Reversal strategies for anticoagulants

1. Prothrombin complex concentrate (PCC)

Indication

- Urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) for patients with acute major bleeding or a need for an urgent surgery/invasive procedure secondary to warfarin therapy.
- Urgent reversal of life threatening bleeding secondary to direct oral anticoagulant therapy

Composition:

Ingredient	Content after reconstitution (IU/mL)	Content per vial (IU)
Active ingredients		
Factor II	14 - 38	280 - 760
Factor VII	9 – 24	180 – 480
Factor IX	25	500
Factor X	18 - 30	360 - 600
Further active ingredients		
Protein C	13 – 31	260 – 620
Protein S	12 - 32	240 – 640
Heparin	0.2 – 0.5	…..

Dosage Regimen: is according to the severity of bleeding and INR elevation

Initial INR	2 - 2.5	2.5– 3	3 – 3.5	➢ 3.5
Approximate Dose (ml Octaplex/ kg)	0.9- 1.3	1.3 – 1.6	1.6 – 1.9	> 1.9

- Multiple doses are allowed if INR is not corrected to the desired level with a previous dose.
- The single dose should not exceed 3000 IU (120 ml Octaplex).

- Consider Vitamin-K 5-10 mg IV concomitantly with PCC dose.

Dose Adjustment:

- No dosage adjustment for renal and hepatic patients.

Monitoring

- INR (baseline and at 30 minutes' post dose)
- Clinical response during and after treatment and signs of thromboembolism.

Contraindications

- Hypersensitivity to active substance
- Known history of heparin induced thrombocytopenia (HIT)
- Coagulation disorders due to chronic liver disease or liver transplantation
- Bleeding associated with hepatic parenchyma disorders

- ❖ Esophageal varices
- ❖ Major hepatic surgery
- ❖ Immunoglobulin A (IgA) deficiency, with known antibodies against IgA

Precautions

- ❖ Benefits of reversing VKA therapy should be weighed against the potential risk of a thromboembolic event.
- ❖ Resumption of anticoagulation should occur once the risk of thromboembolism outweighs the risk of acute bleeding.

Drug interaction:

- ❖ Aminocaproic Acid; Aminomethylbenzoic Acid; Tranexamic Acid

Storage/Stability:

- ❖ Store at 2°C to 25°
- ❖ Do not freeze
- ❖ Protect from light
- ❖ Reconstituted solution should be administered immediately, but may be stored for up to 8 hours at 2°C to 25°C if sterility is maintained

Authorized prescriber

- ❖ Restricted to Thrombosis Team, Hematologists, Cardiology, ICU and Critical Care for life threatening associated hemorrhage as per protocol

2. Fresh Frozen Plasma (FFP)

- Fresh Frozen plasma (FFP) can be prepared from a unit of Whole Blood or collected by apheresis, volume of 1 unit is ~200- 250 mL
- Contains all necessary clotting factors for hemostasis, each with different half life
- Overall half-life of FP in non-bleeding patient is 6-8 hours
- Must be ABO compatible with recipient:

Patient ABO Type (Recipient)	Suitable FFP Types
Group O	Group O, A, B, or AB
Group A	Group A or AB
Group B	Group B or AB
Group AB	Group AB

Indications:

FFP is indicated for the following:

- Bleeding in patients with multiple coagulation factor deficiencies (eg, DIC, liver disease)
- Patients with multiple coagulation deficiencies undergoing invasive procedures
- Iatrogenic coagulopathy associated with massive RBC transfusion* and crystalloid resuscitation
- Trauma patients with associated acute coagulopathy of trauma (ACT)
- Patients on warfarin who are bleeding or at risk for bleeding (examples: Warfarin overdosage; need for invasive procedures before warfarin can be reversed with vitamin K; warfarin-related intracranial hemorrhage)

- Plasma exchange in patients with diseases such as thrombotic thrombocytopenic purpura (TTP) and vasculitis-associated hemorrhage
- Patients with congenital coagulation factor deficiencies for which specific recombinant products are not available (examples factors V and XI)
- Administration as "immune plasma" from donors recovered from viral infections who have developed neutralizing antibodies as in COVID-19 Convalescent Plasma or CCP.
- Patients with plasma protein deficiencies such as C1 inhibitor

Dose:

- A dose of **10-20 mL/kg** of FP will increase all coagulation factors by~**30%,** which is usually adequate for hemostasis and will reduce INR to < 1.5
- Providing smaller doses will be ineffective

Storage:

- Plasma is stored in a frozen state (-18C or lower)
- Thawing takes ~30 min
- After thawing, FFP should be infused immediately or stored at 1°C to 6°C for no more than 24 hours

3- Protamine sulphate

Indication

Treatment of Heparin and Low molecular weight heparin overdosage.

❖ **Heparin overdosage:**

- If patient is not bleeding, consider not administering protamine since risks may outweigh benefits
- Protamine dosage is determined by the amount of heparin administered
  - 1 mg of protamine neutralizes ~100 units of heparin
  - If heparin was administered as a continuous IV infusion, calculate protamine dose based on heparin administered in the previous 2 to 3 hours
  - No dosage adjustments are required for altered renal or hepatic function

Monitoring:

If aPTT remains elevated after 2 to 4 hours after the first dose protamine sulphate, may repeat 0.5 mg of protamine for every 100 units of heparin

❖ **Enoxaparin overdosage:**

- If patient is **not** bleeding, consider **not** administering protamine since risks may outweigh benefits
- The maximum neutralization of the anti-Factor Xa activity is about 60-70%
  - Enoxaparin administered in ≤8 hours
    - Dose of protamine = dose of enoxaparin administered.
    - 1 mg of protamine to neutralize 1 mg of enoxaparin
  - Enoxaparin administered >8 hours to <12 hours ago or if a second dose of protamine is required (eg, clinically significant bleeding continues)
    - 0.5 mg of protamine for every 1 mg of enoxaparin
  - Enoxaparin administered ≥12 hours
    - Protamine administration may not be required.

Administration:

Slow IV injection over ~10 minutes; maximum single dose: 50 mg)

Precaution:
Hypersensitivity reaction

Storage/Stability:
Store at 20°C to 25°C. Do not freeze. Diluted solutions should not be stored.

4) Vitamin K (Phytomenadione)

Indication:
Vitamin K corrects coagulopathy due to vitamin K deficiency and antagonism (eg., malnutrition, therapy with warfarin)

Reversal of Anticoagulation From Warfarin		
Indication	**Management considerations**	**Vitamin K administration**
Supratherapeutic INR and no evidence of bleeding		
INR above therapeutic range but <4.5	Consider holding the next dose of warfarin and/or reduce maintenance dose; increase INR monitoring.	Routine administration of vitamin K is not recommended.
INR 4.5 to 10	Discontinue warfarin, monitor INR frequently, and resume an appropriately reduced warfarin dose when INR is in desired range. May consider administering oral vitamin K if additional risk factors for bleeding exist.	Routine administration of vitamin K is not recommended. If administered, one dose of **oral** vitamin K 1 to 2.5 mg is recommended.
INR >10	Discontinue warfarin, monitor INR frequently, and resume an appropriately reduced warfarin dose when INR is in desired range. Consider administering oral vitamin K depending on bleeding and thrombotic risks.	If administered, one dose of **oral** vitamin K 2.5 to 5 mg is usually recommended; recheck INR after 12 to 24 hours; may administer a second dose if necessary. For patients with a mechanical prosthetic heart valve, a lower **oral** vitamin K dose of 1 to 2.5 mg may be administered to avoid overcorrection of INR. Some data suggest that vitamin K is not routinely needed in the absence of bleeding.
Bleeding		
Minor bleeding	Discontinue warfarin, monitor INR frequently, and resume warfarin at an appropriately adjusted dose when it is safe to do so. Consider administering oral vitamin K depending on INR, site of bleeding, risk of progression to more serious bleeding, and thrombotic risk.	If administered, **oral** vitamin K 2.5 to 5 mg is recommended; if INR remains elevated after 24 hours, may administer another dose.

Reversal of Anticoagulation From Warfarin		
Indication	**Management considerations**	**Vitamin K administration**
Major bleeding into a critical site and/or life-threatening bleeding (including intracranial hemorrhage)	Discontinue warfarin and urgently administer a PCC in combination with IV vitamin K; monitor INR frequently and assess for hemostasis.	Administer **IV** vitamin K 10 mg over 10 to 20 minutes (maximum infusion rate: 1 mg/minute) as soon as possible in combination with PCC; if INR remains elevated after 12 to 24 hours, may administer another dose of vitamin K.

Precaution: Hypersensitivity reaction and Liver disease

Storage/Stability: Store at 20°C to 25°C; Protect from light.

References:

1- *Baugh CW, Levine M, Cornutt D, et al. Anticoagulant reversal strategies in the emergency department setting: recommendations of a multidisciplinary expert panel. Ann Emerg Med. 2019;S0196-0644(19)31181-31183. doi:10.1016/j.annemergmed.2019.09.001*

2- *Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020;76(5):594-622. doi:10.1016/j.jacc.2020.04.053*

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