



Types of fresh plasma with focus on therapeutic plasma exchange

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ABSTRACT

Among blood components for transfusion, plasma for direct therapeutic use is one which has the most diverse presentations as it can either be a labile (fresh) component or a drug when industrially manufactured after pooling of thousands of individual plasma collections. Therapeutic plasma can come in an unmanipulated form or be subjected to chemicals, then may or may not be followed by physical interventions. The question then arises as to whether fresh plasma retains all the moieties having therapeutic virtue and whether the manipulations (aimed at eradicating or at least eliminating infectious agents) favor adverse reactions, the major one being typical allergy or allergic type reactions (that can be severe when presenting as anaphylaxis). These questions become crucial when patients are exposed to hundreds of therapeutic plasma units while being subjected to therapeutic plasma exchange (TPE). This short review aims to present the various types and presentations of therapeutic plasma and to update information on fresh plasma use in TPE programs, both in terms of efficacy and tolerance.

It is expected that plasma for direct therapeutic use—the new name for fresh plasma (referred in this paper as FP)—contains elements or factors that are missing in certain pathologies and restores physiological functions. FP brings clotting and antifibrinolytic factors to control hemostasis [1]. In Therapeutic Plasma Exchange (TPE), FP exchange removes deleterious antibodies (Abs) and provides non-pathogenic (normal) immunological soluble factors [2]. Most FP types currently licensed for therapeutic use fulfill these roles; furthermore, manufacturers, either blood establishments or industry, file with notifying and authorizing bodies or agencies to guarantee that the final products (industrial processes) or components (blood establishment processes) match official criteria issued as standards by the European Commission or others, for example, the FDA [3]. Meanwhile, FP is not uniform and can come in distinct presentations (types) [4]. One may thus question whether those distinct types are functionally different or alike, bearing in mind that differences can be revealed both quantitatively (efficacy) and qualitatively (tolerance).

As has been presented in recent reviews [4–6], FP can be obtained from centrifuged whole blood or by apheresis procedures and further differ because the variation in devices may affect outcome. FP units can be processed from single donations, or result from pools either from a small number of donations (mini pools) or a large number of donations

(often a very large pool of several thousand). The latter is, in general, provided by industry while the former is processed by blood establishments. The number of residual leukocytes which leads to residue after freezing varies considerably from normal (no leukoreduction) to as low as technically possible (below $10^4/L$). In most blood establishments, the target is below $10^6/L$; theoretically, industrial processes further eliminate virtually all leukocyte residues. FP present as truly or virtually universal (the AB group stands for the truly universal and mixes from various ABO groups stand for likely universal) [7]. A and B donors are selected as having low titer anti-B and -A Abs and no isoagglutinins. Further, FP can come as fresh frozen plasma (FFP), thawed at the time of being issued (delivered) to a given recipient, under pre-defined conditions, preserving sentinel proteins; FFP is currently the most frequent FP form. FP can come from rapidly frozen plasma (6–8 h after collection) or from plasma frozen later and held as a liquid for 24 h at room temperature (24RTH plasma). Alternatively, FP can come as a liquid; the liquid FP presentations can result from the thawing of a previously frozen plasma, kept liquid for several days, or from never frozen plasma kept liquid for different periods at 4 °C, defining their usability [8]. Dried FP was made available a long time ago and was recently rehabilitated to serve patients in extreme conditions such as in military or civilian disasters [9]. (Fig. 1). In theory, there is no specific

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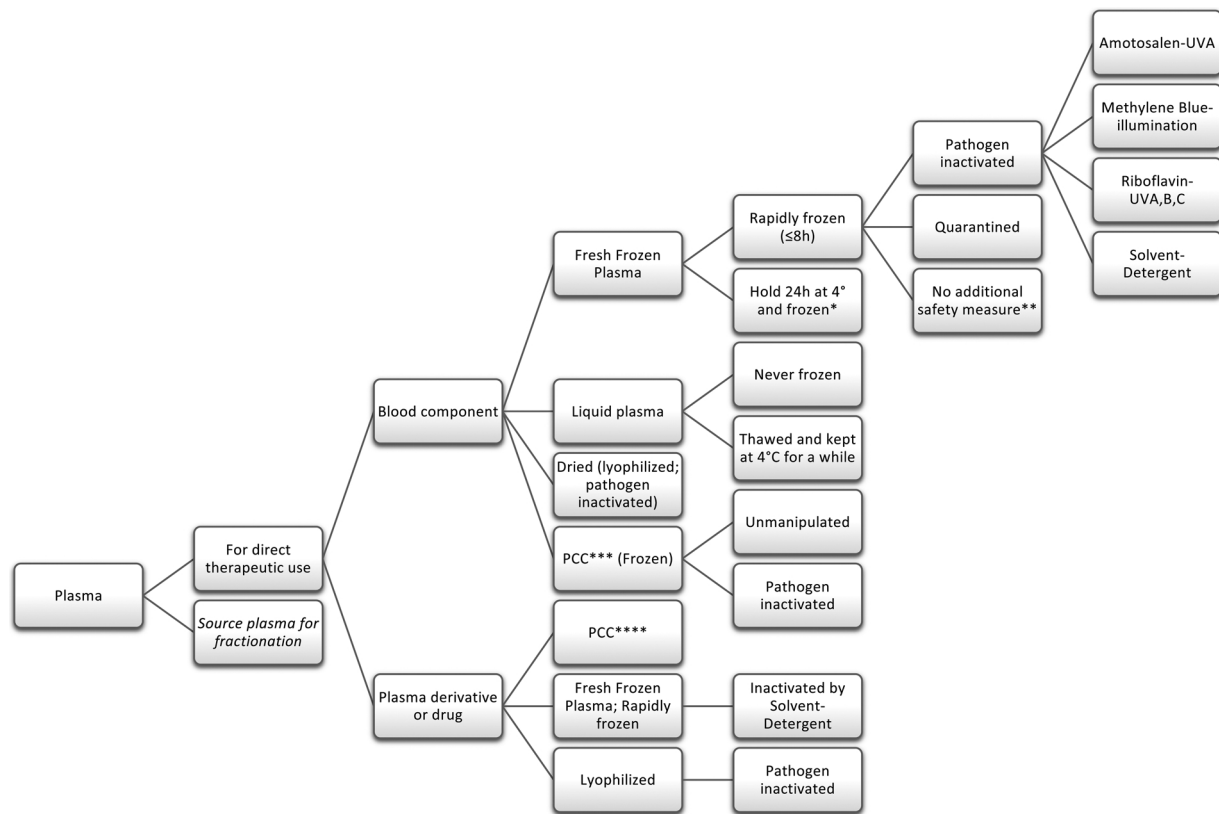


Fig. 1. Different fresh plasma types and categories. The major types and presentation of plasma for therapeutic use are presented, irrespective of implementation of safety measures relative to testing and quality control (that are captured in Fig. 2). *24HRTH plasma may be subjected to safety measures similar to rapidly frozen plasma (not pictured here for space constraint). **In certain blood establishments, fresh plasma is issued after processing (freezing and thawing, or hold liquid) without a cleansing procedure or quarantine. ***PCC stands for Prothrombin Complex Concentrates, which are either a labile blood component or a plasma derivative (drug), depending on systems. ****PCC can be subjected to additional safety measures such as Pathogen Reduction Technologies.

purpose in having such a variety of processes apart from offering flexibility. All FP must contain of desired content in therapeutic factors; flexibility is also expected at the bedside or in the field, which is, for example, the main driver for dried or liquid plasma.

Methods to ensure safety from infections are also strikingly different, despite a universal platform that has been defined, such as one agreed to by the European Community [10]. FP can then also be assayed with nucleic acid and acid testing against HIV, HBV, HCV and additional viruses, depending on epidemiological situations. Nucleic acid testing is applied either to individual donations or mini pools. Additional serological testing may be available depending on the epidemiological conditions.

Filtration, deep freezing, thawing, and preservation, can affect quantitative parameters (defining efficacy) while donor selection, leukoreduction and filtration, and testing can impact qualitative parameters (occurrences or non- occurrences of adverse reactions).

FP is made safer via chemical and physical methods collectively termed Pathogen Reduction or Inactivation Technologies [11]. These methods rely on distinct processes but mainly aim at reducing or eliminating infectious pathogens. They have all proven to be highly effective against most enveloped viruses and parasites (bacteria are not of major concern relative to FP transfusion); however, their efficacy varies against non-enveloped viruses such as HAV, HEV and parvovirus B19. The next question is whether or not these Pathogen Reduction or Inactivation Technologies have a significant impact on quality [12]. Quality is measured after the testing of sentinel proteins such as fibrinogen and FVIII; however, proteins needed in FP used in TPE protocols are often not routine and must be validated separately from the validation file submitted to obtain clearance from licencing bodies. Another safety tool exists that does not use Pathogen Reduction or

Inactivation Technologies, but a quarantine (in general of 2 months) prior to issuing the component. The donor must come back and either donate blood or a test tube for lab work; the quarantined FP can only be released in the subsequent absence of infectious markers. Quarantined FP is thus unmanipulated and expected to maintain all proteins, it is only altered by the freezing and thawing process as for Pathogen Reduction or Inactivation Technologies-treated FP (Fig. 2). Of note, it has been observed that alloimmune anti-HLA Abs are present in numerous female donors having had one or more pregnancies (between 20–30% of multiparous female donors, depending on the studies and test sensitivity) [13,14]. Policies have thus been made available in many countries to either defer multiparous females or to test for anti-HLA Abs, and have proven to be effective in lowering the risk of so-called immunological Transfusion Associated Lung Injury (TRALI) [15,16].

Over time however, some complaints have been made by users reporting intolerance to at least one type of FP, particularly for allergic type adverse reactions. Allergy is indeed the major adverse reaction reported [17]. This has led, in particular, to the discontinuation by the French authorities of Methylene Blue inactivated FP. Occasionally, there have also been reports of post transfusion HEV contamination despite the fact that the FP was Pathogen inactivated [18]. Post transfusion HVA contamination has recently been reported as well, calling attention to the inactivation methods used and contributing to improvements. In spite of this data, large surveys comparing the tolerance of different types of FP failed to identify statistical differences [19–21]. However, it should be stated that this result is probably more valid for severe adverse reactions than for mild ones since they are not rigorously reported, even in countries where this is mandatory by law, such as in France (according to our experience and interviews of many colleagues).

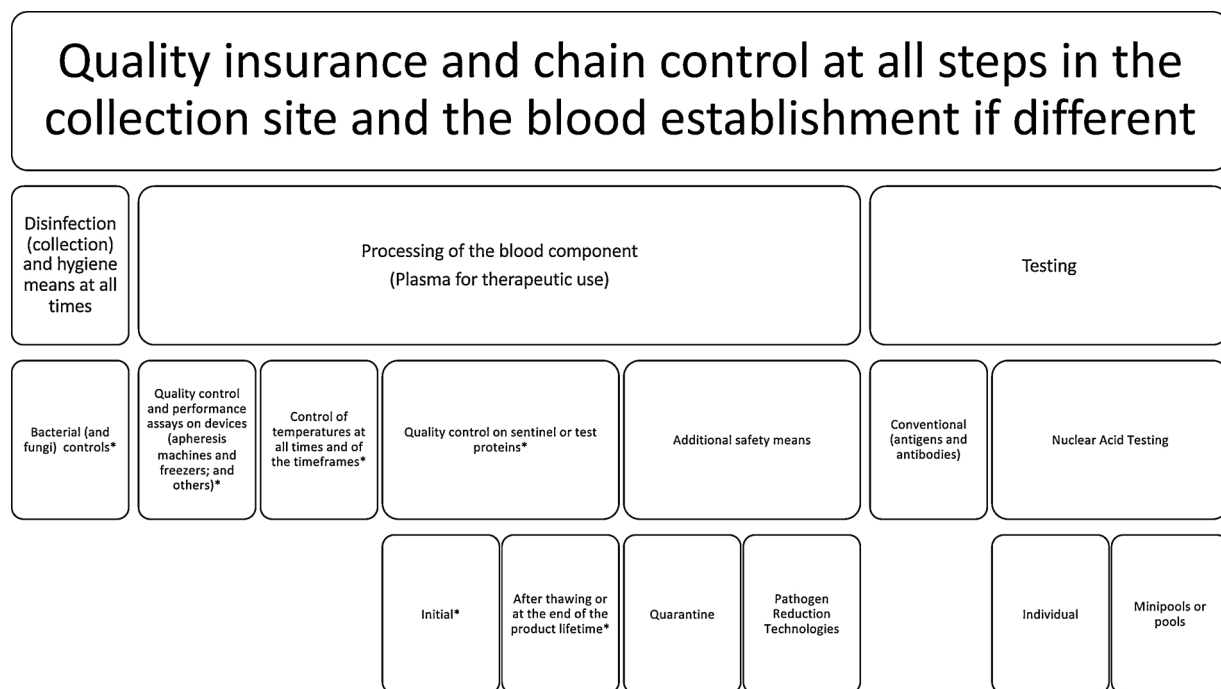


Fig. 2. Safety measures that apply to fresh plasma. Summary of the safety measures that are applied at the different steps of the fresh plasma life circuit. * The controls can be stochastic and on demand or re-qualified or re-certified.

In general, indications for prescribing plasma are restricted and should follow expert recommendations [22]. In hemorrhage and shock, PF transfusion is prescribed more rapidly, after clinical evidence obtained from large clinical trials [23]. In clinical settings in general, FP is used to assist global hemostasis and therefore adequate levels of clotting factors are required compressing all factors that are essential at all stages of the hemostasis and fibrinolysis. All types of FPs available have proven to fulfill this goal to obtain clearance from licensing bodies. It must be noted that FP is comprised of more than three hundred proteins with identified biological activity; consequently, crystalloids and colloids, as well as other volume expanders cannot replace them. There are evidence-based indications for FP transfusion in traumatology, intensive care, anesthesiology, and surgery with novel indications of ratios respective to red blood cell concentrates (and platelet concentrates) as well as the timeframe of the resuscitation protocols [23–25]. There are additional evidence-based medical indications for medical emergencies, such as in TPE protocols for Thrombotic Microangiopathies [26], and particularly thrombotic thrombocytopenic purpura (TTP) [27]. TTP is a rare pathology that requires urgent TPE to bring sustainable levels of ADAMTS13, the enzyme that cleaves multimerized VWF [28]. Besides evidence-based indications, there are also emerging ones. The restoration of endothelium glycocalyx and the prevention of vessel leakage in diverse infectious pathologies have proven to benefit from FP transfusion independent of the infusion of neutralizing antibodies [29,30]; the immunomodulatory and rejuvenating capacity of FP has recently been demonstrated but deserves further clinical study [31].

As novel preparations of FP are made available by blood establishments, they must be evaluated. Liver transplantation remains one of the most reliable models to evaluate global hemostasis and to license or evaluate new FP types [32]. TTP remains the best model for evaluating the types of FP that can be considered to be used in very high volumes of patients, as the treatment of this disease is increasingly standardized worldwide [33]. Currently, retrospective studies have evaluated several types of FP and in particular quarantined, solvent-detergent (SD)- and Amotosalen-inactivated FP. It has been shown that each type of FP could safely treat TTP patients [34]. Two recent studies however observed that TPE regimens based on the use of Amotosalen-inactivated

plasma enabled a moderately but significantly faster platelet count recovery and minimized the global need of FP (in terms of volume) [35,36]. This data deserves a closer look in larger studies to be confirmed; however, it states that ADAMTS13 is likely as robust as Pathogen Reduction Technologies. It also states that there is likely an equal chance of success of TPE for TTP, using any type of FP available at a blood bank. It does not state that the latter assumption holds true for other pathologies, as pathophysiology is different and treatment may rely on factors that may be more or less vulnerable to the various Pathogen Reduction Technology processes. Regarding tolerance, as TPE exposes the patient to a variety of events each carrying a risk of being allergenic, preference is generally given to the standard, which is SD-FP (though AI-FP can be a possibility) over Quarantined FP. The quite exhaustive French hemovigilance network, which reports major but also minor adverse reactions has shown that individual, quarantined FP might be slightly less tolerated than Pathogen-inactivated FP and lead to more frequent reports of allergic-type reactions or anaphylaxis [37]. There is no clear-cut explanation for this observation as pro-allergenic factors are not diluted in pathogen-inactivated individual FP units; pooled FP units may bring dilution of allergenic factors. It has been proposed that the processes can interfere with the complement cascade, though this remains to be formally ascertained. Mini pools of FP units could be another interesting option.

In total, the majority of observations reported so far are in favor of the efficacy equivalence of all types of FP for TPE regimens (despite doubts that are regularly cast on MB-FP, though that is debatable [38]). Caution should be shown for newer types of FP (liquid, dried) that are basically designed for trauma and hemorrhagic emergencies rather than for medical resuscitation. Validation per component is recommended per pathology to ensure that the FP type appropriately provides the needed factors accordingly.

Disclosures

Both authors have received invitations to attend key opinion leader seminars by industrial societies promoting pathogen reduction technology solutions; the TTP-study having compared Amotosalen-

inactivated plasma to solvent- detergent inactivated plasma (Ref: [x]) benefited from sponsorship by Cerus-Europe, Amersfoort, NL.

References

- [1] Bryan Jr. AW, Staley EM, Kennell Jr. T, Feldman AZ, LA 3rd. Williams, Pham HP. Plasma transfusion demystified: a review of the key factors influencing the response to plasma transfusion. *Lab Med* 2017;48:108–11.
- [2] Winters JL. Plasma exchange in thrombotic microangiopathies (TMAs) other than thrombotic thrombocytopenic purpura (TTP). *Hematol Am Soc Hematol Educ Program* 2017;1:632–8.
- [3] MacLennan S. Focus on fresh frozen plasma - facilitating optimal management of bleeding through collaboration between clinicians and transfusion specialists on component specifications. *Presse Med* 2016;45(7-8 Pt 2):e299–302.
- [4] Garraud O, Aubron C, Ozier Y, Coppo P, Tissot JD. Plasma for direct therapeutic use, for today and tomorrow: a short critical overview. *Transfus Clin Biol* 2018;25:281–6.
- [5] Garraud O. Are all therapeutic plasma preparations the same: Is it worth assessing them in clinical trials? *Transfus Apher Sci* 2017;56:920–3.
- [6] Garraud O, Tissot JD. Blood and blood components: from similarities to differences. *Front Med (Lausanne)* 2018;5(84).
- [7] Yazer MH, Seheult J, Kleinman S, Sloan SR, Spinella PC. Who's afraid of incompatible plasma? A balanced approach to the safe transfusion of blood products containing ABO-incompatible plasma. *Transfusion* 2018;58:532–8.
- [8] Cardigan R, Green L. Thawed and liquid plasma—what do we know? *Vox Sang* 2015;109:1–10.
- [9] Sailliol A, Martinaud C, Cap AP, Civadier C, Clavier B, Deshayes AV, et al. The evolving role of lyophilized plasma in remote damage control resuscitation in the French Armed Forces Health Service. *Transfusion* 2013;53(Suppl 1):65S–71S.
- [10] 19th edition European directorate for the quality of medicines & HealthCare. Guide to the preparation, use and quality assurance of blood components. Recommendation No. R (95) 15. *HealthCare*; 2017.
- [11] Seltsam A, Müller TH. Update on the use of pathogen-reduced human plasma and platelet concentrates. *Br J Haematol* 2013;162(August (4)):442–54. <https://doi.org/10.1111/bjh.12403>.
- [12] Prudent M, Tissot JD, Lion N. Proteomics of blood and derived products: what's next? *Expert Rev Proteomics* 2011;8:717–37.
- [13] Saw CL, Hannach B, Petraszko T, Nickerson P. Blood donors implicated in transfusion-related acute lung injury with patient-specific HLA antibodies are more broadly sensitized to HLA antigens compared to other blood donors. *Transfusion* 2013;53:518–25.
- [14] Kakaiya RM, Triulzi DJ, Wright DJ, Steele WR, Kleinman SH, Busch MP, et al. National Heart, Lung, and Blood Institute (NHLBI) Retrovirus Epidemiology Donor Study-II. Prevalence of HLA antibodies in remotely transfused or alloexposed volunteer blood donors. *Transfusion* 2010;50:1328–34.
- [15] Andreu G, Boudjedir K, Muller JY, Pouchol E, Ozier Y, Fevre G, et al. Analysis of transfusion-related acute lung injury and possible transfusion-related acute lung injury reported to the French hemovigilance network from 2007 to 2013. *Transfus Med Rev* 2018;32:16–27.
- [16] Otrrock ZK, Liu C, Grossman BJ. Transfusion-related acute lung injury risk mitigation: an update. *Vox Sang* 2017;112:694–703.
- [17] Dewachter P, Castro S, Nicaise-Roland P, Chollet-Martin S, et al. Anaphylactic reaction after methylene blue-treated plasma transfusion. *Br J Anaesth* 2011;106:687–9.
- [18] Hauser L, Roque-Afonso AM, Beylouné A, Simonet M, et al. Hepatitis E transmission by transfusion of Intercept blood system-treated plasma. *Blood* 2014;123:796–7.
- [19] Bost V, Odent-Malaure H, Chavarin P, Benamara H, Fabrigli P, Garraud O. A regional haemovigilance retrospective study of four types of therapeutic plasma in a ten-year survey period in France. *Vox Sang* 2013;104. 337–4.
- [20] Bost V, Chavarin P, Boussoulade F, Fabrigli P, Chabre C, Benamara H, et al. Independent evaluation of tolerance of therapeutic plasma inactivated by amotosalen-HCl- UVA (Intercept™) over a 5-year period of extensive delivery. *Vox Sang* 2015;109:414–6.
- [21] Saadah NH, van Hout FMA, Schipperus MR, le Cessie S, et al. Comparing transfusion reaction rates for various plasma types: a systematic review and meta-analysis/regression. *Transfusion* 2017;57:2104–14.
- [22] Green L, Bolton-Maggs P, Beattie C, Cardigan R, Kallis Y, et al. British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding. *Br J Haematol* 2018;181:54–67.
- [23] Pavenski K, Stanworth S, Fung M, Wood EM, Pink J, Murphy MF, et al. International collaboration for transfusion medicine guidelines (ICTMG). Quality of evidence-based guidelines for transfusion of red blood cells and plasma: a systematic review. *Transfus Med Rev* 2018;1(June (18)):30017–8. <https://doi.org/10.1016/j.tmr.2018.05.004>. pii: S0887- 7963.
- [24] Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. PROMMTT Study Group. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg* 2013;148:127–36.
- [25] Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. PROPPR Study Group. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2019;3(313):471–82.
- [26] Schwartz J, Padmanabhan A, Aquil N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-Based approach from the writing committee of the American society for apheresis: the seventh special issue. *J Clin Apher* 2016;31:149–62.
- [27] Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood* 2017;129:2836–46.
- [28] Coppo P. French Reference Center for Thrombotic Microangiopathies. Management of thrombotic thrombocytopenic purpura. *Transfus Clin Biol* 2017;24:148–53.
- [29] Barelli S, Alberio L. The role of plasma transfusion in massive bleeding: protecting the endothelial glycocalyx? *Front Med (Lausanne)* 2018;5(91).
- [30] Garraud O, Heshmati F, Pozzetto B, Lefrere F, Girot R, Sailliol A, et al. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. *Transfus Clin Biol* 2016;23:39–44.
- [31] Castellano JM, Mosher KI, Abbey RJ, McBride AA, James ML, Berdnik D, et al. Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. *Nature* 2017;544:488–92.
- [32] Cinquabre J, Kientz D, Remy E, Huang N, Corash L, Cazenave JP. Comparative effectiveness of plasma prepared with amotosalen-UVA pathogen inactivation and conventional plasma for support of liver transplantation. *Transfusion* 2015;55:1710–20.
- [33] Lee LJ, Roland KJ, Sreenivasan GM, Zypchen LN, Ambler KLS, Yenson PR. Solvent-detergent plasma for the treatment of thrombotic microangiopathies: a Canadian tertiary care centre experience. *Transfus Apher Sci* 2018;57:233–5.
- [34] Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, et al. International Working Group for Thrombotic Thrombocytopenic Purpura. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost* 2017;15:312–22.
- [35] Toussaint-Hacquard M, Coppo P, Soudant M, Chevreux L, et al. Type of plasma preparation used for plasma exchange and clinical outcome of adult patients with acquired idiopathic thrombotic thrombocytopenic purpura: a French retrospective multicenter cohort study. *Transfusion* 2015;55:2445–51.
- [36] Herbrecht R, Ojeda-Urbe M, Kientz D, Fohrer C, Bohbot A, Hirschberger O, et al. Characterization of efficacy and safety of pathogen inactivated and quarantine plasma in routine use for treatment of acquired immune thrombotic thrombocytopenic purpura. *Vox Sang* 2018(May 21). <https://doi.org/10.1111/vox.12663>.
- [37] Française Agence. du Médicament et des Produits de Santé. [Annual Hemovigilance Report, 2016] published Dec 2017 last accessed Nov 29, 2018 https://ansm.sante.fr/var/ansm_site/storage/original/application/eb4a3a3c16eefcd5743fe0931100a01.pdf.
- [38] Lozano M, Cid J, Müller TH. Plasma treated with methylene blue and light: clinical efficacy and safety profile. *Transfus Med Rev* 2013;27:235–40.