Principles and Practice of Surgery

A Surgical Supplement to
DAVIDSON'S PRINCIPLES AND PRACTICE OF MEDICINE

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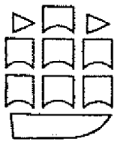

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9. Blood Transfusion

The administration of blood in medical practice has been on record for at least 400 years. Early efforts often ended in disaster, primarily because the concept of blood group specificity was unknown. The definition of human ABO blood groups by Landsteiner in 1901 led to the recognition of many other blood groups and to the provision of safe compatible blood. An important recent development has been the introduction of blood component therapy in which different parts of a donation of blood are separated and concentrated for administration.

EFFECTS ON BLOOD DURING STORAGE

As with all therapies, students must understand the basic properties of transfused blood. Particularly relevant are the changes which occur during storage.

Blood for routine transfusion is collected in citrate anticoagulant to which dextrose is added to prolong red cell viability. Many Blood Transfusion Services still use acid citrate dextrose (ACD); others add phosphate ions (CPD) or adenine (CPD-adenine) to further increase the life of the red cells. Approximately 425 ml of donated blood is added to 75–120 ml of anticoagulant mixture.

The changes which occur during routine storage at 2–6°C with ACD anticoagulant are summarised in Table 9.1. Red cell viability falls sharply after 4 weeks storage and for this reason the routine shelf-life of blood stored in ACD is 21 days (maximum permissible 28 days). Particular attention should be paid to the lability of certain haemostatic factors (notably platelets), to the increase in potassium and ammonia concentration in the plasma, and to the fall in pH during storage.

SEROLOGICAL CONSIDERATIONS

Recent increase in our knowledge of blood group serology, affecting red cells, white cells, platelets and plasma proteins, has made blood transfusion a complex and highly technical procedure. However, the student must be familiar with the basic principles for clinical practice.

RED CELL SEROLOGY

ABO system

The most important red cell antigens are of the *ABO blood group system*. An incompatible ABO blood transfusion can cause immediate and fatal intravascular haemolysis. This occurs because many individuals have circulating natural (allo-) antibodies to ABO red-cell antigens (Table 9.2). The group O patient is at highest risk because his plasma contains both anti-A and anti-B antibodies. As approximately half of the patients who require transfusion are likely to be group O, the potential danger of a blood transfusion is considerable.

Antigens of the ABO system are present on all cells in the body. As they affect histocompatibility they are taken into account when selecting donors for organ or marrow transplantation (see Ch. 14). Both A and B antigens have sub-groups (A_1, A_2,

Table 9.1 Mean changes in some characteristics of blood stored at 4 ± 2°C in ACD.

Parameter	Days stored			
	0	7	14	21
Red cell viability (%)	95	90	84	75
* Platelet viability (%)	95	0	0	0
† White cell viability (%)	95	0	0	0
‡ Coagulation Factor V and VIII (%)	95	30	30	30
Free haemoglobin (g/L)	0–0.10	0.25	0.50	1.0
Lactic acid (g/L)	0.20	0.70	1.20	1.40
pH	7.00	6.85	6.77	6.65
Sodium (mmol)	150	148	145	142
Potassium (mmol)	3.4	10	24	32
Ammonia (μg %)	50	260	470	680

* The fall in viability of platelets occurs in the first 48 hours.
† Figures refer to polymorphonuclear white cells: the fall occurs over the first 72 hours. A significant number of lymphocytes are viable at 21 days.
‡ All other coagulation factors are stable during storage.

Table 9.2 The antigens and antibodies in each of the four main groups of the ABO system.

Blood Group	Frequency in Population* (%)	Antigens on Red Cells	Natural ABO Antibodies	Compatible Donor Blood
O	50	Nil	Anti-A and Anti-B	*Only* O
A	35	A	Anti-B	A or O
B	10	B	Anti-A	B or O
AB	5	A and B	Nil	A, B, AB or O

* These frequencies differ in other counries and even slightly within the United Kingdom. Asian people have an incidence of group B which is between 30–40%. This can create problems in Caucasian communities with pockets of immigrants.

Notes:
1. REMEMBER — O — the universal donor, AB — the universal recipient.
2. REMEMBER — the plasma in the transfusion of donor blood is so dilute that it rarely causes agglutination of the recipient's cells.
3. REMEMBER — blood should never be transfused without careful cross-matching except in the most extreme emergency; incompatibilities other than those due to the ABO system may cause reactions or sensitisations.

A_3, B_1, B_2 etc), and occasionally blood of an exact sub-group is required.

Rhesus blood group system (Fig. 9.1)

This follows the ABO system in importance. There are five detectable antigens (D, C, c, E and e), but the most immunogenic, and therefore most relevant to transfusion, is D. For routine transfusions, only the D group is taken into account and patients and donors are classified as Rh(D) positive or Rh(D) negative; the most common combination of Rhesus antigens in Rh(D) negative individuals is cde.

The Rhesus system is important to the clinician for four reasons.

1. Although natural antibodies to the Rh antigen are rare, immune (iso-) antibodies can be generated which can cause compatibility problems and haemolytic reactions. These are usually less severe than from ABO incompatibility.

2. Rh(D) incompatibility is the most frequent cause of haemolytic disease of the new-born. *RhD*

RHESUS INCOMPATIBILITY

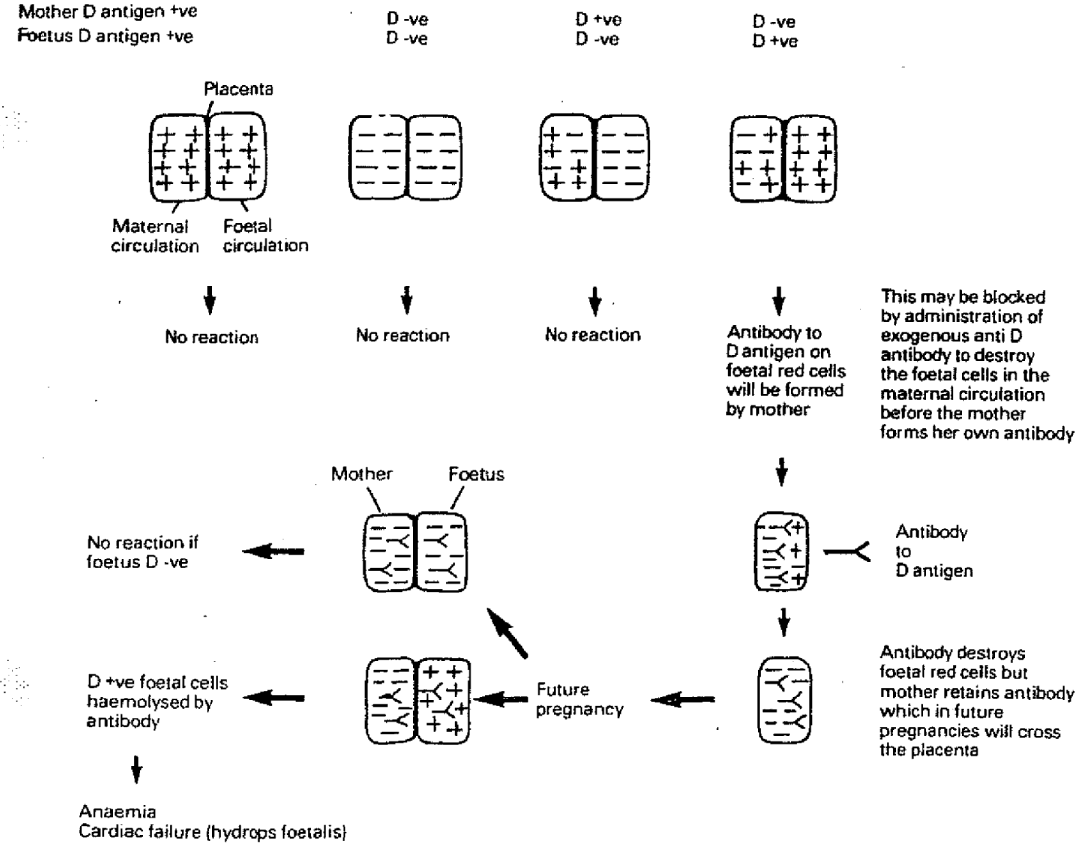

Fig. 9.1 RH incompatibility

negative women in the child-bearing age should not receive Rh(D) positive blood.

3. Patients with circulating anti-D (i.e., an Rh negative patient who has received Rh positive blood) must receive Rh(D) negative blood. This can be difficult to supply, particularly when the patient has a rare ABO group (see Table 9.3).

4. The most common identifiable antibodies in acquired (autoimmune) haemolytic anaemia are Rhesus in specificity. Serious transfusion problems are frequently encountered.

Table 9.3 Availability of ABO Rh(D) negative blood in typical Caucasian community.

O Rh(D) Negative	10%
A Rh(D) Negative	6%
B Rh(D) Negative	2%
AB Rh(D) Negative	0.5%

Other red cell antigens

Many other red cell antigen systems and specific antibodies have been identified, but their incidence is low. Such antibodies may cause clinical problems equal to those found with the Rh(D) system. Commonest are anti-E, anti-c and anti-e (of the Rh system), anti-K (Kell/cellano system), anti-Fy (Duffy system) and Jk (Kidd system). In such patients one must only give donations which do not contain the specific antigen.

The universal donor

With the discovery of the Rhesus blood group system the concept of the 'universal donor' was extended to group O Rh(D) negative rather than just group O. The apparent advantage was that 'universal donor' blood could be given safely without the need for grouping and crossmatching.

However, there are considerable disadvantages to the use of uncrossmatched group O Rh(D) negative blood. Antibodies to other antigen systems may be present and cause transfusion reactions; some group O donations have high natural titres of anti-A which if the recipient is group A cause acute haemolysis; group O Rh(D) negative blood is rare and is essential for the transfusion of Rh negative women in the child bearing age. It should be used as universal donor blood only in dire emergency. If there is a shortage of O Rh(D) negative blood, O Rh(D) positive may have to be used.

In less extreme conditions (see Table 9.4) it is acceptable to use uncrossmatched but group-specific (homologous) blood. In all other circumstances only crossmatched blood of the appropriate group should be used.

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Practical considerations (Fig. 9.2)

The house-surgeon need no longer be familiar with the techniques of providing compatible blood for individual patients. However, he must be familiar with some of the procedures used in the Blood Bank and the principles underlying them.

1. The major cause of incompatible blood

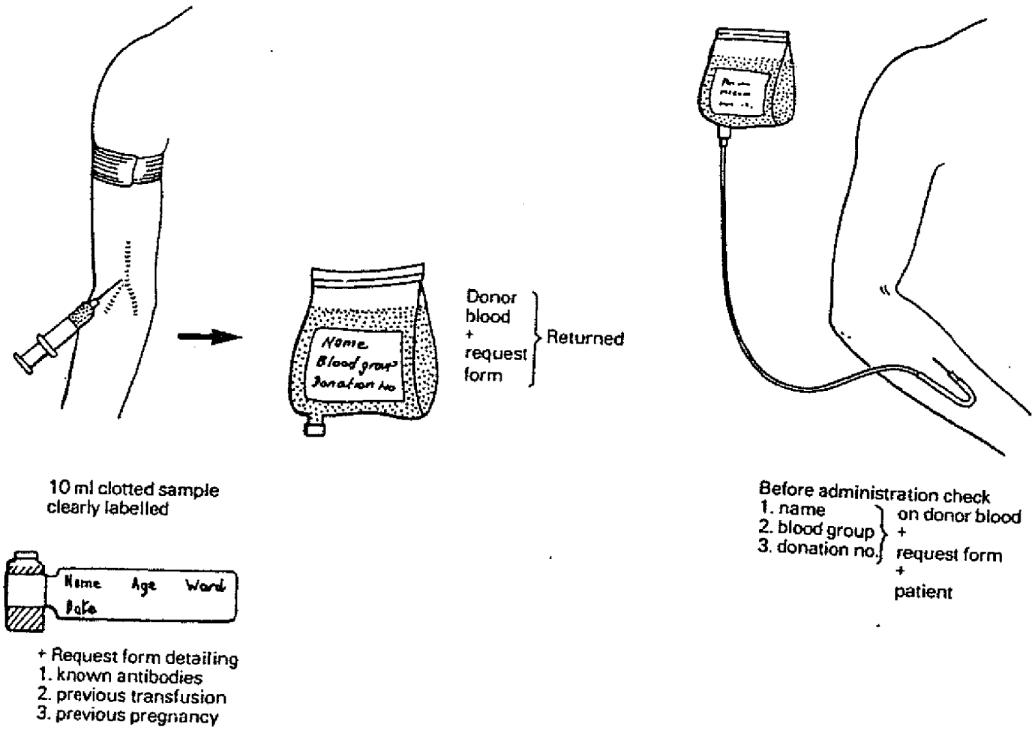

Fig. 9.2 Practical considerations

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Table 9.4 Response times* to requests for blood.

Time	Product/procedure	Comments
Immediate	Not crossmatched (O Rh(D) Negative Universal Donor)	Use only in extreme life-threatening haemorrhagic situations or when grouping and/or crossmatching facilities are not available (Obstetric Flying Squad)
20–30 min	Not crossmatched (Homologous blood ABO Rh(D) compatible)	Less extreme situations as described above. Also permissible in on-going massive transfusion when crossmatching becomes academic (after 12 donations administered in 6 hours)
1 hour (30 min in some Centres)	Emergency crossmatched	Limited technical procedures involved occasionally results in missing an antibody.
2–3 hours	Fully crossmatched	Detection of antibodies can lead to further delay to identify the antibody and provide compatible donations. This can take several hours, days or weeks, depending on the rarity of the antibody or antibodies.

* To these times must be added transport time, to and from the Blood Bank

transfusion is administration of wrong blood to the patient due to mistakes in documentation during the initial request (the blood in the tube does not correspond to the name on the label) or failure to check before administration that the *name, blood group* and *donation number* on every crossmatched donation corresponds exactly with those on the completed request form.

2. The house-surgeon should appreciate the time required to provide compatible blood for an individual patient (Table 9.4). He must also know the expected transport times and appreciate that these can vary in different localities.

3. Patients requiring repeated transfusions of blood require special consideration. Leucocyte, platelet and plasma protein antibodies apart (see below), red cell antibodies may be produced in the interval between the first and subsequent transfusions. A new serum specimen from the recipient must be provided each time a request is made. If during the administration of a transfusion compatible blood is held for more than 72 hours, a re-crossmatch should be requested against a fresh serum sample.

4. Delay in the provision of fully compatible blood can result from taking too small a sample of serum for cross-matching. For every unit requested at least 1 ml of blood is required. In practice it is advisable to take a 10 ml clotted sample: this will provide sufficient serum for rechecking should a transfusion reaction occur.

5. In requesting blood, particular attention must be paid to the labelling of specimens and informing the Blood Bank personnel of known pre-existing immune antibodies, pregnancies and previous transfusions. They are then alerted to potential difficulties. If problems are known to exist, early consultation with the Blood Bank staff will facilitate correct therapy.

WHITE CELL AND PLATELET SEROLOGY

Human white cells and platelets have genetically determined surface antigens which are part of the human leucocyte antigen (HLA) system. The HLA system is complex with a major histocompatability role in organ and marrow transplants. Antigens of the HLA system are not expressed on mature red cells but are found on reticulocytes. Other (non-HLA) antigens specific to neutrophils, lymphocytes or platelets have been recognised.

Routine blood transfusion, or pregnancy, can stimulate the development of leucocyte and/or platelet antibodies which may cause significant reactions during further transfusions. They may also impair the efficiency of subsequent transfu-

stons of white cells or platelets and the function of transplanted organs.

PLASMA PROTEIN SEROLOGY

Approximately one person in 2500 lacks IgA. If repeatedly transfused they may develop allo-antibodies directed against normal IgA, or against different determinants on the IgA molecule. Patients who have developed these antibodies may suffer reactions to subsequent transfusions of blood or blood products containing the specific plasma-protein antigen.

COMPLICATIONS OF BLOOD TRANSFUSION

The morbidity and mortality of blood transfusion may be greater than that of general anaesthesia (Fig.9.3). The list of potential complications is formidable:

Febrile reactions

Pyrogens and minor bacterial contamination used to be a common cause of febrile reactions; this is no longer the case. The occasional febrile reaction now seen is more likely to be due to interactions between pre-existing recipient antibodies and transfused leucocytes, platelets or immunoglobulins. These are usually minor but as some are severe and even fatal all should be investigated. A significant number remain unexplained. They are best managed by stopping the transfusion and the intravenous administration of an antihistamine (chlorpheniramine sulphate, 20 mg) and hydrocortisone (sodium succinate, 100 mg). Further transfusions should be similarly covered, filtered, washed or frozen/thawed/washed/red cells (products with reduced white cells, platelets and plasma protein) may be necessary for patients who require continued transfusion or who continue to react despite antihistamine cover.

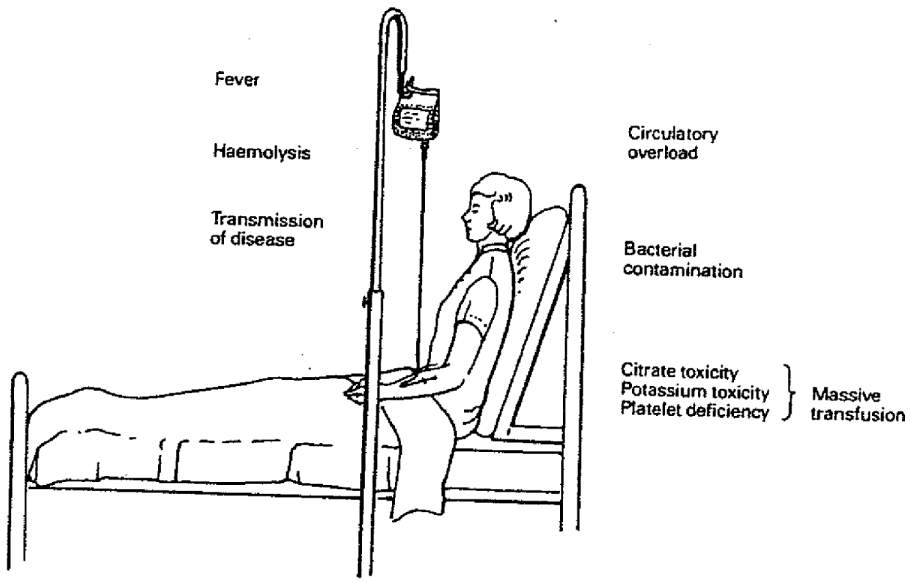

Fig. 9.3 Complications of blood transfusion

Bacterial contamination

Bacterial contamination of blood donations is rare. However, during donation a small number of skin bacteria can pass into the blood and if it is not stored at 4°C heavy growth may occur. Heavily ntaminated blood is almost black and on transrusion causes sudden and severe endotoxaemia, which is usually fatal. Treatment is by intravenous infusions of antibiotics to cover both aerobic and anaerobic organisms and other supportive measures (see shock). The offending blood must be returned immediately to the Blood Bank for investigation.

Circulatory overload

This complication occurs in severely anaemic elderly patients, particularly with cardiac insufficiency. Such patients should be transfused only with red cell concentrates. If blood loss and anaemia is not acute, only one unit of red cells should be given every 24 hours accompanied by 20 mg frusemide intravenously. In some patients xchange transfusion may be required.

Haemolytic reactions

The most common form of immune (non-haemolytic) transfusion reaction is due to incompatible leucocytes, platelets or immunoglobulins (see above). The most sinister are those due to ABO incompatibility. Less than 50 ml of ABO incompatible blood can give rise to sudden and severe back pain, marked dyspnoea and profound hypotension. Haemoglobinuria and haemoglobinaemia occur and the patient becomes icteric in 24 hours. Within one hour of transfusion, acute renal failure may have developed. Disseminated intravascular coagulation (DIC), initiated by antigen/antibody complexes formed on the red cell membranes, may cause a bleeding diathesis.

General anaesthesia may mask many of these signs and symptoms, but sudden unexplained hypotension is an important marker.

Most other antibodies do not cause intravascular haemolysis: the antibody-coated red cells are destroyed more slowly by the reticulo-endothelial system, principally spleen and liver. Jaundice usually develops, but renal failure and DIC are rare.

Massive haemolysis can follow administration of compatible blood which is heavily contaminated, accidentally frozen and thawed, or heated above 40°C.

It cannot be sufficiently stressed that *the most common cause of incompatible blood transfusions are mistakes made in the wards: errors in identification of crossmatching blood samples and/or failure to check blood prior to administration.*

Investigation and management of major intravascular haemolytic transfusion reactions are outlined in Table 9.5.

Transmission of disease

Transmission of viral hepatitis remains the most serious and frequent complication of the administration of blood and blood products. A survey in the United Kingdom, before hepatitis (B surface antigen) testing became routine, indicated that the morbidity and mortality were 27 and 8 respectively per 10 000 units transfused.

Viral hepatitis from blood transfusions rarely arises from hepatitis type A (infectious hepatitis), cytomegalovirus (CMV) and Epstein Barr virus (EBV).

Type B hepatitis virus remains an important cause but the major aetiological agent is unknown and currently called non-A, non-B hepatitis.

The best preventative measure is to avoid unneccessary transfusions.

All donations are now screened for hepatitis B virus, using the surface antigen (HBsAg) as a marker. This reduces the overall risk of hepatitis by about 25%. Two blood products only are without risk: albumin and immunoglobulins.

All donations are also screened for syphilis. As spirochaetes have limited viability, blood stored for more than 4 days at 4°C is safe. Other infectious diseases which can be transmitted by blood transfusion include brucellosis, toxoplasmosis, malaria and trypanosomiasis.

Recent studies have indicated that blood donations and some blood products may rarely transmit an infectious agent which gives rise to the development of severe (often fatal) acquired

Table 9.5 Management of intravascular haemolytic transfusion reactions.

Investigations	Therapy
1. Check for evidence of incompatible blood on bottle (bag) labels. Return suspect donation to Blood Bank for immediate investigation.	1. Stop transfusion.
2. Withdraw 30 ml blood and send to laboratories immediately. Inform Blood Bank medical staff.	2. Hydrocortisone 100 mg I.V.
a. Serological investigations at Blood Bank (10 ml)	3. Insert urinary catheter, empty bladder and monitor urine flow.
b. Blood Urea and electrolytes (10 ml)	4. 100 ml Mannitol (20%) and 100 ml of 0.9% saline.
c. Coagulation screen (10 ml)	5. 150 mg Frusemide I.V.
3. Electrocardiogram. ? evidence of hyperkalaemia.	6. If 2 hours after mannitol and saline the urine flow is less than 100 ml/h, then repeat 100 ml (20%) mannitol. If at the end of next 2 hours urine flow is less than 100 ml/h, assume acute renal failure and treat accordingly.
4. Coagulation and biochemical screens repeated 2–4-hourly until stabilised.	7. If evidence of hyperkalaemia (clinical, ECG or laboratory evidence) institute resonium/insulin/glucose therapy.
	8. If evidence of D.I.C., contact specialist for advice: patient may require systemic heparinisation.

* Every attempt must be made to avoid further blood transfusion until Blood Bank staff have checked compatibility of subsequent donations. In the meantime manage significant hypovolaemia with albumin solutions (SPPS), pooled plasma or artificial colloids.

immune deficiency (AIDS) in recipients. This problem is currently under intense investigation.

Massive transfusion (Fig. 9.4)

If four units of blood are transfused consecutively into patients at a rate in excess of 100 ml/minute complications may arise. These include:

Citrate toxicity. Patients who are hypotensive or have liver or renal damage fail to metabolise or excrete the large load of citrate in transfused blood. It combines with ionised calcium leading to muscle tremor, tetany and cardiac arrhythmias. Citrate is also cardiotoxic.

Potassium toxicity. Potassium leaks out of red cells during storage. Rapid administration of large volumes of old blood may elevate the serum potassium to cardiotoxic levels. This is particularly liable to occur in patients with renal damage or severe crush injuries with extensive muscle damage. Excessive hydrogen ions in stored blood potentiate this effect.

Platelet deficiency. Stored blood has few viable platelets. Massive transfusions may lead to dilution thrombocytopenia and bleeding.

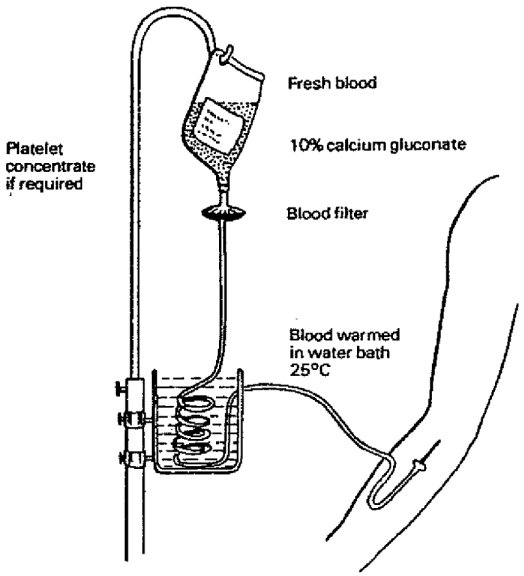

Fig. 9.4 Precautions with massive transfusions

These problems are prevented and/or treated by:

1. Warming blood (25°C) prior to transfusion. This will increase citrate metabolism and avoid the need for calcium adminstration. Otherwise, if more than 2 litres of blood have been administered, 10 ml of 10% calcium gluconate should be given for every two further units.

2. Using blood which is less than 5 days old and so reducing the risk of potassium toxicity.

3. Administering platelet concentrates if there is significant oozing due to failure of haemostasis.

Micro-aggregates of platelets and leucocytes are formed during the storage of blood and it has been suggested that when transfused in large amounts they may contribute to the adult respiratory distress syndrome. The use of in-line micro-aggregate blood filters has become popular but there is little evidence of their benefit, certainly in patients receiving less than 5 units of blood.

BLOOD PRODUCTS AND THEIR CLINICAL USES

The introduction of plastic blood bags, large capacity centrifuges and plasma fractionation have permitted the production of several specific therapeutic products from blood donations. Low volume and highly concentrated derivatives, e.g. platelet and coagulation factor concentrates, can provide effective and specific treatment without the risk of circulatory overload. The use of such *blood component therapy* also reduces waste and increases safety (Table 9.6).

BLOOD REPLACEMENT

Acute haemorrhage

An average healthy adult can lose 500 ml of blood rapidly without ill effect. Provided circulatory

Table 9.6 Examples of products which contribute to blood component therapy

Blood product		Shelf life	Main indications
Whole blood		21 days (ACD) 28 days (CPD)	Severe life-threatening haemorrhage: component of a transfusion policy (see text)
Red cell concentrates		As Whole Blood	All routine transfusions; and part of a transfusion policy (see text)
White cell concentrates		12 hours	Severe leucopenia associated with life-threatening infection; ? to cover surgery in such patients
Platelet concentrates		72 hours	Non-immune severe thrombocytopenia
Transfer factor		5 years	Chronic mucocutaneous candidiasis
Interferon		Not established	Virus infections and malignancy — not yet defined
Albumin	5%	4 years	Acute volume expansion
	15–20%	4 years	Severe symptomatic hypoproteinaemia
Factor VIII	Cryoprecipitate	6 months	Haemophilia A management. von Willebrand's Disease. Hypofibrinogenaemia. Factor VIII Deficiency.
	AHF	1 year	Haemophilia A management
Factor IX	II,VII,IX,X	2 years	Haemophilia B factor replacement. Acquired deficiencies (liver disease, oral anticoagulant reversal)
	II,IX,X	2 years	As above
Factor II (Fibrinogen)		1 year	Hypofibrinogenaemia when cryoprecipitate is unacceptable (see text)
Gammaglobulin		4 years	
Normal			Prophylaxis hepatitis A virus infection
Hyperimmune	(anti-D)		Prevention Rh disease of newborn
	(anti-Tetanus)		Prevention of tetanus
	(anti-Vaccinia)		Prevention and treatment of vaccinia
	(anti-Zoster)		Prevention and treatment of zoster
Fresh frozen plasma		1 year	Some bleeding conditions (see text)

volume is maintained, with crystalloids and/or colloids, the loss of 1–2 litres of blood will not lead to irreversible hypotension. Children, the elderly and those with cardiopulmonary disease tolerate haemorrhage less well; they are also more susceptible to over-transfusion.

The assessment of blood loss is difficult, particularly following acute haemorrhage. Measurements of blood volume are time-consuming and often inaccurate, particularly in anaemic and/or debilitated patients. Estimations of haemoglobin and haematocrit are notoriously misleading when plasma and red cells are lost in the same proportion. Serial clinical observations of increasing pulse-rate, falling blood pressure, irritability, sweating, cold extremities, intolerance to exertion and frequent changing of posture are the best indications for blood transfusion in haemorrhage. Hasty action from a single clinical observation should be avoided unless additional information such as evidence of major internal haemorrhage into muscle or abdomen is available. A systolic pressure of less than 100 mm Hg following blood loss indicates a deficit of greater than 30% of the circulating volume, and the need for transfusion.

There is no need for specific action to replace coagulation factors, unless they are congenitally deficient, there is impaired liver function or the patient is on oral anticoagulant therapy. Rarely a deficit of 50% in coagulation factors may arise in severe haemorrhage, but this is still compatible with normal haemostasis. Release and resynthesis of coagulation factors by a normal liver readily compensates for losses associated with haemorrhage.

Oxygen-carrying capacity must be considered. In patients *without* cardiopulmonary disease an ideal balance between capillary flow and tissue oxygenation is achieved by a haematocrit of 30%. Because of the absence of fibrinogen, crystalloids and colloids are more beneficial to blood viscosity than plasma. Haematocrits below 30% are compatible with normal tissue metabolism, provided oxygen is also administered.

In planning a transfusion policy, it is no longer appropriate to replace blood loss ml for ml. If there is clinical evidence of hypovolaemia then up to 2 litres of crystalloid and colloid solutions should initially be transfused. Those which do not transmit hepatitis virus are ideal. Re-constituted freeze-dry plasma is an acceptable alternative, but its contained fibrinogen may increase blood viscosity and thus reduce capillary flow. It is also potentially icterogenic and its potassium content is high. Administration of red cell concentrates and whole blood can follow. The first two units can be red cell concentrates, but thereafter whole blood may be used. Useful guidelines are summarised in Table 9.7.

Chronic anaemia

The risks associated with blood transfusion contraindicate its routine use for the treatment of chronic anaemia. Blood transfusion should only be considered when haematinics have failed. Impending and uncontrolled acute haemorrhage in the severely anaemic patient is potentially hazardous and every effort must be made to maintain the haemoglobin level above 7 g/dl, using blood transfusions. Delaying surgery, whilst awaiting a response to haematinics in preference to transfusion, may also be unacceptable.

Although successful major surgery can be performed on patients with haemoglobin levels of less than 5 g/dl with appropriate pre-operative transfusion, many surgeons and anaesthetists still prefer an initial haemoglobin of 10 g/dl before commencing an elective major operation. Provided surgical haemorrhage and pre-operative transfusions can be controlled and the pre-existing anaemia is asymptomatic a lower figure, eg. 7 g/dl, can be accepted. The blood product of choice for transfusion to the anaemic patient is red cell concentrate. Each donation (250 ml of concentrate) should raise the haemoglobin by 1.0 to 1.5 g/dl. Transfusion may be hazardous in the extremely anaemic patient (less than 5 g/dl), the elderly, or when significant cardio pulmonary disease is present. In these circumstances it is wise to cover each unit of concentrate with 20 mg frusemide i.v. Ideally, all pre-operative transfusions should be completed 24 hours before surgery.

An overall transfusion policy

Over the last 15 years the administration of whole blood for most routine transfusions has been

recognised as wasteful. The demand for special blood products, derived from plasma, now exceeds the requirement of red cells by a factor of almost two.

This problem can be resolved by the following policy:

1. Red cell concentrates should be used for all forms of chronic anaemia.

2. In acute haemorrhagic situations (including intra-operative blood loss following crystalloid administration) the first two donations of blood should be as red cell concentrates. This is followed by whole blood, as required, over the subsequent 24-hour period (see Table 9.7).

In paediatric cases and burns whole blood is more appropriate.

BLOOD COMPONENTS

Whole blood

Whole blood should be reserved for those patients with severe uncontrolled haemorrhage and clinical signs of hypovolaemia, and as part of a general transfusion policy (see above). Fresh (less than 6 hours old) whole blood to ensure haemostasis is no longer indicated: specific and more highly concentrated haemostatic components are preferred. Fresh whole blood should be administered to the bleeding patient with a systemic haemorrhagic diathesis only when specific concentrates are not available.

Red cell concentrates

Red cell concentrates are prepared by removing plasma from donations of whole blood and resuspending the cells to give a haematocrit of 70%. They are the product of choice for routine transfusions and should account for 60–70% of all units transfused.

Packed red cell concentrates. This product has a haematocrit in excess of 90%. It is reserved for patients with severe anaemia and cardiac failure.

Washed and frozen red cells. Some patients (see p.91) may require donations with minimal leucocytes, platelets and plasma protein contamination. These are prepared by extensive saline washing of red cells. Washed red cells must be transfused within 12 hours.

A more effective but costly method is to use frozen-thawed-washed red cells. After thawing they are washed extensively to remove the cryoprotective agent, glycerol.

Frozen cells can be stored for many years and provide stocks of blood of rare groups.

Filtered red cells. Some patients require leucocyte poor or only red cell preparations. These are best prepared by filtration through special filters.

Platelet concentrates

Platelet concentrates contain 60–70% of the platelets present in the original donation, suspended in approximately 40 ml plasma. An adult requir-

Table 9.7 Transfusion options associated with haemorrhage.

Previously healthy adults:	Begin with 1000 ml crystalloids; followed by 1000 ml colloids; followed by 2 Red Cell Concentrates; followed by Whole Blood as required
Elderly and/or significant cardio-pulmonary disease:	Begin with 500 ml crystalloids; followed by 500 ml colloids; followed by 2 Red Cell Concentrates; followed by Whole Blood as required.

1. By using these regimes the majority of patients transfused for blood loss associated with elective surgery will not require *blood* transfusion.
2. Dextrans and gelatin solutions are the colloid preparations of choice. They are contra-indicated in patients with a pre-existing systematic haemostasis failure and plasma or albuminoid should be used.
3. Patients with severe liver disease or those on full doses of oral anticoagulants should receive 500 ml fresh frozen plasma (FFP) along with the 2 Red Cell Concentrates. Further doses of FFP may be required.

ing this form of therapy usually needs a pool of platelets from 5–6 donations to achieve haemostasis. Platelet concentrates should be administered as rapidly as possible (within 15 minutes).

Platelet therapy is indicated in patients with an active haemorrhagic diathesis due to thrombocytopenia (less than 20×10^9/l) or those with clinical evidence of platelet malfunction. Platelet concentrates are also of value following massive transfusion of stored blood in which the platelets are non-functioning (Table 9.1 and page 93). They are of little value in patients with immune thrombocytopenia or those with obvious splenomegaly, for they are rapidly removed from the circulation before they can exert their haemostatic effects. Prophylactic platelet therapy (5–6 donations per day) aids patients receiving intensive chemotherapy.

As platelet concentrates are contaminated by small amounts of red cells, it is advisable, but not essential, to provide ABO Rhesus compatible donations. Efficiency is best assessed by clinical observation: post-transfusion platelet counts are unreliable. Repeated transfusions of platelet concentrates should be avoided; patients develop an immune refractory state. Should this arise platelets from HL-A compatible donors can be given. This is very expensive.

White cell concentrates

The number of granulocytes required to achieve a therapeutic effect is approximately $2–5 \times 10^{10}$ cells. They are prepared by an extracorporeal device known as a Blood Cell Separator, which continually removes the buffy coat from the circulating blood of a single donor. An ABO and HL-A compatible donor is preferred, usually a relative.

In surgical practice granulocyte transfusions are indicated only in patients with an uncontrolled infection and leucopenia of less than 1.0×10^9/l. They are given daily in a volume of 150–200 ml for 3–4 consecutive days. Donor leucocytes are an important source of a new range of blood products. Transfer factor, extracted from normal leucocytes, may enhance cellular immune mechanisms in certain deficiency states. Interferon is obtained from virus-stimulated leucocytes and is currently under clinical investigation for the treatment of viral and malignant disease.

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Fresh frozen plasma

Plasma separated from fresh blood and stored at −30°C contains all coagulation factors. Thawing takes approximately 60 minutes. The thawed plasma should be used within 4 hours as coagulation factors V and VIII deteriorate rapidly. Fresh frozen plasma should be ABO compatible with the recipient.

Fresh frozen plasma is not a panacea for all bleeding states. Its main indication in surgical practice is when patients on anticoagulant therapy or with severe liver disease require emergency operations or continue to bleed. 800 ml (four donations) are infused in 60 minutes. In elderly patients, circulatory overload may be prevented by frusemide (40 mg i.v.). Fresh freeze-dried plasma is available in some parts of the world. It has the advantage that it can be stored in a domestic refrigerator. Before use it is redissolved in a small volume of distilled water.

Outdated (freeze-dried) plasma

This is prepared from a pool of 10 donations of varied ABO blood groups. It can be administered to a recipient of any blood-group. One unit is made up with 400 ml distilled pyrogen-free water. As the potassium content is high (up to 30 mmol/l) it should be given with caution in patients with renal impairment. The risk of hepatitis is increased by pooling.

Outdated freeze-dried plasma once had a major role in the management of hypovolaemia; with the introduction of safer colloids (dextrans, gelatins) and preparations of human albumin, its use has declined. Its main indication now is in the management of burns; but even then it may be replaced by albumin preparations.

As freeze-dried outdated plasma can be stored for up to 5 years it is still useful as an acute volume expander in countries without facilities for plasma fractionation. In concentrated form (made up in 150 ml distilled water) it provides a useful source of coagulation factors, except the labile factors V and VIII.

Factor VIII concentrates

There are two available concentrates of human factor VIII; cryoprecipitate and antihaemophilic fraction (AHF). When fresh plasma is frozen to −40°C and then allowed to thaw at 4–8°C, a precipitate forms which contains 20–80% of the Factor VIII, fibrinogen and Factor XIII of the original plasma. It also contains clinically significant quantities of the factors which stimulate synthesis and release of Factor VIII and increase platelet adhesion in patients with von Willibrand's disease. The cryoprecipitate from each donation is stored at −30°C in a small volume (20–50 ml) of the plasma supernatant. It dissolves rapidly at 37°C and should be used within 4 hours of reconstitution. Material from several donations is usually pooled prior to administration. Each donation of cryoprecipitate contains 50–150 units of Factor VIII.

Antihaemophilic fraction (AHF) is obtained as a freeze-dried product of plasma fractionation. It has significant advantages over cryoprecipitate: a standard and stated dose is available, it can be stored in a domestic refrigerator, and its administration is much more convenient. Currently, it is more expensive than cryoprecipitate. As it is prepared from large plasma pools it carries a high risk of transmitting hepatitis.

The main use of these preparations is in the management of haemophilia. Minor episodes of joint or muscle pain usually require a single intravenous dose of Factor VIII; more serious haematomas need to be treated for 2–4 days. If major surgery is required Factor VIII must be administered 8-hourly for the first two days and 12-hourly for the next 10–14 days. Major surgery on an adult haemophiliac may require the Factor VIII content of over 1000 donations.

Home therapy is a recent development in the management of haemophilia. The patient or relative administers a small dose (250–500 units) of Factor VIII concentrate as soon as pain is felt in a joint or a muscle, thus aborting a more serious bleed and subsequent hospital admission. AHF is ideal for this form of treatment. All Factor VIII concentrates carry the risk of transmitting hepatitis. As there are trace amounts of anti-A and anti-B in most preparations large doses occasionally cause mild haemolysis in those of group A, B or AB.

Factor IX concentrates

There are two types of Factor IX concentrates available. Both are fractionation products and available as freeze-dried preparations. One is a mixture of coagulation factors II, IX and X and the other of II, VII, IX and X. They are used primarily in the management of hereditary coagulation factor deficiencies, particularly Factor IX deficiency (Christmas disease or haemophilia B). The principles of replacement therapy in Christmas disease are similar to those in haemophilia A.

More recently these concentrates have been used to reverse excess oral anticoagulant therapy and to prepare patients for liver biopsy. However, this practice should be avoided, if possible, in view of the risk of hepatitis.

Factor IX concentrates carry the same risk of transmitting hepatitis as concentrates of Factor VIII. Some preparations may be thrombogenic, particularly in patients with severe liver disease. Thrombogenic activity increases if the concentrates are left standing after reconstitution with distilled water. They should be used immediately.

Fibrinogen concentrates

Large pool fractionated concentrates of fibrinogen are still available, but cryoprecipitate, available as a single donation (0.1–0.3 g of fibrinogen per pack), has considerably less risk of transmitting hepatitis. This form of therapy is used in patients with hereditary fibrinogen deficiency and is only rarely indicated in surgical practice for patients with disseminated intravascular coagulation.

Albuminoid preparations

Preparations of human albumin are available in two forms. A 4.5–5% solution (stable purified protein solution, S.P.P.S., salt content approximately 140 mmol/l), used for acute volume expansion; and a 15% or 25% solution poor in salt (salt poor albumin; S.P.A.), used to correct hypoproteinaemia.

Human albumin preparations are heated to

destroy hepatitis viruses: some have a significant kinin content which may produce transient hypotension. Such reactions are rare and invariably benign.

Preparations of human albumin are very expensive. The 5% preparation costs at least 10 times as much as colloid volume expanders such as dextrans. S.P.P.S. should be reserved for those hypovolaemic patients likely to develop significant hypoproteinaemia (i.e. crush injuries, septic peritonitis, severe acute pancreatitis, prolonged intestinal obstruction and mesenteric vascular occlusion) and those with systemic failure of haemostasis in whom artificial colloids are contraindicated. S.P.P.S can be used in the management of hypovolaemia associated with burns, but many still prefer plasma with its content of biologically active proteins.

Albumin infusions should not be used to supply nutritional requirements. Albumin must be broken down to amino acids before incorporation into body proteins and this process is slow (half-life 18 days). Moreover, the essential amino acid content is poor (particularly tryptophan) and infused albumin increases the catabolic rate. Its main value in hypoproteinaemia is as an acute oncotic agent.

Patients are at risk from low oncotic pressure when total serum protein falls below 52 g/l (albumin less than 25 g/l). Salt-poor albumin should be administered in amounts calculated as 2 × (desired - actual albumin level) × (plasma volume), assuming a plasma volume of 40 ml/kg. This calculation allows for the extravascular deficit which will consume approximately half the administered dose.

Immunoglobulin preparation

Immunoglobulin preparations consist of IgG with only trace amounts of IgM and IgA. The concentration of protein is usually 15 g/100 ml, but antibody content is variable and depends on the donors used. Immunoglobulin preparations are usually administered intramuscularly, do not transmit viral hepatitis, and only rarely cause untoward reactions. There are two types.

1. Human normal immunoglobulin (HNI) is prepared during routine fractionation of large pools from over 2000 ordinary donations. It is used as replacement therapy in hypogammaglobulinaemia and for passive protection against hepatitis A infection or measles.

2. Human specific immunoglobulin (HSI) is produced by fractionation of donations known to have particularly high titres of a specific antibody. They include anti-D, anti-tetanus, anti-vaccinia and anti-varicella (zoster), anti-HBV and anti rabies fractions.

Anti-D immunoglobulin has proved outstandingly successful in preventing immunisation against the Rhesus D antigen during pregnancy. It is also indicated if Rh(D) positive blood is transferred accidentally to a Rh(D) negative recipient. The dose is 10 *μg/ml of red cells administered.*

Anti-tetanus fraction is available as a 250 i.u. dose for prophylactic therapy. It should be given to patients who have not had appropriate active immunisation (full initial course or a booster) within 5 years, and who present with a dirty (soil-contaminated) wound, or one which has not received medical attention for over 72 hours. A more concentrated preparation (5000 i.u.) is available for use in established tetanus.

Anti-HBV. Current evidence suggests that prophylactic use of this specific immunoglobulin can diminish the severity of hepatitis B viral infections. The recommended dose is 10–20 mg/kg body weight given within 5 days of exposure. The material is inevitably in short supply and most frequently used for health service staff who accidentally innoculate themselves with the body fluids of a patient known to be HBs-Ag positive. This occurs from needle pricks or from splashes onto cuts or mucous membranes.

Anti-rabies. This preparation is now available as prophylactic therapy for those who receive animal bites in continental countries.