Is solvent/detergent plasma better than standard fresh-frozen plasma? A systematic review and an expert consensus document

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Background. Only a few studies have compared solvent/detergent plasma (SD-plasma) to standard fresh-frozen plasma (FFP) in terms of efficacy and safety.

Materials and methods. A systematic review was performed in order to develop a consensus document on the use of SD-plasma. Moreover, a pharmacoeconomic study was performed in order to assess whether the use of SD-plasma can be cost-effective with respect to the use of FFP. A multidisciplinary panel used the systematic review and the GRADE methodology to develop evidence-based recommendations on this topic.

Results. Based on moderate to very low quality evidence, the panel developed the following consensus statements: (i) the panel suggested that SD-plasma is safer than FFP; (ii) the panel could not express for or against a greater efficacy of SD-plasma as compared to FFP; (iii) the panel suggested that in patients undergoing liver transplantation SD-plasma can be preferred over FFP; (iv) the panel suggested that SD-plasma can be preferred over FFP in patients with thrombotic thrombocytopenic purpura undergoing plasma-exchange procedures; (v) the panel could not recommend for or against preferring SD-plasma over FFP in critical care patients; and (vi) the panel suggested that the use of SD-plasma can be cost-effective with respect to the use of FFP.

Discussion. Data from additional randomised studies are needed to establish more definitive guidelines on the use of SD-plasma.

Keywords: liver transplantation, TRALI, thrombotic thrombocytopenic purpura, fresh-frozen plasma, SD-plasma.

Introduction

The use of fresh-frozen plasma (FFP) has increased steadily over the last years in many countries¹. In Italy, the National Blood Centre reports the use of 2.4 L/1,000 inhabitants/year, which means 140,000 litres or 600,000 plasma units.

Many guidelines have been published about the clinical use of FFP²-⁵, but most of the recommendations are weak because they are not supported by strong evidences.

There are relevant inconsistencies in the practice of transfusing plasma⁶ and a more appropriate use of FFP is needed, because administration of this blood component is associated with a non-negligible risk of adverse events⁷.

Solvent/detergent-treated plasma (SD-plasma) has been developed in order to reduce the risks associated with the use of untreated FFP⁸. Solvent/detergent technology virtually eliminates the risk of transmission of enveloped viruses, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The SD-plasma manufacturing process, which involves pooling thousands of single-donor plasma units, reduces the virus load through dilution and neutralising antibodies present in the plasma pool, lowers the antibody titres against blood cells and plasma proteins, and allows a more standardised content of plasma proteins⁹.

Despite the widespread use of SD-plasma all over the world¹⁰-¹², only one guideline on its use is available¹³.

In order to fill this knowledge gap, the authors decided to perform a systematic review of the literature on SD-plasma, and to formulate recommendations based on the available scientific evidence or, if unavailable or weak, on experts' opinion.
Material and methods

The principal author (MM), after discussion with transfusion experts (MF, FP, GDS), decided to set up an ad-hoc working panel between January and April 2013 aimed at developing a consensus document on the use of SD-plasma. The other panel members were selected in order to ensure a multidisciplinary approach to the topic of the document. An anaesthesiologist with relevant experience in the field of liver transplant (LB), and an health economist (MR), in order to address issues of economic efficiency, were, therefore, included in the group.

The panel members were asked to formulate questions about the clinical use of SD-plasma. After discussion, the panel agreed to limit the present guidelines to the four questions perceived as the most relevant ones.

Each question was assigned to one or more panel members, who were asked to perform a systematic review of the available evidence. MEDLINE, PubMed, the Cochrane Library and EMBASE were systematically searched for publications without language restriction from January 1980 to June 2015. The Medical Subject Heading and key words used were the following: "solvent/detergent treated plasma", "SD-plasma", "Plasmasafe", "Octaplas", "virus-inactivated plasma", "thrombotic thrombocytopenic purpura", "liver transplant", "fresh frozen plasma", "adverse reaction", "haemovigilance", "TRALI", "thrombotic microangiopathy", and "adverse reaction". Randomised clinical trials, longitudinal studies, case series and reports from regulatory agencies were considered if relevant to the issue. Hand-searches from the reference lists of the most relevant items were also performed to identify further eligible studies not captured in the initial literature search. Search terms were also applied to abstracts from the latest international congresses on this issue. The results of the literature search are shown in Figure 1.

The panel used the GRADE method for guideline development. In the GRADE system the strength of recommendations depends on considerations in addition to the quality of evidence, including trade-offs between desirable (benefits) and undesirable effects (harm), uncertainty or variability in values and preferences, practice setting, and uncertainty about whether the intervention represents a wise use of resources (costs).

The strength of the recommendation represents the extent to which confidence in an estimate of the effect is adequate to support the recommendation. If 70% or more of the members voted strongly for (or against) any intervention the panel agreed to issue a strong recommendation (e.g., "The panel recommends..."). A weak recommendation (e.g., "The panel suggests...") was issued if there were insufficient votes for a strong recommendation, but the total votes strongly and weakly for (or against) the intervention comprised 70% or more of the panel. No recommendation was issued if at least 70% of the panel was neither for nor against an intervention, (e.g., "The panel cannot express for or against...").

Question 1. Is solvent/detergent plasma safer than standard fresh-frozen plasma?

Recommendation 1

The panel recommends considering SD-plasma safer than standard plasma (FFP) with regards to the risk of infectious disease transmission and of immunological reactions, namely transfusion-related acute lung injury (TRALI).


Background

Adverse events associated with the transfusion of FFP include TRALI, transfusion-associated circulatory overload, and allergic and/or anaphylactic reactions (ATR). Other less common risks include transmission of infections, febrile non-haemolytic transfusion reactions, red blood cell alloimmunisation and haemolytic transfusion reactions.
Haemovigilance reports reflect a largely variable incidence of adverse events, because the reporting is passive and only optional in many countries. In France, where the reporting of transfusion-associated adverse events is mandatory, the overall incidence of plasma transfusion-associated adverse events in the year 2008 was 1 every 1,346 transfused units. In Australia, STIR 2008 data show an incidence of one serious adverse event every 5,522 plasma units transfused.

The risk of infectious disease transmission dropped in the last two decades because of extensive donor medical screening and infectious disease testing. In the developed Western world, risk estimates for traditional transfusion-associated viruses (HBV, HCV and HIV) vary between 1 in 10^6 and >10 in 10^6.

The risk of prion transmission by plasma transfusion is unclear. Although no case of transmission via plasma transfusion has been reported, animal studies have shown that plasma can contain the infective prion. In the USA and other non-UK countries, potential donors with prion-related risk factors are permanently deferred from donation.

Finally, bacterial contamination of plasma is reported, although rarely. Only five cases of bacterial contamination of FFP were reported in Canada from 2002 to 2003 and five cases in Germany from 1997 to 2007.

As the risk of infectious disease transmission has been greatly reduced by the previously described strategies, non-infectious complications are now in the forefront. The most serious of these complications is TRALI, which is characterised by acute hypoxaemia and non-cardiogenic pulmonary oedema during or within 6 hours of transfusion. Most patients recover within 3 days with respiratory support, but 5-25% of cases are fatal. The primary mechanism of TRALI is the accumulation and activation of neutrophils within the pulmonary endothelium, mainly because of the infusion of donor-derived antibodies against human leucocyte antigens and human neutrophil antigens. A further, but uncommon, non-immune mechanism for TRALI has been described to occur when bioactive substances (e.g. lysophosphatidylcholine, non-polar lipids, and CD40 ligand) that accumulate during the storage of cellular components can induce lung injury in already sensitised patients. The reported rates of TRALI are approximately the same in Sweden and Finland (respectively, 1.8 and 1.5 cases per 100,000 plasma units transfused), and lower in Denmark and the UK (0.4 cases per 100,000 plasma units transfused).

Apart from TRALI, FFP and platelet transfusions are also associated with ATR; in two retrospective studies the rate of these reactions varied from 45 to 169 cases per 100,000 plasma units transfused.

Evidence summary

The low absolute risk of adverse events, both infectious and immunological, associated with plasma infusions can explain the lack of randomised controlled trials directly comparing the safety of FFP with that of any other intervention, including SD-plasma. It seems very unlikely that such trials will be performed in the near future, and clinical recommendations have to rely on indirect inferences.

SD treatment prevents transmission of lipid-enveloped viruses (HIV, HCV, HBV), and no documented case of infection with HBV, HCV or HIV as a result of transfusion with SD-plasma has been reported in the last 20 years. SD treatment has no effect on non-enveloped viruses, but the use of a donor pool for the production of SD-plasma ensures low virus loads in the starting plasma units, dilution through pooling of single plasma units, and neutralisation of immune antibodies already present in the initial plasma pools.

No cases of prion infection following plasma transfusion have been reported, although very recently a case of variant Creutzfeld-Jacob disease transmission by blood products was reported. The theoretical risk of prion transmission is further reduced by the SD treatment process.

Unlike FFP, SD-plasma does not contain antibodies against human leucocyte antigens. Some countries have recently overcome the problem of antibodies in FFP by using FFP from non-transfused males, but this choice creates many logistic challenges, and does not avoid the infusion of microvesicles, cell fragments and bioactive lipids, which are removed by the double filtration used in the production of SD-plasma. The removal of platelet microparticles and the dilution of mediators of ATR may also contribute to a decreased risk of allergic reactions with SD-plasma. Moreover, SD-plasma has been demonstrated to contain smaller quantities of cytokines responsible for adverse immunomodulation reactions (tumour necrosis factor-α, interleukin-8, and interleukin-10) as compared to FFP.

According to published haemovigilance data from Norway, there were no cases of TRALI and a very low incidence of ATR after the exclusive use of SD-plasma in that country. Another haemovigilance report from France shows that pathogen inactivation procedures (solvent/detergent, methylene blue, amotosalen hydrochloride/UVA inactivated) for plasma can reduce adverse events compared to those associated with quarantined plasma; however, the differences were significant for SD-plasma but not for plasma
treated with the other two pathogen inactivation procedures (7 vs 1 adverse event per 10,000 units of FFP or SD-plasma transfused, respectively; p=0.0009)12. Italian Haemovigilance data also show a lower incidence of reported adverse events with SD-plasma than with standard FFP (respectively, 0.1 vs 1.02 adverse events/1,000 units transfused)13.

In brief, the panel members concluded that SD-plasma is safer than standard plasma (FFP) with regards to the risk of infectious disease transmission, TRALI and ATR.

**Question 2. Is solvent/detergent-plasma more effective than standard fresh-frozen plasma?**

**Recommendation 2**

The panel cannot express for or against a greater efficacy of SD-plasma as compared to FFP.

*Strength of recommendation: not applicable. Quality of evidence: very low.*

**Background**

Despite the widespread use of plasma transfusion all over the world, strong evidence of its efficacy is lacking34 because only a few randomised controlled trials, with relevant methodological biases, are available on this topic. Moreover, most of the trials did not consider strong, clinical end-points such as mortality or cessation of bleeding, but evaluated only surrogate, non-clinical end-points such as the improvement of coagulation tests.

**Evidence summary**

We found only six prospective randomised controlled trials comparing SD-plasma with other types of plasma (Table I). All these studies had some methodological flaws and were underpowered to detect clinical differences between the treatments35-40. There was, therefore, no direct evidence of a greater efficacy of SD-plasma with respect to standard FFP.

However, some features of SD-plasma are worthy of attention. Because of its origin from very large pools of donors, SD-plasma has a greater standardisation of plasma protein concentrations, with lower batch-to-batch variations of plasma protein levels as compared to single-donor units41.

Thrombin generation capacity, as evaluated by thrombin generation tests, of SD-plasma and standard FFP is significantly higher than that of methylene-blue-treated plasma42, probably because of the reduced content of functional fibrinogen in the plasma treated with white-light in the presence of methylene-blue dye43. The importance of fibrinogen for clot firmness is well known, and in recent years its crucial role in ensuring sufficient and stable haemostasis during serious bleeding has also emerged44,45.

Hacquard et al. demonstrated that SD-plasma also has smaller ranges of peak thrombin concentrations, areas-under-the curve and lag times than FFP in thrombin generation tests46. These laboratory findings may indicate a more predictable effect of the infused plasma when SD-plasma is used. It is well known that the increases of coagulation factor levels after FFP infusion are highly variable, probably because of the variability in the coagulation factor content between single units of FFP47. In SD-plasma, the pooling of several hundred single-donor FFP units provides a highly standardised product, thus avoiding the variance demonstrated by single-donor...

**Table I - Prospective, randomised studies comparing SD-plasma with other types of plasma.**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wieding, 1999</td>
<td>71 coronary artery bypass patients</td>
<td>SD-P vs MB-FFP</td>
<td>Equal clinical efficacy</td>
</tr>
<tr>
<td>Williamson, 1999</td>
<td>49 patients with coagulopathy of liver disease and liver transplantation</td>
<td>SD-P vs FFP</td>
<td>Equal clinical efficacy; Equal correction of PT</td>
</tr>
<tr>
<td>Beck, 2000</td>
<td>40 patients with coagulopathy</td>
<td>SD-P vs FFP</td>
<td>Equal clinical efficacy; Equal correction of PT</td>
</tr>
<tr>
<td>Lerner, 2000</td>
<td>45 patients with prolonged PT</td>
<td>SD-P vs FFP</td>
<td>Equal clinical efficacy; Equal correction of PT</td>
</tr>
<tr>
<td>Bindi, 2013</td>
<td>63 liver transplant patients</td>
<td>SD-P vs FFP</td>
<td>Equal clinical efficacy; Equal efficacy on TE; SD-P: reduction in volume transfused</td>
</tr>
<tr>
<td>Bartelmaos, 2013</td>
<td>293 liver transplant patients</td>
<td>FFP MB-FFP SD-P</td>
<td>MB-FFP: moderate increase in volume transfused</td>
</tr>
</tbody>
</table>

SD-P: solvent/detergent-treated plasma; MB-FFP: methylene-blue-treated plasma; FFP: fresh-frozen plasma; PT: prothrombin time; TE: thromboelastography.
plasma units. Furthermore, the solvent/detergent process of viral inactivation preserves the function of clotting factors.

In conclusion, the panel members could not express for or against a greater efficacy of SD-plasma compared to FFP. However, the panel members suggested that SD-plasma can be preferred over FFP because of its greater standardisation of coagulation factor content.

**Question 3. Which patients are likely to benefit most from the use of solvent/detergent plasma?**

**Recommendation 3.1**

The panel suggests that in patients undergoing orthotopic liver transplantation, SD-plasma can be preferred over standard FFP because it reduces the amount of plasma transfusions.

*Strength of recommendation:* weak. *Quality of evidence:* moderate.

**Recommendation 3.2**

The panel suggests that SD-plasma can be preferred over standard FFP for patients with thrombotic thrombocytopenic purpura or haemolytic-uraemic syndrome with associated factor H deficiency requiring a high volume of transfusions annually. In patients who have experienced an allergic reaction to FFP or who have a pre-existing lung disorder or are likely to be at high risk of developing TRALI, or other immunological reactions to FFP, SD-plasma may reduce the incidence of TRALI and allergic and febrile reactions.

*Strength of recommendation:* weak. *Quality of evidence:* low.

**Recommendation 3.3**

The panel cannot express for or against a greater efficacy of SD-plasma compared to standard plasma in critical care patients.

*Strength of recommendation:* not applicable. *Quality of evidence:* very low.

**Liver transplant recipients**

Despite substantial improvements in clinical experience and knowledge, orthotopic liver transplantation (OLT) is still associated with a significant risk of bleeding and massive transfusion, which in turn carry a relevant risk of adverse events, above all TRALI, which is very frequent in this context (occurring in up to 29% of cirrhotic patients undergoing surgery).

Three randomised controlled trials compared SD-plasma to standard FFP for the correction of the coagulopathy associated with liver disease and OLT. The first included both patients with liver disease who received plasma for correction of coagulopathy prior to elective invasive procedures (n=24) and patients who underwent OLT (n=25). OLT patients showed equivalent correction of coagulopathy with the same doses of FFP and SD-plasma, and equal requirements of other blood components.

Bindi et al. compared SD-plasma to standard FFP in 63 cirrhotic patients undergoing OLT. Plasma transfusions were guided by a thromboelastography-based protocol. At the end of surgery, the international normalised ratio, activated partial thromboplastin time, antithrombin, factor V and XII and S protein levels were lower in the group of patients who received SD-plasma. However, a significantly smaller quantity of plasma was required in the SD-plasma group in order to attain the same clinical and thromboelastography goals (2,617±1,297 mL in the FFP group vs 1,187±560 mL in the SD-plasma group, p<0.0001). No difference in the incidence of hyperfibrinolysis was observed between the two groups, contrasting with the findings of previous studies, possibly because of the higher content of α,-antiplasmin in the SD-plasma used in this study.

These findings were only partially confirmed by another recently published randomised controlled study comparing SD-plasma, methylene-blue-treated plasma and standard FFP. The authors found that the use of methylene-blue-treated plasma was associated with a moderate increase in volume transfused in comparison to both SD-plasma and standard FFP, but no differences were reported between the latter two.

The discrepancy in the findings of the more recent studies can be explained by differences in evaluating the need for plasma transfusion and in assessing its efficacy. In the study by Bindi et al., stricter criteria were used for the transfusion of plasma, which was decided by the attending anaesthesiologist according to a pre-specified protocol based on both clinical and thromboelastographic data. By contrast, in the study by Bartelmaos et al., the decision to transfuse plasma was left to the anaesthetist.

In conclusion, the panel members suggest the use of SD-plasma in OLT patients, because it could reduce the amount of plasma infused. This may be clinically relevant, because plasma transfusions in such patients increase the rate of respiratory and infectious complications with a trend towards higher mortality.

**Patients with thrombotic thrombocytopenic purpura or haemolytic-uraemic syndrome**

Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterised by thrombocytopenia and
microangiopathic haemolytic anaemia, associated with a deficiency of the metalloprotease ADAMTS13, and may be congenital (Upshaw-Schulman’s syndrome) or acquired.

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. Daily plasma exchange has reduced the mortality rates from over 90 to 10-20%.

The replacement fluid used in plasma exchange has to contain sufficient amounts of ADAMTS13 but must also be free of high molecular weight multimers of von Willebrand factor which are likely to trigger the pathological platelet aggregation. SD-plasma does not contain high molecular weight multimers because of the industrial process used to produce it, whereas its content of ADAMTS13 and of factor H122, a plasma glycoprotein involved in the control of the complement cascade which has a pathogenic role in atypical haemolytic uraemic syndrome, is normal.

Several reports have confirmed the efficacy of SD-plasma in the treatment of TTP, although a direct comparison with standard FFP has not been performed in this setting.

The UK Department of Health recommends the use of SD-plasma in TTP patients to reduce the risk of transfusion-transmitted infection and adverse immune responses, and the same recommendation has been made by the Transfusion System of the Region of Tuscany. SD-plasma contains lower levels of protein S with respect to the levels in FFP, but no increase in the rate of thrombosis was observed in cases in which thromboprophylaxis with low molecular weight heparin and low-dose aspirin was used once the platelet count was >50×10⁹/L.

In 2011 a panel of experts convened on behalf of the Canadian Agency for Drugs and Technologies in Health recommended that SD-plasma be considered for patients affected by TTP or haemolytic uraemic syndrome who require large volumes of transfusions annually because they have factor H deficiency, have experienced an allergic reaction to FFP or have a pre-existing lung disorder.

The panel members agreed with both these recommendations.

**Critically ill patients**

Intensive care patients often require plasma transfusions, but are at high risk of TRALI and ATR. The true incidence of TRALI in intensive care patients is unknown, and it is likely that the number of reported cases is a great underestimate. The only prospective cohort clinical surveillance study which used current diagnostic guidelines for TRALI reported that the incidence of this adverse event, mainly associated to plasma and platelet transfusions, was 8% in the intensive care population.

Lepri et al. recently reported their experience with the use of SD-plasma (Plasmasafe; Kedrion SpA, Castevecchio Pascoli, Italy) in a prospective cohort of intensive care patients compared with a homogeneous historical cohort of patients who were administered FFP. The average volume of SD-plasma transfused per patient was significantly lower than that of standard FFP (503.45 mL vs 1,549 mL, p<0.001), with similar clinical efficacy. No adverse events were observed in any of the patients treated. An economic analysis, with reference made to regional service rates, showed lower individual treatment costs in patients who received SD-plasma than in those administered standard FFP (€ 152.5 vs € 464.7, p<0.001). This study had several limitations, such as the small number of patients and the historical cohort taken as the control group, but it did suggest that the use of SD-plasma in intensive care patients can offer some advantages in terms of transfusion safety and infection reduction, as well as of reduction of transfused plasma volumes and treatment costs.

In conclusion, although there is no direct evidence of greater safety or efficacy of SD-plasma compared to FFP in critically ill patients, the panel suggests that the use of SD-plasma is advisable in intensive care patients in order to reduce the risk of TRALI and ATR in these subjects who are already at high risk of such complications.

**Question 4. Is solvent/detergent plasma cost-effective with respect to standard fresh-frozen plasma?**

**Recommendation 4**

The panel suggests that the use of SD-plasma can be cost-effective with respect to the use of standard FFP.

**Strength of recommendation: weak. Quality of evidence: low.**

**Background**

Pharmacoeconomic evaluations imply a comparative analysis between two treatment strategies, both in term of clinical effectiveness and costs. The incremental cost-effectiveness ratio (ICER), expresses the incremental cost due to an incremental effectiveness as a consequence of an innovative strategy. It also indicates whether the new alternative is sustainable for the healthcare system, depending on a certain threshold representing the willingness to pay for a quality adjusted life year (QALY). This threshold is usually between € 20,000 and € 30,000 per QALY gained.
Evidence summary

A British study evaluated the cost-effectiveness of SD-plasma by using a simulation model based on infectious and non-infectious adverse events deriving from transfusion\(^6\). The reduction of probable adverse events, of deaths or of a substantial deterioration of quality of life following SD-plasma infusion has a potential impact on QALY. Based on the cost-effectiveness ratio for QALY as a function of age and on the incremental cost of SD-plasma vs FFP, the authors concluded that SD-plasma has an acceptable cost-effectiveness ratio when transfused subjects are under 30 years of age\(^6\).

Another model focused on some transfusion complications such as hepatitis B and C, and evaluated percentage risk of onset and risk factors triggering the specific complications. The cost-effectiveness ratio of SD-plasma vs FFP in critically ill patients in the UK was also evaluated based on an analytical decision-making approach. SD-plasma transfusion, compared to FFP had a QALY score of 0.03 with 0.03 life-years saved\(^6\).

These data indicate that SD-plasma is cost-effective compared to standard FFP. However, they do not provide information on budget impact analysis. We, therefore, conducted a pharmacoeconomic analysis of the use of SD-plasma from an Italian perspective based on data on transfusion reactions obtained from the Coordinating Centre for Transfusion Activities of the region of Veneto (Supplementary Table I). Although unpublished, these data fit well with those reported by the Italian Institute for Health\(^3\) showing 10-fold fewer adverse events associated with SD-plasma as compared to standard-FFP.

Deterministic and a probabilistic analyses were performed.

Deterministic analysis

In order to quantify savings resulting from a decrease in the number of transfusion reactions, all resources in terms of diagnostic tests, treatments and additional days in hospital due to the adverse reaction were identified and evaluated for each level of severity, and their costs referred in euros according to the standard rates (see Supplementary Tables II-IV). Multiplying the number of reactions by the cost of the identified issue, it was possible to estimate the costs and the possible savings related to SD-plasma use.

Probabilistic analysis

The range of variation of results observed was subsequently analysed in probabilistic terms based on a Bayesian approach in order to identify minimal saving thresholds. Since fixed rates do not allow for uncertainties, the most important sources of variability of results needed identification.

The variability was hypothesised as being related to: (i) the number of reactions and related symptom distribution; and (ii) the number of hospital days in the case of therapeutic intervention and of resuscitation procedures.

Variability was thus modelled based on the hypothesis of an \textit{a priori} GAMMA-type distribution of numbers of reactions as well as numbers of hospital days. The GAMMA-type distribution led to the identification of three different scenarios: (i) scenario A (probability of 85%) - there was no more than one additional day in hospital or in the intensive care unit (ICU); (ii) scenario B (probability of 10%) - there were no more than two additional days in hospital or in the ICU; and (iii) scenario C (only a 5% probability) - no more than three additional days in hospital or in the ICU.

Results were expressed as minimal and maximal values and relative to the 25th and 75th percentiles of the hypothesised distribution patterns. As a final step, probabilistic curves were developed to illustrate the distribution of potential savings for each of the three scenarios considered. All values are aggregates and refer to 120 patients.

The results of the deterministic analysis, reported in Supplementary Table V, confirm that the use of SD-plasma reduces costs because it reduces mild reactions and avoids reactions requiring therapeutic interventions or resuscitation procedures.

The results of the probabilistic analysis, reported in Supplementary Table VI, demonstrate that:

- in scenario A, values clustered between the 25th and 75th percentiles lead to estimated savings with SD-plasma use in the range of €2,800 to 3,200 in patients with mild reactions, of €2,500 to 4,600 in patients with moderate reactions and of €34,000 to 44,000 in patients requiring resuscitation procedures;
- in scenario B, values clustered between the 25th and 75th percentiles lead to estimated savings in the range of €2,800 to 3,200 in patients with mild reactions, of €5,000 to 9,000 in patients with moderate reactions and of €66,000 to 86,000 in patients requiring resuscitation procedures;
- in scenario C values clustered between the 25th and 75th percentiles lead to estimated savings in the range of €2,800 to 3,200 in patients with mild reactions, of €7,000 to 13,000 in patients with moderate reactions and of €99,000 to 128,000 in patients requiring resuscitation procedures.

The pharmacoeconomic analysis led to the conclusion that SD-plasma is cost-effective as compared to FFP because it lowers costs by reducing transfusion reactions. The savings can range from about €3,000 in the milder scenarios to €100,000 in
patients staying 3 days in an ICU for reactions requiring resuscitation procedures.

Conclusions
This consensus document is aimed to improve the appropriateness of SD-plasma use in common clinical scenarios. However, most of the recommendations are weak because of the lack of strong evidence on this topic. Additional randomised, carefully designed and well-conducted studies considering strong clinical end-point are, therefore, needed in order to establish more definitive guidelines for the use of SD-plasma.

Authorship contributions
MM and MF: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. MLB, FP and GDS: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. MR: study concept and design, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, supervision of the pharmacoeconomic section.

The Authors declare no conflict of interest.

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