Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER

31

Blood, blood components, plasma, and plasma products

Seohyun (Claudia) Choi, BS, PharmD, BCCCP[*,†,1], *Michael Casias, PharmD, BCIDP, AAHIVP*[*,‡], *Danielle Tompkins, PharmD, BCCCP*[*,§], *Jimmy Gonzalez, PharmD, BCPS*[*,¶], *Sidhartha D. Ray, PhD, FACN*[‖]

*Department of Pharmacy Practice and Administration, Rutgers, The State University of New Jersey, Piscataway, NJ, United States

†Medical Intensive Care Unit, Saint Barnabas Medical Center, Livingston, NJ, United States

‡Hunterdon Medical Center, Flemington, NJ, United States

§Hackensack University Medical Center, Hackensack, NJ, United States

¶Jersey Shore University Medical Center, Neptune City, NJ, United States

‖Department of Pharmaceutical & Biomedical Sciences, Touro College of Pharmacy, New York, NY, United States

[1]Corresponding author: seohyun.choi@pharmacy.rutgers.edu

ALBUMIN AND DERIVATIVES [SEDA-15, 54; SEDA-37, 403; SEDA-38, 335; SEDA-39, 331; SEDA-40, 415]

Albumin

Benefits of albumin administration for large volume resuscitation have been controversial for many years. Although a recent review stated that albumin might have immunomodulatory and anti-inflammatory, antioxidant properties, the evidence of albumin for fluid resuscitation is still inconclusive [1R]. A multicenter, randomized, parallel, open-label, pragmatic trial evaluated the efficacy of long-term human albumin administration in decompensated cirrhosis. A total of 431 patients included in the study received standard treatment (combination of aldosteronic drugs and furosemide) or standard treatment plus long-term human albumin for up to 18 months. Overall, 18-month survival rate was higher in the standard treatment plus long-term albumin than standard treatment alone group (77% vs 66%; $P = 0.028$), and there were no difference in non-liver related adverse events [2C].

In a prospective single-blinded study with non-critical illness patients ($n = 100$) undergoing elective cystectomy showed no difference in renal function when 5% albumin was compared to balanced 6% hydroxyethyl starches for volume replacement. Renal function was assessed and analyzed with serum cystatin C concentrations; estimated glomerular filtration rate; risk, injury, failure, loss, and end-stage renal disease criteria; and neutrophil gelatinase-associated lipocalin [3C].

BLOOD TRANSFUSION [SEDA-15, 529; SEDA-37, 404; SEDA-38, 336; SEDA-39, 331; SEDA-40, 415]

Erythrocytes

Infection

An 18-year-old patient with sickle cell disease who was receiving monthly red blood cell (RBC) transfusions presented with veno-occlusive crises and multi-organ failure. Patient was diagnosed with hemolytic transfusion reactions and transfusion-transmitted infections, which was confirmed to be *Plasmodium falciparum* [4A].

Cardiovascular

A meta-analysis of 17 observational studies demonstrated that RBC transfusion was associated with higher risk for all-cause mortality and acute coronary syndrome (adjusted RR 2.23; 95% CI 1.47–3.39; HR 1.93; 95%

Side Effects of Drugs Annual, Volume 41
ISSN: 0378-6080
https://doi.org/10.1016/bs.seda.2019.07.007

CI 1.12–3.34; RR 2.61; 95% CI 2.17–3.14, respectively) when compared to no blood transfusion. However, hemoglobin-stratified analyses showed that RBC transfusion might have either beneficial or neutral effects on mortality at hemoglobin below 8.0 g/dL (RR 0.52; 95% CI 0.25–1.06) [5M].

A prospective randomized trial performed in Finland evaluated two study groups who had RBC transfusion threshold of either hemoglobin 80 or 100 g/L perioperatively in cardiac surgical patients. There was no significant difference in intraoperative or postoperative bleeding, and baseline coagulation laboratory values. However, patients in the hemoglobin threshold 100 g/L group received significantly more RBC transfusions during the operations. Two patients from each group required re-sternotomies due to bleeding during the first 24 h of surgeries. One patient in the hemoglobin 80 g/L group had postoperative myocardial infarction with ST-elevation [6C].

Pulmonary

A review of post-liver transplantation pulmonary complications identified RBC transfusion as an independent risk factor that prolongs ventilation time and mortality. The pulmonary complication was related to pulmonary edema and viral pneumonia with RBC transfusion greater than 10 units [7R].

Neurologic

A case report of an 18-year-old patient with known factor X deficiency with menorrhea received 4 units of RBC for anemia and 10 units of fresh frozen plasma (FFP) for menorrhagia, who subsequently developed hypertension, generalized tonic–clonic convulsions with magnetic resonance imaging finding consistent with posterior reversible encephalopathy syndrome (PRES). Derangements in blood glucose and liver function tests were also noted [8A].

Neonates

A recent review identified oxidative injury, necrotizing enterocolitis, severe intraventricular hemorrhage, retinopathy of prematurity, transfusion related acute lung injury, and iron overload as potential risks of the RBC transfusion for the preterm baby. Thus the need for the restrictive transfusion guideline was emphasized to minimize those risks [9R]. A meta-analysis of 17 observational studies reported that there is no association between RBC transfusion and necrotizing enterocolitis in preterm infants (OR: 0.96; 95% CI: 0.53–1.71; $P = 0.88$). The studies included in the meta-analysis are predominantly low-to-moderate quality observational studies [10M].

Granulocytes

A retrospective analysis of granulocyte transfusion evaluated 47 patients with neutropenia secondary to chemotherapy, hematopoietic stem cell transplantation or underlying diseases and proven or probable bacterial or fungal infection that did not improve after treatment with antimicrobials, or an expected duration of neutropenia for at least 5 days. Of the 47 patients, 72.3% had improvements regarding infections with overall survival rates at 30 and 120 days were 66% and 57.5%, respectively. Two patients experienced dyspnea, increased heart rate and decreased blood pressure. There were a total of 8 patients who received granulocyte transfusions before hematopoietic stem cell transplantation. One patient suffered grade IV acute graft-vs-host disease (aGVHD), and 2 patients suffered grade I aGVHD. One patient had died of severe pulmonary infection and 1 patient died due to myocarditis. There were 2 patients who received granulocyte transfusions after hematopoietic stem cell transplantation. One patient suffered grade II aGVHD, and the other patient experienced limited chronic graft-vs-host disease (cGVHD). One of them did not recover and died of multiple organ dysfunction syndrome, and the other patient died due to thrombotic thrombocytopenic purpura [11c].

Platelets

Mortality

In a recent Cochrane review of 12 randomized controlled trials, a trial of 190 participants compared platelet transfusion to open control for acute spontaneous intracerebral hemorrhage associated with antiplatelet drugs. In this trial, platelet transfusions were associated with a significant increase in death or dependence (modified Rankin Scale score 4–6) at day 90 (70/97 vs 52/93; RR 1.29, 95% CI 1.04–1.61) [12M].

Infection

Infection risk with platelet transfusion had been a concern for patients with myelodysplastic syndrome and hemato-oncology conditions. In the United Kingdom, implementation of bacterial screening significantly reduced the risk of transfusion related infections; however, there is still a risk for complications such as hepatitis B, hepatitis C, human immunodeficiency virus, hepatitis E, human T-lymphotropic virus, and cytomegalovirus [13R].

Storage

Previous evidence suggested that platelets stored at room temperature might increase bacterial proliferation, which leads to transfusion-related infection. A recent

clinical trial of temperature cycling during platelet cold storage showed improvement in vivo recovery and survival in healthy volunteers. Temperature cycling platelets had in vivo recovery of 42.6% ± 16.4%, survival of 48.1% ± 14.4% hours, and area under curve (AUC) of 1331.3 ± 910.2 while the room temperature platelets in vivo recovery were 55.7% ± 13.9%, survival of 161.3 ± 28.8 h, and AUC of 5031.2 ± 1643.3 ($n = 12$, $P < 0.05$). In a separate paired comparison, cold temperature stored platelets had recovery of 23.1 ± 8.8%, survival of 33.7 ± 14.7 h, and AUC of 540.2 ± 229.6 while temperature cycling platelets had recovery of 36.5 ± 12.9%, survival of 49.0 ± 17.3 h, and AUC of 1164.3 ± 622.2 ($n = 4$, $P < 0.05$). In conclusion, temperature cycling storage for 7 days produced platelets with better in vivo circulation kinetics than cold storage [14E].

In an observational study of platelet transfusion reactions in the Netherlands, a total of 2407 transfusion reactions were reported during 2006–2015. Platelet concentrates stored in plasma (plasma-PLT) were compared to platelet concentrate stored in platelet additive solution (PAS) from two different manufacturers (PAS-B-PLT, PAS-C-PLT). The study found that there were statistical difference in rates of transfusion-related circulatory overload, transfusion-related acute lung injury, acute hemolytic reaction, delayed hemolytic reaction, and suspected infection. When PAS-B-PLT transfusions were compared to plasma-PLT transfusions, the overall relative risk (RR) of transfusion reactions was 0.99 (CI 95% 0.88–1.11). When PAS-C-PLTs were compared to plasma-PLTs, the RR was 0.56 (CI 95% 0.46–0.68) for all transfusion reactions. When PAS-C-PLTs were compared to PAS-B-PLTs, for all reactions the RR (95% CI) was 0.56 (0.45–0.70). Overall, PAS-C-PLT was associated with fewer transfusion reactions compared to plasma-PLT or PAS-B-PLT [15C].

BLOOD SUBSTITUTES [SEDA-15, 84; SEDA-37, 406; SEDA-38, 339; SEDA-39, 333; SEDA-40, 417]

Hemoglobin-based oxygen carrier (HBOC)

While RBC transfusions are the mainstay of treatment for life-threatening anemia, management of patients who cannot accept RBC transfusion remains as a medical challenge. HBOC is an alternative therapy for those who cannot receive RBC transfusions, and its use has been published in multiple clinical trials in recent years; however, the evidence of HBOC administration in critically ill patients with sickle cell disease is scarce. A case series of 3 critically ill patients who received HBOC during sickle cell crisis was reported. Two patients received more than 20 units of HBOCs, and the other patient received 6 units of HBOCs. The first patient experienced hypertension with the first unit administration, then methemoglobinemia to 10.2% after receiving 3 units, which were resolved with appropriate treatment. The second patient also developed hypertension to mean arterial pressure of 95 mmHg, which was resolved without any treatment. Lastly, the third patient had developed a carboxyhemoglobinemia to 10.4% and a methemoglobinemia to 6% after 23 units of HBOCs. The patient was treated with oral ascorbic acid. All three patients survived and were discharged from the hospital [16A].

PLASMA AND PLASMA PRODUCTS [SEDA-15, 84; SEDA-37, 407; SEDA-38, 340; SEDA-39, 333; SEDA-40, 417]

Alpha 1-antitrypsin

Alpha 1-antitrypsin deficiency is a genetic condition that affects multiple organ systems including lung and liver. It was first recognized in patients with emphysema, and purified alpha 1 proteinase inhibitor (A1P1) has been implicated to slow the progression of emphysema. Previous studies reported chills, urticarial rashes, fatigue, nausea, and vomiting as the most common adverse effects of A1P1 [17]. In addition, rare episodes of IgE-mediated anaphylaxis and IgA related anaphylaxis were reported in patients with IgA deficiency [18]. Recent review of anti-protease and alpha-1 antitrypsin augmentation therapy did not identify additional adverse events [19R].

C1 esterase inhibitor concentrate

Hereditary angioedema is a genetic deficiency or dysfunction in C1 esterase inhibitor protein, which leads to a laryngeal edema associated with upper airway swelling in the most severe cases. A case report of a 48-year-old female who presented with oropharyngeal and facial swelling was successfully treated with 1000 units C1 esterase inhibitor protein concentrate. Initially, the patient did not respond to intramuscular epinephrine, intravenous fluids, antihistamines and steroids. Measurement of serum C4 and C1 esterase inhibitor before administration of C1 esterase inhibitor protein concentrate was lower than the reference range, 12.7 and 14.3 mg/dL, respectively. No adverse events were noted after administration of C1 esterase inhibitor protein concentrate [20A].

The use of C1 esterase inhibitor protein was evaluated in non-hereditary angioedema with normal C1 esterase inhibitor through its inhibition of bradykinin formation.

Review of 61 articles included therapies with ecallantide, icatibant, C1 esterase inhibitor, fresh frozen plasma (FFP), tranexamic acid, and omalizumab for the treatment of angiotensin-converting enzyme inhibitor-induced angioedema, idiopathic angioedema, and angioedema with wheals. Safety data were available in 25 of 61 articles, of which only 10 patients received C1 esterase inhibitor. None of the patients were reported to experience adverse events [21M].

Cryoprecipitate

Cryoprecipitate is a commonly used plasma product for the replacement of fibrinogen in North America. Since cryoprecipitate does not undergo pathogen reduction process, there was a risk associated with infections. Due to the safety concern, European countries utilize purified human fibrinogen concentrate as a therapeutic choice; however, head-to-head comparison of cryoprecipitate with purified human fibrinogen concentrate has not been established. A phase III non-inferiority, randomized comparison of a new fibrinogen concentrate vs cryoprecipitate for treating acquired hypofibrinogenemia in bleeding cardiac surgical patients is an ongoing study that may help solve the curiosity of both efficacy and safety of fibrinogen replacement therapies. Fibrinogen Replenishment in Surgery (FIBRES) aims to recruit approximately 1200 patients to provide >90% power to detect non-inferiority of fibrinogen concentrate to cryoprecipitate [22C].

Fresh frozen plasma (FFP)

Infection

A single center retrospective analysis of outcomes was conducted comparing fresh frozen plasma to OctaplasLG, a solvent-detergent blood group specific plasma, in pediatric cardiac surgical patients. A total of 105 pediatric patients <2 years of age were included in the analysis with 65 patients in the OctaplasLG group and 40 patients in the FFP group. There were no statistical differences in amounts of intraoperative RBCs, platelets, or cryoprecipitate transfusions used. Immediate postoperative coagulation such as international normalized ratio (INR) and activated partial thromboplastin time (APTT) was significantly lower in the OctaplasLG group vs FFP group (INR 1.26 vs 1.35, $P < 0.0001$; APTT 1.35 vs 1.63, $P = 0.0353$). More patients in the FFP group received additional plasma transfusion in the first 12 h vs the OctaplasLG group (50% vs 18.5%; $P = 0.001$), and there was a higher rate of postoperative infections in the FFP group than the OctaplasLG group (30% vs 10.8%, $P = 0.0185$) [23c].

PLASMA SUBSTITUTES [SEDA-37, 408; SEDA-38, 341; SEDA-39, 334; SEDA-40, 418]

Esterified starches

Kidney injury

A randomized controlled trial compared balanced 10% hydroxyethyl starch (HES) with balanced 6% HES and balanced crystalloid use during pancreatic surgery. Primary endpoints were intraoperative volume of HES and time until full oral diet. When patients' body weights were adjusted, patients receiving 6% HES required more volume of HES than patients receiving 10% HES (24.0 [21.6; 28.3] vs 33.3 [28.2; 46.2] mL kg BW, $P = 0.002$). Both HES solutions resulted in similar efficacy in reducing intraoperative fluid administration when compared to crystalloids, and there were no difference in gastrointestinal outcomes. However, patients in the 10% HES group had higher incidence of acute kidney injury compared to patients in the crystalloid group (86.7% vs 45%, $P = 0.01$) [24c].

A review of 7 randomized controlled trials evaluated the efficacy and safety of 6% HES vs normal saline in critically ill patients. The results showed that more patients in the 6% HES group met the RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria for risk and injury ($P < 0.05$). Two randomized controlled trials compared 10% HES to normal saline did not show any statistical difference in all-cause mortality or numbers of patients who met the RIFLE criteria [25M].

A randomized single-center trial was conducted to compare HES to acetated Ringer's solution as cardiopulmonary bypass priming solution. A total of 40 patients were included in the trial, 20 patients in each group. The results showed that priming with HES lowered fluid loading during bypass (HES group 3374 mL vs acetated Ringer's solution group 4328 mL, $P = 0.024$) and improved cardiac function in early postoperative period (HES group 2.7 (0.4) L/min/m^2 vs acetated Ringer's solution group 2.1 (0.3) L/min/m^2, $P < 0.001$). Ten patients in the HES group and 9 patients in the acetated Ringer's solution group experienced atrial fibrillation. Six patients in the HES group and 4 patients in the acetated Ringer's solution group received erythrocyte concentrate transfusions during the perioperative and postoperative period, which was not statistically different. However, three patients who developed acute kidney injury were all in the HES group [26c].

Hematologic

An exploratory post hoc subgroup analysis of a prospective trial evaluated functional renal parameters and the structural biomarkers (alpha-glutathione S-transferase,

kidney injury molecule-1, liver fatty acid-binding protein, and neutrophil gelatinase-associated lipocalin) in 44 patients after coronary artery bypass grafting who received either 6% HES (130/0.4) or crystalloid solution. There were no differences in mortality, acute kidney injury, need for renal replacement therapy, and most of functional and structural renal parameters between the two groups. Liver fatty acid-binding protein was higher in the HES group than the crystalloid group at 24 h postoperatively (6.47 vs 2.15; $P = 0.0002$), and blood coagulation parameters were significantly more compromised in the HES group (median factor II HES 80.9% vs crystalloid 105.4%, $P = 0.0012$; median factor X HES 70% vs crystalloid 95.7%, $P = 0.031$; median thrombocytes HES 207.2 gpt/L vs crystalloid 252.8 gpt/L, $P = 0.001$). Blood loss and vasopressor doses were reported to be higher in the HES group; however, it was not statistically significant [27c].

Gelatin

Gelatin is a synthetic colloid plasma expander used for fluid resuscitation. Although recent systematic reviews have stated that gelatin is not associated with increased mortality during resuscitation for critically ill patients, there were clinical concerns for gelatin reducing clot strength. In vitro analysis of succinylated gelatin (SG) solution compared with normal saline in hemodilution was conducted using rotational thromboelastometry. Whole blood samples from 20 healthy volunteers were obtained, and they were diluted with either SG solution or normal saline by 10%, 20%, and 40%. Coagulation time (CT), clot formation time (CFT), alpha angle, and maximum clot firmness (MCF) were measured. CT was prolonged at 40% dilution with SG solution when compared to whole blood (Mean SG solution 84.3 s vs whole blood 71.75 s; $P = 0.003$), and CFT was progressively prolonged with each dilution. At 40% dilution, mean CFT in SG was 179.1 s vs 87.9 s in whole blood ($P = 0.003$). The mean alpha-angle was decreased with 40% hemodilution with SG when compared with whole blood (SG 58.1° vs whole blood 72.4°; $P = 0.001$), and mean MCF was reduced with SG 40% hemodilution compared to whole blood (SG 47.7 mm vs whole blood 62.5 mm; $P = 0.001$). MCF analysis was also reduced at 20% hemodilution with SG compared with whole blood (mean SG 9.1 mm vs whole blood 13.9 mm; $P = 0.0001$). MCF was reduced only at 40% hemodilution with normal saline (normal saline mean 7.5 mm vs whole blood 13.9; $P = 0.001$). The study concluded that impaired coagulation might occur with SG solutions at 40% hemodilution [28E].

IMMUNOGLOBULINS [SEDA-15, 1719; SEDA-37, 409; SEDA-38, 342; SEDA-39, 335; SEDA-40, 419]

Intravenous immunoglobulins

Neurologic

A case of an immunoglobulin-induced aseptic meningitis was reported in a patient with a past medical history of Systemic Lupus Erythematosus (SLE), associated Sjogren syndrome, and recently worsened asymptomatic hypogammaglobulinemia secondary to rituximab. The patient was started on 10% intravenous immunoglobulin (IVIG) 2 g/kg over 5 consecutive days for replacement therapy. Thirty-six hours after the first infusion, the patient presented to the emergency department with headache, photophobia, nausea, vomiting, fever, along with neck stiffness without focal neurological signs. Lumbar puncture was conducted and revealed CSF analysis of neutrophilic pleocytosis with 1547 cells/mm^3 (87.5% neutrophils), hyperproteinorrachia (15.3 mg/dL) and mildly reduced glucose (50 mg/dL), which were consistent with aseptic meningitis. Infectious disease laboratory results were all negative, and repeated lumbar puncture result on day 5 showed normal CSF analysis [29A].

Commercially available IVIG products include lyophilized formulations that require time to reconstitute, and 5% liquid formulation that require higher volume of fluid for infusion. A new 10% IVIG solution was introduced to augment the limitations of older products, yielding high-purity and glycine-stabilized human IVIG. The pharmacokinetic and safety profile of the new product was analyzed in a prospective, open-label, nonrandomized, multicenter, phase III trial that included 51 patients with common variable immunodeficiency or X-linked agammaglobulinemia. Depending on the previous IVIG doses, patients either received IVIG 10% infusion every 3 ($n = 21$) or 4 weeks ($n = 30$) for 12 months. The adverse events occurred during 38 infusions (5.1% of total number of infusions), and headache was the most abundant and reported in 22 infusions (3.0%). Patients in the 4-week group had a higher incidence of serious adverse events (13% vs 5%) including death, persistent or significant disability/incapacity, requirement of hospitalization or prolongation of existing hospitalization, or other important medical event. However, more patients in the 3-week group had severe adverse events (24% vs 7%) defined as the marked limitation in activity with required assistance, medical intervention or therapy. Two patients required premedication for 3 infusions [30c].

In a post-authorization tolerability and safety analysis of IVIG Octagam® 10%, a subgroup of patients ($n = 112$)

with immune thrombocytopenia (ITP) was observed and monitored with a focus on thromboembolic events. Mean dose of Octagam® 10% was 0.4 g/kg/infusion, and a total of 10 events were reported resulting in adverse drug reaction occurrence rate at 0.8% of all infusions. The most common adverse drug reactions were back pain ($n=3$) and headache ($n=2$); in addition, nausea, dizziness and a sensation of heaviness were also reported. There were no thromboembolic events or other serious adverse drug reactions [31C].

Pulmonary

Kawasaki disease is a rare disease state associated with acute vasculitis that leads to multiple organ dysfunction. The disease carries a potential to cause pleural effusion as one of its complications; however, a case from Japan was reported after a 1 year 3-month-old pediatric patient developed pleural effusion right after infusion of IVIG while other acute symptoms were subsiding. The patient received 2 g/kg IVIG and significant pleural effusion was noted on the chest radiography and computed tomography 48 h after the completion of therapy. The patient experienced a mild dyspnea and low oxygen saturation of 96% at room air. A total of 130 mL of exudative pleural fluid was drained with fluid to serum ratio of 0.53 [32A].

Infusion reactions and infections

IVIG therapy is used for the initial therapy for Kawasaki disease. Although evidence is not well established in current clinical practice, infliximab was shown to be well tolerated in these patients. A phase III, randomized, open-label, active-controlled, parallel-group, multicenter trial was conducted to compare infliximab with IVIG in 31 Japanese patients with Kawasaki disease who had persistent fever after an initial dose of IVIG. Patients received a single dose of infliximab 5 mg/kg ($n=16$) or polyethylene glycol-treated human immunoglobulin (VGIH; $n=15$) 2 g/kg on day 0. Defervescence rate within 48 h was greater with infliximab than VGIH (76.7% vs 37%, $P=0.023$), and defervescence was achieved earlier in infliximab ($P=0.0072$). Adverse events were reported in 15/16 patients in infliximab group (93.8%) and 15/15 patients in VGIH group (100%). Relapse of Kawasaki disease occurred in one patient in VGIH group, and more infusion reactions and infections were reported in VGIH group (2/15 (13.3%) and 10/15 (66.7%), respectively) compared to the infliximab group (0/16 and 6/16 (37.5%), respectively) [33c].

Hematologic

A patient with splenic marginal zone lymphoma developed acute thrombocytopenia upon administration of Intratect IVIG for hypogammaglobulinemia. The nadir counts for platelets were 27×10^9, 50×10^9, and 9×10^9/L, and an immunofluorescence test applying flow cytometry and monoclonal antibody immobilization of platelet antigens assay showed that there was a strong direct binding reaction between the patient's platelets and Intratect IgG.

Subcutaneous immunoglobulin

Subcutaneous immunoglobulin (SCIG) provides an alternative delivery method for patients who cannot tolerate intravenous administration or require a formulation that can be administered at home. Studies utilizing SCIG as compared to IVIG for primary immunodeficiency syndromes report fewer adverse effects; however, heterogeneity in SCIG formulation and studied populations lead to a large variance in reported incidences [34M]. Additional advantages include opportunities for ambulatory infusion, lower health care costs, and no need for premedication [35M].

van Schaik and colleagues conducted an international, multi-centered, randomized, double-blinded, placebo-controlled study of Hizentra® 20% in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). The PATH study randomized 172 patients 1:1:1 to placebo, low-dose SCIG (0.2 g/kg), and high-dose SCIG (0.4 g/kg). Both low and high doses demonstrated statistically lower probabilities of disease relapse in 24 weeks relative to placebo. However, the low and high dose SCIG groups experienced greater incidences of any treatment emergent adverse effects (37% vs 58% and 52%; placebo vs low and high dose, respectively); general disorders and conditions such as fatigue (11% vs 28% and 31%); local site reactions (7% vs 19% and 29%); infections (14% vs 23% and 10%); and musculoskeletal disorders (7% vs 18% and 10%). A total of six patients (3%) presented with serious adverse effects. One was observed in the placebo group, three in the low dose, and two in the high dose group; however, only one acute allergic dermatologic reaction in the low dose group was deemed causally related [36MC].

A large retrospective cohort study sponsored by the US Food and Drug Administration (FDA) identified health care claims from over 20 000 commercially insured patients in the United States who were exposed to IVIG and/or SCIG from January 1, 2008 to May 31, 2014. Using Gammagard Liquid® (IVIG) as a reference, the investigators did not find a statistically significant difference in the adjusted rate of hemolytic reactions with Hizentra®, the only SCIG included in this analysis (OR 1.19, 95% CI 0.21–6.69). The study suggested Hizentra® was associated with a lower risk of hemolytic reaction compared to the IVIG products, but further studies would be needed for confirmation [37C].

Dimou and colleagues described a single-center retrospective review of SCIG 10% administered to 33 patients with hypogammaglobulinemia secondary to hematologic

malignancies. SCIG was dosed at 0.4–0.8 mg/kg/month (with recombinant human hyaluronidase pretreatment) to achieve IgG trough levels near 600 mg/dL, and 444 uncomplicated infusions were recorded. Infection was documented in six patients (18.1%)—all had IgG levels <600 mg/dL at time of infection. Three patients (9%) presented with mild (grade 1) ADRs, consisting of low-grade fever and headache the evening following initial or second SCIG infusion. Local edema following subcutaneous infusion was mild and resolved within 48 h of infusion; one male patient reported unilateral scrotal edema hours after infusion, which resolved in less than 24 h [38c].

Anti-D immmunoglobulin

The FDA has addressed concerns raised by the US Environmental Protection Agency (EPA) regarding mercury in plasma-derived products. No currently in-date anti-D (Rho D) immunoglobulin product contains any quantity of thimerosal, a preservative that can decompose to form ethyl mercury in small quantities [39S].

COAGULATION PROTEINS [SEDA-37, 411; SEDA-38, 344; SEDA-39, 336; SEDA-40, 421]

Factor I (fibrinogen)

Fibrinogen concentrate is a preferred therapeutic treatment for fibrinogen replacement in congenital fibrinogen deficiency. A prospective, multinational phase III trial of a new plasma-derived, double virus-inactivated human fibrinogen concentrate was conducted to evaluate the efficacy and safety in use for on-demand treatment of bleeding episodes and surgical prophylaxis in congenital afibrinogenemia patients. Thirteen patients were included in the evaluation, and resulted in 95.7% treatment success (90% CI, 0.81–1.00), and no deaths, thromboses, or seroconversions were reported [40c].

In a single-center, retrospective study evaluated the outcome of prophylactic fibrinogen concentrate infusion in 53 patients who had undergone heart transplantation. Of 53 patients, 23 patients received preoperative fibrinogen concentrate 2 g after the termination of cardiopulmonary bypass pump and complete reversal of heparin, and 30 patients did not. Compared to the control group ($n = 30$), the fibrinogen group had a shorter length of hospital stay (20 vs 16 days; $P = 0.005$) and fewer number of packed RBC infused (2 vs 0 unit; $P < 0.001$). However, patients in the fibrinogen group developed more AKI after surgery (30.4%) compared to the control group (10%) though the number was not statistically significant ($P = 0.059$) [41c].

A study by Négrier et al. evaluated the safety of Clottafact® in current medical practice. Clottafact® is a human plasma-derived fibrinogen concentrate obtained by plasma fractionation from cryosupernatant and precipitation by ion-exchange chromatography. Patients were included if they had acquired fibrinogen deficiency, acute bleeding, and agreed to sign the informed consent form. The study included 156 patients according to the type of treatment (curative or preventive) and origin of the bleed. There were 150 patients who received curative treatment in which 117/159 (73.6%) were considered successful, 35 as moderate (22%), and 7 as no response (4.4%). Overall, there were two patients who experienced adverse drug events: 1 case of pulmonary embolism, and the other with a 4-site venous thromboembolism [42C].

Factor II (thrombin)

A case series was compiled to evaluate the efficacy of managing spontaneous hemoptysis or procedure related bleeding via instillation of endobronchial gelatin and thrombin slurry (GTS). There were 13 cases identified over a period of 10 years in which the GTS was used when standard of care such as cold saline, epinephrine, or balloon occlusion failed. Of the 13 cases, 8 were due to spontaneous bleeding and 5 from diagnostic or therapeutic procedures. Overall, hemostasis was achieved in 10/13 (77%). There were no patient adverse events noted at 30 days [43c].

Jhajharia and colleagues evaluated the use of human thrombin injection in patients who presented with gastric variceal bleeding. The study included a total of 20 patients with the majority having underlying hepatic disease. Patients in the study received 1–3 sessions and a mean total dose of 700 IU. All 20 patients achieved hemostasis on initial presentation with 4/20 requiring a repeat endoscopic session upon follow-up. There were no adverse reactions related to thrombin injection [44c].

Factor VII

A single center, retrospective, cohort study was conducted to assess the overall incidence of thromboembolic (TE) events in patients who received recombinant factor VIIA (rFVIIa) compared to those who did not for refractory coagulopathic bleeding during orthotopic heart transplant (OHT). Out of 62 patients evaluated, 27 received rFVIIa and 35 patients were identified for the control group. The study found no significant difference between patients who received rFVIIa and those in the control group (14.8% vs 11.4%; $P = 0.69$). However, within 14 days, 14.81% of rFVIIa patients suffered a TE event compared to 5.7% in the control group ($P = 0.23$). Authors concluded there were no differences in the rate of TE events in OHT patients, but there was a

non-significant trend towards higher risk of early TE development in the rFVIIa group [45c].

A retrospective collection of data of patients with traumatic brain injury (TBI) were acquired from 11 level 1 US trauma centers over the period of 11 years. The primary outcome was in-hospital mortality. Propensity scoring was conducted to overcome the differences noted between the patients receiving recombinant factor VIIa (rFVIIa) due to TBI compared to those who did not. A total of 4284 patients were analyzed, with 129 who received rFVIIa. There were no differences in mortality between the groups. However, improvement in the Glascow Coma Scale (GCS) from admission to discharge was less among those who received rFVIIa (5.5–2.4; $P = 0.001$) [46C].

Harper and colleagues conducted a retrospective propensity-matched analysis to assess 30-day mortality following cardiac surgery in patients who received three-factor inactive prothrombin complex concentrate (PCC) vs recombinant activated factor VII (rFVIIa). A total of 263 patients received rFVIIa while 72 received PCC while undergoing cardiac surgery requiring cardiopulmonary bypass. There was no significant difference in 30-day mortality between the groups, but rFVIIa was significantly associated with renal failure requiring dialysis ($P = 0.022$), increased need for fresh frozen plasma transfusions ($P = 0.028$), and platelet transfusions ($P = 0.027$) [47C].

Tiede and Worster compiled literature to complete a systematic review of the effectiveness of recombinant factor VIIa (rFVIIa) in acquired haemophilia patients. Overall, 12 studies met the inclusion criteria which encompassed 1244 patients and 1714 bleeds (671 patients received rFVIIa for 1063 bleeds). The initial dose of rFVIIa was $90 \pm 10\,\mu g/kg$. rFVIIa had a favorable safety profile with low risk of general adverse events and thromboembolic-associated events, in addition to demonstrated effectiveness [48M].

Factor VIII

Haemophilia A patients are at a high risk of excessive bleeding during surgeries. Zozulya and colleagues conducted a propensity planned analysis of Nuwiq® (simoctocog alfa, human-cl rhFVIII), a 4th generation rFVIII. The analysis assessed the efficacy and safety in 36 previous treated patients (PTP) with severe haemophilia A (FVIII activity <1%) who underwent surgery. Patients received surgical prophylaxis with Nuwiq®. The efficacy was evaluated for 52 surgeries (25 major and 27 minor) with a success rate of 98.1%. Hemostatic efficacy was assessed as excellent or good in all but one major surgery. The study did not identify any serious treatment-related adverse events, and none of the patients developed FVIII inhibitors [49c].

Factor IX

A multi-phase study was conducted that included a pharmacokinetic (PK) phase that was a randomized, double-blinded, crossover comparison of IB1001 (trenonacog alfa) to nonacog alfa (recombinant FIX). This was followed by a 5-day washout period, then treatment with 75 ± 5 IU/kg followed by a second washout period of 5 days. Patients then entered an open-label treatment phase to receive IB1001 prophylactically or on-demand. Prophylaxis dosing consisted of 50–75 IU/kg twice weekly compared to 50–100 IU/kg for on-demand treatment of bleeding based on severity. The most commonly seen side effect was headache (2.6%) and with no reports of FIX inhibitors. Prophylaxis dosing was deemed effective in preventing bleeds with a median annual bleed rate of 1.52, and 1 or 2 on-demand infusions resolved 84% of bleeds. Overall, the authors concluded that IB1001 was safe and efficacious for routine prophylaxis or treatment of bleeds [50c].

Mahlangu compiled a review of the literature regarding extended half-life (EHL) recombinant factor IX (rFIX) products for the treatment of haemophilia B. Multiple clinical trials assessing EHL rFIX have indicated that the safety profiles of these products are acceptable with no allergic reactions, thromboembolic phenomena or neutralizing antibodies. Additionally, these agents can reduce treatment burden in those with haemophilia B. Further studies are ongoing regarding the safety and efficacy in previously untreated patients. The role in therapy compared to other novel agents remains to be established [51R].

Prothrombin complex concentrate

Thromboembolism

Four-factor prothrombin complex concentrate (4F-PCC) contains coagulation factors II, VII, IX, and X, and is indicated for the reversal of vitamin K antagonist associated bleeding. While 4F-PCC is effective for rapid INR correction, risk of both venous and arterial thromboembolic events is present. Manufacturers recommend against the use of repeat dosing for this reason, as well as lack of clinical data. In an adult patient who was anticoagulated with apixaban, the patient received two doses of 4F-PCC dosed at 35 units/kg, approximately 1 day apart for pulmonary hemorrhage. The patient experienced cardiac arrest on day 4 of admission and was presumed to have a massive pulmonary embolism based on echocardiogram findings [52A].

In addition to on-label use of 4F-PCC for warfarin reversal, 4F-PCC was recently reviewed for off-label uses, such as patients experiencing coagulopathy while not on warfarin therapy. In a retrospective study of 154 patients, incidence of thromboembolic complications (7.2% vs 6.7%, $P = 1.00$) was not different amongst

patients who received 4F-PCC for on-label or off-label uses. There were 11 thromboembolic events in total, 8 of which were lower extremity symptomatic DVTs, and 3 were upper extremity DVTs [53C].

When 3F-PCC and 4F-PCC were evaluated for off-label uses, 13 patients received 3F-PCC and 48 received 4F-PCC for non-warfarin related INR elevations. There was 1 DVT event amongst this cohort of patients [54c].

In a retrospective study of 74 patients with left-ventricular assist devices undergoing orthotopic heart transplantation, patients requiring warfarin reversal received either 4F-PCC intra-operatively, or other products alone (such as FFP). The 4F-PCC group required less FFP, cryoprecipitate, and packed red blood cells, and no thrombotic events were noted [55c].

An alternative dosing scheme of 4F-PCC includes a fixed-dose strategy. This strategy has recently been evaluated in a retrospective review of 37 patients who received 1500 units of fixed-dose 4F-PCC for warfarin reversal. There were no thrombotic complications noted in this study [56c].

von Willebrand factor (VWF)/factor VIII concentrates

von Willebrand factor (VWF) is a multimeric plasma protein that regulates platelet adhesion to collagen exposed through vascular injury and complexes with FVIII, serving to shield it from premature degradation in circulation. VWF/FVIII concentrates are used to reverse quantitative or qualitative defects in von Willebrand disease (VWD) and hemophilia A, thus restoring hemostatic capacity [57R], [58c].

Hazendonk and colleagues conducted a multicenter retrospective cohort study to evaluate perioperative management of patients treated with Haemate® P in the Netherlands. VWF/FVIII were dosed to achieve preoperative and maintenance levels of >0.80 IU/mL each. Of the 103 patients reviewed, a total of 20 (14%) bleeding events occurred with 19 (95%) associated with hemoglobin drops ≥1.24 mmol/L and/or necessitating blood transfusion. No thrombotic events were recorded despite 18 patients reaching extremely high FVIII levels (>2.70 IU/mL); however, thromboprophylaxis with low molecular weight heparin was initiated in 61% of those patients [59C].

A prospective, open-labeled, nonrandomized multinational study of Octanate®, a human plasma-derived VWF/FVIII concentrate, was conducted in 51 previously untreated Caucasian males with hemophilia A to assess the immunogenicity of the formulation. A mean dose of 38.4 (±28.6) IU/kg/exposure day (ED) was administered for indications of prophylaxis, immune tolerance induction, bleeding, and surgical procedures. Inhibitors were detected in five patients (9.8%), with three (5.9%) presenting with clinically relevant titers of inhibitors. Adverse effects were reported in 45 patients (88.2%), with 21 considered probably or possibly related to VWF/FVIII infusion. Of note, 16 cases of asymptomatic parvovirus B19 seroconversion occurred. However, tolerability was considered "very good" in 99.98% of the 8674 documented infusions [58c].

One observational cohort study examined VWF/FVIII in newborn congenital heart disease (CHD), in which anatomical defects may increase blood shear stress and thus induce an acquired-von Willebrand syndrome (aVWS). Twelve complex CHD patients requiring cardiopulmonary bypass (CBP) surgery were included in the review, and 10 received intraoperative VWF/FVIII in cumulative doses between 45 and 390 IU/kg. No significant relationship was observed between dose of factor concentrate and chest closure time or blood loss; one thrombotic complication (transient cerebral venous sinus thrombosis) was noted in a patient who received also rFVII [60c].

Antithrombin III

Antithrombin III, an alpha2-globulin that inhibits serine proteases within the coagulation cascade (e.g., thrombin, plasmin, factors IXa, Xa, etc.), is available in the United States as a human plasma derivative (Thrombate III®) and as a recombinant antithrombin (ATryn®). ATryn® is indicated solely for the prevention of perioperative and post-partum thrombosis in patients with hereditary antithrombin deficiency while Thrombate III® has an additional indication in the treatment and prevention of thromboembolism. Currently, Japanese clinical practice guidelines on sepsis management recommend antithrombin replacement therapy in patients experiencing sepsis-associated DIC [61M].

In a Japanese case series of five patients with antithrombin deficiency undergoing major cardiovascular surgery, investigators administered antithrombin III concentrate prior to and after surgery to maintain ATIII activity ≥120% and ≥80%, respectively. No early periprocedural complications were noted; however, one patient presented 9 months following bioprosthetic aortic valve replacement with numerous thrombi of the valve leaflets, which necessitated replacement with a mechanical valve [62c].

ERYTHROPOIETIN AND DERIVATIVES [SEDA-37, 413; SEDA-38, 346; SEDA-39, 338; SEDA-40, 422]

Cardiovascular

Erythropoietin (EPO) is a hematopoietic factor most commonly used to treat anemia associated with chronic kidney disease (CKD). EPO has known cardiovascular

adverse effects when used to target hemoglobin levels of 13–15 g/dL. A meta-analysis of 48 studies further reported these findings of increased cardiovascular risk, but there was no difference in this risk amongst the different EPO agents [63M].

In a trial of 120 patients with severe traumatic brain injury who were randomized to either EPO 6000 units at days 1, 3, 5, 10, and 15 vs placebo, there were no differences in either neurologic outcomes or thromboembolic events at 10 weeks [64C].

Immunologic

EPO inhibits apoptosis of erythroblasts, but new studies have demonstrated effects on immune cells such as neutrophils, monocytes, dendritic cells, T cells, Natural killer (NK) cells, and B cells. In a trial of 119 autologous blood donors, 49 were treated with recombinant human EPO. Amongst the EPO treated patients, CD8+ T cells, natural killer cells, and B cells all significantly decreased after a single administration of epoetin 24 000 IU, but no WBC lines decreased amongst non-EPO treated patients. Clinical significance of this effect is unknown at this time [65C].

Cancer progression

In a multicenter, open-label, randomized, phase 3 trial of weekly apixaban alfa in patients with squamous cell carcinoma being managed with radiation therapy, poorer outcomes were found amongst darbepoetin treated patients as compared to placebo. In this trial, there were 254 patients treated with darbepoetin alfa and 259 patients in the control group when the trial was halted early due to more patients in the darbepoetin arm experiencing tumor progression and increased mortality [66C].

THROMBOPOIETIN AND RECEPTOR AGONISTS [SEDA-15, 3409; SEDA-37, 414; SEDA-38, 347; SEDA-39, 339; SEDA-40, 423]

Immune thrombocytopenia (ITP) is a disorder that can be primary in nature, or secondary to autoimmune disease, infections, or drugs. Thrombopoietin receptor agonists (TPO-RA) are one mainstay of treatment for chronic ITP. Available TPO-RA's include eltrombopag and romiplostim and are considered second line agents for chronic ITP. A meta-analysis of 9 randomized, placebo-controlled trials evaluated safety outcomes in eltrombopag, romiplostim, and placebo. Of the adverse events studied (headache, fatigue, thrombosis, arthralgia, nausea, nasopharyngitis, diarrhea, peripheral edema, epistaxis, pain in extremity, dizziness, contusion, upper abdominal pain, upper respiratory tract infection, cough, myalgia, anxiety and back pain), there were no statistically significant differences between the TPO-RA's and placebo [67M].

In a retrospective study of 100 patients treated with either eltrombopag or romiplostim, the most commonly reported adverse events were headache, transient transaminase elevation, or thromboembolism. In the eltrombopag arm, 6.3% experienced headache, 9.5% experienced transaminitis, and 9.5% had thromboembolism (including DVT, acute MI, PE, and superficial thrombophlebitis). In the romiplostim arm, 22% experienced headache, 1.7% experienced transaminitis, and 5.1% had thromboembolism (including DVT and PE). Differences in rates of headache and transaminitis were statistically significant, but thromboembolism was not [68C].

Antiphospholipid syndrome (APS) in systemic lupus erythematous (SLE)

ITP is a possible complication of SLE, which can also be associated with antiphospholipid syndrome. In a retrospective review of 18 patients treated with TPO-RAs for SLE ITP, 28% experienced serious thrombotic adverse events. Arterial thrombosis events (including 2 MIs, 1 stroke, and 1 catastrophic APS) occurred in 4 patients with antiphospholipid syndrome. Two venous thrombosis events occurred in a patient without APS. Based on these results, the authors concluded that alternative therapies for patients with APS should be considered [69c].

Pediatrics

In a systematic review of 5 randomized controlled trials in pediatric patients treated with TPO-RAs, efficacy was similar between eltrombopag and romiplostim, but eltrombopag displayed lower risk of overall as well as clinical significant bleeding when compared to romiplostim, which were statistically significant. This was likely due to underlying disease, rather than a drug effect of the TPO-RAs. The only adverse effect that differed between eltrombopag and romiplostim treated patients was cough, which was much more frequent in the eltrombopag arm (RR = 14.40, $P < 0.05$) [70M].

Newly studied indications

Aplastic anemia

An observational trial of 20 patients with aplastic anemia was conducted to evaluate the real-world use of high doses (median 150 mg) of eltrombopag in this patient population. The most common adverse events seen were skin hyperpigmentation, and appeared to be dose

dependent, occurring in all patients who were treated with eltrombopag at least 150 mg/day. This effect was fully reversible when eltrombopag was discontinued. Dyspepsia requiring treatment with an acid-suppressing medication occurred in 9 patients (45%), with 1 case requiring discontinuation. Hepatotoxicity requiring eltrombopag discontinuation occurred in 1 patient [71c].

Advanced myelodysplastic syndromes

The ASPIRE study was a phase 2, randomized, placebo-controlled trial of 145 patients that tested eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukemia with severe thrombocytopenia. Serious adverse effects occurred in 58% of eltrombopag treated patients vs 68% of placebo-treated patients. Seven eltrombopag patients had serious adverse events that were thought to be related to the study drug (acute kidney injury, arterial thrombosis, bone pain, diarrhea, myocardial infarction, pyrexia, and retinal vein occlusion) and 2 experienced fatal adverse events (arterial thrombosis and myocardial infarction) [72C].

STEM CELLS [SEDA-37, 415; SEDA-38, 348; SEDA-39, 340; SEDA-40, 424]

Hematopoietic stem cell transplant (HSCT) is an effective treatment option for blood cancers, hematopoietic diseases, and some autoimmune illnesses. There have been significant advances in post-transplant care, which has led to decreased mortality in the immediate period after transplantation. Despite this, patients who undergo HSCT are still at higher risk of death than the general population, both early and late after transplant.

Infection

In a retrospective cohort of 229 pediatric patients who underwent HSCT, patients with allogeneic HSCT were compared to patients who underwent autologous HSCT. In allo-HSCT there were statistically significant higher rates of severe bacterial infection/sepsis when compared to auto HSCT (8.7% vs 1.0%) and viral reactivations (26.2% vs 2.9%) [73C].

In a review of 678 adult patients who underwent HSCT during the study period, 112 (17%) developed human coronavirus infection during the median follow-up period of over 2 years. Patients infected with human coronavirus developed subsequent proven or probable lower respiratory tract infection 30% of the time [74C].

Endocrine

Pediatric patients who undergo HSCT are at risk for several endocrine disorders, including insulin resistance, hypothyroidism, hypogonadism, or hypocortisolism. In a retrospective review of 178 patients, 65.2% developed at least one endocrine disorder. The median follow-up for these patients was 8.5 years. The most common was primary gonadal failure, with 49 (36.0%) patients developing hypogonadism. Permanent hypothyroidism occurred in 38 patients (21.3%), hypocortisolism occurred in 6 patients (3.4%), and type 2 diabetes occurred in 4 patients (2.2%). Dyslipidemia was also common, occurring in 33 patients (18.5%) [75C].

Metabolic syndrome, in addition to being a late complication, can also occur relatively early after HSCT. In a prospective study of 48 allogeneic and 52 autologous HSCT, 24 patients were observed to have metabolic syndrome at baseline, but by day 30, this number had increased to 43 patients. Metabolic syndrome was further associated with insulin resistance, and incidence was higher in patients who underwent allogeneic transplant as compared to autologous transplant [76C].

Cardiovascular

Cardiovascular mortality in HSCT patients is more than double that of the general population. In a retrospective study of 1930 consecutive HSCT patients who had not developed cardiovascular disease within 1 year after transplant (index date), 1271 (~70%) were followed until the onset of cardiovascular disease, death, or 10 years (whichever came first). Overall, 135 patients developed cardiovascular disease (92 heart failure and 43 coronary artery disease) during the 10-year follow-up period [77C].

TRANSMISSION OF INFECTIOUS AGENTS THROUGH BLOOD DONATION [SEDA-37, 414; SEDA-38, 347; SEDA-39, 340; SEDA-40, 423]

Facilities that collect and manufacture blood are under strict guidance from the Food and Drug Administration (FDA) to ensure there is uniform preparation of blood, sterility, and reduced risk of blood contamination with infectious diseases. In the United States, donated blood is tested for a myriad of infectious pathogens such as HIV, hepatitis B virus (HBV), and Zika. Since the inception of testing for diseases transmitted through blood transfusions, the rate of infections has declined tremendously over the years in developed countries. Due to storage at room temperature, platelets possess the highest

risk of bacterial contamination, limiting its storage to up to 5 days in most instances. The risk of a unit of platelets to be contaminated is 1 in 6000, while the risk of septic transfusion reaction is 1 in 100 000 but the reaction can be severe and fatal. There have been advances over the years to reduce pathogen transmission. Due to the screening efforts and pathogen reduction products, the rates of viral pathogen transmission remain quite low with a rate of 1 in 1–2 million; however, bacteria still remains a problem. There are continued efforts to improve blood safety with the use of pathogen reduction systems and new laboratory tests [78r].

An analysis was conducted of American Red Cross blood donations from allogeneic, English-speaking, nonmilitary donors from June 21, 2009 through April 28, 2015 to assess rates of hepatitis B virus (HBV) DNA-positive with recent (RBI) or occult (OBI) HBV infection. Blood donations were tested for HBV surface antigen (HBsAg) and core antibodies (anti-Hbc), and confirmation via neutralization testing for HBsAg and HBV DNA by nucleic-acid amplification test NAT. A total of 34 390 972 allogeneic donations were collected during the aforementioned timeframe. The overall RBI was 0.35 per 100 000 donations ($n = 120$) and OBI rate of 1.70 per 100 000 ($n = 583$). The RBI and OBI rates constituted 26% of all HBV-infected donors ($n = 2735$). The authors concluded that the rates of RBI and OBI continue to be detected which confirms the importance of comprehensive HBV DNA screening [79MC].

After a rapid, pandemic spread of Zika virus (ZIKV), an international public health emergency was enacted in 2015. Due to the possibility of 4 cases transmitted via blood transfusions in Brazil, questions have been raised about a possible risk to blood supply. Initially, the FDA ceased blood donated in areas of the United States where ZIKV was active, but has since implemented screening on all donated blood for ZIKV. Based on previous literature, the current strategy in the United States appears costly with an unclear gain. There have been questions surrounding the appropriateness of screening and the possibility of reversing this requirement. Even though ZIKV has not been eliminated, the epidemic has waned substantially. The number of reported locally acquired cases in the continental United States has decreased from 226 in 2016 to a mere 2 in 2017. However, the precautionary principle and risk-based approaches encourage continuous review of the literature as new data emerges [80r].

References

[1] Ferrer R, Mateu X, Maseda E. Non-oncotic properties of albumin. A multidisciplinary vision about the implications for critically ill patients. Expert Rev Clin Pharmacol. 2018;11(2):125–37 [R].

[2] Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet. 2018;391(10138):2417–29 [C].

[3] Kammerer T, Brettner F, Hilferink S, et al. No differences in renal function between balanced 6% hydroxyethyl starches (130/0.4) and 5% albumin for volume replacement therapy in patients undergoing cystectomy: a randomized controlled trial. Anesthesiology. 2018;128(1):67–78 [C].

[4] Maier CL, Gross PJ, Dean CL, et al. Transfusion-transmitted malaria masquerading as sickle cell crisis with multisystem organ failure. Transfusion. 2018;58(6):1550–4 [A].

[5] Wang Y, Shi X, Du R, et al. Impact of red blood cell transfusion on acute coronary syndrome: a meta-analysis. Intern Emerg Med. 2018;13(2):231–41 [M].

[6] Laine A, Niemi T, Schramko A. Transfusion threshold of hemoglobin 80 g/L is comparable to 100 g/L in terms of bleeding in cardiac surgery: a prospective randomized study. J Cardiothorac Vasc Anesth. 2018;32(1):131–9 [C].

[7] Lui JK, Spaho L, Holzwanger E, et al. Intensive care of pulmonary complications following liver transplantation. J Intensive Care Med. 2018;33(11):595–608 [R].

[8] Verma A, Hemlata, Elhence P, et al. Posterior reversible encephalopathy syndrome following blood transfusion in a patient with factor X deficiency: is it an unusual systemic manifestation of an adverse transfusion reaction? Transfus Apher Sci. 2018;57(1):50–3 [A].

[9] Iskander IF, Salama KM, Gamaledin RM, et al. Neonatal RBC transfusion: do benefits outweigh risks? Transfus Apher Sci. 2018;57(3):431–6 [R].

[10] Garg P, Pinotti R, Lal CV, et al. Transfusion-associated necrotizing enterocolitis in preterm infants: an updated meta-analysis of observational data. J Perinat Med. 2018;46(6):677–85 [M].

[11] Zhou B, Song T, Feng Y, et al. Clinical outcome of granulocyte transfusion therapy for the treatment of refractory infection in neutropenic patients with hematological diseases. Ann Hematol. 2018;97(11):2061–70 [c].

[12] Al-Shahi Salman R, Law ZK, Bath PM, et al. Haemostatic therapies for acute spontaneous intracerebral haemorrhage. Cochrane Database Syst Rev. 2018;4:CD005951 [M].

[13] Ainley LI, Hewitt PE. Haematology patients and the risk of transfusion transmitted infection. Br J Haematol. 2018;180(4):473–83 [R].

[14] Vostal JG, Gelderman MP, Skripchenko A, et al. Temperature cycling during platelet cold storage improves in vivo recovery and survival in healthy volunteers. Transfusion. 2018;58(1):25–33 [E].

[15] van Hout FMA, van der Meer PF, Wiersum-Osselton JC, et al. Transfusion reactions after transfusion of platelets stored in PAS-B, PAS-C or plasma: a nationwide comparison. Transfusion. 2018;58(4):1021–7 [C].

[16] Davis JM, El-Haj N, Shah NN, et al. Use of the blood substitute HBOC-201 in critically ill patients during sick crisis: a three-case series. Transfusion. 2018;58(1):132–7 [A].

[17] Wencker M, Banlik N, Buhl R, et al. Long-term treatment of alpha-antitrypsin deficiency-related pulmonary emphysema with human alpha-antitrypsin. Eur Respir J. 1998;11(2):428–33.

[18] Meyer FJ, Wencker M, Teschler H, et al. Acute allergic reaction and demonstration of specific IgE antibodies against alpha-l-protease inhibitor. Eur Respir J. 1998;12(4):996–7.

[19] Strange C. Anti-protease and alpha-1 antitrypsin augmentation therapy. Respir Care. 2018;63(6):690–8 [R].

[20] Yigit M, Sogut O, Lisar H, et al. Usefulness of C1 esterase inhibitor protein concentrate in the management of hereditary angioedema of oropharyngeal tissue. Niger J Clin Pract. 2018;21(4):531–3 [A].

[21] van der Elzen M, Go MFCL, Knulst AC, et al. Efficacy of treatment of non-hereditary angioedema. Clin Rev Allergy Immunol. 2018;54(3):412–31 [M].

[22] Karkouti K, Callum J, Rao V, et al. Protocol for a phase III, non-inferiority, randomised comparison of a new fibrinogen concentrate versus cryoprecipitate for treating acquired

hypofibrinogenaemia in bleeding cardiac surgical patients: the FIBRES trial. BMJ Open. 2018;8(4)e020741 [C].
[23] Kalsi AS, Al-Azzawi O, Gill R. Comparison of the coagulation effect achieved by OctaplasLG versus fresh frozen plasma in pediatric cardiac surgical patients. Clin Appl Thromb Hemost. 2018;24(8):1327–32 [c].
[24] Werner J, Hunsicker O, Schneider A, et al. Balanced 10% hydroxyethyl starch compared with balanced 6% hydroxyethyl starch and balanced crystalloid using a goal-directed hemodynamic algorithm in pancreatic surgery: a randomized clinical trial. Medicine (Baltimore). 2018;97(17)e0579 [c].
[25] Zhou FH, Liu C, Mao Z, et al. Normal saline for intravenous fluid therapy in critically ill patients. Chin J Traumatol. 2018;21(1):11–5 [M].
[26] Svendsen OS, Fastard M, Mongstad A, et al. Is the use of hydroxyethyl starch as priming solution during cardiac surgery advisable? A randomized, single-centered trial. Perfusion. 2018;33(6):483–9 [c].
[27] Datzmann T, Hoenicka M, Reinelt H, et al. Influence of 6% hydroxyethyl starch 130/0.4 versus crystalloid solution on structural renal damage markers after coronary artery bypass grafting: a post hoc subgroup analysis of a prospective trial. J Cardiothorac Vasc Anesth. 2018;32(1):205–11 [c].
[28] Kam P, Varanasi S, Yang KW. The effects of haemodilution with succinylated gelatin solution on coagulation in vitro as assessed by thromboelastometry and impedance (multiple electrode) aggregometry. Anaesth Intensive Care. 2018;46(3):272–7 [E].
[29] Graca L, ALves J, Nuak J, et al. Immunoglobulin-induced aseptic meningitis: a case report. BMC Neurol. 2018;18(1):97 [A].
[30] Melamed IR, Borte M, Trawnicek L, et al. Pharmacokinetics of a novel human intravenous immunoglobulin 10% in patients with primary immunodeficiency diseases: analyses of a phase III, multicentre, prospective, open-label study. Eur J Pharm Sci. 2018;118:80–6 [c].
[31] Wietek S, Svorc D, Debes A, et al. Tolerability and safety of the intravenous immunoglobulin Octagam® 10% in patients with immune thrombocytopenia: a post-authorisation safety analysis of two non-interventional phase IV trials. Hematology. 2018;23(4):242–7 [C].
[32] Koizumi K, Hoshiai M, Toda T, et al. Marked pleural effusion after i.v. immunoglobulin therapy for Kawasaki disease. Pediatr Int. 2018;60(3):307–8 [A].
[33] Mori M, Hara T, Kikuchi M, et al. Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. Sci Rep. 2018;8(1):1994 [c].
[34] Guo Y, Tian X, Wang X, et al. Adverse effects of immunoglobulin therapy. Front Immunol. 2018;9:1299 [M].
[35] Navarro-Triviño FJ, Pérez-López I, Ruíz-Villaverde R. Dermatology and immunoglobulin therapy: who to treat and how to administer immunoglobulins. Actas Dermosifiliogr. 2018;109(4):323–30 [M].
[36] van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2018;1:35–46 [MC].
[37] Sridhar G, Ekezue BF, Izurieta HS, et al. Occurrence of hemolytic reactions on the same day as immune globulin product administrations during 2008 to 2014. Transfusion. 2018;58(1):70–80 [C].
[38] Dimou M, Iliakis T, Maltezas D, et al. Efficacy-safety of facilitated subcutaneous immunoglobulin in immunodeficiency due to hematological malignancies. A single-center retrospective analysis. Anticancer Res. 2018;38(7):4187–91 [c].
[39] Food and Drug Administration. Mercury in plasma-derived products [internet]. [updated 2018 March 3; cited 2019 Feb 26]. Available from: https://www.fda.gov/biologicsbloodvaccines/safetyavailability/bloodsafety/ucm095529.htm.
[40] Lissitchkov T, Madan B, Khayat CD, et al. Efficacy and safety of a new human fibrinogen concentrate in patients with congenital fibrinogen deficiency: an interim analysis of a Phase III trial. Transfusion. 2018;58:413–22 [c].
[41] Jahangirifard A, Ahmadi ZH, Naghashzadeh F, et al. Prophylactic fibrinogen decreases postoperative bleeding but not acute kidney injury in patients undergoing heart transplantation. Clin Appl Thromb Hemost. 2018;24(6):998–1004 [c].
[42] Négrier C, Ducloy-Bouthors AS, Piriou V, et al. Postauthorization safety study of Clottafact®, a triply secured fibrinogen concentrate in acquired fibrinogen deficiency: a prospective observational study. Vox Sang. 2018;113:120–7 [C].
[43] Peralta AR, Chawla M, Lee RP. Novel bronchoscopic management of airway bleeding with absorbable gelatin and thrombin slurry. J Bronchol Intervent Pulmonol. 2018;25:204–11 [c].
[44] Jhajharia A, Wanjari SJ, Ashdhir P, et al. Role and safety of human thrombin injection for the treatment of bleeding gastric varices. Indian J Gastroenterol. 2018;37(4):321–5 [c].
[45] Winstead RJ, Pandya K, Flynn J, et al. Factor VIIa administration in orthotopic heart transplant recipients and its impact on thromboembolic events and post-transplant outcomes. J Thromb Thrombolysis. 2018;45(3):452–6 [c].
[46] Lombardo S, Millar D, Jurkovich GJ, et al. Factor VIIa administration in traumatic brain injury: an AAST-MITC propensity score analysis. Trauma Surg Acute Care Open. 2018;3:e000134 [C].
[47] Harper PC, Smith MM, Brinkman NJ, et al. Outcomes following three-factor inactive prothrombin complex concentrate versus recombinant activated factor VII administration during cardiac surgery. J Cardiothorac Vasc Anesth. 2018;32(1):151–7 [C].
[48] Tiede A, Worster A. Lessons from a systematic literature review of the effectiveness of recombinant factor VIIa in acquired haemophilia. Ann Hematol. 2018;97(10):1889–901 [M].
[49] Zozulya N, Kessler CM, Klukowska A, et al. Efficacy and safety of Nuwiq® (human-cl rhFVIII) in patients with severe haemophilia A undergoing surgical procedures. Haemophilia. 2018;24(1):70–6 [c].
[50] Collins PW, Quon DVK, Makris M, et al. Pharmacokinetics, safety and efficacy of a recombinant factor IX product, trenonacog alfa in previously treated haemophilia B patients. Haemophilia. 2018;24(1):104–12 [c].
[51] Mahlangu JN. Updates in clinical trial data of extended half-life recombinant factor IX products for the treatment of haemophilia B. Ther Adv Hematol. 2018;9(11):335–46 [R].
[52] King GS, Cottingham LG, Hughes RE, et al. Probable pulmonary embolism with repeat administration of prothrombin complex concentrate in a factor Xa inhibitor patient. J Clin Pharm Ther. 2018;43(6):903–5 [A].
[53] Scharman CD, Shatzel JJ, Kim E, et al. Off-label use of 4-factor prothrombin complex concentrate is common despite little known benefit: a retrospective study. Eur J Haematol. 2018;101(3):349–53 [C].
[54] Mohan S, Howland MA, Lugassy D, et al. The use of 3- and 4-factor prothrombin complex concentrate in patients with elevated INR. J Pharm Pract. 2018;31(3):262–7 [c].
[55] Sun GH, Patel V, Moreno-duarte I, et al. Intraoperative administration of 4-factor prothrombin complex concentrate reduces blood requirements in cardiac transplantation. J Cardiothorac Vasc Anesth. 2018;32(1):161–7 [c].
[56] Astrup G, Sarangarm P, Burnett A. Fixed dose 4-factor prothrombin complex concentrate for the emergent reversal of warfarin: a retrospective analysis. J Thromb Thrombolysis. 2018;45(2):300–5 [c].

[57] O'Sullivan JM, Ward S, Lavin M, et al. von Willebrand factor clearance—biological mechanisms and clinical significance. Br J Haematol. 2018;183(2):185–95 [R].
[58] Klukowska A, Komrska V, Vdovin V, et al. Low incidence of factor VIII inhibitors in previously untreated patients with severe haemophilia A treated with Octanate: final report from a prospective study. Haemophilia. 2018;24(2):221–8 [c].
[59] Hazendonk HCAM, Heijdra JM, de Jager NCB, et al. Analysis of current perioperative management with Haemate P/Humate P in von Willebrand disease: identifying the need for personalized treatment. Haemophilia. 2018;24(3):460–70 [C].
[60] Icheva V, Nowak-Machen M, Budde U, et al. Acquired von Willebrand syndrome in congenital heart disease surgery: results from an observational case-series. J Thromb Haemost. 2018;16:2150–8 [c].
[61] Nishida O, Ogura H, Egi M, et al. The Japanese clinical practice guidelines for management of sepsis and septic shock 2016 (J-SSCG 2016). Acute Med Surg. 2018;5(1):3–89 [M].
[62] Nishimura Y, Takagi Y. Strategy for cardiovascular surgery in patients with antithrombin III deficiency. Ann Thorac Cardiovasc Surg. 2018;24(4):187–92 [c].
[63] Arantes LH, Crawford J, Gascon P, et al. A quick scoping review of efficacy, safety, economic, and health-related quality-of-life outcomes of short- and long-acting erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anemia and chronic kidney disease anemia. Crit Rev Oncol Hematol. 2018;129:79–90 [M].
[64] Bai XF, Gao YK. Recombinant human erythropoietin for treating severe traumatic brain injury. Medicine (Baltimore). 2018;97(1) e9532 [C].
[65] Nagashima T, Yokohama A, Nagai K, et al. Short-term administration of recombinant human erythropoietin decreases B cell number in human peripheral blood. Transfus Apher Sci. 2018;57(2):208–14 [C].
[66] Overgaard J, Hoff CM, Hansen HS, et al. DAHANCA 10—effect of darbepoetin alfa and radiotherapy in the treatment of squamous cell carcinoma of the head and neck. A multicenter, open-label, randomized, phase 3 trial by the Danish head and neck cancer group. Radiother Oncol. 2018;127(1):12–9 [C].
[67] Zhang J, Liang Y, Ai Y, et al. Eltrombopag versus romiplostim in treatment of adult patients with immune thrombocytopenia: a systematic review incorporating an indirect-comparison meta-analysis. PLoS One. 2018;13(6):e0198504 [M].
[68] Mingot-castellano ME, Caparrós IS, Fernández F, et al. Treatment characteristics, efficacy and safety of thrombopoietin analogues in routine management of primary immune thrombocytopenia. Blood Coagul Fibrinolysis. 2018;29(4):374–80 [C].
[69] Guitton Z, Terriou L, Lega JC, et al. Risk of thrombosis with anti-phospholipid syndrome in systemic lupus erythematosus treated with thrombopoietin-receptor agonists. Rheumatology (Oxford). 2018;57(8):1432–8 [c].
[70] Zhang J, Liang Y, Ai Y, et al. Eltrombopag versus romiplostim in treatment of children with persistent or chronic immune thrombocytopenia: a systematic review incorporating an indirect-comparison meta-analysis. Sci Rep. 2018;8(1):576 [M].
[71] Hwang YY, Gill H, Chan TSY, et al. Eltrombopag in the management of aplastic anaemia: real-world experience in a non-trial setting. Hematology. 2018;23(7):399–404 [c].
[72] Mittelman M, Platzbecker U, Afanasyev B, et al. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): a randomised, placebo-controlled, phase 2 trial. Lancet Haematol. 2018;5(1):e34–43 [C].
[73] Hierlmeier S, Eyrich M, Wölfl M, et al. Early and late complications following hematopoietic stem cell transplantation in pediatric patients—a retrospective analysis over 11 years. PLoS One. 2018;13(10)e0204914 [C].
[74] Eichenberger EM, Soave R, Zappetti D, et al. Incidence, significance, and persistence of human coronavirus infection in hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2019;54:1058–66 [epub ahead of print]. [C].
[75] Shalitin S, Pertman L, Yackobovitch-Gavan M, et al. Endocrine and metabolic disturbances in survivors of hematopoietic stem cell transplantation in childhood and adolescence. Horm Res Paediatr. 2018;89(2):108–21 [C].
[76] Annaloro C, Airaghi L, Giannarelli D, et al. Prospective evaluation of metabolic syndrome and its features in a single-center series of hematopoietic stem cell transplantation recipients. Ann Hematol. 2018;97(12):2471–8 [C].
[77] Armenian SH, Yang D, Teh JB, et al. Prediction of cardiovascular disease among hematopoietic cell transplantation survivors. Blood Adv. 2018;2(14):1756–64 [C].
[78] Jacquot C, Delaney M. Efforts toward elimination of infectious agents in blood products. J Intensive Care Med. 2018;33(10):543–50 [r].
[79] Ramachandran S, Groves JA, Gl X, et al. Recent and occult hepatitis B virus infections among blood donors in the United States. Transfusion. 2018;9999:1–11 [MC].
[80] Bloch EM, Ness PM, Tobian AAR, et al. Revisiting blood safety practices given emerging data about Zika virus. N Engl J Med. 2018;378(19):1837–41 [r].