Treatment of Diffuse Alveolar Hemorrhage: Controlling Inflammation and Obtaining Rapid and Effective Hemostasis

Jeong A Park*

Department of Pediatrics, Memorial Sloan Kettering Cancer Center, USA

*Corresponding Author: Jeong A Park, Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

Published June 09, 2021

This Book Chapter is a republication of an article published by Jeong A Park at International Journal of Molecular Sciences in January 2021. (Park, J.A. Treatment of Diffuse Alveolar Hemorrhage: Controlling Inflammation and Obtaining Rapid and Effective Hemostasis. Int. J. Mol. Sci. 2021, 22, 793. https://doi.org/10.3390/ijms22020793)

How to cite this book chapter: Jeong A Park. Treatment of Diffuse Alveolar Hemorrhage: Controlling Inflammation and Obtaining Rapid and Effective Hemostasis. In: Letizia Giampietro, editor. Prime Archives in Molecular Sciences: 2nd Edition. Hyderabad, India: Vide Leaf. 2021.

© The Author(s) 2021. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License(http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Authors' Contributions: Jeong A Park conceptualized the scope of manuscript and performed the literature search, analysis, and wrote the manuscript.

Funding: This research received no external funding

Acknowledgements: I would like to thank the library service at MSKCC for assistance in literature search.

Conflicts of Interest: The author declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Abstract

Diffuse alveolar hemorrhage (DAH) is a life-threatening pulmonary complication in patients with hematologic malignancies or systemic autoimmune disorders. Pathologic findings show pulmonary capillaritis, bland hemorrhage, diffuse alveolar damage, and hemosiderin-laden macrophages, but in the majority of cases pathogenesis remains unclear. Despite the severity and high mortality, the current treatment options for DAH remain empirical. Systemic treatment to control inflammatory activity including high-dose corticosteroids, cyclophosphamide, and rituximab and supportive care have been applied, but largely unsuccessful in critical cases. Activated recombinant factor VII (FVIIa) can achieve rapid local hemostasis and has been administered either systemically or intrapulmonary for the treatment of DAH. However, there is no randomized controlled study to evaluate the efficacy and safety, and the use of FVIIa for DAH remains open to debate. This review discusses the pathogenesis, diverse etiologies causing DAH, diagnosis, and treatments focusing on hemostasis using FVIIa. In addition, the risks and benefits of the off-label use of FVIIa in pediatric patients will be discussed in detail.

Keywords

Coagulopathy; Corticosteroids; Diffuse Alveolar Hemorrhage; Hematopoietic Stem Cell Transplantation; Hemostasis; Lung
Injury; Pediatric; Recombinant Factor Viia; Rituximab; Vasculitis

Abbreviations

AAV- ANCA Associated Vasculitis; ANA- Antinuclear Antibody; ANCA- Antineutrophilic Cytoplasmic Antibody; APL- Antiphospholipid Antibody; ARDS- Acute Respiratory Distress Syndrome; BAL- Bronchoalveolar Lavage; β2GP- β2 Glycoprotein1; CL- Anticardiolipin Antibody; CR- Complete Response; CT- Chest Computed Tomography; DAH- Diffuse Alveolar Hemorrhage; DAMPs- Dangerassociated Molecular Patterns; ACA- Epsilon Aminocaproic Acid; ESRD- Endstage Renal Disease; ETT- Endotracheal Tube; GBM- Glomerular Basement Membrane; GVHD- Graftversushost Disease; HCT- Hematopoietic Stem Cell Transplantation; HLH- Hemophagocytic Lymphohistiocytosis; ICU- Intensive Care Unit; IPH- Idiopathic Pulmonary Hemosiderosis; NET- Neutrophil Extracellular Traps; NR- No Response; PEEP- Positive Endexpiratory Pressure; PR- Partial Response; RDS- Respiratory Distress Syndrome; FVIIa- Recombinant Factor VIIa; RF- Rheumatoid Factor; TF- Tissue Factor; TFPI- Tissue Factor Pathway Inhibitor; TXA- Tranexamic Acid

Introduction

Diffuse alveolar hemorrhage (DAH) is a clinical syndrome characterized by acute onset of alveolar infiltrates and hypoxemia which result in progressive diffuse alveolar bleeding, requiring immediate treatment [1]. Many systemic diseases can cause DAH, but the pathogenesis is not well understood in the majority of cases, and the standard treatment for DAH has not been established even for the systemic autoimmune disorders. The treatment includes supportive cares such as correction of hemodynamic instability or coagulopathy and ventilatory support, high-dose corticosteroids, immunosuppressants, and plasmapheresis. Though, the overall mortality still remains high. To control systemic inflammation, subsequent cytokine storm, and life-threatening bleeding, multidisciplinary treatment is required. Although the role of systemic immunosuppressive
treatment has been emphasized, systemic immunosuppressive treatment alone is not enough to stop the life-threatening bleeding, and it takes times to work: these single-disciplinary approaches often lead to treatment failure.

Recombinant factor VIIa (FVIIa) was developed for the management of bleeding in hemophilic patients with inhibitors or in FVII-deficient patients. Despite this narrow indication, the off-label use of FVIIa has been increasing in non-hemophiliac patients to prevent or to treat uncontrolled bleeding in adults, children, neonates, and even preterm neonates [2,3]. The FVIIa has been reported to have a significant hemostatic effect in DAH as well [4-7]. However, there is no randomized controlled study to evaluate the efficacy in various conditions but also no consensus on the formulations, routes of administration, doses, and dosing regimens of FVIIa for the treatment of DAH. In addition, few studies have been reported in children. This review discusses the pathogenesis, pathologic findings, diagnosis and underlying etiologies of DAH, treatment strategies, hemostatic treatments including FVIIa, and the off-label use of FVIIa for DAH in adult and pediatric patients.

Pathogenesis of DAH

The DAH syndrome is attributed to the injury to the lung microvasculature including the capillaries, arterioles and venules lining the alveoli. DAH can be clinically categorized into 4 major groups: immune associated [ANCA-associated vasculitis (AAV) and connective tissue disease], congestive heart failure associated, miscellaneous [infection, trauma, clotting disorder, drugs, malignancy, and hematopoietic stem cell transplantation (HCT)], and idiopathic. The major pathologic findings of DAH include antibody-mediated pulmonary capillaritis, bland alveolar hemorrhage, and diffuse alveolar damage [8-10]. Pulmonary capillaritis is the most common pattern and is defined by neutrophilic infiltration of the perivascular interstitium (alveolar septae) of the capillaries, endothelial edema, injury, and fibrinoid necrosis [9,11,12]. It is associated with systemic vasculitides, connective tissue disorders, immune complex mediated disorders, and post-transplant hemorrhages, and systemic immune suppressive treatment is effective to control DAH [12]. Hemosiderin-laden macrophage accumulation is characteristics
in 24-48 hours after the initial vessel injury [8,13]. Bland alveolar hemorrhage is not directly linked with inflammation or destruction of the alveolar capillaries, venules, and arterioles but with widespread leaking of RBCs into the alveoli [8,10]. It is observed in drug-induced DAH, SLE, DIC, cardiac originated DAH (mitral stenosis or mitral regurgitation), and infections such as HIV or infective endocarditis[8, 9].Generally, systemic immunosuppressants are not indicated except in cases of systemic autoimmune disease. Diffuse alveolar damage, the primary lesion in acute respiratory distress syndrome (ARDS), is characterized by interstitial and intra-alveolar edema, capillary congestion, microthrombi, epithelial necrosis and sloughing, the presence of fibrinous exudates in alveolar air spaces, and hyaline membrane formation [14]. It is associated with ARDS, cytotoxic drugs, radiation treatment, SLE, and cocaine inhalation [15,16].

Systemic inflammation involving pulmonary vasculature triggered by overactive autoimmune response and cytokine storm deemed to be the primary cause of DAH. Macrophage activation and high ferritin and IL-6 levels have been implicated in the pathogenesis of acute lung injury, inflammation and pulmonary hemorrhage [17]. Pulmonary capillaritis associated DAH bears on fibrin thrombi occluding the intra-alveolar capillaries and fibrinoid necrosis of the small blood vessels. It is often accompanied by inflammation of large blood vessels, IgG/C3 deposition in the alveolar walls, and erythrocytes extravasation into the alveolar spaces [18]. In animal models, DAH is mediated by opsonin-dependent uptake of dead cells by natural IgM and subsequent activation of the early classical complemet pathway [19]. During inflammation, bone marrow-derived macrophages are recruited to the alveoli and differentiate into proinflammatory (M1-like) macrophages [20], and the IgM/C3-opsonized dead cells engage CR3/CR4 (a component of C3b receptor 3 and 4) on macrophages, expediting the development of DAH[19]. Neutrophil extracellular traps (NETs), fibrous networks which protrude from the membranes of activated neutrophils, also have a detrimental role in both autoimmune disorders and acute lung injury [21]. NETs accelerate the inflammatory processes by releasing a wide range of active molecules like danger-associated molecular patterns (DAMPs), histones, active lytic-enzymes, and multiple cytokines.
in the extracellular space [22]. Imbalance between NETs formation and degradation exacerbates immune responses and tissue injury [23], and prolonged exposure to NETs-related cascades increases systemic organ damage [24]. NETs are closely associated with development of DAH in murine autoimmune disease models, and targeting NETs with DNase-I reduced severity of DAH lesions and improved survival [25,26].

DAH after HCT is also closely associated with lung injury and subsequent vasculopathy. High-dose chemotherapy, thoracic or total body irradiation, and undocumented infections have been implicated as the initial injury to the lung leading to post-transplant DAH [27]. Animal models suggest that alveolitis develops during the acute phase of graft-versus-host disease (GVHD), and it is characterized by alveolar hemorrhage, increase in the alveolar leukocytes, platelet microthrombi, damage of alveolar endothelial and epithelial cells, increased turnover rate of alveolar cells, and increased cell counts and protein concentration of the bronchoalveolar lavage (BAL) fluid [28,29]. Irrespective of post-transplant leukopenia, neutrophils and neutrophil products are detected in the lower respiratory tract of HCT recipient at the time of DAH [30]. Besides, vasculitis of small muscular arteries and thrombotic microangiopathy in the form of endothelial swelling and thrombi are frequently observed in acute hemorrhagic pulmonary edema after transplantation [9,31]. The vasculopathy manifests as concentric intimal or medial hyperplasia with luminal narrowing, prominent myxoid changes, extravasated RBCs, and the presence of foamy histiocytes apart from thrombotic microangiopathy [31-33]. Add on, hematopoietic growth factors (G-CSF) and cytokine storms make worse the alveolar damage and capillary leakage by increasing neutrophil infiltration into the lungs [30]. Dysregulated cytokine release including both TH1 (IL-2, IL-6, IFN-γ, and TNF-α) and TH2 (IL-9 and IL-15) cytokines further potentiates the inflammatory response [34].

**Diagnosis of DAH**

The differential diagnosis of DAH is broad, and the etiologies of DAH can be broadly divided into immune- and non-immune-mediated causes (Table 1) [35]. A careful history, physical examination, and laboratory tests can often help to establish the
risk factors and most likely etiology of the alveolar hemorrhage. Bronchoscopy is the key investigation needed to diagnose DAH by lavage and to exclude other associated infections. Bronchoscopy has higher yield if performed within the first 48 hours. Persistent or increasing blood on three sequential lavage aliquots from one affected area of lung supports the diagnosis of DAH [36]. The number of hemosiderin-laden macrophages should be counted in cases of subacute or recurrent DAH [8,16]. The finding of ≥20% hemosiderin-laden macrophages in BAL fluid is commonly regarded as diagnostic of DAH and closely associated with severity [36-38]. BAL specimens should be sent for routine bacterial, mycobacterial, fungal, and viral cultures, and Pneumocystis stains to exclude infections. The role of transbronchial lung biopsy is not established in the diagnosis of DAH as the area of involvement is often patchy [8], but in any patients presenting with DAH of unclear causes a lung biopsy is strongly recommended to determine the underlying etiologies [10,39,40]. Imaging studies including chest radiographies and high-resolution chest computed tomography (CT) scans provide additional information to support a diagnosis of DAH. Typical pattern of DAH includes focal or diffuse areas of ground glass opacities or consolidations as a consequence of alveolar filling. Laboratory tests include a complete blood count with differential; coagulation studies; serum BUN and creatinine analysis; ANCA testing (c-ANCA and p-ANCA); antigen-specific ELISA [proteinase 3(PR3) and myeloperoxidase (MPO)], analysis of anti-phospholipid antibodies (APL), lupus anticoagulant, anti-cardiolipin (CL) antibodies, anti-β-2 glycoprotein1 (β2GP) antibodies, anti-glomerular basement membrane (GBM) antibodies, anti-nuclear antibodies (ANA), and rheumatoid factor (RF); urinalysis with urine sediment assessment; and a urine drug screen [9,41].
Table 1: Etiologies of diffuse alveolar hemorrhage and treatment options.

| Classification                  | Etiology                                      | Nonspecific findings | Specific findings                                      | Treatment                |
|---------------------------------|-----------------------------------------------|----------------------|-------------------------------------------------------|--------------------------|
| **Immune-mediated**             | ANCA-associated vasculitis                    | Granulomatosis with polyangiitis (Wegener granulomatosis) | Prolonged PT/aPTT/PT INR | c-ANCA,                   | Immunosuppressants, Corticosteroids |
|                                 | Microscopic polyangiitis                      |                      | p-ANCA (MPO-antibody)                                 |                          | Cyclophosphamide            |
|                                 | Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) |                      | Leukocytosis                                          |                          | Rituximab                   |
|                                 | Anti-phospholipid antibody syndrome           |                      | Eosinophilia                                          |                          |                          |
| SLE                             |                                               |                      | Increased ESR                                         |                          |                          |
| RA                              | Hematuria                                     |                      | APL, lupus anticoagulant, anti-CL, anti-β2GP1 antibody |                          |                          |
| Inflammatory myopathies         | Patch diffuse alveolar infiltrates or         |                      | Anti-CL IgA antibody                                   |                          |                          |
| Henoch-Schönlein purpura        |                                               |                      | Removal of autoantibodies                              |                          |                          |
| Ig A nephropathy                | Air bronchogram on chest radiograph          |                      | Anti-CL IgA antibody                                   |                          |                          |
| Anti-GBM antibody syndrome      |                                               |                      | Procoagulation                                         |                          |                          |
| Cryoglobulinemia                |                                               |                      | Platelet transfusion                                   |                          |                          |
| Behçet's disease                |                                               |                      | Cryoprecipitates                                       |                          |                          |
| Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis) |                    |                      | Vitamin K supplement                                   |                          |                          |
| Lung transplant rejection       |                                               |                      | TXA                                                   |                          |                          |
| Drug-induced vasculitis         |                                               |                      | ACA                                                   |                          |                          |
| Medications: warfarin, aspirin, amiodarone, phenytoin |                     |                      | FVIIa                                                 |                          |                          |
| Idiopathic pulmonary capillaritis|                                               |                      | Thrombin                                               |                          |                          |
| **Non-immune mediated**         | Coagulopathy                                  |                      |                                                       |                          |                          |
| Non-cardiovascular disease      | Pseudomonas aeruginosa                        |                      |                                                       |                          |                          |
|                                 | Aspergillus spp.                              |                      |                                                       |                          |                          |
|                                 | CMV and herpes pneumonitis                    |                      |                                                       |                          |                          |
|                                 | Diffuse alveolar damage                       |                      |                                                       |                          |                          |

Diffuse alveolar damage

Radiation
| Cytotoxic drugs | Acute respiratory distress syndrome | Hematopoietic stem cell transplantation |
|----------------|-----------------------------------|----------------------------------------|
|                |                                   | Idiopathic pulmonary hemosiderosis     |
|                |                                   | Diuresis                               |
| Cardiovascular disease | Pulmonary SOS | Kerley B lines on chest radiograph |
| Mitral stenosis |                                | Cardiovascular disease |
| Arteriovenous malformation |    | Mitral stenosis |
| Pulmonary lymphaangiomyomatosis | | Arteriovenous malformation |
| Pulmonary hypertension |    | Pulmonary lymphaangiomyomatosis |
| Pulmonary capillary hemangiomatosis | | Pulmonary hypertension |
| Left ventricular dysfunction | | Pulmonary capillary hemangiomatosis |

**Abbreviations:** ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; anti-β2GPA, anti-β-2 glycoprotein1 antibody; anti-CL antibody, anti-cardiolipin antibody; anti-dsDNA antibody, anti-double stranded DNA antibody; anti-MPO, anti-myeloperoxidase antibody; APL, anti-phospholipid antibody; anti-SM antibody; anti-smooth muscle antibody; C1q, complement 1q; c-ANCA, cytoplasmic-ANCA; CMV, cytomegalovirus; ACA, epsilon aminocaproic acid; ESR, erythrocyte sediment rate; GBM, glomerular basement membrane; INR, international normalized ratio; IPH, idiopathic pulmonary hemosiderosis; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; p-ANCA, perinuclear-ANCA; PT, prothrombin time; aPTT, a partial thromboplastin time; RA, rheumatoid arthritis; RF, rheumatoid factor; FVIIa, activated recombinant factor VII; SLE, systemic lupus erythematosus; SOS, sinusoidal obstruction syndrome; TXA, tranexamic acid.
Treatment of DAH

DAH, especially acute macroscopic hemorrhage, has a high mortality rate, requiring prompt and aggressive multidisciplinary management. Treatment for DAH involves three major disciplines: (1) supportive care including hemodynamic correction, transfusion, and ventilator support, ranging from oxygen supplementation to mechanical ventilation with high positive end-expiratory pressure (PEEP) producing a tamponade effect to limit capillary bleeding, (2) treatment of underlying disease including intensive immunosuppressive treatments to control disease activity, plasmapheresis to remove autoantibodies, and antivirals or antibiotics for infection-associated pulmonary hemorrhages, and (3) rapid and effective local hemostasis [7].

The most immediate life-threatening complication of DAH is acute hypoxemic respiratory failure. When severe DAH results in ARDS, high levels of FiO₂ and PEEP are often needed to achieve acceptable oxygenation. Although there is no consensus on ideal PEEP levels for DAH and it should be adjusted by the severity of respiratory failure and lung recruitability, DAH has been managed with high PEEP and permissive hypercapnia to reduce the active bleeding and prevent lung collapse[42]. The PEEP used in severe ARDS lies around 8.5cm H₂O[43], but the PEEP level should be selected by carefully considering oxygenation advantage and the putative benefits on lung protection[44].

To control the inflammatory activity, high-dose corticosteroids are recommended to start promptly, along with treatment for underlying disease. Corticosteroids have been accepted as a mainstay of treatment aimed at reducing acute inflammatory responses such as lung alveolar epithelial swelling, thrombotic microangiopathy, and increased inflammatory cells and cytokines [10,40,45]. Based on anecdotal reports and retrospective studies, systemic high-dose corticosteroids (500mg to 2g/day or 30mg/kg/day of intravenous (iv) methylprednisolone for 3-5 days followed by gradual tapering over 4 weeks) are recommended to treat DAH [4,40,46,47].
However, steroid treatment alone is not sufficient to stop acute macroscopic pulmonary bleeding and is often fatal if the etiology is infectious or if the patient is in an immunocompromised status; the benefit of high-dose corticosteroids in critically ill patients remains undefined. Despite the widespread use of high-dose corticosteroids for DAH, the mortality exceeds 50%, especially in patients requiring intensive care unit (ICU) admission or in patients received HCT [48]. For the treatment of AAV, reduced-dose glucocorticoids had comparable efficacy to standard-dose corticosteroids with respect to mortality or incidence of end-stage renal disease (ESRD) but also reduced the incidence of serious infections at 1 year [49]. A study investigating the dose effect of corticosteroids for DAH suggested that patients treated with low-dose methylprednisolone (<250 mg/day) had a significantly lower ICU mortality rate compared to the patients treated with medium-dose (250-1000 mg/day) or high-dose (>1000 mg/day) methylprednisolone, and overall mortality did not differ by the doses of corticosteroids, raising questions about the validity of high-dose corticosteroids for DAH [48].

To eliminate autoreactive antibodies or triggering factors rapidly, plasmapheresis has been used as an adjunctive therapy particularly in autoimmune connective disorders, such as anti-GBM disease, AAV or SLE-associated pulmonary capillaritis. Plasmapheresis is performed daily or on alternating days for 14 days. Each exchange involves 1-1.5 times the total plasma volume and is replaced with albumin or FFP. Although retrospective studies reported excellent patient outcome and safety [50], long-term follow-up data or matched analyses to compare the efficacy of plasmapheresis to methylprednisolone have failed to show significant benefit [51-53]. The evidence-based guidelines of the American Society for Apheresis recommend to use plasmapheresis in AAV patients with DAH presenting with hypoxemic respiratory failure requiring either high-flow supplemental oxygen or mechanical ventilation [54]. Recently released data of randomized controlled trial of plasma exchange and glucocorticoids for treatment of AAV (NCT00987389) suggested that the use of plasmapheresis did not reduce the mortality or the incidence of ESRD [49].
Rituximab, a chimeric monoclonal antibody targeting CD20, has been used as another viable alternative. Antibody-mediated modification and/or depletion of ANCA producing CD20(+) plasma cells is a proposed mechanism for rituximab to decrease autoantibody production and to control disease activity [55, 56]. Although most of the studies have been limited, they suggest that rituximab is an effective therapeutic option for DAH in connective tissue disease or autoimmune disorders. Rituximab on a compassionate use basis for patients with refractory AAV reported successful treatment outcomes [57-60]. These encouraging results led to randomized controlled trials evaluating the effect of rituximab as a remission induction therapy in patients with severe AAV (NCT00104299, NCT01731561). Comparison between rituximab and cyclophosphamide pulse therapy for AAV showed a similar efficacy [61]. A randomized trial comparing the effect of combination therapies of glucocorticoids plus rituximab (375mg/m² once weekly for 4 weeks) and glucocorticoids plus cyclophosphamide (2mg/kg/day) also demonstrated comparable efficacy of rituximab for the remission induction in severe AAV, and rituximab showed a better effectiveness for recurrent disease, major renal disease or alveolar hemorrhage [58]. For long-term remission, rituximab was compared to azathioprine maintenance (NCT00748644), and rituximab treatment showed significantly longer remission duration and improved overall survival [61].

For obtaining rapid hemostasis, coagulopathy should be closely monitored and quickly corrected. Commonly accepted targets are platelet counts more than 50,000/μL and a prothrombin time-international normalized ratio (PT-INR) less than 1.5. Depending on the causes, platelet transfusions, vitamin K supplementation, cryoprecipitates, and fresh frozen plasma should be supplemented. Besides, in order to stop the bleeding, various prothrombotic treatments including antifibrinolytics, particularly lysine analogues tranexamic acid (TXA) and epsilon aminocaproic acid (ACA), thrombin, and FVIIa have been used for DAH and reported with a variety of success rates. Mechanisms of the hemostatic agents are described in Figure 1.
Figure 1: Coagulation and fibrinolytic cascades and the mechanisms of hemostatic agents.

TXA prohibits conversion of plasminogen into plasmin inhibiting fibrinolysis and stabilizes blood clots [62]. In addition to intravenous use, intrapulmonary or aerosolized TXA has been used for DAH [63-65]. Nebulized TXA led to complete or near cessation of bleeding in 10/18 pediatric patients with DAH [65], and recently, Neil et al. published a successful treatment outcome in 19 pediatric patients with DAH: 18 out of 19 patients had stopped bleeding after TXA inhalation [64]. However, TXA therapy failed to show significant effect on reducing bleeding associated mortality in patients with hematologic malignancies [66] but also increased risk of post-operative seizures [67] and showed limited efficacy on profound and recurrent bleedings [65]. ACA, another option for hemostatic treatment, is a lysine analog that binds competitively to plasminogen, blocking plasminogen from binding to fibrin and the subsequent conversion to plasmin, resulting in the inhibition of fibrin degradation (fibrinolysis) [68]. ACA has been used in addition to corticosteroids in patients with post-transplant DAH and reported to reduce 100-day mortality rate from 83% to 44% in patients treated with corticosteroids [69]. Though, a recent follow-up study reported that adjuvant treatment with ACA did not yield a significant difference in the outcomes of patients with DAH after HCT. The overall mortality on day 100 was still high at 85% [48].
In addition, the effects of thrombin or fibrinogen-thrombin for treatment of severe hemoptysis have also been reported [70,71]. Recently, Lee et al. has published the efficacy of intrapulmonary thrombin treatment for DAH in patients with hematologic malignancies. Intrapulmonary thrombin stopped bleedings rapidly in 13 of 15 patients refractory to corticosteroids with TXA treatment and significantly improved oxygenation status without thromboembolic complications [72]. Thrombin production is the final coagulation step required to convert fibrinogen to fibrin which produces a hemostatic lattice for platelet aggregation and thrombus formation at the site of injury [73]. Besides to the coagulation cascade, thrombin causes vasoconstriction at the smooth muscle cell level and promotes platelet aggregation at the site of the thrombus [74].

**Recombinant FVIIa treatment for DAH**

Recombinant FVIIa (FVIIa) is also used as an alternative ‘broad spectrum hemostatic agent’ to enhance hemostasis in patients with life-threatening intractable bleeding. Given that tissue factor (TF) pathway inhibitors (TFPI) increased in inflamed alveoli and these TFPIs prevent FVIIa-TF formation and FX activation, the inflamed lungs are more susceptible to bleeding [75]. FVIIa can overcome the effect of TFPI and restore thrombin generation. It promotes hemostasis via both TF-dependent pathway at the sites of endothelial injury and a TF-independent pathway which directly activate factors IX and X on the surface of activated platelets in the absence of TF (Figure 1). Factor X converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin. Alveolar TF remains high in inflammatory pulmonary conditions, including DAH, acute respiratory distress syndrome (ARDS) and pneumonia, as well as after lipopolysaccharide local challenge in the alveoli [5,76-78]. Alveolar TF-FVIIa complex activates coagulation factors IX and X, which in turn initiates a cascade of reactions, leading to thrombin burst and fibrin formation at the site of injury [5]. However, due to the separation between the alveolar and systemic compartments of the lung, FVIIa, similarly to most biologics, requires a high systemic concentration to affect specific receptors in the alveolar compartment. This requires higher and repeated doses of
intravenous FVIIa, associated with a higher risk of thromboembolic complications [7,79,80]. On the other hand, intrapulmonary locally administered FVIIa has been reported to have successful outcomes with a relatively small dose (50μg/kg) and less frequent administration [5,81,82]. Intrapulmonary (ip) administration can ensure that FVIIa reaches its alveolar receptor, TF, and it decreases systemic adverse effects because the alveolocapillary membrane does not allow the transmembranous passage of FVIIa. Pulmonary-administered FVIIa combines with TF and forms TF-FVIIa complex which activates coagulation factor IX and X, inducing balanced hemostasis. With relatively small doses, FVIIa results in both durable hemostasis and a significant improvement in oxygen transport capacity [7]. Moreover, TFPIs produced by alveolar macrophages is highly expressed in the airspace in inflammatory conditions secondary to acute lung injury and contributes to the balanced hemostasis without the theoretical risk of intra-alveolar thrombotic complications with intrapulmonary FVIIa [7,83,84]. Accordingly, treatment with FVIIa has a potentially high benefit-to-risk ratio in DAH when administered via the local intrapulmonary route.

Case reports and clinical studies have reported the effectiveness of FVIIa in various conditions, including thrombocytopenia, functional platelet defects, hemorrhagic complications after HCT (e.g., DAH and hemorrhagic cystitis), gunshot wounds, and coagulopathy of liver failure [85-92]. However, the efficacy and side effects of FVIIa in non-hemophiliac settings are largely anecdotal, and many questions still remain regarding the appropriate indications and guidelines for use, risks of thrombotic complications, monitoring, dosing, and integration with transfusion therapy. A Cochrane review of the off-label use of FVIIa reported that FVIIa did not have a significant mortality benefit over placebo but showed a trend toward control of bleeding, a lower number of transfusions, and arterial thromboembolic events [93].

There is a growing literature supporting the use of FVIIa to stop acute pulmonary hemorrhage following various diseases and injuries, including pneumonia, HCT, metastatic cancer,
idiopathic pulmonary hemosiderosis (IPH), and immune-associated vasculitis. Due to lack of randomized controlled studies, FVIIa has been used as a final effort to stop the bleeding, and many studies have reported the successful use of FVIIa for life-threatening DAH [5,81,82,94,95]. Although the optimal dose and dosing intervals remain to be determined, systemic administration usually entails the intravenous administration of 35-200 µg/kg as either a single dose or repeated doses every 2-4 hours [4,6,95,96], and intrapulmonary therapy typically involves bronchoscopy with a total dose of 50-90µg/kg of FVIIa diluted in normal saline as either a single dose or, if bleeding continues, as repeated doses over 24 hours [7,81,97,98]. The FVIIa treatment for pulmonary hemorrhage in adults is listed in table 2. 29 in 111 cases were related to immune disorders, and the rest 82 cases were non-immune related DAH where hematopoietic stem cell transplant (HCT)-related DAH showed a majority (75%, 62 cases). While the mortality of immune-mediated DAH was 25% (7 in 28 patients), that of non-immune-mediated DAH showed a higher mortality rate, 47% (27 in 58 patients: the outcome for the other 24 patients was not specified). Although the mean dose of FVIIa for iv injection was 427µg/kg/episode for immune-related DAH and 167µg/kg/episode for non-immune related DAH, most of the fatality cases were not directly related to DAH, and the complete response rate was similar in both groups; 19 in 21 patients and 23 in 23 patients. For iv use, approximately 250µg/kg/episode of FVIIa was administered, while, 50µg/kg/episode of FVIIa was used for ip administration. The response rate did not differ by the administration route or administered dose: 42 in 44 patients with iv FVIIa and 19 in 21 patients with ip FVIIa showed complete response.
Table 2: Published data on recombinant factor VIIa treatment for diffuse alveolar hemorrhage in adults.

| References          | Year  | Patients | Previous history                          | Route | Dose of FVIIa | Additional therapies          | Outcome | Thromboembolic complication | Case of death |
|---------------------|-------|----------|-------------------------------------------|-------|---------------|-------------------------------|---------|-----------------------------|---------------|
| Immune related      |       |          |                                           |       |               |                               |         |                             |               |
| Henke et al.[6]     | 2004  | M/53     | ANCA-vasculitis (n=2), viral infection    | IV    | 120µg/kg x 3 doses | CS, CPM, MMF, plasmapheresis | CR      | none                        | 0             |
|                     |       | M/25     | SLE, APS, nephritis, pleural effusion     | IV    | 90µg/kg x 3 doses | CS                            | CR      | none                        | 0             |
| Heslet et al.[5].    | 2006  | M/63     | Sarcoidosis, septic shock                 | IV    | 90µg/kg x 1 dose | TXA, aprotinin, desmopressin  | CR      | none                        | 1             |
|                     |       | F/34     | Wegener's granulomatosis, Churg-Strauss vasculitis | IP    | 50µg/kg x 1 doses | TXA, aprotinin                | CR      | none                        | 0             |
| Dabar et al.[97]    | 2011  | NA       | ANCA-vasculitis                           | IV    | 90µg/kg x 1 dose | none                          | CR      | none                        | 0             |
| Mandal et al.[106]  | 2012  | F/23     | Microscopic polyangitis                   | IV    | 90µg/kg x 2 doses | Plasmapheresis, MMF           | CR      | none                        | 0             |
| Esper et al.[82]    | 2014  | F/37     | SLE, Sjogren syndrome                     | IV    | 50µg/kg x 1 dose | CS, RTX                       | CR      | none                        | 0             |
| Alabed et al.[107]  | 2014  | F/37     | SLE, lupus nephritis                      | IV    | 75µg/kg x 1 dose | CS, CPM                       | CR      | none                        | 0             |
| Khoulani et al.[108] | 2014 | F/51     | NHL, lupus nephritis, cryoglobulinemia, bacterial pneumonia | IV    | 90µg/kg x 3 doses | CS, RTX, plasmapheresis       | NR      | none                        | 1             |
| Pathak et al.[109]  | 2015  | Age 47±19 years | ANCA vasculitis (n=9) | IV    | 75µg/kg x 4 doses | CS, CPM or RTX, IVIG Plasmapheresis | CR (9/9) | none                        | 1/9           |
|                     |       |          | Good pasture's syndrome (n=3)              |       |               |                               |         |                             |               |
|                     |       |          | SLE (n=2)                                 |       |               |                               |         |                             |               |
|                     |       |          | ITP (n=1)                                 |       |               |                               |         |                             |               |
|                     |       |          | Cryoglobulinemia (n=1)                    |       |               |                               |         |                             |               |
|                     |       |          |                                           |       |               |                               |         |                             |               |
| Baker et al.[75]    | 2016  | F/23     | SLE                                       | IV    | 50µg/kg x 1 dose | CS, ACA, IVIG, CPM, RTX, plasmapheresis | PR      | none                        | 1             |
| Diaz et al.[110]    | 2019  | M/67     | Wegener's granulomatosis, bacterial pneumonia | IP    | 30µg/kg x 1 dose | CS, desmopressin              | CR      | none                        | 0             |
|                     |       | F/61     | SLE, pulmonary HTN, pneumonia              | IP    | 50µg/kg x 1 dose | CS, plasmapheresis            | CR      | none                        | 1             |
|                     |       | F/22     | Pulmonary sarcoidosis, pulmonary embolism, pneumonia | IP    | 50µg/kg x 1 dose | ECMO                          | CR      | none                        | 1             |
| Non-immune related                                                                 |   |   |   |   |   |   |   |
|-----------------------------------------------------------------------------------|---|---|---|---|---|---|---|
| Meijer et al.[111] 2000 M/49 ALL, fungal pneumonia                                  | IV| 90µg/kg x 1 dose               | TXA, antifungal agents | CR | none | 1 |
| White et al.[112] 2001 M/ns MDS, AML, Aspergillus pneumonia                       | IV| 90µg/kg x 4 doses              | Antifungal agents      | CR | none | 0 |
| Hicks et al.[113] 2002 F/35 AML, HCT, GVHD, fungal pneumonia                      | IV| 90µg/kg x 4 doses              | CS, ACA, desmopressin | CR | none | 0 |
| Pastores et al.[4] 2003 M/48 NHL, HCT, GVHD                                      | IV| 90µg/kg x 2 doses              | CS                      | CR | none | 0 |
| Henke et al.[6] 2004 M/28 Acute leukemia, HCT                                     | IV| 120µg/kg→180µg/kg             | CS                      | CR | none | 1 |
| Yildirim et al.[114] 2006 M/23 Pulmonary renal syndrome                           | IV| 90µg/kg x 3 doses              | none                    | CR | none | 0 |
| Macdonald et al.[115] 2006 M/52 CAP                                               | IV| 90µg/kg x 1 dose               | none                    | CR | none | 0 |
| Heslet et al.[5] 2006 M/46 CLL, HCT, GVHD, CMV pneumonia                         | IV/IP| 50µg/kg x 3 doses, 50µg/kg x 2 doses | TXA, aprotinin          | PR | none | 1 |
| M/44 AML, pneumonia                                                              | IP | 50µg/kg x 1 dose               | TXA, aprotinin          | CR | none | 0 |
| F/44 AIDS, C. difficile colitis, Pseudomonas pneumonia, CMV infection            | IP | 50µg/kg x 1 doses              | TXA, aprotinin          | PR | none | 1 |
| M/63 AML, HCT, GVHD, pneumonia                                                   | IP | 50µg/kg x 1 dose               | TXA, aprotinin          | CR | none | 0 |
| Shenoy et al.[116] 2007 F/NA AML, HCT, pneumonia                                | IV| 90µg/kg x 2 doses              | CS                      | CR | none | 0 |
| Gupta et al.[117] 2007 24 patients HCT                                            | NA | NA                          | CS (n=24), desmopressin (n=4), ACA (n=3) | NA | none | NA |
| Estella et al.[98] 2008 F/39 AML, renal failure                                  | IP | 50µg/kg x 1 dose               | None                    | CR | none | 0 |
| M/46 IV drug abuse, hepatitis B and C, HIV, myocarditis, aspirin & clopidogrel    | IP | 50µg/kg x 1 dose               | None                    | CR | none | 0 |
| Lau et al.[118] 2009 M/33 Cystic fibrosis                                       | IV| 90µg/kg x 1 dose               | BAE                     | CR | none | 0 |
| M/22 Cystic fibrosis, liver failure, liver TPL, pneumonia                        | IV| 90µg/kg x 1 dose               | BAE                     | CR | none | 1 |
| F/23 Cystic fibrosis, lung infection, ARDS                                       | IV| 120µg/kg x 2 doses             | BAE                     | CR | none | 1 |
| M/27 Cystic fibrosis, supplicative lung disease                                  | IV| 90µg/kg x 2 doses              | BAE                     | PR/CR | none | 0 |
| Tatopoulous et al.[119] 2010 M/53 Leptospirosis, ARF, ARDS                      | IV| 105 µg/kg x 1 dose             | CS                      | CR | none | 0 |
| Dabar et al.[97] 2011 NA Leukemia                                               | NA | 90µg/kg x 1 dose               | none                    | CR | none | 0 |

18 www.videleaf.com
| Study                | Year | Patients | Diagnosis | Preceding conditions | Treatment | Outcome | Other |
|----------------------|------|----------|-----------|----------------------|-----------|---------|-------|
| Elinoff et al. [96]  | 2014 | 23       | ALL (n=1), AML (n=3), CLL (n=2), HD (n=1), AA (n=6), MDS (n=1), other (n=5). preceding conditions: HCT (n=23), CMV infection (n=14), aGVHD (n=1), cGVHD (n=8), DLI (n=6), stem cell boost (n=5), ARDS. | IV | 41 µg/kg x 3 doses, total dose 16 mg, (4.8-37.6 mg) | CS (n=23), Desmopressin (n=8), ACA (n=2), Estrogen (n=1) | NA | 4/43 episodes: blood clot obstruction an e-tube (n=1), basilic vein thrombosis (n=1). DIC (n=2) |
| Pathak et al. [109] | 2015 | years    | HCT (n=7) | IV | 75 µg/kg x 4 doses | CS, CPM or RTX, IVIG Plasmapheresis | CR (7/7) | none | 6/7 |
| Baker et al. [75]   | 2016 | F/49     | MDS, HCT  | IP | 30 µg/kg x 2 dose  | CS, ACA | CR | none | 0 |
|                     |      | M/64     | End-stage liver disease, clopidogrel treatment | IP | 30 µg/kg x 2 dose  | CS | CR | none | 0 |
|                     |      | F/68     | Metastatic anal cell carcinoma, ARDS | IP | 30 µg/kg x 2 dose  | CS | CR | none | 0 |
|                     |      | F/23     | HCT | IP | 30 µg/kg x 1 dose  | CS | CR | none | 0 |
|                     |      | F/84     | Burn, inhaled injury | IP | 60 µg/kg x 1 dose  | CS, ACA | CR | none | 0 |
| Diaz et al. [110]   | 2019 | F/46     | Septic shock | IP | 50 µg/kg x 1 dose  | none | CR | none | 0 |
| Shimizu et al. [120]| 2020 | M/68     | Acute ischemic stroke, t-PA treatment | IV | 75 µg/kg x 1 dose  | CS | CR | none | 0 |
|                     |      | M/54     | Acute ischemic stroke, t-PA treatment | IP | 75 µg/kg x 1 dose  | CS | CR | none | 0 |

**Abbreviations:** AA, aplastic anemia; ACA, aminocaproic acid; aGVHD, acute graft-versus-host disease; AIDS, acquired immune deficiency syndrome; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ANCA, anti-neutrophil cytoplasmic antibody; APS, anti-phospholipid syndrome, ARDS, acute respiratory distress syndrome; BAE, bronchial artery embolization; CAP, community-acquired pneumonia; CLL, chronic lymphocytic leukemia; cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; CR, complete response; CPM, cyclophosphamide; CS, corticosteroids; DLI, donor lymphocyte infusion; ECMO, extracorporeal membrane oxygenation; MDS, myeloid dysplastic syndrome; HCT, hematopoietic stem cell transplantation; HD, Hodgkin disease; HIV, human immune deficiency virus; HTN, hypertension; IP, intrapulmonary; ITP, idiopathic thrombocytopenic purpura; IV, intravenously; MMF, mycophenolate mofetil; NA, not available; NHL, non-Hodgkin lymphoma; NR, no response; SLE, systemic lupus erythematosus; PR, partial response; RTX, rituximab; TPL, transplantation.
Recombinant FVIIa Treatment for DAH in Children

The off-label use of FVIIa in pediatric patients has also been expanding despite the absence of adequate studies addressing safety and efficacy. According to a multi-center cohort study, 83% of FVIIa use was off-label, and the off-label use of FVIIa increased 10-fold between 2000 and 2007 [99]. The Haemostasias Registry reported the results of the off-label use of FVIIa in 388 children [100]. The median age was 12 months, and the medians of the first dose and total dose were 114 μg/kg and 1.2 mg, respectively. They observed a reduction in the number of transfusions after the use of FVIIa ($P<0.01$) and a subjective response rate of 82%; thromboembolic complications were reported in 5.4% to 10.9% of the patients, which were similar to the published incidence in adults [79,101,102]. These results suggest that FVIIa is an effective hemostatic agent in severely ill pediatric patients experiencing life-threatening hemorrhage, and FVIIa can reduce blood product requirements [2,100,103]. However, its benefit for neonates and infants less than 1 year of age remains unclear. Young et al reported that neonates had a lower response rate of 47% and a higher risk of thrombosis (17.6%) than older aged groups (more than 1 month) [103]. The SeveNBleeP registry, a web-based registry of FVIIa use in non-hemophiliac pediatric patients including 42 infants less than 1 year reported that there was no significant reduction in requirements for blood products after FVIIa treatment and no significant increase in thromboembolic complication (2.4%) [2]. The FVIIa has a shorter half-life and more rapid clearance in children compared with adults; therefore, higher and more frequent doses of FVIIa are often required to control significant bleeding in children, especially in neonates and infants [2,100,103]. Considering the relatively poor results of FVIIa and the low levels of natural anticoagulants (proteins C and S and antithrombin-III), the risk of thromboembolic complication can increase in neonates and infants, and the risk-to-benefit ratio can be higher, requiring careful decision.

Many causes such as perinatal asphyxia, very low birth weight (VLBW), mechanical ventilation, respiratory distress syndrome
(RDS), exogenous surfactant therapy, sepsis, hypothermia, patent ductus arteriosus, and coagulopathies can trigger pulmonary hemorrhage in pediatric patients including neonates [3,104]. The FVIIa treatment for pulmonary hemorrhage in pediatric patients is listed in table 3. Data on 45 children are available, the majority was classified as non-immune related DAH, and only 3 cases were immune related DAH. Among 33 pediatric cases with past history information, 16 cases were associated with hematologic malignancies, 5 cases were associated with HCT, 4 cases were preterm, and 5 cases were related to cardiovascular disease. The overall mortality was 30% (10 of 33 cases with detailed information), and the pediatric patients with hematologic malignancies showed a high mortality (9 in 16 patients, 56%). Complete response after treatment of FVIIa was observed in 64.4%, and a partial response (bleeding improved but not ceased) was in 24.4%, with 11.1% having no response to treatment. Two thromboembolic complications were reported (4.4%) [103,105]. Among 45 cases, 29 patients received iv rFVIIa and 16 patients received ip rFVIIa treatment. The mean dose of rFVIIa was 400µg/kg per episode (range, 60-3,150 µg/kg) for iv treatment and 46µg/kg per episode for ip treatment, respectively. But the outcome for ip rFVIIa was not infer to iv rFVIIa: among 29 patients who received iv rFVIIa, 15 achieved complete response, 9 showed partial response, and 5 had no response (82% of response rate); among patients received ip rFVIIa, 14 had complete response and 2 had partial response (100% of response rate). The patients received iv FVIIa required multiple doses to achieve satisfactory hemostasis. Although these data cannot represent the effect of FVIIa for DAH in pediatrics, iv FVIIa appears to be less effective for DAH than other life-threatening bleedings [95, 103]. Due to pharmacokinetic characteristics of children, higher and multiple doses of FVIIa may be needed. On the other hand, the patients treated with ip FVIIa showed a significant improvement in their oxygenation capacities (PaO2/FiO2 ratio) on subsequent days after FVIIa treatment [89,107], and one child experienced thrombotic obstruction in his endotracheal tube (ETT); there was no evidence of intra-alveolar thrombotic deposition (hyaline membrane formation) [106]. We experienced successful immediate hemostasis after treatment of ip FVIIa in pediatric
patients with refractory severe DAH which did not respond to other treatments including TXA, high-dose corticosteroids, rituximab, and multiple transfusions [89]. These data showed that pulmonary hemostasis can be induced more easily from the alveolar side than from the endothelial side with reduced systemic risk of complication, suggesting intrapulmonary administration of FVIIa as an effective strategy for DAH in children as well as in adults.
Table 3: Published data on recombinant factor VIIa treatment for diffuse alveolar hemorrhage in children.

| Reference                  | Year  | Patients (Sex/Age) | Previous history                                         | Route | Dose of FVIIa              | Additional therapies | Outcome    | Thromboembolic complication | Case of death |
|----------------------------|-------|--------------------|----------------------------------------------------------|-------|-----------------------------|----------------------|------------|-------------------------------|---------------|
| Immune-related             |       |                    |                                                          |       |                             |                      |            |                               |               |
| Bafaquih et al.[120]       | 2015  | 3/8 patients, (M:F=4:4), 2 (0.5-9) years | Connective tissue disorder (n=3), respiratory infection (n=3), MOF (n=1) | IP    | 35-50µg/kg x 3-6 dose       | TXA                  | 3CR        | none                          | 0             |
| Congestive heart failure associated |       |                    |                                                          |       |                             |                      |            |                               |               |
| Veldman et al.[121]        | 2002  | M/preterm          | VLBW, RDS, PDA, IVH, PDA ligation                        | IV    | 200µg/kg x 2 doses          | none                 | CR         | none                          | 0             |
| Olomu et al.[122]          | 2002  | M/preterm          | VLBW, RDS, PDA, sepsis, DIC, PIE                         | IV    | 50µg/kg x 6 doses           | none                 | CR         | none                          | 0             |
|                           |       | F/preterm          | VLBW, RDS, PDA, Sepsis, DIC                             | IV    | 50µg/kg x 16 doses          | none                 | CR         | none                          | 0             |
| Leibovitch et al.[123]     | 2003  | F/2 months         | Down syndrome, CHD, cardiac surgery                      | IV    | 100µg/kg x 4 doses          | TXA                  | CR         | none                          | 0             |
| Bafaquih et al.[120]       | 2015  | 1/8 patients       | Cardiovascular disease, ARDS, infection                  | IP    | 35-50µg/kg x 3-6 dose       | TXA                  | 1CR        | none                          | 0             |
| Miscellaneous              |       |                    |                                                          |       |                             |                      |            |                               |               |
| Blatt et al.[124]          | 2001  | F/8 years          | AML, HCT, HC                                             | IV    | 270µg/kg x 1 dose →90µg/kg x 28 doses | CS                  | PR         | none                          | 1             |
| Cetin et al.[3]            | 2006  | M/preterm          | LBW, RDS, sepsis, DIC                                   | IV    | 120µg/kg x 3 doses          | none                 | PR         | none                          | 0             |
| Brady et al.[94]           | 2006  | F/2 days           | MMA, DIC, HD for hyperammonemia                         | IV    | 90µg/kg x 2 doses           | CR                   | none       | 1                             |               |
|                           |       |                    | Pseudomonal sepsis                                      | IV    | 90µg/kg x 1 dose            | CR                   | none       | 0                             |               |
| Grizelj et al.[125]        | 2006  | NA/0 days          | MAS, ventilator care                                    | IV    | 170µg/kg x 1 dose           | ACA                  | CR         | none                          | 0             |
|                           |       | NA/13 days         | HLH, postsurgical resuscitation                         | IV    | 130µg/kg x 1 dose           | ACA                  | CR         | none                          | 0             |
|                           |       | NA/2 days          | HLH, postsurgical resuscitation                         | IV    | 222µg/kg x 1 dose           | ACA                  | CR         | none                          | 0             |
| Young et al.[103]          | 2009  | 12 patients        | NA                                                       | IV    | 90µg/kg x 1 dose (range, 20.3-353µg/kg) | 4CR, 5PR, 3NR       | 1 LV thrombus | NA                          |               |
| Bhat et al.[95]            | 2011  | M/14 years         | DSS, sepsis                                             | IV    | 70µg/kg x 1 dose            | Anti-D               | CR         | none                          | 0             |
|                           |       | M/13 years         | AML, TLS, ARF, acute pancreatitis                       | IV    | 90µg/kg x 1 dose            | none                 | PR         | none                          | 1             |
|                           |       | F/9 years          | Thalassemia, major, HCT, ARDS                           | IV    | 90µg/kg x 1 dose            | octreotide           | CR         | none                          | 0             |
| Sex/Age/Condition                          | Pathogens/Complications       | Route | Dose (µg/kg) x # doses | Ancillary Treatments | Response | NR | # responders |
|------------------------------------------|-------------------------------|-------|------------------------|----------------------|----------|----|--------------|
| F/13 years, ALL, febrile neutropenia, sepsis | IV                            | 70µg/kg x 1 dose | none                  | NR                   | none     | 1  |              |
| M/10 years, AML                          | IV                            | 75µg/kg x 1 dose | none                  | NR                   | none     | 1  |              |
| Colin et al. [126] 2010                  | M/17 years, AML, pancytopenia, sepsis | IP    | 50µg/kg x 1 dose       | CS                   | CR       | none | 0            |
| Larcombe et al. [105] 2014               | M/2 years, AML, HCT, hepatic SOS, GVHD | IP    | 50µg/kg x 1 dose       | None                 | CR       | ETT thrombus | 0 |
| Park et al. [81] 2015                    | F/11 years, MDS, HCT, HC, TMA | IP    | 60µg/kg x 1 dose       | CS, TXA, RTX         | CR       | none | 1            |
| Park et al. [81] 2015                    | M/15 years, AML, DIC, cytarabine syndrome | IP    | 45µg/kg x 1 dose       | CS                   | CR       | none | 0            |
| M/6 years, T-LL, chickenpox infection, hepatic sinusoidal obstruction syndrome | IP | 43µg/kg x 1 dose | CS | CR | none | 0 |
| Park et al. [81] 2015                    | M/14 years, AML, DIC           | IP    | 52µg/kg x 1 dose       | CS                   | CR       | none | 0            |
| F/10 months, HLH, HCT, CMV infection, hepatic sinusoidal obstruction syndrome | IP | 63µg/kg x 1 dose | CS, TXA, RTX         | CR       | none | 1  |
| Bafaquih et al. [120] 2015               | 4/8 patients, (M:F=4:4), 2 (0.5-9) years | IP | 35-50µg/kg x 1 dose | TXA | 2CR, 2PR | none | 2/8 |

**Idiopathic**

| Sex/Age/Condition                          | Pathogens/Complications       | Route | Dose (µg/kg) x # doses | Ancillary Treatments | Response | NR | # responders |
|------------------------------------------|-------------------------------|-------|------------------------|----------------------|----------|----|--------------|
| Bhat et al. [95] 2011                    | F/6 years, IPH, pneumothorax and septic shock | IV | 60µg/kg x 1 dose | none | PR | none | 1  |
| Park et al. [81] 2015                    | F/11 years, IPH               | IP    | 57µg/kg x 1 dose       | CS                   | CR       | none | 0  |

**Abbreviations:** ALL, acute lymphocytic leukemia; ACA, aminocaproic acid; AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; CHD, complex heart disease; CMV, cytomegalovirus; CR, complete response; CPM, cyclophosphamide; CS, corticosteroids; DIC, disseminated intravascular coagulation; DSS, Dengue shock syndrome; ETT, endotracheal tube; GVHD, graft-versus-host disease; HC, hemorrhagic cystitis; HCT, hematopoietic stem cell transplantation; HD, hemodialysis; HLH, hemophagocytic lymphohistiocytosis; HLHS, hypoplastic left heart syndrome; IP, intrapulmonary; IPH, idiopathic pulmonary hemosiderosis; IV, intravenously; IVH, intraventricular hemorrhage; LBW, low birth weight; LV, left ventricle; MAS, meconium aspiration syndrome; MDS, myelodysplastic syndrome; MMA, methylmalonic aciduria; NA, not available; NR, no response; PDA, patent ductus arteriosus; PIE, pulmonary interstitial emphysema; PR, partial response; RDS, respiratory distress syndrome; SOS, sinusoidal obstruction syndrome; T-LL, T-cell lymphoblastic lymphoma; TLS, tumor lysis syndrome; TMA, thrombotic microangiopathy; VLBW, very low birth weight.
**Conclusion**

DAH should be suspected in any patient with alveolar infiltrates on chest radiographs, hypoxemia, anemia, and hemoptysis. DAH is a clinical syndrome that can be a manifestation of multiple different etiologies, and identifying the underlying etiology is important to determine treatment strategy. In life-threatening DAH, rapid and effective hemostasis along with the appropriate treatment for the underlying disease contributes to patient survival. Considering the substantial risk of thromboembolic complications with the use of a large amount of FVIIa, intrapulmonary administration of relatively small-dosed FVIIa could be an effective and reasonable treatment option for DAH in pediatric patients as well as in adults, requiring prospective or randomized trial to verify the effect and standardize the FVIIa treatment. But most importantly, many studies including our case series have suggested that instant hemostasis alone cannot ensure successful treatment outcome without successful treatment of primary disease or inflammation. We have experienced a refractory hemophagocytic lymphohistiocytosis (HLH) pediatric case presented with severe DAH (unpublished data). Although immediate and near complete hemostasis was achieved after intrapulmonary FVIIa instillations, the patients experienced multiple episodes of profound DAH and expired with sepsis and multiorgan failure, strongly implicating the importance of multidisciplinary treatment approach for successful outcome.

**References**

1. Collard HR, Schwarz MI. Diffuse alveolar hemorrhage. Clin Chest Med. 2004; 25: 583-592.
2. Blatny J, Mathew P, Monagle P, Ovesna P, Fiamoli V. Safety and efficacy of recombinant activated factor VII in nonhemophilia children with severe or life-threatening bleeding: a report from the SeveNBleeP registry. Blood Coagul Fibrinolysis. 2014; 25: 326-332.
3. Cetin H, Yalaz M, Akisu M, Karapinar DY, Kavakli K, et al. The use of recombinant activated factor VII in the treatment of massive pulmonary hemorrhage in a preterm infant. Blood Coagul Fibrinolysis. 2006; 17: 213-216.
4. Pastores SM, Papadopoulos E, Voigt L, Halpern NA. Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: treatment with recombinant factor VIIa. Chest. 2003; 124: 2400-2403.

5. Heslet L, Nielsen JD, Levi M, Sengelov H, Johansson PI. Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage. Crit Care. 2006; 10: R177.

6. Henke D, Falk RJ, Gabriel DA. Successful treatment of diffuse alveolar hemorrhage with activated factor VII. Ann Intern Med. 2004; 140: 493-494.

7. Heslet L, Nielsen JD, Nepper-Christensen S. Local pulmonary administration of factor VIIa (rFVIIa) in diffuse alveolar hemorrhage (DAH) - a review of a new treatment paradigm. Biologics. 2012; 6: 37-46.

8. Ioachimescu OC, Stoller JK. Diffuse alveolar hemorrhage: diagnosing it and finding the cause. Cleve Clin J Med. 2008; 75: 258, 260, 264-265.

9. Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest. 2010; 137: 1164-1171.

10. Newsome BR, Morales JE. Diffuse alveolar hemorrhage. South Med J. 2011; 104: 269-274.

11. Colby TV, Fukuoka J, Ewaskow SP, Helmers R, Leslie KO. Pathologic approach to pulmonary hemorrhage. Ann Diagn Pathol. 2001; 5: 309-319.

12. Cordier JF, Cottin V. Alveolar hemorrhage in vasculitis: primary and secondary. Semin Respir Crit Care Med. 2011; 32: 310-321.

13. Maldonado F, Parambil JG, Yi ES, Decker PA, Ryu JH. Haemosiderin-laden macrophages in the bronchoalveolar lavage fluid of patients with diffuse alveolar damage. Eur Respir J. 2009; 33: 1361-1366.

14. Castro CY. ARDS and diffuse alveolar damage: a pathologist's perspective. Semin Thorac Cardiovasc Surg. 2006; 18: 13-19.

15. Parambil JG, Myers JL, Aubry MC, Ryu JH. Causes and prognosis of diffuse alveolar damage diagnosed on surgical lung biopsy. Chest. 2007; 132: 50-57.

16. Park MS. Diffuse alveolar hemorrhage. Tuberc Respir Dis (Seoul). 2013; 74: 151-162.
17. Aggarwal NR, King LS, D'Alessio FR. Diverse macrophage populations mediate acute lung inflammation and resolution. Am J Physiol Lung Cell Mol Physiol. 2014; 306: L709-725.
18. Franks TJ, Koss MN. Pulmonary capillaritis. Curr Opin Pulm Med. 2000; 6: 430-435.
19. Zhuang H, Han S, Lee PY, Khaybullin R, Shumyak S, et al. Pathogenesis of Diffuse Alveolar Hemorrhage in Murine Lupus. Arthritis Rheumatol. 2017; 69: 1280-1293.
20. Short KR, Kroeze E, Fouchier RAM, Kuiken T. Pathogenesis of influenza-induced acute respiratory distress syndrome. Lancet Infect Dis. 2014; 14: 57-69.
21. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, et al. Neutrophil extracellular traps kill bacteria. Science. 2004; 303: 1532-1535.
22. Mistry P, Carmona-Rivera C, Ombrello AK, Hoffmann P, Seto NL, et al. Dysregulated neutrophil responses and neutrophil extracellular trap formation and degradation in PAPA syndrome. Ann Rheum Dis. 2018; 77: 1825-1833.
23. Kaplan MJ, Radic M. Neutrophil extracellular traps: double-edged swords of innate immunity. J Immunol. 2012; 189: 2689-2695.
24. Lee KH, Kronbichler A, Park DD, Park Y, et al. Neutrophil extracellular traps (NETs) in autoimmune diseases: A comprehensive review. Autoimmun Rev. 2017; 16: 1160-1173.
25. Jarrot PA, Tellier E, Plantureux L, Crescence L, Robert S, et al. Neutrophil extracellular traps are associated with the pathogenesis of diffuse alveolar hemorrhage in murine lupus. J Autoimmun. 2019; 100: 120-130.
26. Liu S, Su X, Pan P, Zhang L, Hu Y, et al. Neutrophil extracellular traps are indirectly triggered by lipopolysaccharide and contribute to acute lung injury. Sci Rep. 2016; 6: 37252.
27. Afessa B, Tefferi A, Litzow MR, Krowka MJ, Wylam ME, et al. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med. 2002; 166: 641-645.
28. Sisson JH, Thompson AB, Anderson JR, Robbins RA, Spurzem JR, et al. Airway inflammation predicts diffuse alveolar hemorrhage during bone marrow transplantation in
patients with Hodgkin disease. Am Rev Respir Dis. 1992; 146: 439-443.

29. Piguet PF, Grau GE, Collart MA, Vassalli P, Kapanci Y. Pneumopathies of the graft-versus-host reaction. Alveolitis associated with an increased level of tumor necrosis factor mRNA and chronic interstitial pneumonitis. Lab Invest. 1989; 61: 37-45.

30. Capizzi SA, Kumar S, Huneke NE, Gertz MA, Inwards DJ, et al. Peri-engraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. Bone Marrow Transplant. 2001; 27: 1299-1303.

31. Srivastava A, Gottlieb D, Bradstock KF. Diffuse alveolar haemorrhage associated with microangiopathy after allogeneic bone marrow transplantation. Bone Marrow Transplant. 1995; 15: 863-867.

32. Agustí C, Ramirez J, Picado C, Xaubet A, Carreras E, et al. Diffuse alveolar hemorrhage in allogeneic bone marrow transplantation. A postmortem study. Am J Respir Crit Care Med. 1995; 151: 1006-1010.

33. Roychowdhury M, Pambuccian SE, Aslan DL, Jessurun J, Rose AG, et al. Pulmonary complications after bone marrow transplantation: an autopsy study from a large transplantation center. Arch Pathol Lab Med. 2005; 129: 366-371.

34. Koh H, Nakamae H, Koh KR, Ohsawa M, Nakane T, et al. Serum cytokine profiles at the onset of severe, diffuse alveolar hemorrhage complicating allogeneic hematopoietic stem cell transplantation, treated successfully with pulse intravenous cyclophosphamide. Acta Haematol. 2010; 124: 171-175.

35. Krause ML, Cartin-Ceba R, Specks U, Peikert T. Update on diffuse alveolar hemorrhage and pulmonary vasculitis. Immunol Allergy Clin North Am. 2012; 32: 587-600.

36. De Lassence A, Fleury-Feith J, Escudier E, Beaune J, Bernaudin JF, et al. Alveolar hemorrhage. Diagnostic criteria and results in 194 immunocompromised hosts. Am J Respir Crit Care Med. 1995; 151: 157-163.

37. Perez-Arellano JL, Losa Garcia JE, Garcia Macias MC, Gomez Gomez F, Jimenez Lopez A, et al. Hemosiderin-laden macrophages in bronchoalveolar lavage fluid. Acta Cytol. 1992; 36: 26-30.
38. Golde DW, Drew WL, Klein HZ, Finley TN, Cline MJ. Occult pulmonary haemorrhage in leukaemia. Br Med J. 1975; 2: 166-168.
39. Travis WD, Colby TV, Lombard C, Carpenter HA. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol. 1990; 14: 1112-1125.
40. Susarla SC, Fan LL. Diffuse alveolar hemorrhage syndromes in children. Curr Opin Pediatr. 2007; 19: 314-320.
41. Park JA. Diffuse alveolar hemorrhage and recombinant factor VIIa treatment in pediatric patients. Korean J Pediatr. 2016; 59: 105-113.
42. Kirby RR, Downs JB, Civetta JM, Modell JH, Dannemiller FJ, et al. High level positive end expiratory pressure (PEEP) in acute respiratory insufficiency. Chest. 1975; 67: 156-163.
43. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016; 315: 788-800.
44. Gattinoni L, Collino F, Maiolo G, Rapetti F, Romitti F, et al. Positive end-expiratory pressure: how to set it at the individual level. Ann Transl Med. 2017; 5: 288.
45. Heggen J, West C, Olson E, Olson T, Teague G, et al. Diffuse alveolar hemorrhage in pediatric hematopoietic cell transplant patients. Pediatrics. 2002; 109: 965-971.
46. Raptis A, Mavroudis D, Suffredini A, Molldrem J, Rhee FV, et al. High-dose corticosteroid therapy for diffuse alveolar hemorrhage in allogeneic bone marrow stem cell transplant recipients. Bone Marrow Transplant. 1999; 24: 879-883.
47. Majhail NS, Parks K, Defor TE, Weisdorf DJ. Diffuse alveolar hemorrhage and infection-associated alveolar hemorrhage following hematopoietic stem cell transplantation: related and high-risk clinical syndromes. Biol Blood Marrow Transplant. 2006; 12: 1038-1046.
48. Rath NK, Tanner AR, Dinh A, Dong W, Feng L, et al. Low-, medium- and high-dose steroids with or without aminocaproic acid in adult hematopoietic SCT patients with diffuse alveolar hemorrhage. Bone Marrow Transplant. 2015; 50: 420-426.
49. Walsh M, Merk PA, Peh CA, Szpirt WM, Puéchal X, et al.
Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med. 2020; 382: 622-631.

50. Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, et al. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis. 2003; 42: 1149-1153.

51. Gallagher H, Kwan JT, Jayne DR. Pulmonary renal syndrome: a 4-year, single-center experience. Am J Kidney Dis. 2002; 39: 42-47.

52. Nishimura K, Waki D, Kadoba K, Mukoyama H, Yokota T, et al. Efficacy of Plasma Exchange in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis. Ther Apher Dial. 2019; 23: 248-252.

53. Walsh M, Casian A, Flossmann O, Westman K, Höglund P, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int. 2013; 84: 397-402.

54. Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, et al. Guidelines on the use of therapeutic apheresis in clinical practice--evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010; 25: 83-177.

55. Walsh M, Jayne D. Rituximab in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis and systemic lupus erythematosus: past, present and future. Kidney Int. 2007; 72: 676-682.

56. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2009; 60: 2156-2168.

57. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005; 52: 262-268.

58. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010; 363: 221-232.

59. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, et al. Rituximab for refractory Wegener's
granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med. 2006; 173: 180-187.
60. Cartin-Ceba R, Fervenza FC, Specks U. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis with rituximab. Curr Opin Rheumatol. 2012; 24: 15-23.
61. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010; 363: 211-220.
62. Mannucci PM. Hemostatic drugs. N Engl J Med. 1998; 339: 245-253.
63. Solomonov A, Fruchter O, Zuckerman T, Brenner B, Yigla M. Pulmonary hemorrhage: A novel mode of therapy. Respir Med. 2009; 103: 1196-200.
64. O'Neil ER, Schmees LR, Resendiz K, Justino H, Anders MM. Inhaled Tranexamic Acid As a Novel Treatment for Pulmonary Hemorrhage in Critically Ill Pediatric Patients: An Observational Study. Crit Care Explor. 2020; 2: e0075.
65. Bafaqih H, Chehab M, Almohaimed S, Thabet F, Alhejaily A, et al. Pilot trial of a novel two-step therapy protocol using nebulized tranexamic acid and recombinant factor VIIa in children with intractable diffuse alveolar hemorrhage. Ann Saudi Med. 2015; 35: 231-239.
66. Sanz MA, Montesinos P. Open issues on bleeding and thrombosis in acute promyelocytic leukemia. Thromb Res. 2010; 125: S51-54.
67. Sander M, Spies CD, Martiny V, Rosenthal C, Wernecke KD, et al. Mortality associated with administration of high-dose tranexamic acid and aprotinin in primary open-heart procedures: a retrospective analysis. Crit Care. 2010; 14: R148.
68. Marshall A, Li A, Drucker A, Dzik W. Aminocaproic acid use in hospitalized patients with hematological malignancy: a case series. Hematol Oncol. 2016; 34: 147-153.
69. Wanko SO, Broadwater G, Folz RJ, Chao NJ. Diffuse alveolar hemorrhage: retrospective review of clinical outcome in allogeneic transplant recipients treated with aminocaproic acid. Biol Blood Marrow Transplant. 2006; 12: 949-953.
70. Tsukamoto T, Sasaki H, Nakamura H. Treatment of
hemoptysis patients by thrombin and fibrinogen-thrombin infusion therapy using a fiberoptic bronchoscope. Chest. 1989; 96: 473-476.

71. de Gracia J, de la Rosa D, Catalán E, Alvarez A, Bravo C, et al. Use of endoscopic fibrinogen-thrombin in the treatment of severe hemoptysis. Respir Med. 2003; 97: 790-795.

72. Lee J, Rhee CK, Kim SC, Kim YK, Kim HJ, et al. Use of intrapulmonary administration of thrombin in hematological malignancy patients with alveolar haemorrhage: A case series. Medicine (Baltimore). 2020; 99: e20284.

73. Göbel K, Eichler S, Wiendl H, Chavakis T, Kleinschnitz C, et al. The Coagulation Factors Fibrinogen, Thrombin, and Factor XII in Inflammatory Disorders-A Systematic Review. Front Immunol. 2018; 9: 1731.

74. Lew WK, Weaver FA. Clinical use of topical thrombin as a surgical hemostat. Biologics. 2008; 2: 593-599.

75. Baker MS, Diab KJ, Carlos WG, Mathur P. Intrapulmonary Recombinant Factor VII as an Effective Treatment for Diffuse Alveolar Hemorrhage: A Case Series. J Bronchology Interv Pulmonol. 2016; 23: 255-258.

76. Schultz MJ, Haitsma JJ, Zhang H, Slutsky AS. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia--a review. Crit Care Med. 2006; 34: 871-877.

77. Schultz MJ, Millo J, Levi M, Hack CE, Weverling GJ, et al. Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator associated pneumonia. Thorax. 2004; 59: 130-135.

78. Levi M, Schultz MJ, Rijneveld AW, van der Poll T. Bronchoalveolar coagulation and fibrinolysis in endotoxemia and pneumonia. Crit Care Med. 2003; 31: S238-242.

79. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010; 363: 1791-1800.

80. Stanworth SJ, Birchall J, Doree CJ, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev. 2007; CD005011.

81. Park JA, Kim BJ. Intrapulmonary recombinant factor VIIa for diffuse alveolar hemorrhage in children. Pediatrics. 2015;
82. Esper RC, Estrada IE, de la Torre Leon T, Gutierrez AO, Lopez JA. Treatment of diffuse alveolar hemorrhage secondary to lupus erythematosus with recombinant activated factor VII administered with a jet nebulizer. J Intensive Care. 2014; 2: 47.

83. Ellery PE, Adams MJ. Tissue factor pathway inhibitor: then and now. Semin Thromb Hemost. 2014; 40: 881-886.

84. Wood JP, Ellery PE, Maroney SA, Mast AE. Biology of tissue factor pathway inhibitor. Blood. 2014; 123: 2934-2943.

85. Kristensen J, Killander A, Hippe E, Helleberg C, Ellegard J, et al. Clinical experience with recombinant factor VIIa in patients with thrombocytopenia. Haemostasis. 1996; 26: 159-164.

86. Al Hammadi AM, Sallah S. Efficacy and safety of recombinant factor VIIa in the treatment of bleeding episodes in patients with aplastic anemia. J Thromb Haemost. 2007; 5: 435-436.

87. Farah RA, Hamod D, Melick N, Giansily-Blaizot M, Sallah S. Successful prophylaxis against intracranial hemorrhage using weekly administration of activated recombinant factor VII in a newborn with severe factor VII deficiency. J Thromb Haemost. 2007; 5: 433-434.

88. Tengborn L, Petruson B. A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. Thromb Haemost. 1996; 75: 981-982.

89. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. Lancet. 1999; 354: 1879.

90. Pihusch M, Bacigalupo A, Szer J, von Depka Prondzinski M, Gaspar-Blaudschun B, et al. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. J Thromb Haemost. 2005; 3: 1935-1944.

91. Yadav SP, Sachdeva A, Bhat S, Katewa S. Successful control of massive gastrointestinal bleeding following umbilical cord blood transplantation (UCBT) by use of recombinant activated factor VII (rFVIIa) and octreotide infusion. Pediatr
92. Harkensee C, Vasdev N, Gennery AR, Willetts IE, Taylor C. Prevention and management of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation—a systematic review and evidence-based guidance for clinical management. Br J Haematol. 2008; 142: 717-731.

93. Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, et al. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database Syst Rev. 2012; 3: CD005011.

94. Brady KM, Easley RB, Tobias JD. Recombinant activated factor VII (rFVIIa) treatment in infants with hemorrhage. Paediatr Anaesth. 2006; 16: 1042-1046.

95. Bhat S, Yadav SP, Anjan M, Dinand V, Sachdeva A. Recombinant activated factor VII usage in life threatening hemorrhage: a pediatric experience. Indian J Pediatr. 2011; 78: 961-968.

96. Elinoff JM, Bagci U, Moriyama B, Dreiling JL, Foster B, et al. Recombinant human factor VIIa for alveolar hemorrhage following allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2014; 20: 969-978.

97. Dabar G, Harmouche C, Jammal M. [Efficacy of recombinant activated factor VII in diffuse alveolar haemorrhage]. Rev Mal Respir. 2011; 28: 106-111.

98. Estella A, Jareno A, Perez-Bello Fontaina L. Intrapulmonary administration of recombinant activated factor VII in diffuse alveolar haemorrhage: a report of two case stories. Cases J. 2008; 1: 150.

99. Witmer CM, Huang YS, Lynch K, Raffini LJ, Shah SS. Off-label recombinant factor VIIa use and thrombosis in children: a multi-center cohort study. J Pediatr. 2011; 158: 820-825 e1.

100. McQuilten ZK, Barnes C, Zatta A, Phillips LE. Off-label use of recombinant factor VIIa in pediatric patients. Pediatrics. 2012; 129: e1533-1540.

101. MacLaren R. Weber LA, Brake H, Gardner MA, Tanzi M. A multicenter assessment of recombinant factor VIIa off-label usage: clinical experiences and associated outcomes. Transfusion. 2005; 45: 1434-1442.
102. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA. 2006; 295: 293-298.

103. Young G, Wicklund B, Neff P, Johnson C, Nugent DJ. Off-label use of rFVIIa in children with excessive bleeding: a consecutive study of 153 off-label uses in 139 children. Pediatr Blood Cancer. 2009; 53: 179-183.

104. Fekete M, Nemeth A. Neonatal pulmonary haemorrhage, birthweight, gestational age and intrauterine growth. Acta Paediatr Hung. 1985; 26: 65-73.

105. Larcombe PJ, Kapur N, Fraser CJ, Coulthard MG, Schlapbach LJ. Intrabronchial administration of activated recombinant factor VII in a young child with diffuse alveolar hemorrhage. Pediatr Blood Cancer. 2014; 61: 570-571.

106. Mandal SK, Sagar G, Sahoo M, Jasuja S. Recombinant activated factor VII for diffuse alveolar hemorrhage in microscopic polyangiitis. Indian J Nephrol. 2012; 22: 130-132.

107. Alabed IB. Treatment of diffuse alveolar hemorrhage in systemic lupus erythematosus patient with local pulmonary administration of factor VIIa (rFVIIa): a case report. Medicine (Baltimore). 2014; 93: e72.

108. Khoulani D, Rao B, Khanshour A, Kuriakose P, Yessayan L. Failure of Recombinant Activated Factor VII in Treatment of Diffuse Alveolar Hemorrhage due to Cryoglobulinemic Vasculitis. Case Rep Hematol. 2014; 2014: 283086.

109. Pathak V, Kuhn J, Gabriel D, Barrow J, Jennette JC, et al. Use of Activated Factor VII in Patients with Diffuse Alveolar Hemorrhage: A 10 Years Institutional Experience. Lung. 2015; 193: 375-379.

110. Diaz R, Almeida P, Alvarez M, Ferrer G, Hernandez F. Life-Threatening Pulmonary Hemorrhage Responds to Recombinant Factor VIIa: A Case Series in South Florida Hospitals. Cureus. 2019; 11: e6202.

111. Meijer K, de Graaff WE, Daenen SM, van der Meer J. Successful treatment of massive hemoptysis in acute leukemia with recombinant factor VIIa. Arch Intern Med. 2000; 160: 2216-2217.
112. White B, Martin M, Kelleher S, Browne P, McCann SR, et al. Successful use of recombinant FVIIa (Novoseven) in the management of pulmonary haemorrhage secondary to Aspergillus infection in a patient with leukaemia and acquired FVII deficiency. Br J Haematol. 1999; 106: 254-255.

113. Hicks K, Peng D, Gajewski JL. Treatment of diffuse alveolar hemorrhage after allogeneic bone marrow transplant with recombinant factor VIIa. Bone Marrow Transplant. 2002; 30: 975-978.

114. Yildirim H, Ucgun I, Yalcin AU, Gulbas Z, Sahin G, et al. Recombinant factor VIIa treatment for life-threatening haemoptysis. Respirology. 2006; 11: 652-654.

115. Macdonald JA, Fraser JF, Foot CL, Tran K. Successful use of recombinant factor VII in massive hemoptysis due to community-acquired pneumonia. Chest. 2006; 130: 577-579.

116. Shenoy A, Savani BN, Barrett AJ. Recombinant factor VIIa to treat diffuse alveolar hemorrhage following allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2007; 13: 622-623.

117. Gupta S, Jain A, Warneke CL, Gupta A, Shannon VR, et al. Outcome of alveolar hemorrhage in hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2007; 40: 71-78.

118. Lau EMT, Yozghatlian V, Kosky C, Moriarty C, Dentice R, et al. Recombinant activated factor VII for massive hemoptysis in patients with cystic fibrosis. Chest. 2009; 136: 277-281.

119. Tatopoulos A, Herbain D, Kazmierczak C, Bollaert PE, Gibot S. Parenteral use of recombinant activated factor VII during diffuse alveolar hemorrhage secondary to leptospirosis. Intensive Care Med. 2010; 36: 555-556.

120. Shimizu Y, Tsuchiya K, Fujisawa N. Risk factors of diffuse alveolar hemorrhage after acute ischemic stroke treated with tissue-type plasminogen activator. The effectiveness of activated recombinant factor VII treatment. Surg Neurol Int. 2020; 11: 129.

121. Veldman A, Fischer D, Voigt B, Beyer PA, Schlosser R, et al. Life-threatening hemorrhage in neonates: management with recombinant activated factor VII. Intensive Care Med.
2002; 28: 1635-1637.
122. Olomu N, Kulkarni R, Manco-Johnson M. Treatment of severe pulmonary hemorrhage with activated recombinant factor VII (rFVIIa) in very low birth weight infants. J Perinatol 2002; 22: 672-674.
123. Leibovitch L, Kenet G, Mazor K, Matok I, Vardi A, et al. Recombinant activated factor VII for life-threatening pulmonary hemorrhage after pediatric cardiac surgery. Pediatr Crit Care Med. 2003; 4: 444-446.
124. Blatt J, Gold SH, Wiley JM, Monahan PE, Cooper HC, et al. Off-label use of recombinant factor VIIa in patients following bone marrow transplantation. Bone Marrow Transplant. 2001; 28: 405-407.
125. Grizelj R, Vukovic J, Filipovic-Grcic B, Saric D, Luetic T. Successful use of recombinant activated FVII and aminocaproic acid in four neonates with life-threatening hemorrhage. Blood Coagul Fibrinolysis. 2006; 17: 413-415.
126. Colin AA, Shafieian M, Andreansky M. Bronchoscopic instillation of activated recombinant factor VII to treat diffuse alveolar hemorrhage in a child. Pediatr Pulmonol. 2010; 45: 411.