Clinical and practical aspects of indications and administration of blood products in inherited and acquired bleeding disorders

L. Walterová

(Liberec, Czech Republic)

Transfusions of blood products -both blood components and plasma derivatives- can be life-saving procedures if used rationally

Blood components/labile blood products/cells, plasma and cryo/ are provided by blood services and produced from single individual donations or pooled from several (up to 10-20) donations. Stable blood products/albumin, clotting factors, immunoglobulins , coagulation inhibitors, etc., are procured from human plasma from large numbers of individual donations. Even though provision of these products by transfusion services and pharmaceutical industry has become safe, standard and accessible in most countries, good clinical practice -i.e. proper use of these quality products- is often still inadequate. This has been proved by a number of studies documenting large variations in the use blood components for identical sets of patients in different countries or even institutions having comparable access to blood products. It has been recognised by the Council of Europe and a publication dealing with optimal use of blood *("Summaries of Product Characteristics")* has been published in 2005. Another source of information is the *Manual of Optimal Use of Blood* published as an EU project in 2010 by the Scottish National BTS (www.optimalblooduse.eu) or available guidelines of the BCSH *(British Comm. on Standards in Haematology)*.

Component therapy, i. e. providing the specific part of blood (cells, plasma, cryo) that patient actually needs, has become routine decades ago. The general trend is to overtransfuse, in the sense that too many patients are transfused. Often, though, individual patient does not get large enough dose.

Plasma derivatives, products from plasma pools, undergo further testing and treatment to eliminate potential infectious risks. These are used in situation, when one or a specific range of factors or inhibitors is to be replaced, in both inherited and acquired deficiencies or for immunologic effects. Plasma is then generally unsuitable, even though quite often still used for the lack of sources or sometime even lack of knowledge.

As the blood safety of the products has ceased to be the major problem, focus is moving to the clinical side of the process: the proper indications and correct administration of the products. In the clinical setting, though, it is much more difficult to find the indicators of the quality of the treatment. Adverse reactions after administration of the blood products can be followed, but that does not give an information of the appropriatness of indication and profit for the patient. Numerous guidelines have been issued in the era of evidence-based medicine, but these are often not followed and may not be suited for the specific patient in a given situation.

The indication of every blood component and/or blood derivative should be thus clearly stated before ordering it, with consideration not only of the profit but also of the risks it may bring to the individual patient. The indication of each administration must be stated in patients documentation in writing before the order, with the exception of life-threatening situations.

Indications of blood products

Blood components are mainly used for the following purposes:

- to maintain oxygen transport;
- to correct bleeding and coagulation disorders;
- rarely to correct immunological disorders.

Plasma derivatives: albumin, immunoglobulins, concentrates of coagulation factors and coagulation inhibitors are used as substitutions for the missing plasma component or for their immunomodulatory or regulatory effect.

The choice of the optimal blood product depends on:

- clinical situation of the patient;
- awareness of the clinician as to the optimal product;
- availability of the chosen product.

Administration of the products

Administration of **blood components** is unique in the sense of each component being prepared for individual patient by the process of pre-transfusion testing and can be used solely for this individual person. The component that is life-saving for one patient may be detrimental to another individual. Thus utmost attention must be paid to the transfusion pathway. Also, as blood components are of human origin, there can never be zero risk and 100% standardisation of these products.

Key elements of the peritransfusion process

Before the process of transfusion starts, the patient must be informed on the reason for and expected benefit of transfusion as well as possible risks and -where relevant- patient consent to transfusion must be obtained.

Steps to be followed during the clinical transfusion process:

1) identification of the patient when taking the sample for the pre-transfusion testing;
2) correct labeling of the tube with patient sample, preferably at the bedside, with unique identification of the patient and the health care provider taking the sample;
3) correct completion of blood order form with information of:
   - patient identity,
   - date and time of blood sample withdrawal,
   - type and amount of blood components being ordered,
   - indicating physician,
   - reason for component order (i.e.: Hb level, coagulation disorder, platelet number, active bleeding or preoperative order),
   - identification of the person taking the sample,
   - relevant information on previous transfusion and pregnancy history,
   - information on previously known irregular antibodies, application of anti-D globulins,
   - information on previous adverse reactions to transfusion;
4) timely and correct transport of the sample to the laboratory;
5) proper laboratory pre-transfusion testing and choice of correct component with documentation of the pre-transfusion testing outcome;
6) timely transport of the component to the patient with the provision of cold chain where necessary;
7) correct identification of the patient;
8) check on necessary vital signs: heart rate, blood pressure, temperature, urine;
9) check on delivered blood component: type, amount, expiration date, visual control, color, possible leak, swirling of platelets, thawing of plasma, temperature irregularities, etc.; check on accompanying documentation;
10) bedside blood group check, where required;

11) timely and correct administration at a pre-set velocity with monitoring of the patient/repeated check on vital signs of the patient 15 minutes after the start of each component transfusion/pulse, blood pressure and temperature, if there is a change from baseline values, then respiratory rate. Post-transfusion check on vital signs and urine, not later than 1 hour after completion of transfusion;
12) documentation of the administration;
13) record of the outcome of the transfusion after completion;
14) assessing the need for further applications;
15) monitoring the patient late transfusion reactions: if patient is transfused on out-patient bases, i.e. cannot be monitored for 24 hours post-transfusion, he must be counselled on the signs of possible adverse reaction and a contact for immediate clinical advise must be given.

Every step of the process has its importance and deviating from its completion may have deleterious consequences for the patient. Misidentifications of the recipient both at the time of taking the sample as well as at the time of administration have been shown as a cause of vast majority of life-threatening adverse effects.

Administration of plasma derivatives is simpler as the products are not prepared for individual patients. On the other hand, due to the procurement from human plasma, they still may carry small but inherent risk of both infection or immune adverse reactions. Thus it is important to indicate these also with caution, when the expected benefit overweighs possible risk. Administration should be carried out exactly according to the instructions in SPC leaflet to minimise the risk of allergic or other adverse reactions. Some of the products must be tempered first at room temperature, dissolved and filtered by provided filter and then only applied at a pre-set rate.

The batch number must be noted in the patient documentation for possible later use: withdrawal of certain batch, checking on late effects of the derivative, etc.

Clinical assessment / diagnosis

Medical history is a key element in diagnosis of bleeding disorder. Careful family and personal history must be taken. It is useful to have a standard questionnaire for the patiens that covers:

a) bleeding history in the larger family, personal history of spontaneous bleedings: epistaxis, gingival bleeding, haematemesis and melena, objectivisation of meno/metrorhagia, prolonged wound healing, haematuria;
b) bleeding during medical interventions: vaccinations and other injections, dental care, surgeries, delivery;
c) onset of the bleeding and possible accompanying disease distinguishes often inherited versus acquired disorders, infection within last weeks can point toward autoimmune origin of thrombocytopenia in children and young adults (AITP);
d) drug intake.

Physical examination helps to distinguish among coagulation/vascular/platelet defects. Also, signs of underlying disease can be spotted.

Careful examination of possible presence of petechiae, mucosal bleedings, spontaneous haematomas, late bleedings, haemangiomas and teleangiectasias must be performed as well as examination of possible bleeding into joints, abdominal cavity or CNS. Neurological signs may be consequence of either bleeding or microvascular thrombosis, i.e. in heparin-induced thrombocytopenia (HIT) or haemolytic/uremic syndrome.

Laboratory tests

Screening tests

1) Blood count with smear analysis to assess the possible reason of thrombocytopenia (platelet clumping in pseudothrombocytopenia, large platelets in disorders with increased platelet turnover (HIT, AITP) Dohle inclusions in May-Hegglin syndrome, giant platelets in Bernard Soulier syndrome). Presence of schistocytes may lead to the diagnosis of MAHA (microangiopathic haemolytic anaemia present in

HIT). Blood count with smear analysis would in most cases rule out other underlying haematological disorders causing bleeding (leukaemias, myeloproliferative disease, aplastic anaemia, etc.).

2) Coagulation screening: PT, APTT, fibrinogen, selectively antithrombin, DDimers for assessing activation of coagulation/fibrinolysis and possible diagnosis of DIC (disseminated coagulopathy). It must be understood, though, that the global tests as PT, which was primarily developed to monitor anticoagulant therapy, poorly predict the risk of bleeding when moderately prolonged. Their prolongation points to the proper further testing though in differential diagnosis of coagulation disorders.
3) Consider bleeding time/in vitro-bleeding time/PFA 200, better than obsolete in-vivo bleeding time.

Specialised coagulation tests

1) Mixing/correction/assays (mixing normal and patient plasma in different ratios with subsequent incubation) distinguishes between factor defects and presence of inhibitors/antibodies, i.e. lupus anticoagulants.
2) Specific factors assays.
3) von Willebrand disease diagnostics: antigen and activity (RiCo-ristocetin cofactor activity, CB- collagen binding activity, RIPA (ristocetin-induced platelet aggregation), multimeric structure, F VIII binding activity.
4) Inhibitor testing.
5) Fibrinolysis testing.

Platelet functions testing/aggregation assays, platelet function analyser (PFA)

POCT (point of care testing)

Thrombelastography (TEG), thrombelastometry (ROTEM): measuring global coagulation state. These analysers, usually located right next to the patients in the operating room or anaesthesiology department, are used for critically ill patients -trauma and massively bleeding patients- where quick decisions for substitution are needed. These devices measure the start of clot formation, its velocity, maximal amplitude and lysis, enabling immediate substitution of the required component/plasma or platelets or derivative/fibrinogen. Other POCT device, as i. e. haemoglobinometer, may guide attending intensivists in substitution of red blood cells for desired haematocrit in critically ill and bleeding (30%) patients before the result of whole blood count is known from the laboratory.

Inherited bleeding disorders

Inherited bleeding disorders vary in prevalence in population, from relatively often seen -as i. e. von Willebrand disease (if the mild forms are included, in population studies, with no bleeding manifestation, may be found in up to 1% of population)- to very rare F V deficiency, dys/afibrinogenemia, etc.

The severity of the diseases differ vastly, from mild cases with no need of substitution with the exception of large invasive procedures, to severe, spontaneously bleeding patients requiring regular substitution.

Inherited disorders of platelet function are rare and in most cases do not cause life-threatening spontaneous bleeding. Their manifestation can be dangerous during invasive procedures.

Overview of most common inherited bleeding disorders

Defects of coagulation factors

Haemophilia

X/linked bleeding disorder, frequency 1:10 thousands births.

Patients are nearly always males (females only as double heterozygotes or hemizigotes, i.e. Turner syndrome X0) with affected X chromosome. In all other cases, females are carriers.

Deficiency in F VIII cause haemophilia A, deficiency in F IX haemophilia B.

80-85% of patients suffer from haemophilia A, only 15-20 % from haemophilia B

Clinical presentations of both diseases are identical, with severity according to residual amount of functional factor (% of normal).

Severe form: under 1% with spontaneous bleedings in joints and muscles from early age.

Moderate form: 1-5% occasional spontaneous bleeding, severe bleeding in trauma or surgery.

Mild form: 5-40% bleeding with major trauma or surgery.

Carriers may bleed during surgery. Menstrual bleeding may be heavier than normal (in patients with factor level below 30%).

Treatment

Goal of treatment is the prevention of bleeding. Once bleeding occurs, it should be treated early, within 2 hours. In mild cases treatment with desmopressin in combination with RICE, rest, ice (applied 20 minutes every 4-6 hours), compression may be sufficient possibly augmenting the effect with tranexamic acid (exception is prolonged haematuria, where antifibrinolytics are generally contraindicated).

Most bleedings in severe and moderate haemophiliacs must be treated by factor concentrate.

Existing factors are either plasma-derived or recombinant. The strategy of treatment does not differ. In vivo recovery of F VIII/IX should be considered for each patient when calculating the dosage. In principle, half-life of both recombinant and plasma-derived factor VIII is in 8-12 hours, in adult population tends to be a bit longer. For that reason, paediatric population, especially newborns, is dosed 10-25% higher doses per Kg of body weight than adults. F IX has a longer half-life, 16-18 hours.

Roughly, in F VIII concentrates, 1 IU /Kg of body weight of F VIII rises the level by 2%, 1 IU of F IX/1 Kg of body weight rises the level of F IX by 1%.

The desired levels of factors are calculated for each invasive procedure. It must be counted on quicker turnover of the factor during bleeding and invasive procedures, so the intervals perioperatively are generally 8 hours for F VIII and 12 hours for F IX, with prolongation of the intervals in post-operative period. Bolus application results more expensive (by about 30%) than continual infusion during surgeries. Lately it has been shown, though, that continual infusion in combination with surgery may result more often in inhibitor development. The desired levels of factors for different type of bleedings and invasive procedures, as well as duration of substitution for both haemophilia A and B, are published in the *Guidelines for Management of Haemophilia*, edited by the Word Federation of Haemophilia (for both countries with and without financial constraints), as well as in a number of National Guidelines.

The choice of factor depends often on national policies. Recombinant factors are considered safer in the context of blood-borne diseases; the price though may be a limitation of its use. Also, it is not quite clear whether they are not involved in development of inhibitors more often, even though there has been no definite conclusion in this issue. Studies have been ongoing especially in haemophilia A patients, where inhibitors are more common and of major concern. Also, frequent changes of types of plasma-derived coagulations factors have raised suspicions about higher frequency of inhibitor development, in some studies, due to different immunological stimuli of each factor type. Plasma-derived products purity is measured by number of IU per mg of protein: concentrates of low, intermediate and high purity. There is variable content of vonWillebrand factor (vWF) present in different products.

Recombinant factors should be the treatment of choice in the previously untreated patients (PUPs), and in the second line in patients without hepatitis and HIV infections.

For haemophilia B patients, it is advantageous to use pure factor IX concentrates as opposed to prothrombin complex (PCC), which may be associated with l higher risk of thrombosis or DIC in larger doses.

In countries with very limited financial resources are still used blood components for haemophilia treatment with the major concern as to the standardisation of the content of coagulation factors and safety. Cryoprecipitate is source for F VIII, von Willebrand factor, fibrinogen, F XIII. Fresh-frozen plasma and cryo-poor plasma contain F IX and F XI as well as F VII and X. These components though are not the products of choice to be recommended.

Treatment strategies

1) On demand treatment, concentrate is given as soon as possible after development of bleeding. Most patients who are bleeding frequently are educated to inject themselves the correct amount of factor as soon as possible after bleeding occurs. They are educated in the indication of amount and in self-application. For minor bleedings, they do not need to see the physician, but only record the time, reason for application, amount and batch number of the concentrate, to discuss with the attending physician later.
2) Prophylaxis: indicated in severe haemophiliacs with frequent bleedings, especially in paediatric population. The dose is 25-40 IU per Kg three times a week in haemophilia A and twice a week in haemophilia B. Other regimens (i. e. daily, every other day, or weekly) only are possible and practiced in some countries. The aim is to keep the factor level ove 1-2% to prevent spontaneous bleeding events.
   a) Primary prophylaxis begins at the latest after the first bleed, always before 2 years of age.
   b) Secondary prophylaxis is initiated after more than one major bleeding, or later than at two years of age.
   c) Short-term prophylaxis is performed during and after surgery, during rehabilitation, etc., in patients usually on on-demand treatment.

Inhibitors

Development of inhibitor is of major concern especially in haemophilia A patients (10-15%, more often in paediatric population), less in haemophilia B (1-3%). The majority of inhibitors develop within the first 10-50 exposure days. Also, high initial doses of factor concentrate (over 50 IU/ Kg for more than 5 days), application to the newborns and children before 6 months of age may enhance inhibitor development. More inhibitors develop in conjunction with infections, vaccinations, intercurrent bleedings. Patients prone to development of inhibitors are those with severe gene defects (i. e. deletion or inversion). Inhibitors may be transient if the titre is low (below 5 BU-Bethesda Units). High responders, whose titre of inhibitor is high, tend to have persistent inhibitors and, even when the titre falls during the time of absence of application of the concentrate, it develops quickly after the next infusion.

It is advantageous to start prophylaxis with lower doses, in absence of bleeding or infections, to minimise the risk of inhibitor development.

A specific problem in haemophilia B patients with inhibitor is the possible development of severe allergic reactions (in nearly 50%). The most severe manifestations occur in the first 20 applications, so it is advisable that the patients predisposed for such a reaction get the initial treatment with factor at a petting where severe allergies can be treated.

Treatment of patients with inhibitors

Bleeding in patients with inhibitors is always a major challenge. In low-responders, with inhibitor titre less than 5 BU, administration of high doses of coagulation factor concentrate can overcome the presence of inhibitors. For patients with high inhibitor level, or those waiting for the start of immune tolerance induction therapy, bypassing agents -activated prothrombin complex concentrate (aPCC) or recombinant F VIIa (rFVIIa)- are the treatment of choice. Sequential use of both has been shown of benefit in refractory bleeding with no evidence of development of thrombosis, thrombocytopenia or DIC.

Immune-tolerance induction (ITI) is the only strategy known to eradicate inhibitors. It can be successful in 60-80% of patients with haemophilia and about one third of patients with haemophilia B when correctly managed. Dose regimens vary widely from 50 UI/Kg three times a week to 200 IU/Kg

daily. Also, the best products types are still under discussion: plasma-derived are usually the product of choice. The best candidates are children with recently diagnosed inhibitor: for them it is a cost-effective option, because there is a good chance of inhibitor eradication and return to prophylaxis that can prevent arhtropathy. The titre of the inhibitor at the onset of ITI should be at least below 10 BU, ideally below 5 BU. ITI should continue until there is no further decrease for at least 6 months. Careful consideration must be given to haemophilia B patients who rarely develop inhibitor but can have high risk of anaphylaxis and nephritic syndrome development. Patients with mild haemophilia and inhibitor should be preferentially treated with bypass therapy on demand before considering ITI.

Newly emerging problems in elderly haemophiliacs

As haemophiliacs average age is nearing to the one of general population, new problems arise. Co-morbidities as osteoporosis, obesity, hypertension diabetes and cardiovascular disease must be dealt with. Haemophilia patients have statistically higher risk of hypertension development and generally lower risk of cardiovascular disease, and progressive reduction of cancer incidence with the increasing severity of haemophilia has been observed. In case of acute coronary syndrome requiring PCI, optimal factor level should be achieved to prevent not only bleeding but also formation of occlusive thrombi. Thrombolytic therapy can be performed only with full replacement therapy. During the dual antiaggregation therapy, factor level should be held at 30% and a prolonged use of aspirin is not recommended. If indicated, patient must be on regular prophylaxis. If anticoagulation is indicated, i. e. for atrial fibrillation prophylaxis, administration of factor concentrate should be given to maintain factor level over 30%. Higher development of inhibitors has been observed in elderly haemophiliacs in conjunction with larger doses of F VIII replacement during invasive procedures.

Literature is scarce in this area though and further studies will be needed to assess the optimal therapy in these situations.

Von Willebrand disease

It is the most common of inherited bleeding disorders, afflicting both sexes. The vast majority of cases are type I, i. e. partial quantitative defect with rarely bleeding phenotype, requiring no or only occasional treatment with plasma-derivatives, as most bleedings can be treated with desmopressin and adjuvant therapies, as antifibrinolytics. Even though there is primary defect or deficiency of von Willebrand factor (vWF), there is secondary deficiency of F VIII, as vWF factor acts as its plasma-carrier and stabiliser. The defect is both in platelet plug formation and in fibrin formation.

Mainstays of therapy, in cases not relieved by desmopressin, are plasma-derived concentrates with variable ratio of vWF and F VIII content. It must be appreciated that the concentrates with high ratio of vWF/FVIII content are more advantageous, as the infusion of vWF factor results in endogenous production of FVIII. In derivatives where there is vWFr and F VIII both in high concentrations, infusion may result in high FVIII levels as endogenous F VIII is produced in the presence of infused vWF and it may result in possible risk of thrombosis several hours after infusion. Patients that undergo elective surgery should receive concentrate infusion 6-8 hours before intervention, in order to allow enough time for new synthesis of endogenous F VIII. On the other side, in a bleeding patient with initial low level of F VIII, F VIII concentrate can be added initially with von Willebrand factor in the first dose for immediate effect. The dosage is still often calculated in F VIII levels to reach the proper F VIII levels, as many plasma products still declare F VIII content rather than von Willebrand Factor content. Administration of the substitution during surgeries is usually performed once daily. In major surgeries, twice infusions per day may be considered. In vivo recovery of both F VIII and vWF is similar: 1 IU of vWF results approximately in 2% elevation of plasma level.

If bleeding is not controlled despite adequate F VIII levels, platelet transfusion is indicated. Transfused platelets localise vWF at the site of vascular injury and thus enable haemostatic effect.

Plasma concentrates and platelets are always part of complex therapy, relying also on local measures and antifibrinolytics as tranexamic acid or aminocaproic acid.

Prophylaxis is not used widely in vWD, but it has been shown that there is a cohort of patients (especially type III, with spontaneous joint bleeds or severe repeated epistaxis), which profit from regular prophylaxis. Another target group would be patients with type II A and B with functional defect of VWF and severe gastrointestinal bleeds. Prophylaxis is given 1-3 times a week.

Recombinant VWF are emerging, mostly used in studies.

Other factor deficiencies

A number of other hereditary disorders is managed by plasma products (mostly in conjunction with invasive procedures). If the relevant factor does not exist (i. e. F V) or is unavailable, there is a place for the use of plasma, with the preference of virally inactivated FFP.

F XI deficiency under 20% should be managed with FXI concentrate after injury or surgery. Tranexamic acid should not be given concurrently due to the risk of thrombotic complications. In patients with pre-existing risk of thrombosis, and in patients with cardiovascular disease, concentrate should be avoided and plasma used.

F VII deficiency can be treated both with plasma-derived F VII or with rF VIIa.

PCC should be avoided due to the potential thrombogenicity.

F II and X deficiencies are rare disorders with no specific concentrate available. PCC is generally used.

F XIII deficiency is treated by specific plasma-derived factor.

Fibrinogen deficiencies comprise a large number of mutations, both hypo- and a-fibrinogenemia and dysfibrinogenemia. In the latter, it is often difficult to predict whether there would be a bleeding problem during invasive procedure. Fibrinogen concentrate is available in most countries. In its absence, cryoprecipitate can be used. If there is not a problem with volume overdose, virally inactivated plasma is the product of choice in some countries.

A number of other plasma products is used for rare deficiencies in coagulation inhibitors (antithrombin, protein C, protein S) or other rare inherited defects (i. e. hereditary angioedema, inherited defect in protein C1 inhibitor which allows unchecked activation of complement pathway). The availability of some of these products can be a problem even when the diagnosis is made.

Defects in platelets

Hereditary thrombocytopathies and thrombocytopenias do not as a rule bleed spontaneously. The treatment of choice in invasive procedure is platelet transfusion. For Glanzmann thrombasthenia, rF VIIa has been approved as the treatment option of choice.

Defects in vascular wall

Rendu-Osler-Web er disease/hereditary haemorrhagic teleangiectasia. Bleeding due to anatomic malformations of the vessel wall, severe cases require RBC transfusions when therapy with oral or parenteral iron is not sufficient.

Acquired bleeding disorders

Patiens with normal coagulation in the past may require substitution for either trauma and surgical bleeding, or due to chronic disease predisposing to bleeding. Often bleeding is caused by intake of drugs -anticoagulants or antiaggregants- causing bleeding either when overdosed or combined with a situation predisposing to bleeding: fever, infection, combination with antipyretics, NSAID, some antibiotics, hypolipidemics, etc. Detailed medical history is necessary as often patients would not consider some medication, i. e. non-prescription analgesics relevant.

Coagulopathy in massive bleeding

Trauma patients with massive bleeding develop coagulopathy that has a decisive influence on survival. Incidence of coagulopathy is strongly associated with severity of injury. Degree of tissue injury and hypoperfusion as well as hypothermia may be causative factors of coagulation derangement as they add to impaired thrombin generation. Increased expression of thrombomodulin leads to activation of protein C pathway with subsequent inactivation of F V and F VIII, depletion of fibrinogen and activation of fibrinolysis. Fibrinogen is the critical factor in bleeding patient and must be supplemented adequately.

Diagnosis with POCT and treatment should be initiated immediately after admission. Every institution should have a specific protocol for massive transfusion. Adequate body temperature is necessary for normal haemostasis as well as prevention of metabolic acidosis and hypocalcemia.

In massive prolonged bleeding, the ratio of infused RBC and plasma infusions should be nearing to 1:1 with adequate substitution of fibrinogen and platelets, keeping haematocrit over 30%.

Disseminated intravascular coagulopathy

Disseminated intravascular coagulation (DIC) is a complex systemic thrombohaemorrhagic disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets. The resultant clinical condition is characterised by intravascular coagulation and haemorrhage. DIC is always secondary to an underlying disorder and is associated with a number of clinical conditions, generally involving activation of systemic inflammation. DIC has several consistent components including activation of intravascular coagulation, depletion of clotting factors, and end-organ damage. Typically, DIC results in significant reductions in platelet count and increases in coagulation times (PT and aPTT). Despite these abnormalities, routine platelet and coagulation factor replacement is not indicated in acute DIC, unless ongoing bleeding is present or invasive procedures are planned.

In DIC, treatment of underlying disease is of utmost importance. At bleeding onset, replacement therapy with blood components and plasma products is necessary. Caution must be taken to limit the risk of enhancing thrombotic risks.

Platelet replacement in non bleeding patients may be considered if platelet counts drop below 20 x 10^6/mL, though the exact levels at which platelets should be transfused is a clinical decision based on each individual patient clinical state. Consumption-induced deficiency of coagulation factors can be partially rectified by the administration of FFP, particularly in those patients with prolonged PT, elevated INR (> 2,0), twice prolonged aPTT and/or low fibrinogen levels. The suggested starting dose is 15-20 mL/Kg of FFP. If volume overload is suspected, PCC could be considered in rare cases with serious bleeding. It is an off-label treatment and risk of its possible thrombotic potential must be taken into account. Fibrinogen should be supplemented when approaching critical level of 1 g/L, with the dose of 2-4 g. Antithrombin is recommended when falling below 60%. Dosage calculation formula uses the actual level of antithrombin (% AT) measured and body weight (BW), repeated daily or more often according to actual test results and clinical situation.

Dose of antithrombin to be administered = 120 – actual % AT x BW/2

Treatment with plasma components and derivatives must always be only one part of the complex therapy.

Anticoagulation therapy overdose

The number of patients treated with anticoagulation therapy for different reasons has been rising dramatically in the last decade. Bleeding complications due to this therapy are thus more frequent. Warfarin overdose due to concurrent change of medication, infection, diarrhea or chance-overdosing resulting in major bleedings. Vitamin K is effective in warfarin overdose reversal, but does not stop bleeding immediately. In case of serious bleeding complication or need of urgent surgery, vitamin K must be supplemented by coagulation factors missing in warfarin therapy (F II, VII, IX, X, C, S).

Both plasma and PCC can be used for replacement of the missing factors, both with limitations.

Not all prothrombin complex concentrates are the same and it must be taken into consideration: there are 3-factors concentrates, more properly termed F IX concentrates (these contain useful levels of F II, IX and X), while 4-factors concentrates also contain F VII, protein C and S and are more suitable for replacement therapy in warfarin reversal. PCC has an advantage in delivering high concentration of factors in smaller volume, which is advantageous especially for elderly patients to prevent volume overload and development of transfusion-associated cardiovascular overload (TACO). PCCs have also an advantage in more rapid delivery. On the other hand, PCC is associated with higher risk of thrombosis, which is dangerous in patients who have had indication for long-term anticoagulant therapy. rF VII a and aPCC are not recommended in this indication.

PT/INR does need to be reversed to normal range: INR approximately up to 1,6 represents presence of approximate clotting factor levels of 30% which is sufficient for haemostasis.

New oral anticoagulants**,** i.e.direct antagonists of thrombin (dabigatran) and drugs with anti-Xa activity (rivaroxaban and apixaban), first introduced as a prophylaxis of thromboembolic complications after major orthopedics surgeries, have recently become routine in long-term anticoagulant therapy and prophylaxis. Unlike Warfarin, the effect of these drugs is not expected to be routinely controlled. Incessantly, one can encounter situations of unexpected bleeding or need of reversal of the effect for acute surgery. At the moment, there is no known specific antidote. There is one study suggesting that rivaroxaban could be possibly influenced by PCC. Otherwise, possible overdose could be treated just by dialysis (dabigatran) and symptomatically (gastric lavage, oral charcoal, etc.).

Acquired vWD

It is associated with underlying serious disease: lymphoproliferative diseases, myeloproliferative syndromes (predominantly essential thrombocytaemia), myeloma, valvular heart disease. The prevailing mechanisms of pathogenesis are the accelerated clearance of vWF from plasma due to the absorption on the surface of abnormal cells, formation of complexes with other plasma proteins, and heightened in-vivo proteolysis. The most successful form of treatment is removal of the underlying cause. Other options may be desmopressin, factor substitution or i.v. immunoglobulin: the choice usually must be done after administration of test doses.

Acquired haemophilia

It is caused by autoimmune depletion of inhibition of coagulation factor, most often F VIII of vWF. Inhibitors to other factors have been described. It usually leads to severe bleeding with sudden onset. It may be associated with malignancy, autoimmune disease or pregnancy, but 50% of cases have no known underlying disease. Immunosuppressives are the first line of therapy. Bleeding is managed by aPCC (75 IU/Kg/12-24 hours), rFVIIa or porcine FVIII.

Thrombocytopenia with bleeding

It is managed according to its causes.

Severe thrombocytopenia due to aplasia of bone marrow after chemotherapy is generally substituted by platelet concentrates.

In autoimmune thrombocytopenia, if first-line therapy with corticosteroids fails, there is a role of high dose i.v. immunoglobulins, especially in preparation for splenectomy. Platelet concentrates are given only in life-threatening bleedings.

Bleeding in thrombocytopenia in TTP/HUS, which is due to increased platelet turnover and activated coagulation) should not be treated by platelet substitution. Plasma-exchange is the treatment of choice. It has ben suggested by some studies, that cryo-poor plasma should be superior due to its low content of high molecular weight von vWF, but it has never been proven by large cohorts of patients. Also, as pathogen-reduced plasma products as i.e. solvent/detergent (SD)-treated plasma have become available, some countries have included them as a product of choice in patients requiring large exposures. On the other hand, there are suspicions of increased thrombogenic potential in this product, mostly due to decreased protein S content.

Acquired thrombocytopathies

After antiaggregation drugs, should be treated in case of acute surgery by platelets. In-vivo bleeding time - PFA test can be used to judge the need of platelet substitution.

Patients with chronic diseases with predisposition to bleeding: liver disease, uremia

Liver disease impacts on both primary haemostasis and plasma coagulation. Majority of bleedings occur as a result of porto-systemic varices. Impairment of haemostasis in liver disease and uremia is very complex and bleeding is often unpredictable. Global coagulation tests poorly reflect the risk of bleeding. In liver disease, there is reduced synthesis of both: coagulation factors (F II, V, VII, IX, XI, fibrinogen) as well as coagulation inhibitors (antithrombin, protein C and S). Thrombocytopenia due to reduced megakaryopoiesis, reduced platelet survival and splenic sequestration. Levels of F VIII and VWF are

increased, fibrinolysis is enhanced. There may be vitamin K deficiency due to poor intake or loss of vitamin K-producing intestinal bacterial flora.

There is insufficient evidence to support prophylactic transfusion of FFP in non-bleeding patients even when considering liver biopsy. In patient s with DIC associated with liver disease, FFP administration can be useful and fibrinogen should be considered. Platelet concentrates are indicated in case of very low platelet counts. For substitution on acute bleeding or invasive procedures, FFP, PCC and platelets are given (if under $50x10^9$/L) and selectively rFVIIa in life-threatening bleeding. All these plasma products must be used with considering their limitations mentioned earlier.

Patients with inherited bleeding disorder manifesting during invasive procedure

Patients with mild inherited bleeding disorders, which do not have history of bleeding under normal conditions, can bleed profusely when this fact is overlooked and patients are operated. These patients (i. e. carriers of haemophilia) may bleed heavily when anticoagulation therapy is introduced for intercurrent thrombosis or cardiologic reason. Careful personal and family history is thus always one of the mainstays of diagnosis.

Conclusions

Bleeding, especially massive, is always a medical emergency. In known case of inherited coagulation disorders, it is possible to predict the effects and thus substitute the correct amount and type of given blood product. Problems arise with patients with rare bleeding disorders, where there is no available concentrate on the market, or in the setting of financial constraints. In these cases, there is still place for the use of blood components: plasma or cryoprecipitate. Complex therapy with use of other pharmaceutical and non-pharmaceutical measures is not to be forgotten. In common inherited bleeding disorders, recombinant clotting factors are used widely. Recombinant F VII has its place in the setting of patients with inhibitors and Glanzmann thrombocytopathy and off label in life-threatening bleeding in polytrauma, post-partum, etc.

Platelet concentrates for inherited platelet disorders are the treatment of choice in bleeding or in preparation to invasive procedures.

Substitution of erythrocytes in bleeding in these patients is needed to keep appropriate haematocrit above 30% to prevent further bleeding. It must be accompanied by timely diagnostic work-up and causal therapy.

In acquired bleeding disorders, diagnosis should be made on basis of patient history, former and actual blood tests (coagulation, blood count and biochemistry) before administering blood products which influence the results of especially clotting assays taken during or after administration. Monitoring of the effects of the treatment should be done repeatedly both by classical laboratory tests and POCT device (thrombelastography) for the possiblity of quick reactions to actual situation.

Even in emergency situations, attention should be paid to pre-transfusion measures if blood components are used, as well as to documentation of administered blood products to assure the safety of the patient.

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