A COMPLETE REVIEW ON PURPURA FULMINANS: A THROMBOTIC DISORDER OF SKIN

Sarvana Sravya*[1], Dhondge Sai Sundar[1] and Dr. Mehraj Fatima[2]

[1]Pharm-D IV year, Department of Pharmacy Practice, Mallareddy Institute of Pharmaceutical Sciences, Secunderabad- 500100, Telangana, India.

[2]Assistant Professor, Department of Pharmacy Practice, Mallareddy Institute of Pharmaceutical Sciences, Secunderabad- 500100, Telangana, India.

*Corresponding Author

Sarvana Sravya

Pharm-D IV year, Department of Pharmacy Practice, Mallareddy Institute of Pharmaceutical Sciences, Secunderabad- 500100, Telangana, India.

ABSTRACT

Purpura fulminans (PF) is a hematological emergency characterized by skin necrosis and disseminated intra-vascular coagulation. It was first described by Guelliot Hjort et al. were the first to clearly define its characteristic features in 1884. Purpura fulminans is not a single disease, but a common clinical and histopathological manifestation of several distinct disease processes. This syndrome usually occurs in children, but it has also been noted in adults. Neonatal purpura, Idiopathic purpura and Acute infectious purpura are the three basic prototypes of purpura fulminans. This article gives a brief discussion regarding symptoms, causes, pathology, diagnostic tests and treatment of various types of purpura. Purpura fulminans occur due to congenital or adapted factors that alter the anticoagulants level in the body.Protein C deficiency is common, it may be associated with deficiency of other anticoagulants, protein S and antithrombin-III. Purpura shows thrombotic occlusions of small and medium blood vessels in the body leading to extra-vascular bleeding. Symptoms like well-demarked ecchymosis patches/ maculae are seen initially, followed by irregular central blue-black necrotic areas representing cell death. In neonates, the symptoms appear abruptly with-in 2-3 days of birth and rapid progression of condition leads to increased risk of multi- organ failure and mortality. In adults, the progression is slow comparatively. Physical examination of lesions and protein C levels are useful for immediate treatment or preventive measures to be followed. Management strategies are made based on diagnostic results. The general management consists of fresh frozen plasma (FFP); plasma concrete and anticoagulants.

KEYWORDS: purpura, skin necrosis, thrombocytopenia, anticoagulants, thrombosis, Ceprotin.

INTRODUCTION

Purpura fulminans is a rare syndrome of intravascular thrombosis and hemorrhagic infarction (bleeding due to ruptured capillaries) of the skin that is rapidly progressive and is accompanied by vascular collapse and disseminated intravascular coagulation (widespread cascade of coagulation pathways).[1] It was first described by Guelliot in 1884. Hjort et al. were the first to clearly define its characteristic features:[2]

1. Usual occurrence in young children.
2. Recurrent bacterial or viral infections involving skin.
3. Sudden development of progressively enlarging, purplish-black areas of hemorrhagic skin necrosis sharply demarcated from surrounding healthy skin by a narrow red border.
4. Histopathological findings involved skin of dermal vascular thrombosis and secondary hemorrhagic infractions.
5. Usual absence of thrombo-hemorrhagic manifestations in organs other skin.
6. Association with hypofibrinogenemia and thrombocytopenia, all due to DIC.

This syndrome usually occurs in children, but it has also been noted in adults. Purpura fulminans is not a single disease, but a common clinical and histopathological manifestation of several distinct disease processes.[3] The pathological cause is mainly alteration in levels of anticoagulants (protein-C, protein-S and antithrombin-III) present in body. Deficiency of protein-C levels is common which is associated with decreased levels of protein-S or antithrombin-III.

Neonatal purpura, Idiopathic purpura and Acute infectious purpura are the three basic prototypes of purpura fulminans. Neonatal purpura shows an inherited protein-C deficiency, idiopathic purpura is associated with protein-S deficiency and acute infectious purpura is a common prototype caused due to bacterial infections (mainly gram-negative bacteria) and viral infections. Diagnosis of purpura is primarily targeted in finding the underlying etiological factor, this can be done by physical examination of lesions, complete blood picture analysis, blood culture tests, coagulopathy study, antiphospholipid antibody testing and examination of protein C and protein S levels in individual. Treatment of purpura involves symptomatic relief and complete eradication or decreasing the effect of underlying cause. Different classes of drugs are used in treatment of purpura: anticoagulants,

antithrombolytics, fibrinolytics, immunosuppressants, steroids, cyclophosphamide and antimicrobials. Plasma concretes (CEPROTIN) and fresh frozen plasma (FFP) are used for improving protein C levels. Supportive therapy is needed in case of infections, toxin induced purpura and in complicated cases like sepsis associated purpura fulminans where multiple organ- failure is common.

CLASSIFICATION

Different types of classifications are used for distinguishing purpura fulminans, one of the commonly used classification is based on triggering factors: Neonatal purpura, idiopathic purpura and acute infectious purpura. Other classifications are: **A)** on clinical and epidemiological criteria and laboratory findings,[4] the patients of purpura are classified into nine categories: Congenital protein C or protein S deficiency, Acute infectious purpura fulminans, Post- infectious purpura fulminans, acquired protein C or S deficiency due to drugs and diseases, Antiphospholipid antibody syndrome, Vasculitis disorders, Platelet mediated purpura fulminans, Toxin/ poison induced purpura fulminans. **B)** Based on types of lesions: Palable purpura and Non-palable purpura.[5] **C)** Based on platelet involvement: Thrombotic thrombocytopenic purpura and Idiopathic thrombocytopenic purpura. The patient may present purpura that can be categorized into one or more classifications.

EPIDEMIOLOGY

Purpura fulminans, of which the incidence is increasing, has a death rate of 20–25%; 5 to 20% of the survivors need skin grafts and/or amputations. Neonates and infants are at greater risk of purpura compared to adults. The age distribution of purpura fulminans indicated in the % patients (y-axis) vs age (x-axis) graph, (figure-1):
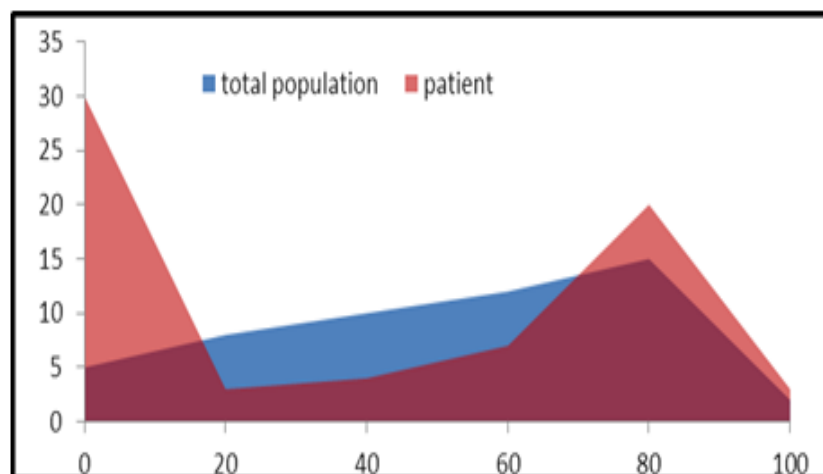

Figure 1: Age distribution of purpura fulminans.

Purpura associated with congenital (inherited) protein C deficiency occurs in 1:500,000–1,000,000 live births.[6] It shows an equal distribution among male and female. Neonatal purpura and idiopathic purpura are more common in children whereas acute infectious purpura is common among adults. Chronic meningococcal and streptococcal infections are most often associated with purpura. Despite of having highly developed neonatal therapy, meningococcal infectious purpura accounts about 10%- 15% cases among children. Acute infectious purpura shows 20%-40% mortality rate and post-infectious purpura shows 15%-20% mortality rate.

ETIOLOGY

Disorders of the coagulation system and purpuric lesions may occur due to various causes, but purpura fulminans implies a major coagulation disorder and has been observed in the following conditions:

(1) Disseminated intravascular coagulation (DIC) -Abnormal and excessive generation of prothrombotic factors in the circulation can occur because of various reasons, including infections, surgical complications, malignant diseases, and enzyme deficiencies. Depending on the rate and severity of DIC, it may either cause venous thrombosis, pulmonary embolism, with low rates of bleeding (slowly evolving), or it may cause thrombocytopenia and depletion of clotting factors (rapidly evolving), leading to bleeding and multiorgan failure. Regardless of the type, purpura fulminans can arise as a manifestation of this disorder.

(2) Micro-organisms - S.pneumoniae *(but mainly in asplenic patients),* S.aureus, beta-hemolytic streptococci, Pseudomonas aeruginosa, Varicella zoster *(severe chicken pox),* Rubella, measles, H.influenzae, Rickettsia, Candida albicans cause infections (Acute infectious purpura). Meningococcal infection[7] and the development of sepsis-induced purpura caused by *Neisseria meningitides* is a life-threatening infection that is most commonly encountered in children. In 15-25% of the cases, abrupt development of disseminated purpuric lesions is observed. Despite all treatment strategies, this infection can still be fatal, due to its abrupt onset and severe damage to blood vessels and coagulation system.

(3) Congenital deficiency of protein C or S - neonates who are born with a deficiency of either protein C or S develop extensive purpuric lesions on their first day of life, and the condition (neonatal purpura fulminans) may be life-threatening if not supplemented with appropriate enzymes.[8]

(4) Drugs - medications including excess use of vasopressor, sulfonamides, belladonna, procaine penicillin, amino phenazone, aspirin, chloral hydrate, sedatives and phenytoin have been mentioned as potential causes of this disorder, through mechanisms still not fully understood. Prolonged use of anticoagulants like warfarin and heparin is associated with purpura.[9]

(5) Thrombocytopenia - Any disease which accelerates platelet consumption, or decreases platelet production can predispose patients to purpura fulminans, including idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), and malignant diseases which deplete platelets.[10]

(6) Clotting factor deficiencies - Purpura can often be a manifestation of clotting factor deficiencies, and purpura fulminans can be observed in severe cases. Examples include von Willebrand disease, hemophilia A and B, antithrombin III deficiency, and other clotting factor deficiencies.

(7) Diseases- amyloidosis, microangiopathic hemolytic anemia (MAHA), bone marrow transplantation, cholestasis, renal failure, atherosclerosis, endocarditis, polyarteritis, other systemic vasculitis, nephrotic syndrome, Cushing's syndrome, Henoch-Schonlein purpura, Gardner- Diamond syndrome (psychogenic purpura), cancers (lymphomas, leukemia) and Post-infectious purpura fulminans (due to autoimmune destruction of proteins C or S).

(8) Psychogenic purpura- also termed painful bruising syndrome, auto-erythrocyte sensitization syndrome or Gardner-Diamond syndrome is characterized by spontaneous painful ecchymoses in patients who often have psychologic instability.[11]

CLINICAL PRESENTATION (SYMPTOMS)

Purpura may appear abruptly in adults and within 2-12h after birth in neonates born with congenital protein C deficiency. In adults, PF may be preceded by malaise, headache, nausea, drowsiness, and pains. PF initially shows well-demarcated stigmata, petechiae (figure-2), ecchymosis, rashes (figure-3) and erythematous macules that are confined to dermis.
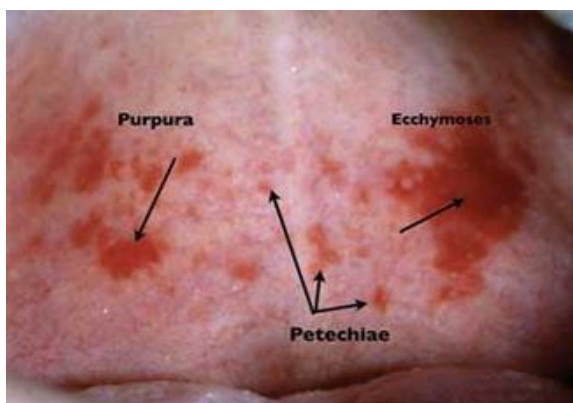

Figure-2: Purpura on fingers.

Figure3: Dermal symptoms of purpura

Figure-4: Purpuric rashes

They progress rapidly to develop irregular central areas of blue-black hemorrhagic necrosis (figure-4).[12] In chronic cases, blood accumulation causes PF lesions to become painful, dark and raised, sometimes with vesicle or bullae formation.

Figure-5: Ophthalmic manifestation of purpura.

Figure-6: Neonatal purpura.

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. This progression of PF correlates with 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 ischemic injury with extravasation of blood cells into the dermis and gangrenous necrosis (figure 5) sometimes with secondary infection.[13] The distribution of PF lesions may be different according to the underlying pathogenesis. 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. Ophthalmologic complications (figure 6) including vitreous hemorrhage and retinal detachment that may result in partial or complete blindness.

Specific Manifestations[14] are seen in different types of purpura fulminans, neonatal purpura fulminans include the following: symptoms develop within the first 72 hours after birth; Purpuric lesions are seen over different skin sites (including the perianal region, the flexor surface of the thighs, and abdominal skin); Skin lesions soon enlarge and become vesiculated, producing hemorrhagic bullae with subsequent necrosis and black scar formation; thrombocytopenia and possible signs of a urinary tract infection (UTI) are seen. Idiopathic purpura fulminans shows sudden development of purpuric symptoms 7-10 days after onset of the precipitating infection; progressively enlarging, well-demarcated purplish areas of hemorrhagic cutaneous necrosis with derangements in coagulation factors; Erythematous macules that progress within hours to sharply defined areas of purpura; Impaired perfusion of limbs and digitals; Major organ dysfunction (e.g., lungs, heart, or kidneys). The 4 primary features of acute infectious purpura fulminans are large purpuric skin lesions, fever, Hypotension and Disseminated intravascular coagulation (DIC).

PATHOLOGY

Purpura fulminans is a hematological skin disorder that occurs due to imbalance in hemostasis. Hemostasis is a process involving coagulation (formation and stabilization of clot) and clot retraction or dissolution. Coagulation is activated through intrinsic pathway or extrinsic pathway involving activation of several proteins or clotting factors. Through both pathways a common clotting factor is activated that is factor X. The activated factor X (Xa) converts prothrombin to thrombin. This thrombin activates many other clotting factors (VIII, V and XIII) and converts fibrinogen to active fibrin, factor XIIIa helps in formation of cross-bridges among the fibrin molecules leading to formation and tightening of clot. Thus, coagulation causes healing of any internal or external injuries. After healing, the fibrin clot must be dissolved, and coagulation must be stopped because uncontrollable coagulation may lead to development of thrombus, embolism and other blood disorders at an early age. The control over coagulation takes place by two mechanisms: fibrin clot degradation and negative feedback mechanism. Thrombin (through negative feedback) and tissue plasminogen activator causes degradation of fibrin clot by conversion of an inactive protein called plasminogen into active form plasmin. Plasmin dissolves the cross-bridges among the fibrin molecules leading clot retraction and the free fibrin molecules are degraded. The negative feedback mechanism involves activation of anticoagulants like antithrombin-III, protein C and protein S, these activated anticoagulants inhibit the coagulation cascade at different steps. The complete coagulation mechanism and activity anticoagulants is briefed in figure-7.
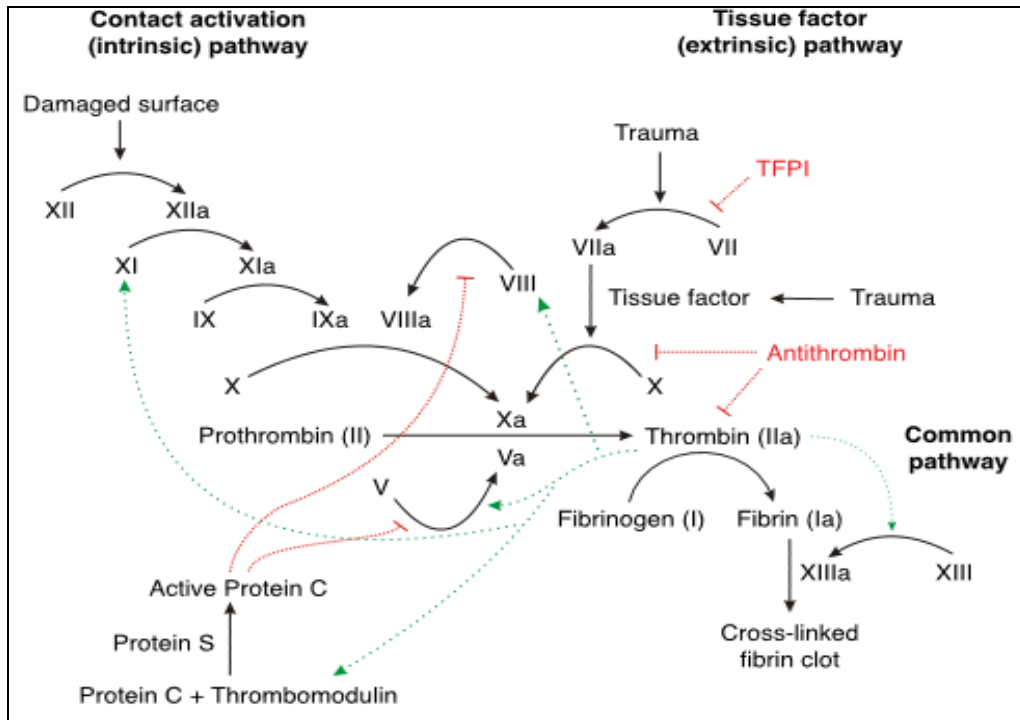
Figure-7: coagulation cascade and activity of protein C, protein S and antithrombin-III.

Protein C

Protein C is a major component in anticoagulation in the human body. The activation of protein C is strongly promoted by protein S, thrombomodulin and endothelial protein C receptor (EPCR), the latter of which is found primarily on endothelial cells (cells on the inside of blood vessels).[15] The presence of thrombomodulin accelerates activation by several orders of magnitude and EPCR speeds up activation by a factor of 20. On the endothelium, activated protein C(APC) performs a major role in regulating blood clotting, inflammation, and cell death (apoptosis). Because of the accelerating effect of thrombomodulin on the activation of protein C, the protein may be said to be activated not by thrombin but the thrombin–thrombomodulin (or even thrombin–thrombomodulin–EPCR) complex. Once in active form, APC may or may not remain bound to EPCR. APC proteolysis peptide bonds in activated Factor V and Factor VIII (Factor V_a and Factor $VIII_a$), and one of the amino acids in the bond (serine). These proteins that APC inactivates, Factor V_a and Factor $VIII_a$, are highly procoagulant cofactors in the generation of thrombin, which is a crucial element in blood clotting; together they are part of the prothrombinase complex. Cofactors in the inactivation of Factor V_a and Factor $VIII_a$, include protein S, Factor IIa, high-density lipoprotein, anionic phospholipids and glycosphingolipids.

Factor V_a binds to prothrombin and Factor X_a, increasing the rate at which thrombin is produced by four orders of magnitude (10,000x). Inactivation of Factor V_a thus practically halts the production of thrombin.[16] Factor VIII, on the other hand, is a cofactor in production of Factor Xa, which in turn converts prothrombin into thrombin. Factor $VIII_a$ augments Factor X activation by a factor of around 200,000. APC inactivates Factor V_a by making cleavages thus diminishing the molecule's attraction to factor X and factor II (prothrombin). The inactivation of Factor $VIII_a$ is not as well understood. The half-life of Factor $VIII_a$ is only around two minutes unless Factor IX_a is present to stabilize it.

Protein C in zymogen form is present in normal adult human blood plasma at concentrations between 65–135 IU/dL. Activated protein C is found at levels approximately 2000 times lower than this. Mild protein C deficiency corresponds to plasma levels above 20 IU/dL, but below the normal range. Moderately severe deficiencies describe blood concentrations between 1 and 20 IU/dL; severe deficiencies yield levels of protein C that are below 1 IU/dL or are undetectable. Protein C levels in a healthy term infant average 40 IU/dL. The concentration of protein C increases until six months, when the mean level is 60 IU/dL; the level stays low through childhood until it reaches adult levels after adolescence.[17] The half-life of activated protein C is around 15 minutes.

Protein S

Protein S is a vitamin K-dependent glycoprotein, synthesised by endothelial cells and hepatocytes. It exists in plasma as both free (40%) and bound (60%) forms (bound to C4b-binding protein). The anticoagulant activity is by virtue of free form while the bound form acts as an inhibitor of the complement system and is up regulated in the inflammatory states, which reduce the Protein S levels thus resulting in procoagulant state. It functions as a cofactor to APC in the inactivation of Va and VIIIa. It also causes direct reversible inhibition of the prothrombinase (Va–Xa) complex.[18]

Mutations in the PROS1 gene can lead to Protein S deficiency which is a rare blood disorder which can lead to decreased anticoagulation (thus, increased risk of thrombosis), clumping of apoptotic cells, inflammatory reactions due to production of anti-phospholipid antibodies. Protein S levels are low at birth and do not reach adult values until approximately age 6 months. The protein S level is greater than 73 U/dL in males whereas it is greater than 63 U/dL in females. Elevated protein S levels are not usually associated with medical problems and are not clinically significant. A low level of protein S activity can cause excessive or

inappropriate blood clotting. If the protein is not functioning properly (i.e., normal protein levels but improper function), insufficient regulation of the coagulation process ensues, which can result in an increased risk of clot development and vein blockage. The severity of the risk is dependent on the magnitude of the deficiency and/or the degree of dysfunction of the protein.

Anti-thrombin III

Antithrombin is a natural serine protease inhibitor. The physiological target proteases of antithrombin are those of the contact activation pathway(formerly known as the intrinsic pathway), namely the activated forms of Factor X (X_a), Factor IX (IX_a), Factor XI (XI_a), Factor XII (XII_a) and, to a greater extent, Factor II (thrombin) (II_a), and also the activated form of Factor VII (VII_a) from the tissue factor pathway (formerly known as the extrinsic pathway). The inhibitor also inactivates kallikrein and plasmin, also involved in blood coagulation. The Plasma concentration: 0.15-0.2 mg/mL. Newborn shows 60%-90% protein S level while it is up to 80%-120% in children and adults. An increased antithrombin level is not a clinical problem. Inherited types of antithrombin deficiency are as follows: Type I - Decreased functional and immunological antithrombin level, Type II - Decreased functional antithrombin activity, while protein concentration is normal. Acquired antithrombin deficiency may be associated with: coagulation, Unfractionated heparin therapy, Liver disease, Nephrotic, Protein, Estrogen, L-asparaginase treatment and Cardiac surgery.

Purpuric lesion development

The development of purpuric lesions is seen due to disseminated intravascular coagulation which is characterized by massive, sustained and excessive activation of coagulation with the eventual inundation (overwhelming) of the anticoagulant and fibrinolytic systems. This leads to disseminated microthrombi formation and tissue ischemia; consumption of platelets, coagulation factors and natural anticoagulants; and variable bleeding. Ultimately free, circulating, unopposed thrombin and plasmin are generated (the two key agents responsible for DIC) which then leads to[19]

- Activation and consumption of platelets, coagulation factors, fibrinogen and fibrin.
- Consumption and depletion of anticoagulant proteins (protein C, protein S and antithrombin).

- Generation of D-dimers and fibrin degradation production. Formation of microthrombi leading to tissue ischemia (large thrombi can also be formed, particularly in chronic purpura fulminans).

- Schistocytes (fragmented red blood cells) are formed as red blood cells are severed flowing through fibrin strands (microthrombi within vasculature) and variable bleeding.
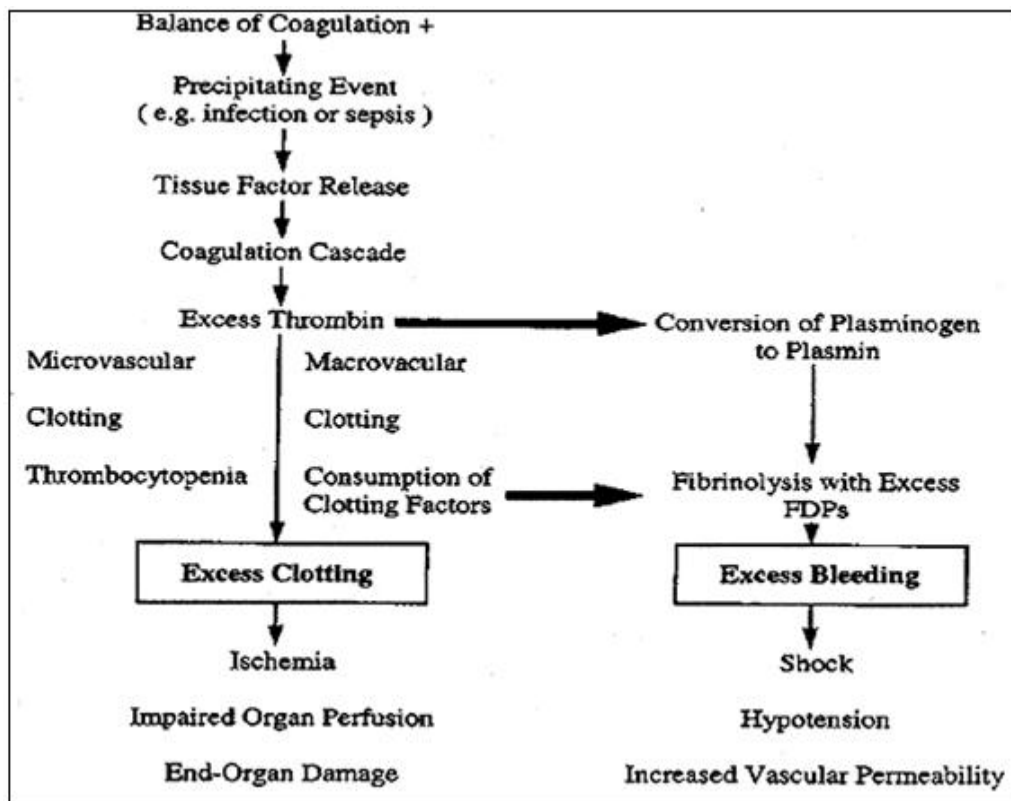

Figure-8: Description of how any disturbances in coagulation pathway causes multi-organ damage.

DIAGNOSIS

During the acute phase, the laboratory findings are that of DIC: thrombocytopenia, hypofibrinogenemia, increased fibrin degradation products and prolonged prothrombin (PT) and activated partial thromboplastin (aPTT) times. There are reports of associated microangiopathic anemia. Distinction between congenital and acquired causes of protein C and S deficiency is often challenging in the setting of acute thrombosis. Genetic testing of the child and family members can be useful to confirm the diagnosis of neonatal purpura, but it is not readily available in most centers, and the results would not be timely enough to guide management of these critically ill neonates. Testing of a citrated plasma sample, collected prior to initiation of treatment, is therefore crucial for accurate diagnosis. Functional (activity) assays are recommended for initial screening. Antigen levels may be contributory if

interfering factors (e.g. factor V Leiden mutation, antiphospholipid antibodies, direct thrombin inhibitors) are present. Unlike testing in adults, the interpretation of protein S levels in neonates is not complicated, which is present at very low levels at birth. Protein C and S activity levels are undetectable in homozygotes. Levels of protein C and S in healthy neonates are significantly below adult reference ranges, as low as 0.12 and 0.14 U/mL respectively. These physiologically low levels combined with acquired causes can lead to abnormal results. The usual recommendation of repeat testing in three to six months for confirmation is clearly impractical in this setting; testing of parents is therefore essential.

Prenatal diagnosis:[20] If the causative mutation of protein C or S deficiency within a family is known, prenatal diagnosis is available for women at risk of having a child with homozygous deficiency. This requires chorionic villous sampling that is associated with a 1% risk of fetal loss. Fetal blood sampling offers an alternative method; however, fetal protein C levels in the second trimester may be as low as 8% and the detection limit for many of the commercially available assays is 3%. This, combined with the risk of sample contamination with maternal blood, makes the distinction between heterozygous and homozygous states challenging.

TREATMENT

In neonatal purpura fulminans, which is often congenital, testing of blood samples of infant and parent for protein C and protein S levels is recommended before therapy. The initial treatment includes replacement with fresh frozen plasma (FFP) and plasma concretes, which is followed by use of anticoagulants alone or in combination with protein C concretes. FFP should be given at a dose of 8–12 mL/kg every 6–12 h until a protein C concentrate is available.[21] The most common side-effect is fluid overload. There is an increased risk of exposure to blood-borne pathogens and allergic reactions to donor proteins in case of varying donors. A total of 1 mL/kg of FFP/FP will increase the plasma protein C concentration by 1 IU/dL. The aim is to have a trough protein C activity of >10 IU/dL while awaiting the protein C concentrate. Ceprotin and Protexel are the two protein c concretes available. Initial dose of 100 U/kg followed by 50 U/kg every 6 h is indicative therapy. The target protein C activity is a trough level of 50 IU/dL. They are used in both congenital and severe acquired protein C deficiency. 100 U/kg as an initial bolus, then 30–50 U/kg every 12–24 h is recommended for surgical prophylaxis. Recombinant activated protein C (APC) is not recommended to treat neonatal purpura fulminans due to the possible increased risk of bleeding. The treatment

during the acute phase should continue until all lesions, including skin, CNS and ocular lesions, have resolved. Liver transplant is performed in case of homozygous PROC mutation when replacement therapy is readily unavailable. Maintenance therapy consists of either secondary prophylaxis with oral anticoagulation alone or protein C concentrate: 30–50 U/kg every 1–3 days with warfarin therapy.

Anticoagulation therapy should be initiated with administration of protein C replacement therapy and is an effective long term secondary prophylaxis. Initial heparin therapy is considered to avoid warfarin induced thrombosis. Unfractionated heparin (UFH) should be administered at a dose of 28 U/kg/h with a target anti-Xa level of 0.3–0.7 U/mL. The recommended dose of low molecular weight heparin (LMWH) is 1.0–1.5 mg/kg/dose every 12 h with a therapeutic target anti-Xa level of 0.5–1 U/mL. Warfarin is recommended for maintenance therapy. If protein C concentrate is not concurrently administered as prophylaxis, then international normalized ratio (INR) between 2.5 and 3.5 should be reached. A smaller dose of warfarin, to maintain a target INR of 1.5–2.5, is recommended with protein C replacement therapy.[22]

Due to the risk of bleeding or recurrent purpura fulminans, INRs often need to be monitored on a weekly basis. D-Dimer is a helpful indicator of adequate replacement and anticoagulation therapy in neonates. A raising or elevated D-dimer may be the first sign of recurrent purpura fulminans. In-case of acquired protein C deficiency; management of DIC should be based on the clinical and associated laboratory findings. The platelet count should be maintained $>50,000 \times 10^9$/L and the fibrinogen level >1 g/L. Protein C concrete is commonly used; the doses are similar but must be adjusted in case of renal failure. If the etiology is secondary to severe infection, appropriate intravenous antibiotics should be administered. Cases with comorbid pathological bleeding may require additional transfusions with platelet concentrate (10–15 mL/kg) or cryoprecipitate (5 mL/kg). Established soft tissue necrosis may require surgical removal of the dead tissue, fasciotomy, amputation or reconstructive surgery.

In acute infectious purpura, the initial management is directed at treatment of the infection and main complication (circulatory failure and shock). Patients with severe disease should be treated with broad spectrum antibiotics and resuscitated with fluid to correct circulatory failure. They may often need tracheal intubation and mechanical ventilation with inotropic support to improve multiple organ dysfunction. FFP or cryoprecipitate infusions are used for

correcting coagulopathy and to reduce risk of hemorrhage associated with hypofibrinogenemia. Support care is needed in-case of multiple organ failure. May require skin grafting and amputation of digits and limbs. Long-term orthopedic complications including disruption of bone may be seen if not treated properly.

In post-infectious purpura fulminans, most frequent regimen followed is administration of FFP on daily basis (10-20mL/kg) and immediate intravenous heparinization (100 units/kg) should be undertaken followed by a constant infusion of 25units kg/h until levels of protein S return to normal (2-6 weeks). As there is a risk of superinfection with group A streptococcus or S. aureus which may lead to systemic sepsis and shock, necrotizing fasciitis and DIC, recognition of these complications and appropriate antimicrobial and surgical therapy is mandatory. Immunosuppression with steroids and plasmapheresis are contraindicated as they result in a decline of protein S antibodies levels much rapidly.

CONCLUSION

Purpura fulminans, a skin disorder caused due to downregulation of anticoagulant pathway in hemostasis. The main etiology of purpura is protein C deficiency that may occur in an individual due to various reasons like microbial infections, drugs, diseases, toxins, snake bite or it may be a congenital deficiency. The pathology behind purpuric symptoms and progression of disorder solely depends on the underlying cause, but the conditions accompanied by it are usually extremely severe. Neonatal forms of purpura fulminans are 100% fatal without replacement of deficient clotting factors, while meningococcal sepsis can still be a fatal condition, even despite therapy. The therapeutic strategies are developed based on the diagnosis outcomes. The drug of choice of purpura is Ceprotin, a protein C plasma concrete. Along with these fresh frozen plasma and anticoagulants are used, drugs like fibrinolytics; thrombolytics; antibiotics; antivirals; antifungals; antitoxins; antidotes are used for eradication of underlying cause. A continuous monitoring of INR levels, clotting time, prothrombin time is needed for follow-up of management of purpura fulminans. Improvements in supportive therapy have been made within the last few decades and have improved patient outcomes, including prevention of secondary infections, and transfusion of necessary blood products.

REFERENCES

1. Pino PA; Román JA; Fernández F. Delayed Surgical Debridement and Use of Semiocclusive Dressings for Salvage of Fingers After Purpura Fulminans. *Hand (N Y),* Dec, 2016; 11(4): NP34-NP37.

2. Acute, Severe Disseminated Intravascular Coagulopathy. Robert W. Colman (eds.), Hemostasis and Thrombosis: Basic Principles and Clinical Practice, Philadelphia, Lippincott Williams and Wilkins, 2006; 1577.

3. Saul N. Faust and Simon Nadel. Life threatening dermatoses and emergencies in dermatology. (eds.). Purpura fulminans, Springer, Berlin, Heidelberg, 45.

4. Herbert P. Goodheart, Diseases of Vasculature. Sonya seigafuse, Kerry Barrett (eds.), Goodheart's photo guide to common skin disorders, Philadelphia, USA. Lippincott Williams and Wilkins, 2009; 313-14.

5. Manco-Johnson MJ, Abshire TC, Jacobson LJ, Marlar RA. Severe neonatal protein C deficiency: prevalence and thrombotic risk. J Pediatric, 1991; 119(5): 793-98.

6. Chantal P. Bleeker, Henry JC De Vries, Dermatological manifestations of systemic infections. Cohen J, William G, Steven M. Opal (eds.), Infectious Diseases, area, pub name, 2017; 1(4): 113-21.

7. James W. Patterson, The Vasculopathic Reaction Pattern, Patterson (eds.). Weedon's Skin Pathology, USA, Churchill Livingston Elsevier, 4th edition, 2006, 223.

8. Alan R. Cohen, Rash-Purpura, Gary R. Fleisher, Stephen Ludwig, Benjamin K. Silverman (eds.). Synopsis of Pediatric Emergency Medicine. Philadelphia, Lippincott William and Wilkins, 2002; 211.

9. Leung AK, Chan KW. Evaluating the child with purpura. Am Fam Physician, 2001; 64(3): 419-28. PMID:11515831

10. J. Nolan, R. Sinclair. (Review of management of purpura fulminans and two case reports). British Journal of Anesthesia, 2001; 86 (4): 581-6.

11. Chalmers E, Cooper P, Forman K, et al. (Purpura fulminans: recognition, diagnosis and management). ACD-BMJ, 2011. doi: 10.1136/adc.2010.199919.

12. emedicine.medscape.com/article/2202749-overeview

13. *Nicolaes GA, Dahlbäck B. (Congenital and acquired activated protein C resistance). Seminars in Vascular Medicine, February 2003; 3(1): 33–46.* doi*:10.1055/s-2003-38331.* PMID 15199491.

14. *Mosnier LO, Griffin JH. "Protein C anticoagulant activity in relation to anti-inflammatory and anti-apoptotic activities". Frontiers in Bioscience, 2006; 11: 2381–99.* doi*:10.2741/1977.* PMID 16720321.

15. *Goldenberg NA, Manco-Johnson MJ. "Protein C deficiency". Haemophilia, November 2008; 14(6): 1214–21.* doi*:*10.1111/j.1365-2516.2008.01838.x. PMID 19141162*.

16. Palta S, Saroa R, Palta A. (Overview of the coagulation system). Indian Journal of Anaesthesia, 2014; 58(5): 515-523. doi:10.4103/0019-5049.144643.

17. http://www.pathologyoutlines.com/topic/coahulation dic.html

18. Klodiana Mrishaj. (NEONATAL PURPURA FULMINANS). Flipper e nuvola, 7077.

19. Talwar A, Kumar S, Gopal M G, Nandini A S. Spectrum of purpura fulminans: Report of three classical prototypes and review of management strategies. Indian J Dermatology Venereal Lepro, 2012; 78: 228.

20. Adya KA, Inamadar AC, Palit A. Anticoagulants in dermatology. Indian J Dermatol Venereol Leprol, 2016; 82: 626-40.