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NEONATAL PURPURA FULMINANS: A NARRATIVE REVIEW

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ABSTRACT Neonatal purpura fulminans (NPF) is a life-threatening thrombotic disorder characterized by rapidly progressive cutaneous necrosis and disseminated intravascular coagulation. This narrative review synthesizes current evidence on its etiology, pathophysiology, clinical management, and outcomes. NPF most commonly results from severe protein C/S deficiency or sepsis, manifesting with painful purpuric lesions that evolve to gangrene within hours. Diagnosis requires coagulation studies, genetic testing, and exclusion of mimics. Immediate treatment with protein C replacement and anticoagulation is critical, though mortality remains high (20-50%). Long-term sequelae include limb loss and neurodevelopmental delays. Emerging therapies like gene editing and immunomodulators offer future promise. Early recognition and multidisciplinary care are essential to improve outcomes.

KEYWORDS : neonatal purpura fulminans, protein C deficiency, thrombosis, newborn.

INTRODUCTION

Neonatal purpura fulminans (NPF) represents a catastrophic thrombotic disorder characterized by rapidly progressive cutaneous hemorrhage and necrosis, disseminated intravascular coagulation (DIC), and high mortality (30-60%) despite intensive care (1). This thrombohemorrhagic emergency typically manifests within 72 hours of life, with dramatic ecchymotic lesions evolving into full-thickness necrosis, often signaling underlying severe protein C/S deficiency or septic shock (2). The condition serves as a critical model of developmental hemostasis gone awry, where the immature neonatal coagulation system - with physiologically low vitamin K-dependent proteins - collides with genetic or acquired thrombotic triggers. While rare (1:50,000-100,000 live births), NPF demands urgent recognition, as outcomes hinge on timely protein C replacement and anticoagulation (1). Beyond its hematologic complexity, NPF poses unique diagnostic challenges, mimicking conditions like neonatal lupus or thrombocytopenia syndromes, yet carrying far graver implications if misdiagnosed (2). This review synthesizes current evidence on NPF's evolving pathophysiology, evidence-based interventions, and controversial management areas, aiming to equip clinicians with actionable knowledge for this time-sensitive neonatal crisis.

Methods

We conducted a comprehensive literature search to identify relevant publications on neonatal purpura fulminans (NPF) without systematic study selection or quality assessment, consistent with narrative review methodology. Four major databases (PubMed, Scopus, Web of Science, and Embase) were searched using key terms including "neonatal purpura fulminans," "protein C deficiency," "neonatal DIC," and "newborn thrombophilia" (publication years 2000-2023). Through iterative analysis and thematic synthesis, we selected 15 particularly informative references that provided meaningful insights into NPF pathophysiology, clinical presentation, or management approaches.

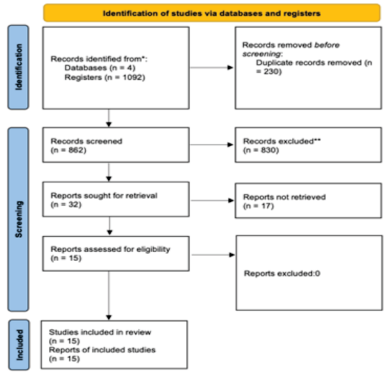

Figure. PRISMA.

Etiology and Classification

Neonatal purpura fulminans (NPF) arises from severe disruptions in the anticoagulant pathway, classified into hereditary and acquired forms based on underlying etiology (2).

Hereditary Forms

The most common cause is congenital protein C or S deficiency, with homozygous protein C deficiency (levels <1% of normal) presenting within hours of birth with widespread cutaneous necrosis and thrombosis (3). These vitamin K-dependent proteins are crucial for inactivating factors Va and VIIIa; their deficiency leads to unchecked thrombin generation. Less frequently, antithrombin III deficiency may trigger NPF, though it typically manifests later in infancy due to partial placental transfer of maternal antithrombin (4). Genetic testing confirms these diagnoses, with SERPINC1 (antithrombin), PROC (protein C), and PROS1 (protein S) being key candidate genes (5).

Acquired Forms

Sepsis-associated NPF predominates in preterm infants, with Neisseria meningitidis and group B Streptococcus being prime culprits (2). Bacterial endotoxins activate the protein C pathway while simultaneously inducing endothelial injury and DIC. In contrast, maternal autoimmune disorders (e.g., antiphospholipid syndrome) may cause transplacental transfer of prothrombotic antibodies, resulting in NPF despite normal infant protein C/S levels (4). These cases often coincide with intrauterine growth restriction or placental infarction.

Pathophysiology

Neonatal purpura fulminans represents a devastating thrombohemorrhagic disorder where the pathophysiology centers on three interconnected pathological processes: coagulation cascade failure, inflammatory mediator storm, and microvascular occlusion (5). At its core, the disease manifests through a catastrophic imbalance between procoagulant and anticoagulant pathways. In hereditary forms, this stems from severe deficiencies of natural anticoagulants, particularly protein C or S, which normally serve as critical brakes on the coagulation cascade by inactivating factors Va and VIIIa (6). The neonatal period presents a uniquely vulnerable state for thrombotic complications as developing hemostatic systems normally operate with baseline reductions in vitamin K-dependent factors, including protein C levels that are only 30-50% of adult values (5).

The inflammatory component of purpura fulminans,

particularly in sepsis-associated cases, adds another dimension to the pathophysiology. Microbial pathogens trigger an overwhelming cytokine release, with tumor necrosis factor-alpha and interleukins 1 and 6 playing prominent roles (5,7). These inflammatory mediators induce widespread endothelial activation and injury, further promoting thrombosis through multiple mechanisms. They upregulate tissue factor expression while simultaneously downregulating crucial anticoagulant proteins like thrombomodulin (6). The inflammatory milieu also stimulates release of plasminogen activator inhibitor-1, effectively shutting down the fibrinolytic system that might otherwise help mitigate the developing thrombotic process (7).

Clinical Features

Neonatal purpura fulminans (NPF) presents with distinctive clinical manifestations that evolve rapidly, often within hours of birth. The hallmark cutaneous findings begin as discrete erythematous macules that progress to irregular petechiae and ecchymoses within 6–12 hours (7). These lesions subsequently develop central hemorrhagic necrosis, forming blackened eschars with surrounding erythema, most commonly affecting dependent areas (buttocks, extremities) and pressure points (8). The progression from petechiae to full-thickness gangrene may occur in as little as 24–48 hours, reflecting the underlying microvascular thrombosis. Unlike other neonatal rashes, NPF lesions are painful and demonstrate rapid centrifugal expansion, a feature that helps distinguish them from benign ecchymoses (9).

Systemic involvement is nearly universal in severe cases. Renal failure develops in 40–60% of patients due to cortical necrosis from glomerular microthrombi, manifesting as oliguria and rising creatinine (8). Pulmonary hemorrhage occurs in 30% of sepsis-associated NPF, resulting from alveolar capillary thrombosis and presenting as bloody endotracheal secretions with hypoxemia (10). Neurological complications (seizures, stroke) may arise from cerebral sinovenous thrombosis, particularly in protein C-deficient infants (7). Laboratory findings consistently reveal consumptive coagulopathy: thrombocytopenia (<50,000/μL), prolonged PT/aPTT, hypofibrinogenemia, and elevated D-dimers (9).

The differential diagnosis requires careful consideration of other neonatal thrombotic and inflammatory disorders. Neonatal lupus may mimic NPF's cutaneous findings but lacks coagulopathy and demonstrates maternal anti-Ro/La antibodies (8). Thrombocytopenia disorders (e.g., NAIT, Kasabach-Merritt syndrome) show petechiae but not progressive necrosis or DIC. Congenital protein C/S deficiency can be confirmed by functional assays showing <1% activity, while sepsis-associated NPF typically presents with positive cultures (usually GBS or meningococcus) and more prominent inflammatory markers (10).

Diagnostic Approach

The diagnosis of neonatal purpura fulminans (NPF) requires a systematic approach integrating laboratory, genetic, and histopathological findings to distinguish between hereditary and acquired forms. Initial laboratory evaluation typically reveals profound coagulation abnormalities, including markedly prolonged PT (often >30 sec) and aPTT (>60 sec), hypofibrinogenemia (<100 mg/dL), and elevated D-dimers (>10 μg/mL), consistent with disseminated intravascular coagulation (10). Thrombocytopenia (<50,000/μL) is nearly universal, while protein C activity levels <20% (or <1% in homozygous deficiency) provide critical diagnostic specificity (11). Serial monitoring of these parameters is essential, as dynamic changes reflect disease progression and response to therapy.

Genetic testing should be pursued emergently when hereditary NPF is suspected. Targeted sequencing panels for thrombophilia genes (PROC, PROS1, SERPINC1) can identify causative mutations within 24-48 hours using rapid PCR techniques (12). Of particular importance is the differentiation between homozygous and compound heterozygous protein C deficiency, as this impacts both prognosis and long-term management. Concurrent maternal testing for protein C/S levels helps distinguish true congenital deficiency from transient postnatal depression, while also identifying potential carrier parents for genetic counseling (10).

Histopathological examination of skin lesions, though rarely required for diagnosis, demonstrates characteristic features when performed. Punch biopsies reveal microvascular thrombosis with fibrin deposition in dermal vessels, accompanied by hemorrhagic necrosis of surrounding tissue (11). Immunohistochemistry may show endothelial protein C receptor depletion in sepsis-associated cases. Notably, the absence of inflammatory infiltrates helps differentiate NPF from vasculitic processes (12). While biopsy is generally avoided in acute management due to bleeding risk, it may be valuable in atypical presentations or when considering alternative diagnoses.

Management

The management of neonatal purpura fulminans (NPF) requires a multidisciplinary approach addressing the acute thrombotic emergency, underlying etiology, and long-term complications. During the acute phase, prompt administration of protein C replacement is critical. Recombinant human activated protein C concentrate (10-80 IU/kg every 6 hours) demonstrates superior efficacy to fresh frozen plasma (FFP) in hereditary cases, achieving therapeutic protein C levels (>25%) within 4 hours versus 12-24 hours with FFP (10). However, FFP (10-20 mL/kg every 12 hours) remains essential in resource-limited settings and provides additional coagulation factors. The role of heparin therapy remains controversial; while unfractionated heparin (10-15 U/kg/h) may prevent thrombus extension, it carries significant bleeding risks in DIC and should only be considered after protein C repletion (11).

Infection control is paramount in sepsis-associated NPF. Broad-spectrum antibiotics (typically ampicillin plus cefotaxime or gentamicin) must be initiated immediately, with adjustment based on culture results and local resistance patterns (12). Meningococcal PCR from blood/CSF should be obtained given its strong NPF association. Adjunctive therapies like IVIG (0.5-1 g/kg) may be considered in refractory septic shock, though evidence remains limited to case reports (13).

Surgical management focuses on meticulous wound care. Early consultation with pediatric surgery is recommended, as escharotomy may be required for compartment syndrome in extremity involvement (10,11). Debridement of necrotic tissue is typically delayed 2-3 weeks to allow demarcation, with vacuum-assisted closure devices proving beneficial for large defects (11,12). Skin grafting is often necessary but should be postponed until coagulation parameters stabilize.

Long-term anticoagulation protocols vary by etiology. Hereditary NPF requires lifelong warfarin (target INR 2-3), with transition from heparin beginning once skin lesions stabilize (13). Novel direct oral anticoagulants lack neonatal data. For sepsis-associated NPF, anticoagulation is generally continued for 3-6 months post-resolution (14,15). All patients require regular monitoring for post-thrombotic complications including growth disturbances and neurodevelopmental delays.

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