Meningococcal septicaemia and purpura fulminans in children – surgical management and outcome: a 22 year review of 68 patients

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Abstract
Meningococcal septicaemia complicated by purpura fulminans remains a devastating illness with rapid onset, debilitating morbidity and high mortality. The clinical course of management of 68 children (average age 3.4 years) with purpura fulminans seen over a 22 year period is described. All patients received maximum systemic support. Standard surgical techniques were utilised for skin grafting and amputations.

Overall mortality was 10 per cent. Demarcation of necrotic areas was evident at 5.5 days and the average area of skin necrosis was 14 per cent body surface area. The lower limbs were predominantly affected. Purpura fulminans resolved in 13 children (19 per cent) without skin necrosis. Skin grafting was required in 39 children.

The following factors were associated with a poor outcome for peripheral extremity salvage; progressive irreversible skin changes, early disappearance of distal pulses, tense cold swollen extremities and intense pain on passive movement of the affected extremity. Amputations were performed proximal to the area of necrosis, on average 27 days post injury. Soft tissue releasing incisions were not performed.


Introduction
Purpura fulminans is a rare catastrophic childhood illness occurring after an initial apparently benign infection. It has a rapid progression and symptoms include development of a purpuric skin rash, disseminated intravascular coagulation (DIC) and frequently multiple organ failure. It can follow viral, rickettsial and bacterial infections and typically is seen following Neisseria meningitides septicaemia. Children with meningococcaemia are at greatest risk of developing purpura fulminans, with an incidence of 10-33 per cent, while surgical complications occur in up to 72 per cent, often with long-term sequelae. The established disease has a case fatality rate of 8-50 per cent. Rifampicin prophylaxis to all household contacts is advisable to eradicate bacteria from the nasopharynx and to prevent contacts from developing the disease.

Medical management includes systemic support, antibiotics, correction of plasma deficiencies and, when required, anticoagulant and thrombolytic therapy. Surgical treatment depends on the nature and extent of tissue damage and may include decompression during the acute phase and, subsequently, debridement of necrotic tissue, skin grafts, local microvascular flaps and amputations. This study reports our experience with the management of children with purpura fulminans seen in our hospital since 1977, with a view to developing a surgical management protocol which could perhaps limit the extent of tissue injury.
Material and methods
A retrospective review of records was conducted of patients admitted to the intensive care unit with a clinical diagnosis of purpura fulminans seen during the 22 year period (1977-1999). Purpura fulminans was defined as clinical evidence of extensive purpura, intravascular thrombosis and the presence of septic shock. Timing and extent of surgical interventions were documented especially as a conservative policy was pursued during this time.

Wound care was determined by local pathology and, in principle, was dealt with similar to full thickness burns. Small necrotic areas were left to heal or were covered with non adhesive dressings. Larger areas were covered with an antiseptic solution and extensive wounds were regarded as full thickness necrosis requiring regular hydrotherapy, topical antiseptics, occlusive dressings, bacteriological surveillance and debridement when fully demarcated.

Standard surgical principles were followed. Debridement and primary or delayed skin grafting were done only in stable patients with well demarcated necrotic tissues. Levels for amputation were likewise defined and standard principles were used. Standard pain control measures were used including intravenous morphine and oral analgesics.

Results
Seventy five children with an admission or discharge diagnosis of purpura fulminans were identified. In total, seven children with non-meningococcal purpura were excluded from the study. Of the 68 children with meningococcal purpura fulminans, there were 44 females and 24 males with an average age of 3.4 years (range 3 months – 12 years). Eight of these children were aged less than 1 year.

The Glasgow meningococcal septicaemic prognostic score points, used to stratify patients, was not used due to missing information related to the coma scale score. Skin necrosis (dark black areas) was observed within 24 hours of admission and involved an average of 14 per cent total body surface area (range 2-85 per cent). The lower limbs were involved in 37 children, upper thighs in six, gluteal area in three, trunk in 17, arms in 18 and face and head in eight. Multiple areas were usually involved and demarcation of necrotic tissue was clinically completed at 5.2 days (range 3-17 days).

All 68 patients presented with septicaemic shock, intravascular coagulation and purpuric skin lesions. Gram-negative intracellular Diplococci were cultured from skin scrapings in two children and from blood cultures in 49. Seventeen children had negative blood cultures, 10 of whom received antibiotics prior to admission.

The meningococcal isolates were not typed but all showed 100 per cent sensitivity to penicillin, cefotaxime and chloramphenicol. Ten children (14 per cent) died between 8 and 120 hours post admission and death occurred within 24 hours of admission in eight children. Heparin was used in seven and tissue plasminogen activator and streptokinase were used in an additional three patients, but did not prevent amputations in seven of the 10 children.

Purpura fulminans resolved in 13 children without skin necrosis. Spontaneous healing of necrotic tissue occurred in six and surgical skin grafting to the legs, arms, trunk and face was required in 39 (Table 1). Five primary skin grafts were performed of which four were lost due to the infected necrotic nature of the wounds which was an unsuitable base for primary skin grafting.

Quantitative tissue cultures of necrotic tissue always yielded a heavy growth of Gram-positive and Gram-negative organisms, especially Staphylococcus aureus, Beta haemolytic Streptococcus, Pseudomonas, Proteus, Enterobacter, Klebsiella and Escherichia coli. No fungal elements were identified. The subsequent 34 wounds were all excised and allowed to establish a healthy granulation tissue base followed by delayed skin grafting. Excellent skin graft take was observed.

Allografts were used in two children with extensive skin necrosis and unsuitable donor sites as temporary biological dressings. A temporary Hartman’s type colostomy was required in two children with 6 and 85 per cent skin loss to prevent ongoing faecal soiling of extensive necrotic gluteal and upper thigh areas.

Amputations were performed in 14 children (24 per cent) proximal to the areas of necrosis after completion of demarcation, on average 27 days (range 19-50 days) post admission. The toes were amputated at the metatar-
sophalangeal joints in five children and interphalangeal joint in one child. One child required a transmetatarsal foot amputation. Bilateral below knee amputations were performed in two children, a through knee amputation in one and an emergency above knee amputation, as part of a life saving procedure for peripheral gangrene with exposed bone, in another.

In addition, one child had extensive areas of necrosis involving 85 per cent of her total body surface area which included both legs up to the knees. Bilateral amputations were contemplated as both anterior and posterior muscle compartments were involved, but a Technetium 99m limb perfusion scan showed evidence of distal perfusion.

After extensive debridement of necrotic tissue, sufficient functional muscle tissue was left to justify limb preservation. Subsequently, she regained limited plantar and dorsiflexion function of her feet and achieved reasonable locomotive activity. One adipose fascial dermal flap was used to cover exposed bone and deep structures of the plantar surface of the right foot.

Major soft tissue and muscle necrosis of the lower limbs developed in four children, exposing joint cavities leading to septic arthritis in two, and the loss of most anterior and posterior compartment lower leg muscles in the other. None of these children required lower leg amputations but all have limited locomotive function.

Necrotic fingers were amputated at mid-phalangeal joint level in five children (bilaterally in three) and at metacarpal level in both hands of one child with bilateral feet amputations. Two earlobes were involved with excision of necrotic tissue and primary closure in one and subsequent reconstruction in another. The tip of the nose was amputated in one child.

Factors associated with a poor outcome for peripheral extremity salvage were progressive irreversible skin changes, early disappearance of distal pulses and clinical evidence of a non perfused, swollen, cyanotic, cold and painful extremity.

Histological evaluation of amputated specimens showed widespread damage to both soft tissue and bone. The primary and predominating process appeared to be a result of vascular occlusion by fibrin thrombi. This result of the DIC caused ischaemic damage to the surrounding tissue with extensive coagulative necrosis of skin, subcutaneous tissue and muscle. The bones examined showed evidence of severe damage to cortex, medulla and metaphysis with areas of infarction and bony repair. A second, less impressive process appeared to be infective in nature. Focal vascular inflammation, acute periostitis and acute osteomyelitis were all features which seemed to indicate a direct suppurative effect by the meningococcus.

**Discussion**

Meningococcaemia is a destructive form of Gram-negative sepsis and in 10-33 per cent of cases, the disease process is complicated by purpura fulminans.

The pathogenesis of purpura fulminans is thought to be due to an endotoxin induced vasculitis with associated thrombosis and haemorrhage, manifesting initially as petechial spots which rapidly progress to larger purpuric areas with haemorrhagic bullae and finally to skin and subcutaneous tissue necrosis and infarction (Figure 1 & 2). The skin rash is usually of sudden onset and rapid spread, and must be differentiated from purpura occurring in other illnesses, i.e. viral infections and *Haemophilus influenzae*. Histologically there is necrosis, thrombosis and haemorrhage with an intense vasculitis and occlusion of small vessels with aggregates of platelets and erythrocytes (Figure 3). In addition, marked extravasation of fluid and red blood cells are striking features and contribute to local swelling and further impairment of tissue perfusion. The demarcation of the necrotic areas is usually complete within 3-17 days and has a predilection for extremities.

The process, however, varies and affected areas do not always become necrotic. Necrosis was present on admission in all and progressed rapidly to involve on average 14 per cent of the body surface area (range 2-85 per cent). Spontaneous

**Figure 1.** Typical rash of meningococcal septicaemia with small to large or confluent purpuric lesions.
healing of small necrotic areas was observed in 18 per cent of children with little residual scarring.

To prevent the devastating consequences of meningococcaemia, the diagnosis should be made promptly with immediate appropriate treatment instituted (Table 2) 8, 9. *Neisseria meningitides* is very sensitive to penicillin although strains less sensitive to other antibiotics are becoming more common (vide infra). Of 183 strains, isolated from either cerebrospinal fluid or blood cultures during a recent survey in our laboratories, 100 per cent of *N. meningitides* were sensitive to cefotaxime, chloramphenicol and rifampicin, 98 per cent were sensitive to penicillin and 37 per cent to co-trimoxazole.

Hypovolaemia must be corrected as soon as possible, preferably with the use of colloids and blood components (fresh frozen plasma, cryoprecipitate and platelets) to replace coagulation factors as well as protein C, protein S and antithrombin III. Cardiac function must be optimised with inotropic support and ventilation support introduced when required. The use of peripheral vasoconstrictors to maintain blood pressure may be necessary, but theoretically can exacerbate peripheral limb ischaemia.

Other methods to improve peripheral circulation such as the use of nifedipine and trinitrates have been used, but it is difficult to judge their effects in the presence of the developing pathophysiological consequences of purpura fulminans 14. There is no indication at present that immunotherapy in meningococcaemia has a significant role to play. The administration of steroids, although shown not to improve outcome, may be beneficial in physiological doses in patients with relative or absolute adrenal insufficiency9.

New therapeutic options have been developed for the coagulopathy associated with purpura fulminans. Protein C concentrates should be given early in the progression of purpura fulminans to normalise protein C levels and to reverse coagulopathy 15. Depletion of protein C, a naturally occurring anti-coagulant, is a major factor causing microvascular thrombosis 6. We have used fresh frozen plasma as a substitute in an attempt to replenish presumed anticoagulative factor deficiencies.

The use of heparin has been advocated for many years and a recent retrospective study found that heparin used within the first 72 hours reduced the number of digit and extremity necrosis, skin grafting procedures and amputations 16. We used heparin early on in seven children but unfortunately five of these progressed to peripheral ischaemia. Thus its use was of doubtful efficacy.

As an alternative, Epoprostenol (PG 12), a potent inhibitor of platelet aggregation and powerful vasodilator at a dose of 10-20mg/kg/min has been showed to improve the microcirculation to the skin and subcutaneous tissues 17. The use of recombinant bactericidal/permeability-increasing protein (rBPI21) as adjunctive treatment for severe meningococcal septicemia was recently introduced in clinical practice and was shown to decrease the long-term sequelae including death and amputations. This treatment should be given at the time of administering antibiotics on diagnosis of the disease 18.

Purpura fulminans is characterised by vessel thrombosis and fibrinolytic therapy offers the potential of a reversal of this process. In addition, tissue plasminogen activator (TPA) is a physiological endothelial activator of fibrinolysis responsible
for local clot dissolution. We have used both TPA and streptokinase in an effort to improve small vessel circulation (patients 7, 9 and 18). Amputations were still required in two of the three children where fibrinolytic therapy was used but in one, an immediate and sustained improvement in perfusion of purpuric areas was seen.

Although it may be difficult to assess peripheral limb viability during the resuscitation and septic phases of purpura fulminans, it remains vitally important to closely monitor these critical areas (Figure 4). In our experience, all children with progressive dermal ischaemic change, disappearance of arterial pulses and severe limb pain on passive extension have developed major digital or limb losses. Linear skin and subcutaneous decompression incisions, with or without fasciotomy, done before irreversible ischaemic changes occur may improve the chances of limb preservation, similar to escharotomies done for circumferential limb burns (Figure 5).

In a recent case with threatening peripheral ischaemia, soft tissue pressure measured at 68cmH₂O reduced to 25cmH₂O after two releasing incisions with immediate and dramatic improvement in distal perfusion. Bleeding was easily controlled with bipolar cauterisation. The extensive subcutaneous capillary leak and oedema, which was contained by relatively inelastic skin and subcutaneous tissue, clearly contributed to peripheral limb ischaemia.

<table>
<thead>
<tr>
<th>Table 2. Purpura fulminans – treatment algorithm (adapted).</th>
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<tr>
<td><strong>Antibiotics</strong></td>
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<tr>
<td>Achieve adequate circulation</td>
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<tr>
<td>Assess indications for releasing incisions</td>
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<tr>
<td>Pain on passive extension</td>
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<td>Conservative support</td>
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<td>Await demarcation of ischaemic tissue</td>
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<td>Topical therapy for necrotic areas</td>
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<td>Serial debridement of necrotic tissue</td>
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<td>Skingrafting – delayed</td>
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<td>Second look surgery for questionable tissue viability</td>
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<tr>
<td>Conservative amputations</td>
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<tr>
<td>– preserve epiphyses</td>
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<td>– conserve length</td>
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<tr>
<td>Wound coverage</td>
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<tr>
<td>– reconstruction with local &amp; regional flaps</td>
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<tr>
<td>– skin grafts or vacuum assisted closure</td>
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<td>Long term surveillance</td>
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<td>Active mobilisation/splinting</td>
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<tr>
<td>Residual morbidity</td>
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<tr>
<td>– skin cover/scars</td>
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<tr>
<td>– bone-joint contractures</td>
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<tr>
<td>– angular deformities</td>
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<td>– epiphyseal damage</td>
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Treatment of hypovolaemia
Inotrope therapy (± ventilatory support)
Vasodilatory therapy – if required
Coagulation support
Skin care

= ‘Threatening ischaemia’
Disappearing pulses
‘Compartment syndrome’
Figure 4. Peripheral limb ischaemia with a clear demarcation line with absent perfusion in the lower limbs. Emergency soft tissue decompression was not done. Both lower limbs were amputated.

Our reluctance in the past to decompress ischaemic extremities with skin and subcutaneous releasing incisions was based on the presence of DIC, bleeding and a developing disease with an uncertain end point. However, early fasciotomies were instrumental in salvaging severely compromised distal extremities in one small series; therefore, continuous subcutaneous and compartment pressure monitoring and early soft tissue releasing incisions have been proposed to reduce the consequences of peripheral ischaemia. Concomitant sympathectomy to improve peripheral circulation has not been recommended.

Management of skin necrosis presents a difficult problem. It is important to allow the necrotic area to demarcate fully which can be delayed for more than 2 weeks. The lesion is usually a thick necrotic eschar. Favourable conditions for bacterial growth in the necrotic areas lead to rapid bacterial multiplication and invasive sepsis. A polymicrobial infection within the necrotic and surrounding viable tissue is seen on histology and quantitative bacterial counts.

Both Gram-positive and Gram-negative organisms predominate in the eschar and surrounding tissues. Small areas can be left to heal through a process of spontaneous separation, wound contraction and healing by secondary intention. This was the process of healing in 18 per cent of our children. Alternatively, the areas can be excised with primary closure if they are located in cosmetically and functionally important areas. If left to heal spontaneously, unsightly scars may develop.

The surgical management is labour intensive and children required an average of 4-5.3 procedures per patient to complete the healing process. These procedures consisted of debridement of necrotic tissue, skin grafting – either primary or secondary – and amputations.

Larger necrotic areas required either single or serial debridement procedures of all necrotic tissue including non viable skin, subcutaneous skin and even muscle. Necrotic tissue should only be excised in stable patients. Resection of questionable tissue should be deferred until clear demarcation is evident in order to minimise tissue loss.

Histological assessment of tissue viability may be helpful, as clinical assessment cannot always determine the extent of subcutaneous muscle and bone necrosis with accuracy. Limb perfusion scans, magnetic resonance imaging (MRI) and magnetic resonance (MR) angiograms may be valuable adjuvants in delineating the level of arterial occlusion, soft tissue and bone necrosis. In one of our cases, a Technitium scan showing distal limb perfusion aided the decision to conserve the lower limb.

Although primary skin grafting has been advocated, it is seldom successful. Delayed split skin grafting on an adequate bed of granulation tissue is preferred. Allografts can be used as temporary biological dressings to cover extensively excised wounds where donor sites are deficient or where the development of a vascularised bed for skin grafting is awaited. The use of cultured epithelial autografts has been reported, and although the ‘take’ rate is only in the order of 50 per cent, their application can stimulate wound healing, especially in children with massive skin loss.
We have not used local, random or pedicle fasciocutaneous or subcutaneous flaps to cover large defects or amputation stumps initially as the underlying vasculitis and wound infection preclude their use. The need for flaps to cover bone and deep muscular structures was required in only one of our children (2 per cent). Skin and muscle loss can also expose joints resulting in septic arthritis. Two of our children had knee joints exposed, which required treatment with antibiotics, local debridement and skin grafts. Functional ability returned in these joints.

Of major concern is the progressive ischaemic changes to peripheral structures which may culminate in digital or extremity loss. The incidence varied from 23-71 per cent in reported series and up to 38 per cent of surviving children have amputations of two or more limbs. High level quadruple limb amputations may be required in up to 23 per cent. The need for amputations must be evaluated with great circumspection. The basic principle is to preserve useful function as much as possible. The most appropriate level of amputation is determined by functional and reconstructive considerations, especially in growing children as residual limb lengthening may provide useful function at a later date. This might require multiple skin grafts, the use of allografts or transposition flap coverage for wound closure. If the epiphysis has to be sacrificed, as much diaphyseal length as possible should be left.

In our experience, amputations could always be covered initially by local anterior and posterior muscular flaps with either primary or secondary closure obtained using skin grafts. Most amputations involve the lower extremities and quadruple amputations were rare, with only one child in our series requiring both hands and feet amputations. Amputation levels frequently required revision; stump revision and surgical repair of deformities may become necessary, making ongoing surveillance essential.

Conclusion
In conclusion, purpura fulminans is a common disease with devastating consequences. We advocate early surgical consultation. Skin and soft tissue releasing incisions, which were only used recently in our series, should be considered early on to reduce the incidence of extremity necrosis.

Small necrotic areas usually separate spontaneously with secondary healing or can be excised and sutured. Larger necrotic areas should be excised only after demarcation has been established and can be covered with delayed skin grafting. Amputation should be conservative and may require revision. Growth disturbances in long bones are not uncommon and scar revision and surgical repair of deformities may become necessary, making ongoing surveillance essential.

References


