ORH Radcliffe Hospitals NHS Trust
Guidelines for the transfusion management of massive bleeding

Definitions of massive bleeding

- 50% loss of blood volume within 3 hrs,
- Blood loss at a rate of loss of 150mL per minute.

Examples of clinical features associated with massive blood loss are:

- Profound shock e.g. due to blunt or penetrating trauma
- Systolic blood pressure lower than 70mm Hg on admission or less than 90mm Hg after initial fluid challenge

Transfusion resuscitation in adults with major bleeding due to trauma

Alongside planning for damage control resuscitation/surgery and urgent radiological investigations/interventions, the flow chart on the next page illustrates one recommended strategy for transfusion support in acute major bleeding due to trauma. Although the evidence base for the use of any specific ratios of blood components is poor, the rationale for early treatment with plasma appears appropriate and is being used in many hospitals.

Transfusion resuscitation in adults with major bleeding not associated with trauma e.g. medical, surgical or obstetric patients

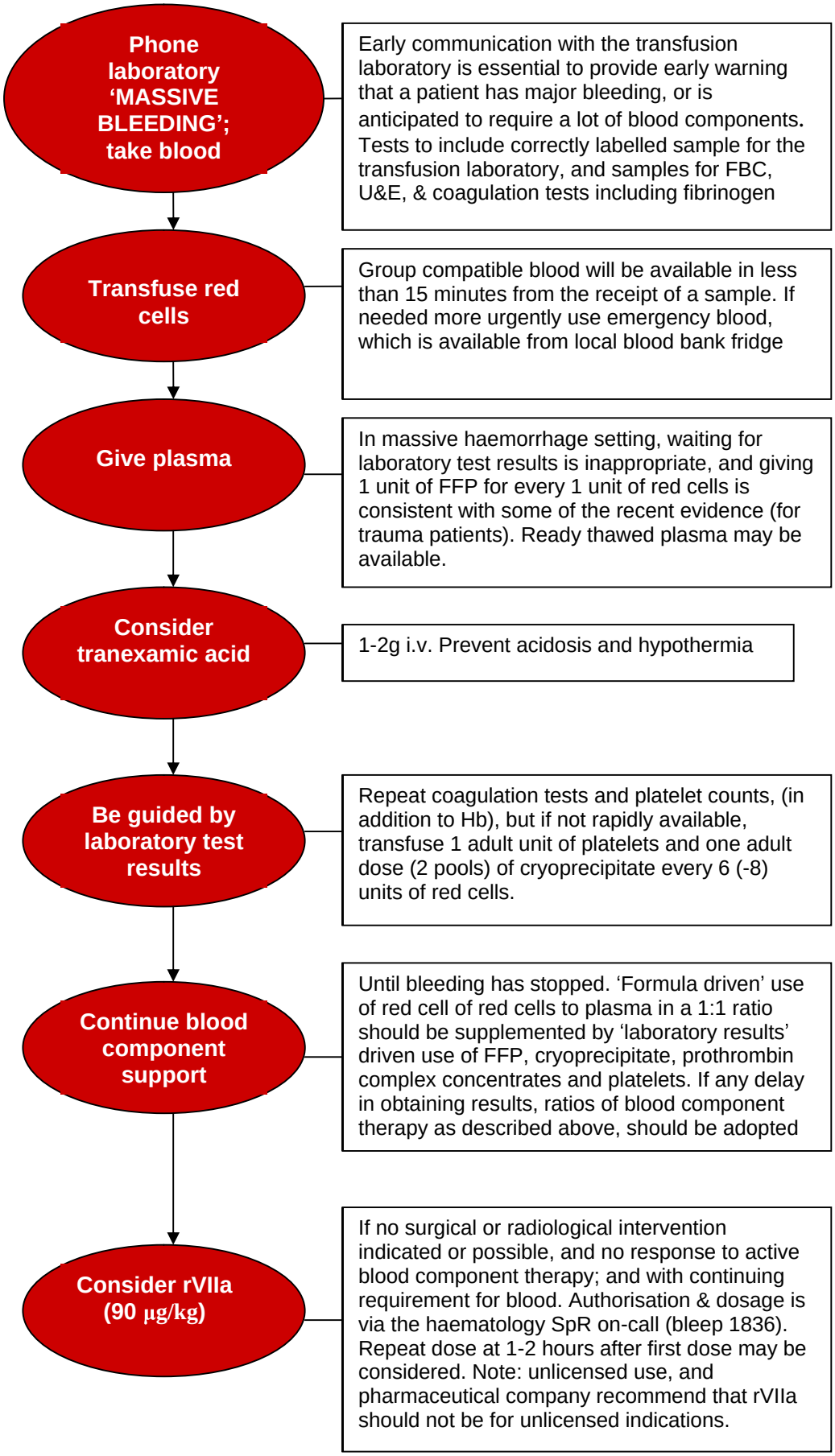
The principle of early use of plasma has not been evaluated in these patients groups, but it seems appropriate for cases of major acute life-threatening bleeding. However, the majority of patients in these settings (including surgical patients who also receive cell salvaged blood) require large volume (not 'massive') transfusion characterised by steady and on-going replacement of blood volume over 24 hrs. These patients may not be shocked, and the recommendation for early use of plasma as described above, in this type of controlled setting is inappropriate. Additional blood component therapy should be guided by regular laboratory test results (or near patient results) for coagulation tests and platelet counts.

In the patients described above, it is essential for early recognition of major blood loss and effective action to prevent shock and its consequences. Avoidable deaths of patients with major haemorrhage are well recognised, and locally agreed guidelines such as those described in this document are needed to ensure effective management.

Blood components carry serious risks e.g. acute lung injury, and are also a scarce resource. Excessive use can mean fewer components are available for other patients.

Useful contact numbers

1. **Blood Transfusion Laboratory**
    a. **JR and Churchill sites:**
        i. **Routine hours (M-F 08.30-17.00) extension 20339**
        ii. **Out of routine hours : bleep 1719**
    b. **Horton site**
        i. **Routine hours (M-F 09.00-17.30) extension 29236**
        ii. **Out of routine hours : via switchboard**
2. **Haematology/transfusion SpR**
        i. **Routine hours (M-F 08.30-17.00) bleep 4366 or call 07764 280706 – the transfusion registrar may be available to attend patients requiring massive transfusion once contacted**
        ii. **Out of routine hours: bleep via switchboard**
3. **Cell Salvage Team via bleep (routine hours only)**


Phone laboratory 'MASSIVE BLEEDING'; take blood
Early communication with the transfusion laboratory is essential to provide early warning that a patient has major bleeding, or is anticipated to require a lot of blood components. Tests to include correctly labelled sample for the transfusion laboratory, and samples for FBC, U&E, & coagulation tests including fibrinogen
Transfuse red cells
Group compatible blood will be available in less than 15 minutes from the receipt of a sample. If needed more urgently use emergency blood, which is available from local blood bank fridge
Give plasma
In massive haemorrhage setting, waiting for laboratory test results is inappropriate, and giving 1 unit of FFP for every 1 unit of red cells is consistent with some of the recent evidence (for trauma patients). Ready thawed plasma may be available.
Consider tranexamic acid
1-2g i.v. Prevent acidosis and hypothermia
Be guided by laboratory test results
Repeat coagulation tests and platelet counts, (in addition to Hb), but if not rapidly available, transfuse 1 adult unit of platelets and one adult dose (2 pools) of cryoprecipitate every 6 (-8) units of red cells.
Continue blood component support
Until bleeding has stopped. 'Formula driven' use of red cell of red cells to plasma in a 1:1 ratio should be supplemented by 'laboratory results' driven use of FFP, cryoprecipitate, prothrombin complex concentrates and platelets. If any delay in obtaining results, ratios of blood component therapy as described above, should be adopted
Consider rVIIa (90 µg/kg)
If no surgical or radiological intervention indicated or possible, and no response to active blood component therapy; and with continuing requirement for blood. Authorisation & dosage is via the haematology SpR on-call (bleep 1836). Repeat dose at 1-2 hours after first dose may be considered. Note: unlicensed use, and pharmaceutical company recommend that rVIIa should not be for unlicensed indications.

Background

Trauma and massive bleeding - evidence

Evidence of clinical effectiveness of transfusion in massive bleeding consists largely of uncontrolled observational studies and consensus of expert opinion. The recommendations contained in these guidelines are therefore based on limited evidence. There is a need for controlled clinical trials in this important area of transfusion medicine. New developments, such as use of fibrinogen concentrate and prothrombin complex concentrate (PCC) will be described in updates of these guidelines, as appropriate.

Overall priorities in management

1. Communication

Early communication with a senior Biomedical Scientist (BMS) in the blood transfusion laboratory is essential to provide early warning that a patient has major bleeding, or is anticipated to require a lot of blood components. This protocol is activated by communicating to blood transfusion laboratory that a patient has 'MASSIVE BLEEDING'. In turn, the blood transfusion laboratory will inform either the haematology SpR covering transfusion, or one of the senior transfusion haematologists.

Early consultation with relevant surgical, anaesthetic and radiological colleagues is advisable and the importance of good communication and co-operation in this situation cannot be over-emphasised. Damage control resuscitation/surgery and urgent planning for any radiological investigations/interventions or surgery is a key factor in improving outcomes, but is beyond the scope of this document.

A member of the clinical team should be nominated to act as co-ordinator responsible for liaison with the blood transfusion laboratory. Responsibilities include ensuring the first blood samples are taken, including a correctly labelled sample for cross-match, and liaison with the transfusion laboratory. Such individuals may be required to act as an assistant porter to ensure rapid transfer of samples and blood components.

When the acute bleeding is under control, the co-ordinator will inform the blood transfusion laboratory, to 'stand down'.

2. Initial blood samples

Blood samples should be sent at the earliest possible opportunity for:

- blood grouping, antibody screening and crossmatching (EDTA tube, purple top)
- baseline blood count (EDTA tube, purple top)
- coagulation screen including fibrinogen estimation (Citrate tube, blue top, filled to line)
- biochemistry investigations (yellow top).

It is **essential** that patients are identified and that samples are labelled correctly. This hospital uses an electronic patient identification system, "Safe Tx", which should be used routinely when sending blood samples to the transfusion laboratory.

3. Restoration of circulating volume

Restoration of circulating volume is most effectively achieved by rapid infusion of (warmed) blood components or crystalloids or colloids, through large bore peripheral cannulae. A central line or interosseous needle may provide suitable alternative routes for fluid resuscitation.

But, the use of albumin and non-albumin colloids versus crystalloids for volume replacement has been the subject of debate following meta-analyses and clinical trials. In addition, concerns have been raised about the excessive early use of crystalloids. Therefore, current recommendations are now aimed at moving rapidly onto emergency red cell transfusion (see below) if there is bleeding and haemodynamic instability, with full 'up-front' use of blood components including FFP, platelets and cryoprecipitate, described below.

4. Transfusion of Red cells

Red cell transfusion is nearly always likely to be required when 30% to 40% blood volume is lost; whilst over 40% blood volume loss is immediately life-threatening. **Hypothermia** increases the risk of disseminated intravascular coagulation and other complications, and may be prevented by pre-warming of resuscitation fluids and the use of a temperature controlled blood warmer.

Blood loss is usually underestimated and it must be remembered that haemoglobin and haematocrit values do not fall for several hours after acute haemorrhage unless there has been volume replacement with fluids other than red cell concentrates.

Intraoperative blood salvage may be of great value in reducing requirements for allogeneic blood, but bacterial contamination of the wound is a relative contraindication. The cell salvage service is available within normal working hours (bleeps 4171 or 4169).

In an extreme situation it may be necessary to use Group O uncrossmatched red cells (emergency stock) if the blood group is unknown. Emergency red cell stocks are maintained in fridges located:

- JR site: Delivery Suite, Main theatres, West wing theatres and from the laboratory
- Churchill site: Porters lodge fridge
- Horton site: from the laboratory

If emergency stock is taken from a blood fridge, inform the laboratory to ensure it is replaced. Green tags on the emergency stock units must also be completed and returned to the laboratory.

In an emergency, premenopausal females whose blood group is unknown should be given ORhD negative red cells in order to avoid sensitisation and the risk of haemolytic disease of the newborn in subsequent pregnancy. It is acceptable to give ORhD positive cells to males and postmenopausal females of unknown blood group, and current stocks of emergency red cells may include both ORhD negative and positive red cells.

If the clinical status of the patient allows, fully compatible blood should be used. If this is not possible, red cells of the same group as the patient should be used as soon as the patient's blood group is known as group O blood is a scarce resource.

5. Administration of fresh frozen plasma (FFP) and cryoprecipitate

Ready thawed units of FFP are sometimes available in the transfusion laboratory at the John Radcliffe, to facilitate rapid collection without the need for controlled thawing. If not available, FFP will take 20-30 minutes to thaw from the time of request. In massive haemorrhage setting, waiting for laboratory test results is inappropriate, and giving 1 unit of FFP for every 1 unit of red cells is recommended.

The other main recognised delay in transfusion of FFP is transport, and for that reason, members of the attending clinical team may be expected to help act as porters, if the situation requires this.

Laboratory tests of coagulation should be monitored frequently. When dealing with an evolving process, or with concerns about the development of DIC, it is important to check parameters frequently (at least four hourly and after each therapeutic intervention) to monitor the need for and the efficacy of component therapy.

The level of fibrinogen falls first in massive bleeding, ahead of other labile coagulation factors. Although critical levels of 1g/L are often referenced in earlier guidelines, recent work suggests higher target levels may improve outcomes.

Although FFP alone, if given in sufficient quantity, may correct and improve fibrinogen and most coagulation factor deficiencies, large volumes may be required. If fibrinogen levels remain critically low despite FFP (<1.0 and possibly 2.0g/L), cryoprecipitate therapy must be considered. If laboratory results not rapidly available, transfuse one adult dose (2 pools) of cryoprecipitate every 6 (-8) units of red cells, and 1 adult unit of platelets every 6 (-8) units of red cells (see next section).

There is some evidence that fibrinogen levels fall rapidly in major obstetric bleeding and early use of cryoprecipitate is specifically recommended in these patients.

The role of fibrinogen concentrates and specific coagulation factor concentrates such as prothrombin complex concentrate PCC, in the setting of major haemorrhage is as yet unproven, although these products may have important advantages. Further clinical evaluations are required before their wider use will be considered in updated versions of these guidelines.

6. Administration of platelets

A platelet count of 50 x 10^9/L is to be anticipated when approximately two blood volumes have been replaced by red cells concentrates, but there is marked individual variation. In assessing the requirement for platelets, frequent measurements of the patient's platelet count may be necessary. Platelet function can also be expected to be abnormal in a case of massive transfusion.

Expert consensus suggests that platelets should not be allowed to fall below the critical level of 50 x 10^9/L in acutely bleeding patients. A higher target level of 100 x 10^9/L has been recommended for those with multiple high energy trauma or central nervous system injury. Empirical platelet transfusion may be required when platelet function is abnormal such as is found after cardiopulmonary by-pass or when a patient takes anti-platelet therapy.

If laboratory results not rapidly available, transfuse one adult unit of platelets every 6-8 units of red cells.

7. Use of rVIIa

A recombinant form of activated factor VII (rVIIa, NovoSeven, Novo Nordisc, Denmark) has been used for a number of years in the approved clinical setting to manage bleeding in haemophiliacs with inhibitory antibodies to factors VIII or IX. With greater knowledge of its mechanism of action has come the appreciation that rVIIa may enhance haemostasis at the local site of injury without systemically activating the coagulation cascade (and with the associated risk of wide spread thrombosis). However, a Cochrane systematic review indicated that evidence for effectiveness of rFVIIa as a more general haemostatic drug,

either prophylactically or therapeutically, remains uncertain. “Unrestricted, unevaluated use of rFVIIa outside licensed uses of rFVIIa does not seem justified on the basis of the RCTs identified and analysed, and the results of further ongoing studies are ideally required to clarify whether rFVIIa is effective, and the size of any effects.”

The pharmaceutical company now state: “***Safety and efficacy of NovoSeven have not been established outside the approved indications and therefore NovoSeven should not be used.*** When NovoSeven is administered to patients outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (5.6% in patients treated with NovoSeven versus 3.0% in placebo-treated patients) has been shown in a meta-analysis of pooled data from placebo-controlled trials conducted outside current approved indications in various clinical settings, each of these having distinct patient characteristics and hence different underlying risk profiles. Thromboembolic events may lead to cardiac arrest.”

Vials of rVIIa, will be stored in the transfusion laboratories on all sites (John Radcliffe, Churchill and Horton Hospitals) It can be requested by contacting the laboratory or technician on-call, who will record the name of the requester and check that these guidelines have been followed including authorisation (see below). Cross-charging of rVIIa will operate to the 62 clinical areas, as for all blood products.

Authorisation and guidance on correct dose of rVIIa will be through the on-call haematology SpRs who will liaise/inform their appropriate consultants as indicated. (Aim for 90mg/kg, but round up to next whole vial - 1mg, 2mg and 5mg vials are available from the blood transfusion laboratory: for example rVIIa dose by IV bolus - 55kg = 5mg, 55-75kg = 7mg, 76-100kg = 9mg, 101-120kg = 11mg). The primary role of this authorisation step is to offer advice and ensure that measures to correct patient factors such as acidosis and thrombocytopenia are corrected implemented before rVIIa is given (ie to minimise inappropriate requesting). The laboratories are not able to issue the product without this authorisation.

Because of the associated increased risk from thrombotic complications following rVIIa administration, its use should be considered more cautiously in the following patients:

- history of venous or arterial thrombosis,
- coronary artery disease
- cerebrovascular disease.
- caution should also be applied for patients with persisting haemorrhage and with established laboratory evidence of disseminating intravascular coagulation (because there is a generalised activation of the coagulation system and therefore a greater risk of thrombotic complications)

8. Laboratory tests

It is essential to send correctly labelled initial samples as soon as possible. Avoidable delays in provision of blood components continues to occur because initial samples for blood grouping, antibody screening and cross matching are incorrectly labelled.

Repeat testing as practical and at least every 4 hours, but if laboratory results not rapidly available, transfuse FFP, cryoprecipitate and platelets as advised in this protocol.

Results for arterial blood gas sampling may also be important in guiding on-going red cell transfusion support, and near-patient testing by thromboelastography is under evaluation at present.

9. Complications of massive bleeding and transfusion/fluid treatment

Use of blood components are associated with recognised risks e.g. transfusion related acute lung injury (TRALI), haemolysis. Blood must be used appropriately even in a massive transfusion setting.

Mis-labelling and incorrect administration of components continues to occur. It is essential to adhere to usual best practice for patient identification and sample labelling including the use of the electronic system for sample collection and blood administration.

Other risks such as hypothermia can be minimised by the use of fluid warmers and active patient warming. Biochemistry changes must be monitored, including for hypocalcaemia, hyperkalaemia, acid–base disturbances (e.g. metabolic alkalosis associated with administration of large volume of citrate containing red cells, metabolic acidosis or hyperlactataemia associated with tissue hypoperfusion, hyperchloraemic acidosis associated with the use of large volume chloride-containing crystalloids).

10. Monitoring and audit

Introduction of the protocol will be accompanied by a monitoring and auditing programme. Information will be gathered prospectively, to include:

1. appropriateness of activation of MASSIVE BLEEDING alert to the transfusion laboratory
2. collection of baseline demographic information on patients treated according to the protocol
3. blood component supply (eg detailing time from laboratory receipt of a correctly labelled specimen to availability of group-specific and fully cross matched blood), overall usage and any wastage.
4. patient outcome data
5. adverse events and incident report forms

Further Reading

1. British Committee for Standards in Haematology, Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. Br J Haematol. 2006;135:634-41
2. Stansbury LG, Dutton RP, Sterin DM et al. Controversy in trauma resuscitation: Do ratios of plasma to red cells matter? TMR 2009 255
3. Lin Y, Stanworth SJ, Birchall J, Doree CJ, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia (Cochrane Review). The Cochrane Database of Systematic Reviews. 2009 (Updated)

Version Control & Authors

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