CASE ILLUSTRATION

- It was a breezy Friday night call when I received a code red buzz
- 36 Malay Lady
- Brought into yellow zone HTAA by a young nephew complaining of giddiness following a fall
- Upon attending, noted patient slowly losing her consciousness with acidotic breathing
- She was pale
Clinically:

- Unresponsive to call
- Acidotic breathing with undetectable BP, SPo2 and a feeble pulse
- Blood soaked sarong. With severed cord at perineum. Mysteriously, baby was missing
What are your initial priorities in managing this case?
C) Linen protectors

d) Quarter filled

ii) Half filled

iii) Almost fully soaked

500mls 1000mls 1500mls
Hemorrhage- a preventable death

- While hemorrhage is the #2 cause of mortality, hemorrhage is the #1 reversible cause for mortality.

- Almost all mortality from hemorrhage occurs within 1st 24 hours.

![Bar chart showing percentage of deaths by type over time.](chart.png)

- Percentage of deaths by type:
  - Hemorrhage
  - CNS
  - Other

- Prehospital: Hemorrhage (40%), CNS (20%), Other (40%)
- First 24 hours: Hemorrhage (40%), CNS (20%), Other (40%)
- After 24 hours: Hemorrhage (20%), CNS (20%), Other (60%)
Major haemorrhage is variously defined as:

- Loss of >1 blood volume within 24 hours (around 70 mL/kg, >5 litres in a 70 kg adult)

- 50% of total blood volume lost in less than 3 hours

- Bleeding in excess of 150 mL/minute.

- A pragmatic clinically based definition is:
  - bleeding which leads to a SBP < 90 mm Hg or HR>110 bpm.
Understanding Haemostasis

• Primary haemostasis
  – Platelets plug formation
  – Immediately within seconds

• Secondary haemostasis
  – Plasma coagulation system
  – Fibrin
  – Strengthen primary hemostatic plugs
  – Occurs within minutes.
Primary hemostasis

3 critical events

- Platelet adhesions
- Granule release
- Platelet aggregation
Primary haemostasis

Platelets adhere to vWF-collagen
Secondary hemostasis

- Intrinsic/contact factor phase
- Extrinsic/tissue factor dependent pathway
- FX activation complex cascade
- Conversion of prothrombin to thrombin and stimulates fibrinogen to form fibrin monomer
Secondary haemostasis

TF-VIIa triggers Xa production
Thrombin generation proceeds on PL (platelet) surface

M. Laffan
Stable clot formation

fibrin

platelets

Stable fibrin-platelet clot is formed

M. Laffan
After clot formation

Thrombin binds to TM and activates PC and TAFI
Excess thrombin is neutralized by AT
Fibrinolysis is activated by plasmin (P)

M. Laffan
Fibrinolysis system

- Plasminogen
- Antifibrinolytic agents
- t-PA
- Urokinase
- PAI-1
- α2-Antiplasmin
- Fibrin(ogen)
- Fibrin(ogen) degradation products
Pathophysiology

The Lethal Triad

- Hypothermia
- Acidosis
- Coagulopathy

Bleeding

Crystalloid & PRBC Administration
Early trauma induced coagulopathy (ETIC) or Acute coagulopathy of Trauma

Historically, ETIC was attributed to crystalloid and RBC transfusion without administration of platelets, plasma, or both.

However, subsequent studies in both adult and paediatric trauma patients demonstrated that ETIC was present in 24%, and up to 56% in severely injured patients, usually within 30 min of injury, even before receiving RBC and fluid resuscitation.
Dilutional coagulopathy, activation of inflammatory mediators, hyperfibrinolysis, thrombocytopenia, and metabolic abnormalities (hypothermia, hypocalcaemia, and acidosis) all contribute to the pathogenesis of the haemostasis abnormality in massive haemorrhage.
Breaking the “Bloody Vicious Cycle”

- Control hemorrhage
- Use best possible resuscitation products
- Prevent hypothermia
- Prevent hemodilution
- Treat coagulopathy

Figure 12  The so-called bloody vicious cycle is a syndrome that has a multifactorial pathogenesis. The usual manifestations include coagulopathy, hypothermia, and metabolic acidosis.118
RATIONALE

• DIVC REGIME??

Damage Control! We need Massive Amounts of Blood!!
• In the past, trauma patients were given colloid or crystalloid fluid initially.

• Blood products were administered after 2 litre of fluid resuscitation, usually guided by laboratory results to keep haemoglobin >10 g/dl, platelet count >50000, and INR ≤1.5.
Recent studies with consideration of resuscitation, and better understanding the pathophysiology of ETIC has led to early use of RBCs, plasma, and platelets and reduced crystalloid use in resuscitation.
• The administration of RBC:plasma:platelets at 1:1:1 ratio was first proposed by the US military.

• Records of 466 MT patients treated at 16 major level 1 trauma centre between July 2005 and June 2006 were reviewed.
24 hr mortality of 466 massively transfused trauma patients seen in 2006 at 16 academic trauma centers by units of plasma to units of RBC ratio.
CONCLUSIONS: Conventional MT practices vary widely at Level 1 Trauma centers, while survival after massive transfusion differs greatly.

Survival in MT civilian patients is improved by increasing plasma and platelet ratios.

Prospective trials should aim for a 1:1 ratio of plasma: RBC.

Resuscitation with a 1:1:1 ratio of RBCs, plasma, and platelets is the recommendation of the Army Surgeon General and his Trauma Consultant.

However, these studies, and multiple others, are retrospective, and are affected by survival bias which is resulting from the fact that surviving patients are more likely to receive more plasma and platelets in relation to RBCs compared with nonsurviving patients because they lived long enough to receive those blood products.
In June 2011, the Canadian National Advisory Committee on Blood and Blood Products determined that the retrospective evidence available at the time was insufficient to recommend a RBC:Plasma:Platelet transfusion ratio of 1:1:1 as the standard of care for MT.

They also stated that subsequent retrospective studies would be unlikely to overcome survivorship bias and would not be able to make further contributions to the determination of the most effective ratio.
• Prospective observational study of all adults patients with major haemorrhages who survive >30minutes of admission to the hospital

• 1245 pts were transfused with 1 pint PC within 6 H
• 905 pts were transfused with 3pint PC within 24 H
• RBC:plasma and RBC:platelet ratios 1:1 or 1:2 cohorts

1 July 2009 - 15 Oct 2010
RESULTS

• In the first 6 hours, patients with ratio <1:2 has 3-4x likelihood to die from bleeding than patients with ratios of 1:1 or higher.

• Conclusions:
  • High plasma and platelets ratio early in resuscitation were associated with significant lesser mortality in patients transfused with 3 pint PC within 24H admission
The follow-up Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial is a randomized trial to evaluate ratios, MT patients receive either a 1:1:1 (higher ratio) or a 2:1:1 (lower ratio) RBC: Plasma: Platelet with primary outcome of survival, and also complications and length of hospital stay.

- No significant difference in mortality at 24H or 30 days
What are the 5 common causes of critical bleeding?

• Trauma
• Gastrointestinal bleeding
• Ruptured aortic aneurysm
• Obstetric haemorrhage
• Surgical procedures
Massive Blood Transfusion

- Transfusion of ≥10 red blood cell (RBC) units, which approximates the total blood volume (TBV) of an average adult patient, within 24 h,
- Transfusion of >4 RBC units in 1 h with anticipation of continued need for blood product support
- Replacement of >50% of the TBV by blood products within 3 h.
- Transfusion support to loss of blood >150ml/min

In Paediatric pts

- Transfusion of >100% TBV within 24 h,
- Transfusion support to replace ongoing haemorrhage of >10% TBV /min
- Replacement of >50% TBV by blood products within 3 h.
What is MTP?

- Designed to interrupt the lethal triad of acidosis, hypothermia and coagulopathy that develops with massive transfusion thereby improving outcome.

- The process of management of blood transfusion requirements in major bleeding episodes, assisting the interactions of the treating clinicians and the blood bank and ensuring judicious use of blood and blood components.

- Develop locally: agreed on specific guidelines that include clinical, laboratory, blood bank and logistic responses.
A practical guideline for the haematological management of major haemorrhage

Beverley J. Hunt,1 Shubha Allard,2 David Keeling,3 Derek Norfolk,4 Simon J. Stanworth,5 Kate Pendry6 and on behalf of the British Committee for Standards in Haematology

1Department of Haematology, GSTT, St Thomas’ Hospital, 2Department of Haematology, Royal London Hospital, London, 3Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals, Churchill Hospital, Oxford, 4Department of Haematology, Leeds Hospital, Leeds, 5NHSBT/Department of Haematology, John Radcliffe Hospital, Oxford, and 6Patients’ Clinical Team, NHSBT, Manchester, UK

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Algorithm for the management of major haemorrhage
(adapted from the BCSH Practical Guideline for the Management of Those With, or At Risk of Major Haemorrhage (2014) with permission)

Recognise blood loss and trigger major blood loss protocol

Take baseline blood samples before transfusion for:
- Full blood count, group and save, clotting screen including Clauss fibrinogen
- Near-patient haemostasis testing if available

If trauma and <3h from injury, give tranexamcic acid 1 g bolus over 10 minutes followed by IV infusion of 1 g over 8h (consider tranexamic acid 1 g bolus in non-traumatic)

Team leader to coordinate management and nominate a member of team to liaise with transfusion laboratory
- State patient unique identifier and location when requesting components
- To limit use of Group O NEG: until patient group known, use O NEG units in females and consider O POS in males
- Use group-specific blood as soon as available
- Request agreed ratio of blood components (e.g. 6 units RBS and 4 units FFP). Send porter to lab to collect urgently

If bleeding continues

Until lab results are available:
- Give further FFP 1L (4 units) per 6 units red cells
- Consider cryoprecipitate (2 pools)
- Consider platelets (1 adult therapeutic dose (ATD))

If lab results are available:

<table>
<thead>
<tr>
<th>IF</th>
<th>GIVE</th>
</tr>
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<tbody>
<tr>
<td>Falling Hb</td>
<td>Red cells</td>
</tr>
<tr>
<td>PT ratio &gt;1.5</td>
<td>FFP 15–20 mL/kg</td>
</tr>
<tr>
<td>Fibrinogen &lt;1.5 g/L</td>
<td>Cryoprecipitate (2 pools)</td>
</tr>
<tr>
<td>Platelets &lt;75×10⁶/L</td>
<td>Platelets 1 ATD</td>
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</tbody>
</table>

Continue cycle of clinical and laboratory monitoring and administration of ‘goal-directed’ blood component therapy until bleeding stops
Figure 7.2 Algorithm for the management of major haemorrhage
(adapted from the BCSH Practical Guideline for the Management of Those With, or At Risk of Major Haemorrhage)

1. Recognize blood loss and trigger major blood loss protocol
2. Take baseline blood samples prior to transfusion for:
   - Full blood count, Group and Save, clotting screen including Clauss fibrinogen or
   - Near-patient haemostatic testing if available
   - Give FFP:RBCs in at least 1:2 ratio
3. If trauma and < 3 h from injury, give tranexamic acid 1 g bolus over 10 min followed by IV infusion of 1 g over 8 h and FFP:RBC in 1:1 ratio; consider a dose of platelets. Consider tranexamic acid 1 g bolus in non-traumatic bleeding
4. TEAM LEADER to further co-ordinate management and nominate a member of team to liaise with transfusion laboratory
   - State patient unique identifier & location
   - Limit use of Group O RhD Neg RBC; until group known use O RhD Neg units in females < 50 years and consider O RhD Pos in males
   - Use group-specific RBC as soon as available
   - Request pre-agreed ratio of blood components, e.g., 4 units RBC and 4 units FFP; Send porter to laboratory to collect urgently
   - Consider blood warmer
Figure 7.2 Algorithm for the management of major haemorrhage
(adapted from the BCSH Practical Guideline for the Management of Those With, or At Risk of Major Haemorrhage)

IF BLEEDING CONTINUES

Until Laboratory results are available:
- Give FFP and red cells in a ratio of 1:1
- Consider Cryoprecipitate (2 pools)

When laboratory results are available:

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<td>Platelets 1 adult dose (order when &lt; 100 x 10^9/l)</td>
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Continue cycle of monitoring and giving appropriate blood components until bleeding ceases
RECOGNIZE AND TRIGGER

• When and who should initiate MTP.
• Identify the key role team leader and coordinator
• Often the most senior doctor directing resuscitation of the patient
• Responsible for communicating with laboratories and other support services to prevent time-wasting and often confusing duplicate calls
NOTIFY TRANSFUSION SERVICE

• For immediate transfusion, group O red cells should be issued after samples are taken for blood grouping and crossmatching.

• ABO-group-specific red cells can usually be issued within 10 minutes of a sample arriving in the laboratory.

• Fully crossmatched blood is available in 30 to 40 minutes after a sample is received in the laboratory.
LABAROTORY TESTING

- GXM and FBC
- DIC screen- PT/APTT, Se Fibrinogen, d-Dimer, FDP
- Se Calcium
- RFT/ ABG – acid base status
- Bedside haemostatic testing if available
- thromboelastography (TEG) and rotational thromboelastometry (ROTEM),
BLOOD PRODUCT PREPARATION AND DELIVERY

- Bleeding 2L or more
- Give upfront at least 1:2 ratio FFP:RBC
- 6-8u (15 - 20mls/kg) FFP
- 2- 4u emergency Group O (O negative)
- Females <50 years of age should receive RhD negative red cells to avoid sensitisation
• Use group specific red cells as soon as available

• GXM samples must be obtained and labelled before administration of Group O red cells.

• Regular haemostatic monitoring (FBC/PT/APTT/Fibrinogen) every 30-60m to assess severity and guide appropriate use of haemostatic blood components
Investigation results not available

- Consider another FFP:RBC in 1:1 ratio
- Consider hypofibrinogenaemia
- Consider cryoprecipitate 2 pools
  - 1 pool = 1u/10kg
- 10u contains 3-6g fibrinogen may increase plasma fibrinogen level by 1g/L
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When laboratory results are available:
Recommendation

In major haemorrhage aim to keep platelets $>50 \times 10^9/l$ (1B); we suggest that platelets should be requested if there is on-going bleeding and the platelet count has fallen below $100 \times 10^9/l$ (2C).
Recommendations

Adult trauma patients with, or at risk of, major haemorrhage, in whom antifibrinolytics are not contraindicated, should be given tranexamic acid as soon as possible after injury, at a dose of 1 g intravenously over 10 min followed by a maintenance infusion of 1 g over 8 h (1A).

The use of tranexamic acid should be considered in non-traumatic major bleeding (1B).

The routine use of aprotinin is not recommended (1B).

If trauma and < 3 h from injury, give tranexamic acid 1 g bolus over 10 min followed by IV infusion of 1 g over 8 h and FFP:RBC in 1:1 ratio; consider a dose of platelets. Consider tranexamic acid 1 g bolus in non-traumatic bleeding...
The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

The CRASH-2 collaborators*

- 10096 were randomized to TXA and 10115 were assigned to placebo

\[ p < 0.0001 \]. Early treatment (≤1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5.3%] events in tranexamic acid group vs 286/3704 [7.7%] in placebo group; relative risk [RR] 0.68, 95% CI 0.57–0.82; \( p < 0.0001 \)). Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4.8%] vs 184/2996 [6.1%]; RR 0.79, 0.64–0.97; \( p = 0.03 \)). Treatment given after 3 h seemed to increase
Tranexamic acid (TXA), were demonstrated to reduce mortality in trauma patients in both civilian and military settings, especially if given early in the resuscitation process (<3 h from injury to treatment, preferably within 1 h from injury).

In the military setting, the MATTERs study, mortality in the TXA group was lower than in the group not receiving TXA.
Conclusion:
In blunt trauma, RBC transfusion was significantly reduced with rFVIIa (estimated reduction 2.6 RBC units, \( p=0.02 \)) and the need for massive transfusion was reduced (14% vs. 33% of patients, \( p=0.03 \))
**Recommendation**

The use of rVIIa is not recommended in the management of major haemorrhage unless as part of a clinical trial (1D).

**Recommendation**

The use of PCC is not recommended in the management of major haemorrhage unless as part of a clinical trial (1D).
OTHERS IN A NUT SHELL

- Intravenous access – 2 large bore IVs and CVC
- FFP:RBC 1:1 ratio with expected loss
- Limit crystalloid - avoid dilutional coagulopathy
- Labs: GXM, CBC, Platelets, INR, PT, PTT, Fibrinogen, Electrolytes, BUN/Creatinine, ionized calcium
- Continuous monitoring: Volume Status, U/O, Acid-base status
- Aggressive re-warming.
- Prevent / Reverse acidosis
- Correct hypocalcemia: CaGluconate 1 gm iv 10 slowly (Target goal ionized calcium 1.2 – 1.3)
- Transfuse with unmatched group O RBCs on hand.
- Repeat lab testing to evaluate coagulopathy
Trauma patients in particular have a high rate of hospital-acquired venous thromboembolism (VTE) (Geerts et al, 1994) and there is also evidence from obstetrics that those who bleed excessively have a higher rate of VTE (Jacobsen et al, 2008). Current thromboprophylaxis protocols reduce the rate of VTE significantly and should be applied (NICE, 2010).

**Recommendation**

Thromboprophylaxis should be given after major haemorrhage and should be started as soon as possible after bleeding ceases (1A).
Transfusion reactions:

- **Allergic**: Range from simple urticarial to anaphylaxis. Steroid and diphenhydramine might be given to patients with allergic transfusion.

- **Haemolytic transfusion reaction (acute and delayed)**: Might be reduced by giving group O RBCs and AB plasma for emergency release of blood products.

- **Febrile non-haemolytic transfusion reaction**: Diagnosis of exclusion.
Immunological reactions:

- **Transfusion-related acute lung injury (TRALI):** Incidence can be reduced by transfusing male-only plasma.

- **Transfusion-related immunomodulation (TRIM):** Might be responsible for increased risk of bacterial infection.

- **Transfusion-associated graft vs host disease (Ta-GVHD):** Irradiation of cellular blood products in patients at risk (such as neonates and immunosuppressed patients) to prevent Ta-GVHD.

- **Post-transfusion purpura (PTP):** Can be treated with IVIg infusion, steroid, or plasma exchange.
Metabolic complications

• **Hypocalcaemia:** Because of citrate overload from rapid transfusion of blood products. (Each unit PRBCs – approx 3gm citrate)

• **Hypomagnesaemia:** Because of large volume of magnesium-poor fluid and citrate overload. Monitor ionized magnesium level and correct if necessary

• **Hyperkalaemia:** Because of haemolysis of RBC from storage, irradiation, or both.

• **Hypokalaemia:** Because of re-entry into transfused RBCs, release of stress hormones, or metabolic alkalosis. Monitor potassium level and correct if necessary
• **Metabolic alkalosis:** Because of citrate overload. Monitor acid–base status

• **Acidosis:** Because of hypoperfusion, liver dysfunction, and citrate overload. Monitor acid–base status

• **Hypothermia:** Because of infusion of cold fluid and blood products, opening of body cavities, decrease heat production, and impaired thermal control. Neonates and infants are at increased risk. Blood warmer should be used

• **Other:** infections
Massive transfusion protocol (MTP) template

Senior clinician determines that patient meets criteria for MTP activation

**Baseline:**
Full blood count, coagulation screen (PT, INR, APTT, fibrinogen), biochemistry, arterial blood gases

Notify transfusion laboratory *(insert contact no.*) to: ‘Activate MTP’

**Laboratory staff**
- Notify haematologist/transfusion sp
- Prepare and issue blood components as requested
- Anticipate repeat testing and blood component requirements
- Minimise test turnaround times
- Consider staff resources

**Haematologist/transfusion specialist**
- Liaise regularly with laboratory and clinical team
- Assist in interpretation of results, and advise on blood component support

**Senior clinician**
- **Request:**
  - 4 units RBC
  - 2 units FFP
- **Consider:**
  - 1 adult therapeutic dose platelets
  - tranexamic acid in trauma patients
- **Include:**
  - cryoprecipitate if fibrinogen < 1 g/L

*a Or locally agreed configuration

Bleeding controlled?

**YES**

**NO**

Notify transfusion laboratory to: ‘Cease MTP’

**Optimise:**
- oxygenation
- cardiac output
- tissue perfusion
- metabolic state

**Monitor** *(every 30–60 mins)*:
- full blood count
- coagulation screen
- ionised calcium
- arterial blood gases

**AIM FOR:**
- temperature > 35°C
- pH > 7.2
- base excess < –6
- lactate < 4 mmol/L
- Ca^{2+} > 1.1 mmol/L
- platelets > 50 × 10^9/L
- PT/APTT < 1.5 × normal
- INR ≤ 1.5
- fibrinogen > 1.0 g/L
The routine use of rFVIIa in trauma patients is not recommended due to its lack of effect on mortality (Grade B) and variable effect on morbidity (Grade C). Institutions may choose to develop a process for the use of rFVIIa where there is:

- uncontrolled haemorrhage in salvageable patient,
- failed surgical or radiological measures to control bleeding,
- adequate blood component replacement,
- pH > 7.2, temperature > 34°C.

Discuss dose with haematologist/transfusion specialist. rFVIIa is not licensed for use in this situation; all use must be part of practice review.

### Initial management of bleeding
- Identify cause
- Initial measures:
  - compression
  - tourniquet
  - packing
- Surgical assessment:
  - early surgery or angiography to stop bleeding

### Special surgical considerations
- If significant physiological derangement, consider damage control surgery or angiography

### Cell salvage
- Consider use of cell salvage where appropriate

### Dosage

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Platelet count &lt; 50 x 10^9/L</td>
<td>1 adult therapeutic dose</td>
</tr>
<tr>
<td>INR &gt; 1.5</td>
<td>FFP 15 mL/kg^a</td>
</tr>
<tr>
<td>Fibrinogen &lt; 1.0 g/L</td>
<td>cryoprecipitate 3–4 g^a</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>loading dose 1 g over 10 min, then infusion of 1 g over 8 hrs</td>
</tr>
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</table>

^a Local transfusion laboratory to advise on number of units needed to provide this dose

### Considerations for use of rFVIIa

The routine use of rFVIIa in trauma patients is not recommended due to its lack of effect on mortality (Grade B) and variable effect on morbidity (Grade C). Institutions may choose to develop a process for the use of rFVIIa where there is:

- uncontrolled haemorrhage in salvageable patient, and
- failed surgical or radiological measures to control bleeding, and
- adequate blood component replacement, and
- pH > 7.2, temperature > 34°C.

Discuss dose with haematologist/transfusion specialist. rFVIIa is not licensed for use in this situation; all use must be part of practice review.

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**ABG** arterial blood gas  
**INR** international normalised ratio  
**DIC** disseminated intravascular coagulation  
**RBC** red blood cell  
**BP** blood pressure  
**PT** prothrombin time  
**INR** international normalised ratio  
**FBC** full blood count  
**APTT** activated partial thromboplastin time  
**MTP** massive transfusion protocol  
**rFVIIa** recombinant activated factor VII
"Heads, you get a transfusion"

"Tails, you take a baby aspirin."
Summary

1. Hemorrhagic shock requiring MT is associated with high mortality.

2. MTP are associated with improved outcomes.

3. Early blood product transfusion with plasma:platelet:RBC ratio close to 1:1:1 is associated with reduced 6-hour mortality.

4. Goal-directed transfusion with TEG/TEM is feasible.

5. Fibrinogen concentrates, PCC and other factor concentrates require further study.

6. When hemorrhage control is complete, stop transfusion.
Thank you...