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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomized controlled trial (PLACID Trial). Agarwal A, Mukherjee A, Kumar G, et al. BMJ 2020;371.

Although there is questionable efficacy, plasma from recently ill but recovered patients ("convalescent plasma") has been considered as a treatment for a number of viral diseases. There is limited high-quality data assessing this intervention for patients with COVID-19. In this setting, Agarwal et al have conducted a randomized controlled trial.

The authors enrolled patients from 39 different tertiary care hospitals in India. The focus was on individuals with COVID-19 infection and moderate disease defined as either an arterial partial pressure of oxygen and/or fraction of inspired oxygen (PaO2/FiO2) ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of more than 24/min with an oxygen saturation of 93% or less on room air. Exclusion criteria included a PaO2/ FiO2 <200 mm Hg or shock. Patients randomized to the treatment arm received 2 units (each 200 mL) of convalescent plasma spaced 24 hours apart and those in the control arm received standard of care. The convalescent plasma was taken from donors with an RT-PCR confirmed diagnosis of COVID-19 with symptoms of at least fever and cough. The donors had to be symptom free for 28 days or, if 2 negative RT-PCR COVID-19 tests, 14 days. Samples were taken from the donor units for post-transfusion analysis of neutralizing antibody titers. The composite primary outcome included progression to severe disease (PaO2/FiO2 ratio <100 mm Hg) or death by 28 days. Assuming a baseline rate of 18% for the primary outcome, the study had 80% power to detect a 50% drop to 9%.

There were 1210 patients assessed for eligibility with ultimately 235 allocated to the convalescent plasma arm and 229 to the control arm. There were 11 patients who did not complete the study and only 2 patients in the treatment arm that did not receive convalescent plasma. Participants were similar in regard to age (median of 52 years), time from symptom onset to enrollment, types of symptoms, baseline vital signs (mean SpO2 on room air of 88%) and other treatments utilized. In intention-to-treat analysis, there was no significant difference in the primary outcome (18% in control, 19% in intervention). In regard to secondary outcomes, at day 7, more patients in the treatment arm (approximately 10% absolute difference) had resolution of fatigue or shortness of breath, but not other symptoms, and had a negative COVID-19 test compared to the control arm. There were no differences in length of stay (LOS) or type of respiratory support.

In the post-transfusion analysis, the median donor antibody titer was 1:40. The median time to donation after a confirmed COVID-19 diagnosis was 41 days and 71% of patients received at least 1 plasma unit with a detectable antibody titer (≥1:20). There was no difference in the primary outcome when looking at subgroups who received convalescent plasma with a detectable neutralizing titer (n = 160) or titer of 1:80 or greater (n = 67). There were 12 patients with possible transfusion reactions but apparently minor symptoms (eg, dizziness, nausea).

Agarwal et al should be commended for carrying out a well-designed study. Their randomized control trial of a relatively large cohort showed essentially no benefit from convalescent plasma in patients with moderate illness. While one could argue the study was only powered to detect a 50% difference, there was not even a hint of benefit in the treatment arm in regard to the primary outcome. One might also argue that perhaps the titers were not high enough to see a benefit but most donors had a detectable titer and there was no apparent benefit even when limiting analysis to patients receiving higher titer products. It is critical that quality studies are performed prior to universally implementing experimental therapies ("primum non nocere"). It is perhaps not surprising that convalescent plasma may not be effective in treating viral illness. Even currently available anti-viral antibody concentrates are mainly used for prophylaxis and not treatment. (RH)

Impact of autologous blood transfusion after bone marrow harvest on unrelated donor’s health and outcome: a CIBMTR analysis. Farhadfar N, Murthy HS, Logan BR, et al. Bone Marrow Transplant 2020; 55:2121-31.

Bone marrow (BM) donation may involve significant blood loss. In the 1980’s, due to the risk of transfusion-transmitted disease, autologous red cell unit donation was recommended prior to BM harvest to try and avoid allogeneic transfusion. Fortunately, there is now improved safety of the blood supply. In addition, there is

* Corresponding author.
 E-mail address: simon.stanworth@nhsbtt.nhs.uk (S. Stanworth).
1 Co-Author: Richard Haspel and Johnny Mack.
growing recognition of risks of autologous donation and transfusion including lowering preprocedure hemoglobin (Hb), circulatory overload and mis-transfusion. In this context, in 2016, the National Marrow Donor Program (NMDP), stopped recommending autologous unit collection and left the decision up to individual sites. While there have been small center studies questioning the need for autologous blood donation, Farhadfar et al explore this issue on a larger scale using NMDP data.

The study included first-time unrelated BM donors from the United States between 2006 and 2017. As there was only data on transfusion and not collection, donors were divided by those who received an autologous transfusion and those who did not. The primary outcome was donor symptoms based on the National Cancer Institute’s Common Terminology Criteria for Adverse Events. This assessment method had been previously validated and includes a number of potential adverse effects including skeletal pain, fatigue, insomnia and nausea. Data was collected 2 days, 1 month, and 6 months after donation and donors were also contacted 2 days after BM donation and then weekly until complete recovery of any symptoms. Time to recovery was a secondary outcome.

During the study period, there were 4211 donors that received and 2813 that did not receive an autologous transfusion. Of note, the 25 donors that received an allogeneic transfusion were excluded. Over time, there was a shift in not transfusing autologous units from approximately 70% in 2006 to 35% in 2017. Donors receiving autologous transfusion underwent longer harvests (median of 57 vs 37 minutes) and had a greater percent of total blood volume (TBV) removed (median 25% vs 15%). They also collected a lower total nucleated cell/kg of the recipient (median: 4.0 vs 5.6). The precollection Hb level was also approximately 1 g/dL lower in donors who were subsequently transfused autologous products. The median Hb levels postcollection were 11 g/dL in the transfused group (pretransfusion) and 12 g/dL in donors who were not transfused.

In regard to symptoms, in multivariable analysis, there was no difference at the measured time points between those who received or did not receive an autologous transfusion. There were some associations at various time points with duration of harvest, donor sex and age. The percent of TBV blood volume removed was divided into quartiles with >27% of TBV in the highest group. For these donors, 82% received autologous transfusions. In multivariable analysis, there were more reported toxicities at 48 hours (OR: 0.73, P = .01) for the high-volume donors who did not receive transfusion but not at the other time points. These donors who received transfusion recovered faster than those who had not (median: 21 vs 26 days, OR = 1.175; P = .0089).

Farhadfar et al provide some important large cohort data on the utility of autologous red cell unit collection for BM donors. Overall, it appears that there is little benefit. It appears that donors were being transfused at median Hb levels that would not normally merit transfusion in other settings. There was also a very low number of allogeneic transfusions suggesting that some of the autologous units may have been transfused simply because they were available and not based on symptoms. If there was data on all the patients who had autologous units collected but not used, we might have gotten a better sense of the waste in time and effort.

While there is the limited data suggesting some potential benefit for those who will lose a lot of blood volume, it is difficult to account for all potential confounders in the analysis and such practice of very large collections “violates NMDP safe BM harvest policy.” Taken together, as noted by the authors, “the results of this study do not support the routine use of autologous blood transfusion for all unrelated BM donors.” (RH)

Allogeneic cord blood transfusions prevent fetal haemoglobin depletion in preterm neonates. Results of the CB-THP study. Teofili L, Papacci P, Orlando N, et al. Br J Haematol 2020. Epub ahead of print.

Premature neonate may receive a lot of blood transfusions. While there are associations between more transfusions and adverse outcomes (eg, retinopathy of prematurity [ROP]), it is difficult to separate out cause and effect. That is, do the transfusions cause sicker patients or are sicker patients just more likely to be transfused? Neonates also have fetal Hb while the adult units transfused have Hb A with each having different properties especially in regard to oxygen affinity. Could providing neonates the more “physiologic” HbF improve outcomes? In this setting, Teofili et al carried out a study transfusing cord red blood cell (RBC) units into preterm neonates.

The authors included patients at a gestational age ≤30 weeks and/or ≤1000 g who were then followed until 36 weeks. When transfusion was ordered, the neonates received, if available, an ABO and Rh(D) matched cord red blood cell unit or, if a cord blood unit (CBU) was not available, an adult unit. The CBUs were collected, prior to the delivery of the placenta, from neonates born at >37 weeks’ gestation from a mother with no evidence of infection or fever. Red cell concentrates, suspended in additive solution, were made from units >60 ml with <20% erythroblasts and no evidence of hemolysis or clots. They were tested for transfusion-transmitted infections and cultured for bacteria and fungi. The units were leukoreduced, stored for up to 14 days and released after being irradiated. The primary end point was median Hb levels at 32 weeks.

There were 25 patients enrolled in the study with a median gestational age of 29.4 weeks and a weight of 1030 g. The median hematocrit and Hb at birth were 47.5% and 93.4%. At 32 weeks, there were 9 patients who received a total of 20 transfusions with 2 patients receiving exclusively CBUs (1 transfusion each) and 3 patients receiving only adult units (1 transfusion each). The other 4 patients received a total of 15 transfusions. At 32 weeks, as might be expected, patients not receiving any transfusions or only CBUs had a median HbF% >90%. When compared to these patients, those receiving only adult units or a combination had a significantly lower median HbF% of 58% and 69%, respectively. The median time between transfusions was 8 days following a CBU and 7 days following an adult unit. The change in hematocrit post-transfusion was 9% for CBUs and 11.5% for adult units.

In regard to other outcomes, for all 23 patients completing the study (36 weeks, 2 patients died), 8 developed ROP, 7 had nonsurgical necrotizing enterocolitis, 5 had bronchopulmonary dysplasia and 3 had an intraventricular hemorrhage. For the 10 of these patients receiving 26 transfusions (12 cord and 14 adult), 6 had ROP, 5 had necrotizing enterocolitis and 4 had bronchopulmonary dysplasia with a median HbF% at 36 weeks of 67.1. There was no association between number or type of unit (adult or CBU) received and any of the adverse outcomes. There was an association with a HbF% below the median at 36 weeks and ROP (P = .048).

In this study, building on their prior work, the authors show that transfusion of CBUs appears to maintain HbF levels in premature neonates – more so than standard transfusions, which is not that surprising given adult units have HbA. There are, however, many unanswered but related questions such as whether giving HbA is harmful in neonates. While HbF is “physiologic,” it has stronger oxygen affinity than HbA which serves a purpose in pulling oxygen from the placenta but is it better than HbA after birth? The authors comment that lower HbF is associated with ROP perhaps due to increased oxygen delivery leading to issues with vascu larization. As noted above, this data may be confounded by the fact that sicker neonates may be more at risk for ROP and will receive more transfusions. There also may be instances where the
lower oxygen affinity of HbA may be helpful such as a neonate with any ischemia related issues.

Furthermore, while cord blood is normally discarded and collection is of no harm to mother or child, the effort required in collecting and standardizing use of such products is not trivial. The paper does not appear to describe how the collection solution and storage time of the products were validated in regard to variables such as hemolysis, hematocrit and red cell survival. Another important question is what percent of collected products met the authors’ criteria for use (eg, volume requirements, culture positive)? An adult unit, given its larger size, can also be reserved for multiple transusions to a single neonate allowing for reduced donor exposures. Taken together, while a potentially interesting idea, there are significant logistical (and cost) hurdles for use of these products let alone showing they have any advantage in regard to standard adult units. (RH)

Cord blood CD8+ T-cell expansion following granulocyte transplants eradicates refractory leukemia. Hiwarkar P, Adams S, Gilmour K, Nataraj R, Bonney D, Poulton K, et al. Blood Adv 2020;4(17):4165-74. doi:10.1182/bloodadvances.2020001737.

This paper caught my attention as it so nicely illustrates the importance of observation and serendipity. Cord blood is a preferred donor cell source for children with poor-risk or refractory leukemia disease undergoing haemopoietic stem cell transplanation. A central immunological pathway for mediating the graft-versus-leukemia effect is mediated through cytotoxic T-cell responses with donor T cells directed against residual recipient malignant cells. Considerable research is on-going testing different strategies to enhance this effect. The challenge is that techniques to augment these grafts versus leukemia effects may come at the expense of graft-versus-host disease.

This group of researchers made some unique observations in a small case series of children with high-risk pediatric leukemia undergoing T cell-replete CB transplantation (CBT), who also received transfusions of granulocytes. In this case series, 5 children received third-party, pooled granulocytes. The exact reasons for receiving these transfusions were not clearly stated. It is likely to reflect a combination of treatment and secondary prophylaxis for children with a complicated history of severe complications of infection, mostly fungal chest infections. At this center in England, these granulocytes are not apheresis derived from a single donor but are only provided as a pooled product from National Health Service Blood and Transplant. This component is thus very heterogeneous in content, including neutrophils and mononuclear cells such as lymphocytes and monocytes, and characterized by multiple donors and exposure to many different major and minor histocompatibility complex antigens.

The researchers nicely monitored a T-cell expansion that was transient but robust, including expansion of CD8+ T cells. This was contrasted to the more typical slower CD8+ T-cell expansion ordinarily observed after T cell-replete CB transplantation, which for this study was defined by a historical cohort of children undergoing immune reconstitution monitoring after transplantation and who did not receive granulocyte transfusions. The CD8+ T cells were further investigated using standard immunological techniques of flow cytometry and molecular assessments, and these expansions was shown to be polyclonal, rapidly switching to memory phenotype, and with the ability to mediate cytotoxicity. Of clinical significance, the children fared very well. There was no evidence of viral reactivation and immune suppression could be stopped early. There were no reports of chronic graft-versus-host disease. Four of the patients were reported to be in continued remission after a median of 26 months.

At level, a novel anti-leukemia therapy based on fetal-derived cord blood CD8+ T cells that translates into long-term remission without GVHD for children with refractory leukemia disease appears very important but needs to be open to review and repeating by the transplant community. For me, the other lesson, is surely about the powers of observation by clinicians and a willingness to explore unexpected results. Many transplantation colleagues may consider a granulocyte component derived from whole blood (WB) to be a “dirty” component with no role – but in this case, it’s use may have benefits in addition to those suspected for the treatment of refractory infection. (SJ)

Limited effect of red blood cell transfusion on long-term mortality among anaemic cardiac surgery patients. Tran L, Greiff F, Wahba A, et al. Interact Cardiovasc Thorac Surg 2020;31:375-82.

RBC transfusion during cardiac surgery has been associated with inferior short- and long-term patient survival in some observational studies, but not in others. The contrasting observations may be due to confounding by severity of illness, since “sicker” patients are more likely to be transfused and also less likely to survive. The authors of this study focus specifically on patients with preoperative anemia to explore the relationship between perioperative transfusion and long-term survival in patients undergoing cardiac surgery.

This is a single center, retrospective cohort design using a surgical database. Patients that underwent cardiac surgery with cardiopulmonary bypass were included if they had preoperative anemia (Hb <130 g/L [men] and <120 g/L [women]). The primary outcome of the study was all-cause mortality from 30 days to 5 years postoperatively. Using Cox proportional hazards regression, survival was compared between patients transfused ≥1 RBC unit during hospitalization and those that were not transfused. Patients that died within 30 days of surgery or with <30 days observation were. Adjustment for confounders was reported in 4 steps, starting from an unadjusted model. With each step, a “block” of covariates was added: (1) patient risk factors and perioperative lab values, (2) operative variables associated with risk of transfusion, and (3) postoperative complications.

Over a 17-year period, 10 288 cardiac surgery patients were identified. 2278 were anemic prior to surgery and 1859 were included in the analysis: 1525 (82%) were transfused ≥1 RBC unit. Preoperative Hb was <110 g/L in 21.4% and <100 g/L in 5.8%. Men (65.8%) were less likely to be transfused RBCs than women (95.8%). A total of 370 deaths (19.9%) occurred during a mean observation time of 4.1 years, 37 (11.1%) in the nontransfused group and 333 (21.8%) in the transfused group. Almost all the deaths that occurred up to 1 year postoperatively were in transfused patients (95.5%).

Prior to adjustment, RBC transfusion was associated with higher hazard of death (HR 2.09, 95% CI 1.49-2.93 overall; HR 4.70, 95%CI 1.72-12.81 from 30-days to 1 year; HR 1.77, 95%CI 1.23-2.55 from 1-5 years). After adjusting for confounders, RBC transfusion was not associated with long-term mortality (HR 1.16, 95%CI 0.80-1.68 overall; HR 1.79, 95%CI 0.63-5.12 from 30-days to 1 year; HR 1.11, 95%CI 0.75-1.65 from 1-5 years). Sensitivity analyses including deaths <30 days and emergency surgeries (HR 1.19, 95%CI 0.82-1.71), excluding patients on warfarin, ticagrelor, or clopidogrel (HR 1.00, 95%CI 0.65-1.53), and evaluating number of transfused units (HR 1.14, 95%CI 0.75-1.75 for 1-2 RBC units; HR 1.08, 95%CI 0.70-1.65 for ≥3 RBC units [both compared with no transfusions]) did not change the overall results.

These findings suggest that the relationship between long-term postcardiac surgery survival and RBC transfusion may primarily be due to confounding factors that both increase the risk of transfusion and mortality. Although the study included a large number of patients, it is a single center study, which limits generalizability. The authors appropriately emphasize that very few untransfused patients died in the first year of follow-up and the apparent lack
of effect may be due to insufficient power. This study highlights a challenge in addressing the question of harm from transfusion in an observational study design. The focus was placed on anemic patients to minimize bias arising from severity of illness, but only a minority of anemic patients are not transfused. (JPM)

Whole blood administration: comparison of in vitro platelet function of pressure bag, pressure bag with fluid warming device, and rapid infuser methods. Alley T, Taylor G, Owens A, et al. J Trauma Nurs 2020;21(6):351-54.

Platelet concentrates are the divas of the conventional blood components: their storage temperature cannot be too cold or too hot, they have to be gently rocked at all times, must not be transported in a cooler with the other components, and cannot be heated with a warming device or transfused under high pressure. With the increasing use of WB in trauma resuscitation, the question arises of how the delicate platelets in WB handle being treated like plasma and RBCs. The objective of this study was to evaluate in vitro function of platelets from WB units after mock transfusion using 3 different methods: pressure bag (PB), PB with fluid warming line (HL), and rapid infused with warming line (RI).

Ten units of nonleukoreduced WB, stored in CPD, were each divided into 3 aliquots. Each aliquot was infused into an empty blood collection bag using the 3 methods. Control samples were collected from each aliquot prior to infusion and 2 samples were collected from the collection bag following transfer. Temperature, rapid thromboelastography, and platelet aggregation studies were performed on each aliquot.

The evaluated WB units had an average storage time of 5.8 (4-7) days, platelet count of 135 (91-179 × 10^9/L). Infusion time was shortest with RI (29 seconds [25-32] vs 105 seconds [91-113] for PB and 118 seconds [93-133] for HL). The temperature increased by 19.5°C (16-21°C) with RI, 17.1°C (15-20°C) with HL, and 4.3°C (2.7°C) with PB. “Multivariate test analysis” (not described further) was reported not to show a significant difference pre- and postinfusion on thromboelastography values. The maximum amplitude was 55.6 mm (IQR 50.6-63.5) re-infusion, 54.9 mm (IQR 47.6-61.4) with PB, 55.5 mm (IQR 48.1-63.9) with HL, and 56.1 mm (IQR 50.6-61.2) for RI (P = .72 for group). Platelet aggregation with arachidonic acid, adenosine diphosphate, epinephrine, and collagen were evaluated. No statistically significant differences were noted from preinfusion to postinfusion for any of the agonists except arachidonic acid, which showed increased maximum aggregation following infusion (P = .021), but the increase was similar with each infusion method (preinfusion 13.0% [3.7-22.6], PB 25.5% [2.7-43.4], HL 23.7% [3.7-43.8], and RI 23.0 [12.1-44.6]).

This study attempts to answer an important question regarding platelet function following WB transfusion using methods that are often not used for platelet concentrates. While the results are encouraging, the study did not use a power calculation to determine the number of samples that would be required to confidently answer the question. Additionally, details on the statistical analysis are lacking, leaving the reader to guess at the tests used for comparison. (JPM)

Red blood cell tension protects against severe malaria in the Dantu blood group. Karluki SN, Marin-Menendez A, Introvini V, et al. Nature 2020;585:579-83.

While the SARS-CoV-2 virus has certainly left its mark on human life in 2020, this paper is a nice reminder that malaria has been shaping the evolution of human RBCs for centuries. The Dantu antigen is in the MNS blood group and is the result of a rearrangement of glycoprotein A (GYPA) and glycoprotein B (GYPB) genes that results in a hybrid protein with a GYPB extracellular domain and a GYPB intracellular domain. Dantu-positive individuals are protected from severe malaria in a dose-dependent fashion, but the mechanism of protection is unknown. In this study, the investigators explore the mechanism of malaria resistance by the Dantu blood group. RBC samples were collected from 42 children from the town of Kilifi in Kenya, where the allele is more frequent. The children were negative for the sickle mutation.

Invasion into Dantu-homozygous, Dantu-heterozygous, and non-Dantu RBCs by 5 different strains of Plasmodium falciparum was measured using fluorescence-activated cell sorting. A dose-dependent reduction in 

Whole blood is superior to component transfusion for injured children. A propensity matched analysis. Reeser CM, Yazer MH, Triulzi DJ, et al. Ann Surg 2020;272(4):590-94.

The vast majority of the modern published experience using WB in trauma comes from its use in adult patients. The safety of efficacy of WB in pediatric patients is not well defined. WB offers the same hypothesized advantages in pediatric trauma resuscitation as it does in adults: more convenient administration, physiologic ratios of blood components, and cold-stored platelets. The objective of this study was to explore the effectiveness of WB with
conventional component (CC) resuscitation in critically injured pediatric trauma patients at a single center. The study uses a single-center, retrospective cohort design. Patients <18 years of age were identified from a trauma database. A WB program was introduced at the center in June 2016, with group O, low-titer (anti-A and anti-B <50), cold-stored (1-6°C, for up to 14 days) WB replaced uncrossmatched RBC units for initial trauma resuscitation. The maximum WB dose was 20-40 mL/kg and components would be used once this volume was reached.

Any patients transfused ≥1 blood component in the emergency room during the 3 years prior to introduction of the WB program were included in the CC group and any patients that received any WB as part of their resuscitation in the 3 years after the program was introduced were included in the WB group. Exclusion criteria included pre-existing coagulopathy, receipt of components before arrival, and death in the trauma bay after prehospital cardiac arrest. Patients that received WB were matched 1:1 to controls that received component resuscitation using propensity scores. There were 3 “primary” outcomes: time to resolution of base deficit, volume of products transfused, and persistent post-transfusion coagulation dysregulation (defined by highest INR in the 48 hours after admission). Secondary outcomes included functional disability at discharge, hospital and ICU LOS, time on mechanical ventilation, and total transfusion volume.

The cohort consisted of 185 children, 153 in the CC group and 32 in the WB group. There were 33 exclusions, leaving 28 WB patients, who were matched to 28 CC patients. The average age was 11 vs 8 years (WB vs CC), the majority male (68% vs 61%) and injured by blunt trauma (72% vs 78%). In the WB group, the time to resolution of base deficit was shorter (median [IQR] 2 hours [1-2.5] vs 6 hours [1-24], WB vs CC, P < 001), the maximum post-transfusion INR was lower (1.6 [1.4-2.2] vs 1.4 [1.3-1.5], P = 0.01), and lower volumes of RBCs (15 mL/kg [0-28] vs 24 [10-62], P = 0.01), plasma (5 mL/kg [0-15] vs 11 mL/kg [5-35], P = 0.04), and platelets (0 mL/kg [0-2] vs 3 mL/kg [0-8], P = 0.03) were transfused. Total transfusion volumes were similar (29 mL/kg [11-55] vs 48 mL/kg [17-122], P = 0.08). Mortality (29% vs 43%, P = 0.40), functional disability (57% vs 50%, P = 0.75), hospital LOS (8 days [1-18] vs 8 days [4-13], P = 0.74), ICU LOS (4 days [2-7] vs 3 days [1-9], P = 0.89), and days on ventilator (2 days [0-5] vs 1 day [0-6], P = 0.8) were not different between groups.

The authors provide a high-quality analysis of observational data in an area lacking in published evidence. Given the relatively broad eligibility criteria for WB resuscitation at the center, it is surprising that there was such a large discrepancy in the number of patients included in each group, with 121 more patients in the CC group over a similar period of time, raising concern about selection bias. This is addressed through the use of propensity score matching, which improved imbalances in baseline characteristics, but residual bias is possible. Few details are provided regarding the covariates included in the propensity score. It is not surprising that higher volumes of RBCs, plasma, and platelets were given in the CC group, since WB transfusions were not taken into account, and the differences in median volumes of plasma and RBCs is close what would be expected from the median volume of WB given, assuming a hematocrit of 50%. The title is eye-catching but perhaps a little misleading: the main difference observed with WB was a faster time to base deficit correction, but the clinical significance of achieving this milestone is uncertain. Mortality, hospital and ICU LOS, and time on ventilator were similar between the groups. (JPM)

Feasibility assessment for use of Rh-positive blood products during emergency resuscitation in the North Texas trauma population. Edmundson, P, Vandertulip, KR. Proc (Bayl Univ Med Cent) 2020;33:532-35.

Blood transfusion can be life-saving in trauma. There are a number of approaches, based primarily on observational data, that are being considered in trauma that wouldn’t be currently used in other patient populations. These include use of WB and ABO incompatible plasma products. Due to logistical issues, it is difficult to provide O negative WB for trauma patients. As a result, some have put forth the idea that the benefits of providing WB to women of childbearing age outweighs the risk of using units that are O positive. The argument is that women represent a minority of trauma patients, the risk of developing anti-D isn’t that high and we can now treat anti-D related HDFN. In this milieu, Edmundson and Vandertulip present their local experience to try and support the use of O positive WB for all patients.

The authors, at their level II trauma center, reviewed patients in their trauma registry from January 2016 through July 2019. To try and narrow down to patients who might have been transfused emergency release O negative blood, they then specifically looked at patients who received a transfusion within 4 hours of arriving in the hospital.

Of the 7681 patients in their trauma registry, 883 received blood products. Of these, 277 received transfusions within the first 4 hours of transfusions. After excluding 15 patients with no blood type, 262 patients were analyzed with approximately 25% female, 50% having blunt trauma, and a median age of 37 and injury severity score of 22. Of the 64 women in the cohort, 4 (6%) were Rh negative with 1 being of childbearing age. The authors conclude that “the prescription against Rh-positive blood as an emergency release blood product only minimally reduces the risk of development of future HDFN in our trauma population.”

There are major caveats to broadly applying these findings. It is a very small cohort of patients with a lower-than-expected percentage of Rh-negative individuals. Even if it were true that only 0.4% of the millions of trauma patients are at risk, that still adds up to thousands of patients. In addition, only 35% of patients in the reported cohort received more than 10 units of blood demonstrating that it is not always possible to predict when a trauma patient will require massive transfusion. In fact, while O negative blood is a valuable resource, only 9 units of red cells were transfused to the female Rh-negative patients over 3 years. It would be very unfortunate if an Rh-negative woman had a child with HDFN because she had received only 1 or 2 units of Rh-positive blood.

There are a number of areas in blood banking where we make an effort to prevent an adverse outcome even if the risk may be relatively small. For example, we do antibody screens even though most patients have not made antibodies and, those that have, will not develop acute hemolysis if transfused incompatible blood. For the alloimmunized pregnant female patient with anti-d, intrauterine transfusions are not a trivial intervention and HDFN can lead to significant morbidity and mortality. If there was high quality evidence regarding the benefits of WB and we could somewhat confidently predict who would need massive transfusion, then perhaps routinely giving Rh positive blood to women of childbearing age should be considered. Until then, while there may be situations where such a patient requires so much blood that a switch to Rh positive red cell units is required, up front providing Rh- blood to this patient population seems ill-advised. (RH)

Incidence of thromboembolic events following administration of four-factor prothrombin complex concentrate (4F-PCC) for oral anticoagulation reversal. Makhoul T, Kelly G, Kersten G, et al. Thromb Res 2020;194:158-64.

Prothrombin complex concentrates (PCC) are routinely sometimes used in the emergency reversal of both vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs). While the risk of thromboembolic events (TEs) of PCCs compared with plasma have been evaluated in randomized, controlled trials in the rever-
sal of VKAs, the same quality data is not available for PCC use in the reversal of DOACs. The objective of this study was to measure the frequency of TE following 4-factor PCC (4F-PCC) for the reversal of VKA and DOACs.

This study is a retrospective, cohort study conducted at 2 tertiary-care academic centers in the USA. Adult patients that were treated with 4F-PCC between 2013 and 2017 and that survived ≥6 hours from the time of administration were included in the cohort. The primary outcome of the trial was the incidence of TE (arterial, venous, or mixed/unspecified vessel type thrombosis or embolism) prior to discharge. TE events were identified by ICD-9 or ICD-10 codes and clinical/imaging data extracted from medical record review. Patients that developed TEs were compared with patients who did not, and predictors of TE were identified using logistic regression. Patients taking VKA and DOACs were analyzed separately in a preplanned subgroup analysis.

The cohort consisted of 542 patients, with a mean age of 73 ± 14 years and the majority were male (58%). Approximately three-quarters received PCC for VKA reversal (76%), and most patients were anticoagulated for atrial fibrillation (58.6%). Intracerebral hemorrhage was the most common reason for reversal (68.5%), followed by need for an emergent procedure (13.4%). A median dose of 2000 units (IQR 2000-2500) was given overall and in both VKA and DOAC subgroups.

TE occurred in 9.2% of patients. The incidence of TE was similar between both treatment sites, as well as anticoagulation types (9.9% on VKA vs 7.1% on DOAC, P = 0.34). Deep vein thrombosis was the most common TE (62%) followed by stroke (28%). The median time to TE was 116 hours (IQR 41-252), 62% occurred within 7 days of PCC and 42% within 3 days. Time to initiation of VTE prophylaxis was similar between TE and no TE groups. The multivariable analysis identified indication for anticoagulation and hospital LOS were associated with risk of TE. Patients with an indication of “DVT or PE” (OR 2.03 95%CI 0.99-4.18 compared with atrial fibrillation) or “other” (antiphospholipid antibody syndrome, Factor V Leiden, superior mesenteric vein thrombus, carotid artery stenosis, left atrial thrombus, or protein C-deficiency) for anticoagulation (OR 3.84 95%CI 1.25-11.79), and patients with a hospital LOS ≥7 days (OR 3.06 95%CI 1.47-6.38) were more likely to have a TE.

This paper offers an estimate of thrombomelobitic risk following use of PCC to reverse oral anticoagulation in a “real world” setting among a relatively large cohort of patients. Compared with previously published estimates, the incidence of TE was higher in both VKA and DOAC groups. The risk of TE was similar between patients taking VKAs and patients taking DOACs. Despite a lack of high-quality evidence, PCCs have become relatively routine in the reversal of DOACs. This study provides some reassurance that patients being treated with PCC are not being exposed to an increased risk of thrombosis compared with VKA patients. However, the efficacy of PCC for DOAC reversal is still an unknown and needs to be defined for the risk-benefit of PCCs for DOAC reversal to be understood. [JPM]

Pharmacokinetics of intramuscular tranexamic acid in bleeding trauma patients: a clinical trial. Grassin-Delyle S, Shakur-Still H, Piccetti R et al. Br J Anaet 2020. 10.1016/j.bja.2020.07.058.

There is a challenge with delivery of tranexamic acid (TXA), in that the large informative trials in trauma and postpartum bleeding have tested intravenous TXA to test on any reduction of deaths due to bleeding. The data also indicates that TXA is most effective when given early. Yet, intravenous medications are more logistically challenging, in the military environment and for prehospital care, including if administered as an infusion. Indeed, in many countries, prehospital care is provided by health care professionals and other staff who cannot give intravenous injections. So, the group from the London School of Hygiene and Tropical Medicine with collaborators, assessed the potential role of an intramuscular formulation of TXA.

The aim of this study was to characterize the pharmacokinetics of intramuscular TXA in bleeding trauma patients. The hope was that an intramuscular formulation could support more rapid and likely delivery in situations of bleeding from trauma or childbirth. This was an open-label pharmacokinetic study in 2 UK hospitals. Thirty bleeding trauma patients received a loading dose of TXA 1 g intravenous (i.v.), as per guidelines based on the randomized trial data. The second TXA dose was given as two 5 mL (0.5 g each) intramuscular injections. Blood samples were collected at intervals and the injection sites monitored. TXA concentrations were measured using liquid chromatography coupled to mass spectrometry, and the time course plotted using nonlinear mixed-effect models allowing for age, sex, ethnicity, body weight, type of injury, signs of shock, and glomerular filtration rate as possible covariates.

Intramuscular TXA was well tolerated with only mild injection site reactions in 30 patients who received the test drug, from whom 239 serum samples were obtained. A nonlinear mixed effect modelling approach was fitted to the data and presented in the paper. The time to reach therapeutic concentrations after a single intramuscular TXA 1 g injection was described with simulation for 5 or 10 mg/L. After a single TXA dose 1 g intramuscular (i.m.), a TXA concentration of 5 mg/L or 10 mg/L would be achieved in about 4 minutes or 11 minutes, remaining above the (lower) level for 10 hours. After a TXA dose 0.5 g intramuscular, a TXA concentration of 5 mg/L would be achieved in about 10 minutes, remaining above this level for 5.8 hours. Overall, a TXA concentration of 10 mg/L would be achieved in 22 out of 30 patients in about 20 minutes, remaining above this level for 2.8 hours.

Overall, the data were reassuring – the findings supported the conclusion of drug being rapidly absorbed. The results suggest that an intramuscular formulation of TXA could have a role for many clinical settings, and for example trauma care in low or middle resource countries settings. Interestingly, if one is concerned about the challenges of giving an infusion of TXA, the recent Study of Tranexamic Acid During Air and Ground Medical Prehospital Transport Trial (STAAMP Trial) trial reported on trauma patients who received 1 g of TXA before hospitalization (447 patients) or placebo (456 patients) infused for 10 minutes in 100 mL of saline. This schedule of prehospital administration of TXA after injury did not result in a higher incidence of thrombotic complications or adverse events and appeared safe (Guyette FX, et al TXA During Prehospital Transport in Patients at Risk for Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. JAMA Surg. Taken together, these results indicate some flexibility in dosing and formulation for TXA that could support more timely and pragmatic administration in many different clinical settings (SJS)

Audit and feedback to improve laboratory test and transfusion ordering in critical care: a systematic review. Foster M, Presseau J, McCleary N, Carroll K, McIntyre L, Hutton B, et al. Implement Sci 2020;15(1):46. Published 2020 Jun 19. doi:10.1186/s13012-020-00981-5.

We all want to know more about how to change behavior in pathology, including requests for laboratory unnecessary tests or blood transfusions. Two recent papers review evidence for different approaches to this conundrum. The article after this one in the journal club addresses what we know for computerized clinical decision support systems. This recent review by contrast addresses the role Audit and Feedback for modifying behaviors in clinical practice. The paper describes a well-conducted systematic review of the Audit and Feedback literature for improving test or transfusion requesting in the critical care setting.
Five databases, 2 registries, and the bibliographies of relevant articles were comprehensively searched. Eligibility was assessed for critical care studies that assessed the use of A&F targeting health care provider behaviors, alone or in combination with other interventions. Studies were included only if they reported laboratory test or transfusion orders, or the appropriateness of orders, as outcomes. The comparison was to historical practice, no intervention, or another health care behavior change intervention. There were no restrictions based on study design, date of publication, or follow-up time. Intervention characteristics and absolute differences in outcomes were summarized. The quality of individual studies was assessed using a modified version of the Effective Practice and Organization of Care Cochrane Review Group’s criteria for nonrandomized studies, which is the most common expected study design for this area of research.

The researchers identified 16 studies, and the majority were uncontrolled before-after studies, as perhaps to be expected; 3 were reported to be a randomized controlled trial, a controlled before-after study, and a controlled (quasi-experimental) clinical trial. Only 1 study assessed audit & feedback in isolation. Audit and feedback are not as we know a homogeneous single intervention and is often one part of a behavior change programme – in total the research group indicated that the identified studies described 17 interventions, mostly (88%) multifaceted interventions with an A&F component. Interestingly, feedback was most often provided in a written format only (41%). Moreover, this feedback was only provided more than once in around half of the studies. Often aggregated data was used as well, rather than more individualized reporting. Overall study quality was low, with studies often lacking a concurrent control group. What was the effect size? Well, some studies found a benefit, but this varied and was not seen in all published reports (of course publication bias could be also a concern here).

As for the broader audit & feedback literature, it appears we really don’t know enough about how to plan and deliver to obtain the best effect in clinical practice. Some of the lessons mirror other findings in the wider literature – for example, the need for multi-faceted strategies, the need to explore the barriers to practice change prior to just doing a cycle of “audit & feedback,” the need for individual feedback and delivered more than once. Audit & feedback can help, but needs to be well designed, and ideally in the context of a clinical study evaluation – perhaps conducted as part of an “implementation laboratory” (SJS)

Computerised clinical decision support systems and absolute improvements in care: meta-analysis of controlled clinical trials. Kwan JL, Lo L, Ferguson J, Goldberg H, Diaz-Martinez JP, Tomlinson G, et al. BMJ 2020;370:m3216. Published 2020 Sep 17. doi:10.1136/bmj.m3216.

This paper described an ambitious review aimed at understanding the role and impact of clinical decision support systems across clinical care. Such systems embedded in electronic health records are generating a lot of interest in transfusion. As for audit and feedback, we may learn more about these implementation strategies when considering the breadth of health care, not just selected topics like pathology and transfusion. The aim of this review was to describe the improvements achieved with clinical decision support systems and explore factors relevant to the heterogeneity of results across diverse clinical settings.

The systematic review was well conducted, although only 1 database was searched (Medline up to August 2019). Eligible studies included randomized or quasi-randomized controlled trials reporting changes in the proportions of patients receiving care recommended by clinical decision support systems. Quantitative meta-analysis was undertaken and meta-regression explored factors such as the characteristics and types of clinical decision support systems as well as study details. Specific attention was paid to study that incorporated reporting of clinical end points.

A large number of studies were identified: 108 studies reporting 122 trials. This represented data from 1203053 patients and 10790 providers. Most studies were conducted in the outpatient not inpatient setting, across topics like prescribing, test ordering and even vaccination. The pooled results suggested that clinical decision support systems increased the proportion of patients receiving desired care by 5.8% (95% confidence interval 4.0%-7.6%). However, as might be expected, there was considerable variability and evidence of substantial heterogeneity (I² was very high at 76%). Many studies reported very little effect benefit; the variation in effect sizes for the top quartile of reported improvements ranged from 10% to 62%. In 30 trials reporting clinical end points, clinical decision support systems increased the proportion of patients achieving guideline-based targets (eg, blood pressure or lipid control) but only by a median of 0.3% (interquartile range -0.7% to 1.9%), which does not appear clinically significant. Interestingly, some features of baseline adherence appeared to be important predictors of better change with implementation of clinical decision support systems, for example, low baseline compliance to recommended practice.

So, the authors found little evidence that clinical decision support systems were overall helpful – indeed in many studies the performances were rather disappointing. This has several implications (and please read the accompanying commentary related to this article). It would be really helpful to have more information on why there might be poor uptake and engagement with clinical support systems – is this a problem of the interface with clinicians or for other reasons. If I was investing in this technology at my hospital, I might want to undertake some background work first, including to really explore clinician input and satisfaction, as well as understanding if the system could be designed alongside stronger patient engagement. The overall findings mirror the literature for audit and feedback: clinical decision support systems appear to achieve often only small to moderate improvements in targeted processes of care. We really need to understand what makes a particular clinical decision support system deliver more substantial enhancements in care, so we can apply the best means of delivering better clinical care (SJS).

Micro-environmental sensing by bone marrow stroma identifies IL-6 and TGFβ1 as regulators of hematopoietic ageing. Valletta, S., Thomas, A., Meng, Y. et al. Nat Commun 2020;11:4075. https://doi.org/10.1038/s41467-020-17942-7.

The management of aging in the elderly is getting more complicated. In addition to uncertainties about the optimal transfusion management of outpatient MDS, there are a group of disorders linked to MDS which include anemia defined as idiopathic cytopenia/dysplasia of unknown significance, or clonal cytopenia of unknown significance. These disorders are likely characterized by an inflammatory process and also appear to be associated with cardiovascular disease, which remains a major cause of death in these populations. But why do haemopoietic changes occur as we get older? Hematopoietic ageing is often defined by declining erythropoiesis and lymphopoiesis, leading to well recognized changes in levels of Hb and evidence of decreased adaptive immunity (we perhaps have also seen this more clearly during the recent and on-going COVID19 pandemic). This elegant series of experiments started to probe whether these changes were intrinsic to the hematopoietic stem cells, or represented a major cause due to external factors such an altered microenvironment.

The methods reported described gene expression and cell profiling, at scale, of stromal populations from young and aged BM, using a well-defined mouse model. The mouse “competitive repopulation” model was a stem cell transplantation experiment
in which haematopoietic stem cells were isolated from young or old mice, and then injected into lethally irradiated recipient animals. Peripheral blood reconstitution experiments were performed at 16 weeks after transplantation. In these studies, BM stromal cells were acting as sensors of age-associated changes to the BM microenvironment. Additional experiments explored the effects of different inhibitors, for example interleukin-6 in aged mice, to test whether these factors could revert any age-dependent changes in haematopoietic progenitor activity.

As might be expected, and as observed in aging in humans, aged mice develop lower Hb levels compared to young mice (although platelet count seems to increase). A key overall finding was that reduced lymphoid lineage output appeared to be an intrinsic property of aged haematopoietic stem cells, but this was not the case for erythroid output. The researchers reported on assessments of function of erythroid progenitors through analysis of a range of cell makers and found that expression of genes normally associated with erythroid-lineage specification was significantly decreased compared to young mice. Interestingly, inhibition of IL-6 appeared to “improve” aged erythroid progenitor function. Inhibition of TGFβ signaling led to reversal of age-associated haematopoietic stem cells platelet lineage bias, increased generation of lymphoid progenitors and rebalanced haematopoietic stem cells lineage output in transplantation assays.

In summary, for haematopoietic stem cells, intrinsic and extrinsic mechanisms appear to be involved in age-associated haematopoietic decline. However, for decreased age-related erythropoiesis, the findings suggest that the main cause is an external factor, less so being an intrinsic property of aged haematopoietic stem cells. Moreover, further experiments highlighted the potential importance of immune pathways to mediate this effect, through (transforming growth factor) TGFβ-receptor and IL-6 inhibition. These results raise the potential role of multiple new therapeutic options through targeted immunomodulatory/immune-suppressive drugs to affect an improvement in age-related changes in erythropoiesis in the future – top-up transfusions of red cells are clearly a very “crude” approach. (SJS)

Racial/ethnic and gender disparities in the use of erythropoiesis-stimulating agents and blood transfusions: cancer management under Medicare’s reimbursement policy. Li M, Schulz R, Chisholm-Burns M, et al. J Manag Care Spec Pharm 2020;26:1477-86.

There is important growing awareness of health care in regard to race/ethnicity and gender. The goal should be to eliminate such differences when due to conscious or unconscious bias. Another important consideration is the effect of governmental regulations on changes in medical practice. In this context, Li et al analyze the effect of a Medicare-policy change on use of erythropoiesis stimulating agents (ESA).

Medicare, overseen by the United States Centers for Medicare and Medicaid Services (CMS), is the federal health insurance program for individuals 65 years and older. In 2007, due to increasing safety concerns when targeting high Hb levels, CMS created a new reimbursement policy for ESAs in cancer. To receive payment, a Hb level of <10 g/dL was established as the threshold. The authors analyzed use of ESAs in cancer patients before and after the policy change with January 1, 2003, to June 30, 2007 as the prepolicy period and May 1, 2008 to December 31, 2009 as the postpolicy period. Chronic kidney disease (CKD) patients served as a control as these patients also are relatively frequently prescribed ESAs but there was no similar CMS policy change. All patients were identified through the Surveillance, Epidemiology, and End Results-Medicare linked database. Gender and race ethnicity were collected from Medicare enrollment data and use of transfusions and ESAs were determined through CPT and ICD-9 codes in Medicare claims. Results were adjusted for cohort differences and analyzed using an interrupted time series design which allows for not only identification of changes in level, but changes in trend.

This study identified 54,370 ESA users (44,322 prepolicy and 10,048 postpolicy) and 48,165 patients who received blood transfusions (32,179 prepolicy and 15,986 postpolicy). There were significant differences between the cancer and CKD patients including age, gender, ethnicity and/or race, education and poverty level. ESAs were used by about 5% of both cancer and CKD patients in the prepolicy period. Post policy, there was only a slight drop in the CKD group but, after accounting for the control group in the regression analysis, the use of ESA in the cancer group dropped by 50% (P < .0001). Approximately 1% of patients in both groups received blood transfusions prepolicy change. Postpolicy, after accounting for the control group, there was a 10% increase in the cancer group (P = .02). When looking at differences by gender, the decrease in ESA use was greater in females than males (60% vs 30%) as was the increase in transfusion (10% vs no significant change). In regard to race/ethnicity, the amount of ESA use dropped in whites, Latinos and African-Americans to the same extent (approximately 50%). However, transfusions only increased in African Americans and by 50%.

While one limitation of this study is the possibility of unaccounted confounders, the authors should be commended for trying to answer important questions. Their use of a control group helps emphasize the major effect a governmental policy change can have on health care including hematology-related areas. Furthermore, there may be gender and racial and/or ethnic disparities in how ESAs and transfusions are utilized. The change in one intervention, ESA use, also had an effect on a different intervention, transfusions. We do not know the reasons for the authors’ findings. Are they related to biases or potential differences in Hb levels in different cohorts? Regardless, transfusion medicine specialists should further explore possible health care disparities in our practice. In addition, we should recognize how incorporating evidence-based guidelines into reimbursement policies may be an effective way to bring out positive changes in patient care. (RH)