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Transfusion in massive haemorrhage in Neonates & Paediatrics (birth -16years)

Guideline Detail

Ownership Fran Hartley, Transfusion Practitioner (contact for review)
Dr Marina Karakantza, Consultant Transfusion Medicine
Dr Lawrence Miall, Consultant Neonatal Medicine
Dr Mike Richards, Consultant Paediatric Haematologist
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NB: Page 11 should be printed and displayed in relevant clinical areas.

Summary

In line with recent evidence on the benefits of using a higher plasma to red cell transfusion ratio in adults with massive haemorrhage, these guidelines extend this concept to neonatal and paediatric patients.

NB: It is not appropriate to use this guideline for the treatment of meningococcal sepsis or for treatment of controlled bleeding or correction of anaemia.

Aims

To improve outcome in neonatal and paediatric patients with massive haemorrhage through the use of appropriate and timely blood component transfusion.

To optimise blood component use and minimise wastage of blood components.

Objectives

To provide clear guidance to clinical teams managing neonatal and paediatric patients with massive haemorrhage on what to transfuse, when to give it and how to request it.

Background

This document must be used in conjunction with the:
LTHT Policy on Safer Transfusion,
http://nww.lhp.leedsth.nhs.uk/common/guidelines/detail.aspx?ID=1864
and the Policy for the use of written informed consent for transfusion of blood and blood components (section 6.7)
http://nww.lhp.leedsth.nhs.uk/common/guidelines/detail.aspx?ID=1217

Complications of major blood loss and massive transfusion may jeopardise the

survival of patients from many different specialities, and challenge haematological and blood transfusion resources.

An accumulating body of evidence and expert opinion supports earlier use of blood components in the resuscitation of patients with massive haemorrhage. **Red blood cells and fresh frozen plasma (FFP)/octaplasLG® should be given in a ratio of 1:1(1 dose:1 dose)**[1,2,3,4] Platelets and Methylene Blue (MB) cryoprecipitate are also necessary following large volume blood component resuscitation. It is vital that scarce blood component resources are used appropriately.

To improve confidence and maintain best practice when managing massive haemorrhage and to comply with NPSA SPN RRR017 which stipulates teams hold regular (at least annually) 'dry-runs' / 'drills' to practice individual team member roles in a massive haemorrhage scenario and to ensure a cohesive team approach in managing patient care.

A member of the clinical team should be nominated to act as co-ordinator responsible for overall organisation, liaison, communication and documentation during a massive haemorrhage episode. This is a critical role for a designated member of the permanent clinical staff.

Diagnosis

The massive haemorrhage guideline for neonatal & paediatric patients (birth -16 years) should be activated when:

There is active massive haemorrhage as defined by any of:

- a loss of one blood volume (80ml/kg) within a 24 hr period or,
- 50% blood volume loss (40ml/kg) within 3 hrs or,
- a rate of blood loss of 2 – 3ml / kg per minute

Or, signs of continuing shock following 40ml/kg crystalloid and/or colloid resuscitation for acute haemorrhage

AND a consultant with experience in the management of massive haemorrhage authorises its use – usually a surgeon, anaesthetist, intensivist, neonatologist or A&E consultant.

Investigation

This guideline does not cover the investigation of the source of the bleeding but assumes that all appropriate measures to identify and stop the bleeding are ongoing.

Treatment / Management

This guideline does not cover the management of bleeding in neonates or paediatrics per se but rather the appropriate use of blood components for the resuscitation of victims of massive haemorrhage. The guideline assumes that all necessary measures to identify and control bleeding sites are on-going. Furthermore effort must be directed at preventing hypothermia by the use of fluid warmers and external warming devices (e.g. Bair hugger or overhead warmer).

For Information:

octaplasLG®

- All patients born after 1/1/1996 should receive octaplasLG® instead of fresh frozen plasma. octaplasLG® is solvent detergent treated virally inactivated blood group specific pooled product and sourced from vCJD free countries and is used as a vCJD control measure for those not exposed to environmental factors related to vCJD

- octaplasLG® is used and administered in the same way as FFP but should be prescribed as octaplasLG

- **NB:** *pre-thawed* octaplasLG® is not stored in Blood Bank. It is a clinical decision whether or not the massive haemorrhage situation requires pre-thawed standard FFP or if can wait up to 30 minutes for octaplasLG® to be thawed.

octaplasLG® is obtained from Blood Bank by telephone detailing the patient's name, date of birth and ID number.

To help with the decision whether to use FFP or wait for octaplasLG®;

- octaplasLG® and FFP have similar constituents/properties
- octaplasLG® is virally inactivated and has a lower risk than FFP of transfusion reactions such as TRALI (Transfusion Related Acute Lung Injury)
- In the UK there is no risk ratio for developing vCJD from transfusion. Since the outbreak of vCJD there have been 177 cases of vCJD in UK, 4 of which were confirmed as transfusion transmitted

Δ see below for further information

NB: Both FFP and octaplasLG® once thawed must not be warmed further so must not be given via a Level One or Belmont infuser or other fluid warming device.

In event of massive haemorrhage:

Red cells: FFP (Fresh Frozen Plasma)/octaplasLG should be administered on a 1:1 ratio i.e. 1 dose:1 dose (20 ml/kg Red Cells to 20 ml/kg FFP/octaplasLG®)

1. Call blood bank (LGI: x23398 or SJUH: x65559). Give details (including "this is a neonatal / paediatric massive haemorrhage", urgency of request, full name, ID (NHS) number and Date of birth of patient & location). Request blood components by volume. The initial request will be for **red cells 20ml / kg & Fresh Frozen Plasma/octaplasLG® 20ml / kg** - you will need to calculate the volume to request e.g. for a 10kg child "I need 200ml red cells and 200ml FFP/octaplasLG®". Blood bank will not calculate blood volumes. Avoid any further calls to blood bank unless the situation changes.

2. Ensure CORRECTLY LABELLED patient ID wristband is in place (detailing the patient's NHS number as the primary identifier, first name, last name and date of birth. **No wristband, no transfusion**).

3. Ensure CORRECTLY LABELLED transfusion sample taken
    - Children >4months old a minimum of 2mls of blood in a 6ml EDTA sample tube,
    - Children less than 4months old, a 1-2 ml EDTA sample
        - Children <4 months old ensure a 6ml EDTA sample of Mums blood has previously been received in Blood Bank, if not, send one.
        - If Mum is not available and a sample of her blood has not previously been received in Blood Bank, send at least 2ml EDTA sample of baby's blood

Samples should be taken to Blood Bank on A-Floor of Jubilee Wing or, Blood Bank on Level Zero of Bexley Wing **by hand** as this is the fastest route and allows immediate confirmation that the sample is acceptable.

4. At the same time, take samples for FBC, clotting screen and U&E and send to LGI Blood Sciences Lab in Old Medical School or to the SJUH main Pathology laboratory on the link corridor between Chancellor Wing and Lincoln Wing. Send by Airtube or hand deliver.

5. On receipt of a correctly labelled sample, group-specific red cells can be available within 10-15 minutes

6. If immediate red cell transfusion is essential, use Emergency O D-negative blood (20ml/kg) from the Blood Bank supply or delivery suite (neonatal haemorrhage).

    Once the decision to activate the massive transfusion in neonates / paediatrics protocol has been taken, aim to avoid using additional crystalloid or colloid unless the patient is in shock.

    If there is a delay in blood arrival, use emergency O D-negative red cells. If this is the case the total number of mls/kg of O D-negative red cells must

count towards the total number of mls/kg red cells given in the first instance to maintain the 1 dose:1 dose ratio.

NB: SJUH: Remember to call for porters at the beginning of the emergency if you require them to collect / deliver samples or blood components, **OR** you may need to consider nominating a departmental member of staff to act as 'runner'.
LGI: Blood Bank will automatically arrange for porters to collect / deliver urgent blood components

7. Give red cells and FFP/octaplasLG® in a 1:1 ratio i.e. 1 dose:1 dose[1]. Administer red cells 20 ml / kg & FFP/octaplasLG® 20ml / kg. In a controlled situation, the rate of transfusion can be over minutes, depending on clinical picture. Administer FFP/octaplasLG® alongside red cells using separate IV access.

8. When initial resuscitation with red cells and fresh frozen plasma/octaplasLG® is complete, administer intravenous tranexamic acid (within 3 hours of the start of haemorrhage)[5] (dose depends on age & weight of the child, see appendix 1) over ten minutes then further doses every 8 hours as necessary, see appendix 1. Also, administer intravenous phytomenadione (vitamin K) to help prevent coagulopathy, (dose depends on age/weight of the child, see appendix 1)

9. After each transfusion of 20ml / kg of red cells, ionised hypocalcaemia may occur, especially if there is liver synthetic dysfunction because of the large citrate load from anticoagulated blood components. This may interfere with coagulation and have other adverse metabolic consequences. Ionised calcium can be reliably measured on a blood gas machine. This must be corrected by intravenous infusion of calcium gluconate. See appendix 1 for recommended dose of calcium gluconate, this dose should be followed by repeat of the assay. (See appendix 2 for further risks of transfusion).

10. After one 80ml / kg total volume (crystalloid/ colloid/ red cells/ FFP/ octaplasLG®) or, 20 ml / kg red cells has been given **AND** there is still evidence of continuing haemorrhage, the senior clinician must decide whether further transfusion is required. Contact blood bank as soon as this decision is made and request components outlined below in point 11.

11. After initial resuscitation, platelets and MB cryoprecipitate must be considered if active bleeding persists. Appropriate aliquots to be transfused are as follows[1]:

    - RBCs 20 ml/kg aliquots (maximum 4 adult units), O D-negative or ABO and D-specific (ideally, cross-matched)
    - FFP/octaplasLG® in 20 ml/kg aliquots (maximum 4 adult units)
    - Platelets in 15 ml/kg aliquots (maximum 1 adult therapeutic dose) to

be considered after every 40 mL/kg RBCs

- MB Cryoprecipitate 10 ml/kg (maximum 1 adult therapeutic dose)

These aliquots should be repeated in recommended 1:1(i.e. 20 ml/kg Red Cells to 20 ml/kg FFP/octaplasLG® to 15ml/kg Platelets to 10ml/kg MB Cryoprecipitate) ratio as necessary until bleeding is controlled. Once laboratory parameters are available ratios should be modified accordingly.

The therapeutic aims should be:

- Hb 80 g/L
- Fibrinogen >1.5 g/L
- PT ratio <1.5
- Platelets >75 x 109/L.

Careful monitoring for adequacy of resuscitation and for circulatory overload is essential.

In order to prevent over-transfusion of blood components all prescriptions should be ordered and prescribed in millilitres rather than units. The maximum prescribed volume should not be greater than the volume for equivalent adult transfusions.

12. Details of the patients receiving any emergency O D-negative Red Blood Cells (RBC) used must be communicated to Blood Bank as soon as possible. This will also inform them of the need to replace O D-negative units as necessary.

13. Any unused blood components MUST be returned to blood bank immediately

14. All red cells received in areas with a satellite blood fridge must be scanned into the blood fridge. If blood arrives in a cool box it should be kept in the cool box in which it arrives for up to the maximum length of time stated on the transport slip. Each blood unit should be removed and used one at a time, between each removal ensure the lid is securely positioned on the cool box at all times. Platelets, FFP/octaplasLG®, MB cryoprecipitate MUST NOT be stored in a cool box. See Safer Transfusion Policy: http://nww.lhp.leedsth.nhs.uk/common/guidelines/detail.aspx?ID=1864

15. All blood components must be recorded on a transfusion prescription and fated (for “traceability”) using the Autofate system or by signing and sending the manila tag attached to each blood component to the issuing blood bank. See Safer Transfusion Policy: http://nww.lhp.leedsth.nhs.uk/common/guidelines/detail.aspx?ID=1864

16. Patients on warfarin with significant bleeding should be given 25 international units / kg of intravenous Octaplex (requested on the Octaplex

request form: http://lthweb/sites/hospital-transfusion-team/how-to-order-blood-and-blood-products/how-to-order-blood-and-blood-products) - see appendix 1 and assuming they do not have an absolute contraindication to reversal. Do not wait for an INR result before giving the Octaplex. Remember that Octaplex has a short half life (4-6 hours)

17. Successful patient outcome requires prompt action and good communication between clinical specialties, diagnostic laboratories and blood bank staff

18. All activations of the massive transfusion protocol in neonates and paediatrics must be reviewed as part of the departmental clinical governance procedure. See below re: de-briefing.

19. In a life threatening massive haemorrhage do not wait to obtain written consent for use of blood components. However it is good practice to gain verbal consent at the earliest opportunity. If parents have specifically objected to use of blood components (e.g. on religious grounds) then you must act in what you consider to be the best interests of the patient. See Written Informed Consent for Transfusion Policy: http://nww.lhp.leedsth.nhs.uk/common/guidelines/detail.aspx?ID=1217

Δ For Information: The currently imported FFP by the National Blood Service is a "single donor" blood component produced from US male donors. It is treated with methylene blue and light as a viral inactivation method and is primarily intended for use in patients born since Jan 1st 1996
Sixteen of the Member States of Council of Europe employ Pathogen Reduced technologies for plasma while seven have introduced a universal pathogen plasma inactivation practice. The most frequently used PR technology is the Solvent Detergent (SD) treatment.
In SHOT report 2011, the estimated risk of acute reaction to octaplas was 1 to 24,809 while that of severe reactions was 1 in 86.832. The rate of acute reaction to octaplas was significantly lower to standard FFP (p=0.006), while the rate of severe reactions was also lower but did not reach statistical significant.

Provenance: Fran Hartley, Transfusion Practitioner
Dr Lawrence Miall, Consultant Neonatal Medicine
Dr Marina Karakantza, Consultant Transfusion Medicine
Dr Mike Richards, Consultant Paediatric Haematologist

Clinical condition: Massive haemorrhage

Target patient group: Neonatal and paediatric massive haemorrhage: Emergency Dept, Surgical haemorrhage, Neonatal Unit, Paediatric Intensive Care Unit

Target professional group (clinical competence): Medical / Nursing / Theatre / Laboratory staff involved in the management of massive haemorrhage

References / Evidence Bases:

1. New HV et al. Guidelines on transfusion for foetuses, neonates and older children. British Committee for Standards in Haematology 2016 British Journal of Haematology v175, Issue 5 p784–828 (for massive haemorrhage

see section 5): http://onlinelibrary.wiley.com/doi/10.1111/bjh.14233/full

2. Johansson PI, Stensballe J. Hemostatic resuscitation for massive bleeding: the paradigm of plasma and platelets - a review of the current literature. Transfusion 2010 v50 p701-710

3. Shaz BH, Dente CJ, Nicholas J et al. Increased number of coagulation products in relationship to red blood cell products transfused improves mortality in trauma patients. Transfusion 2010 v50 p493-500

4. Pham HP, Shaz BH. Update on massive haemorrhage. Br. J. Anaesth. 2013, 111 (suppl 1): i71-i82. doi: 10.1093/bja/aet376

5. Crash 2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010 DOI:10.1016/S0140-6736(10)60835-5

6. Royal College of Paediatrics & Child Health: Evidence Statement Major Trauma & the use of Tranexamic Acid in Children, Nov 2012 http://www.rcpch.ac.uk/child-health/childrens-medicines/childrens-medicines

7. National Patient Safety Agency: Rapid Response Report, NPSA/ 2010/RRR 017

All uses of this guideline will be audited internally and by the Hospital Transfusion Team.

Evidence level:

B. Robust experimental or observational studies

De-briefing

It is recommended that the clinical areas involved hold a joint 'de-brief'/audit after each massive haemorrhage case to establish any learning points and/or if any changes in practice are required to improve the outcome in future massive haemorrhage situations. The de-brief should be initiated by the Consultant in charge and/or the Hospital Transfusion Team. Feedback on any lessons learned will be circulated to relevant stakeholders by the Consultant in charge and/or the Hospital Transfusion Team.

The de-brief group should consist of all key stakeholders including representation from the Hospital Transfusion Team and Transfusion lab to enable a full and robust analysis of the approach to the massive haemorrhage case.

Appendix 1

Tranexamic Acid[5,6]

Loading Dose – 15mg/kg (max 1g) diluted in a convenient volume of Sodium Chloride 0.9% or Glucose 5% and given over 10 minutes

Maintenance infusion: 2mg/kg/hour. Suggested dilution 500mg in 500ml of sodium chloride 0.9% or glucose 5% given at a rate of 2mls/kg/hour for at least 8 hours. The infusion should be stopped if investigations show that no significant bleeding has occurred.

MAXIMUM infusion dose of 1g

Contraindications:

Relative (assess risk vs benefit on an individual patient basis). If there is a realistic suspicion of significant bleeding the benefits will most likely outweigh the risks.

- Patients with previous deep vein thrombosis (DVT), pulmonary embolism (PE) or arterial thrombosis
- History of convulsions
- Patients with indwelling cardiac stent
- Severe renal impairment due to risk of accumulation -the risk of accumulation even in severe renal impairment is very slight (see National Poisons Information Service Toxbase).

Absolute

- Hypersensitivity to tranexamic acid or any of the ingredients
- Greater than 3 hours between time of injury and initial bolus dose

Tranexamic acid is associated with an increased risk of thrombosis. However in the CRASH 2 study the treatment group had a lower incidence of thrombotic events. The risks are felt to be very small.

Calcium Gluconate: by slow intravenous injection over 5-10 minutes.

Neonate (less than 1 month): 0.11 mmol / kg (0.5mL/kg of calcium gluconate 10%)

Aged 1 month – 16 years: 0.11 mmol / kg (0.5mL/kg of calcium gluconate 10%) -- maximum dose of 4.5 mmols (20mL of 10% calcium gluconate)

Phytomenadione (Vitamin K): by slow intravenous injection

Neonate (less than 1 month): 1mg as a single dose

1month - 18 years 250-300 micrograms/kg (max 10mg) as a single dose

Octaplex (Prothrombin Complex Concentrate): by slow intravenous injection.

Dose: 25 international units / kg (requested from blood bank on an Octaplex request form).

N.B.: The only indication to use Fresh Frozen Plasma (10-20 ml/kg) to reverse warfarin is if octaplexLG® is not available.

Appendix 2

Risks of massive transfusion

Clinicians should be aware that there are risks associated with massive transfusion and blood component therapy; including:

- Incorrect Blood Component Transfused (IBCT)
- Transfusion Associated Circulatory Overload (TACO)
- Transfusion Related Acute Lung Injury (TRALI)
- Immune complications and acute reactions
- Hyperkalaemia due to high extracellular potassium in stored red cell units and ionised hypocalcaemia due to citrate toxicity especially if there is liver synthetic dysfunction. This may interfere with coagulation and have other adverse metabolic consequences. It cannot be diagnosed from a routine plasma calcium measurement but many modern blood gas analysers accurately measure ionised calcium, or send a blood sample to the Clinical Biochemistry laboratory for analysis. This may be corrected by slow intravenous bolus of calcium gluconate.

All suspected transfusion reactions MUST be reported to the Hospital Transfusion Team immediately to comply with MHRA investigation & reporting requirements.

Algorithm for the Generic Transfusion Management of Neonatal/Paediatric Massive Haemorrhage

-Adapted from BCSH Guidelines (2016): Guidelines on transfusion for foetuses, neonates and older children

Recognise blood loss and trigger massive haemorrhage protocol:

- the loss of one blood volume (80 ml/kg) within a 24 hour period or
- 50% blood volume loss (40 ml/kg) within 3 hours or
- a rate of loss of 2-3 ml/kg per minute

AND a consultant with experience in the management of massive haemorrhage authorises its use

Contact Key Personnel as appropriate e.g. Duty or On-Call Consultant caring for the patient, Anaesthetist, Interventional Radiologist, Endoscopist, Haematologist (if clotting is a concern)

Team Leader to co-ordinate further management and appoint 1 person to liaise with Blood Bank
LGI: 23398 (24h) or 22413 (9-5pm), SJUH: 65559 (24h) or 67513 (9-5pm)

State: **"this is massive neonatal/paediatric haemorrhage"** and give the patient's name, date of birth and ID Number

- Inform Blood Bank of the **TOTAL VOLUME of mls of red cells/octaplasLG®/FFP required** (in a ratio of 20mls/kg red cells to 20mls/kg octaplasLG®/FFP) and to where you want the blood components issuing
- Use group-specific RBC as soon as possible

NB: SJUH: on CARPS make an 'urgent' request for blood collection, LGI: blood will be delivered

Send CORRECTLY LABELLED baseline blood samples prior to transfusion for:

- Full blood count, Crossmatch, Clotting screen including Clauss Fibrinogen, U&E, LFT, Calcium, ABG

Administer RBC:FFP/octaplasLG® in a ratio of 1 dose:1 dose

(NB: Include any O D-negative used in the initial total ratio & inform Blood Bank when used)

NB: octaplasLG® should be used for patients born after 1/1/1996 but is NOT stored pre-thawed, it is a clinical decision whether or not to wait for thawing

Prevent hypothermia: use fluid warming device / keep the patient warm

Administer I.V. Tranexamic Acid: Loading Dose – 15mg/kg (max 1g) diluted in a convenient volume of Sodium Chloride 0.9% or Glucose 5% and given over 10 minutes within 3 hours of start of haemorrhage. Maintenance infusion: 2mg/kg/hour. Suggested dilution 500mg in 500ml of sodium chloride 0.9% or glucose 5% given at a rate of 2mls/kg/hour for at least 8 hours.

ADMINISTER I.V. VITAMIN K by slow intravenous injection: - Neonate (less than 1 month): 1mg as a single dose **or** 1month - 18 years 250-300 micrograms/kg (max 10mg) as a single dose

IF BLEEDING CONTINUES

These aliquots should be repeated in the recommended 1(dose):1 (dose) ratio i.e.

- 20 ml/kg Red Cells to
- 20 ml/kg FFP/octaplasLG® to
- 15ml/kg Platelets to
- 10ml/kg MB Cryoprecipitate

Repeat as necessary until bleeding is controlled. Once laboratory parameters are available ratios should be modified accordingly.

After each transfusion of 40ml /kg of red cells, ionised hypocalcaemia may occur. This can be corrected by intravenous infusion of calcium gluconate: appendix 1

Ionised Calcium can be checked with an appropriate blood gas sample (venous, capillary or arterial); ideally an Hb measurement should also be monitored.

Stand Down:

- Inform Blood Bank
- Return unused blood components
- Fate blood units.

Continue cycle of monitoring and giving appropriate blood components depending on laboratory results until bleeding stops.

Aims for Therapy:

Hb	80 g/L	**Fibrinogen**	>1.5g/L
Platelets	>75 x 10^9 /L	**Ca** $^{2+}$	>1 mmol/L
PT ratio	< 1.5	**pH**	> 7.35 (on ABG)
APTT ratio	<1.5	**Temp**	>36°C

Monitor for hyperkalaemia

Glossary

Activated Partial Thromboplastin Time (APTT) - a laboratory test that measures the activity of clotting factors in the intrinsic pathway of coagulation. It is commonly prolonged in DIC and following dilution of normal clotting factors by massive red cell transfusion.

Disseminated intravascular coagulation (DIC) occurs when there is generalised activation of the coagulation and fibrinolytic pathways with consumption of multiple clotting factors and platelets. Common causes include sepsis and traumatic tissue injury. The laboratory profile typically includes prolongation of both the Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT), reduced plasma fibrinogen level and elevation of D-dimer (a breakdown product of fibrin clots). There is often thrombocytopenia due to consumption of platelets and evidence of red cell fragmentation on the blood film. Decompensated DIC may be associated with clinical signs of both bleeding and thrombosis in the same patient.

FFP - Fresh Frozen Plasma - obtained from normal blood donors and used as a therapeutic source of clotting factors.

Prothrombin Time (PT) - a laboratory test that measures the activity of clotting factors in the extrinsic pathway of coagulation. It is commonly used to monitor warfarin therapy and is often prolonged in liver disease and DIC and following dilution of normal clotting factors by massive red cell transfusion.

Prothrombin Time Ratio (PT Ratio) - the ratio of the patient's PT to the PT of normal plasma. It provides a measure of the degree of clotting abnormality.

Thrombocytopenia - a reduction in the peripheral blood platelet count (normally 150-400x10(9)/l). A level of 75x10(9)/l is adequate for most surgery and is the minimum target for patients requiring massive transfusion or bleeding from DIC. Requests for platelet transfusion therapy are initiated at 100x10(9)/l in patients with massive bleeding (predictable when 2 blood volumes have been replaced by red cells and plasma transfusion) as platelets have to be ordered from the Regional Blood Transfusion Centre.