Local pulmonary administration of factor VIIa (rFVIIa) in diffuse alveolar hemorrhage (DAH) – a review of a new treatment paradigm

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Background: Diffuse alveolar hemorrhage (DAH) is a clinical syndrome with typical symptoms dyspnea and hemoptysis. DAH is a complication of specific diseases, in some cases with acute catastrophic hemoptysis, while other patients present low grade alveolar bleeding with a need of chronic transfusion as in pulmonary hemosiderosis.

Methods: Current literature in the PubMed database and other sources was reviewed in order to evaluate the current treatment recommendations, efficacy of this treatment, and finally the risk of complications after off-label use of rFVIIa in respect to DAH.

Objectives: (i) To elucidate the clinical aspects of alveolar hemorrhage, (ii) to develop a simple diagnostic algorithm in order to separate DAH from other important pulmonary diseases with similar clinical picture and comparably high mortality. Such an algorithm has important therapeutic consequences because these diseases: acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and bronchiolitis obliterans organizing pneumonia (BOOP) have different therapies, (iii) to evaluate and discuss whether local pulmonary administration may improve outcome and reduce mortality in DAH, and (iv) to suggest a treatment schedule.

Results: Hitherto the diagnosis and treatment of DAH has been based on anecdotal reports. The treatment has relied on different unspecific treatment modalities based on a mixture of treatment of the underlying disease and treatment without evidence targeted to stop the alveolar bleeding. However, recently a number of publications have advocated the use of intrapulmonary rFVIIa. Even in severe bleeding DAH has been shown to respond promptly without thromboembolic complication when FVIIa was administered locally via the air side, because the FVIIa does not penetrate the alveolo-capillary membrane to the blood-side. The incidence of DAH (in the US and Europe is 100,000–150,000, and 50,000 patients annually are at risk of developing DAH following hematopoietic stem cell transplant (HSCT) and autoimmune diseases. Finally 50,000–100,000 patients may be falsely categorized as having acute respiratory distress syndrome/acute lung injury (ARDS/ALI) because DAH and ARDS cannot be separated clinically. A new treatment paradigm of DAH is proposed as no other intervention has been able to ensure pulmonary hemostasis in DAH. The diagnosis of DAH is simple, a series of broncho-alveolar washes which become increasingly bloody. This test should be performed in all patients with pulmonary opacities in order to separate ARDS/ALI from DAH. FVIIa administrated via pulmonary route is “drug of choice”, because it stops bleeding in the life-threatening syndrome DAH. Hemostasis is obtained after only one to two small doses of FVIIa (50 µg/kg body weight per dose) and after hemostasis the oxygen transport quickly improves.
**Conclusion:** Intrapulmonary administration of rFVIIa is recommended as the treatment of choice for DAH and blast lung injury (BLI) because the treatment has been shown to be successful and uncomplicated in spite of the fact that only a small series of DAH has been documented.

**Keywords:** coagulation factor FVIIa, diffuse alveolar hemorrhage, hemosiderosis, blast lung injury, local pulmonary treatment, biologics, bronchoalveolar lavage, diagnosis, algorithm, new treatment recommendation

**Introduction**
There is a general lack of understanding of the gap between, on the one hand, the “air side”, where the effective drug-related receptors are located and, on the other hand, the vascular compartment. When administered intravenously biological drugs like FVIIa do not reach the receptors in the alveoli, because they do not pass the alveolo-capillary membrane. “Biologics” refer to biologically manufactured drugs, similar to endogenously key signaling proteins, like FVIIa.

Traditionally, biologics are administered intravenously with the hope that a sufficient concentration of the drug reaches the specific receptors. This requires a high systemic concentration of the drug and is associated with a higher risk of adverse systemic effects than local application at the target site.

**The syndrome of diffuse bleeding DAH**
The diffuse alveolar hemorrhage (DAH) syndrome has a number of clinical characteristics similar to a number of well-pulmonary documented conditions like acute respiratory distress syndrome (ARDS), acute lung insufficiency (ALI), and bronchiolitis obliterans organizing pneumonia (BOOP) (Table 1).

**Diffuse alveolar hemorrhage related to pulmonary receptors in perspective**
For many years it has been known that even the air side of the lung has receptors. Rose et al made a functional study of the granulocyte macrophage colony stimulating factor (GM-CSF) receptor, documenting that it was necessary to inhale the drug in order to reach the receptor on the air side (Figure 1). Intravenous administration of GM-CSF had no effect on the alveolar macrophages whereas the inhaled drug increased the number of macrophages with no interference with systemic monocytes.

In the normal airspace the hemostatic balance is skewed toward anticoagulation due to increased expression of plasminogen activator and low expression of tissue factor (TF). As soon as the lungs are exposed to an inflammatory process, the anticoagulatory state will swiftly be turned into a procoagulatory state – a primitive host defense reaction in order to stop the invasiveness of bacteria and to hinder bacterial multiplication and dissemination.

On the air side a whole host of receptors are placed. The complex cross talk between the dynamic receptor expression and the overall effect is hard to predict. It is known that pulmonary receptors ensure pulmonary host defense, ie, the TF and GM-CSF-receptors, both placed on the airside isolated from the blood side. The different biologics must fulfill certain qualities in order to be able to penetrate the biological membranes. First of all the molecular size must be small, most likely smaller than 15–20 kDa, like insulin with a molecular size of 8 kDa. Secondly, the drug must be lipophilic in order to cross the alveolo-capillary membrane to reach the peripheral airways. However, no newly developed therapeutic recombinant drug fulfills the low size criteria.1

**Table 1 DAH – the key points**

<table>
<thead>
<tr>
<th>Clinical picture</th>
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<tr>
<td>• DAH is characterized clinically by alveolar bleeding, from mild with chronic transfusion need to the catastrophic alveolar bleeding with hemoptysis.</td>
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</table>

**The DAH presents with three subsets**

| • Macroscopic bleeding – mortality of >70%. |
| • Chronic microscopic alveolar bleeding, falling hematocrit, sputum filled with hemosiderin laden macrophages. The mortality is low, however, the life expectancy is reduced due to pulmonary fibrosis. |
| • Blast lung injury after a major blast. The subset seemingly has a “window of opportunity” of 3 hours. |

**The diagnosis of DAH**

| • Bronchoalveolar lavage with aliquot with successive lavage fluid bloodier macro/microscopically than the previous one. In this way DAH may be separated from ARDS/ALI and BOOP. |

**Treatment of DAH**

| • Alveolar bleeding may be treated successfully provided the DAH syndrome is treated locally intrapulmonarily, by lavage or inhalation. |
| • Prophylaxis of DAH is only based on the specific optimization of the multiple underlying diseases and conditions. |

**Abbreviations:** ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia; DAH, diffuse alveolar hemorrhage.
in as much as all the wild type proteins are all hydrophilic FVIIa and GM-CSF.

Pathophysiology of DAH

DAH is characterized by damage to the alveolar-capillary basement membrane allowing red blood cells to enter the alveolar spaces. Most frequently DAH is a symptom of pulmonary capillaritis as seen in autoimmune diseases or after hematopoietic stem cell transplant (HSCT). DAH may also occur as a result of diffuse alveolar damage in acute respiratory distress syndrome/acute lung injury (ARDS/ALI). Further the damage may be the result of physicochemical factors like blast lung injury (BLI), toxic drug effects (eg, cytotoxic drugs, crack cocaine inhalation), and radiation therapy (Figure 2).

Epidemiology of DAH

In hematological stem cell transplantation (HSCT) recipients, DAH is an infrequent cause of death both in early and late phases after transplantation.5,6 DAH after HSCT is a devastating complication that carries an overall mortality of 16%–70%.7,6 As a result of life-threatening multiple organ dysfunctions, 15%–40% of HSCT recipients receive intensive care unit support, the majority of whom require mechanical ventilation.9–11 The mortality rate of HSCT recipients receiving invasive ventilation used to exceed 90%.10,12 Although more recent studies have shown improvement in outcome, the mortality rate of HSCT recipients receiving mechanical ventilation is still high.10–15 It is estimated that 50,000 HSCT procedures took place in 2007 in the USA, and 80,000 worldwide, and that 25%–40% of HSCT recipients are admitted to the medical intensive care unit (ICU) for the management of pulmonary complications to HSCT.7,11,16,17

A considerable number of patients will also develop DAH due to other causes than HSCT, eg, infections, bronchoscopy, autoimmune diseases, HIV (Kaposi’s sarcoma), and transplantations, ie, DAH has been reported in 75% of patients with Kaposi’s sarcoma, in 66% of patients with SLE,19 in 5%–10% of patients with Goodpasture syndrome.20 Fatal DAH has been reported in approximately 10%–41% of lung autopsies of HSCT patients that succumbed to HSCT related complications.9,21 Further, DAH is reported to develop in 40% of patients admitted to the ICU for respiratory failure (ARDS/ALI). The annual incidence of ARDS/ALI in the USA and EU admitted to ICU is over 500,000 patients.

The syndrome of DAH

The multiple causes of DAH are shown in Table 222 together with the treatment of the underlying cause of DAH and symptomatic treatment of the ongoing alveolar bleeding. Formerly, the management strategy was limited to the optimization of each of the specific diseases and underlying disorders
as a prophylactic measure toward prevention of DAH syndrome. Most of such prophylactic interventions have been treatment with steroids, anti-infective measures, eg, anti-cytomegalovirus pneumonia therapy, plasmapheresis, platelet transfusion, and coagulation factors. These interventions are alone focused on prophylaxis of the stereotype syndrome alveolar bleeding.

The diagnosis of DAH

The algorithmic scheme is depicted in Figure 3, based on the fact that the signs and symptoms are a common denominator of DAH, ARDS and BOOP: acute pulmonary insufficiency with reduced $O_2$ transport capacity and confluent opacities on chest film. It is imperative to distinguish between the specific diagnoses of these conditions, and in as much as they have a very high mortality, it is of utmost importance to diagnose correctly because the specific therapies are different. The key to the diagnosis, as it appears in Figure 3, is the finding of (i) a macroscopically progressively hemorrhagic aliquot in a series of bronchoalveolar lavage fluid (BALF) findings that denote a severe DAH syndrome, or (ii) measurements of an increased hemoglobin concentration in the BALF corresponding to a slow bleeding (pulmonary hemosiderosis), or (iii) absence of bloody return in the BALF excluding the DAH diagnosis. The remaining two conditions are separated by a simple flow-cytometry (FC) on the BALF, where the BOOP is characterized by abundant inflammatory cells, and the ARDS diagnosis is based on a BALF without inflammatory cells and without bloody return.

### DAH in childhood and adolescence

DAH occurs in any age group secondary to the same underlying diseases and conditions. However, the major difference

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<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Clinical presentations</th>
<th>Classic options of treatment</th>
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<tbody>
<tr>
<td>Pulmonary capillaritis or autoimmune diseases</td>
<td>Systemic lupus erythematosus  Goodpasture’s syndrome  Antiphospholipid syndrome  Wegner’s granulomatosis  Scleroderma rheumatoid arthritis  Henoch Schönlein purpura  Acute lung allograft rejection  Bone marrow transplantation</td>
<td>Immunosuppressants  • Steroids  • Methotrexate  • Retuximab  Removal of autoantibodies  • Plasmapheresis  Procoagulation  • Plasma</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>Radiation therapy  Cytotoxic drugs  ARDS</td>
<td>Trasxenic acid  Platelet transfusion  Coagulation factors</td>
</tr>
<tr>
<td>Traumatic alveocapillary membrane</td>
<td>Blast lung injury  Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Subacute bacterial endocarditis  Negative pressure pulmonary edema  Mitral stenosis  Idiopathic pulmonary hemosiderosis  Coagulation disorders  Pulmonary veno-occlusive disease</td>
<td></td>
</tr>
<tr>
<td>Drug induced alveocapillary membrane</td>
<td>Warfarin  Isocyanates  Nitrofurantoin  Propylthiouracil  Clopidogrel  Fibrinolytics  Aspirin  Amiodarone  Phenytion</td>
<td>Discontinuation of treatment  Broad spectrum antibiotics and antiviral therapy</td>
</tr>
<tr>
<td>Infections</td>
<td>Bacteria  Pseudomonas aeruginosa  Leptospirosis  Mycoses  Aspergillus spp.  Viruses infections  CMV and herpes pneumonitis</td>
<td></td>
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</table>

**Abbreviations:** ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; DAH, diffuse alveolar hemorrhage.
is that the DAH syndrome is characterized by microscopic alveolar bleeding with chronic transfusion need. Hemoptysis is seldom. The chronic erythrocyte intraalveolar bleeding often surpasses the metabolic clearance of iron originating from the erythrocyte metabolism of the alveolar macrophage. This leads to an alveolar iron overload. These patients don’t have a considerable acute mortality, but a severely reduced long term life-expectancy due to pulmonary fibrosis secondary to accumulated iron in the alveolar space.

Pulmonary hemosiderosis
The idiopathic pulmonary hemosiderosis syndrome (IPH) is a DAH condition, however, without known underlying cause, ie, the incidence and prevalence of IPH is unknown. There are approximately 500 cases reported in the literature, primarily in children (80%). The etiology of IPH is not clear, in spite of many theories. Clinically, the signs and symptoms of IPH are identical to other microalveolar bleedings like the acquired pulmonary hemosiderosis secondary to known underlying diseases, ie, exacerbations concomitantly with cough, dyspnea to fulminant respiratory failure. The chronic state is accompanied with variable degrees of iron deficiency anemia, present in most patients. Spirometry shows a restrictive pattern due to pulmonary fibrosis in the chronic condition. Lung biopsies from both IPH and secondary pulmonary hemosiderosis patients often show severe thickening of the alveolar wall and hemosiderin-loaded alveolar macrophages that also appear in sputum.

The blast lung injury – a dynamic process with a “window of opportunity”
A blast lung injury (BLI) is based on the disruption of the alveolo-capillary membrane after an explosion, with a significant pressure wave entailing diffuse alveolar bleeding (Table 3). Based on the pathophysiology, BLI can be characterized into distinct phases of a dynamic process (Table 4). This leads to (i) diffuse bleeding and (ii) hemolysis which quantitatively surpasses the clearance rate of free iron (Fe++) from the alveoli unless the diffuse alveolar bleeding is stopped early.

It seems that there is a “window of opportunity” of 3 hours in which the BLI is reversible (Table 5). If the
Table 3 Overview of BLI – a dynamic condition

| Definition and pathogenesis | The traumatic DAH secondary to primary blast BLI is a special form of DAH but triggered (i) By a “blast wave” secondary to a high explosive detonation. The expanding high pressure wave induces destructive interaction between the pressure wave, the lung tissue and pulmonary vasculature leading to a disruption of tissues at the air-blood interface. (ii) With a subsequent resonance inducing hemolysis of the intra-alveolar space. |
| Natural course of BLI | From the early phase with bleeding over mild hemolysis to the end stage with irreversible lung injury based on insufficient iron clearance. Reversible provided therapy is initiated within the first 3 hours – “the window of opportunity.” |
| Treatment window | The blast injury secondary to high-explosives is life-threatening and the window of opportunity is narrow which means that time for treatment is of essence. The time window for intervention is only 3 hours. Preemptive* inhalation of FVIIa can eliminate the risk of mortality or permanent lung dysfunction secondary to BLI. |
| Battlefield and homeland security | Inhalation of FVIIa implies that BLI casualties may be evacuated from the war zone by helicopter and ensure a safe home transport to acquire final treatment in an allied hospital. |

Note: *Preemptive is predefined prophylaxis based on (i) a major blast exposure within the 3 hours open window, most preferably 30 minutes after the exposure. 
Abbreviations: BLI, blast lung injury; DAH, diffuse alveolar hemorrhage.

Hemorrhage is not brought to a halt, the severity of the pulmonary dysfunction increases over the next 4 days into irreversible BLI and fatal pulmonary failure. The BLI occurs when soldiers in the battlefield or the civilian population are exposed to bomb attacks. Inhalation of FVIIa is an obvious measure to treat the BLI within the window of opportunity, which could be an indication for use of FVIIa in respect to the military and homeland use, because BLI affects soldiers in the battlefield as well as victims of terror attacks.

BLI – signs, symptoms and outcome

BLI secondary to high explosives causes life-threatening dysfunction of the lungs of soldiers exposed to a blast. The incidence of BLI is not known, but may be as high as 1000–5000 persons annually.

There are to date no reports of the prevalence of DAH in blast lungs because it is a military secret. BLI may occur in the absence of any external signs of trauma, as seen in a series of 517 blast casualties, where approximately 20% were immediately fatal.

Table 4 After a major blast the three phases have their own distinct problems

<table>
<thead>
<tr>
<th>Timing</th>
<th>Pathophysiology of the post blast pulmonary injury phases</th>
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<tbody>
<tr>
<td>Phase 1</td>
<td>Hemorrhagic phase</td>
</tr>
<tr>
<td>0–3 hours</td>
<td>• Transmigration of inflammatory leucocytes, inflammatory stress and destruction of endothelial integrity</td>
</tr>
<tr>
<td></td>
<td>• Window of opportunity</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Alveolar inflammation</td>
</tr>
<tr>
<td>4–12 hours</td>
<td>• Extravasation of blood with transmigration of inflammatory leucocytes into the hemorrhagic lesions</td>
</tr>
<tr>
<td></td>
<td>• Subsequent biodegradation of hemoglobin with deposition of iron in alveoli accompanied by degranulation of neutrophils</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Pulmonary destruction</td>
</tr>
<tr>
<td>13–56 hours</td>
<td>• Increased transferrin – bound Fe (3+) and non-transferrin complexes of Fe (3+)</td>
</tr>
<tr>
<td></td>
<td>• Subsequently disruption of alveolar capillary network and necrotic changes in the pulmonary epithelial cells</td>
</tr>
</tbody>
</table>

Treatment of DAH

Hitherto the separation between symptomatic intervention towards life threatening DAH and the optimization of the underlying disease has not been properly addressed – a fact which has caused confusion concerning the discussion of the best way to administer FVIIa as an intravenous infusion or as an airway deposition, ie, as a BALF administration or as an inhalation (Figure 4).

A common denominator for these studies is that the trials generally have only a very small number of patients included, thereby evading proper statistical evaluation. In 2006 a study was published with a sufficient number of patients to reach a statistical significant effect of local FVIIa. Before this time treatment was a mixed intervention of questionable effect with steroids, anti-infective measures, plasmapheresis, platelet transfusion, and intravenous infusion of FVIIa and other procoagulation factors in spite of the fact that DAH bleeding is not due to factor deficiency.

As late as in 2011 it is still suggested that treatment of DAH should be based “on the underlying cause of hemorrhage,
with corticosteroids as a mainstay of therapy in most cases22 despite of the first series of a systematic treatment of DAH with local intrapulmonary FVIIa in 2006.31 This study documented an effect of administering a small intrabronchial dose of FVIIa. The effect of intrabronchial lavage with a simple saline solution of FVIIa demonstrated (i) that no patient succumbed after the treatment due to alveolar bleeding, (ii) a significantly improved oxygen gas exchange \( P = 0.024 \), and (iii) a balanced hemostasis \( P = 0.031 \). These findings were subsequently reproduced by three later publications from three independent centers using the identical treatment protocol, however, each study had only a few patients included.32–34 None of the four studies adverse effects (AE) were reported, probably because there was no detectable transmembraneous FVIIa passage from the air side into the blood as evaluated by the prothrombin time. The pathophysiological understanding of the mechanism of action, the marked effect, and the fact that no patients died or were encountering adverse effects as a consequence of the local treatment with FVIIa was most likely the reason for being granted the orphan drug (OD) designation in both Europe (European Medicines Agency [EMEA]), Canary Wharf, London and secondly in the USA (Food and Drug Administration [FDA], Virginia, USA) in spite of the theoretical risk of intra-alveolar thrombotic com-

### Table 5 Diffuse alveolar hemorrhage – the treatment paradigm

<table>
<thead>
<tr>
<th>DAH subtype</th>
<th>Clinical signs and symptoms</th>
<th>Route of administration</th>
<th>Effective dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic alveolar bleeding</td>
<td>Hemoptysis and severely reduced oxygen transport capacity and confluent opacities on chest films</td>
<td>Bronchoalveolar lavage with 25 mL saline via each main bronchus(^a)</td>
<td>75 µg/kg FVIIa(^{31-34})</td>
</tr>
<tr>
<td>Microscopic alveolar bleeding or hemosiderosis</td>
<td>Chronic transfusion requirement and hemosiderin laden macrophages in expectorate</td>
<td>Inhaled FVIIa(^a)</td>
<td>75 µg/kg FVIIa(^{31})</td>
</tr>
<tr>
<td>Blast lung injury</td>
<td>Initial dyspnea after the blast</td>
<td>No information</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Increasing symptoms and eventually leading to hemoptysis or microscopic DAH</td>
<td>Animal proof of concept at DSTL</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Window of opportunity of 3 hours</td>
<td>Most likely the intervention would be inhalation of FVIIa, at least as a prehospital treatment</td>
<td>–</td>
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</table>

Notes: The total effective dose is dissolved in 50 mL. Using a micropump nebulizer interference with the two active sites of FVIIa is avoided. This treatment option was effectively administered in one patient who presented with recurrent bleeding after extubation; no further published experience exists. Note that the treatment regime is based on a limited number of patients.

Abbreviation: DSTL, British Defence Science and Technology Laboratory.
plications, when treating DAH with FVIIa as a pulmonary deposition.22

However, the systemic administration of FVIIa for off-label use for the treatment of uncontrollable life-threatening hemorrhage has been increasing since the introduction of FVIIa (NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark),35 but concomitantly a concern for potential thromboembolic complications has equally been increasing, especially after the publication of several meta-analyses recommending caution due to ongoing reports of fatal complications.36,37

A suggestion for the treatment of the three conditions, DAH, pulmonary hemosiderosis and blast lung injury, is shown in Table 531–34 based on published documentation. Patients suffering from chronic DAH as IPH, often children, are at present generally placed on high-dose steroids, and then weaned to the lowest dose that keeps them from having exacerbations. The use of chronic high dose steroids is problematic because the treatment induces multiple adverse effects both in children but also in the adolescent. The 5-year mortality rate in pediatric patients ranges from 24% to 60%.38 Since no treatment is known at present to be effective, clinical trials with inhaled FVIIa are warranted. It is suggested that the end point could be a fall in numbers of hemosiderin-loaded macrophages in sputum combined with reduced transfusion need. Since FVIIa has a very high degree of efficacy in DAH and is without adverse effects, inhaled FVIIa in a small low daily dose will most likely serve as a prophylactic measure. Such a treatment scheme could make invasive procedures like single-lung transplantation superfluous as this treatment has shown no lasting effect because IPH recurred.38

However, to date no information on treatment of pulmonary hemosiderosis and BLI has been published. In as much as pulmonary hemosiderosis and BLI share the same pathophysiological background alveolar bleeding, treatment suggested in Table 5 is an extrapolation from the published effective dose in DAH.

Every time the clinician encounters a condition where no documentation exists it should be considered whether the disease is worse than the treatment. In the case of using air side treatment of FVIIa in microalveolar bleeding, inhalation by a simple inhalation device seems to be the treatment of choice, ensuring swift deposition of FVIIa into the alveolar space, without the need for invasive procedures such as bronchoscopy. Using a micropump nebulizer ensures that there will not be any interference with the active site of the FVIIa molecule. The only documented case of inhalation of FVIIa by a micropump where the DAH has been treated with success was a patient with Wegener's granulomatosis.31 The patient had been extubated a few hours earlier after a bout of hemoptysis and had presented with recurrence of the DAH through bloody tinged expectorator. Instead of reintubation she was treated with an FVIIa dose of 50 µg/kg BWT inhaled via a jet nebulizer. After 5 minutes the patient spontaneously exclaimed that the dyspnea had defervesced, and there were no further episodes of DAH.

Discussion

Biologics are relatively new approaches to treat hitherto untreatable diseases like the DAH syndrome. The immediate and positive effect of local FVIIa administered from the air side is due to the fact that the combined FVIIa and its receptor tissue factor (TF) will bring about a balanced hemostasis, ie, with both durable hemostasis for a remarkably small dose of FVIIa, and an improvement in oxygen transport capacity. These facts also explain the lack of systemic adverse effects (Figure 5).

DAH is a syndrome, not a disease, with three subsets. It is easily conceived that the acute macroscopic hemorrhage has a very high mortality >75%. The microscopic DAH subset has on the contrary a small acute mortality; however, with a severely reduced life expectancy. Lastly the DAH subset associated with blast injuries has anecdotally been

![Figure 5 Rationale for local pulmonary treatment of DAH with FVIIa. Intravenous rFVIIa does not reach the alveoli (1) in contrast to the airway route (2) where a direct access to the receptor TF is obtained. The TF-FVIIa complex activates coagulation factor IX and X. Finally the activated TF-FVIIa complex induces a perfect “balanced” hemostasis ie, sufficient fibrin deposition without interference with the oxygen transport. The TFPI are constitutively expressed in the airspace in inflammatory conditions, secondary to alveolar inflammation. The TFPI is usually of less importance as compared to the procoagulatory factors. However, this might be the explanation for the balanced hemostasis.](image)

Abbreviations: DAH, diffuse alveolar hemorrhage; TF, tissue factor; TFPI, tissue factor inhibitors.
successfully treated with inhaled FVIIa (pers comm; Danish Medical Center in Helmand province, Afghanistan and Lars Heslet, 2009).

The clinical picture, “white lungs” on chest film and severely reduced oxygen transport capacity, is a common denominator of the high mortality pulmonary diseases DAH, ARDS and BOOP. Diagnostically they may be separated by a simple algorithm: when an aliquot series of BAL fluid washes shows increasingly bloody return, irrespective of whether it is from macro- or microscopic bleeding.

Therapy of the DAH syndrome seems to be simple because DAH is the common denominator of multiple underlying diseases and conditions. It is most important to separate the treatment of the alveolar bleeding from the optimization of underlying disease like plasmaferesis, steroids, and antibiotics. Administration of FVIIa into the airways via local administration is suggested as an adjuvant therapy to treatment of the underlying disease (Figure 5). Taking into consideration the adverse effects of high-dose steroids often used in children with DAH or IPH and further the risk of acquiring irreversible pulmonary fibrosis due to insufficient iron clearance, a trial with inhaled FVIIa seems to be far less risky in spite of such an intervention.34

Conclusions
1. The documented therapy from four independent centers of instillation of FVIIa or inhalation of the drug into the airways has demonstrated a sustained and immediate hemostatic effect in DAH, however, still only in a small number of patients.
2. There is an obvious indication for this treatment in patients with the syndrome DAH and with BLI, being the first line intervention to treat the catastrophic high mortality of DAH. This treatment is also safe because the drug does not penetrate from ‘air’ to ‘blood’.
3. Lastly, patients with confluent opacities on chest film and reduced oxygenation capacity like DAH, ARDS and BOOP, may according to a simple algorithm BALF wash test be categorized into distinctive groups and treated accordingly. It has been estimated that ARDS is likely to be over-diagnosed in 20%, an important issue because the treatments are different.
4. Larger, however, not necessarily placebo-controlled studies are warranted, taking into account the high mortality when utilizing the above mentioned treatment recommendations and based on the simple diagnostic algorithm to systematically separate the DAH syndrome from the conditions ARDS/ALI and BOOP.

Disclosures
SNC and JDN declare that they have no competing financial or other interests related to the preparation or the content of the manuscript. LH has shares in the pharmacompany Serendex, Copenhagen, Denmark that holds a patent in pulmonary treatment with rFVIIa, but has not received reimbursements, fees, funding, or salary from any organization relating to the content or the preparation of the manuscript. LH declares that he has no other competing interests.

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