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Blood, Blood Components, Plasma, and Plasma Products

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ALBUMIN AND DERIVATIVES [SEDA-15, 54; SEDA-33, 670; SEDA-34, 509; SEDA-35, 583; SEDA-36, 483]

Albumin [SEDA-15, 54; SEDA-33, 670; SEDA-34, 509; SEDA-35, 583; SEDA-36, 483]

Exogenous administration of human albumin has been used primarily for volume expansion. Albumin accounts for 70–80% of the oncotic pressure in plasma. Other properties of albumin include carrying hydrophobic substances, antioxidant activity, antithrombotic effects, anti-inflammatory effects, and endothelial stabilization. A recently published review article highlights these properties and indications for exogenous albumin administration [1r].

Comparative Studies

Albumin was compared to normal saline in 841 patients with acute ischemic stroke in the following international study. Albumin 25% at a dose 2 g/kg with a maximum volume of 750 mL or the equivalent volume of normal saline was administered within 5 hours of symptom onset. The study was terminated early for futility after finding no difference in the primary endpoint of neurological outcome at 90 days. Patients treated with albumin experienced more pulmonary edema (RR 10.8, 95% CI 4.37–26.72), shortness of breath (RR 2.58, 95% CI 1.09–6.12), and symptomatic intracranial hemorrhage within 24 hours (RR 2.42, 95% CI 2.42–5.78) [2C].

The randomized, multi-center, open-label ALBIOS trial compared 20% albumin, administered to maintain a serum albumin level of 3.0 g/dL, to crystalloid solution. The study of patients with severe sepsis found no

difference in mortality at 28 or 90 days. Despite no difference in volume of fluid administered to the two groups, in the first 7 days of the study the net fluid balance was lower and the arterial blood pressure was higher in the albumin group compared to crystalloid group [3C].

A cohort study of 62 patients with bleeding peptic ulcers compared the following three groups: patients with normal serum albumin, patients with serum albumin less than 3 g/dL, and patients with serum albumin less than 3 g/dL treated with 1 or 2 days of 10 g of 20% albumin every 8 hours. Rebleeding was significantly lower in the patients with normal serum albumin compared to both groups with hypoalbuminemia. Duration of hospitalization was 7 versus 15 days ($p=0.01$) for patients treated with albumin compared to the untreated patients with low albumin [4c].

Systematic Reviews

Crystalloid versus colloid resuscitation including albumin was the subject of systematic reviews. A meta-analysis of 14 studies demonstrated possible benefit of albumin over crystalloids for mortality in sepsis with over 18000 patients. The odds ratio for mortality was 0.83, 95% CI 0.65–1.04, not statistically significant [5M]. In patients with severe sepsis, a British meta-analysis of 16 trials with over 4000 patients demonstrated no mortality benefit for albumin over crystalloids and no signal for harm [6M].

Albumin for plasma expansion following paracentesis in patients with cirrhotic liver disease was associated with less circulatory dysfunction (OR 0.26, 95% CI 0.08–0.93) and no statistically significant effect on mortality, hyponatremia, encephalopathy, readmission, or renal

dysfunction. A statistically significant difference in death (OR 0.46, 95% CI 0.25–0.86) and renal dysfunction (OR 0.34, 95% CI 0.15–0.75) was found in cirrhotic patients with infection. This meta-analysis included 16 studies with 1518 patients [7M].

Respiratory

There is debate over resuscitation with crystalloids versus colloids, such as albumin, and the effect on the lungs. Pathophysiology, historic perspectives, and evidence are reviewed in a recent article. The authors concluded, despite theoretical benefit, resuscitation with albumin does not prevent respiratory dysfunction [8r].

Immunologic

Anaphylactic shock due to the human albumin found in fibrinogen and erythrocytes concentrates which was reported in a 40-year-old male patient under general anesthesia for prolapsed mitral valve replacement. Skin prick and intradermal testing was used to confirm reaction to albumin [9A].

Drug–Drug Interaction

Administration of human albumin with furosemide compared to furosemide alone was reviewed in a meta-analysis of 10 studies. At 8 hours, the combination of albumin and furosemide resulted in an increase of 231 mL (95% CI 135.5–326.5) urine output and 15.8 mEq (95% CI 4.9–26.8) of sodium excretion. There was no difference at 24 hours of treatment [10M].

BLOOD TRANSFUSION [SEDA-15, 529; SEDA-34, 509; SEDA-35, 583, SEDA-36, 483]

Erythrocytes

The clinical decision to transfuse patients should not be based solely on a single hemoglobin number. According to the American Cancer Society, blood transfusion can be life-saving; however, they are not without risks [11S]. There is substantial overutilization of transfusions based on the available hemovigilance programs. Blood transfusions have been cited as one of the top five most overutilized therapeutic procedures in the United States [12c]. The establishment of hemovigilance programs started over 20 years ago in France with the initiation of various monitoring systems by Blood Transfusion Committees which laid the foundation for a national hemovigilance system [13r]. Some of the most important factors to consider when evaluating a patient for transfusion suggested by hemovigilance systems include: goals of therapy, prior experiences with transfusions, and individualized risk–benefit analysis [14C]. Institutional experience and national databases suggest that a more

restrictive blood transfusion approach is being increasingly implemented as best practice [15R].

According to the Red Cross Blood Service organization, each blood product that is transfused carries a potential risk of causing a side effect [16r]. Typically, this risk or incidence is fairly small. The organization further classifies these reactions as acute, occurring within 24 hours of transfusion, or delayed, occurring 24 hours post-transfusion. The common acute immunological reactions are: hemolytic ABO/Rh mismatch which can occur in up to 1:40 000 patients and febrile nonhemolytic transfusion reactions which may affect 0.1–1% of patients. The latter can be treated with antipyretics. Other considerations include mild allergic reactions (urticaria) with up to 3% of patients being affected to more serious severe reactions of anaphylaxis with a much lower incidence of 1:50 000. Urticaria can be treated with antihistamines (diphenhydramine) or steroids. Reported delayed immunologic reactions include post-transfusion-related purpura and transfusion-associated graft versus host disease (TA-GVHD), both of which are reported to be rare [16r] but patients with weaker immune systems are more susceptible to TA-GVHD reactions [11S]. The more notable and commonly cited transfusion reactions that can occur are transfusion-related acute lung injury (TRALI) with a 1:1200–1:190 000 incidence and transfusion-associated circulatory overload (TACO) with a less than 1% reported incidence. Both of these reactions have been reported in adults and pediatric patient populations.

Respiratory

A recent retrospective Canadian study sought to evaluate the similarities and differences between adult and pediatric patients presenting with symptoms of TRALI after recent transfusions. A total of 284 cases of TRALI were reported and out of those 6% ($n=17$) occurred in children. This retrospective trial demonstrated that the symptomatic presentation of TRALI in both of these patient populations is very similar and should not be overlooked. Although the numbers were small, there did not appear to be a difference in presentations or outcomes between adults and children with TRALI [17c]. By further stratifying the pediatric patients into age groups, the authors noted that most of the children who presented with TRALI were either teenagers or less than 1-year olds, potentially concluding that these two pediatric patient populations are at a higher risk. The American society of Hematology highlights that there is no single test to diagnose TRALI. It should be suspected if the patient has clinical findings (ex: hypoxemia, hypotension, fever, transient leucopenia and bilateral pulmonary edema) typically within 6 hours of transfusion [18S]. The treatment should include discontinuation of transfusion (if applicable) and supportive care where applicable including: ventilator support, maintenance

of hemodynamic status and fever reducing agents. Most patients demonstrate clinical improvements within 96 hours from symptom onset. The reported overall fatality rate post-TRALI is 5% [18S].

Immunologic

Human Leucocyte Antigen (HLA) is one clinically implicated pathway in which TRALI is suspected to occur. Both the United Kingdom and the United States have demonstrated the benefit of excluding plasma collected from female donors as a means to reduce incidence of TRALI in the recipient [19r]. This resulted in a reduction of approximately half to two-thirds in TRALI incidences with fatalities almost disappearing [20S]. Previous studies have concluded that with each pregnancy comes an increased probability for HLA alloimmunization and this formed response appears to be long-lasting. These allo-antibodies tend to be present more frequently in females who have given birth to at least two children. Further reports indicate that the prevalence of HLA antibodies in the donor population is 2.3% in men and 17% in women [21c].

Hematologic

Hemosiderosis (iron overload) is another potential complication of transfusions. The incidence of iron overload typically increases with number of transfusions. A retrospective chart analysis to determine the prevalence and risk factors for liver toxicity associated with Transfusion Related Iron Overload (TRIO) in pediatric oncology patients was recently published. The authors of this study also report their experience with Iron Chelating Therapy (ICT). The single major risk factor for TRIO was number of transfusions with a prevalence of greater than 35% in patients receiving over 10 transfusions. Four patients with TRIO and elevated liver function tests received chelation therapy. The study authors concluded that there was a significant decrease in serum ferritin levels and an improvement in liver function tests was observed with no serious adverse effect from iron chelation therapy [22c].

Death

Aggressive blood transfusion may affect long-term mortality. One hypothesis is that changing the immune function can potentially increase the risk of infections and risk of certain cancers. The authors sought to find a difference between a liberal transfusion strategy in which they received blood transfusion to maintain hemoglobin level at 100 g/L (10 g/dL) or higher vs. restrictive transfusion strategy in which they received blood transfusion when hemoglobin level was lower than 80 g/L (8 g/dL) or if they had symptoms of anemia [14C]. Over 2000 patients were enrolled in the study and randomly assigned in a 1:1 ratio to the liberal transfusion strategy

or restrictive transfusion strategy. The follow-up duration was 3 years, during which over 40% of patients died. However, the long-term mortality did not differ significantly between the liberal transfusion strategy (432 deaths) and the restrictive transfusion strategy (409 deaths) (hazard ratio 1.09 [95% CI 0.95–1.25]; $p=0.21$). These findings did not support idea that blood transfusions lead to long-term immunosuppression severe enough to affect long-term mortality rates [14C].

Another study provides interesting insight into a unique patient populations who otherwise are not candidates for blood transfusions but who are at the same time severely anemic. This was a retrospective study which analyzed the clinical outcomes of 293 patients 18 years and older who could not be transfused and had at least one hemoglobin measurement of ≤ 8 g/dL after surgery. The majority of the patients were self-identified as Jehovah's witnesses (98%) and female (74.1%). The odds ratio of death after adjustment for other significant factors was 1.82 with an overall mortality rate of 8.2%. This study confirms a very important clinical point that there is a low risk of mortality in patients with hemoglobin ranges from 7 to 8 g/dL. The risk substantially increases with lower hemoglobin ranges. The unadjusted odds ratio (OR) of death per each 1 g/dL decrease in the nadir post-operative Hgb was 2.04 (95% CI 1.52–2.74) although the number of patients who fell into this hemoglobin group was extremely small [23c].

Technology and Transfusions

The recent use of technology in medicine worldwide has substantially decreased the risks of side effects with many medications including therapeutic procedures such as blood transfusions. An observational study evaluated the impact of a computerized clinical decision support system to see if it would promote proper decision making strategies for transfusions of red blood cells (RBCs) by physicians. Patient outcomes (overall mortality, 30-day readmissions and length of stay) as well as the number of RBC transfusions were assessed before and after implementations of the computerized alert trigger for transfusions when hemoglobin levels were higher than 7 g/dL. The results were overwhelmingly positive [12c]. There was a significant improvement in RBC utilization and the clinical patient outcomes showed improvement as well (mortality, $p=0.034$; length of stay, $p=0.003$) or remained stable (30-day readmission rates, $p=0.909$). The mean number of units transfused per patient also declined (3.6 to 2.7, $p<0.001$). This also led to a reduction in acquisition costs of RBC units. The authors concluded that there was a statistically significant improvement in clinical patient outcomes when combined with an improved blood utilization protocol based on a computerized clinical decision support system [12c].

Granulocytes

Neutrophil granulocytes are the most abundant (50–75%) type of white blood cells in humans and form an essential part of the innate immune system. They are formed from stem cells in the bone marrow. Neutrophils play a critical role in preventing infections as part of the innate immune system. Reduction in neutrophils below an absolute count of 500 cells/pL is termed severe neutropenia or agranulocytosis [24H]. Neutrophils are able to phagocytize foreign substances such as bacteria. This blood product is used for patients with functionally defective granulocytes as well as neutropenic patients with life-threatening microbial infections. Occasionally, when transfused, this product is associated with hypoxia secondary to the high concentration of degrading cells.

Observational Study

In a study involving 128 patients with prolonged neutropenia and suspected invasive pulmonary aspergillosis (IA) patients were subdivided into two treatment groups. Group one received both granulocyte transfusion with antifungal therapy and group two only received antifungal therapy. Patients who received granulocyte transfusion were less likely to respond to antifungal therapy ($p=0.03$) and had a higher mortality rate ($p=0.009$). Among patients who received the granulocyte transfusion, 53% developed a pulmonary reaction characterized by worsening shortness of breath and pulmonary infiltrates within 48 hours of receiving the transfusion. This study suggests that granulocyte transfusion did not improve response to antifungal therapy and was associated with worse outcomes of invasive aspergillosis [25c].

Platelets

Observational Studies

Platelet transfusions prevent major haemorrhage and improve survival in thrombocytopenic patients [26c]. For many decades, advances in the preparation of platelets, including the introduction of pathogen reduction techniques, have been improved. Additionally, indications have been extended, for example to patients with drug-induced platelet dysfunction. However, platelet shortage is a serious medical concern. In November of 2014, the American Association of Blood Banks published guidelines for the administration of platelet transfusions in adult patients. These guidelines included only one strong recommendation on moderate quality evidence: platelets could be transfused prophylactically to reduce the risk of spontaneous bleeding in adult patients admitted to hospital with platelet counts of 10×10^9 cells/L or less, and low doses are equally effective as high doses [27r]. In 2012, the Society of Thoracic Surgeons recommended that patients should have transfusions after a

coronary artery bypass only if their hemoglobin concentrations fell to less than 70 g/L (7 g/dL); before this time, some patients would automatically be transfused after surgery or when hemoglobin was at 100 g/L (10 g/dL). Due to these and other similar guidelines, the total number of transfusions each year has been falling according to the American Red Cross, which covers about 40% of the US blood bank market. This both decreases the medical costs as well as decreases the risk of unnecessary side effects [27r].

Allergic Reactions and Fever

Plasma constituents have been implicated in several types of platelet (PLT) transfusion reactions. Leukoreduced apheresis platelets stored in InterSol have 65% less plasma than apheresis platelets stored in 100% plasma (PPs). This open-label, nonrandomized retrospective study compared transfusion reaction rates in InterSol PLTs versus PPs. Over 14000 transfusions from several sites were included with majority (9845 transfusions given to 2202 patients) were the apheresis platelets stored in 100% plasma (PP). A total of 165 adverse reactions were reported with majority appearing in the PP arm. The highest incidence transfusion reactions were allergic in nature as well as febrile nonhemolytic transfusion reactions (FNHTR's) at 0.66% and 0.40% of total transfusions reported, in the PP and InterSol groups, respectively [28c].

BLOOD SUBSTITUTES [SEDA-33, 672; SEDA-34, 511; SEDA-35, 586; SEDA-36, 485]

Hemoglobin-Based Oxygen Carriers [SEDA-33, 672; SEDA-34, 511; SEDA-35, 586; SEDA-36, 485]

Review of the properties of hemoglobin and the potential blood substitutes are discussed. While the authors offer no direct link to side effects, the potential for adverse outcomes could be linked to viscosity, vessel wall stress, and nitric oxide delivery [29r].

Comparative Studies

HBOC-201, a cell-free purified glutaraldehyde, cross-linked, and polymerized bovine hemoglobin, was compared to red cell transfusion in non-cardiac surgery patients during a study conducted from 1998 to 1999. Patients received up to seven units of HBOC-201 or red cells. The proportion of HBOC-201 group who avoided RBC transfusion was 0.427. There was no difference in 30-day mortality, serious adverse events, or time to hospital discharge between groups [30c].

PLASMA AND PLASMA PRODUCTS [SEDA-15, 84; SEDA-34, 512; SEDA-35, 586, SEDA-36, 486]

α 1-Antitrypsin

Alpha-1 antitrypsin (AAT) has broad anti-inflammatory and immunomodulating properties. Administration of human plasma-derived AAT is protective in models of acute myocardial infarction in mice. The objective of this prospective open-label, single-arm treatment study was to determine the safety and tolerability of human plasma-derived AAT and its effects on the acute inflammatory response in non-AAT deficient patients with ST-segment elevation myocardial infarction (STEMI). Ten patients with acute STEMI were enrolled and received AAT at 60 mg/kg IV within 12 hours of admission. C-reactive protein (CRP) and plasma AAT levels were determined at admission, 72 hours, and 14 days, and patients were followed clinically for 12 weeks for the occurrence of new onset heart failure, recurrent myocardial infarction, or death. Compared with historical controls, the area under the curve of CRP levels was significantly lower 14 days after admission in the study group (75.9 vs. 205.6 mg/L, $p=0.048$). In conclusion, a single administration of study agent in patients with STEMI was well tolerated and was associated with a blunted acute inflammatory response [31c].

C1 Esterase Inhibitor Concentrate

Observational Studies

Hereditary angioedema (HAE) due to C1 esterase inhibitor (HAE-C1-INH) deficiency is a rare genetic disorder presenting with recurrent episodes of skin swellings, abdominal pain, and potentially fatal laryngeal edema. An observational study was designed to review the safety and efficacy of human, plasma-derived C1-INH concentrate for the treatment of patients with HAE-C1-INH. A systematic review of nearly 90 studies (2000 patients) was performed which investigated C1-INH for HAE. Replacement therapy with C1-INH significantly shortened time to onset of symptom relief in HAE attacks compared with placebo in many of the reviewed studies. C1-INH has been shown to be effective for patients receiving home therapy and short- and long-term prophylaxis. Treatment with C1-INH was generally well tolerated and administration of C1-INH was not associated with transmission of viruses or development of autoantibodies irrespective of treatment duration [32R]. Another observational study wanted to get a physician perspective on what they thought was a "true" incidence of side effects when administering C1-INH for HAE in their patients. This study was done via a survey to physicians

who manage patients with HAE. The study was designed to determine the risk of thrombosis associated with C1-inhibitor (C1-INH) via a survey. The survey queried physicians about their observations while treating HAE. Of the 66 physicians who participated in the survey, 37 had patients (856 patients) who were on C1-INH but only 4 (total of 5 patients) had patients on C1-INH who experienced a thromboembolic episode [33c].

Dose Escalation Studies

Another study sought to evaluate the safety of escalating doses of Cintyze[®], a nonfiltered C1 inhibitor, in patients who were not previously controlled on the standard doses (1000 units every 3–4 days). Eligible patients had to have >1 HAE attack/month. Dose escalation went up to 2500 units (max dose) in 12 of the 20 patients based on continued number of attacks per month. Eighteen of the patients experienced common and previously reported side effects. Four patients reported serious reactions including cerebral cystic hygroma, laryngeal angioedema attack, anemia, and bile duct stone) but these effects were considered by investigators to be unrelated to treatment. Notably, there were no systemic thrombotic events or discontinuations due to adverse events. Dose escalation of nanofiltered C1 inhibitor (human) up to 2500 units was well tolerated and reduced attack frequency in the majority of patients [34c].

Cryoprecipitate

Cryoprecipitate was originally developed as a therapy for patients with antihemophilic factor deficiency or hemophilia A and has been used for nearly 50 years. With the production of recombinant and purified factor concentrates, the classical indications of hemophilia A and von Willebrand disease are no longer appropriate. Cryoprecipitate is now most commonly used to replenish fibrinogen levels in patients with acquired coagulopathy (ex: hemorrhage including cardiac surgery, trauma, organ transplantation, or obstetric hemorrhage).

This agent is a blood product that is manufactured from fresh frozen plasma. It contains a subset of coagulation factors namely: fibrinogen (minimum of 150 mg/unit), factor VIII (minimum 80 IU/unit), von Willebrand factor, and factor XIII. Currently, cryoprecipitate is used to treat hypofibrinogenemia [35r].

Observational Study

The objective of this retrospective, non-controlled observational study was to determine the safety and efficacy of cryoprecipitate in improving plasma fibrinogen levels, coagulation parameters and clinical status in both acute and chronic acquired hypofibrinogenemia. The average fibrinogen level before administration of

cryoprecipitate was similar in the two disease groups (acute vs. chronic), and the amount of cryoprecipitate administered was comparable in the two cohorts. At 24 hours post-cryoprecipitate, the mean fibrinogen level was higher in the acute group when compared to the chronic group (2.02 vs. 1.45 g/L; $p=0.0009$). Despite cohort differences, the increase in fibrinogen level was statistically significant for both cohorts between baseline and 24 hours (acute, $p\leq 0.0001$; chronic, $p=0.0001$). On another very important note, there were no acute adverse transfusion reactions reported as a direct result of the cryoprecipitate administration; no cases of transfusion-associated circulatory overload (TACO) or transfusion-transmitted infection (TTI) were noted indicating that cryoprecipitate is an effective and safe method of increasing the plasma fibrinogen level in hypofibrinogenemic patients [36c].

Fresh Frozen Plasma [SEDA-34, 513; SEDA-35, 587; SEDA-36, 487]

Systemic Review

A retrospective analysis was performed to identify the frequency of adverse reactions after transfusion on both per transfused patient and per transfused unit basis. The study evaluated red blood cells (RBCs), fresh frozen plasma (FFP), and platelet concentrates (PCs). The incidence of adverse reactions to RBCs, FFP, and PCs per transfused unit was 0.6%, 1.3%, and 3.8%, respectively. The incidence of adverse reactions to RBCs, FFP, and PCs per patient was 2.6%, 4.3%, and 13.2%, respectively—almost threefold higher. Most RBC associated adverse reactions were febrile nonhemolytic transfusion reactions and allergic reactions; whereas most FFP and PC associated adverse reactions were allergic reactions. This is consistent with what was found in prior literature [37R].

PLASMA SUBSTITUTES [SEDA-33, 675; SEDA-34, 513; SEDA-35, 587; SEDA-36, 487]

Dextrans [SEDA-15, 1082; SEDA-33, 675; SEDA-34, 513; SEDA-35, 587; SEDA-36, 487]

Hematologic

Thrombolastometry analysis and extrinsic coagulation assay (EXTEM) was performed on blood samples from 10 healthy volunteers diluted first with 3% dextran 60, 6% dextran 60, buffered and unbuffered hydroxyethyl starch (HES) 130/0.4, 5% albumin and Ringers acetate. Correction of dilutional coagulopathy was then performed using fibrinogen concentrate on each sample. Samples diluted with HES or dextran demonstrated

decreased correction of coagulopathy compared to those diluted with albumin ($p\leq 0.001$). The platelet component of clot strength was decreased more by the dextran solutions than albumin ($p\leq 0.001$) [38E].

Etherified Starches [SEDA-15, 1237; SEDA-33, 675; SEDA-34, 513; SEDA-35, 587; SEDA-36, 487]

Comparative Studies

Mortality in patients with hypovolemic shock treated with crystalloids or colloids was compared in the CRIS-TAL trial. In the colloid group, 68.8% of patients received HES. At 28 days, there was no difference in mortality but at 90 days, mortality was 30.7% in colloids group vs. 34.2% in crystalloids group (RR 0.92, 95% CI 0.86–0.99; $p=0.03$) [39C].

Systematic Reviews

Crystalloid versus colloid resuscitation including use of HES was the subject of several systematic reviews [5M,6M]. One analysis included two studies which compared starch to albumin for sepsis and found albumin was associated with decreased risk of mortality OR 0.71 (95% CI 0.54–0.94) with moderate quality evidence. Comparisons between starches with gelatin and crystalloids were not statistically significant [5M].

Cardiovascular

Administration of 500 mL of 6% HES 130/0.4 and 500 mL of Ringer's Lactate (RL), was compared to 1000 mL of RL in 168 healthy mothers for elective caesarian section with spinal anesthesia. Use of HES+RL was associated with lower incidence of hypotension 36.6% compared to 55.3% ($p=0.025$) in pure RL group. There was no difference in phenylephrine requirements, post-operative maternal hemoglobin, or neonatal outcomes. HES concentrations were undetectable in umbilical cord samples obtained from six of the neonates assigned to the HES group [40c].

Fluid Balance

Administration of 6% HES for volume replacement in a study of 61 pediatric open heart surgery patients resulted in less positive fluid balance than patients treated with albumin ($p=0.050$) [41c].

Hematologic

Coagulation competence measured with thrombolastography and perioperative blood loss were compared in patients undergoing cystectomy administered 35 mL/kg of HES 130/0.4 or RL. There was reduced development and strength of clot in patients treated with HES. Perioperative blood loss was 2191 mL in the HES

group compared to 1370 mL in the group treated with RL ($p=0.038$) [42c]. In a similar comparison, cardiac surgery patients received HES, albumin, and RL as the major perioperative fluid with a maximal dose of 50 mL/kg/day. There was no difference in volume of chest tube drainage however 64% of patients treated with HES required transfusion compared to 62% and 35% of patients treated with albumin and RL, respectively (p -value HES vs. RL = 0.0003) [43c]. In a *post hoc* analysis of a Scandinavian starch for sepsis database, HES administration was associated with increased risk of bleeding when compared to Ringer's acetate (RR 1.55, 95% CI 1.16–2.08). This was also associated with an increased risk of death (RR 1.36, 95% CI 1.04–1.79; $p=0.03$) [44c].

Urinary Tract

The role of HES in development of renal dysfunction was explored in a recent review in the surgical population [45r]. One study of on-pump cardiac bypass surgery patients compared normal saline to 7.2% NaCl/6% HES 200/0.5 resuscitation at a dose of 4 mL/kg in 30 minutes after the start of anesthesia. There was no difference in the rate of acute kidney injury between groups [46c]. However, in another a meta-analysis of 10 studies with more than 4600 patients with sepsis, the rate of acute kidney injury, requirement for renal replacement therapy was higher in treatment with HES. There was no difference in ICU or 28-day mortality but an increased rate of mortality in patients treated with HES compared to crystalloids [47R].

Skin

A retrospective study of 70 patients with electron microscopy-proven HES induced pruritus between 1993 and 2008 sought to characterize latency, duration, and severity. The majority of patients received HES 200/0.5 6% solutions. Patients experienced an average of 3.5 attacks per day with an onset of 3 weeks after HES administration. No clinical differences were seen between 200/0.5 and 130/0.4 HES associated pruritus nor in cumulative HES dose [48A].

Gelatin [SEDA-34, 514; SEDA-35, 584; SEDA 36–487]

Systematic Reviews

Crystalloid versus colloid resuscitation including use of gelatin was the subject of systematic reviews. Gelatin was compared with starch in one study included in the meta-analysis and no difference in mortality for sepsis resuscitation was noted [5M].

GLOBULINS

Immunoglobulins [SEDA-15, 1719; SEDA-33, 677; SEDA-34, 514; SEDA-35, 588; SEDA-36, 488]

Intravenous Immunoglobulin

The mechanism of immunoglobulin in primary and secondary immunodeficiency disorders is delivery of mature antibodies in adequate concentrations against a variety of pathogens. The mechanism of action in other conditions is less understood but anti-inflammatory and immunomodulation effects are present. A variety of intravenous immunoglobulin (IVIG) products are available, each with different studied indications, formulations, and potential toxicities. The volume load, sugar content, osmolality, sodium content, IgA content, and pH of preparations all influence these potential reactions [49R]. There are a variety of adverse reactions and management strategies for them related to intravenous immunoglobulin (IVIG). Infusion reactions such as headache, nausea, vomiting, musculoskeletal pain, flushing, and tachycardia many be prevented with premedication using NSAIDs, corticosteroids, antihistamines, and acetaminophen. These anaphylactoid reactions can appear like anaphylaxis but are differentiated due to a lack of hypotension and release of IgE. Anaphylaxis due to the IgA in IVIG products has also occurred. Thromboembolic events following treatment with IVIG have been associated with patient specific risk factors and formulations contaminated with coagulation factors XI, XIIa, and kallikrein. Acute renal dysfunction has been further linked with age, diabetes, sepsis, concomitant nephrotoxic agents, and products containing sucrose. Prehydration has been employed to decrease the chances of this toxicity. Hematologic adverse events including neutropenia and hemolysis have been described as well [50R,51R]. A series of proposed European consensus statements were published following the Kreuth III meeting [52R].

OBSERVATIONAL STUDIES

A single center retrospective review of 77 patients treated with IVIG over a 10-year period demonstrated an adverse event rate in 32% in this patient population. The most common reported adverse event was fever (30.5%) followed by rash (22.2%). Onset of fever was most frequently observed between 61 minutes and 6 hours from the initiation of the infusion [53c].

COMPARATIVE STUDIES

A prospective cohort of 1765 infusions of IVIG for 117 patients with primary immunodeficiency in Brazil was analyzed for adverse events. The incidence of reactions

was 2.15% of infusions and 23.8% of patients. Pretreatment, infusion rate, and number of batches were not found to be significantly associated with increased or decreased infusion reactions. Only 7.9% of reactions were severe and there were no significant findings with respect to latency of reaction. There was a higher incidence of reactions with Tegeline[®] compared to Octagam[®] [54c].

MAJOR REVIEWS

In neonates, synthesis of immunoglobulin occurs several months after birth. Transfer of material immunoglobulin occurs after 32 weeks of gestation. Administration of exogenous IVIG in neonates with suspected sepsis was hypothesized to reduce morbidity and mortality. In a Cochrane review of 8 studies with 3871 infants, mortality was not improved in patients treated with IVIG (RR 0.94, 95% CI 0.80–1.12). No difference in morbidity at 2 years or length of stay was reported [55R]. A similar review of adult patients with sepsis and severe sepsis reviewed polyclonal IVIG and IgM-enriched polyclonal IVIG separately. In 10 trials of polyclonal IVIG trials with 1430 patients, reduction in mortality was confirmed when compared to placebo (RR 0.81, 95% CI 0.70–0.93). In the seven trials of 528 patients treated with IgM-enriched polyclonal IVIG reduction in mortality was also reported (RR 0.66, 95% CI 0.51–0.85). However, in those studies of low bias no mortality reduction was demonstrated [56R]. In a Cochrane review of seven trials with 623 patients with Guillain-Barre syndrome improvement, there was no difference, when compared to control treatments, in mean change in a validated disability scale. There was no difference in adverse effects between patients treated with IVIG or plasma exchange but more patients completed IVIG treatment [57R].

HEMATOLOGIC

The incidence of thromboembolic events in a retrospective cohort of 303 patients was 16.9% (95% CI 13–21.6). The study reviewed patients at a tertiary care center in Madrid over a 2-year period. The outcome of fatal thromboembolic events was observed in 16 patients, 32% of total thromboembolic cases. Patients who experienced thromboembolic events tended to be older, male gender, and treated with higher doses of IVIG ($p < 0.001$) [58C]. Hemolytic anemia was characterized in a study of 34 *de novo* and 50 maintenance patients treated for neurologic conditions. The fall in hemoglobin was 0.9 and 0.4 mM for the *de novo* and maintenance groups, respectively. There were no significant changes in reticulocytes, haptoglobin, and bilirubin. Lactate dehydrogenase was significantly increased [59c].

URINARY

A case report of severe antibody mediated rejection following IVIG for BK virus nephropathy in a Caucasian

female recipient of a deceased donor transplant is discussed below. There were no donor specific antibodies present prior to IVIG infusion. Nephrectomy was performed and antibodies were present. Following IVIG infusion donor specific antibodies to HLA DR11 and HLA DQ7 were present in the recipient's serum. Twenty-five days after nephrectomy serum was negative for donor specific antibodies [60A].

SKIN

Erythematous rashes on the palms and chest are described in recipients of IVIG [61A,62A].

IMMUNOLOGIC

A prospective study of 21 patients receiving IVIG for primary antibody deficiency's tested plasma samples and drug lots of different IVIG products for antibodies to tetanus, diphtheria, measles and varicella. There was no significant difference between products or drug lots of IVIG with respect to antibodies for these diseases. There was fluctuation in the patients' plasma antibodies titers in the four blood samples drawn every 3 months [63c].

DRUG FORMULATIONS

BIVIGAM, a new IVIG formulation from Behring is reviewed [64r]. IVIG formulation is often implicated with renal toxicity. Osmotic nephrosis has been associated with glucose solutions. Maltose solutions are degraded in the brush boarder of the proximal tubule and therefore also implicated with nephrotoxicity. Mannitol, as an IVIG excipient, is suspected to cause renal vasoconstriction and osmotic nephrosis. Finally, D-sorbitol, glycine and L-proline IVIG products have little association with nephrotoxicity [65r].

Subcutaneous Immunoglobulin

OBSERVATIONAL STUDY

A prospective, open-label, multi-center, study of 24 adult and pediatric Japanese patients with primary immunodeficiency assessed serum IgG trough levels with IVIG treatment or IgPro20 (Hizentra[®], L-proline stabilized 20% human subcutaneous IG). Patients were treated for three mandatory IVIG infusions, followed by a 12-week wash-out period with conversion to the IgPro20, followed by the 12-week study period of IgPro20. Dose equivalence was established as the primary efficacy endpoint. During the subcutaneous IG (SCIG) period, 52% of patients experienced a serious bacterial infection, with one patient requiring hospitalization. Overall, adverse event rates were 0.461 and 0.653 per treatment for the SCIG and IVIG, respectively. Local infusion site reactions occurred in 80% of patients during the SCIG treatment with decreasing incidence over time [66c].

SKIN

Two patients are described to have necrotic skin ulcers at the site of SCIG infusion. A 13-year-old boy treated with 20% SCIG for common variable immunodeficiency. After 3 years, with only local erythema at the site of injection the patient experienced a blister with necrotic center on the thigh which grew oxacillin-sensitive *Staphylococcus aureus*. He was treated with trimethoprim-sulfamethoxazole and erythromycin. The second patient, an 11-year-old girl treated for trichothiodystrophy and associated hypogammaglobulinemia. After 4 years of treatment, a blister at the site of infusion developed into a 4.5 × 5 cm area of induration with 1 cm necrotic center. She was hospitalized and treated initially with clindamycin, fluconazole, and piperacillin-tazobactam. She had resolution of infection after 9 days of antibiotic treatment. One month after her SCIG treatment she developed a blister at the injection site again, treated with clindamycin, but no development of necrosis of the skin [67A].

Anti-D immunoglobulin

The British Committee for Standards in Hematology (BCSH) published a guideline for use of Anti-D immunoglobulin to prevent hemolysis in newborns and fetuses. This statement reviews indications, dosage, administration, and monitoring. The low incidence of adverse events is emphasized with recommendations for surveillance for severe hypersensitivity reactions [68R].

COMPARATIVE STUDIES

A single center study comparing pediatric patients treated for immune thrombocytopenia before and after the March 2010 FDA warning regarding treatment with Anti-D immunoglobulin, demonstrated no statistical difference in adverse effects. Headache, nausea, vomiting, hematuria, anemia, fever, and chills were most frequently reported adverse events in 2186 patients before and 1782 patients after the warning [69c].

IMMUNOLOGIC

In a retrospective analysis of the Leukocyte Antibody Prevalence Study Database previously pregnant RhD negative and positive women were compared. HLA sensitization rate was lower in RhD negative women less than or equal to 40 years old (RR 0.58, 95% CI 0.40–0.84). Authors concluded this effect was associated with the routine use of RhIG prophylaxis [70c].

Suspected hypersensitivity reactions to Anti-D immunoglobulin in three pregnant women are described. A 18-year-old primigravida Rh(–) woman developed wheezing, severe dyspnea, and periorbital edema within 3 minutes of administration of Anti-D 500 IU (Rhopylac; CSL Behring, Haywards Health, UK). Upon subsequent pregnancy, skin prick and intradermal testing was

negative. Empiric protocol was used with 10%, 30%, 60% of total 1500 IU if Rhophylac was administered on a subsequent Rh(–) pregnancy. A 25-year-old woman, Rh(–) primigravida was administered 1500 IU Rhophylac at 28 weeks and 500 mcg of D-GAM (Anti-D; Bio Products Laboratory, Elstree, UK) upon delivery. Upon development of maternal hemorrhage, 7500 IU of Rhophylac was administered over 20 minutes. After 1 hour, the patient developed tremor, tachycardia, dyspnea, and desaturation to 80% on room air. After 6 months skin prick testing, intradermal testing, and challenge with 1500 IU of Rhophylac elicited no reaction. A 19-year-old Rh(–) female who received three separate doses of Anti-D immunoglobulin. After the first dose of 250 IC D-Game she felt “unwell”. Next she received 1500 IU of Rhophylac with reports of light-headedness, blurred vision, facial edema and pruritus. Skin prick testing and intradermal testing were negative 5 months later. After 300 IU of Rhophylac, she became dizzy with a headache and ocular pruritus. The additional 1200 IU of the full dose were well tolerated with no further reported reactions [71A].

DRUG INTERACTIONS

There is a risk of inadequate response to live vaccines, such as the influenza and MMR vaccines, when administered with Anti-D immunoglobulin. Because the obstetric population is a risk of co-administration of these products reminding patients to follow-up vaccine titers was the subject of a nursing quality initiative [72r].

COAGULATION PROTEINS [SEDA-15, 845; SEDA-33, 679; SEDA-34, 518; SEDA-36, 493]

Factor I

Fibrinogen (factor I) concentrate may be either plasma-derived or a recombinant product. It is the final protein in the common coagulation cascade.

Systemic Review

A systematic review identified 12 articles reporting fibrinogen concentrate (FC) usage in trauma patients: 4 case reports, 7 retrospective studies, and 1 prospective observational study were evaluated. Some of the available studies suggested that FC administration was associated with a reduced blood product requirement with minimally reported adverse events [73R].

Impact of Meals and Lab Levels

The authors of this research study hypothesized that fasting time for coagulation tests is not standardized and that this can decrease patient safety. The study evaluated the impact of whether a light meal (i.e. breakfast) can jeopardize laboratory coagulation tests. A blood

sample was first collected from 17 fasting volunteers (12-hour fast). Immediately after blood collection, the volunteers consumed a light meal. Then samples were collected at 1, 2 and 4 hours after the light meal. Several coagulation tests were evaluated including, fibrinogen (Fbg) levels. The results of Fbg and PS test were not influenced by a light meal. The authors concluded that a light meal does not influence the laboratory coagulation tests, but they suggested that the laboratory quality managers standardize the fasting time for all blood tests at 12 hours, to completely metabolize the lipids intake [74c].

Factor II

A wide variety of topical agents are approved as potential therapies in the maintenance of hemostasis during surgical procedures. A multidisciplinary approach to the selection and application of these agents requires input from all members of the surgical team [75R].

Topical thrombin may be either from a bovine or recombinant source. Thrombin plays a central role in coagulation, both activating platelets and cleaving fibrinogen. It is often used intraoperative for hemorrhage control, but may also be used on superficial wounds.

Factor VIIa [SEDA-15, 1318; SEDA-34, 518; SEDA-35, 592; SEDA-36, 493]

Observational Studies

Severe bleeding, defined as the loss of 20% or more of the total blood volume, is associated with a markedly increased risk of morbidity and mortality [76c].

In severe post-partum hemorrhage refractory to standard treatment, the use of rFVIIa has been considered. Even though case reports suggest a potential benefit of this agent in this clinical setting, the lack of randomized controlled trials greatly limits the value of available favorable data [76c]. In a recent report published by the World Health Organization "Recommendations for Prevention and Treatment of Postpartum Hemorrhage", the group concluded that there is insufficient evidence to recommend rFVIIa for the treatment of post-partum hemorrhage, and that its use should be limited to women with licensed hematological indications. The group regarded rFVIIa as a potentially life-saving drug but noted that it is also associated with life-threatening adverse effects [77S].

Thromboembolic Events (TEs)

A *post hoc* analysis assessed the safety of rFVIIa dosing in congenital haemophilia and the impact of >240 µg/kg dosing. A total of 61734 rFVIIa doses were reported in 481 patients treated for 3947 bleeding events. Over half (52%) exceeded 120 µg/kg, 37% exceeded 160 µg/kg

and 15% exceeded 240 µg/kg. No TEs were reported. The findings of this analysis show that high doses of rFVIIa are utilized clinically for treatment of patients [78R].

Factor VIII [SEDA-15, 1319; SEDA-34, 518; SEDA-35, 592; SEDA-36, 494]

Neurologic

Among 148 cases in a stroke registry, patients with acute ischemic stroke (AIS) were included if both FVIII and vWF were measured during admission. Out of the total 148 cases, 51 patients (34.5%) had FVIII+/vWF+. Patients with FVIII+/vWF+ had increased odds of inpatient complications (odds ratio, 8.6; 95% confidence interval, 1.58–46.85; $p=0.013$) and neurological worsening (odds ratio, 3.2; 95% confidence interval, 1.18–8.73; $p=0.022$) versus patients with FVIII–/vWF–. These findings suggest that FVIII and vWF levels may serve as clinically useful stroke biomarkers by providing risk profiles for patients with AIS [79E].

Factor IX [SEDA-15, 1324; SEDA-34, 518; SEDA-35, 592; SEDA-36, 494]

Drug Formulations

Multinational, randomized, single-blind trial investigated the safety and efficacy of a recombinant glycoPE-Glylated factor IX (FIX) with extended half-life, in 74 previously treated patients with Hemophilia B. Patients received prophylaxis for 52 weeks, randomized to either 10 or 40 IU/kg once weekly or to on-demand treatment of 28 weeks. Once-weekly prophylaxis with 40 IU/kg resolved target joint bleeds in 66.7% of the affected patients and improved health-related quality of life. No safety concerns were identified [80C].

Factor IX Gene Therapy

Another study evaluated long-term safety and efficacy of Factor IX gene therapy in Hemophilia B patients where gene therapy that is mediated by a novel adeno-associated virus serotype 8 vector has been shown to raise factor IX levels. The authors sought to evaluate if patients with severe Hemophilia B can benefit from gene therapy to raise factor IX levels and decrease rates of bleeding. The effects were found to be clinically positive with a significant decrease in rates of acute bleeding episodes with no reported acute or late toxic effects [81c].

Prothrombin Complex Concentrate [SEDA-34, 518; SEDA-35, 518; SEDA-36, 494]

There are three main types of Prothrombin Complex Concentrates (PCC) that are available on the market

worldwide. The first one is an activated-PCC which contains activated forms of factors II, VII, IX, and X. Activated PCCs are used for bypass therapy in hemophilia patients who have developed inhibitor antibodies. The second type is a four-factor PCC which contains nonactivated forms of factors II, VII, IX, and X. And finally, three-factor PCC contains non-activated forms of factors II, IX, and X (while lacking factor VII). These three- and four-factor non-activated PCCs are most often used for anticoagulation reversal and severe hemorrhage in clinical practice.

Cardiac Surgery

Twenty-five patients who underwent cardiac surgery with coagulopathy and life-threatening bleeding refractory to conventional treatment received activated prothrombin complex concentrate FEIBA (factor VIII inhibitor bypassing activity). The mean FEIBA dose was 2154 units. The need for fresh frozen plasma and platelet transfusion decreased significantly after FEIBA administration ($p=0.0001$ and $p<0.0001$, respectively). The mean internationalized normalized ratio decreased from 1.58 to 1.13 ($p<0.0001$). The study investigators report that the clinical outcomes were excellent with no patient returning to the operating room for re-exploration. There was no hospital mortality and all patients were discharged home [82C].

Haematologic

PCC is used as a reversal option for warfarin anticoagulation. This study compared warfarin reversal in patients who received either three-factor PCC (PCC3) or low-dose rFVIIa (LDrFVIIa) for reversal of warfarin anticoagulation. Seventy-four PCC3 and 32 LDrFVIIa patients were analyzed. Baseline demographics, reason for warfarin reversal, and initial INR were equivalent. There was no difference in the number of thromboembolic events (2 LDrFVIIa vs. 5 PCC3, $p=1.00$), mortality, length of hospital stay, or cost [83c]. Similar results were found in a study from Spain which evaluated the use of PCC for reversal of vitamin K antagonists. The study reported that no infusion reactions were detected, and only 1 thrombotic episode was observed out of 31 patients who were included in the study [84c]. Another study sought to evaluate the safety and efficacy of nonactivated four-factor PCC versus plasma in patients experiencing major bleeding while taking vitamin K antagonists. The outcomes were both clinically and statistically positive in favor of using four-factor PCC. The safety profile was similar between groups; 66 of 103 (4F-PCC group) and 71 of 109 (plasma group) patients experienced ≥ 1 adverse event [85C].

von Willebrand Factor (VWF)/Factor VIII Concentrates [SEDA-34, 519; SEDA-35, 594; SEDA-36, 494]

Comparative Studies

Most studies on immune tolerance induction (ITI) therapy in haemophilia A patients are focused on primary ITI in children. The authors of this study report on the ITI outcome in a large retrospective cohort, including adult patients with rescue ITI, treated with a pdFVIII/VWF concentrate. Success rate of 87% was achieved in primary ITI and 74% in the higher risk profile of rescue ITI. Several safety concerns were observed including venous access complications consisting of seven infections, one case of haemarthrosis (bleeding into the joint spaces), one case of allergy to the pdFVIII/VWF concentrate that was considered a failure of therapy, and one case of pleural haemorrhage that resolved after treatment [86c].

Observational Study

The safety of recombinant von Willebrand factor (rVWF) combined at a fixed ratio with recombinant factor VIII (rFVIII) was investigated in 32 subjects with von Willebrand disease (VWD) in a prospective phase 1, multi-center, randomized clinical trial. The authors concluded that rVWF was well tolerated and no thrombotic events or serious adverse events were noted [87C].

ERYTHROPOIETIN AND DERIVATIVES [SEDA-34, 520; SEDA-35, 594; SEDA-36, 494]

Systematic Reviews

Erythropoiesis-stimulating agents are often used to attenuate blood transfusions among anemic patients receiving chemotherapy or those with chronic kidney disease (CKD). However, these agents are not without potentially serious side effects. They have been shown to be associated with venous thromboembolism and increased mortality. For these reasons, a recent Cochrane review discussed the potential adverse effects of these agents when used in the setting of CKD. Clinical guidelines recommend ESA treatment to avoid blood transfusions and anemia-related symptoms for patients with CKD. However, whether all the available ESAs are equally effective and safe has not been adequately evaluated by individual RCTs [88R].

Data for the effects of ESA treatment compared to placebo or no treatment on all-cause mortality was provided in 10 studies involving over 5000 participants. Three agents (epoetin alfa, epoetin beta and darbepoetin alfa) were assessed against placebo or no treatment with patients with underlying CKD. The odds of all-cause

mortality, cardiovascular mortality and MI were not statistically significant with all three agents. However, when considering the odds of stroke, the results were not statistically significant in the epoetin alfa and beta groups, but were increased in darbepoetin alfa group when compared to placebo. Similar results were found with hypertension, where all three agents had a higher propensity to increase blood pressure in comparison to placebo [88R].

THROMBOPOIETIN AND RECEPTOR AGONISTS [SEDA-15, 3409; SEDA-36-495]

The ideal selection of thrombopoietin receptor agonists is an area of ongoing research. Eltrombopag and romiplostim are both efficacious in increasing platelet counts but differ in route of administration, dose titration, and potentially adverse effects [89r].

Observational Studies

An open-label extension trial of eltrombopag in Japanese patients with chronic immune thrombocytopenia (ITP) followed patients until the drug was commercially available or serious adverse events occurred. Median duration of therapy was 27.5 months with 15 patients treated for more than 2 years. Concomitant treatment was required in 79% ($n = 15$) of patients with 14 of those patients who were treated with corticosteroids. Adverse events included nasopharyngitis and headache. Two events of chest pain with normal ECG were determined to be associated with eltrombopag. Four events of cataract progression were reported in three patients during treatment and two were considered serious adverse events related to treatment. Five patients experienced elevation in liver enzymes. A total of 10 bone marrow biopsies were obtained from 7 patients which were normal or showed grade 1 bone marrow fibrosis [90c].

Systematic Review

A review of the French Pharmacovigilance Database from January 2009 to December 2013 identified 53 adverse drug reactions with romiplostim and 37 adverse drug reactions with eltrombopag. Twelve cases of venous thromboembolism occurred with romiplostim and 7 with eltrombopag, however 83% of the patients had at least one risk factor for thrombosis. Romiplostim was implicated with hematologic adverse reactions more frequently than eltrombopag, while eltrombopag was associated with gastrointestinal events [91R]. A systematic review of thrombopoietin receptor agonists (TPOs) for treatment of myelodysplastic disorder included 4 studies of romiplostim and 1 of eltrombopag.

Romiplostim was associated with decreased bleeding events and platelet transfusions when adjusted for time exposure. There was no increase in AML progression. The authors emphasized possible bias in reported data [92C].

Hematologic

Sixty six patients treated with TPOs were followed for a median of 29 months of treatment. At the beginning of treatment 67% of bone marrow biopsies showed no fibrosis which decreased to 22% at the end of treatment. High grade myelofibrosis, either 2 or 3, was associated with older age. Grade of myelofibrosis was not associated with initial marrow grade, TPO dose, TPO agent, or immature platelet fraction [93M].

Skin

Eltrombopag-induced hyperpigmentation of the skin is described in two patients. Tissue biopsies were Fontana-Masson stain and Prussian blue stain positive demonstrating increased melatonin deposition and hemosiderin deposition from red blood cell leakage, respectively [94A].

Pregnancy

Romiplostim was used in two pregnant patients with steroid resistant immune thrombocytopenia for 10 and 22 weeks during gestation. No neonatal complications were reported [95A].

Interference with Diagnostic Tests

Serum of patients treated with eltrombopag appears dark reddish brown and alters based on drug concentration and pH. Erroneous results for serum total bilirubin were described in patients treated with eltrombopag [96A].

TRANSMISSION OF INFECTIOUS AGENTS THROUGH BLOOD DONATION [SEDA-34, 521; SEDA-35,596; SEDA-36, 495]

In 2009, the American Association of Blood Banks released a statement identifying emerging infectious disease agents with transfusion safety risks. The author of a recent review summarizes emerging infectious disease since the 2009 statement including MERS-CoV, Dengue viruses, Chikungunya virus, and Hepatitis E virus [97r].

Bacteria

Borrelia burgdorferi transmission by transfusion has not been widely described. Authors postulate, that is, it due to low bacterial load in infected humans and inability of host-adapted spirochetes to survive under blood storage conditions [98H].

Virus

Risk of arbovirus in South-East Asia is emerging due to limited resources and high incidence of the infection [99r]. In French Polynesia, during the 2013 outbreak of Zika virus, testing of 1505 asymptomatic blood donors was carried out. Three percent of donors were Zika virus positive using PCR testing [100c].

Transmission of hepatitis C virus from an Anti-HCV negative donor to two recipients in Turkey was described. The donor, a 33-year-old woman, was found to be HCV-RNA virus and Anti-HCV positive 3 weeks after donation. Initial donated blood was then tested for HCV-RNA with a viral load of 22 039 549 IU/mL. Two recipients were diagnosed with hepatitis C virus. One of the recipients, a 44-year-old female who received red blood cells for hemoglobin of 6.7 g/dL was successfully treated with interferon alpha. The other recipient, a 19-year-old male with myeloid leukemia, received platelets and was not treated for Hepatitis C virus due to comorbid disease. Authors highlight the need for nucleic acid amplification testing of donors to decrease risk of transmission [101A]. Hepatitis E virus was identified in 79 of 225 000 blood donations in England between October 2012 and September 2013. Follow up of 43 recipients identified 18 recipients or 43% with Hepatitis E viral infection [102R]. In the United States, testing of 1939 donated blood samples from 2006 to 2012, identified positive Ig Anti-HEV in 18.8% samples but no donations with HEV RNA. Two patients of the 362 recipients (0.6%) had positive post-transfusion blood samples for Hepatitis E virus however direct link to transfusion is not clear [103R].

Prion

Using predictive modeling based on United Kingdom prevalence of variant Creutzfeldt-Jakob disease (vCJD) estimates of transfusion-transmitted vVJD in the United States range from 1 in 134 million transfusions to 1 in 480 000 transfusions [104r].

STEM CELLS [SEDA-34, 522; SEDA-35, 597; SEDA-36, 496]

Endocrinology

At one center, 32 patients with history of type-2 diabetes and varying diabetic complications were

administered autologous stem cells and observed for changes before and after therapy (improvement of symptoms, HgbA1c levels and 24 hours urine protein quantity). The researchers reported clinical improvement in hemoglobin levels and 24 hours urine protein quantity with no toxic side effects [105c].

Respiratory System

Literature suggests that hematopoietic stem cell transplantation (HSCT) is associated with more respiratory infections due to immunosuppression. In a retrospective trial, the researches aimed to investigate the frequency of rhinosinusitis after HSCT, and the association between rhinosinusitis and chronic graft vs. host disease (GVHD). Patients with GVHD had a higher frequency and recurrence of rhinosinusitis, in addition to more frequent need for endoscopic sinusotomy and decreased overall survival [106c].

Cardiovascular System

Hematopoietic cell transplantation (HCT) is an accepted treatment for many malignant disorders but may have side effects for several major organs, including the cardiovascular system. In this study, cardiac function was evaluated using echocardiography and levels of NT-proBNP in 18 patients, and in 18 matched controls. Patients in the HCT group had cardiac dimensions, and left ventricular ejection fractions within normal range. However, they also had lower measurements of left ventricular diastolic function and a significantly higher NT-proBNP levels. The investigators also reported that heart rate was significantly higher in the HCT group [107c].

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