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Editorial

Surgical treatment of acute infectious purpura fulminans in neonates

Paola Parisi, Diego Ribuffo

Unit of Plastic and Reconstructive Surgery, Department of Surgery "P. Valdoni", Sapienza University of Rome, Policlinico Umberto I, Rome, Italy

"The future belongs to those who believe in the beauty of their dreams."
Eleanor Roosevelt

Keywords

Skin necrosis, purpura fulminans, pediatric reconstructive surgery, skin grafting, dermal substitute, tissue engineering.

Corresponding author

Paola Parisi, MD, Unit of Plastic and Reconstructive Surgery, Department of Surgery "P. Valdoni", Sapienza University of Rome, Policlinico Umberto I, Viale del Policlinico 155, 00161, Rome, Italy; phone: +393881557327; e-mail: paola.parisi86@gmail.com.

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Introduction

Skin and soft tissue necrosis rarely occurs in neonates, although pediatric and plastic surgery services should be aware of this urgent condition [1]. Plastic surgeons are frequently consulted regarding management of soft tissue or open wounds to perform debridement, plan reconstruction or proceed with amputation. Several situations may lead to this condition. Predisposing factors include prematurity, hypercoagulability state, umbilical artery cannulation, thrombosis, hyperosmolar fluid infusions, sepsis [1], thermal abnormality, dry labor and purpura fulminans (PF) [2, 3]. Additional cases have been described as a consequence of intrauterine compression [4], as well as in newborns of diabetic mothers, who have a higher tendency to develop intravascular coagulation [5].

Neonatal PF (NPF) is a clinical-pathological entity characterized by dermal microvascular thrombosis associated with disseminated intravascular coagulation (DIC) and perivascular hemorrhage, occurring in the newborn period. It can be categorized into three forms based on etiology [6]. Congenital PF (CPF) stems from a coagulopathy, most commonly due to the homozygous absence of anticoagulant proteins C or S. Acute infectious PF (AIPF) occurs in sepsis and is most commonly associated with meningococcal infection, though other bacteria such *Pneumococcus spp.* and viruses have also been described [7-12]. The most commonly associated pathogen in the neonatal period is group B *Streptococcus spp.* [13-15]. PF can also present itself in an idiopathic form in which, as the name implies, diagnosis is by exclusion and usually has a less severe clinical presentation.

The clinical severity varies according to the underlying cause (i.e., genetic variability of severe congenital protein C and S deficiencies, acquired conditions, etc.). The onset of symptoms is usually within 2-12 hours from birth. Nevertheless, infants presenting with a delayed onset of PF, between 6 and 12 months of age, have been reported [16, 17]. AIPF occurs during acute illness, usually sepsis with endotoxin-producing Gram-negative bacteria. It is the most common type and is associated with an acquired deficiency of protein C. The mechanism involves an imbalance of the coagulation cascade, where bacterial endotoxin triggers consumption of proteins C, S and antithrombin III. This pro-coagulative state leads to thromboses of microvascular dermal vessels and is associated with DIC [17]. The skin lesions may present early as petechial rashes. These rapidly progress to larger ecchymoses. Later in the course, hemorrhagic bullae may form, which contribute to the classic presentation consisting in hard eschars [17]. Limbs are the most commonly involved areas. With time, necrosis and gangrene may ensue, potentially resulting in necrosis that extends beyond the skin into soft tissues and even bone [18, 19]. Differential diagnosis should be made with necrotizing fasciitis (NF). In PF, skin manifestations are not a direct result of organism soft tissue penetration.

PF can lead to loss of extremities, and in fact results in amputation of distal limbs (i.e., fingers, toes) in 19% of cases. More proximal amputations, above the knee and elbow, are also well-documented. Previously published case reports suggest that significant tissue loss in patients with AIPF results from missed extremity compartment syndromes [20, 21]. This is likely compounded by significant delays in surgical referral and intervention, which can be in excess of 3 weeks [20, 22]. Therefore, early recognition with prompt investigation of the principal cause and treatment is key. A multidisciplinary approach should always be performed, with a team that includes specialists in critical care medicine/pediatrics, infectious disease, plastic surgery, orthopedic surgery, physical medicine/rehabilitation, psychology, and nutrition service, along with dedicated nurses. This is a rare condition, but it is often fatal if it is not treated as soon and as effectively as possible.

The mortality rate of AIPF ranges from 10% to 50% [23-26]. The most common causes of death are multisystem organ dysfunction, DIC, and adrenal hemorrhage [22]. The aim of this editorial is to expose the available options in the surgical management of neonatal AIPF.

Initial local management of skin and soft tissues

If limbs are affected by PF, they should be elevated to allow the reduction of edema and should be carefully examined for compartment syndrome. In case the latter were to be diagnosed, the affected extremity must be immediately decompressed to achieve maximal soft tissue salvage. The measurement of a compartmental pressure of 30 mmHg or above poses the need for fasciotomies. In hypotensive patients, compartment syndrome could be present with intra-compartmental pres-

sures below 30 mmHg. Fasciotomy should be performed within 6 hours of the onset of ischemia.

The presence of skin abscess should be assessed and, if purulence is present, an early debridement should be performed when the medical condition allows for surgery to be performed. If surgery is not possible, the abscess should still be drained as much as possible, and dressing changes should be performed frequently. After debridement, the subsequent open wounds can be treated with wet-to-dry dressing changes until reconstructive surgery can be planned. When purulence is absent, and the skin is ischemic but not frankly necrotic (i.e., purpuric skin), local skin care with an antibiotic ointment is recommended. When only skin necrosis or eschar is present, diluted iodopovidone or sodium hypochlorite solutions should be used to decrease the risk of infection.

Surgical debridement is advocated after the demarcation of soft tissue necrosis: an aggressive debridement performed too early has been shown to increase the number of repeat debridement surgeries and to be related to a more proximal level of amputation [27, 28]. If there are no signs of local infection, the not completely demarked areas should be evaluated for possible salvage or conservative recovery. On the other hand, an early debridement, with removal of non-viable tissues and reduction of inflammatory byproducts from the necrotic area, contributes to an improvement in renal function [29]. Hirudin therapy with leeches has vasodilating properties which could be used in ischemic digits to reduce the hypercoagulable state and increase blood flow [30]. This treatment would be most appropriate in patients with isolated digital ischemia.

Early local debridement in stabilized neonates

After initial critical care and stabilization of the patient, a more aggressive surgery can be performed to manage necrotic tissues. The aim is to preserve as much tissue as possible, especially from the joints, obtaining the total resection of non-viable tissue. To better evaluate vital or non-vital tissue, magnetic resonance imaging with or without contrast medium can help surgeons determine the level of debridement or amputation [31]. Also, an intraoperative tissue biopsy can demonstrate the viability of tissues. Skin and soft tissue debridement should be more aggressive (with the exception of the face), while it is advocated to be more conservative in resection of bone, preserving its length and the articular surfaces as much as possible. Different studies are weighing the role of enzymatic escharectomy in the management of these patients, to potentially avoid complications related to surgery, bleeding and anesthesia [32, 33].

Reconstructive options

Skin grafts are usually the first option for skin defect coverage. Skin grafts can be used at split thickness (split-thickness skin grafts, STSG), and can even be meshed, to expedite the healing process by easing evacuation of tissue exudation and fluids, all the while reducing the size of harvested skin. More complex defects with exposed bone or joint will require reconstruction with pedicled or free flaps, either musculocutaneous or fasciocutaneous [20, 34].

Timing of reconstruction is crucial: an early coverage could lead to graft failure [35] or flap failure [20, 36] due to residual inflammatory response or to continued perfusion dysfunction.

Most authors agree to perform major reconstructive surgeries when the patient is in a stable general and local condition and the wound bed is well perfused and vital: this process may take up to 4 weeks from the initial presentation. In this early period, dressing change should be performed with care until definitive coverage can be achieved. Another option is to cover the wound with allograft skin [37], especially when bone or articular surfaces are exposed. The benefit is that the allograft can be maintained for weeks, as a bridge to major surgery.

Another option is to use negative pressure therapy (NPT), which has recently been applied for the treatment of complex wounds even in neonates [38, 39] and premature babies [40]. It is an effective and well-tolerated method, indicated when it is impossible to achieve immediate wound closure with flaps or STSG. The technique may also be used as a bridge to definitive coverage of wounds or to induce secondary intention healing (SIH), alone or associated with complementary dressings. NPT promotes granulation tissue formation and wound contraction [41], prevents and treats wound infections [42] and improves tissue vascularization [41-43].

Pediatric guidelines are lacking: adult techniques have currently been readapted to children. Some authors suggest that children are unable to tolerate the pain associated with intermittent mode and exclusively recommend continuous negative

pressure, which may also be more advantageous to generate granulation tissue [44-46] Negative pressures recommended for adults (-125 mmHg) are generally used for children 4-year-old or above. Lower suction pressures are advised for premature newborns, neonates, infants and small children, as well as for wounds presenting exposed viscera or related to delicate tissues [42]. Pressures of -50 mmHg (prematures) or -75 mmHg (neonates and small children) have been empirically recommended. If the defect is circumferential, it is necessary to reduce the negative pressure even further due to the risk of compressive effect on sensible peripheral blood circulation of a newborn. Some authors recommend "wall" or automated aspirators to generate less negative pressures in premature newborns and neonates, as the proprietary device's minimum level of negative pressure is -50 mmHg [47-53]. Other researchers opted for customized NPT systems based on gauze/surgical towels/customized sponges, multi-fenestrated catheters connected to automated/wall aspirators and adhesive transparent dressings with good results, mostly, but not exclusively, before the availability of proprietary devices [48-51]. Complications of NPT are uncommon and mostly manageable, and they mainly include foam retention and dermatitis/skin maceration [52-54].

NPT is contraindicated over major blood vessels. In fact, hemorrhagic deaths have been reported in adults where NPT was used directly over blood vessels [45]. Nevertheless, this recommendation has been put into discussion by authors who describe specific regimes of low vacuum protocols for usage over exposed blood vessels [55]. The presence of coagulopathy also represents a contraindication [52]. However, many Pediatric Cardiac Surgery patients have received NPT while being administered anticoagulants and no bleeding complications were reported. Surgical hardware exposure is not a contraindication [45, 56]. Debridement is needed before considering NPT in necrotic wounds with eschars. Unsurprisingly, malignancy in the wound contraindicates the procedure, in adults and children alike [53].

Biomaterials

With the current advances in tissue bio-engineering, different innovative biomaterials (dermal and skin substitutes) have been developed for wound management and reconstruction. Dermal substitute biomaterials are capable of providing a new dermal layer suitable for the subsequent application of an STSG. Such materials can be divided into cellular and acellular. The latter can be based either on allogeneic, xenogeneic or synthetic materials.

Many dermal substitutes are available in the market, such as Integra® Dermal Regeneration Template (Integra LifeSciences Corp., Plainsboro, NJ, USA), MatriDerm® (MedSkin Solutions Dr. Suwelack AG, Billerbeck, Germany), etc. They are usually composed of one or more layers. Integra® Dermal Regeneration Template is a bilaminate acellular dermal substitute based on allogeneic materials. It presents an internal layer of collagen chondroitin sponge, which is in contact with the wound bed and activates the dermal regeneration, while an external layer acts as a silicon semi-permeable barrier to external agents, also preventing liquid loss [57]. MatriDerm® is a single layer composed of bovine collagen type I, III and V coated with 3% bovine elastin hydrolysate. One or more layers may be stacked on top of each other according to the type of defect [58]. The newly formed dermis is usually ready for epidermal autograft in 15-20 days from application. After this period, the neodermis is ready for skin grafting or SIH [59].

Using these biomaterials in the setting of neonatal wounds has different advantages: application is very quick and easy, providing stable and tension-free coverage; reduction in fluid and protein loss and prevention of bleeding from the wound surface expedite the healing process; risk of infection is contained by providing coverage to the exposed wound; dressings are simple and require minimal analgesia; management can be performed at the bedside for several weeks; procedures yield excellent long-term aesthetic and functional results with better quality scars and less contracture than simple and direct skin grafting alone [60].

In an attempt to achieve a single-stage coverage, these biomaterials have been seeded with disaggregated cultured [61] or non-cultured [62] autologous keratinocytes, in experimental studies. Results were promising, but further clinical follow-up studies are required.

Additionally, skin substitutes have been used to manage open wounds in infants and children, such as the graftskin (Apligraf®, Organogenesis Inc., Canton, MA, USA), an alloplastic tissue-engineered skin substitute that contains living neonatal foreskin-derived keratinocytes and fibroblasts as well as bovine collagen [63]. The

morphologic, biochemical, and metabolic composition of this skin equivalent is similar to that of normal human skin; however, blood vessels, melanocytes, and appendages are not present. The exact mechanism of action is unknown, though different mechanisms have been suggested according to the type of wound [64].

Plastic surgery late treatment

Most of these patients require extensive rehabilitation and further surgical revision. One of the most frequent problems is scar contracture. First treatments are based on pressure garments and physical therapy. Frequently, surgical scar release is required, especially if the contracture is across a joint. Scar release surgery can include procedures, such as Z-plasties, local rotation flaps or even major procedures such as free-tissue transfer [29]. The unique peculiarity of managing these patients is that the reconstructive process must take growth into consideration. As the patients grow, cosmetic surgical treatment becomes more important. Of note, the principles for surgical intervention in these patients with late-term sequelae are the same as for those in burn patients.

Future advancements and innovations

The clinical introduction of the widely-used dermal regeneration templates has pushed the boundaries of reconstructive and regenerative surgery, now carrying the potential for improved functional and aesthetic results. However, these templates are still limited by the fact that they require coverage with an overlying autologous STSG [65].

Nowadays, research focuses on culturing epidermis from the patient's own cells. The first attempts were performed 40 years ago by Rheinwald and Green [66, 67], but cultured epithelial autografts presented considerable problems when used for the coverage of deep skin defects. The main problems were: graft fragility, poor take, instability of healed grafts, and unsatisfactory long-term functional and aesthetic results [68]. Then, in the early 1990s, Hansbrough et al. [69] developed the first cultured autologous dermo-epidermal skin substitute, with successful clinical application in severe burns patients; it has more recently been investigated in a clinical trial setting [70].

Autologous cultured skin substitutes allow surgeons to obtain viable tissue from a skin biopsy of the patients, reducing morbidity of donor sites for STSG. This is of great importance in dramatically ill preterm neonates and in patients with extensive loss of substance. One of the major problems in skin tissue engineering is the finding of optimal scaffolds for cell cultures. Research will continue to focus on finding the optimal scaffold for cell growth. Recently, Meuli et al. [71] reported a phase I prospective trial on the use of a cultured autologous dermal epidermal skin substitute on hydrogel scaffold for pediatric patients with acute or elective deep partial- or full-thickness skin defects with excellent initial results. The paper by Nagaichuk et al. published in this issue also explores new directions and could be useful for all the physicians involved in this field [72].

Declaration of interest

The Authors have no financial interest and conflict of interest to disclose.

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