

## ***Recombinant activated Factor VII (rFVIIa; NovoSeven) usage protocol in emerging indications***

This suggested rFVIIa protocol has been endeavored to assist clinicians in the appropriate use of rFVIIa in life-threatening massive bleeds, in particular coagulopathic diffuse bleeding that could occur in various traumatic, medical and surgery-related settings which has proved unresponsive to all other conventional methods of intervention. Multidisciplinary groups of clinicians from the fields of medicine, surgery, obstetrics, anesthesia, cardiac surgery, critical care and hematology specialties have evolved an opinion and rFVIIa usage protocol based on their experience, knowledge and published international literature. Ensuing information is intended to be used as a guideline though any use should be tailored to local hospital practice and resources.

### **Important considerations<sup>1,2</sup>**

- In massive bleeding, every attempt should be made to control bleeding by conventional measures. rFVIIa should not replace and/or delay surgery or any other methods used to control the source of bleeding, such as angiography with embolization.
- As rFVIIa arrests coagulopathic bleed rather than surgical bleed, it should be administered as an adjunctive therapy to concomitant surgical measures.
- rFVIIa should be considered only if first line treatment with a combination of blood products (RBCs, platelets, FFP and cryoprecipitate/fibrinogen) and surgical approaches fails to control bleeding.
- Efforts to achieve the correction of factors such as hypothermia, severe acidosis, low hematocrit and hypocalcemia, which may interfere with coagulation, should be made.
- Before administering rFVIIa, the patient, or the patient's next of kin, should be informed about the type of treatment that they are receiving.

### **Indication<sup>2,3</sup>**

Any salvageable patient suffering from massive, uncontrolled hemorrhage\*in whom there is failure to arrest hemorrhage despite appropriate surgical measures and blood component replacement therapy\*\*. Massive bleeding could occur in the context of varied clinical settings some of which are enlisted below, though the list in itself is not claimed to be complete and exhaustive.

### **Specific disease entities**

- Polytrauma-related hemorrhage
- Postpartum hemorrhage

- Cardiac surgery bleeds
- Anticoagulant related bleeding
- Dengue hemorrhagic fever
- Liver disease-related bleeds
- Thrombocytopenia with refractory bleeding

## Definitions

**Massive hemorrhage\*** is defined as one of the following<sup>2</sup>:

- Loss of entire blood volume within 24 h (10 U of packed RBC in a patient weighing 70 kg)
- Loss of 50% of blood volume within 3 h
- Blood loss at a rate of 150 mL/min
- Blood loss at a rate of 1.5 mL/kg/min for  $\geq 20$  min

## Failure to arrest the hemorrhage despite<sup>2</sup>

- Application of all accepted and available surgical measures (e.g. ligation of damaged vessels, tamponading, or packing of the bleeding site, and induction of localized thrombosis).
- Appropriate replacement therapy<sup>2:\*\*</sup>
  - Packed red blood cells (PRBCs): 8-10 U
  - Fresh frozen plasma (FFP): 10–15 mL/kg (4–6 U for a patient weighing 70 kg)
  - Cryoprecipitate: 1–2 U/10 kg (10–15 U for a patient weighing 70 kg)
  - Platelets: 1–2 U/10 kg (10–15 U for a patient weighing 70 kg)

## Contraindications<sup>2</sup>

**Absolute:** Unsalvageable patients, as identified according to the clinical evaluation of the treating medical team.

**Relative:** History of thromboembolic events (e.g. pulmonary emboli, myocardial infarction, cerebrovascular accident, deep vein thrombosis) within the previous 6 months.

## Administration guidelines<sup>2,4,5</sup>

rFVIIa is currently available in India as room temperature stable NovoSeven 1 mg and 2 mg lyophilized powder vials with corresponding dedicated diluents and a comprehensive infusion kit.

- rFVIIa could be considered if there is no response to transfusion of 8-10 U of PRBCs, conventional replacement therapy and surgical interventions
- Appropriate timing of rFVIIa usage is critical as its usage as a ‘last resort’ could minimize the chances of consistent positive clinical outcomes
- An initial dosage of 90-100 mcg/kg could be considered for most of the clinical situations; nevertheless specific dosage for relevant disease entities are mentioned in the ensuing pages; dosage usually rounded to a nearest vial and administered as a slow IV bolus over 2-5 minutes
- If bleeding persists beyond 20 minutes, a second dose could be repeated up to a maximum of total 3 doses
- Before considering the third dose, hypocalcemia to be corrected along with empirical replacement therapy
- Preferably rFVIIa should be used soon after reconstitution as slow IV bolus over 2-5 min. It should not be mixed with infusion solutions
- Response to rFVIIa should be assessed on clinical grounds (i.e. reduction or cessation of hemorrhage)

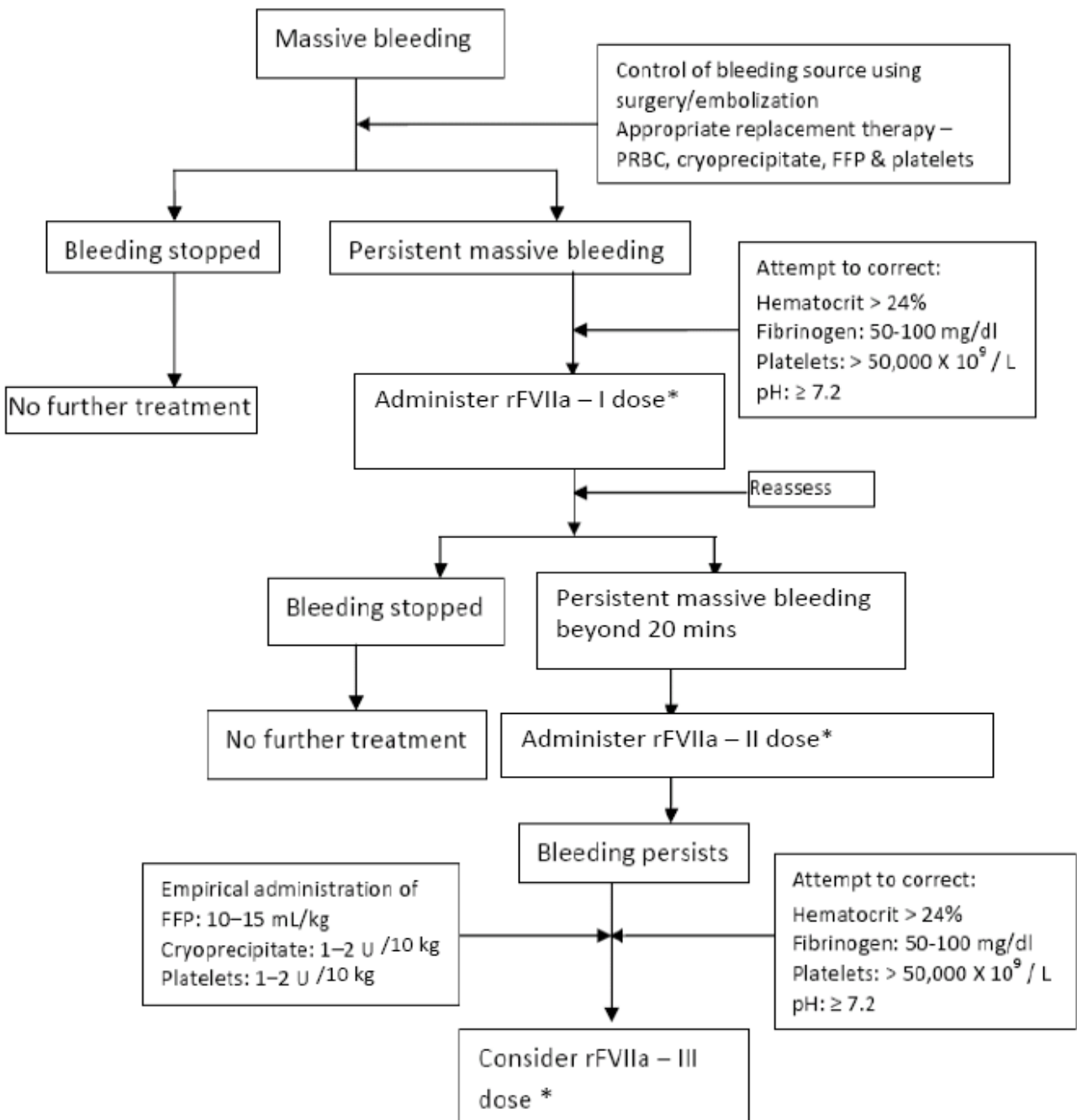
## Preconditions for rFVIIa administration<sup>2,4,5</sup>

All standard measures for the management of massive hemorrhage will have to be undertaken before the potential use of rFVIIa including

- Adequate correction of hypovolemia
- Achieving hematological parameters which include
  - Fibrinogen levels of  $\geq 50$  mg/dL (preferably 100 mg/dL)
  - Platelet levels of  $\geq 50\,000 \times 10^9$  per L (preferably  $100\,000 \times 10^9$  per L – for head trauma or neurosurgery) desirable; haemostatic response to rFVIIa however has been documented even with lower platelet counts.

- Hemoglobin > 80 g/L (to optimize hemostasis)
- Hematocrit of 0.24 (to facilitate clot formation)
- Attempts to correct acidosis (aim for pH =7.20 or higher as poor response to rFVIIa is seen if pH  $\leq$ 7.1)
- Attempts to prevent and/or correct hypothermia (not mandatory for functioning of rFVIIa though)

## Algorithm for use of rFVIIa






Note: \*General dosage recommended in majority of indications is about 90-100 mcg/kg; however in anticoagulant-related bleeds, lower doses of 60-90 mcg/kg are preferred; doses of 20-40 mcg/kg have been used for non-emergent anticoagulant reversal.<sup>6</sup>

NICE Data: According to 188 cases reviewed at NICE-review meet held on Mar28-29, 2009, the median dose for majority of the indications was 60mcg/kg though the median dose for

DHF was 90mcg/kg and those for ICH, Cardiac surgery and Thrombocytopenia respectively were 44, 40 and 45mcg/kg.

## Specific disease entities

Indications	Recommendation	Suggested doses*
<p>Polytrauma – related bleed<sup>1,6,7</sup></p> <p>Polytrauma bleed.doc</p>	<p>Ongoing bleeding and coagulopathy despite surgical intervention and replacement therapy – <b>Appropriate</b><sup>6</sup></p> <p>Level of recommendation – <b>Grade B</b><sup>1</sup></p>  <p>Recommendation.doc</p> <p style="text-align: center;">c</p>	<p>Initial dose of 90 - 100 mcg/kg IV bolus</p> <p>If bleeding persists: Consider II and III dose after 1 h and 3 h respectively following administration of I dose<sup>7</sup></p>
<p>Postpartum hemorrhage<sup>1,6,8</sup></p>  <p>Flow chart PPH.doc</p>	<p>Attempted significant clotting factor replacement; Prior to hysterectomy – <b>Appropriate</b><sup>6,8</sup></p> <p>Level of recommendation – <b>Grade E</b><sup>1</sup></p>	<p>Initial dose of 90 mcg/kg IV bolus</p> <p>If bleeding persists: Consider II dose after 20 mins</p> <p>If bleeding persists after 2 doses – Consider hysterectomy</p>
<p>Cardiac surgery bleed<sup>1,6,9,10</sup></p>  <p>Flow chart.doc</p>	<p>Intractable nonsurgical bleeding unresponsive to attempted significant clotting factor replacement – <b>Appropriate</b><sup>6</sup></p> <p>Level of recommendation - <b>Grade B</b><sup>9</sup></p>	<p>Initial dose of 70-90 mcg/kg IV bolus</p> <p>If bleeding persists, repeat dose up to 3 times</p>
<p>Anticoagulant-related bleed<sup>6,11</sup></p>	<p><b><i>Non-traumatic intracranial bleeding</i></b><sup>6</sup></p> <p>&lt; 4 hours since symptom onset</p> <p>On anticoagulant therapy - <b>Appropriate</b></p> <p><b><i>Isolated traumatic head injury with evidence of expanding bleeding</i></b><sup>6</sup></p> <p>Taking anticoagulant therapy - <b>Appropriate</b></p> <p>Level of recommendation - <b>Grade B</b></p>	<p>Initial dose of 60 – 90 mcg/kg IV bolus</p> <p>If bleeding persists, repeat up to 3 doses</p>

Dengue hemorrhagic fever <sup>12,13</sup>	Adjunctive therapy to significant blood component transfusion for controlling active bleeding – <b>Appropriate</b>  Level of recommendation - <b>Grade C</b>	Initial dose: 100 mcg/kg repeated at 15-30 mins interval (usually 1-2 doses) till reduction of bleeding  Repeat dose: 100 mcg/kg, repeated at 2-4 intervals (usually 2-4 doses) till cessation of bleeding  Final dose: 100 mcg/kg after bleeding completely stops
Liver disease-related bleeds <sup>1,11</sup>	Ongoing hemorrhage despite attempted significant clotting factor replacement in patients with liver disease (variceal, non-variceal and liver transplantation related bleed) – <b>Inappropriate</b>  Level of recommendation – <b>Grade B<sup>1</sup></b>	Not applicable
Thrombocytopenia with refractory bleeding <sup>14</sup>	Severe bleeding despite attempted significant clotting factor replacement – <b>Could be appropriate</b>  Level of recommendation - <b>Grade E</b>	Initial dose of 50-100 mcg/kg  Dose to be repeated if necessary

## Monitoring

Currently, the best available indicator of rFVIIa efficacy is the arrest of hemorrhage judged by visual evidence, hemodynamic stabilization and a reduced demand for blood components.<sup>2</sup>

### \*rFVIIa Dosage as per NICE Data:

According to 188 cases reviewed at NICE-review meet held on Mar28-29, 2009, following are the dosages (mcg/kg) used in clinical hemorrhage of various etiologies. The median dose for majority of the indications was 60mcg/kg though the median dose for DHF was 90mcg/kg and those for ICH, Cardiac surgery and Thrombocytopenia respectively were 44, 40 and 45mcg/kg.

Indications	Median Dose(mcg/kg)	Dose Range(mcg/kg)
DHF	90	40 – 120
OBG. BLEEDING	60	20 – 100
OTHER SURGERY	60	20 – 100
LIVER DISEASE	60	9 – 120
UGI / LGI BLEED	60	20 – 100
TRAUMA	60	40-120
ANTICOAG - BLEED	60	40 – 90
OTHERCOAGULOPATHIES	60	20 – 80
THROMBOCYTOPENIA	45	20 – 100
ICH	44	20 – 90
CARDIAC SURGERY	40	32 – 80

## References

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