Pathogen reduced plasma products: a clinical practice scientific review from the AABB

Melissa M. Cushing,[1] *Monica B. Pagano*,[2] *Jessica Jacobson*,[3] *Joseph Schwartz*,[4] *Brenda J. Grossman*,[5] *Steven Kleinman*,[6] *Mi Ah Han*,[7] *Claudia S. Cohn*,[8] *on behalf of the AABB Clinical Transfusion Medicine Committee*

BACKGROUND: A small body of literature assessing the efficacy and safety of pathogen reduced (PR) plasma has been published.

STUDY DESIGN AND METHODS: An AABB committee systematically reviewed the literature and graded the clinical trial evidence with the assistance of a GRADE expert.

RESULTS: Most studies identified were low quality and had a small sample size; in addition, efficacy and safety were monitored in many different ways making it difficult to quantify therapeutic benefit and risk. The data analyzed in this systematic review showed that pathogen inactivation did not adversely affect the efficacy of S/D or amotosalen plasma transfusions in any patient population studied. In addition, there were no significant safety issues for these patient populations, other than the specific contraindications noted in their respective package inserts.

CONCLUSION: Larger, well-designed trials are needed to further evaluate the efficacy and safety of all of the PR plasma products.

Plasma has been used since the 1940s as a volume expander and to correct or prevent coagulopathy. Despite the millions of units transfused globally each year, the dose, indications, and therapeutic efficacy of plasma are yet to be defined.[1–3] The reasons for this include the lack of adequately powered clinical trials, a scarcity of well-designed retrospective studies and the currently available laboratory testing, which poorly predict risk of bleeding.[4–6]

A small body of literature assessing the efficacy and safety of pathogen reduced (PR) plasma has been published. Due to the potential of these products to provide important safety improvements by decreasing infectious disease transmission, an AABB committee has completed a systematic review of this literature.

From the [1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, the [3]Department of Pathology, NYU Langone Health, the [4]Department of Pathology & Cell Biology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York; the [2]Department of Laboratory Medicine, University of Washington Medical Center, Seattle, Washington; the [5]Department of Pathology & Immunology, Washington University School of Medicine in St. Louis, St. Louis, Missouri; the [6]Department of Pathology & Laboratory Medicine, The University of British Columbia, Vancouver, British Columbia; the [7]Department of Preventive Medicine, College of Medicine Chosun University, Gwangju, Republic of Korea; and the [8]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota.

Address reprint requests to: Melissa M. Cushing, MD, Transfusion Medicine and Cellular Therapy, Weill Cornell Medicine, 525 East 68th St, Box 251, New York, NY 10065; e-mail: mec2013@med.cornell.edu.

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HISTORY OF POOLED-SOLVENT/DETERGENT PLASMA

S/D treated plasma is manufactured by combining plasma units from 630 to 1520 individual healthy volunteer or paid donors.[7] The pooled plasma is filtered to remove residual cells then treated with a combination of solvent and detergent (1% Tri(n-butyl)-phosphate [TNBP] and 1% Octoxynol) to inactivate enveloped viruses. The residual solvent and detergent are removed by oil extraction and chromatography steps. The final product is sterile-filtered, aliquoted, and stored frozen.[8]

Different preparations of S/D plasma have been developed (Table 1). The first S/D plasma licensed in Europe was Octaplas, manufactured by Octapharma, and has been available since 1992. This plasma is S/D treated for 4 hours at 30°C and extracted with medicinal quality castor oil for 60 to70 minutes at 20°C.[9] This product is still used in some countries. A version of first-generation S/D plasma manufactured by Sanquin from 1996 to 2002 showed an increased risk of hyperfibrinolysis when used in liver transplant cases, raising safety concerns and leading to market withdrawal.[10,11]

The first S/D plasma available in North America in 1998 was Plas+SD, manufactured by V.I Technologies Inc. (VITEX). It was discontinued in 2003 after reports of bleeding and thromboembolic complications. Analysis showed that a longer S/D treatment time coupled with an ultrafiltration step caused a greater reduction in plasmin inhibitor (also known as α2-antiplasmin), protein S (PS), and citrate when compared to other S/D plasma preparations. The very low plasmin inhibitor might have increased the risk of bleeding, whereas the reduced levels of PS and citrate likely increased the risk of thromboembolic events.[12]

The second-generation of Octaplas (known as OctaplasLG in Europe and Octaplasma in Canada) has been available since 2009. The main differences that distinguish this second-generation product include a shorter S/D incubation time, which may improve the concentration of S/D labile plasma proteins such as plasmin inhibitor and PS and passage of the S/D plasma over an affinity ligand column designed to bind and remove prion protein.[13] The same product is licensed in the US but the FDA has not allowed for the claim regarding the mitigation of prion-transmission.[9] Although the currently available product in the US is also called Octaplas, it should not be confused with the first-generation product with the same name that is still available in a few places in Europe.

Uniplas is a non-blood group specific (i.e., "universal") version of Octaplas. Specific ratios of plasma of different blood groups are mixed prior to S/D treatment, leading to the neutralization of anti-A and anti-B by binding to free A or B antigens. This product is currently used in select European countries.[14]

PATHOGEN REDUCED PLASMA (NONPOOLED)

By 2009, there were three licensed plasma PI technologies available in Europe, each using heterocyclic compounds

TABLE 1. A comparison of S/D plasma products

Product	Other names	Status	Years available	Countries available	Plasma pool size	Distinctive manufacturing step(s)	Company
1st gen S/D	Octaplas	Currently in use	1992 - present	European countries	Variable	4 hours S/D treatment	Octapharma
	Plasmasafe	Currently in use		Italy	380 liters		Kedrion
VF plasma	N/A	Discontinued	1998-2003	Germany	200 liters		Deutsches Rotes Kreuz
Plas+SD	VITEX	D/C due to thromboembolic complications	1998-2003	US and Canada	650 liters	4 hours S/D treatment; 15′ oil extraction	V.I. Technology
2nd gen S/D	Octaplas LG in Europe	Currently in use	2009 - present	US and some European countries	380 liters	1-1.5 h S/D treatment; 60-70′ oil extraction; prion removal step	Octapharma
	Octaplas in US	Currently in use		Canada	380 liters		Octapharma
	PVA-SD	Currently in use		France	60 liters		Etablissement Francais du Sang
Uniplas	N/A	Currently in use	2010	European countries	380 liters	ABO dilution	Octapharma

S/D = solvent/detergent; Gen = generation; VF = Virusinaktiviertes Frischplasma [virus inactivated fresh plasma]; D/C = discontinued.

that disrupt nucleic acids upon photoactivation. These techniques are: i) amotosalen and UVA (Intercept; Cerus Corp; ii) riboflavin and UV (Mirasol; Terumo BCT); and iii) methylene blue (MB) plus visible light (multiple manufacturers). Intercept plasma was FDA approved in 2014, but it is not currently in use in the US. More detailed information about the production process for Intercept and Mirasol was recently reviewed.[15]

MB was developed by the German Red Cross in Springe, Germany in 1992.[16] The Springe method begins with a freeze–thaw step to lyse leukocytes and potentially release viruses. MB solution is added directly to a fresh frozen plasma (FFP) unit followed by one-sided illumination with fluorescent light for 1 hour.[17] The Springe method, which is used commercially by Grifols, has been modified by Baxter and Macopharma. The Baxter method replaces the freeze/thaw step with a 0.8 μm filtration to remove residual cells and aggregates. Then MB is added, and the unit is exposed to double-sided fluorescent light for 30 minutes. Macopharma, which manufactures Theraflex MB, uses a 0.65 μm filter instead of the freeze/thaw step, adds MB via an anhydrous pill, illuminates both sides of the unit using either sodium lights or light emitting diodes (LED), and removes the residual MB at the end.[18,19]

METHODS

Target patient population

A systematic review of the evidence available was performed to compare the safety and efficacy of PR plasma components compared to non–pathogen reduced plasma in adult and pediatric patients.

Development process

The AABB commissioned and funded this scientific review.

Panel composition

A panel of six experts was convened: five members of the AABB Clinical Transfusion Medicine Committee with expertise in transfusion medicine and a methodology expert in the GRADE process (MH). The panel created multiple questions related to the efficacy and safety of these products in evaluated populations, and then narrowed the questions down to the five most important questions after multiple discussions on conference calls.

Systematic evidence review

A manual and systematic search, from January 1998 through June 2018, of PubMed and Embase was performed in triplicate by MP, CC, and MC using terms associated with pathogen inactivation and solvent/detergent treatment (for full list of search terms see "Appendix" below). Study abstracts were reviewed by at least two committee members for selection based on predefined inclusion criteria.

Inclusion and exclusion criteria

Only studies with full manuscripts available and published in the English language were considered. Trials of products no longer manufactured and trials reporting on patient subsets from other trials were excluded. Only randomized controlled trials (RCT) were included in the efficacy analysis. RCT and observational studies were included in the adverse event analysis. Figure 1 provides a full description of studies included and excluded.

Definitions

A PR plasma product refers either to a pooled, S/D plasma unit, or a plasma product treated with a photoactive agent (amotosalen, riboflavin, or MB) plus ultraviolet or visible light. Conventional plasmas include FFP and quarantined FFP (qFFP).

Evidence grading

Evidence from the RCTs involving PR plasma was graded[20] using the following domains: risk of bias (allocation concealment, blinding, loss of follow-up), inconsistency/unexplained heterogeneity (wide variance of point estimates across studies, deviations from intended interventions, minimal/no overlap in confidence intervals, low p-value for test of heterogeneity), indirectness (differences in population or intervention, indirect comparison, or surrogate outcomes), imprecision (confidence interval of absolute effect), and publication bias (e.g., challenging to assess, all studies small, or industry funded).

To determine the relevance and importance of the outcomes studied in the RCTs, the transfusion experts on the panel each independently graded the trial outcomes for clinical relevance (critical; important, but not critical; limited importance). Each transfusion medicine expert member of the panel was sent a comprehensive list of all outcomes listed in any of the included trials. The list was derived from a group meeting where all outcomes were generated. These results were then reviewed and graded for relative importance by the panel and the number of trials evaluating each important outcome are in Table 2.

SCIENTIFIC REVIEW

During the 20-year interval, there were seven randomized controlled trials evaluating the safety and efficacy of S/D plasma versus various comparators (see Table 3): three in liver transplant/liver disease patients,[21–23] two in open heart surgery,[14,24] one in thoracic aortic dissections,[25] and one in healthy volunteers.[9] Two additional reports were excluded: one described a subset of patients included in another trial[30] and one studied a product that is no longer manufactured and was withdrawn from US and Canadian markets in the 2000s.[31] There were five clinical trials[17,22,26,27,29] evaluating PR plasma in: liver transplant, acquired coagulopathy due to liver disease, thrombotic thrombocytopenic purpura (TTP), anticoagulated patients, and in healthy volunteers. One trial was

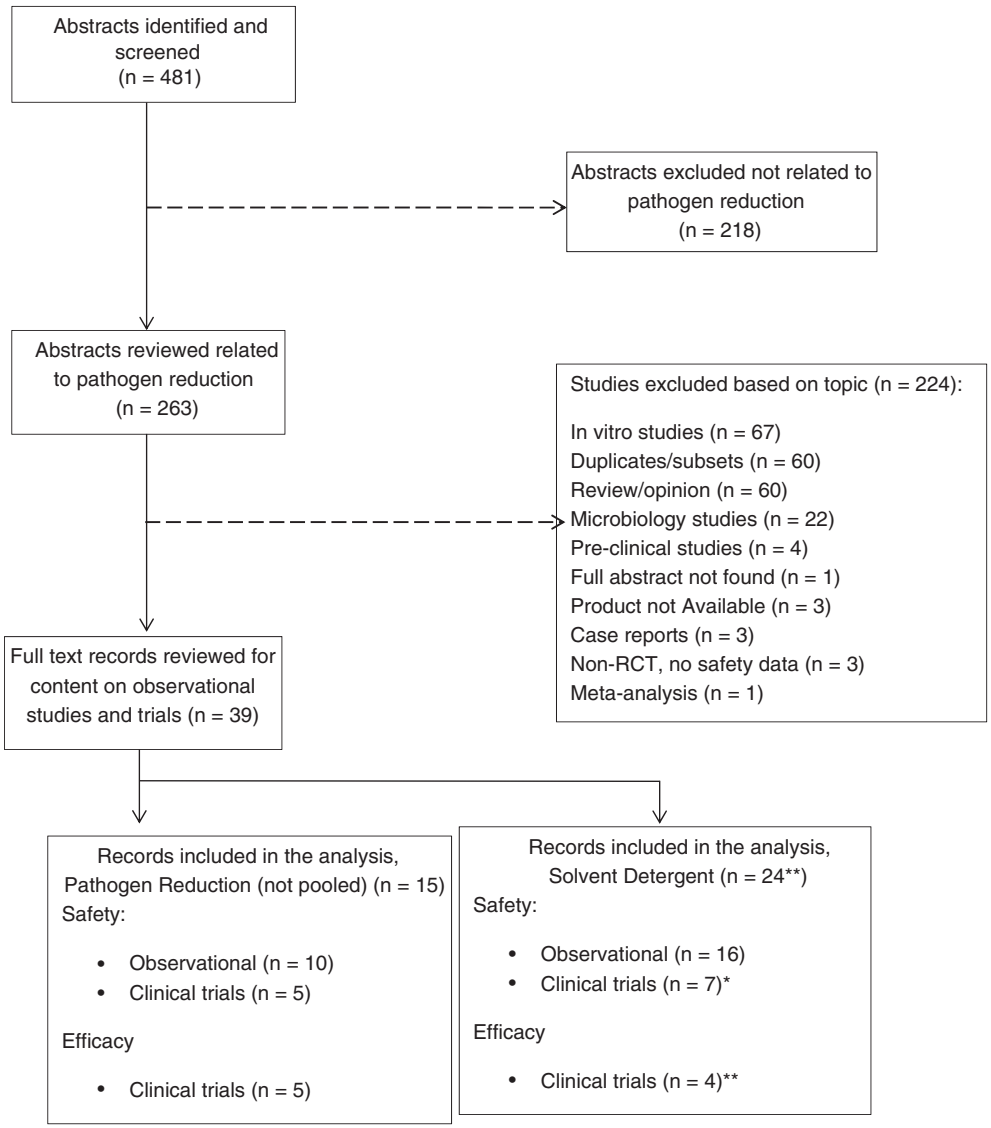

Fig. 1. Literature search and manuscript inclusion.

excluded due to lack of a control group.[32] Efficacy outcomes are stated in Table 2. An overview of trial designs is presented in Table 3. The panel evaluated the appropriateness of the study design(s) and compared the efficacy of the plasma products as a group in Table 4. The overall grading of the efficacy evidence available is provided in Table 5 (S/D plasma) and Table 6 (PR plasma).

PRODUCT EFFICACY

Question 1: Is the currently available version of S/D plasma as effective as conventional plasma?

Population: Patients undergoing liver transplantation or with end-stage liver disease.

Intervention: S/D plasma.

Comparator: Conventional plasma.

Quality of evidence: Low.

Synopsis: Three trials[21–23] evaluated S/D versus conventional plasma in end-stage liver disease or liver transplantation patients. These trials found overall equivalence for efficacy between the two plasma types as measured by volume of plasma transfused and post-transfusion recovery of coagulation factor levels.

Detailed results: Two prospective RCTs enrolled patients undergoing liver transplantation,[21,22] and a third RCT enrolled patients with coagulopathy associated with liver disease undergoing liver transplantation or other surgical intervention.[23] The three trials, which included a total of 408 patients (for N of each trial see Table 3), were successfully randomized so that cohorts were equivalent in terms of age, gender, and severity of disease.

In the first trial,[22] the primary endpoint was the volume of plasma transfused during liver transplantation, with a

TABLE 2. Relevance of outcomes studied in PR and S/D clinical trials

Relevant outcome	Panel grading of relative importance* – mean (standard deviation)	Number of PR clinical trials including outcome	PR references	Number of S/D clinical trials including outcome	S/D references
Surgical & medical coagulopathies					
Serious adverse reactions (including hyperfibrinolysis and thrombosis)[9,17,21–28]	1 (0)	4 of 4	[17,22,26,27]	7 of 7	[9,21–25,28]
Achievement of clinical hemostasis[24,25,27]	1.2 (0.45)	1 of 4	[27]	2 of 7	[24,25]
Infectious disease transmission[23,28]	1.2 (.45)	0 of 4	N/A	2 of 7	[23,28]
Mortality[9,21,23–25,27,28]	1.4 (0.55)	1 of 4	[27]	6 of 7	[9,21,23–25,28]
Extent of correction of factor levels[9,17,21–25,27]	1.4 (0.55)	3 of 4	[17,22,27]	5 of 7	[9,21–24]
Plasma volume transfused[9,21–25,27]	1.6 (0.55)	2 of 4	[22,27]	6 of 7	[9,21–25]
Transfusion reaction rate[9,17,23–26,28]	1.6 (0.55)	2 of 4	[17,26]	5 of 7	[9,23–25,28]
Blood loss[14,22,25,27]	1.8 (0.84)	2 of 4	[22,27]	3 of 7	[14,22,25]
Number of plasma units transfused[14,21,22,25–27]	1.8 (0.84)	3 of 4	[22,26,27]	4 of 7	[14,21,22,25]
RBC unit usage[14,21,22,25,27]	1.8 (0.45)	2 of 4	[22,27]	4 of 7	[14,21,22,25]
Extent of correction of PT/PTT/INR[9,14,17,21–24,26,27]	2 (1)	4 of 4	[17,22,26,27]	6 of 7	[9,14,21–24]
Seroconversion of viral markers[23,28]	2 (1)	0 of 4	N/A	2 of 7	[23,28]
Platelet unit usage[14,21,22,25,27]	2.(0.45)	2 of 4	[22,27]	3 of 7	[14,21,25]
Length of stay[21,25]	2.2 (0.45)	0 of 4	N/A	2 of 7	[21,25]
Complement activation (Uniplas)[28]	2.2 (0.55)	0 of 4	N/A	1 of 7	[28]
Renal failure[21,22,25,27]	2.6 (0.55)	2 of 4	[22,27]	2 of 7	[21,25]
Impact on glycocalyx and endothelium[25]	3 (0)	0 of 4	N/A	1 of 7	[25]
TTP studies					
Time to remission[29]	1 (0)	1 of 1	[29]	No studies	N/A
Thrombosis[29]	1 (0)	1 of 1	[29]	No studies	N/A
Proportion of patients in remission[29]	1.2 (0.45)	1 of 1	[29]	No studies	N/A
Relapse rate[29]	1.4 (0.55)	1 of 1	[29]	No studies	N/A
Number of TPEs[29]	1.4 (0.55)	1 of 1	[29]	No studies	N/A
Time until relapse[29]	1.8 (0.45)	1 of 1	[29]	No studies	N/A
Inhibitor level[29]	1.8 (0.45)	1 of 1	[29]	No studies	N/A

* Panel Grading Relative Importance: 1) Critical; 2) Important, but not critical; 3) Limited Importance (average score submitted by reviewers and standard deviation between reviewers). This table only includes clinical trials, not observational studies nor hemovigilance reports.

comparison of S/D versus qFFP versus MB plasma (details regarding MB plasma are found in the PR section). The decision to transfuse depended on the judgment of the anesthesiologist who was blinded to plasma type. Results showed that the median transfused volume per patient of S/D and qFFP were equivalent; however, fewer qFFP units were transfused (8 units qFFP; 10 units S/D). This was not considered a difference as the equivalence margin was preset at 20%. The comparison of number of transfused units is confounded, as the volume of the units used was not matched (qFFP: 224+/− 15 mL; S/D: 200 mL). There were no differences for secondary endpoints, which included intraoperative blood loss, hemostasis parameters after correction, and AE. No cases of hyperfibrinolysis were reported in either arm and the same number of patients (13 in each group) received tranexamic acid. Study limitations include a lack of generalizability to other patient populations and the differences in volume of S/D versus FFP units.

In the second trial,[21] the primary endpoint was the hemostatic efficacy of S/D plasma vs conventional FFP in cirrhotic patients undergoing liver transplantation.[21] The decision to transfuse was dictated by a TEG-guided algorithm. A significantly greater volume of FFP was transfused when compared to S/D plasma (2617 mL +/− 1297 vs 1187 mL +/− 560.6, respectively) ($p < 0.0001$). In contrast, fewer FFP units were transfused when compared to S/D (4.5 +/− 1.2 vs. 7.5 +/− 3.3 units, respectively) but this was not statistically significant ($p = 0.08$). The volume of conventional plasma units was over twice the volume of S/D units (550 mL vs. 200 mL, respectively) and the difference in the amount of plasma used was probably related to the standard practice of ordering plasma in units rather than by volume for adults. A secondary endpoint was an assessment of coagulation parameters levels after surgery. Although several differences in these coagulation measurements were reported, TEG parameters did not differ, indicating that any difference in initiating fibrin formation was not clinically significant. There were 7 cases of hyperfibrinolysis reported (3 FFP and 4 S/D), which resolved with tranexamic acid administration. Limitations of this trial include a small number of subjects, a single patient population, and lack of generalizability to other patient populations, lack of standard doses or volumes for plasma, RBC and platelet transfusion, and measurement of laboratory tests only at the beginning and end of surgeries with no defined relationship to the timing of plasma transfusions.

The third trial, which compared S/D with FFP, included end-stage liver disease patients who required plasma for liver transplantation or for other surgical procedures.[23] The primary endpoint was correction of coagulopathy, based on a comparison of coagulation lab tests post-transfusion and within 24 hours post- surgery. In both groups (liver transplant and other surgical procedures group) an equivalent correction of coagulopathy, clotting factors, and activated

TABLE 3. Randomized controlled trial descriptions

First author - journal - year	Patient population	Study location	Study type	Intervention-comparison Plasma	Subject number	Primary endpoint	Secondary endpoints
Pathogen reduced plasma studies							
Bartelmaos[22] (2013) Transfusion	Liver transplantation	Multicenter, France	Prospective randomized, blinded	S/D vs. MB vs. FFP	293	Total volume of plasma transfused during liver transplantation	Blood loss; correction of fibrinogen, PT and factor V levels; adverse events. Plasma volume transfused in first transfusion episode.
Mintz[29] (2006) Transfusion	Thrombotic thrombocytopenic purpura (TTP)	Multicenter, USA	Prospective, randomized, controlled, blinded	Amotosalen vs. FFP	35	Proportion of patients in remission within 30 days of first study TPE	Remission, relapse, number of TPEs, volume and number of units exchanged, and VWF activity and inhibitors after TPE
Mintz[27] (2006) Blood	Acquired coagulopathy (mainly liver disease)	Multicenter, USA	Prospective, randomized, controlled, blinded	Amotosalen vs. FFP	121	Changes in PT/PTT after 1st plasma transfusion	FVII level, clinical hemostasis, blood component usage, safety
Simonsen[17] (1999) Vox Sang	Healthy volunteers /autologous	Single Center, Denmark	Prospective randomized, sequential, crossover paired	MB vs. FFP	12	Clinical and biochemical tolerance	Adverse events
Stanojkovic[26] (2012) Transfusion and Apheresis Science	Acquired coagulopathy	Single Center, Serbia	Prospective randomized, controlled, blinded outcomes assessment	Riboflavin vs. FFP	60	Improvement in INR per plasma unit transfused	Adverse events
Solvent/detergent plasma studies							
Bindi[21] (2013) Vox Sang	Liver transplantation	Single Center, Italy	Prospective, unblinded randomized	S/D vs. FFP	63	Hemostatic efficacy (viscoelastic testing and factor levels)	Clinical differences between 2 types of plasma
Haubelt[24] (2002) Vox Sang	Cardiothoracic Surgery	Single Center, Germany	Prospective, consecutive groups of 5 patients receiving one product and then the other	S/D vs. FFP	67	Hemostasis and Fibrinolysis	Adverse events
Jilma-Stohlawetz[9] (2013) Transfusion	Healthy volunteers	Single Center, Austria	Prospective, randomized, open-label crossover	S/D, 2nd gen vs. S/D, 1st gen	60	Recovery of clotting factors, PT, aPTT and Protein C	Adverse events, concentration of plasmin inhibitor after transfusion
Noddeland[14] (2002) Thrombosis Research & Tolllosfrud[28] (2003) Intensive Care Med	Cardiac surgery	Single Center, Norway	Prospective, parallel group, controlled, randomized, blinded laboratories values	S/D vs. Uni-S/D vs. no plasma	84	Bleeding and hemostatic activity (Noddeland)/ Complement activation and incompatibility reactions due to low titer anti-A and anti-B (Tollosfrud)	Safety
Stensballe[25] (2018) Anesth Analg	Emergency surgery for thoracic aortic dissections	Single Center, Denmark	Randomized, blinded, pilot study	S/D vs. FFP	57	Impact of glycocalyx and endothelial injury	Adverse reactions, endothelial markers, biomarkers, bleeding, transfusion, renal failure, organ failure, length of stay, morbidity & mortality
Williamson[23] (1999) Transfusion	Liver disease and liver transplantation	Multicenter, UK	Prospective, randomized, blinded patients	S/D vs. FFP	49	Efficacy of correcting coagulopathy over 24 hours	Adverse events, viral marker seroconversion 6-18 months after treatment

TABLE 4. Panel evaluation of study design and product efficacy

First author - journal - year	Patient population	Major limitations in study design	Panel evaluation of efficacy	Received industry funded
Pathogen reduced plasma studies				
Bartelmaos[22] (2013) Transfusion	Liver transplantation	None identified	Evidence did not demonstrate a difference in efficacy between FFP, S/D, and methylene blue plasma.	No
Mintz[29] (2006) Transfusion	Thrombotic thrombocytopenic purpura (TTP)	Small sample size, not powered to detect small differences	Evidence did not demonstrate a difference in efficacy between FFP and amotosalen-treated plasma	Yes
Mintz[27] (2006) Blood	Acquired coagulopathy (mainly liver dz)	None identified	Evidence did not demonstrate a difference in efficacy between FFP and amotosalen treated plasma	Yes
Simonsen[17] (1999) Vox Sang	Healthy volunteers /autologous	Small sample size, subjects: not blinded, male only, relatively normal coagulation profiles, received small amount of plasma.	Evidence showed that methylene blue plasma can be safely administered. Clinical efficacy not evaluated.	Yes
Stanojkovic[26] (2012) Transfusion and Apheresis Science	Acquired coagulopathy	Minimal information about demographics of patients and underlying disease status, statistical analysis not optimal. Not fully blinded.	Evidence did not demonstrate a difference in efficacy between FFP and riboflavin treated plasma.	No
Solvent/detergent plasma studies				
Bindi[21] (2013) Vox Sang	Liver transplantation	All patients cirrhotic, no standard doses & volumes used for plasma, RBC and platelets transfusion. Laboratory tests only measured at start and end of surgeries with no relations to the plasma transfusions.	Evidence did not demonstrate a difference in efficacy between FFP and S/D plasma	No
Haubelt[24] (2002) Vox Sang	Cardiothoracic Surgery	Demographics data included only minimal parameters to demonstrate well balanced arms. Hemostasis primary endpoint was assessed using a subjective measure. Study was underpowered to detect small differences with no pre-specified difference referred to in the power calculation.	Evidence did not demonstrate a difference in efficacy between FFP and SD plasma. Lower levels of protein S activity were observed following S/D plasma infusion.	No
Stensballe[25] (2018) Anesth Analg	Emergency surgery for thoracic aortic dissections	Inadequately powered for efficacy. Clinical relevance of study biomarkers is unknown.	Preliminary data in a non-adequately powered pilot trial. Clinical relevance of evidence presented remains unknown.	Yes
Williamson[23] (1999) Transfusion	Liver disease and liver transplantation	Small sample size study; one of the transfusion indications was prophylaxis without bleeding or a procedure. Only 2/3 of patients available for follow-up viral testing. Clinicians were not blinded. Use of cryoprecipitate may have confounded outcome interpretation.	Evidence did not demonstrate a difference in efficacy between FFP and S/D plasma	Yes

TABLE 5. Grading of the evidence for solvent detergent plasma (outcomes listed in Table 2)

Is the currently available version of solvent/detergent plasma as effective as conventional plasma in patients undergoing liver transplantation or with end-stage liver disease?

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
N = 405(3 RCT)	Serious (health care providers not blinded in 2/3)	Not serious (consistent results among studies)	Not serious (included products of interest)	Very serious (confidence intervals not provided)	Very serious (1 study industry funded, 2/3 studies small)	Low

Is the currently available version of solvent/detergent plasma as effective as conventional plasma in patients undergoing cardiothoracic and vascular surgery?

Participants/plasma units (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
N = 208 (3 RCT)	Very serious (health care providers not blinded)	Not serious (consistent results among studies)	Serious (one study included Uniplas, not primary product of interest)	Serious (confidence intervals not provided); sample sizes small	Very serious (2/3 studies industry funded, all 3 studies small)	Low

partial thromboplastin time (aPTT) was achieved with the same dose of S/D or FFP. In the S/D plasma cohort, the INR was significantly higher at baseline and also showed a greater correction post-transfusion. The transfusion of other blood components was equivalent in both cohorts. Study limitations include a small sample size, inappropriate transfusion indications (i.e., plasma given for prophylaxis in the absence of bleeding or an invasive procedure), incomplete blinding of clinicians, and use of cryoprecipitate which may have complicated outcome interpretation.

Population: Cardiac surgery.

Intervention: S/D plasma.

Comparators: Conventional plasma.

Quality of evidence: Low.

Synopsis: One trial evaluated efficacy in cardiac surgery patients, comparing S/D to FFP.[24] Similar clinical and hemostatic outcomes were seen between treatment groups. S/D plasma was associated with lower increments in PS activity and plasmin inhibitor, but these differences were not reflected in clinical outcomes. There were markers of active fibrinolysis before and after infusion of S/D and FFP but there was no evidence of fibrinolysis-induced hemorrhage.

Detailed results: A prospective RCT included 67 patients undergoing cardiac surgery and massive transfusion who were randomized to receive 600 mL of FFP (n = 31) or S/D (n = 36).[24] Hemostatic effect was evaluated using post-transfusion changes in PT and/or aPTT, ATIII, fibrinogen, and D-dimer, as well as chest tube output. There were no significant differences in bleeding (39% of patients with S/D; 42% of patients receiving FFP) and both patient cohorts showed equivalent increases of relevant lab values from baseline values, except Protein S (PS) activity. FVIII changes could not be properly evaluated. PS activity was decreased in both groups pre-transfusion but did not demonstrate a significant increment after S/D transfusion. A decrease in plasmin-plasmin inhibitor complex levels and plasmin inhibitor levels occurred after both types of plasma. Study limitations include the low median dose of plasma (8.5 mL/Kg), not all patients met plasma transfusion criteria at the time of the transfusion, and bleeding assessment was not blinded in a small number of patients.

Population: Emergency surgery for aortic dissection.

Intervention: S/D plasma.

Comparator: Conventional plasma.

Quality of evidence: Low.

Synopsis: This pilot randomized trial used glycocalyx and endothelial injury as primary outcomes, as measured by four biomarkers at 24 and 48 hours post-surgery.[21] When compared to patients receiving conventional plasma, patients transfused with S/D plasma had significantly reduced glycocalyx damage at 24 hours and significantly reduced tight junction injury at 48 hours.

Detailed results: This randomized trial investigated the level of glycocalyx and endothelial injury as the primary outcome in a pilot trial of 57 patients. Plasma levels of

TABLE 6. Grading of the evidence for assessment for pathogen reduced plasma (non-pooled) (outcomes listed in Table 2)

Is pathogen reduced plasma as effective as conventional plasma in patients undergoing liver transplantation or with liver disease?						
Participants/ plasma units (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
N = 414 (2 RCT)	Not serious (both blinded)	Serious (inconsistent results among studies, but two different products compared)	Not serious (included products of interest)	Serious (confidence intervals not provided)	Serious (1/2 study industry funded)	Low

Is pathogen reduced plasma as effective as conventional plasma in patients undergoing cardiothoracic and vascular surgery?						
Participants/ products (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
N = 0 (0 RCT)	n/a	n/a	n/a	n/a	n/a	n/a

Is pathogen reduced plasma as effective as conventional plasma in anticoagulated patients?						
Participants/ products (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
N = 60 (1 RCT)	Very serious (unblinded)	n/a (1 study)	Not serious (included products of interest)	Serious (confidence intervals not provided); sample sizes small	Serious (only 60 patients in 1 study)	Low

Is pathogen reduced plasma as effective as conventional plasma in TTP patients?						
Participants/ products (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
N = 35 (1 RCT)	Not serious (blinded)	n/a (1 study)	Not serious (included products of interest)	Serious (confidence intervals not provided); sample sizes small	Serious (study industry funded)	Low

syndecan-1, soluble thrombomodulin, soluble E-selectin, and soluble VE-cadherin were measured at 24 and 48 hours post-surgery and used as indicators of injury. The decline in syndecan-1 at 24 and soluble VE-cadherin at 48 hours was significantly more pronounced in the S/D cohort indicating less glycocalyx respective endothelial cell damage; however, there were higher levels of IL-6 over the 24 hours post transfusions for S/D. There was significantly greater intraoperative bleeding in the conventional plasma cohort, but this difference was not seen post-operatively. Total blood product use and platelet use was significantly higher in the conventional plasma group, as was use of recombinant factor VIIa. Time on ventilator was also reduced. Total costs for blood products were significantly lower in the S/D group ($3114 vs. $4913). Study limitations include the small number of patients, open label design, and the use of biomarkers of glycocalyx injury as the primary endpoint.

Question 2: Is PR plasma (non-S/D) as effective as conventional plasma?

Population: Patients with acquired coagulopathy of liver disease.

Intervention: Amotosalen/UVA-treated plasma.

Comparators: Conventional plasma.

Quality of evidence: The overall level of evidence was low for this category, but the level of evidence in one study[27] was high.

Synopsis: FFP treated with amotosalen-HCl and UVA light was compared to conventional FFP in one RCT in patients with coagulopathy associated with liver disease.[27] The primary endpoint of correction of coagulation parameters after the first plasma transfusion was equivalent in both groups.

Detailed results: The non-inferiority of amotosalen/UVA-treated plasma compared to conventional FFP was assessed in a blinded, multi-site RCT of 121 patients with acquired coagulopathy of liver disease.[27] The primary endpoint was change in the aPTT and PT after the first plasma transfusion. Secondary endpoints included changes in some laboratory values, clinical hemostasis, and blood component usage. When changes in PT and aPTT were adjusted for FFP dose and patient weight, amotosalen/UVA-treated, and conventional plasma were equivalent for all endpoints. Equivalence was also shown in a sub-group analysis of patients undergoing orthotopic liver transplantation. When

the full dataset was analyzed without adjustment for FFP volume, equivalence was maintained for all metrics except for aPTT. The correction in the aPTT showed a wide variance, which led to the rejection of equivalence, with a slight trend favoring amotosalen/UVA-treated plasma. A limitation of this latter finding is that aPTT is not a good marker for assessing correction of coagulopathy in liver disease.

Population: TTP patients.

Intervention: Amotosalen/UVA-treated plasma.

Comparators: Conventional plasma.

Quality of evidence: Low.

Synopsis: Amotosalen/UVA-treated plasma was compared to conventional FFP in an RCT in 35 TTP patients.[29] Using the correction of coagulation factors and a comparison of the volume of plasma transfused, this trial found overall equivalence.

Detailed results: The trial evaluated the efficacy of Amotosalen/UVA-treated plasma in 35 patients with acute TTP who were randomized to undergo plasma exchange receiving FFP or Amotosalen/UVA-treated plasma as replacement fluid. There were no differences in remission within 30 days, time to remission, relapse rates, time to relapse, total volume and number of plasma units exchanged, or number of exchanges between the two groups.[29]

Population: Patients with an elevated INR.

Intervention: Riboflavin/UV-treated plasma.

Comparators: Conventional plasma (quarantined FFP).

Quality of evidence: Low.

Synopsis: FFP treated with riboflavin and UV light was compared to conventional FFP in a clinical trial that enrolled 60 patients with elevated INR but normal aPTT; further patient details were not provided.[26] Outcomes included post-transfusion change in INR and the number of units required to normalize the INR. A significant increase in the number of Riboflavin/UV-treated plasma units was needed to normalize coagulation laboratory values when compared to the number of conventional plasma units needed to achieve this outcome [84 vs. 68 ($p = 0.039$)].

Detailed results: The clinical efficacy of riboflavin/UV-treated plasma was tested in a prospective, single-center RCT with 60 patients randomized to receive riboflavin/UV-treated or conventional plasma.[26] The primary endpoint was the post-transfusion change in INR; in addition, the number of units required to normalize the INR was assessed. The mean improvement in pre-transfusion to post-transfusion INR after a two-unit transfusion was significantly lower when comparing riboflavin/UV-treated plasma (mean 0.66; range 0.33-1.68) versus conventional FFP (mean 0.83; range 0.32-2.40) ($p < 0.001$). There was a significant increase in the number of plasma units that normalized coagulation parameters in the riboflavin/UV-treated plasma group (mean 2.80 vs. 2.24; $p < 0.05$). Study limitations include a small dose of plasma (6.2 mL/kg), a small sample size, and sparse clinical information about the patient population.

Population: Liver transplantation patients.

Intervention: FFP treated with MB and visible light.

Comparators: Conventional plasma (quarantined FFP).

Quality of evidence: Low.

Synopsis: FFP treated with MB and visible light was compared to qFFP in a clinical trial in liver transplant patients.[22] Patients in the MB cohort received significantly more plasma transfusions than those treated with FFP.

Detailed results: A prospective, blinded, multicenter RCT compared MB and conventional FFP in liver transplant patients.[22] This study found that a significantly greater median volume of MB plasma (2254 mL) was transfused when compared to the volume of qFFP (1798 mL). When the data were adjusted for bleeding risk factors, the excess volume of MB plasma transfused compared to qFFP was 14.5%. Since the a priori equivalence margin was established as 20%, the two products were considered equivalent. Study limitations include a lack of generalizability to other patient populations and the differences in volume of S/D versus FFP units.

Question 3: Are there safety concerns for S/D plasma?

Safety of PR plasma products

Our analysis of the safety of PR and S/D products included both RCTs and observational studies. Evidence grading was not applied as only one RCT used safety as a primary endpoint. There was only very low-quality evidence from observational trials for all safety outcomes. The incidence of adverse events (AE) for S/D and PR plasma could not be readily compared across studies as some studies reported AE per patient, some per product, and some per transfusion episode. In most studies, S/D or PR plasma was not the only product transfused, thus making it difficult to determine which product was responsible for an adverse event.

Synopsis: Fifteen observational trials[33–47] and seven RCTs[9,21–25,28] were used to evaluate the safety of S/D plasma. No study reported an increase in AE in S/D plasma compared to conventional plasma and most reported a decrease. Allergic reaction rates were lower with S/D plasma compared to conventional plasma. Three studies found no differences in clinical fibrinolytic episodes or laboratory evidence of hyperfibrinolysis.

Viral transmission

Viral transmission was evaluated in 8 S/D plasma studies. Parvovirus B19 seroconversion was identified in one patient who had received only FFP, not S/D.[23] The remainder of the studies found no infectious disease transmission. In one open-heart surgery trial, a single multi-transfused patient (1/36) on the Uniplas arm had an increase in anti-Hepatitis A IgG, but no IgM antibodies were detected.[28]

Allergic reactions

Seventeen studies using S/D plasma and one using Uniplas reported allergic reactions. Reaction rates were only evaluated for larger studies (defined as 50 or more subjects) since many studies included a small number of patients transfused

multiple times and some individual patients had high reaction rates. Reaction rates ranged from 0.0% to 14.8%; (Table 7) however, the rates were consistently lower with S/D compared to conventional plasma, but the evidence was low quality and the lower rates could have been related to chance alone. Only one study contained data on pediatric or neonatal populations.[46] One crossover trial with healthy volunteers had higher allergic reaction rates compared to other plasma studies, but this may be a result of the use of active surveillance.[9]

In one study of 18 patients with thrombotic microangiopathies,[38] 17 were switched from standard frozen plasma or cryosupernatant plasma to S/D plasma, 15 due to an allergic transfusion reaction during the current treatment course, one due to a history of severe allergic reactions to plasma and one because of a perceived risk of TRALI. After being switched to S/D plasma, 12 patients did not experience any further allergic reactions and five had only one additional allergic reaction during the remaining treatment course. None had recurrent allergic reactions.

TRALI

No case of confirmed TRALI has ever been reported for S/D plasma. One retrospective observational TTP study reported an adverse reaction associated with S/D plasma as "TRALI suspicion," but no details about the reaction were reported, the study did not mention whether patients may have been concurrently transfused other blood products, and that reaction was never reported in a separate case report.[44]

Complement activation and hyperfibrinolysis

Three studies reported on hyperfibrinolytic episodes. One randomized controlled trial and one prospective observational study showed no difference with regard to the number of hyperfibrinolytic episodes and need for antifibrinolytic medications.[21,37] In a comparison of cardiac surgery patients receiving either S/D or FFP, one study found decreased levels of PS and plasmin inhibitor in the S/D plasma cohort (first-generation S/D product with longer S/D incubation time), but no difference in hyperfibrinolysis.[24] Four studies evaluated and found no evidence of complement activation.[28,37,42,43]

TABLE 7. A comparison of allergic reaction rates for SD versus conventional plasma

S/D plasma	Conventional plasma	Study author
Allergic reactions/patients (%)		
0/36 (0%)	0/31 (0%)	Haubelt[24]
1/81 (1.2%)	N/A	Solheim[42]
16/509 (3.1%)	16/172 (9.3%)	Scully[40]
7/81 (8.6%)	8/27 (29.6%)	Toussaint-Hacquard[44]
20/981 (2.0%)	N/A	Vendramin[45]
1/35 (0.3%)	N/A	Witt*[46]
Allergic reactions/10,000 transfusions		
4.86	7.14	Bost[47]

* Pediatric patients.

Thromboembolism

Five single-arm observational studies reported on thromboembolism with S/D plasma: three in TTP patients[38,40,45] and two in liver resection/liver transplant patients.[37,42] While high thromboembolic rates (up to 12%) were reported, these rates are expected in these patient populations. Since these were uncontrolled observational studies, no information is available on the risk of thromboembolism with FFP in the same patient groups.

Question 4: Are there safety concerns for PR plasma (non-S/D)?

Synopsis: Nine observational trials[32,47–55] and six RCTs[17,22,26,27,29] were used to evaluate the safety of PR plasma. No study reported an increase in AE in PR plasma compared to conventional plasma and most reported similar or decreased AE. There were no cases of suspected or confirmed TRALI for PR plasma. In most studies, the allergic reactions rates were lower or similar with PR compared to conventional plasma. No studies found an increase in clinical fibrinolytic or thrombotic episodes.

Viral transmission

No viral transmissions were noted for PR plasma, but only one study[55] monitored this outcome.

TRALI

No cases of TRALI occurred with PR plasma, while TRALI was reported at varying frequencies in the comparator plasma products.

Allergic reactions

Four RCT and seven observational studies reported allergic reaction rates, which ranged from 1.05 per 10,000 units using MB-plasma; 33.2 using riboflavin/UVB-treated plasma; and 853 using amotosalen/UVA-treated plasma (Table 8). Similar to S/D studies, PR allergic reaction rates were only evaluated for larger studies including 50 or more subjects. In each study that included a comparison plasma group, the rates of allergic reactions were lower using PR than for conventional plasma, except

TABLE 8. A comparison of allergic reaction rates for PR versus conventional plasma

Type of PR plasma	PR plasma	Conventional plasma	Study author
Allergic reactions / 10,000 transfusions			
Methylene blue	1.05	7.14	Bost[47]
Methylene blue	3.62	N/A	Noens[54]
Methylene blue	1.18	4.59	Politis[55]
Riboflavin	33.2	69.8	Letowska[53]
Amotosalen	4.16	7.14	Bost[47]
Amotosalen	2.4	3.4	Bost[56]
Allergic reaction rate / patient			
Amotosalen	26%	26%	Mintz[29]
Amotosalen	8%	4.3%	Guignier[50]

for Guignier et al who reported a higher number of allergic reactions in patients with thrombotic microangiopathies receiving amotosalen/UVA-treated plasma versus qFFP (7/65 [8%] vs. 1/23 [4.3%]; this was not statistically significant).[50] Another TTP study reported an equivalent urticarial rate (26%) in the PR and conventional plasma cohorts.[29] No study reported rates specific for pediatric or neonatal populations.

Complement activation and hyperfibrinolysis

Five RCT and 10 observational studies reported no occurrence of complement activation or hyperfibrinolysis for patients receiving PR plasma.

Thromboembolism

One RCT (liver disease) and two observational studies (liver transplant and TTP) reported on thromboembolism as part of AE (none included prospective monitoring). No study reported significant differences in incidence rates of thromboembolism for PR versus conventional plasma.[27,49,51]

Question 5: Are there specific indications, contraindications, or limitations for S/D or PR plasma?

There are no specific indications for S/D or PR plasma versus conventional plasma and virtually no restrictions for the use of PR plasma products with the exception of those listed below. Due primarily to the cost of PR, some blood suppliers/national blood systems have targeted use of these products for persons who are expected to receive large quantities of plasma (e.g, TTP patients) in order to minimize the risk of their acquiring a transfusion-transmissible infection. Some hospitals provide S/D plasma for patients who have had severe or recurrent allergic reactions to conventional plasma.

According to the package insert, PR plasma and S/D plasma should not be the primary replacement product for patients with severe PS deficiency as PS levels are reduced in both S/D and PR plasma.

According to the package insert, amotosalen/UVA-treated plasma is contraindicated for neonatal patients treated with phototherapy devices that emit wavelengths less than 425 nm due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen. However, most phototherapy devices emitting at this wavelength are off the market.[57,58] The wavelength of UV light used for Mirasol PR plasma is 313 nm which does not overlap with wavelengths used for the treatment of jaundice in neonates. PR plasma is contraindicated for patients with a history of hypersensitivity reactions to psoralens.

There are limited data in the pediatric population. Our review did not identify any signals to indicate a problem with use in this population, but further research is needed.

CONCLUSIONS

There are a limited number of clinical trials evaluating either PR or S/D plasma products. Most are low quality and have a small sample size; in addition, efficacy and safety were monitored in many different ways making it difficult to quantify therapeutic benefit and risk. Nevertheless, the available evidence indicates that PR plasma products are as efficacious as conventional plasma products in a variety of patient populations and clinical conditions, except in the case of methylene blue and riboflavin PI plasma where two studies[22,26] found that additional units of PR plasma were administered compared with standard plasma components to achieve similar hemostatic benefit as measured by PT or PTT. The quality of the evidence available to support the efficacy findings was very low.

With regard to non-infectious AE, this review has summarized evidence which, in aggregate, indicates that currently available S/D and PR plasma products have no documented deleterious effects compared to conventional plasma products. Furthermore, they appear to have lower rates of allergic reactions and TRALI.

This review did not include an assessment of the already proven increased safety provided by PR plasma with regard to reducing infectious disease transmission of major transfusion-transmitted pathogens (HIV, HCV, HBV, WNV), which is the original purpose for the development of these products, and which has been documented by in-vitro experiments and by data reported through hemovigilance. This factor, as well as the additional cost of the products, should be considered when deciding whether or not to use these products.

In conclusion, the data analyzed in this systematic review showed that pathogen inactivation did not adversely affect the efficacy of S/D or amotosalen plasma transfusions in any patient population studied. In addition, there were no significant safety issues for these patient populations, other than the specific contraindications noted in their respective package inserts. Larger, well-designed trials are needed to further evaluate the efficacy and safety of all of the PR plasma products.

APPENDIX – SYSTEMATIC REVIEW OF THE EVIDENCE

We combined a manual and systematic search of two databases, PubMed and Embase, from January 1, 1998 through June 2018 using terms associated with pathogen inactivation and solvent/detergent treatment *((“plasma transfusion”/exp AND (“pathogen reduction system”/exp OR “solvent detergent” OR “sd plasma” OR “pi plasma” OR “pathogen inactivated” OR ‘pathogen inactivation’ OR “pathogen reduced” OR ‘pathogen reduction’ OR octaplas OR uniplas OR uniplasma OR mirasol OR intercept OR theraflex OR sd OR “s d” OR hemovigilance OR haemovigilance OR surveillance OR biovigilance OR “methylene blue”) AND (“clinical article”/de OR “clinical trial”/de OR “cohort analysis”/de OR “comparative study”/de OR “controlled clinical trial”/de OR “controlled study”/de OR “major clinical study”/de OR “multicenter study”/de OR “observational study”/de OR “prospective*

study"/de OR "randomized controlled trial"/de OR "randomized controlled trial (topic)"/de OR "retrospective study"/de OR "comparative effectiveness"/de OR "patient safety"/de OR "treatment outcome"/de) AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py)) NOT ("conference abstract"/it OR "conference paper"/it OR "editorial"/it OR "letter"/it OR "note"/it OR "review"/it OR "short survey"/it OR "case report"/de).

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CONFLICTS OF INTEREST

MMC is a consultant for Cerus Corporation and Octapharma.
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SK is a consultant for Cerus Corporation.
BJG, MAH have declared no conflicts of interest.
CSC has served as the site PI for a clinical trial of Octaplas (LAS-213).

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