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4 Plasma for Therapeutic Use

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Four licensed preparations are available in Germany, fresh frozen plasma (FFP); solvent-detergent-treated plasma (SDP); methylene-blue-photoinactivated plasma (MBPIP); as well as lyophilized human plasma (LHP).

4.1 Preparation and Products

FFP is obtained from whole blood from an individual donor by centrifugation and separation of cells or by apheresis (plasmapheresis or as part of a multicomponent donation). If necessary, leukocyte filtration is performed and the plasma is immediately frozen to below 30 °C so that activities of factor V and VIII are optimally preserved [29]. To minimize the risk of transmitting HIV, HBV and HCV, quarantine storage of FFP is mandatory, followed by a second examination of the donor for infection markers of these viruses prior to releasing the plasma for treatment purposes.

Like FFP, LHP is a single-donor plasma that is lyophilized after quarantine storage and cell filtration and is only solubilized immediately before use.

SDP is prepared by pooling 500–1,600 individual donations. Treatment with the solvent TNBP and the detergent triton X-100 completely eliminates lipid-enveloped viruses like HIV, HBV and HCV in SDP. The risk of transmitting the non-enveloped viruses HAV and parvovirus B19 is minimized by testing the individual plasma donations using nucleic acid amplification technique (NAT) and by virus neutralization due to the antibodies present in the plasma pool. As is true for all pooled plasma preparations, the residual risk of transmitting the variant Creutzfeldt-Jakob disease (vCJD) is very low but slightly higher compared to that of preparations from individual donations. Because of ultracentrifugation, SDP is virtually free of blood cells [28, 31].

MBPIP is leukocyte-reduced plasma from individual donors to which methylene-blue was added and which was irradiated by infrared light at a wavelength of 590 nm. After irradiation, methylene-blue is largely removed using a special filter and the plasma is frozen. The methylene-blue/light procedure effectively inactivates most of the clinically relevant viruses. Only viruses that might be present at very high titers, like e.g. parvovirus B19, are possibly not completely inactivated [56].

4.2 Quality Criteria

FFP units contain all pharmaceutically active compounds, the clotting factors and inhibitors, at an average activity of 100 U/dl or 100%, with widely diverging values corresponding to variability between individuals. Levels of the acute-phase proteins fibrinogen and factor VIII in the plasma show particularly wide variation. FFP obtained by apheresis contains substantially greater activities of factors V, VIII, IX and XI than FFP obtained from whole blood [64]. Depending on the manufacturing process, FFP contains small amounts of leukocytes and platelets [9].

Due to the manufacturing conditions, potencies of clotting factors and inhibitor activities in SDP are by approximately 10% lower than in FFP. Activities of factor VIII, plasmin inhibitor (synonym: alpha-2 antiplasmin) and levels of protein S are even lower. Clinical trials, taking into account all indications for plasma except for plasma exchange in neonates, showed that SDP and FFP do not substantially differ in their tolerance and their influence on the levels of clotting factors [30]. However, the studies involved relatively small numbers of cases and therefore lack the statistical power to detect minor differences in efficacy. Like FFP, SDP contains normal activities of von Willebrand factor cleaving protease (vWF:CP; synonym: ADAMTS13; ADAMTS = a disintegrin and metalloproteinase) which is important for treating thrombotic thrombocytopenic purpura (TTP) [71]. Pooling causes a leveling of variation between individuals regarding plasma levels and a dilution of any antibodies that may be present.

Like FFP, MBPIP is a single-donor preparation the plasma protein levels of which are subject to natural variation between individuals. Photo-oxidation of fibrinogen in the presence of methylene-blue and under the influence of light causes a reduction of coagulable fibrinogen levels and of factor VIII activities by 20–35% [70]. Activities of coagulation factors V, IX and XI may also decrease by more than 10%. To date, there are no data derived from large randomized trials regarding MBPIP efficacy and tolerance [70].

In blood group O and A(2) preparations the levels of clotting factor VIII and von Willebrand factor (vWf) are on average lower by approximately 25% than in blood group A(1), B or AB plasma units.

The plasma preparations described are free of activated clotting factors and can therefore also be used in patients with activated hemostasis, e.g. in disseminated intravascular coagulation (DIC).

To date, no data are published regarding LHP.

4.3 Storage, Shelf Life and Transportation

Except for LHP (storage temperature at 4–25 °C), plasma preparations have to be stored in suitable deep-freezers or freezers that continually monitor and document the temperature and are fitted with an alarm device. Under no circumstances may the products be thawed, either partially or completely, during transportation. Therefore, they must be transported in deep-frozen form using validated systems. Deep-frozen plasma units have to be handled with great care to avoid damage to the plastic bags. After thawing or reconstitution with water, plasma preparations must be administered within 6 h.

4.4 Application: General Principles, Mode of Administration, Dosage, Indications

4.4.1 General Principles

Principally plasma therapy is indicated if
- in complex coagulopathies plasma activities of clotting factors and inhibitors have to be raised prior to invasive surgery because of apparent bleeding or the threat of severe hemorrhage and/or
- plasma activities of clotting factors V and XI or of vWF: CP (synonym: ADAMTS13) have to be raised since no licensed concentrates are available yet for substitution.

Other congenital coagulopathies are principally treated with coagulation factor concentrates, e.g. hemophilia A is treated with factor VIII concentrates. If in emergencies the effect of oral anticoagulants or of a severe vitamin K deficiency is to be reversed, the more rapid and more effective prothrombin complex concentrates (PCC) should be used for this purpose. But PCC concentrates are no replacement for plasma when treating complex coagulopathies since they do not contain the following clotting factors: fibrinogen, factor V, factor VIII, vWf, factor XI, and factor XIII.

Requirements for an efficient plasma therapy are
- laboratory confirmation of a suspected coagulopathy by using prothrombin time (PT) and, if necessary, activated partial thromboplastin time (aPTT), level of coagulable fibrinogen as well as determination of the single factors in congenital factor V or factor XI deficiency (exceptions: plasma exchange, urgent indication in massive transfusion),
- specification of the dose according to the objective of the therapy,
- control of transfusion efficacy following plasma transfusion by laboratory analyses,
- specification of suitable transfusion intervals.

For the following reasons it is not very efficient to treat coagulopathy with plasma:
- Some coagulation factors have a short biological half-life (factor V: 12–15 h; factor VII: 3–6 h). The substitution effect is not sustained over long periods of time, therefore short transfusion intervals of 4–12 h are necessary in order to achieve and maintain hemostatically effective levels in plasma.
- Patients with acquired coagulopathies often show increased turnover regarding clotting factors and inhibitors due to consumption and/or loss or dilution and consequently an abbreviated and diminished efficacy of plasma in comparison to patients in the steady-state.
- A significant increase in clotting factor and inhibitor levels in plasma requires the transfusion of large volumes. Often the required dose cannot be administered due to the risk of hypervolemia.

Table 4.1. Compatibility scheme of plasma depending on the ABO blood group of the recipient

Patient blood group	Compatible plasma blood groups
A	A or AB
B	B or AB
AB	AB
O	O, A, B or AB

4.4.2 Mode of Administration

Transfusion is performed intravenously, using peripheral veins if possible, by using a transfusion device standardized according to the Act on Medical Devices that is provided with a standard filter (usually with a pore size of 170–230 μm) to retain blood clots. Several plasma units can be transfused using the same set of transfusion instruments within 6 h after thawing of frozen plasma and resolving of lyophilized preparations. Ready-to-use plasma may not be supplemented with drugs or intravenous fluids. On selecting the speed of transfusion and the dose, the risks of hypervolemia, hypothermia and citrate intoxication must be taken into account. Warming of plasma prior to or during transfusion using licensed equipment is required in patients
- undergoing massive transfusion,
- with hypothermia prior to transfusion,
- with chronic cold agglutinin disease,
- with high titers of cold antibodies,
- who develop vasospasms when given chilled blood, or
- in preterm and full-term infants and children.

ABO-typed FFP, LHP, and SDP are administered as ABO-identical transfusions. Serological compatibility tests are not necessary. Plasma preparations marked as universally compatible can be administered without regard to the ABO blood group. In exceptional cases ABO-typed FFP, LHP, or SDP may also be administered as ABO-non-identical but compatible transfusion. To generally use AB plasma for all patients is out of the question since the amount of AB plasma available is very limited (in Central Europe the prevalence of blood group AB is 4%) (table 4.1).

In case a transfusion is urgent, the physician performing the transfusion has to take into account the time needed for thawing of the frozen plasma (around 30 min) and for transport.

4.4.3 Dosage

The necessary dose is calculated as follows:
1 ml plasma/kg body weight increases the factor and inhibitor levels or the PT
- by 1 U/dl or by 1% in cases when increased turnover is lacking, by 0.5–1.0 U/dl or

– by 0.5–1.0% in cases of increased turnover (level of fibrinogen: by 0.02–0.03 g/l or 2–3 mg/dl).

Example: patient with a PT of 40%; target level: 60% (difference 20%); body weight 75 kg; plasma dose = 75 kg × 20 ml plasma/kg = 1,500 ml, corresponding to 6 units of FFP of 250 ml or 8 units of SDP of 200 ml (dose rounded). When using SDP it is recommended to increase the dose by approximately 10% in comparison to FFP because of a lower concentration of clotting factors.

Even high doses of plasma only result in a moderate increase of clotting factor and inhibitor activities in the recipient [37]. For an effective plasma therapy a sufficiently high dose is therefore required that has to be transfused rapidly: a minimum of 15 ml/kg body weight, infusion rate 30–50 ml/min. In adults any dose below 600 ml (2–3 units) is inadequate. In patients with impaired renal function, severe liver damage or cardiopulmonary insufficiency, the plasma dose is limited due to the risk of hypervolemia.

An acute TTP can only be treated effectively by plasma exchange. For this purpose the major part of patient plasma is removed using automated plasmapheresis and replaced by FFP or SDP. 100 or 150% of plasma exchange requires plasma doses of 40 or 60 ml/kg body weight. Plasma exchange can also be necessary in patients with severe factor V and factor XI deficiency prior to major surgery in order to boost factor V and factor XI levels to hemostatically effective plasma levels [3, 51].

There are wide variations in the biological half-life of clotting factors and inhibitors contained in plasma. When treating severe congenital factor V and factor XI deficiency, replacement intervals are calculated according to the half-life of these clotting factors (factor V 12–15 h; factor XI 60–80 h). Often TTP is caused by an vWf:CP (ADAMTS13) deficiency or by an inhibitor against this protease whose half-life is 2–4 days [22]. Nonetheless, in cases of the very rare congenital TTP prophylactic plasma transfusions every 2–4 weeks are sufficient to avoid TTP episodes [20].

Clinically relevant plasmin inhibitor deficiency has to be treated with antifibrinolytic agents since the concentration of plasmin inhibitor cannot be boosted sufficiently by plasma therapy alone [18].

4.4.4 Indications

As far as there are any controlled trials at all on the treatment of certain clinical pictures with plasma preparations, there are just a few randomized clinical trials on the use of FFP and SDP [67].

4.4.4.1 Loss and Dilution Coagulopathy in Severe Acute Blood Loss

Cohort trials in patients with severe acute blood loss of more than 100% of the circulating blood volume who were transfused with massive amounts of volume replacement fluids and plasma-poor RBC concentrates showed a hemostatically significant drop in the fibrinogen level to below 1.0 g/l and an prothrombin time values below 50% [17, 32, 39, 49, 50]. Below these threshold values diffuse microvascular bleeding is to be anticipated. However, there are no controlled trials on the determination of effective plasma doses.

In patients with hypothermia it is possible to determine false shortened PT, aPTT and false low fibrinogen levels since laboratory analysis is performed at 37 °C [63]. In case patients receive either hydroxyethyl starch preparations or dextran and the fibrinogen level is determined using the so-called 'derived' fibrinogen method, an intervention level of 1.5 g/l instead of 1.0 g/l should be chosen [33].

Based on a number of aspects, plasma transfusion should be indicated early in cases of major continuous blood loss:

– Blood loss is difficult to quantify in routine clinical practice.
– If blood loss is rapid, normovolemia and hemoglobin concentration of at least 60 g/l are difficult to maintain.
– Consumption of coagulation factors at the site of large wound surfaces and/or by DIC as well as hypothermia and acidosis can aggravate loss and dilution coagulopathy derived from crystalloid and colloid volume replacement fluids [15, 27].
– Data on PT, aPTT and levels of coagulable fibrinogen (and platelet count) are not always available in a timely fashion.

In acute blood loss the transfusion of plasma is indicated under the following circumstances:

– Continuous blood loss of more than 100 ml/min or continuous demand for substitution by more than 2 RBC concentrates every 15 min, following transfusion of at least 4–6 RBC concentrates.
– Continuous blood loss, in particular due to apparent microvascular bleeding, following transfusion of 4–10 RBC concentrates, if data on PT, aPTT and possibly levels of coagulable fibrinogen are not available in a timely fashion.
– PT < 50% or aPTT > 45 s and/or fibrinogen <1 g/l (method according to Clauss). In this connection it must be taken into account that different reagents show differences in sensitivity to clotting factor deficiencies as well as other interfering factors, e.g. due to heparin or volume replacement fluids, especially for aPTT. The reference range in different aPTT reagents also varies widely.
– Rapid transfusion of plasma with 15–20 ml/kg body weight at a rate of 30–50 ml/min is preferable to a schematic administration of 1 unit of plasma for every 1–3 units of RBC [34].
– The therapeutic goal is to stop diffuse microvascular bleeding or rather to prevent the occurrence of microvascular bleeding by boosting PT to a minimum of 50% and of the fibrinogen level to a minimum of 1 g/l, and by shortening of aPTT to levels <45 s.

In cardiac surgery the prophylactic postoperative administration of plasma to decrease postoperative blood loss is not indicated [11].

Plasma should be rapidly transfused with a dose of 15–20 ml/kg body weight in patients with severe acute blood loss and apparent or impending diffuse microvascular bleeding that is caused in part by coagulopathy with PT < 50% or aPTT > 45 s and/or fibrinogen levels of <1 g/l.	**1 C**
Plasma shall *not* be transfused postoperatively as prophylaxis in patients undergoing cardiopulmonary bypass surgery if PT >50% and fibrinogen levels >1 g/l and in the absence of diffuse microvascular bleeding.	**1 A**

4.4.4.2 Liver Damage

End-stage liver disease is accompanied by complex failure of hemostasis, also including thrombocytopenia, platelet dysfunction and accelerated fibrinolysis, in addition to coagulopathy due to impaired synthesis and/or increased turnover of clotting factors and inhibitors [37]. In order to determine the severity of coagulopathy, PT is used and can be expressed in seconds, in percent activity of the standard value, as ratio values (of the clotting time of the patient plasma compared to that of normal pool plasma), and as International Normalized Ratio (INR). In liver disease only PT expression in percent of the standard value is comparable between different thromboplastin reagents and should be referred to, rather than seconds or INR [35, 61]. Since not only coagulation factors but also inhibitors have reduced levels, the disposition to bleeding is often less pronounced than expected from the reduced PT level [44, 69]. In patients with liver disease, the following applies for all clinical situations: The threshold value for PT or for other parameters in hemostasis at which bleeding complications are significantly reduced by a therapeutic intervention using plasma has not yet been determined as well as the plasma doses necessary for sufficient hemostasis. Since the intravascular blood volume in patients with liver dysfunctions is often set at high values due to hyperaldosteroism, the risk of hypervolemia is higher after transfusion of large doses of plasma than in other clinical settings.

Liver transplantation is not a mandatory indication for plasma transfusion. In the context of liver transplantation the demand in blood products including FFP or SDP depends primarily on the surgical technique and the duration of surgery. Some centers never require plasma in the context of liver transplantation [14, 55].

In patients with severe liver dysfunction who have to undergo cholecystectomy, laparoscopic cholecystectomy, partial hepatic resection, or other medium or major surgical interventions, there is an association between PT and postoperative bleeding [2, 21, 43, 65]. The purpose of plasma therapy is to raise PT levels to more than 50% [43]. To do this, single doses of at least 20 ml/kg body weight are usually required [72]. Clinical observation of patients without severe liver dysfunction suggest that partial hepatic resection can be performed without plasma transfusion even at PT levels between 35 and 40%, unless major peri- or postoperative bleeding occurs [43, 57, 65].

In acute liver failure the prophylactic administration of plasma apparently does not improve the prognosis [23].

Fine-needle liver biopsy under ultrasound guidance and monitored by laparoscopy is not associated with a higher rate of bleeding complications in patients with liver dysfunction and PT levels of below 50% [12, 16, 46]. Therefore a prophylactic administration of plasma is not indicated prior to liver biopsy at PT levels < 50%, while postoperative monitoring of bleeding from the biopsy channel is advisable. A decrease in the PT level down to 30% does not lead to a higher rate of bleeding in patients after paracentesis or thoracentesis, so that the prophylactic administration of plasma is not indicated in these cases [47]. Central venous cannulation in patients with PT levels < 10% (INR > 5.0) leads to a higher incidence of superficial hematoma, but not to prolonged bleeding from the needle track [19]. The prophylactic transfusion of plasma is not indicated.

In patients with liver dysfunction and coagulation disorders plasma could be transfused when PT is below 50% and major bleeding occurs at a dose of 20 ml/kg body weight. The objective of treatment is to arrest bleeding and to increase PT to at least 50%.	**2 C**
In patients with liver dysfunction and coagulation disorders plasma could be transfused when PT is below 50% and major bleeding occurs at a dose of 20 ml/kg body weight. The purpose of treatment is to increase PT to at least 50% until primary wound healing is complete.	**2 C**
In patients undergoing liver transplantation with PT ≥ 50% plasma should not be administered perioperatively as prophylaxis.	**2 C+**
Plasma shall not be transfused as prophylaxis in patients with liver dysfunction and coagulation disorders in the context of fine-needle liver biopsy, after paracentesis, thoracentesis or central venous cannulation.	**1 C+**

4.4.4.3 Disseminated Intravascular Coagulation

There are no controlled trials on the efficacy of plasma transfusion in patients with DIC except for a small controlled

study in neonates with DIC that found no effect regarding survival of either exchange transfusion or administration of fresh-frozen plasma and platelets [26]. In patients with DIC and severe hemorrhage, that are aggravated among other things by severe coagulopathy, high doses of plasma shall be transfused repeatedly, e.g. 20 ml/kg body weight [48]. The purpose of this treatment is maintenance of hemostatically effective minimum levels corresponding to PT levels of around 50% [10].

Administration of plasma has no beneficial effect on the prognosis of patients with acute pancreatitis without DIC [40, 41].

Plasma could be transfused at a dose of 20 ml/kg body weight in patients with DIC and coagulopathy with PT < 50% and/or fibrinogen levels <1 g/l *and* severe hemorrhage.	**2 C**
Plasma should not be administered prophylactically in patients with DIC and coagulopathy with PT < 50% and/or fibrinogen levels < 1 g/l, who do not have to undergo surgery and have no injuries with a risk of bleeding.	**2 C**
Plasma shall not be transfused in patients with acute pancreatitis without DIC and without coagulopathy with PT < 50%.	**1 A**

4.4.4.4 Thrombotic Thrombocytopenic Purpura and Adult Hemolytic Uremic Syndrome

TTP and adult hemolytic uremic syndrome (HUS) are summarized under the microangiopathic hemolytic anemias (MHA). Probably plasma exchange is only effective in the forms of TTP occurring most frequently that are characterized by a vWf:CP (synonym: ADAMTS13) deficiency or by an inhibitor against vWf:CP. By exchanging plasma, the antibodies against vWf:CP are removed and lacking vWf:CP is substituted. Since the various clinical pictures cannot be safely differentiated at the time when a decision on the therapy is required, in all cases plasma exchange is started. Plasma exchange has led to a significant reduction in the 2-year mortality from >90% down to 20–30% and is clearly superior to plasma transfusion alone [4, 62, 66].

- Daily plasma exchange with 40–60 ml/kg body weight until platelet count is >100/nl and still rising or at least no longer dropping. By this the 2-year mortality of patients with acute TTP could be reduced from >95% down to 20–40%. In contrast to plasma exchange, plasma infusion does not lower the rate of mortality satisfactorily [62].
- Relapses require to repeat a course of daily plasma exchange.
- If the response rate is low an attempt can be made to perform plasma exchange twice per day.
- Plasma infusions are only effective in the very rare congenital form of TTP in preventing relapses during remission. In this connection plasma infusions of 10 ml/kg body weight given prophylactically every 1–3 weeks are sufficient, at a biological half-life of vWf:CP of 50–80 h [38].

In patients with acute TTP or adult HUS daily plasma exchange shall be performed with 40–60 ml/kg body weight until platelet count is >100,000/µl. If the response rate is low an attempt to perform plasma exchange twice per day is indicated.	**1 A**
In patients with severe congenital vWf:CP (ADAMTS13) deficiency and TTP, plasma can be transfused every 1–3 weeks in order to prevent TTP relapses.	**2 C+**

4.4.4.5 Hereditary Factor V Deficiency and Hereditary Factor XI Deficiency

Severe hereditary factor V deficiency with residual activities below 5% is a very rare event. Prior to surgery or invasive procedures and in cases of severe hemorrhage, 15–20 ml plasma/kg body weight are transfused in order to maintain hemostatically effective factor V levels of at least 15–20%. Because of the short biological half-life of factor V (12–15 h) plasma has to be transfused in 12-hour intervals [6]. In cases of severe hemorrhage and a risk of volume overload plasma exchange can be necessary, especially in children [3]. The efficacy of an additional therapy with platelet concentrates because of the high amounts of factor V in platelets is doubtful. A therapy with activated recombinant coagulation factor VIIa alone or in addition to plasma may be reasonable [25].

In severe hereditary factor XI deficiency (residual activity below 5%) and mild factor XI deficiency with a disposition to severe bleeding, 20 ml plasma/kg body weight are transfused prior to surgery, invasive procedures and in cases of severe bleeding in order to achieve a hemostatically effective minimum level of 20%. Because of the long biological half-life of factor XI (around 60 h) plasma transfusions in 24-hour intervals are usually sufficient [6]. In mild factor XI deficiency with a disposition to severe bleeding plasma has to be transfused when fibrin sealant, desmopressin (DDVAP) and antifibrinolytic drugs are insufficient to achieve hemostasis. In rare cases plasma exchange may be necessary to avoid volume overload [51]. In Germany factor XI concentrates are not available and are suspected to cause thromboembolic complications [5]. Recombinant factor VIIa could represent an alternative to plasma [52].

In patients with severe hereditary factor V deficiency (residual activity < 5%) plasma shall be transfused with a dose of 15–20 ml/kg body weight perioperatively, in the context of invasive procedures or in cases of severe bleeding with the objective of maintaining hemostatically effective plasma levels of 15–20%. **1 C+**

Plasma exchange with 40 ml/kg body weight could be performed perioperatively or in the context of invasive procedures in patients with severe hereditary factor V deficiency (residual activity < 5%), in whom a hemostatically effective factor V level in plasma cannot be achieved by plasma transfusion. **2 C**

In patients with severe hereditary factor XI deficiency (residual activity < 5%) plasma shall be transfused with a dose of 20 ml/kg body weight perioperatively, in the context of invasive procedures or in cases of severe bleeding with the objective of maintaining hemostatically effective plasma levels of 20% when local measures (e.g. fibrin sealant), desmopressin (DDVAP) and antifibrinolytic drugs are insufficient to achieve hemostasis. **1 C+**

Plasma exchange with 40 ml/kg body weight could be performed perioperatively, in the context of invasive procedures or in cases of severe bleeding in patients with severe hereditary factor XI deficiency (residual activity <5%), in whom a hemostatically effective plasma factor XI level cannot be achieved by plasma transfusion. **2 C**

In patients with mild hereditary factor XI deficiency and a disposition to severe bleeding plasma shall be transfused with a dose of 20 ml/kg body weight perioperatively or in the context of invasive procedures when local measures (e.g. fibrin sealant), desmopressin (DDVAP) and antifibrinolytic drugs are insufficient to achieve hemostasis. **1 C+**

4.4.4.6 Special Indications in Pediatric Patients

The prophylactic application of 3–20 ml plasma/kg body weight in preterm infants on their first and second day of life has no effect on the frequency and severity of cerebral hemorrhage, mortality and the long-term outcome [54].

Plasma infusions have no beneficial effect on the clinical course of HUS in children [42, 60].

Partial plasma exchange transfusion has no beneficial effect compared to exchange transfusion with volume substitutes when treating the hyperviscosity syndrome in neonates with polycythemia [13, 36, 68].

In newborn infants and small children undergoing cardiopulmonary bypass surgery or extracorporeal membrane oxygenation, RBC concentrates and plasma and possibly platelet concentrates are used as priming fluid, because there is a disparity between the blood volume of the child and the volume used to prime the oxygenator. In a prospective randomized trial comparing plasma with albumin as priming fluid of the heart-and-lung machine there was a tendency to less blood loss in the plasma group [53]. Another very small prospective randomized trial showed no difference between the groups with or without plasma in the prime [45].

For the same reasons as in cardiopulmonary bypass surgery, an exchange transfusion in neonates with severe hemolysis or hyperbilirubinemia is performed using RBC concentrates that are mixed with compatible plasma.

In newborn infants and small children undergoing cardiopulmonary bypass surgery or extracorporeal membrane oxygenation plasma combined with RBC concentrates could be used as priming fluid. **2 C**

An exchange transfusion shall be performed in neonates using RBC concentrates and plasma. **1 C+**

Plasma shall not be transfused in preterm infants as prophylaxis with the objective of preventing intracerebral hemorrhage. **1 A**

Plasma shall not be transfused in children with HUS without coagulopathy. **1 B**

Partial exchange transfusion in neonates with polycythemia and hyperviscosity syndrome shall not be performed using plasma. **1 B**

4.4.4.7 Lack of Indication for Therapy with Plasma ('Non-Indication')

Below clinical pictures and symptom complexes are listed in which plasma should not be applied or is possibly ineffective.

Prophylactic postoperative administration of plasma in patients undergoing cardiopulmonary bypass surgery with PT > 50% or fibrinogen levels > 1 g/l and in the absence of signs of microvascular bleeding [11].	**1 A**
Prophylactic perioperative administration of plasma in patients undergoing liver transplantation if PT ≥ 50% [14, 55].	**2 C+**
Prophylactic administration of plasma prior to liver biopsy, paracentesis, thoracentesis or central venous cannulation in patients with liver dysfunction and coagulopathy [12, 16, 19, 46, 47].	**1 C+**
Prophylactic administration of plasma in acute liver failure without bleeding complications with the objective of improving the outcome [23].	**1 B**
DIC without coagulopathy and/or without bleeding complications [26].	**2 C**
Acute pancreatitis [40, 41].	**1 A**
Prophylactic administration of plasma in preterm neonates [54].	**1 A**
Partial plasma exchange transfusion in neonates with polycythemia and hyperviscosity syndrome [13, 36, 68].	**1 B**
HUS in children [42, 60] .	**1 B**
Burns in the absence of bleeding complications and without coagulopathy [1, 7, 8].	**1 B**
Plasma exchange in patients with Guillain Barré syndrome [58, 59].	**1 A**
– Primary volume substitution – Parenteral nutrition – Substitution of immunoglobulins – Coagulation factor and inhibitor deficiencies that can be treated more effectively and with better tolerance using factor concentrates, e.g. hemophilia A and B, severe coumarin-induced hemorrhage, with the exception of emergency situations if concentrates are not available in time or if there are contraindications against concentrates (e.g. PCC in heparin-induced thrombocytopenia type II) – Disorders of hemostasis that on principle cannot be treated effectively with plasma: thrombocytopenia, platelet disorders, hyperfibrinolysis.	**1 C+**

4.5 Absolute and Relative Contraindications

In patients with plasma intolerance and confirmed IgA deficiency, plasma is contraindicated. In the quite frequent hereditary IgA deficiency (prevalence 1:650) anti-IgA antibodies can be present that were implicated to cause anaphylactic reactions to blood products after application of IgA-containing blood products. However, the association is controversial [24].

4.6 Adverse Reactions

Citrate intoxication occurs following transfusion of high doses of plasma in the context of a massive transfusion or plasma exchange in patients with impaired liver function. This can be accompanied by reduced ventricular function, arrhythmia and increased neuromuscular excitability. Since citrate is metabolized to bicarbonate, quite often during massive transfusion a metabolic alkalosis is observed that is difficult to manage.

There is a risk of volume overload in particular in patients with renal insufficiency, cardiopulmonary insufficiency and liver disease as well as in preterm and full-term neonates.

The development of inhibitors against coagulation factors following the application of plasma is highly unlikely. Patients with severe factor V or factor XI deficiency must be considered to be at risk if the residual activities of these coagulation factors are below 1 U/dl.

For further particulars, especially regarding transfusion-related acute lung injury (TRALI), see chapter 11.

4.7 Documentation

According to article 14 of the German Transfusion Act (Transfusionsgesetz; TFG), there is an obligation to perform a patient- as well as product-related batch documentation for plasma for therapeutic use.

4.8. References

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