PROTOCOL FOR TRANSFUSION SUPPORT IN BLEEDING DISORDERS

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INTRODUCTION

- Patients who have an abnormality of platelets or the coagulation/fibrinolytic system may suffer from severe bleeding due to childbirth, surgery or trauma.

- Recognition that a patient may have a bleeding disorder and the correct diagnosis and treatment can influence the timing and type of elective surgery, reduce the need for transfusion and avoid risks to the patient due to bleeding.

•Coagulation and platelet disorders can be classified as follows:

■ **Acquired coagulation disorders,** arising as a result of disease or drug therapy

•Liver disease,

•Aspirin-induced platelet dysfunction or

•Disseminated intravascular coagulation

■ **Congenital coagulation disorders**

•Haemophilia A or B

•von Willebrand disease

DONOR SCREENING -PROTOCOL

- Age 18-55yrs
- Donor weight :Minimum 50 Kgs
- Hb: >12.5 g/dl

Donated blood and blood components are screened for

oHIV

oHbsAg

oHCV

oSyphilis

oMalaria

DEFINITIONS

BLOOD PRODUCT :

Any therapeutic substance prepared from human blood.

WHOLE BLOOD :

Unseparated blood collected into an approved container containing an anticoagulant preservative solution

BLOOD COMPONENT

1. A constituent of blood , separated from whole blood by differential centrifugation
- Red cell concentrate
- Plasma
- Platelet concentrates

2. Plasma or platelets collected by apheresis
3. Cryoprecipitate prepared from fresh frozen plasma

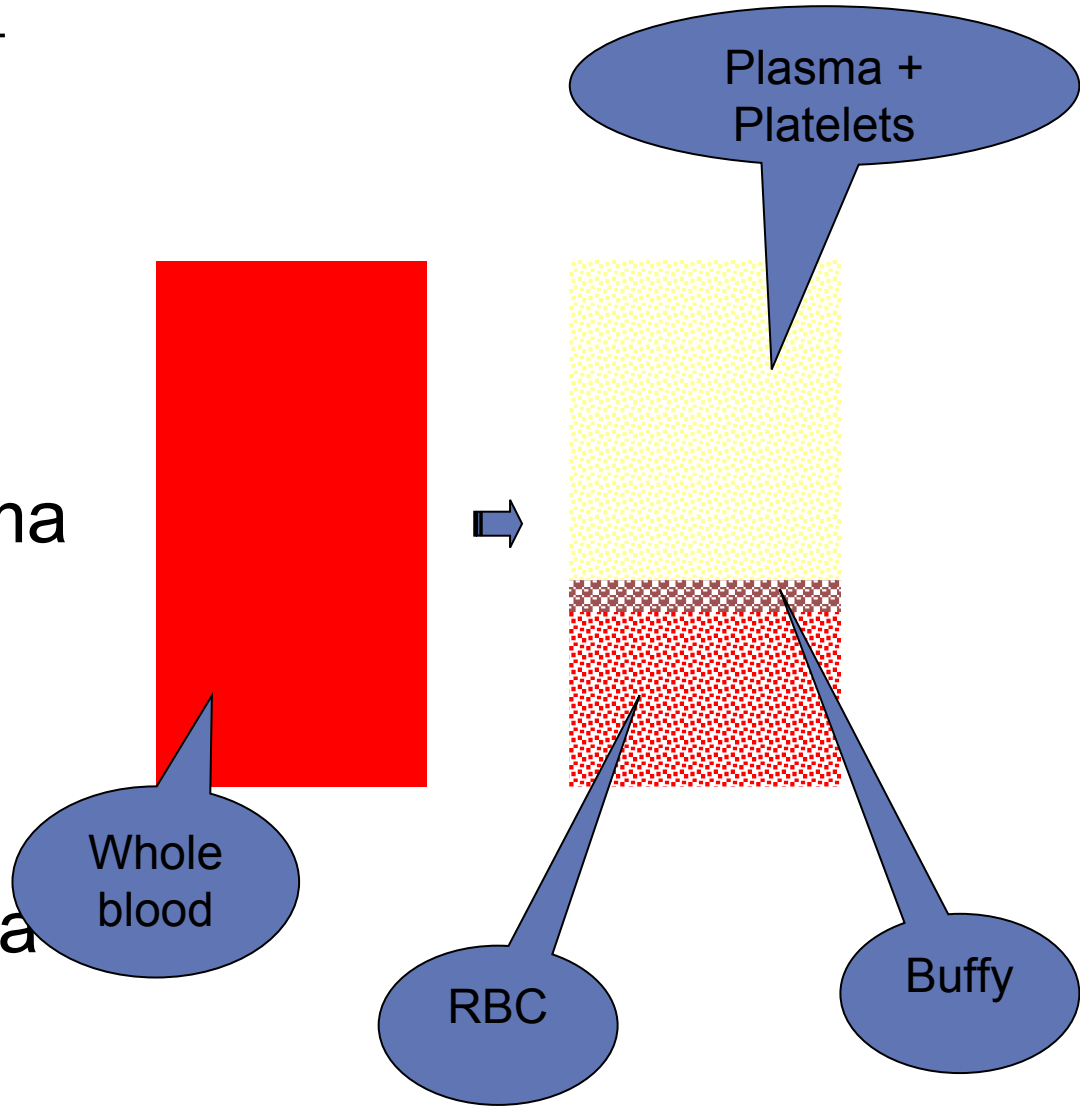
BLOOD COMPONENTS USED IN BLEEDING DISORDERS

- Whole blood
- PRP (Platelet rich plasma)
- Platelet concentrate
- FFP (Fresh frozen plasma)
- Cryoprecipitate

COMPONENT PREPARATION

Principle - Differential centrifugation

- Red cells
  - Packed cells
- Plasma
  - Fresh frozen plasma
- Platelets
  - Platelet rich concentrate
  - Platelet rich plasma
- Cryoprecipitate



WHOLE BLOOD

- Whole blood contains 350+49 ml of blood plus anticoagulant solution(CPDA-1)
- Stored at 2-6 deg C for 35 days
- **Stored blood has no functional platelets and no labile coagulation factors V and VIII after few hours.**
- **Complications :**
  1. Dilutional thrombocytopenia
  2. Congestive cardiac failure

PLATELETS

- Platelet units can be either
  - Random donor units
  - Apheresis units

- 1 random donor unit contains 55 $x10^9$ platelets.

- 1 apheresis unit contains $240x10^9$ platelets.

- Stored at 20-24 deg C in continuous agitation for 5 days in platelet agitator.

PLATELET RICH PLASMA & PLATELET RICH CONCENTRATE

Preparation :

- 450 ml of fresh blood by centrifugation or by Apheresis.

- A unit of platelet concentrate prepared from 450 ml of fresh blood contains:

– Plasma vol.	40-70ml.
– Platelet yield	$5.5x10^{10}$
– RBC	traces to 0.5ml.
– pH	6.0 or more

PLATELET CONCENTRATE

COMPLICATIONS:

1.Chill, Fever, Allergic reaction

2. Alloimmunisation

3. Platelet refractory state

4. Graft vs. host disease

CONTRA INDICATIONS:

1. TTP

2. Heparin induced thrombocytopenia

Fresh Frozen Plasma (FFP)

- Quantity :200 -250 ml
- Also collected by apheresis
- All coagulation factors and other proteins

Storage

- At less than - 20 deg C for 1 yr
- Dose
  – 10-15 mL/kg
- Contains both F VIII and F IX (1 IU /ml)
- Expect 20-30% increase in all factor levels

FRESH FROZEN PLASMA

- Contains labile & non labile clotting factors, albumin and immunoglobulin.
- Factor VIII level at least 70 % of normal fresh plasma level

- Dosage - Initial dose of 15 - 20 ml / kg

FRESH FROZEN PLASMA

- Before use thawed at 37 ^{o} C

Precaution

- Acute allergic reaction are common
- Anaphylactic reaction may occur

Administration

- Must be ABO compatible, Rh not required
- Infuse as soon as possible after thawing
- using standard blood administration set

FRESH FROZEN PLASMA

Contra-indications

1. Should not be used as blood volume expander
2. Hypo-proteinemia
3. Source of immunoglobulin
4. Nutritional support
5. Wound healing

CRYOPRECIPITATE

- Made from 1 unit partially thawed FFP
- Quantity:15 -30 mL
- Fibrinogen, factor VIII, VWF, factor XIII
- Stored 1 year frozen, 6 hours thawed
- If pooled must be given in 4 hours
- Dose
  - 1 unit/10 kg
  - 10-20 units required in adult of 70 kg.

CONGENITAL BLEEDING AND CLOTTING DISORDERS

Deficiencies of Factor VIII and IX

- Haemophilia A and haemophilia B are caused by inherited deficiencies of Factors VIII and IX respectively.
- These two factors interact to activate Factor X, which is needed for the production of thrombin and hence coagulation.
- Both are X-linked recessive disorders affecting males mostly .

SEVERITY OF HEMOPHILIA

Severity	F VIII/ IX level (IU/dl)	Clinical picture	Hemophilia A incidence	Hemophilia B incidence
Severe	<1	Spontaneous bleeding	70	50
Moderate	1-5	Bleeding with minimal trauma/ Surgery	15	30
Mild	6-30	Bleeding with major trauma or Surgery	15	20

World Hemophilia federation/WHO

TRANSFUSION PROTOCOL IN HAEMOPHILIA

Management of a case of acute bleeding

1.Avoid anti-platelet agents such as aspirin and non-steroidal anti-inflammatory drugs.

2 Do not give intramuscular injections.

3.Administer coagulation factor concentrates to treat bleeding episodes as quickly as possible

4 .Do not incise swellings in haemophiliacs.

5. Start physiotherapy early to minimize loss of joint function.

Desmopressin (DDAVP)

•Desmopressin releases stored endogenous Factor VIII and von Willebrand factor, so may be useful in mild or moderate haemophilia A. It is not indicated in Factor IX deficiency.

Replacement with factor concentrates

•It is imperative to use factor concentrates that are licensed and certified to be virus-inactivated.

•If coagulation factor concentrates are not available, use:

■Cryoprecipitate in Haemophilia A

■ Fresh frozen plasma in Haemophilia B.

DOSAGE OF FACTOR VIII IN HAEMOPHILIA A

Severity of bleed	Required Factor VIII dose	Factor VIII concentrate (500 iu/bottle)	Cryoprecipitate* (80–100 iu/pack)
1.Mild bleed: nose, gums, etc.	14 iu/kg	1–2 bottles (adult)	1 pack/6 kg
2.Moderate bleed joint, muscle, gastrointestinal tract, surgery	20 iu/kg	2–4 bottles (adult)	1 pack/4 kg
3.Major bleed: Cerebral bleed	40 iu/kg	4–6 bottles (adult)	1 pack/2 kg
4 Prophylaxis for major surgery	60 iu/kg	6–10 bottles (adult)	1 pack/1 kg

CALCULATION OF DOSE

Cryoprecipitate requirement (No of bags)

•No of bags =

(desired F VIII level-initial FVIII level)X Plasma Vol /FVIII content of each bag (IU)

•1 IU /kg of F VIII increases plasma level by 2 %

•1 IU /kg of F IX increases plasma level by 1 %

CALCULATION OF DOSE OF FVIII

- **Blood volume in adults = wt(in kgs) × 70ml/kg**
- **Plasma volume = blood volume × (1 – pcv)**
- **units of FVIII required = plasma volume × (desired F VIII level-initial FVIII level)**

• As adjunct to factor replacement in mucosal or gastrointestinal bleeding and surgery, give fibrinolytic inhibitor:

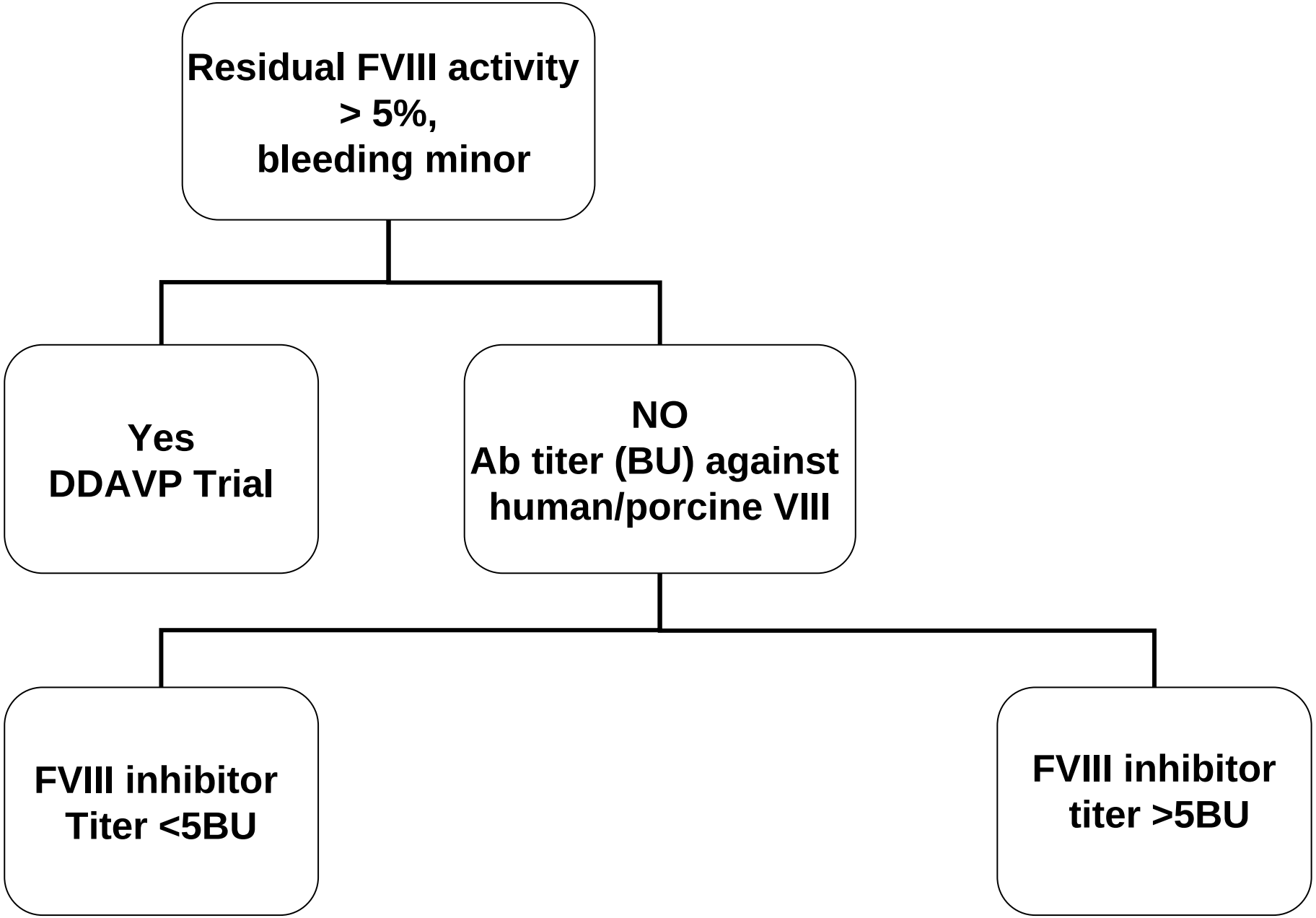
Tranexamic acid (oral): 500–1000 mg

3 times/day. Do not use for haematuria.

•In an emergency, use fresh frozen plasma to treat bleeding in haemophiliacs (give 3 bags initially) if none of the above are available.

•If FFP ,is also not available, transfuse **fresh whole blood** (1 IU of F VIII/IX present in about 2 ml of fresh whole blood)

MANAGEMENT OF PATIENTS WITH FVIII INHIBITORS


Residual FVIII activity
> 5%,
bleeding minor
Yes
DDAVP Trial
NO
Ab titer (BU) against
human/porcine VIII
FVIII inhibitor
Titer <5BU
FVIII inhibitor
titer >5BU

CLASSIFICATION OF PATIENTS WITH FVIII INHIBITORS

Low responders

-Inhibitors < 5 BU

-Inhibitors not ↑ on exposure to F VIII

-Respond to factor replacement therapy

-Sometimes inhibitors disappear

High responders

-Inhibitors > 5 BU

-60-70 % high responders

-Inhibitors ↓ in absence of replacement therapy

-Even become undetectable

-Re -exposure inhibitors ↑over 4-7 days.

MANAGEMENT OF HIGH RESPONDERS

- **Removal & suppression of inhibitors**
  - Plasmapheresis + chemotherapy (cyclophosphamide or steroids or Rituximab)
  - Slow response, time consuming
- **IVIG therapy**
  - For both autoantibodies and alloantibodies to FVIII in some cases of hemophilia A
  - Effect is due to anti- idiotype antibodies
- **Porcine FVIII**
  - Mostly used in high titer FVIII inhibitors when titer <50 BU
  - 100 U/Kg every 24 hourly.

- **Prothrombin complex concentrate (PCC)**
  - Contain varying amounts of vit K dependent factor (II, VII, IX, X), manipulated to get partial activation of factors VII, IX and X.
  - 65-95% effective
  - Used only in mild hemophilia A with FVIII inhibitors and hemophilia B
  - Dose 50-100 U/kg. Max 200 U/kg/day

- **rFVIIa**
  - Dose 90µg/kg
  - Allows FVIIa to attach to activated platelet surface mediating conversion of F X to FXa on platelet surface.

DOSAGE OF FACTOR IX IN HAEMOPHILIA B

Severity of bleed	Required Factor IX dose	Factor IX concentrate (500 iu/bottle)	Fresh frozen plasma
1 Mild bleed	15 iu/kg	2 bottles (adult)	1 pack/15 kg
2 Major bleed	20–30 iu/kg	3–6 bottles (adult)	1 pack/7.5 kg

Note:

1.Repeat in 24 hours if bleeding continues.

2.Factor VIII concentrate and cryoprecipitate are not useful for haemophilia B so accurate diagnosis is essential.

3.As adjunct to replacement therapy:

Tranexamic acid (oral): 500–1000 mg 3 times/day, as for haemophilia A.

VON WILLEBRAND DISEASE(VWD)

•Von Willebrand factor (vWF) is a protein which is involved in platelet adhesion, both to other platelets and to the subendothelium.

• It also acts as a carrier protein for Factor VIII.

• Deficiency of von Willebrand factor is inherited as an autosomal dominant condition affecting both males and females.

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MANAGEMENT OF VWD

The aim of treatment is to normalize bleeding time by

- Increasing endogenous vWF levels with desmopressin (DDAVP)

or

- Replacing vWF using an intermediate-purity Factor VIII product that is known to contain some vWF

or

with Cryoprecipitate.

Dose regime

•Treat as for mild or moderate bleed of haemophilia A, except that the haemostatic dose may be repeated not 12-hourly, but after 24–48 hours, as von Willebrand factor has a longer half-life than Factor VIII.

1.**Desmopressin (DDAVP)**

0.3–0.4 μg/kg IV lasts 4–8 hours and avoids the need to use plasma products.

The dose can be repeated every 24 hours, but the effect is reduced after some days of treatment.

2.**Factor VIII concentrates**

Reserve for patients unresponsive to desmopressin.

3.**Cryoprecipitate**

Dosage:4-6 packs/adult

ACQUIRED BLEEDING AND CLOTTING DISORDERS

- Disseminated intravascular coagulation(DIC)
- Deficiency Vitamin K dependent coagulation factors
- Gastrointestinal bleeding
- Bleeding problems associated with surgery

TRANSFUSION PROTOCOL IN DIC

1 .If the PT or APTT is prolonged and the patient is bleeding:

- Replace red blood cell loss with the freshest whole blood available as it contains fibrinogen and most other coagulation factors

and

- Give fresh frozen plasma as this contains labile coagulation factors: 1 pack/15 kg body weight (4–5 packs in adults)
- Repeat FFP according to the clinical response.

2. If fibrinogen is low or the APTT or thrombin time is prolonged, also give cryoprecipitate (to supply fibrinogen and Factor VIII): 1 pack/6 kg (8–10 packs in adults).

3.If the platelet count is less than 50 x 10^9/L and the patient is bleeding, also give platelet concentrates: 4–6 packs (adult).

4.The use of heparin is controversial.

MANAGEMENT OF DEFICIENCY OF VITAMIN K-DEPENDENT COAGULATION FACTORS

- 1 Remove the underlying cause of vitamin K deficiency:
  - Stop anticoagulants (warfarin)
  - Treat malabsorption or dietary deficiency.
- 2 Replace coagulation factors with fresh frozen plasma, as necessary.
- 3 Reverse warfarin with intravenous vitamin K if the patient is bleeding and the INR is prolonged. Doses of vitamin K exceeding 1 mg may make the patient refractory to further warfarin for up to 2 weeks.

GUIDELINES ON TRANSFUSION IN GASTROINTESTINAL BLEEDING

Severity of bleed	Clinical features	Iv infusion/ Transfusion	END POINT
Mild bleed	Pulse and haemoglobin normal	Maintain with venous access until diagnosis is clear. Ensure blood is available	
Moderate bleed	Resting pulse >100/min *and/or* Haemoglobin <10 g/dl	■ Replace fluid ■ Order compatible red cells (4 units)	Maintain Hb >9 g/dl*

GUIDELINES ON TRANSFUSION IN GASTROINTESTINAL BLEEDING

Severity of bleed	Clinical features	Iv infusion/ Transfusion	END POINT
	History of collapse *and/or* Shock ■ Systolic BP <100 mmHg ■ Pulse >100/min	Replace fluid rapidly ■ Ensure blood is available ■ Transfuse red cells according to clinical assessment and Hb/Hct	Maintain urine output >0.5 ml/kg/hr ■ Maintain SBP >100 mm Hg ■ Maintain Hb >9 g/dl*

PATIENTS FULLY ANTICOAGULATED WITH WARFARIN

- Emergency surgery

1. Give vitamin K, 0.5–2.0 mg by slow IV infusion.
2. Give fresh frozen plasma, 15 ml/kg. This dose may need to be repeated to bring coagulation factors to an acceptable range.
3. Check INR immediately prior to surgery.
4. Commence surgery if INR and APTT ratio are <2.0.

PATIENTS FULLY ANTICOAGULATED WITH HEPARIN

Elective surgery

1 Stop heparin 6 hours preoperatively.

2 Check APTT ratio immediately prior to surgery.

3 Commence surgery if APTT ratio is <2.0.

4 Restart heparin as soon as appropriate postoperatively.

Emergency surgery

•Consider reversal with IV protamine sulphate. 1 mg of protamine

THANK YOU