intravascular coagulation. This may progress rapidly to multi-organ failure caused by thrombotic occlusion of small and medium-sized blood vessels. PF may complicate severe sepsis or may occur as an autoimmune response to otherwise benign childhood infections. PF may also be the presenting symptom of severe heritable deficiency of the natural anticoagulants protein C or protein S. Early recognition and treatment of PF is essential to reduce mortality and to prevent major long-term health sequelae. However, management strategies require accurate identification of the underlying cause. This review focuses on the clinical features, differential diagnosis and laboratory features of the range of PF disorders and includes expert consensus opinion about immediate and on-going management.

Purpura fulminans (PF) is a rapidly progressive thrombotic disorder affecting neonates and children in which there is haemorrhagic infarction of skin and disseminated intravascular coagulation (DIC). PF may also herald multi-organ failure or severe large vessel venous thrombosis and therefore causes high initial mortality and long-term morbidity in survivors. Early recognition and diagnosis of the initiating cause of PF may avert these adverse outcomes although this can present significant challenges to paediatricians and neonatologists without expertise in haemostasis and thrombosis.

Unfortunately, most of the existing PF literature comprises single case reports or short case series and there have been no recent systematic reviews that deal with all causes of PF. In order to correct this, a panel of UK Haematologists and laboratory scientists was assembled to systematically review the previous PF literature and to provide expert opinion to guide diagnosis and management of this disorder. All panel members have direct experience of diagnosis and management of severe heritable protein C (PC) deficiency, which is the major genetic cause of PF. The aim of the panel was to appraise and develop the current practice of diagnosis and management of PF and severe PC deficiency, and to communicate the main findings to a wider audience of clinicians who are likely to be the first point of contact for neonates and children presenting with PF.

## CLINICAL APPEARANCE OF PURPURA FULMINANS

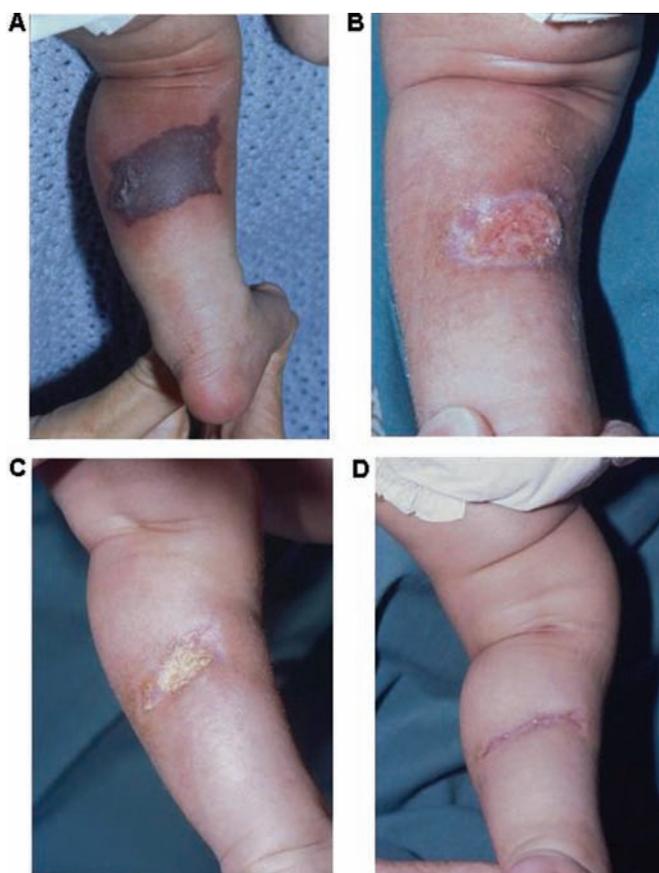
The initial appearance of PF lesions is of well-demarcated erythematous macules that

progress rapidly to develop irregular central areas of blue-black haemorrhagic necrosis. Advancing areas of central necrosis are typically surrounded by a thin border of erythema that fades into adjacent uninvolved skin. Haemorrhage into the necrotic dermis causes PF lesions to become painful, dark and raised, sometimes with vesicle or bulla formation<sup>1</sup> (figure 1). Although early PF lesions may be reversible with therapeutic intervention, established lesions often progress within 24 to 48 h to full-thickness skin necrosis or more extensive soft tissue necrosis that may require surgical debridement, fasciotomies or amputation.<sup>2,3</sup> This progression in the clinical appearance of PF correlates with the histological appearance of occlusion of small dermal vessels with microthrombi causing capillary dilation and congestion with red cells in early PF. In later stage lesions, there is irreversible endothelial ischaemic injury with extravasation of blood cells into the dermis and gangrenous necrosis sometimes with secondary infection.<sup>4</sup> The distribution of PF lesions may be different according to the underlying pathogenesis (see below).

Early PF lesions may be confused with simple traumatic skin bleeds or with other purpuric rashes such as immune thrombocytopenic purpura or thrombotic thrombocytopenic purpura. However, the skin changes in these diagnoses do not progress to necrosis. Henoch-Schönlein purpura may also cause lesions that are similar to PF although tend to be smaller and urticarial and very seldom lead to necrosis.<sup>5</sup> In most circumstances, these differential diagnoses may be readily distinguished from PF by considering associated clinical and laboratory features.

## CAUSES AND PATHOGENESIS OF PURPURA FULMINANS

The appearance of PF in neonates or children may be a presenting feature of severe acute sepsis and is a cardinal feature of meningococcal septicaemia which is complicated by PF in 10–20% of cases.<sup>6</sup> Less commonly, PF complicates *Streptococcus*, *Haemophilus* and *Staphylococcus* sepsis, particularly in asplenic patients (box 1).<sup>2,7</sup> PF may occur as an autoimmune phenomenon after otherwise benign infections such as *Varicella* or may have no identifiable precipitant. Rarely, PF may be the first phenotypic manifestation of severe heritable defects of the PC anticoagulant pathway. In some individuals, a combination of sepsis and a partial heritable defect in the PC anticoagulant pathway is sufficient to initiate PF suggesting synergy between



**Figure 1** Purpura fulminans lesion in severe heritable protein C deficiency. Images show progression of a PF lesion from a well-demarcated area of haemorrhagic infarction shortly after presentation (A) through skin necrosis (B), healing (C) and finally, after surgical repair (D).

these initiators.<sup>8 9</sup> A suggested classification of the causes of PF is shown in box 1.

### PURPURA FULMINANS IN SEVERE SEPSIS

PF may follow the acute inflammatory response in severe sepsis in which there is systemic activation of the coagulation and complement pathways and endothelial dysfunction causing DIC. Widespread coagulation activation leads to consumption of circulating coagulation factors and platelets which may lead to bleeding.<sup>10</sup> The loss of anticoagulant and anti-inflammatory proteins, particularly PC and its essential cofactor protein S (PS) may also promote thrombus formation, inhibit fibrinolysis and lead to further activation of inflammatory pathways.<sup>11 12</sup>

In DIC complicating sepsis caused by some organisms such as meningococcus, there is also a local defect in the activation of PC on endothelium in small vessels leading to further loss of local anticoagulant and anti-inflammatory PC activity. This initiates micro-vascular thrombosis in the dermis causing PF.<sup>13</sup> PF in severe sepsis may be distinguished from PF of other causes by typically developing in the distal extremities and progressing proximally or appearing as a generalised or diffuse rash affecting the whole body surface.<sup>1</sup> PF caused by severe sepsis is also usually accompanied by micro-vascular thrombosis and haemorrhagic infarction in other tissues, especially the lungs, kidneys, central nervous system, adrenal glands. The clinical features of sepsis are therefore accompanied by multi-organ failure that is rapidly progressive and carries high mortality. The clinical manifestations of the systemic inflammatory

### Box 1 Proposed classification of the causes of purpura fulminans

- ▶ Severe acute infections
  - *Neisseria meningitidis*
  - *Streptococcus pneumoniae*
  - Group A and B streptococci
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*
  - Other bacteria
  - *Plasmodium falciparum*
- ▶ Postinfectious purpura fulminans
  - Autoimmune protein S deficiency
  - Autoimmune protein C deficiency
- ▶ Heritable PC pathway defects
  - Severe protein C deficiency
  - Severe protein S deficiency
- ▶ Coumarin induced skin necrosis

response and DIC in severe sepsis have been reviewed in detail elsewhere.<sup>14</sup>

### POSTINFECTIOUS PURPURA FULMINANS

PF lesions may also appear a few days or weeks after a febrile infectious illness. However, in this circumstance, PF lesions tend to occur on the lower body, especially the thighs, lower

legs, buttocks and in males, the scrotum and penis. PF is uncommon on the upper body and arms and is rare on the head and neck.<sup>1</sup> In contrast to PF in severe sepsis, postinfectious PF typically spares the distal extremities. Phenomena such as large vessel venous thrombosis and systemic micro-vascular thrombosis and multi-organ failure are uncommon but may occur later in the course of inadequately treated disease.<sup>1,3</sup>

Postinfectious PF is most commonly associated with *Varicella* and *Streptococcus* infections although a wide range of organisms have been implicated (box 1). In some cases, a history of a febrile illness is not always offered and a causative organism may not be identified. Postinfectious PF should be considered strongly if new PF and DIC develop in an otherwise well child. Affected children typically show a severe acquired deficiency of PS caused by cross-reacting IgG autoantibodies that increase PS clearance from the circulation.<sup>15</sup> PF caused by autoantibodies against PC are reported rarely.<sup>16</sup> Antiphospholipid antibodies are common in children with PF after varicella infection but also after uncomplicated varicella. These are usually transient, correlate poorly with PS levels and thrombosis and are seldom likely to be of clinical significance.<sup>15</sup>

### HERITABLE PC AND PS DEFICIENCY

PF is also a presenting feature of severe heritable deficiency of PC or PS arising from pathological mutations in the *PROC* and *PROS1* genes respectively (box 1). Partial PC deficiency caused by heterozygous *PROC* mutations has a reported incidence of 1 in 200–500 individuals although is a risk factor for adult-onset and childhood venous thromboembolic disease.<sup>17</sup> In contrast, PF arises when there is a severe loss of PC anticoagulant function caused by homozygous or compound heterozygous *PROC* mutations. In view of the observed prevalence of partial PC deficiency, the predicted prevalence of severe PC deficiency is 1 in 40 000–25 000 individuals. However, to our knowledge, there are only eight individuals in the UK who are receiving long-term treatment for this disorder. This marked discrepancy probably reflects the high fetal loss, peri-natal mortality and difficulties in diagnosis of severe PC deficiency in this age group.<sup>18</sup> Severe heritable PS deficiency is exceptionally rare.

Clinical manifestations of severe heritable PC deficiency include PF developing typically within a few hours or days after birth and progressing to widespread skin necrosis, digital and limb gangrene.<sup>19</sup> There is a predisposition of PF lesions to develop on the lower limbs and male genitalia in an identical way to postinfectious PF. The PF lesions may also form at pressure points in neonates such as the heels and buttocks. Affected neonates also typically show significant neurological injuries resulting from antenatal or early postnatal cerebral venous thrombosis with secondary peri-ventricular haemorrhagic infarction and hydrocephalus (figure 2A). Blindness is a common manifestation of severe PC deficiency and may arise from vitreal bleeding, retinal vein, artery or vitreal vein thrombosis with retinal detachment manifesting as leucocoria (figure 2B) or ischaemic optic atrophy.<sup>20</sup> Large vessel thrombosis and multi-organ failure from widespread micro-vascular thrombosis are recognised sequelae.<sup>21</sup> There are occasional reports of severe PC deficiency presenting with extensive large vessel thrombosis without antecedent PF<sup>22</sup> and of severe PC deficiency presenting with PF later in infancy.<sup>23</sup> Parents of a neonates or child with severe heritable PC deficiency are frequently consanguineous and there may be a history of fetal loss in previous pregnancies.

### LABORATORY INVESTIGATION OF PURPURA FULMINANS

The cardinal laboratory features of PF are those of the associated DIC which manifests as prolonged plasma clotting times, thrombocytopenia, reduced plasma fibrinogen concentration, raised plasma fibrin-degradation products and sometimes, microangiopathic haemolysis. However, this pattern of abnormalities is not specific to PF and may occur in DIC of any cause.<sup>24</sup>

Measurement of PC and PS levels are important additional investigations that should be performed at presentation. PF is usually associated with reduced PC or PS levels to <5 IU/dl although it is important to recognise that healthy term neonates show reduced and highly variable physiological levels of PC and PS (approximately 15–55 IU/dl) compared to older children and adults and that these tend to rise progressively through the first six months of life.<sup>24</sup> PC levels may be reduced further to levels of <10 IU/dl in preterm or twin neonates or those with respiratory distress without overt PF or DIC.<sup>25</sup>



**Figure 2** Neurological and ophthalmic manifestations of severe Protein C deficiency. T2-weighted brain MRI of a child with severe heritable PC deficiency showing bilateral peri-ventricular cystic porencephaly that is typical of periventricular haemorrhagic infarction (A). The characteristic ocular manifestation of leucocoria (B) may arise because of ischaemic optic atrophy following vitreal bleeding or retinal venous or vitreal vein thrombosis.

Interpretation of PC and PS levels may be hindered further if plasma samples are obtained after emergency treatments such as fresh frozen plasma (FFP) which contain exogenous PC and PS. The results of PC and PS tests should therefore be compared with age-adjusted laboratory reference ranges and interpreted carefully alongside clinical findings. Early input from a paediatric haematology specialist is recommended.

Neonates or older children with PF often present a significant diagnostic challenge because severe sepsis, heritable PC or PS deficiency and postinfectious PS deficiency are all associated with DIC. The presence of DIC is also typically associated with markedly reduced plasma PC and PS concentration because of consumption of these natural anticoagulants. The demonstration of DIC and low PC and PS alone are therefore usually insufficient to identify the underlying cause of PF. Urgent measurement of PC and PS levels in the parents of a neonate with PF may be informative since demonstration of a partial reduction in PC or PS in both parents is highly suggestive of severe heritable PC or PS deficiency in the affected neonate or child. In contrast, demonstration of normal PC or PS in both parents makes heritable deficiency very unlikely. Paternity should not be assumed when interpreting parental PC and PS levels and it should be recognised that low PS levels may be reduced in healthy women postpartum and does not necessarily indicate partial heritable PS deficiency.

In practice, identification of the cause of PF is usually post hoc and requires careful consideration of the age and circumstances of presentation. Severe sepsis is usually apparent through clinical findings, isolation of a causative organism, laboratory evidence of a severe acute phase response and by demonstration of clinical response to antimicrobial therapy. After the introduction of treatment for severe sepsis, the stimulus for microvascular thrombosis and DIC is typically short lived and no new PF lesions develop as PC replacement therapy is progressively reduced. Postinfectious PF may be more prolonged and should be considered if presentation occurs in infants or older children who are otherwise well or are in convalescence from a febrile illness. Evidence for this diagnosis is strengthened by serological evidence of recent *Varicella* infection or if coagulation assay tests for lupus anticoagulant are positive. Definitive diagnosis requires specialist interpretation of PC and PS assay results because some rare heritable variants may be difficult to identify in commercially available laboratory tests.<sup>26</sup> Diagnosis of severe heritable PC or PS deficiency may be confirmed by demonstration of homozygous or compound heterozygous mutations in the *PROC* or *PROS1* genes.<sup>27 28</sup>

### ACUTE MANAGEMENT OF PURPURA FULMINANS

PF of any cause is a haematological emergency that requires urgent intervention because of the rapidly progressive nature of the multi-organ thrombotic injury and because of the frequent association with severe sepsis. Accordingly, most neonates and older children who present with PF are initially assumed to have a septic cause and are managed with full supportive care, urgent broad spectrum antimicrobial and adjunctive therapies. PF with DIC also requires urgent FFP (10–20 ml/kg every 8–12 h) in order to replace pro-coagulant and anticoagulant plasma proteins that are consumed in the DIC process. In accordance with current UK recommendations, all FFP for paediatric use should be sourced from non-UK volunteer donors and should undergo methylene blue pathogen reduction.<sup>29 30</sup> Additional transfusion with platelet concentrates (10–15 ml/kg) or cryoprecipitate (5 ml/kg) may be necessary

for significant thrombocytopenia (platelet count  $<50 \times 10^9/\text{dl}$ ) and hypofibrinogenaemia (fibrinogen concentration  $<1\text{g}/\text{dl}$ ) respectively, particularly if there is pathological bleeding.<sup>29</sup> An important therapeutic action of FFP in this setting is to replace PC and PS in circulating plasma which are depleted in all causes of PF. Methylene blue treated FFP contains approximately 95 IU/dl PC and PS<sup>31</sup> and a therapeutic dose of 15 ml/kg is therefore anticipated to increase plasma PC and PS levels in recipients by approximately 30 IU/dl.<sup>19</sup>

Empiric replacement therapy with FFP is also appropriate initial therapy for postinfectious PF and for neonates presenting with suspected severe heritable PC or PS deficiency prior to definitive diagnosis. In this circumstance, the intensity of initial therapy is usually adjusted to prevent the appearance of new PF lesions and this is usually accompanied by stabilisation or correction of the laboratory markers of DIC. However, in postinfectious PF there is increased auto-immune clearance of PS and it may be difficult to achieve therapeutic levels of plasma PS with FFP alone. There is currently no commercially available PS concentrate and interventions such as plasma exchange to enable high volume replacement therapy in combination with immune suppression may be considered. For all neonates and older children, sustained PC or PS replacement therapy using FFP may cause significant practical problems relating to fluid overload and immunological complications such as allergy and transfusion related lung injury.

### PC REPLACEMENT THERAPY IN SEPSIS

Reduced activated PC (APC) anticoagulant and anti-inflammatory activity is critical for the pathogenesis of PF and replacement therapy using recombinant APC concentrate (Drotrecogin alfa (activated); Xigris, Eli Lilly, Indianapolis, USA) benefits adults with severe sepsis at high risk of death although increases bleeding risk.<sup>32</sup> In the single randomised controlled trial in children with severe sepsis (RESOLVE study), recombinant APC concentrate did not improve organ failure or 28 day mortality but was associated with increased intracranial bleeding, particularly in children younger than 60 days.<sup>33</sup> Accordingly, recombinant APC is not recommended for children with PF during severe sepsis.<sup>34</sup>

An alternative agent is PC concentrate which is converted to APC in vivo and therefore also has anticoagulant and anti-inflammatory activity.<sup>35</sup> In small single-arm observational studies in adults and children with severe sepsis, infusion of a high purity, plasma derived PC concentrate (Ceprotin; Baxter AG, Vienna, Austria) was associated with better than predicted clinical outcomes.<sup>36</sup> Furthermore, in a dose-finding randomised controlled trial in children with PF complicating severe meningococcal sepsis, PC concentrate caused non-significant improvement in abnormal laboratory parameters of coagulation and was not associated with abnormal bleeding.<sup>37</sup> This study was not powered to demonstrate an effect on efficacy outcomes. Human PC concentrate is not currently licensed for use in PF complicating severe sepsis and the role of this agent requires clarification in larger scale trials.

### PC REPLACEMENT THERAPY IN HERITABLE PC DEFICIENCY

PC concentrate is licensed in Europe and the USA for the short-term prevention of PF in severe heritable PC deficiency and should be considered as an alternative to FFP as soon as this diagnosis is confirmed because of greater efficacy but also to minimise FFP exposure. Experience is greatest with the Ceprotin product (Baxter AG) and we recommend initial

loading with 100 u/kg followed by 50 u/kg every 6–12 h during treatment of active PF.<sup>18</sup> Although the plasma half-life of PC in healthy subjects is approximately 10 h, in patients with active PF, this may be markedly reduced to 2–3 h because of consumption through DIC. Initial replacement regimes may therefore require modification according to clinical response of the PF lesions and laboratory markers of DIC such as D-dimer and PC level (target trough PC activity >25 IU/dl).

In the experience of the panel members and from other expert sources,<sup>18</sup> long term prevention of PF requires on-going treatment with Ceprotrin at doses of 30–50 u/kg given by intravenous infusion every 2–3 days. Subcutaneous infusion of Ceprotrin has been used successfully in some individuals to circumvent line sepsis, which often complicates long-term intravenous regimes. Reported treatment regimes using subcutaneous infusion are typically within the range of 100–350 u/kg administered at up to 3 day intervals.<sup>38–40</sup> The Ceprotrin product has a well-documented safety record with no reported instances of bleeding, inhibitor formation or infection transmission during therapy.<sup>41</sup> An alternative PC concentrate (Protexel; LFB, Lille, France) is also now licensed in some European countries as replacement therapy in severe heritable PC deficiency and early experience suggests that efficacy and safety are similar to the Ceprotrin product.<sup>42</sup>

### ANTICOAGULATION IN PURPURA FULMINANS

Anticoagulation should be used with caution in the treatment of acute PF because of the increased bleeding risk caused by depletion of pro-coagulant clotting factors caused by DIC. However, when PF is accompanied by large vessel venous thrombosis or central venous catheter thrombosis, weight-adjusted unfractionated heparin is usually necessary but should be given concurrently with FFP replacement therapy. This helps reduce bleeding risk and avoids heparin resistance caused by acquired antithrombin deficiency which commonly accompanies severe sepsis. Unfractionated heparin should be monitored using the activated partial thromboplastin time (aPTT) although the anti-Xa assay may offer some advantages if there is a significant additional coagulopathy or heparin resistance caused by depletion of antithrombin. aPTT and anti-Xa test results should be interpreted against locally determined therapeutic ranges.<sup>43</sup>

On-going anticoagulation may be required after resolution of acute PF if there is large vessel thrombosis. In this circumstance, vitamin K antagonists should be used with extreme caution since these agents cause further depletion of PC and PS and may therefore precipitate further micro-vascular thrombosis and PF.<sup>44</sup> Vitamin K antagonists should therefore be started at low dose while unfractionated heparin treatment is continued for at least 48 h after a therapeutic INR is reached. Control of long-term anticoagulation with vitamin K antagonists is often challenging in younger children. There is limited experience of long-term anticoagulation with low-molecular weight heparin in children with severe heritable PC deficiency which may circumvent some of these difficulties.<sup>26 45</sup>

### LONG-TERM OUTCOMES AFTER PURPURA FULMINANS

PF complicating severe sepsis is a self-limiting phenomenon and resolution of acute sepsis eliminates the drive for the formation of new PF lesions. Similarly, in postinfectious PF, the risk of new PF lesions lasts only as long as neutralising PS antibodies are present in the circulation which is typically 1–2 weeks after presentation.<sup>3</sup> However, once PF lesions have progressed to full thickness skin necrosis, healing usually take

4–8 weeks and leaves large scars. Since many children with PF also require surgical debridement, fasciotomy, amputation or plastic reconstruction, multi-disciplinary input is required to facilitate rehabilitation.<sup>2 7 8</sup> Survivors of severe sepsis may show long term neurological, psychological and other long-term health sequelae.<sup>46</sup>

Neonates and children with severe heritable PC deficiency have an on-going risk of PF and therefore require long-term antithrombotic therapy. This usually requires PC replacement therapy either alone, or in combination with coumarins or low-molecular weight heparin.<sup>18</sup> In some cases, recurrent PF may be prevented with anticoagulant drugs alone.<sup>26 45</sup> Liver transplantation offers long term cure of heritable PC deficiency.<sup>47</sup> The additional neurological and ophthalmic injuries associated with severe heritable PC deficiency frequently result in delayed psychomotor development and blindness and sequelae such as epilepsy, hydrocephalus and cerebral palsy. The supervision of PC replacement therapy and the management of these complex chronic health issues usually requires multi-disciplinary expert care that is usually co-ordinated in centres with expertise in paediatric thrombosis and haemostasis.

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