Recommendations from the Tuscan Transfusion System on the appropriate use of solvent/detergent-inactivated fresh-frozen plasma

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Introduction

The availability of methods and systems for inactivating pathogens in fresh-frozen plasma (FFP) for clinical use raises the question of whether and, if so, to what extent, these treatments, notoriously used to reduce the risk of post-transfusion infections, should be introduced.

The level of transfusion safety guaranteed by selecting donors on the basis of their clinical features and personal history, combined with serological tests and genomic amplification to screen for transmissible infections, is very high, while there are adverse events associated with transfusions that, given their morbidity and mortality, deserve greater attention[1-4]. The current level of transfusion safety makes the cost-benefit ratio of introducing the use of pathogen-inactivated FFP unfavourable, even in the most economically developed countries, if the benefit is measured only in relation to the residual risk of infection[5-14]. Furthermore, cost-efficacy analyses show that the use of further economic resources, to improve the already high level of transfusion safety, must be justified by in-depth evaluations of the particular epidemiological context; in this way it is possible to avoid the paradox that the allocation of resources, withheld from other areas in which epidemiological findings suggest a more appropriate use, could even lower the overall safety of transfusions[9].

Between 2004 and 2005, the Transfusion System of the Region of Tuscany carried out an experimental project for the production of contract manufacturing apheresis plasma to be sent to industry for pathogen inactivation with solvent/detergent (S/D). The aim of this project was to obtain locally-collected pathogen-inactivated plasma for clinical use in the Region and involved all the structures constituting the Region's Transfusion System: 15 Services of Immunohaematology and Transfusion Medicine and their peripheral branches, represented by 25 Transfusion Sections.

After a thorough analysis of the characteristics that could make S/D FFP superior to standard FFP, in 2005 the Regional Blood Transfusion Co-ordinating Centre (RBTCC) drew up proposed recommendations for the use of this blood component, which had recently become available (albeit to a limited extent and at a relatively high cost), with the dual aim of reaching a consensus on its clinical utilization and of supplying an instrument to guide appropriate usage of the product. The recommendations, revised in May 2007 by a regional working group co-ordinated by the Technical Committee of the RBTCC, were kept at a low grade given the lack of studies that were methodologically adequate to provide higher levels of evidence.

The expected benefits of spreading and using the recommendations on the correct use of S/D FFP within the Region are more appropriate use of this blood component and a contribution to Regional self-sufficiency in plasma derivatives, possibly as a consequence of the reduced consumption of plasma for clinical use.

Methodology, levels of evidence and grades of recommendation

According to an authoritative definition[15], guidelines are "recommendations on clinical behaviour, produced through a process of systematic review of the literature and experts' opinions, with the aim of helping doctors and patients to decide the most appropriate care in specific clinical situations".

They are, therefore, created with the purpose of ensuring the highest level of appropriateness of interventions and minimising that variability in clinical decisions related to lack of knowledge and subjectivity in the definition of care strategies.

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In accordance with the indications contained in the methodology manual of the national programme for guidelines[16], the process of developing these recommendations was multidisciplinary and based on systematic reviews of the literature or updating already existing guidelines on the subject. Furthermore, an explicit evaluation was made of the quality of the proof and the strength with which the individual recommendations were adopted and implemented.

The methodology used to prepare the grades of recommendations was drawn from that used by the Consensus Conference of the American College of Chest Physicians in 2004[17].

The recommendations are classified by grade, expressed in Arabic numbers (1,2), according to their strength, and in letters (A, B, C), according to the evidence and type of study.

In detail (Table I):

- *Grade 1*: the authors are certain that the benefits are greater (or less) than the costs in terms of risk and financial expenditure. This is, therefore, a strong recommendation.
- *Grade 2*: the authors are less certain concerning the above points and, therefore, make a weaker recommendation.

As far as regards the classification by letters:

- *Grade A*: a recommendation derived from the evidence of numerous, consistent randomised studies.
- *Grade C+*: a recommendation derived from the analysis of observational clinical studies, but with very consistent results, or from results unequivocally extrapolated from randomised studies.
- *Grade B*: the clinical studies providing the evidence were randomised, but had important limitations (discordant results, methodological flaws).
- *Grade C*: the recommendation derives from an analysis of observational studies, with less consistent results, or from results extrapolated with a lower degree of certainty from randomised studies; recommendations based on the clinical experience/opinion of experts are also classified as grade C.

The verb "recommend" is used for the higher grades (1A, 1C+, 1B, 1C), while the verb "suggest" is used for the lower grades (2A, 2C+, 2B and 2C).

In general, any recommendation other than Grade 1A implies that the authors recognise that there are alternative interpretations of the available evidence and other clinical policies that can, supported by alternative reasoning, be considered appropriate. Furthermore, even the Grade 1A recommendations cannot be applied indiscriminately in every circumstance and in every patient.

The characteristics of FFP inactivated using the S/D method

The definition of priority clinical indications for the use of S/D FFP cannot, for ethical reasons, depend on the criterion of limited availability, nor can it be based on the distinction between categories of patients according to factors such as the severity of the pathology, age or prognosis.

The definition of the indications for the use of S/D inactivated FFP and its proven and/or probable greater benefits compared to those of FFP must be based on an evaluation of the particular characteristics of the product, that is: a) inactivation of transfusion-transmitted pathogens; b) removal of cells and their fragments, achieved by the double filtration; c) standardisation and the diluting effect consequent to the formation of pools of plasma that undergo industrial processing.

The S/D method of pathogen inactivation was patented in 1985 for the treatment of concentrates of coagulation factors[18]; since then it has become the most widely spread industrial method for virucidal treatment of plasma derivatives. S/D FFP was introduced for clinical use in Europe in 1991[19]. It is a biopharmaceutical product subject to marketing authorisation by the relevant regulatory bodies and with declared concentrations of the biologically active proteins. Each batch is prepared from a pool of FFP composed of 500-1,600 donations with given ABO specificities.

The S/D treatment requires that the FFP is thawed rapidly and treated for 4 hours with tri-nitrobutyl-phosphate (TNBP) solvent and with Triton X-100 detergent, both at 1%. The TNBP is then removed by extraction with ricin oil and the Triton X-100 by hydrophobic chromatography; these processes are followed by sterile filtration and packaging in units of 200 mL.

The inactivated FFP is subject to the same inappropriate use as FFP and has the same contraindications; the product information leaflet advises against its use in pregnancy and lactation.

The clinical indications for which S/D FFP is considered appropriate are[20-25]:

- correction of congenital deficiencies of coagulation factors for which there is not a concentrate of the specific factor;
- acquired deficiencies of multiple coagulation factors, when the PT and aPTT are more than 1.5 times higher than normal, in the presence of ongoing bleeding or high risk of bleeding;
- use as the replacement fluid in apheretic treatment of thrombotic microangiopathies;

Table I - Grades of Recommendation

Grade of Recommendation	Clarity of Risk/Benefit	Methodological strength of supporting evidence	Implications
1A	Clear	Randomised controlled trials without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	Randomised controlled trials with important limitations (inconsistent results, methodological flaws)	Strong recommendations; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	Randomised controlled trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2C+	Unclear	No randomised controlled trials but strong results from randomised controlled trials can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	Randomised controlled trials with important limitations (inconsistent results, methodological flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendations; other alternatives may be equally reasonable

- reconstitution of whole blood for exchange transfusion;
- hereditary angioedema due to a deficiency of C_1 esterase inhibitor, in the absence of a specific plasma derivative.

The benefits of viral and bacterial decontamination

The decontamination of S/D FFP is guaranteed by the treatment with the solvent and detergent, immunological neutralisation (due to the physiological presence of neutralising antibodies in the pool of plasma sent for industrial processing), and by double filtration (with 1 μ filters and with the so-called sterilising filters of 0.22 μ), which removes cells, cell fragments and bacteria. S/D treatment, therefore, guarantees a high level of safety with regards to all viruses with a lipid envelope (including the West Nile virus), bacteria, protozoa and intracellular viruses, such as cytomegalovirus, Epstein-Barr virus and human T-cell leukemia virus-I and II. It is not, however, active on viruses without an envelope, such as hepatitis A virus and parvovirus B19; the possible transmission of these latter is, however, greatly reduced by the dilution of any initial viral load, the presence of neutralising antibodies in the pools of plasma, and the hydrophobic chromatography to which the product is subject. Furthermore, nucleic acid amplification technology is used to search for viral genomes of hepatitis A virus and parvovirus 19 in the initial pools of plasma or (as occurs for the Italian product) on the individual accompanying samples, representing the single units of plasma[19,26-39].

Haemophiliacs often have variable levels of immune function depression caused, at least in part, by chronic exposure to the foreign proteins contained in clotting factor concentrates[40-42]; in this population, the use of products that have undergone S/D inactivation has been shown, in both *in vitro* and *in vivo* studies, to have a very high level of viral safety[26].

Indications. The use of S/D FFP is suggested in patients with severe acquired or congenital immunodeficiency,

precisely because of the potential advantage of further lowering the risk of post-transfusion infections compared to the risk following the use of FFP that has not undergone pathogen inactivation. Grade of recommendation: 2C+.

Benefits associated with the removal of cells and cell fragments

The Decree from the Ministry of Health, dated 3 March 2005, concerning the characteristics and methods of donation of blood and blood components[43], and the European Recommendation N. R (95) 15, on the preparation, use and quality assurance of blood components[44], consider $< 6 \times 10^9$/L red blood cells, $< 0.1 \times 10^9$/L leucocytes and $< 50 \times 10^9$/L platelets in FFP as acceptable levels of contamination. The microparticles deriving from cell membranes consist of phospholipid microvesicles containing membrane receptors, other proteins and membrane antigens that enable the cell of origin (red blood cells, platelets, leucocytes, endothelial cells) to be identified; these microparticles range from 0.05 to 1.5 μ in size. The microparticles in FFP are predominantly of platelet origin[45-47]; a reduction in the incidence of refractoriness to platelet transfusions is one of the possible advantages deriving from the use of S/D FFP[19]. The double filtration of S/D FFP removes residual cells and many of their fragments, thus reducing the possibility of allo-immunisation and cell-mediated adverse immunological reactions in the recipient[35,38,48-56].

Indications. The use of S/D FFP is suggested to prevent platelet, red cell and leucocyte alloimmunisation in the following groups of patients: a) women of childbearing age; b) candidates for solid organ transplants (excluding the liver) or bone marrow grafts; c) candidates for long-term transfusion therapy. Grade of recommendation: 2C.

Standardisation and dilution effect

The production of a pool of FFP units leads to the dilution and possible neutralisation of antibodies and allergens in S/D FFP and, also, to a high level of final standardisation of the concentrations of the normal constituents of plasma, which overcomes the biological variability present between single units of FFP[19,27,35,38].

It is obvious that it is easier to use a standardised product than the ordinary FFP which, inevitably, is subject to the biological variability associated with single donors.

1. Use in cases of clotting factor deficiencies

The concentration of factor (F) VIII, which is a labile coagulation factor, is considered a suitable index for evaluating the production process of FFP; the variability in the content of clotting factors in FFP, whether produced by apheresis or separation, can have various causes, including the choice of anticoagulant or lack of standardisation of the procedures used for the collection, preparation, freezing and storage of the FFP[32,57-68]. Furthermore, there are reported variations in the levels of von Willebrand factor (vWF) and FVIII in relation to the ABO phenotype and genotype, ABO subgroups, levels of oestrogens, age and stress[69-80].

S/D FFP contains the same labile and stable clotting factors and other plasma proteins as FFP[81], but in standardised amounts in each batch; the values of the clotting activity are comparable to those of FFP and each factor is present at the minimum declared concentration of 0.5 UI/mL.

S/D FFP has been used successively as replacement therapy, in the presence of bleeding, and for prophylaxis prior to invasive procedures, in patients with deficiencies of fibrinogen, FII, FV, FX, FXI, FXIII, or combined FV and FVIII deficiency[81-83]. There have been no reports of the formation of neo-immunogens or of an increase in the development of inhibitors[84]. S/D FFP is, therefore, to be preferred to FFP if specific factor concentrates are not available or, for deficiencies of FII and FX, if prothrombin complex is not available[84-87].

Indications. The use of S/D FFP is suggested for replacement therapy, in the presence of haemorrhagic events, or for prophylaxis prior to invasive procedures in patients with isolated FV deficiency, combined FV and FVIII deficiency, and deficiency of fibrinogen, FXI or FXIII, if the specific concentrates are not available, and in patients with deficiency of FII or FX, if prothrombin complex is not available. Grade of recommendation: 2C.

2. Benefits associated with the prevention of allergic and febrile reactions

Allergic and febrile reactions to transfusions are generally not severe adverse events. The reported incidence of these reactions varies in different haemovigilance studies, depending on the type of blood component transfused[4, 88-90].

The two ends of the spectrum of clinical pictures caused by allergic reactions to transfusions are the anaphylactic reactions, which are more severe and rarer, and the urticarial reactions, which are milder and relatively more frequent[4,88,89]; these latter are attributed to: a) passive transmission of donor's IgE; b) pre-existing antibodies in the recipient active against proteins or HLA antigens in

the donor's serum; c) exposure of the recipient to allergens present in the donor's plasma. These allergens can also derive from the diet and bind to the IgE on mast cells, causing activation of these cells and release of histamine[90].

The process of making pools of plasma for pathogen inactivation leads to a more than 1000-fold dilution of the antigens/allergens and antibodies responsible for immunological reactions and, as indicated by haemovigilance data, can reduce the incidence of allergic reactions in recipients, particularly if large volumes of plasma are transfused[27,35,38,81,91-95].

Non-haemolytic febrile reactions can be caused by: a) the infusion of inflammatory cytokines and other bioactive molecules contained in the transfused blood component[96]; b) interactions between antibodies in the recipient's plasma and antigens on the transfused cells (lymphocytes, granulocytes, platelets or their fragments), with consequent production of cytokines; c) the formation of antigen-antibody complexes, with consequent activation of complement and the release of cytokines[97]. As shown in haemovigilance studies, also the incidence of this type of reaction can be reduced by the effect of dilution and the double filtration step in the production of S/D FFP[19,38,98].

Indications. The use of S/D FFP is suggested in patients with severe allergic or febrile reactions, particularly if they are candidates for transfusion of large volumes of FFP. Grade of recommendation: 2C.

3. Prevention of transfusion-related acute lung injury (TRALI)

TRALI is an acute, non-cardiogenic pulmonary oedema that can complicate, albeit not frequently, transfusion therapy. It is the most important cause of transfusion-related mortality and morbidity[4,88,89]. It often goes unrecognised, but its incidence has been estimated to be between 1.4 and 8 cases per 10,000 allogeneic units transfused or between 4 and 16 cases per 10,000 patients transfused, with an increasing trend[99-103]. Data from Serious Hazards Of Transfusion (SHOT), the haemovigilance system in the United Kingdom, showed that TRALI is between five to seven times more frequent following transfusion of plasma-rich blood components, with the incidence ranging from 1.25 to 5 cases per 10,000 blood components containing plasma.[4] In fact, plasma is the most frequently involved blood component[101]. The risk factors for TRALI are unclear, but some conditions appear to be associated with an increased incidence: thrombotic thrombocytopaenic purpura (TTP), massive transfusion, recent surgery, active infections, solid organ or bone marrow transplants, induction therapy for haematological neoplasms, the reversal of oral anticoagulation with FFP and heart bypass surgery[101,104]. There are two pathophysiological mechanisms involved: a) an immunological mechanism, that is, the infusion of donor's antibodies directed against recipient's granulocytes or HLA antigens or, viceversa, the binding of recipient's antibodies to antigens on the donor's granulocytes; b) a non-immunological mechanism, which involves a predisposing clinical condition in the patient (surgery, trauma or sepsis) able to cause activation of the pulmonary endothelium, and infusion of bioactive lipids, produced during the storage of the transfused blood component. In both cases the final pathway is increased permeability of pulmonary capillaries, with consequent oedema[101,104-108]. Interestingly, the incidence of TRALI seems to be higher among patients admitted to intensive care units, in whom the presence of predisposing conditions is notably more frequent[109]. The measures most commonly proposed to reduce the risk of TRALI are: a) exclusion of donors involved in cases of TRALI; b) the exclusive use of FFP from untransfused male donors or S/D FFP; c) leucodepletion of cellular blood components issued to patients with anti-leucocyte antibodies[19,110-112]. Further studies, such as the multicentre Leukocyte Antibody Prevalence Study (LAPS) currently underway in the USA, are, however, necessary to provide more information on the prevention of TRALI[113]. The use of S/D FFP is currently suggested because the industrial process of pooling units of FFP notably dilutes or neutralises the anti-HLA and anti-HNA antibodies present in single units[4,19,35,38], thus rendering S/D FFP free of these antibodies[114,115]. The use of plasma from untransfused male donors avoids the infusion of donor anti-leucocyte antibodies, but not that of microvesicles, cell fragments and bioactive lipids[38], which are, on the other hand, almost completely removed by the double filtration used in the production of S/D FFP.

Indications. The use of S/D FFP is suggested for the prevention of TRALI in patients with pre-existing lung damage treated in an intensive care setting, for the treatment of TTP, in the case of massive transfusion, sepsis, solid organ or bone marrow transplantation, during induction therapy for haematological neoplasms and during hearth surgery with extracorporeal circulation and high FFP consumption. Grade of recommendation: 2C+.

4. Treatment of thrombotic thrombocytopaenic purpura

TTP is a syndrome characterised by thrombocytopaenia

and microangiopathic haemolytic anaemia; it is associated with a deficiency of ADAMTS13, which may be congenital (Upshaw-Schulman's syndrome) or acquired. ADAMTS13 is a metalloprotease that prevents the accumulation of high molecular weight multimers of vWF. These high molecular weight multimers, which are not cleaved into low molecular weight multimers because of the lack of the specific enzyme, remain anchored in long chains to endothelial cells and, particularly in the microcirculation, promote the adhesion of platelets, which starts the formation of thrombi[116-119]. Other pathogenic mechanisms have been hypothesised; in the idiopathic forms, these mechanisms extend beyond the deficiency of ADAMTS13 and autoantibodies and seem to involve vWF-independent platelet aggregation, vascular apoptosis and activation[120].

The rationale of the treatment of TTP is based on plasma replacement therapy in the congenital forms and on removal of antibodies by plasma-exchange or immunosuppressive therapy in the acquired forms[116,121]. The replacement fluid used in plasma-exchange must, therefore, contain sufficient levels of ADAMTS13 and be free of the high molecular weight multimers of vWF[122]: S/D FFP fulfils both of these requirements. High molecular weight multimers are not present in S/D FFP, precisely because of the industrial process used to produce this blood component, whereas they are present in standard FFP and FFP in which pathogen inactivation is achieved by methylene blue[94]; this last product seems to be less efficient than FFP in the treatment of TTP[123,124]. The levels of the ADAMTS13 metalloprotease in S/D FFP are normal; furthermore, they are stable even after thawing and storage at room temperature for up to 5 hours[94,122,125,126]. The activity of ADAMTS13 in the plasma of patients with blood group O is about 10% greater than that in patients with blood groups A, B and AB explaining the lower levels of vWF in people with blood group O[127,128].

S/D FFP contains normal levels of factor H[122], a plasma glycoprotein involved in the control of the complement cascade and which has a pathogenic role in atypical haemolytic uraemic syndrome (HUS). HUS is a thrombotic microangiopathy that can present with signs and symptoms overlapping those of TTP, but with compromised renal function being a prominent component of the clinical picture[119,129,130]. The familial forms of HUS associated with factor H deficiency are often treated with plasma-exchange, even though this is less effective than in TTP and does not prevent recurrences or progression towards renal failure[92,119,129]. Various studies have confirmed the efficacy of S/D FFP in the treatment of TTP[35,131-134].

Indications. The use of S/D FFP is suggested for replacement therapy in congenital forms of TTP and as the replacement fluid in apheretic treatment of TTP and in familial forms of HUS associated factor H deficiency; in these conditions, in which large volumes of plasma are necessary, S/D FFP has the additional potential benefit of reducing the incidence of TRALI and allergic and febrile reactions. Grade of recommendation: 2C+.

Transfusion therapy in neonates

S/D FFP has been used in neonates with demonstrated efficacy and safety; the data available do, however, derive from a limited number of studies[91,135].

Indications. Collectively, the particular characteristics of S/D FFP make the use of S/D FFP preferable to that of FFP for all indications in neonates[136]. Grade of recommendation: 2C.

Reported adverse reactions

S/D FFP has been used in Europe for over 15 years and more than 6 million units have been transfused (200 mL/unit). In the USA, this product was authorised for use in May 1998, but production was suspended in 2001 following the notification of six deaths caused by thromboembolic complications following orthotopic liver transplantation[137].

In Europe, a retrospective observational study of patients who had undergone orthotopic liver transplantation revealed a higher incidence of hyperfibrinolysis in patients treated with S/D FFP than in those treated with FFP; the red cell transfusion requirements were not, however, significantly different between the two groups of patients[138]. The hyperfibrinolysis, which was initially attributed to reduced levels of α_2-antiplasmin in S/D FFP, was subsequently correlated to the amount of bleeding. Following modifications of the surgical technique and the introduction of low doses of aprotinin no further thrombotic or haemorrhagic complications occurred[139]. In Norway 208 liver transplants were carried out between 1993 and 2001 using S/D FFP and aprotinin, with no reports of thrombotic or haemorrhagic complications[140]. One randomised study in patients with liver disease and impaired haemostasis who underwent invasive procedures or liver transplantation showed that efficacy and tolerability of FFP and S/D FFP were equivalent and that the transfusion needs in the groups treated with the two products were the same[141,142]. Another prospective, randomised trial compared the effects of treatment with standard FFP and S/D FFP on haemostasis and fibrinolysisis in the complex coagulopathy

that follows open heart surgery; the two types of plasma corrected the haemostasis and fibrinolysis equivalently, although they differed in their ability to raise the levels of activity of protein S and plasminogen inhibitor[143].

There is no evidence that a deficiency of plasmin inhibitor can cause haemorrhagic complications in patients with altered haemostasis treated with plasma; furthermore, there have been no descriptions of persistent bleeding in patients with congenital or acquired deficiency of plasmin inhibitor treated with S/D FFP-based replacement therapy[35,144].

S/D FFP was initially reported not to contain α_2-antiplasmin and to harbour reduced levels of antitrypsin[145], but, subsequently, the complete absence of the plasmin inhibitor was not confirmed[143,146-148]. Some authors also reported a significant loss of FV and FVIII[149], not confirmed by others, and a significant reduction of protein S in all studies. The clinical significance of this last finding is unclear[35].

In the USA three cases of deep vein thrombosis have been reported in patients with TTP treated with plasma-exchange using S/D FFP as the replacement fluid[150]. In contrast, in Europe there have been no reports of thromboembolic episodes directly related to treatment with S/D FFP. In a retrospective analysis of 67 patients with TTP treated with plasma-exchange using S/D FFP produced in Europe seven thromboembolic events were found in six patients, all of whom, however, had additional risk factors for thromboembolism[93]. Thrombotic complications have also been described after the use of standard FFP and plasma cryosupernatant[151,152].

A recent comparative analysis of S/D FFP produced in Europe and the USA confirmed similar reductions in the levels of FV, FVIII and α_2-antiplasmin but revealed considerable differences between the two products: the North American plasma shows a greater decrease in antitrypsin activity, contains residues of TNBP, and has high concentrations of lipoprotein (a), fibrin monomers and C3a des-Arg, a marker of complement activation. Furthermore, the concentration of citrate in the American product is lower and it has almost no protein S activity, whereas European S/D FFP has a moderate reduction of protein S activity and antigen. Collectively, these differences could be responsible for the adverse effects notified after the use of S/D FFP produced in the USA[137].

The differences between the two products derive from the fact that the plasma in the USA is obtained by fractionation and not by apheresis, has a low concentration of citrate and is separated within 15 hours of collection; furthermore, it undergoes concentration and ultrafiltration passages that are not used in the European product[35,137].

Conclusions

The analysis of the literature shows that S/D FFP has been extensively investigated; controlled and observational studies have clearly confirmed that the safety and efficacy of this product are the same as those of standard FFP. That said, the lack of adequate randomised clinical trials means that the level of evidence is currently insufficient to be able to make stronger recommendations on the clinical use of S/D FFP.

Reported adverse events must be given extremely careful attention in prospective haemovigilance studies, even if the available evidence seems to indicate chance occurrence rather than a cause-effect relationship between the administration of S/D FFP and the adverse reactions described.

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