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

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Blood and blood treatments

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Abbreviations

AE	adverse event
ARDS	acute respiratory distress syndrome
C	Celsius
CFU-GM	colony-forming unit granulocyte-macrophage
CI	coagulation index
CKD	chronic kidney disease
CP	convalescent plasma
DFX	deferasirox or oral chelating agent
EACA	e-Aminocaproic acid
EAP	Expanded Access Program of the Mayo Clinic
EFS	event-free survival
eGFR	estimated glomerular filtration rates
FDA	Food and Drug Administration
FDI	ferric derisomaltose
FDP	freeze-dried plasma
FERWON	a program initiated to address the safety and efficacy
FGF	fibroblast growth factor
HIG	hyperimmune globulin
HLA	human leukocyte antigen
ICU	intensive care unit
Id	ixazomib-dexamethasone
IDA	iron deficiency anemia
IPSS	International Prognostic Scoring System
IQR	interquartile range
IRd	ixazomib-lenalidomide-dexamethasone
IS	iron sucrose
IVIG	intravenous immunoglobulins
Kg	kilogram
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
ml	milliliter
NDMM	newly diagnosed multiple myeloma
ng	nanogram
NGAL	neutrophil gelatinase-associated lipocalin
PCR	polymerase chain reaction
pmol	picomoles
RBC	red blood cells
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SF	serum ferritin
TACO	transfusion-associated circulatory overload
TEG	thromboelastography
TRALI	transfusion-related acute lung injury
UCB	umbilical cord blood
VRO	varus rotational osteotomy

TRANSFUSIONS

Plasma

Freeze-dried plasma

A systematic review, meta-analysis assessed the mortality outcomes of freeze-dried plasma (FDP) transfusion treatments in patients with major trauma (Mok et al., 2021) [M]. The analysis included 11 observational studies and 1 randomized controlled trial; 7 of the 12 involved military populations. No statistically significant differences in mortality were observed with the use of FDP compared to allogenic blood products. However, FDP treatment was associated with chills, rigor, and erythema, and there were noted complications with the administration and reconstitution of the treatment itself. Due to multiple studies lacking control groups and the evaluations of bias ranging from high to low, the authors concluded a low to moderate level of evidence can be gained from the collection of studies. Consequently, more evidence is needed to determine the safety and benefits of FDP treatment in trauma care.

Platelets

A single-center, two-stage exploratory pilot study was conducted to determine if cold-stored platelets (2° to 6 °C) could replace the current standard of storing platelets at 20° to 24 °C or room temperature during elective and semi-urgent cardiothoracic surgery (Strandenes et al., 2020) [c]. The first stage compared platelets that had been

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cold-stored for up to 7 days ($n = 21$) to those stored at room temperature ($n = 21$). The second stage compared platelets that had been cold-stored for 8 to 14 days ($n = 10$) to the same control. Both stages used median chest drain output as the primary indicator of platelet function. Secondary outcomes of platelet function included changes in multiple electrode impedance aggregometry after platelet transfusion, blood cell counts, conventional coagulation tests, blood usage, and hemostatic viscoelastic assays.

Median chest drain output was 720 mL in the "room temperature" group, 590 mL in the "cold storage for up to 7 days" group, and 595 mL in the "cold storage for up to 8 to 14 days" group. These measurements indicated no statistically significant difference between the room-temperature stored platelets and the cold-stored platelets. Therefore, it was tentatively concluded that cold-stored platelets (up to 14 days) could be used during cardiothoracic surgery and that this study can serve as a model for future pilot trials. The authors recognized that although there were no statistically significant differences between groups, further studies with higher numbers of patients are required before a definitive conclusion can be drawn concerning platelet storage methods.

As for adverse events, arterial thromboembolism occurred in 6/25 (24%) of those treated with room temperature-stored platelets (stored up to 7 days), 6/25 (24%) of treated with cold-stored platelets (stored up to 7 days), and 2/15 (13%) of cold-stored (stored for 8–14 days). Venous thromboembolism occurred in 2/25 (8%), 0/25 (0%), and 2/15 (13%), respectively. 28-day mortality occurred in 3/25 (12%), 2/25 (8%), and 2/15 (3%), correspondingly. Between the three groups, there were no reported transfusion reactions associated with treatment.

Intravenous immunoglobulins

A retrospective, multicenter study and literature review assessed 17 patients (median age 55 years, 10 male, 7 female) who received intravenous globulin (IVIG) treatment for a variety of medical conditions, including Guillain Barre, peripheral neuropathy, neuro-lupus, myasthenia, multiple myeloma with hypogammaglobulinemia, primary hypogammaglobulinemia, autoimmune cytopenias, graft versus host cutaneous disease after allogenic hematopoietic stem cell transplant for acute myeloid leukemia, anti-HLA antibodies after lung transplant, cancer-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, Kawaski disease, and experimental assay (Baudel et al., 2020) [R]. These cases demonstrated a clinically diverse set of patients who experienced transfusion-related acute lung injury (TRALI). Symptom onset occurred during IVIG treatment in 41% of patients and occurred within 10 min to 24 h following infusion in 59%. Additional associated findings included bilateral alveolar opacities, respiratory distress, shock, fever, cough, chills, nausea, vomiting, agitation, and the need for mechanical ventilation. Due to the associated high mortality risk, the authors emphasize transfusion-related acute lung injury is a salient but infrequent (0.5%) adverse event to consider with IVIG treatments.

Umbilical cord blood

A study investigated the impact of post-thaw colony-forming unit granulocyte-macrophage (CFU-GM) on the quality of umbilical cord blood. In this study, researchers retrospectively examined the outcomes of 269 patients with malignant and non-malignant disease who received single umbilical cord blood (UCB) transplant (Hussein et al., 2020) [c]. The cases observed spanned from January 1, 2000, to December 31, 2017. Patients ranged in age from <1 to 66 years old with a median age of 7 years old. The rate and speed of neutrophil and platelet engraftment were used as determinants of clinical outcomes. As a result, increased neutrophil and platelet engraftment correlated with higher levels of post-thaw CFU-GM ($P < 0.01$). From this data, the authors concluded that the quality of a UCB graft could be effectively measured and predicted by post-thaw CFU-GM levels.

Blood coagulation

Thromboelastography

Lin et al. (2020) [c] conducted a retrospective study to evaluate thromboelastography (TEG) as a coagulation assessment of intra-muscular hemocoagulase in postoperative thoracic surgery. TEG is a method for measuring clot development in terms of stabilization, strength, and dissolution. TEG has advantages over aPTT and PY/INR tests, which do not assess the cellular components of the clot. Hemocoagulase agents derived from snake venom have been widely used in the prevention and treatment of surgical bleeding.

The study included 97 patients, 54 of whom (30 males and 24 females with a median age of 59.03 years) had a normal coagulation index, and 43 patients (22 males and 21 females with a median age of 59.3 years) with a lower than normal coagulation index (TEG < -3.0). The group with low CI had two cases of bleeding that were managed uniquely according to their circumstances. The authors noted that prior to thoracic surgery, fibrinogen levels were significantly lower at baseline in the low CI group [2.68 g/L $\pm$ 0.74 ($P < 0.01$)]. Results suggest that patients should be evaluated with thromboelastography technology when receiving hemocoagulase treatment to gauge coagulation activity.

Antifibrinolytic

Tranexamic acid

A single-center, double-blind, parallel group, randomized clinical trial evaluated the intraoperative blood loss of patients treated with tranexamic acid versus a placebo during open aortic aneurysm surgery (Monaco et al., 2020) [c]. The median age of patients undergoing open aortic aneurysm surgery was 70 years old. The participants of this study were dominantly male (93/100). The patients were randomized into two groups of 50 individuals; a placebo group and another to be treated with tranexamic acid. This group received a loading dose of 500 mg/100 mL saline, followed by 250 mg per hour throughout the procedure. The results for intraoperative blood loss, red blood cell transfusions, thromboembolic events and mortality (both at 28 days and 1-year post-op) did not differ significantly between study groups. In analysis, the postoperative (post-op) blood loss was determined as potentially lower in the tranexamic acid treatment group; however, these results were limited by the method of periaortic abdominal drainage used for post-op blood loss collection. Although underpowered for safety analysis, the authors reported no increase in adverse events with tranexamic acid treatment. The post-op outcomes noted acute myocardial infarction, red blood cell (RBC) transfusions, acute kidney injury in each group, and one case in the control group of bleeding requiring intervention. The study groups each had one post-op intensive care unit (ICU) admission for intraoperative hemodynamic instability and one for a major surgical complication. There was no difference in the length of hospital stay between the groups. Although the use of tranexamic acid did not reduce postoperative bleeding in major vascular surgery, it may prove advantageous in controlling postoperative blood loss.

Aminocaproic acid

A randomized, double-blind, placebo-controlled trial was conducted with pediatric patients with cerebral palsy comparing intraoperative blood loss following bilateral varus rotational osteotomy (VRO) surgery (Swarup et al., 2020) [c]. The treatment group, $n = 12$, was given intravenous e-Aminocaproic acid (EACA). The control group, $n = 12$, received saline. Intraoperative blood loss was not significantly different between groups. The patients treated with EACA had a calculated intraoperative blood loss of 535.7 mL (SD 356.6 mL), which was less than the control group's 628.0 mL (SD 235.8 mL) though not significantly less. Transfusion requirements, 24-h drain output, and length of hospital stay between the groups were not statistically different, and no adverse events associated with treatment were reported. The authors concluded that these results do not support the routine use of EACA in pediatric patients for VRO surgery. However, the findings were limited by sample size. Consequently, more extensive studies are warranted.

Plasma substitutes

A triple-blind, non-inferiority, randomized control trial was conducted to compare postoperative urinary neutrophil gelatinase-associated lipocalin (NGAL) concentrations at 1 h and 24 h post-surgery in those administered hydroxyethyl starch (HES) 6% and those given human albumin 5% as the control (Duncan et al., 2020) [C]. During surgery, effective treatment for hypovolemia is plasma volume replacement with HES; however, the FDA has issued warnings regarding HES and a possible risk of increased coagulopathy.

Between June 2015 and February 2018, 141 individuals (age range 40–85 years) who met the inclusion criteria were scheduled for elective aortic valve replacement. Patients experiencing hypovolemia during surgery were administered either 6% HES 130/0.4 ($n = 69$) or human albumin 5% ($n = 72$). The percentage of patients (22%) who had >100 ng/mL urinary NGAL at 1 h did not differ between the HES and albumin groups. Similarly, the percentage of patients with >250 ng/mL was no different between the two groups at 10%, and postoperative kidney function results were similar between groups. Non-inferiority ($P < 0.15$) testing was not demonstrated since wide confidence intervals resulted in a significance value of $P = 30$. There were no differences in adverse outcomes such as long-term mortality and decreased kidney function observed in the study groups.

The authors revealed that other accepted research has employed higher non-inferiority margins (up to 50%) than the differences demonstrated in this study (15%) and acknowledged that broader studies could reduce the wide confidence intervals allowing for a more accurate test for non-inferiority. For this reason, the authors propose further research with a greater number of participants.

Iron chelation

Deferasirox

A retrospective study cohort analyzed 50 patients (32 female, 18 male) with mean serum ferritin (SF) levels <500 μg/L who received iron chelation therapy, deferasirox (DFX), for a diagnosis of transfusion-dependent thalassemia (Scaramellini et al., 2020) [c]. Dose adjustment was based on SF, to 14.5 mg/kg/day if SF < 500 μg/L and 17.7 mg/kg/day if SF > 500 μg/L. Adverse events included three patients with myocardial iron overload (SF < 500 μg/L). There were no reported cases of Fanconi

syndrome associated with treatment. The authors concluded that iron chelation therapy, deferasirox treatment, in patients with SF < 500 μg/L is safe with no evidence of increased renal or hepatic adverse events.

An international randomized, multicenter, double-blind, placebo-controlled trial was conducted at 60 locations to assess iron chelation therapy, deferasirox (DFX), in transfusion-dependent patients classified as low or intermediate 1-risk for myelodysplastic syndrome (MDS) (Angelucci et al., 2020) [MC]. Risk level was based on the International Prognostic Scoring System (IPSS). Patients had serum ferritin levels >2247 pmol/L and were previously treated with 15–75 packed red blood cell units. The median age of the patients was 65 years old (range: 20–80 years). 137 males and 88 females participated in the study. A 2:1 randomization of 225 patients placed 149 patients in the DFX treatment group and 76 in the placebo group. The DFX tablet treatment was increased throughout the trial with the doses ranging 10–40 mg/kg/day. Serum ferritin and 1 week of treatment were used to assess dosage. Overall, DFX treatment was given for a median of 1.6 years (IQR 0.5, 3.1) at a median dose of 14.9 mg/kg/day, and the placebo was administered for 1 year at 23.5 mg/kg/day.

The study assessed event-free survival (EFS), defined as "time from date of randomization to first documented nonfatal event including cardiac or liver dysfunction and transformation to acute myeloid leukemia, or death, whichever occurred first" (p. 513). Those treated with DFX had an EFS of 3.9 years (95% CI 3.2–4.3), which was longer than the placebo group at 3 years (95% CI 2.2–3.7). This trial reported a high volume and diversity of side effects, many of which led to the discontinuation of the study. Of these side effects, 71.6% (8.8% serious adverse events) for the DFX treatment group and were thought to be drug-related. In the placebo group, 51.3% (3.9% serious adverse events) were reported. The most common side effects reported as drug-related were increased serum creatinine (23% DFX, 1.3% placebo), diarrhea (20.3% DFX, 13.2% placebo), and nausea (10.1% DFX, 7.9% placebo). Notably, of these common side effects, five patients treated with DFX had increased serum creatinine resulting in discontinuation in the study. Three DFX patients' diarrhea resulted in their discontinuation of the study drug. Ultimately, the DFX group had 20.3% of patients discontinued due to adverse events than 17.1% in the placebo group. Mortality in the DFX group was 38.3% and 43.4% in the placebo group. The authors concluded that while event-free survival was longer in the deferasirox treatment group, participants experienced a high number of drug-related and drug-unrelated side effects. There were a substantial number of study discontinuations. To patients, the significant number of adverse events may outweigh the relatively short prolongation of life offered by iron chelation therapy or deferasirox.

Ferric derisomaltose and ferric carboxymaltose

The two FERWON trials reported by Wolf et al. (2021) [C] were conducted to assess the efficacy of ferric derisomaltose (FDI) or iron isomaltose 1000 versus iron sucrose (IS) in the treatment of iron deficiency anemia (IDA) in different patient populations. FERWON-IDA evaluated effectiveness for a broad array of etiologies of IDA and FERWON- NEPHRO specifically evaluated IDA from Chronic Kidney Disease (CKD).

Collectively the study evaluated 3050 patients, primarily focusing on serious and severe hypersensitivity reactions and cardiovascular adverse events. Of the 159 patients (256 events) who experienced hypersensitivity, there was a non-inferior risk difference of serious or severe hypersensitivity between the FDI and IS treatments at 0.1% (95%CI −0.57%; 0.48%). Although the most common, cardiovascular adverse events occurred significantly less frequently in the FDI treatment group (FDI 2.5%, IS 4.1%, $P = 0.018$). Cardiovascular adverse events included hypertension, congestive heart failure, and atrial fibrillation in the IS group. Recurrent adverse drug reactions were lower in the FDI treatment group (risk ratio 0.67, 95% CI 0.56; 0.78, $P < 0.001$) compared to the IS group. All cases of mortality were considered unrelated to treatment.

Due to differing administration protocols between FDI and IS treatments, the IS treatment was received in multiple doses and on average in less quantity than FDI (FDI mean dose 984 ± 114 mg, IS mean dose (902 ± 207 mg).

Overall, hypersensitivity was rare in both treatment groups. The difference in treatment protocols may provide convenience advantages for FDI.

The FERWON-NEPHRO study, a randomized, open-label multicenter trial, conducted by Bhandari et al. (2021) [MC], evaluated 1538 (962 women, 576 men) non-dialysis dependent, chronic kidney disease patients with estimated glomerular filtration rates (eGFR) <60 L/min/1.72 m^2 or eGFR <90 L/min/1.73 m^2. The patients had a mean age of 68.6 and mean eGFR 35.5 mL/min/1.73 m^2. The treatment groups were randomized 2:1 with 1027 patients (mean age 68.3, 633 women, 394 men) receiving FDI (single dose 1000 mg, mean ± SD 993 + 71 mg) and 511 patients (mean age 69.3, women 329, men 182) receiving IS (multiple doses of 200 mg, recommended to total 1000 mg, mean ± SD 899 + 198 mg).

A significant number of composite cardiovascular adverse events were reported. Of the 1027 patients in the FDI treatment group, 42 (4.1%) experienced at least one composite cardiovascular adverse event, compared to the 35 (6.9%) patients of 511 in the IS group. Both treatment groups noted hypophosphatemia with 32/1011 treated with FD and 4/500 treated with IS. Several adverse drug events were seen in both groups. The FD treatment group totaled 83 adverse reactions, including

rash and pruritis, identified in 48 patients; four suffered serious adverse drug reactions: drug hypersensitivity, hypersensitivity acute MI, infusion-related reaction. The IS treatment group noted 43 adverse reactions in 27 patients, including rash, pruritus, and serious pyrexia. Each treatment group experienced three unrelated deaths.

The FERWON-IDA study evaluated 1512 (1356 completed the trial) patients 18 years and older with iron deficiency anemia in a 2:1 randomization of FDI treatment (mean dose 975 mg, SD 145 mg) to IS treatment (mean dose 905 mg, SD 217). (Auerbach et al., 2019) The FDI treatment group had 1009 patients (mean age 44.1, 892 women, 117 men), while the IS treatment group had 503 (mean age 43.8, 456 women, 47 men). Those treated with FDI were reported to have an earlier increase in hemoglobin; however, the increase evaluated at the end of treatment was determined to be non-inferior. The calculated risk difference between serious or severe hypersensitivity reactions was not statistically significant between the treatment groups. Nor was the number of patients with composite cardiovascular adverse events statistically significant with eight FDI patients and six IS patients. No severe hypophosphatemia was reported. Overall, 12.5% of patients ($n = 124$) had at least one adverse drug reaction in the FDI group, compared to 12.8% of patients ($n = 63$) in the IS group, with the most common adverse event being nausea. The authors noted rash and chest discomfort most commonly occurring in the FDI treatment group and dysgeusia and overdose more common in the IS treatment group. Additionally, one death was reported in the FDI treatment group, although classified as unrelated to treatment. The authors concluded that the FDI treatment was "well-tolerated" and highlighted the safety similarity to IS.

Iron deficiency anemia treatments were assessed in two open-label, randomized clinical trials that included 245 (18 years and older) patients (mean age 44.1, 892 women, 117 men) assigned to be treated with either ferric derisomaltose ($n = 125$) or ferric carboxymaltose ($n = 117$) (Wolf et al., 2020) [C]. These patients were diagnosed with iron deficiency anemia based on the guideline of hemoglobin levels ≤ 11 g/dL and serum ferritin level ≤ 100 ng/mL. Patients who qualified for this study had previously failed oral iron treatments.

The purpose of these studies was to assess the incidence of hypophosphatemia (serum phosphate <2 mg/dL) comparing two groups during the 5-week post-treatment period. One treatment group was given 1000 mg of IV ferric derisomaltose compared to the second group, given two doses of 750 mg of IV ferric carboxymaltose administered 1 week apart. Hypophosphatema occurred in two patients (1.6%) in the ferric derisomaltose treatment group and in 26 patients (22.2%) in the ferric carboxymaltose treatment group. All severe cases occurred in the ferric carboxymaltose treatment group.

The authors concluded there is a significantly lower incidence of hypophosphatemia in the group treated with ferric derisomaltose. This finding is consistent with previously published studies.

Serious adverse events occurred in one patient treated with derisomaltose; hypersensitivity reaction manifested as unilateral eye swelling. Two patients treated with ferric carboxymaltose experienced hypersensitivity reactions of dyspnea and swelling. Adverse reactions occurred in 55 (47%) patients treated with ferric carboxymaltose compared to 21 (16.8%) patients treated with ferric derisomaltose. Headache was reported in four (3.2%) patients treated with ferric derisomaltose and five (4.3%) treated with ferric carboxymaltose. Of those treated with ferric derisomaltose, nausea occurred in one patient (0.8%) and in eight patients (6.8%) receiving ferric carboxymaltose. There were no patients with increased ferritin or decreased phosphorus in the ferric derisomaltose group. In contrast, six (2.6%) patients had increased ferritin, and 19 (16.2%) patients had reduced phosphorus in the ferric derisomaltose group. Parathyroid hormone increased in four (3.2%) patients receiving ferric derisomaltose and in six (5.1%) patients in the ferric derisomaltose group.

In an open-label randomized, parallel-group controlled, phase 3 trial, hemoglobin normalization in postpartum women with hemoglobin levels <110 g/L and ferritin levels <50 μg/L was evaluated by Vanobberghen et al. (2021) [C]. Between October 8, 2015, and March 14, 2017, 230 women who needed treatment for iron deficiency anemia were randomly assigned to two separate groups in two hospitals located in a resource-deficient area in Tanzania. One group was treated with intravenous ferric carboxymaltose. The comparison group was treated with daily doses of oral iron and folic acid (three 200 mg supplements with 60 mg elemental iron, 5 mg folic acid). Baseline median data for the entire patient group was age 26 years old (IQR 22–30 years), hemoglobin of 94 g/L (IQR 85–104), ferritin 21 μg/L.

Patients treated with IV ferric carboxymaltose (dose adjusted for hemoglobin and weight) 75/94 had hemoglobin normalization to >115 g/L at the 6-week assessment. Of the comparison group, 47/92 patients treated with oral iron daily hemoglobin normalized as anticipated. There was one grade 1 infusion-related reaction and one patient with a grade 2 pruritic reaction in the ferric carboxymaltose group. The patient who experienced grade 2 pruritis did not receive a second 500 mg dose of treatment. Adverse events were reported in 48% of patients receiving IV ferric carboxymaltose and 37% of those treated with oral iron. AEs unrelated to the iron-deficiency anemia treatments occurred in four patients (two in each group) and included adverse events that required hospitalization: gastrointestinal disorder, pain in extremities, urinary fistula, uterine hemorrhage. Adverse events with oral iron included a grade 3 urinary

fistula leading to hospitalization and a grade 3 mediastinal infection.

The authors concluded IV ferric carboxymaltose compared to an oral iron and folic acid combination has a safe and preferable outcome for hemoglobin normalization in a location experiencing economic challenges.

ORAL FERROUS SULFATE HEPTAHYDRATE

A national, multicenter, phase-3, single-arm, open-label cohort study assessed hemoglobin and ferritin normalization in pediatric patients in Poland by Pachuta-Węgier et al. (2020) [c]. In this study, pediatric patients received 2 mg/kg/day of oral ferrous sulfate heptahydrate (20 mg/mL elemental iron) for iron deficiency anemia (IDA). The data set for evaluation was 19 patients with moderate IDA (hemoglobin 7–10.9 g/dL, serum ferritin <12 ng/mL). Of the 21 patients enrolled, two patients were excluded from the analysis for misclassification of moderate iron deficiency but were followed for adverse events. The mean age for the cohort was 10.7 months (16 males, 3 females) with a mean hemoglobin level 10 ± 0.8 g/dL (mean ± SD) g/dL, and serum ferritin 6.5 [4.0;9.0] ng/mL (median [Q1:Q2].

Following 3 months of daily oral iron supplementation, 18/19 patients experienced hemoglobin normalization (12 ± 0.7 g/dL (mean ± SD)) and 16/19 ferritin (31.5 ± 19.4 ng/mL). One patient was treated with oral iron for an additional 3 months to normalize serum ferritin levels. Serum ferritin levels improved but did not exceed 12 ng/mL. Two patients withdrew during the study period: one due to the adverse events of moderate upper abdominal pain and the second for unrelated rotavirus gastroenteritis. Of the 21 patients followed for safety, seven experienced adverse events including upper abdominal pain ($n = 1$), pyrexia ($n = 1$), bronchitis ($n = 1$), *exanthema subitum* ($n = 1$), gastroenteritis rotavirus ($n = 1$), laryngitis viral ($n = 1$), respiratory tract infection ($n = 2$), upper respiratory tract infection ($n = 2$), urinary tract infection ($n = 1$, viral rash ($n = 1$), dermatitis allergic ($n = 1$). The authors concluded 2 mg/kg/day of oral ferrous sulfate heptahydrate had substantial therapeutic benefits and high levels of tolerability in this cohort of pediatric patients with moderate IDA, the findings of which are consistent with other reports.

Newly diagnosed multiple myeloma

This national, multicenter, retrospective cohort observational study of ixazomib-based therapy for patients with newly diagnosed multiple myeloma (NDMM) was conducted at 14 centers in China (Li, Bao, et al., 2020 [c]). The 85 participants had a median age of 67 years (age range from 35 to 87 years). Males composed 56.5% of the cohort. The patients had received no treatment for NDMM prior to being enrolled in the study.

On average, each participant received six cycles of one of three regimens of an ixazomib-based treatment. 38 patients were treated with ixazomib-lenalidomide-dexamethasone (IRd), 25 with ixazomib-dexamethasone (Id), and 22 with Id and chemotherapeutics or monoclonal antibody treatments that were customized with dose reduction, stem cell transplantation, increased treatment length, and ixazomib maintenance. Collectively, the study reported a 95.3% response rate for the study group.

Twelve cases (14.1%) discontinued treatment due to adverse events (AEs). Grade 3 and 4 AEs were reported in nine cases (infection, diarrhea, thrombocytopenia, and abdominal distention). A total of 25 patients reported ≥3-grade AEs. The most common AEs reported were Lymphocytopenia (29), anemia (27), fatigue (25), neutropenia and thrombocytopenia (24), rash/skin/subcutaneous tissue disorder (excluding herpes zoster) (20), diarrhea (16), constipation (15), peripheral edema (11), pneumonia (10), nausea and vomiting (8), peripheral neuropathy (5), upper respiratory tract infection (3), and herpes zoster (2). The dose reduction of ixazomib was attributed to AEs in 3 cases (3.5%). The authors acknowledge the potential for selection and reporting biases in this retrospective cohort analysis which may have under-reported AEs.

The authors concluded that ixazomib-based therapy for NDMM is an effective treatment with acceptable side effects.

References

Angelucci, E., Li, J., et al. (2020). Iron chelation in transfusion-dependent patients with low- to intermediate-1-risk myelodysplastic syndromes: A randomized trial. *Annals of Internal Medicine*, *172*(8), 513–522. https://doi.org/10.7326/M19-0916 [MC].

Auerbach, M., Henry, D., et al. (2019). A prospective, multicenter, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial. *American Journal of Hematology*, *94*(9), 1007–1014. https://doi.org/10.1002/ajh.25564 [MC].

Baudel, J. L., Vigneron, C., et al. (2020). Transfusion-related acute lung injury (TRALI) after intravenous immunoglobulins: French multicentre study and literature review. *Clinical Rheumatology*, *39*(2), 541–546. https://doi.org/10.1007/s10067-019-04832-7 [R].

Bhandari, S., Kalra, P. A., et al. (2021). Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: The FERWON-NEPHRO randomized, open-label, comparative trial. *Nephrology, Dialysis, Transplantation*, *36*(1), 111–120. https://doi.org/10.1093/ndt/gfaa011 [MC].

Duncan, A. E., Jia, Y., et al. (2020). Effect of 6% hydroxyethyl starch 130/0.4 on kidney and haemostatic function in cardiac surgical patients: A randomised controlled trial. *Anaesthesia*, *75*(9), 11801190. https://doi.org/10.1111/anae.14994 [C].

Hussein, E., DeFor, T., et al. (2020). Evaluation of post-thaw CFU-GM: Clinical utility and role in quality assessment of umbilical cord blood

in patients receiving single unit transplant. *Transfusion*, *60*(1), 144–154. https://doi.org/10.1111/trf.15592 [c].
Li, J., Bao, L., et al. (2020). Ixazomib-based frontline therapy in patients with newly diagnosed multiple myeloma in real-life practice showed comparable efficacy and safety profile with those reported in clinical trial: A multicenter study. *Annals of Hematology*, *99*(11), 2589–2598. https://doi.org/10.1007/s00277-020-04234-9 [c].
Lin, C., Zhang, J., et al. (2020). Use of thromboelastography to monitor effects of the hemocoagulase on the blood coagulation in patients after thoracic surgery. *Annals of Palliative Medicine*, *9*(4), 2090095–2092095. https://doi.org/10.21037/apm-20-1221 [c].
Mok, G., Hoang, R., et al. (2021). Freeze-dried plasma for major trauma—Systematic review and meta-analysis. *The Journal of Trauma and Acute Care Surgery*, *90*(3), 589–602. https://doi.org/10.1097/TA.0000000000003012 [M].
Monaco, F., Nardelli, P., et al. (2020). Tranexamic acid in open aortic aneurysm surgery: A randomised clinical trial. *British Journal of Anaesthesia*, *124*(1), 35–43. https://doi.org/10.1016/j.bja.2019.08.028 [c].
Pachuta-Węgier, L., Kubiak, M., et al. (2020). Ferrous sulfate oral solution in young children with iron deficiency anemia: An open-label trial of efficacy, safety, and acceptability. *Pediatrics International: Official Journal of the Japan Pediatric Society*, *62*(7), 820–827. https://doi.org/10.1111/ped.14237 [c].
Scaramellini, N., Consonni, D., et al. (2020). A holistic approach to iron chelation therapy in transfusion-dependent thalassemia patients with serum ferritin below 500 μg/L. *American Journal of Hematology*, *95*(9), E230–E232. https://doi.org/10.1002/ajh.25860 [c].
Strandenes, G., Sivertsen, J., et al. (2020). A pilot trial of platelets stored cold versus at room temperature for complex cardiothoracic surgery. *Anesthesiology*, *133*(6), 1173–1183. https://doi.org/10.1097/ALN.0000000000003550 [c].
Swarup, I., Nguyen, J., et al. (2020). Effect of intravenous aminocaproid acid on blood loss and transfusion requirements after bilateral varus rotational osteotomy: A double-blind, placebo-controlled randomized trial. *Journal of Pediatric Orthopedics*, *40*(6), e454–e459. https://doi.org/10.1097/BPO.0000000000001480 [c].
Vanobberghen, F., Lweno, O., et al. (2021). Efficacy and safety of intravenous ferric carboxymaltose compared with oral iron for the treatment of iron deficiency anaemia in women after childbirth in Tanzania: A parallel-group, open-label, randomised controlled phase 3 trial. *The Lancet. Global Health*, *9*(2), e189–e198. https://doi.org/10.1016/S2214-109X(20)30448-4 [C].
Wolf, M., Auerbach, M., et al. (2021). Safety of ferric derisomaltose and iron sucrose in patients with iron deficiency anemia: The FERWON-IDA/NEPHRO trials. *American Journal of Hematology*, *96*(1), E11–E15. https://doi.org/10.1002/ajh.26015 [C].
Wolf, M., Rubin, J., et al. (2020). Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials. *JAMA*, *323*(5), 432–443. https://doi.org/10.1001/jama.2019.22450 [C].

Further reading

Duan, K., Liu, B., et al. (2020). Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proceedings of the National Academy of Sciences*, *117*(17), 9490–9496. https://doi.org/10.1073/pnas.2004168117 [c].
Joyner, M. J., Bruno, K. A., et al. (2020). Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clinic Proceedings*, *95*(9), 1888–1897. https://doi.org/10.1016/j.mayocp.2020.06.028 [C].
Joyner, M. J., Wright, R. S., et al. (2020). Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *The Journal of Clinical Investigation*, *130*(9), 4791–4797. https://doi.org/10.1172/JCI140200 [MC].
Li, L., Zhang, W., et al. (2020). Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19. *JAMA*, *324*(5), 460. https://doi.org/10.1001/jama.2020.10044 [c].
Morabito, C. J., & Gangadharan, B. (2020). Active therapy with passive immunotherapy may be effective in the fight against COVID-19. *Clinical and Translational Science*, *13*(5), 835–837. https://doi.org/10.1111/cts.12816 [r].
Rajendran, K., Krishnasamy, N., et al. (2020). Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. *Journal of Medical Virology*, *92*(9), 1475–1483. https://doi.org/10.1002/jmv.25961 [M].
Tremblay, D., Seah, C., et al. (2020). Convalescent plasma for the treatment of severe COVID-19 infection in cancer patients. *Cancer Medicine*, *9*(22), 8571–8578. https://doi.org/10.1002/cam4.3457 [c].