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Current advances in transfusion medicine 2020: A critical review of selected topics by the AABB Clinical Transfusion Medicine Committee

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CONFLICT OF INTEREST

CSC has disclosed professional relationships with Grifols, Terumo BCT, and Instrumentation Laboratory. NMD has disclosed financial relationship with Verax Biomedical. TG has disclosed professional relationship with Fresenius Kabi. JSR has disclosed financial relationships with Terumo BCT and Sanofi Genzyme. ESA, SB, CKH, JJ, PML, RAM, CM, MTP, HS, EKS, and MBP have disclosed no conflicts of interest.

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Abstract

Background: The AABB Clinical Transfusion Medicine Committee (CTMC) compiles an annual synopsis of the published literature covering important developments in the field of transfusion medicine (TM), which has been made available as a manuscript published in Transfusion since 2018.

Methods: CTMC committee members reviewed original manuscripts including TM-related topics published electronically (ahead) or in print from December 2019 to December 2020. The selection of topics and manuscripts was discussed at committee meetings and chosen based on relevance and originality. Next, committee members worked in pairs to create a synopsis of each topic, which was then reviewed by two additional committee members. The first and senior authors of this manuscript assembled the final manuscript. Although this synopsis is extensive, it is not exhaustive, and some papers may have been excluded or missed.

Results: The following topics are included: COVID-19 effects on the blood supply and regulatory landscape, COVID convalescent plasma, adult transfusion practices, whole blood, molecular immunohematology, pediatric TM, cellular therapy, and apheresis medicine.

Conclusions: This synopsis provides easy access to relevant topics and may be useful as an educational tool.

Keywords

cellular therapy; therapeutic apheresis; transfusion practices (adult)

1 | INTRODUCTION

The Clinical Transfusion Medicine Committee (CTMC) of the AABB was charged by its Board of Directors to write an annual review of significant developments in transfusion medicine (TM). The committee chose topics based on new developments in the field and/or recent interest within the transfusion community; however, not all topics could be covered. Medical literature for the year 2020 was dominated by the pandemic caused by the novel coronavirus SARS-CoV-2 (COVID-19), and although the majority of publications this year focused on COVID-19, other important developments occurred in areas such as adult and pediatric transfusion practices, molecular immunohematology, cellular therapy, and therapeutic apheresis.

2 | MATERIALS AND METHODS

CTMC members chose topics that were of significant interest and/or had high-impact developments. For each topic, an attempt was made to cover all literature published in English, scour news bulletins, and in some cases, solicit expert input to select manuscripts

that the committee members considered notable in the field; however, this was not a systematic review of the literature, and the risk of bias and strength of the evidence were not addressed. After committee consensus regarding which manuscripts to include, committee members with expertise in that field wrote a synopsis of the literature. These synopses were reviewed by two to three other committee members, and the final manuscript content is reviewed and assembled by the first and last authors of this manuscript.

3 | COVID-19: EFFECTS ON THE BLOOD SUPPLY AND REGULATORY LANDSCAPE

Key Points

- The 2020 pandemic impacted the supply and demand for blood components and led to temporary and permanent changes by the U.S. Food & Drug Administration (FDA) in blood donor eligibility criteria.

When the World Health Organization declared the pandemic a national emergency, there was an initial reduction in blood collections of approximately 30% due to canceled blood drives.[1,2] This decreased supply was matched by a decreased demand as surgeries were canceled.[2] Since the initial decline, there have been sporadic, geographical shortages in the blood supply secondary to an increase in COVID cases along with weather events.

In response to the pandemic, the FDA provided guidance that included revising the donor eligibility criteria.[3,4] In April 2020, the FDA released the guidance “Alternative Procedures for Blood and Blood Components During the COVID-19 Public Health Emergency” to address the urgent need for blood during the public health emergency.[4] The FDA also released guidance on reduced deferral periods and policies relating to human immunodeficiency virus (HIV) risk (August 2020), transfusion-transmitted malaria (April 2020), and revised recommendations regarding Creutzfeldt–Jakob Disease and Variant Creutzfeldt–Jakob Disease (August 2020) (Table 1).[5–7]

SARS-CoV-2 has been investigated for transmissibility by blood transfusion, and studies have demonstrated that the risk of transfusion-transmission is negligible.[8,9] The REDS Epidemiology, Surveillance, and Preparedness of the Novel SARS-CoV-2 Epidemic (RESPONSE) study is evaluating the incidence of SARS-CoV-2 RNA in asymptomatic blood donors and seroincidence of SARS-CoV-2 in blood donors to assist in epidemiologic and longitudinal studies of SARS-CoV-2.[10]

4 | COVID CONVALESCENT PLASMA

Key Points

- Blood centers manufactured and distributed COVID-19 convalescent plasma (CCP) under investigation of new drug (IND) applications, expanded access programs (EAP), and emergency use authorization (EUA) for use in COVID-19 patients and also performed SARS-2-CoV IgG antibody testing on blood donors for seroprevalance studies and to qualify donors for CCP collection.

- Despite widespread CCP use, its efficacy remains controversial, with possible benefit shown for high titer CCP used early in course of disease.
- A major limitation to evaluating CCP efficacy has been widespread use outside of randomized control trials in the US.
- Heterogeneity in CCP antibody measurement and recipient selection remains challenges.

4.1 | Access and regulatory guidance

As convalescent plasma for the treatment of COVID-19 has not yet been approved for use in the U.S., FDA guidance[11] confirmed that it is regulated as an investigational product and administered under IND or EUA; the latter continues to be updated as evidence emerges.[11] During spring 2020, the Mayo Clinic-led National Expanded Access Program (EAP) provided a mechanism for U.S. clinicians to administer CCP as an IND to hospitalized adult patients with moderate to severe COVID-19 disease. Without a control arm or centralized data collection on COVID patients who did not receive CCP, the analysis of EAP data was limited to comparison with previously published rates of COVID-19 mortality as well as transfusion-related adverse events. Reports indicated no unexpected increase in adverse events.[12,13] The EAP ended in late August 2020 with the announcement of EUA by the FDA for hospitalized patients with COVID-19.

Numerous blood donor centers in the US implemented SARS-CoV-2 IgG antibody testing of blood donors in spring/summer 2020 to assist in the recruitment and collection of CCP.[11,14–20] The FDA requires CCP to contain anti-SARS-CoV-2 antibodies; to ensure that the donors have sufficient antibodies, they must have had symptoms of COVID-19 and a positive test for COVID-19 or a reactive (positive) result in two different tests approved, cleared, or authorized by the FDA to detect SARS-CoV-2 antibodies. There is an additional recommendation to measure neutralizing antibody (nAb) titers if possible.[21] Published data report that 82%–93.5% of donors with prior SARS-CoV-2 infection have demonstrable IgG antibodies with a positive correlation detected between the level of SARS-CoV-2 IgG antibodies and nAb titers.[14–20] A time-dependent decline has been shown in both nAb titers and detectable IgG in CCP donors and the general population post-infection. This may impact the maximum time a recovered person may donate CCP and also has important implications for durability of immunity.[20]

4.2 | Retrospective STUDIES

Retrospective case–control studies with or without propensity matching have suggested potential efficacy for CCP.[22,23] Although these studies were limited by selection bias, some showed improved survival (adjusted hazard ratio in plasma recipients 0.13–0.89, $p = .027$).[22] Finally, a retrospective subgroup analysis of patients in the Mayo EAP showed a dose-dependent correlation between 30 days survival and anti-spike IgG antibody levels in administered CCP, but only among patients not receiving mechanical ventilation (relative risk 0.48–0.91 between high titer and low titer CCP recipients).[24]

4.3 | Randomized controlled trials

A limited number of randomized controlled trials (RCT) have been reported investigating the safety and efficacy of CCP in COVID-19 (Table 2).[25–29] The only trial to date that has shown positive effect after CCP administration enrolled patients early in the course of disease, prior to hospitalization or moderate/severe respiratory compromise.[29] Conversely, no improvement in symptoms or survival benefit has been proven for CCP in hospitalized patients with moderate to severe COVID-19 prior to CCP administration. In the largest RCT to date, the RECOVERY trial in the United Kingdom found no mortality benefit to high-titer CCP versus usual care, both in the full study population and in the subgroup of those not receiving invasive mechanical ventilation at randomization.[28]

One significant limitation of these trials is lack of standardization for evaluation of anti-SARS-CoV-2 antibody potency. Most studies used binding anti-spike protein antibody assays, which are correlated, to a degree, with nAb titer. However, due to lack of standardized calibrators, comparing titer results from one assay to another is problematic.

4.4 | Known and potential risks of CCP

The correlation between high burden of disease with COVID-19 and high titer binding anti-spike antibodies raises the question of whether antibody-dependent enhancement (ADE) may play a role in disease progression in a subset of patients.[30] Similarly, it is unclear if a subset of CCP donors may induce ADE in a subset of recipients. Furthermore, anti-interferon-1 autoantibodies have been associated with severe COVID-19 disease and it remains unclear whether transfused anti-INF-1 autoantibodies (or others) within CCP represent a risk to recipients.[31]

5 | ADULT TRANSFUSION PRACTICE

Key Points

- The TRIST trial evaluated a restrictive (7 g/dl) versus liberal (9 g/dl) red blood cell (RBC) transfusion strategy for hematopoietic stem cell transplant (HSCT) patients. The restrictive strategy was noninferior based on the primary outcome, health-related quality of life (HRQOL) at day 100, supporting a restrictive approach to transfusion in this population.
- The Haemorrhage Alleviation with Tranexamic Acid-Intestinal System (HALT-IT) trial was an international, randomized, placebo-controlled trial evaluating the efficacy of tranexamic acid (TXA) in patients with gastrointestinal (GI) bleeding. The primary endpoint, death from bleeding within 5 days of randomization, was not different between the TXA and placebo groups. However, thromboembolic events were greater in the TXA group, suggesting that TXA should not be routinely used to treat GI bleeding outside of a clinical trial.

5.1 | Trist trial

The Liberal Versus Restrictive Red Cell Transfusion Thresholds in Hematopoietic Cell Transplantation (TRIST) RCT evaluated a restrictive transfusion approach in a multicenter,

chronic transfusion-dependent patient population.[32] Investigators used a non-inferiority design and randomized 300 HSCT patients to receive RBC transfusion for hemoglobin levels below either 9 or 7 g/dl. TRIST used HRQOL at day 100 measured by the Functional Assessment of Cancer Therapy—Bone Marrow Transplantation (FACT-BMT) instrument. The restrictive transfusion strategy was noninferior to the liberal strategy with respect to patients' FACT-BMT scores at day 100. The restrictive group also received fewer RBC transfusions (mean 2.73 vs. 5.02). There was no difference in other secondary outcomes, including transplant-related mortality and bleeding.

Most of the large RCTs evaluating RBC transfusion thresholds include mortality as the primary outcome. This crude outcome measure, while important, requires a large sample size because death is infrequent over a short follow-up period and transfusion is one of many interventions and aspects of patient care in this complex patient population. The TRIST trial's sample size of 300 is smaller than many of the well-known RBC transfusion threshold trials, since detecting a clinically significant change in HRQOL in response to transfusion did not necessitate such a large sample size. Importantly, however, by using HRQOL as the primary outcome, TRIST has begun to address a critical question about the effect of transfusion on patient-centered outcomes. The study design involved two-unit transfusions rather than the single-unit transfusion approach that is now standard for hemodynamically stable inpatients. Despite this limitation, the TRIST trial provides much needed evidence in a key patient population and ultimately does not support the need for a liberal transfusion strategy.

5.2 | Halt-It trial

Antifibrinolytic agents, such as TXA, are commonly used to reduce bleeding in the setting of trauma, cardiac surgery, orthopedic surgery, and obstetric hemorrhage. Additionally, several small clinical trials have shown TXA reduces mortality in patients with upper GI bleeding, but were too small to assess the impact of TXA on thromboembolic adverse events. The HALT-IT trial was a large international RCT evaluating the effect of TXA on patients with GI bleeding.[33] Investigators enrolled over 12,000 patients in 15 different countries to receive TXA or placebo. The primary outcome was death from bleeding within 5 days of randomization, which was not different between the control or intervention groups (risk ratio 0.99, 95% confidence interval [CI] 0.82–1.18). Importantly, the TXA group had a higher rate of thromboembolic events compared with the placebo group. Overall, the findings from this study support the author's conclusion that TXA should not be used for treatment of GI bleeding outside of an RCT.

It is worth noting that the primary outcome of HALT-IT was changed during the trial from all-cause mortality to death due to bleeding within 5 days. The authors stated the change was due to a greater proportion of deaths occurring due to reasons other than bleeding than expected and because it was realized that TXA would not be expected to prevent re-bleeding after several days based on its short two-hour half-life.

6 | WHOLE BLOOD FOR TRAUMA RESUSCITATION

Key Points

- Low-titer group O whole blood (LTOWB) was adopted by more institutions, and studies continued to support its safety, with no detectable signal of deleterious effects.
- Multiple prospective and retrospective observational studies suggested that LTOWB may decrease mortality compared with component therapy in adult and pediatric trauma patients and those receiving massive transfusion; most studies were small and will require confirmation in RCTs.

There has been resurgence in the use of whole blood (WB) for trauma and massive transfusions. Advocates state that compared with component therapy, WB contains less anticoagulant, has less dilution of coagulation factors, and is logistically easier to manage.[34] Opponents have been concerned that even with LTOWB, ABO isohemagglutinins could have adverse effects on non-group-O recipients, and that platelets could be lost or become dysfunctional during leukoreduction or storage.[34] Over time, proponents of WB have countered these arguments by developing platelet-sparing leukoreduction filters,[34] showing equivalent safety of WB compared with components,[35,36] and with emerging evidence regarding its efficacy. Overall, WB continues to be validated as safe for adult and pediatric trauma. Recent observational data provides a rationale for current limited use with a trend toward superior outcomes.

6.1 | Safety data

Harrold et al retrospectively examined 77 trauma patients (23 group O, 54 non-group O) at two hospitals who received at least 4 units of LTOWB.[37] Laboratory markers of hemolysis were measured, and there were no statistically significant differences between the group O and non-group O recipients.

The authors cautioned that right-censoring from patients who died within 24 h of transfusion and were excluded could have biased the results. They used ABO antibody titer cutoff of 50, but noted that it would be interesting to see similar data from hospitals that use higher titers for their cutoff and allow unlimited numbers of units of LTOWB for non-group O recipients.

6.2 | Efficacy in adult civilian trauma

Retrospective and prospective observational studies in 2019–2020 have sought to associate WB use with improved outcomes in trauma patients when compared with component therapy. Data drawn from the Trauma Quality Improvement Database showed that trauma patients receiving WB had significantly decreased 24-hour and in-hospital mortality in both unadjusted and adjusted analyses.[38] In another study of 350 patients receiving prehospital or emergency department transfusions, 198 patients received WB and had significantly decreased risk of adjusted 30-day mortality.[39] A third study of 44 patients receiving WB in a massive transfusion setting showed a decrease in adjusted mortality at 24 hours and 28 days.[40]

These three studies are limited by the nature of retrospective or observational design. While all three attempted some degree of adjustment for physiology, low incidence of the outcome of interest limits the generalizability of their adjusted models. Nevertheless, it is compelling that all three studies point in the same direction toward a probable benefit for WB in trauma.

6.3 | Efficacy in pediatric trauma

Leeper et al. performed a propensity-matched analysis of injured pediatric patients who received component therapy (2013–2016, $n = 28$) versus LTOWB (2016–2019, $n = 28$).[41] The groups demonstrated no differences in in-hospital mortality, functional disability, hospital length-of-stay, or intensive care unit length-of-stay. However, the WB group had faster time to resolution of base deficit, lower post-transfusion INR, and lower amounts of RBCs, plasma, and platelets administered after adjusting for body weight.

No mortality benefit was seen in this study, which could be due to the fact that traumatic brain injury rather than hemorrhage was the predominant cause of death, and the relatively small amounts of WB used (median 15 ml/kg) could have been insufficient to yield significant benefit.

7 | MOLECULAR IMMUNOHEMATOLOGY

Key Points

- An array-based test for determining RBC, HLA, and HPA antigens was developed and validated using DNA samples from 7477 European blood donors and demonstrated 99.82% concordance with antigen types using other established methods.
- The genetic bases of several blood group systems were established: CTL2, PEL, and MAM. These systems were provisionally assigned the designations of IBST 039–041.

7.1 | Large-scale genotyping

RBC genotyping is possible by various test platforms,[42,43] and mass genotyping of patients and donors holds the potential for multiple improvements in clinical TM.[44] However, for genotyping platforms to be universally adopted, a test has to be comprehensive, scalable, cost-effective, and paired with a software that can provide automated interpretation.

An international Blood Transfusion Genomics Consortium employed an array-based technology to develop and validate an inexpensive and nearly comprehensive genotyping approach. The UK BioBank version 2 Axiom Array (UKBBv2 array) tests genetic variants known to predict most RBC antigens, human platelet antigens (HPA), and human leukocyte antigens (HLA), reportedly at a cost of about $40 per sample.[45] They tested DNA samples from 7477 blood donors in England and the Netherlands, and analyzed the data using versions of the published bloodTyper algorithm[46,47] and freely available Applied Biosystems HLA Analysis tool. Array-based typing was then compared with the known “clinical” antigen types, which were established by both serological and DNA-based testing methods. The investigators found an overall 99.82% concordance in 103,326 comparisons

across 28 RBC antigens, 10 HPA, and 6 HLA loci. Among the RBC antigen types, only 72 of 89,371 comparisons (0.08%) were discordant, and 33 of those (46%) were ultimately explained by erroneous serologic typing. The authors also attribute six discrepancies to newly identified alleles that they predict alter the expression of the antigens. Additionally, a total of seven ABO-related discrepancies were noted. Given the clinical significance of ABO-misinterpretation, the authors recommend typing for ABO using antibody-based methods.

To examine the clinical impact of the array-based genotyping, investigators retrospectively evaluated 3146 complex immunohematology cases (at least 3 RBC alloantibodies) and searched their pool of array-typed donors for matches. Compared with clinical typing alone, array-based typing yielded a 2.6-fold greater probability of identifying compatible donors. The benefit was greater for patients with rare combinations of antibodies, whereas for common antibody profiles, array-typed and clinically typed approaches were equivalent.

7.2 | New blood group systems

For a blood group antigen to be designated as a new blood group system, International Society of Blood Transfusion (ISBT) requires that the gene encoding the antigen must be identified and sequenced. In 2019, Omae et al. showed that mutations in prion protein (PrP, CD230) are responsible for the KANNO-negative phenotype.[48] Stenfelt et al. and Veldhuisen et al. identified mutations on B4GALNT2-encoded galactosyl transferase as the genetic basis of the Sd(a)-negative phenotype.[49,50] ISBT thus assigned KANNO and SID as ISBT 037 and ISBT 038 blood group systems, respectively.

In 2020, the genetic basis of three additional blood group systems was discovered. Vrignaud et al performed whole exome sequencing on seven serologically compatible individuals to identify mutations in *SLC44A2* gene.[51] Individuals from Moroccan ethnicity had a missense mutation in exon 14 of the gene, while the proband of European ancestry exhibited a large deletion of the gene. Using flow cytometric and western blot analysis, authors demonstrated that the antibody reactivity in the probands was targeted against the SLC44A2 (also known as CTL2) protein. The SLC44A2/CTL2 protein is highly expressed on human neutrophils and bears the human neutrophil antigen 3. ISBT has provisionally assigned the designation of ISBT 039 to the CTL2 blood group system.

Azouzi et al. established the genetic basis for the PEL-negative phenotype.[52] Using a combination of whole exome sequencing on four unrelated PEL-negative French-Canadian individuals, and a comparative proteomics approach to analyze the differential expression of proteins in RBC membranes from three PEL-negative and three PEL-positive individuals, the authors identified a large deletion of the *ABCC4/MRP4* gene as the basis of the PEL-negative phenotype. Using flow-cytometry, CRISPR-Cas9 technology, western blotting, and immunoprecipitation, they demonstrated that mutations in *ABCC4* are responsible for the absence of PEL antigen, and the specificity of the alloantibody seen in the PEL-negative individuals is directed against the ABCC4 protein. The PEL-negative individuals demonstrated impaired platelet aggregation in vitro; however, none showed easy bruising or increased bleeding. PEL blood group has provisionally been assigned ISBT 040 designation.

Thornton et al described the molecular basis of the high-prevalence MAM antigen.[53] Anti-MAM has been shown to cause severe hemolytic disease of the fetus and newborn. Whole exome sequencing on 10 MAM-negative individuals identified a variety of inactivating mutations in the *EMP3* gene, ranging from whole gene deletion to single exon deletion and nonsense mutation. A combination of approaches including short hairpin RNA, CRISPR-Cas9, and transfected cells demonstrated that the expression of MAM antigen is dependent upon intact *EMP3* gene. MAM blood group has provisionally been assigned ISBT 041 designation.

8 | PEDIATRIC & NEONATAL TRANSFUSION

Key Points

- The age of RBC products transfused in pediatric intensive care patients did not impact the incidence of new or progressive multiple organ dysfunction syndrome.
- Liberal blood transfusions compared with restrictive RBC transfusions in extremely low-birth-weight infants did not reduce the likelihood of death or disability at 24 months of corrected age.
- A prophylactic platelet transfusion threshold of 25×10^9/Ldid not increase the likelihood of bleeding in preterm neonates over that of 50×10^9/L.

8.1 | RBC trials

The Age of Blood in Children in Pediatric Intensive Care Unit Trial published by Spinella et al.[54] found that the age of RBCs did not impact the incidence of new or progressive multiple organ dysfunction syndrome including mortality in critically ill children (3 days–16 years). Subjects were followed for up to 28 days or until discharge or death, whichever came first. The primary objective of the trial was to determine whether fresh (≤7 days old) RBCs were superior to standard issue RBCs, and no significant differences were found in 1538 randomized patients. Seven-hundred and twenty-eight subjects who received fresh and 733 who received standard issue RBCs were included in the primary analysis. The median storage duration of RBCs was 5 days (IQR, 4–6 days) in the fresh and 18 days (IQR, 12–25 days) in the standard issue group ($p < .001$). New or progressive multiple organ dysfunction was found in 20.2% of the fresh versus 18.2% of the standard issue groups (unadjusted absolute risk difference 2%, 95% CI, 2.0% to 6.1%, $p = .33$). The prevalence of acute respiratory distress-syndrome was 6.6% in the fresh versus 4.8% of the standard issue group. Intensive care unit mortality was 4.5% in the fresh versus 3.5% in the standard issue group ($p = .34$).

The Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low Birth-Weight Infants Trial published by Franz et al.,[55] demonstrated no statistical difference between outcomes based on receiving liberal or restrictive RBC transfusion therapy in extremely low-birth-weight infants (<1000 g at birth). The incidence of transfusion was 81.3% in the liberal versus 60.5% in the restrictive group. The RBC transfusion threshold varied by the weight of the patient. The median volume transfused was 40 ml versus

19 ml. The mean weekly hematocrit was 3% points higher with the liberal threshold. The primary outcome, defined as death or neurodevelopmental impairment by 24 (+/−1) months of corrected age, was not statistically different between the groups ($p = .72$), nor were the secondary outcomes of death, cognitive deficit, or cerebral palsy. No differences were observed between those that developed necrotizing enterocolitis requiring surgical intervention, bronchopulmonary dysplasia, or treatment for retinopathy of prematurity. Liberal blood transfusions compared with restrictive transfusions did not reduce the likelihood of death or disability at 24 months of corrected age.

8.2 | Platelet trial

The Platelets for Neonatal Thrombocytopenia trial previously reported a 7% absolute-risk reduction using a prophylactic transfusion threshold of 25×10^9/L compared with 50×10^9/L for major bleeding and/or mortality in preterm neonates.[56] Fustolo-Gunnink et al.[57] assessed whether the findings were heterogeneous across different subpopulations. Neonates were categorized into 4 risk quartiles based on their baseline risk of major bleeding and/or death ($N = 653$). A total of 146 neonates died or developed major bleeding. The 25×10^9/L threshold was associated with an absolute-risk reduction in all risk groups varying from 4.9% in the lowest risk group (those predicted least likely to experience major bleeding and/or death) to 12.3% in the highest risk group. The authors concluded that the 25×10^9/L transfusion threshold should be adopted for all neonates.

9 | CELLULAR THERAPY

Key Points

- Allogeneic chimeric antigen receptor (CAR)-NK-cells were successfully used to treat CD19-positive lymphoid tumors without significant toxicity.
- Anti-CD19 CAR-T cells were successful in treating mantle cell lymphoma resistant to Bruton Tyrosine Kinase (BTK) inhibitors.

9.1 | CAR-NATURAL killer (NK) cells in CD19-POSITIVE lymphoid tumors

Autologous derived T-cells engineered to target CD19-positive cells have emerged as a promising new treatment option for patients with B-cell malignancies. This has led to the FDA approval of two CAR T-cell products.[58,59] CAR T-cell therapy, however, has numerous limitations. Typically, it requires a patient with relapsed or refractory disease to forego lymphodepleting chemotherapy for a period in order to undergo autologous collection of mononuclear cells, which then require complex and time-consuming manufacturing.

Liu et al performed a phase-1/2 clinical trial to test the safety and efficacy of engineered NK cells that were derived from an allogeneic source.[60] NK cells from cord blood were transduced with a vector expressing genes that code for anti-CD19 CAR, interleukin-15 to enhance in vivo expansion and persistence, and an inducible caspase 9 to be deployed as a safety switch. Of the 11 patients with relapsed or refractory B-cell malignancies (CLL and non-Hodgkin's lymphoma) who were infused with ex vivo expanded anti-CD19 CAR NK-cells, 8 (73%) patients showed a rapid clinical response with 7 (64%) patients exhibiting a complete remission. No significant toxicities attributable to NK cells were noted in these

patients. Durability of response after CAR NK-cell therapy could not be assessed, as the patients underwent post-remission treatment at the discretion of treating physicians.

While patients in this trial received freshly manufactured CAR NK-cells, the successful use of allogenic derived NK cells creates the possibility of these cellular therapy products being stored and readily administered to a patient in need.

9.2 | CAR-T cells in mantle cell lymphoma

Patients with mantle cell lymphoma resistant to BTK inhibitors have a very poor prognosis. The ZUMA-2 clinical trial was a multicenter, single-arm, phase 2 trial evaluating the safety and efficacy of KTE-X19 in adult patients with refractory or relapsed mantle cell lymphoma who were previously treated with BTK inhibitors.[61] KTE-X19 is an autologous derived in vitro expanded anti-CD19 CAR T-cell therapy. Of the 74 patients enrolled, 68 received KTE-X19 CAR T-cell therapy. Analysis of primary efficacy in 60 patients demonstrated that 93% had an objective response and 67% exhibited complete remission. In an intention-to-treat analysis of all enrolled patients, 85% demonstrated objective response and 59% entered remission. At 12 months, the progression-free and overall survival rates were 61% and 83%, respectively. The authors did report serious adverse events, including grade 3 or higher cytokine release syndrome and neurologic events in 15% and 31% of the patients, respectively. Other serious side effects included cytopenias and infections.

While the trial showed that the majority of patients with relapsed or refractory disease demonstrated a clinical response and went into remission, serious adverse events like those reported with use of CAR T-cell therapies were also noted. The FDA approved KTE-X19 in July 2020.[62]

10 | THERAPEUTIC APHERESIS

Key Points

- The study examining plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (PEXIVAS) demonstrated that plasma exchange did not reduce the incidence of death or end-stage kidney disease (ESKD) among patients with severe disease. This prompted the *Journal of Clinical Apheresis* (*JCA*) Special Issue Writing Committee to release an updated fact sheet changing the category recommendation from I to II.
- A multicenter, double-blind, randomized, placebo-controlled trial of Alzheimer's disease management by plasma exchange with albumin replacement and intravenous immunoglobulin dosing (AMBAR) demonstrated that plasma exchange could slow cognitive and functional decline in mild-to-moderate Alzheimer's disease.

10.1 | PEXIVAS study

The results of the Plasma Exchange and Glucocorticoid Dosing in the Treatment of ANCA-Associated Vasculitis (PEXIVAS) study were recently published.[63] This international RCT

enrolled 704 patients with ages 15 years or older from 95 centers in 16 countries. It is the largest study published to date on the role of therapeutic plasma exchange (TPE) in ANCA-associated vasculitis (AAV). The 2 × 2 factorial study design compared TPE versus no TPE and standard versus reduced-dose steroid regimen on the primary composite outcome of ESKD or death in patients with AAV. The study concluded that TPE did not reduce the incidence of ESKD or death and that a reduced-dose regimen of glucocorticoids was non-inferior to a standard dose regimen. The study included 191 patients with pulmonary hemorrhage (61 severe) and did not observe a beneficial treatment effect in this subset of patients.

There are at least two important limitations of this study that may influence the interpretation of the results.[64] First, kidney biopsy was not required for trial participation. In a chronic disease that leads to irreversible kidney scaring, the effect of TPE on the subset of patients with acute disease that may be more responsive to possible short-term improvement in kidney function, as shown in the MEPEX study,[65] remains unknown. Second, the trial was not designed to assess the role of TPE in patients with pulmonary hemorrhage and may have been underpowered to detect a difference in this subset of patients.[66–68]

Based on the results of this study, the *JCA* Special Issue Writing Committee released an updated fact sheet in August 2020 incorporating this newly available evidence.[69] The category recommendation for rapidly progressive glomerulonephritis (RPGN) and Cr ≥5.7 mg/dl in the setting of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), or renal-limited vasculitis (RLV) was changed from category I to II to support use of TPE in select patients with biopsy-proven acute RPGN. Diffuse alveolar hemorrhage (DAH) in the setting of AAV remained a category I indication for TPE due to the life-threatening nature of this complication and the lack of alternative treatments.

10.2 | AMBAR study

The results of the Alzheimer's Management By Albumin Replacement (AMBAR) study were recently published.[70] This phase 2b/3, double-blind trial randomized 347 Alzheimer's disease (AD) patients from 41 sites in the United States (22) and Spain (19). Subjects between 55 and 85 years of age with a probable diagnosis of mild-to-moderate AD (Mini-Mental State Examination [MMSE] score of 18–26) and receiving stable doses of acetylcholinesterase inhibitors and/or N-methyl-D-aspartate receptor antagonists were assigned to one of three TPE treatment groups with varying doses of albumin and intravenous immune globulin (IVIG) or a placebo group that included sham TPE. The primary endpoint assessed changes from baseline to 14 months in two measures: the AD Cooperative Study-Activities of Daily Living (ADCS-ADL) and the AD Assessment Scale-Cognitive Subscale (ADAS-Cog). The study concluded that the TPE-treated patients had significantly less decline compared with placebo (ADCS-ADL, 52% less decline, $p = .03$; ADAS-Cog, 66% less decline, $p = .06$). In subgroup analysis, there were no significant differences between the three TPE treatment groups, nor between those subjects with mild AD (MMSE 22–26) versus the placebo group. While these results are encouraging, future studies should further investigate the mechanism by which AD progression was slowed, the

necessity of IVIG, the impacts of various demographic and AD parameters on treatment response, and the durability of treatment response after cessation of therapy.[71]

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Abbreviations:

AAV	ANCA-associated vasculitis
AD	Alzheimer's disease
ADE	antibody dependent enhancement
ANCA	anti-neutrophil cytoplasmic antibody
BTK	bruton's tyrosine kinase
CAR	chimeric antigen receptor
CCP	COVID convalescent plasma
CTMC	clinical transfusion medicine committee
DAH	diffuse alveolar hemorrhage
EAP	expanded access protocol
ESKD	end-stage kidney disease
EUA	emergency use authorization
FDA	food & drug administration
GI	gastrointestinal
GPA	granulomatosis with polyangiitis
HLA	human leukocyte antigens
HPA	human platelet antigens
HRQL	health related quality of life
HSCT	hematopoietic stem cell transplant
IND	investigational new drug
INR	international normalized ratio
ISBT	international society of blood transfusion
IVIG	intravenous immunoglobulin

LTOWB	low-titer group O whole blood
MMSE	mini-mental state examination
NK	natural killer
RCT	randomized controlled trial
RLV	renal-limited vasculitis
RPGN	rapidly progressive glomerulonephritis
TM	transfusion medicine
TPE	therapeutic plasma exchange
TQIP	trauma quality improvement database
TXA	tranexamic acid

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TABLE 1

Select changes by the US Food & Drug Administration in donor deferral criteria designed to reduce the risk of transmission of infectious diseases

Infectious disease	Donor category	Previous deferral[a]	Current deferral[a]
HIV[5]	Has exchanged sex for money or drugs	Indefinite	3 months
	Non-prescription injection drug use	Indefinite	3 months
	History of receiving allogeneic transfusion	12 months	3 months
	Nonsterile skin penetration with equipment contaminated with allogeneic blood or body fluids (e.g. needlestick)	12 months	3 months
	Men who have had sex with men	12 months	3 months
	Sexual contact with a person who has tested positive for HIV, or is at high risk of HIV infection (MSM, individuals who have exchanged money/drugs for sex, individuals who used non-prescription injection drugs)	12 months	3 months
Malaria[6]	Travel to a malaria-endemic area	12 months	3 months
CJD and variant CJD[7]	Has a blood relative diagnosed with familial CJD	Indefinite	Permanent

Abbreviations: CJD, Creutzfeldt–Jakob Disease; HIV, human immunodeficiency virus; MSM, men who have sex with men.

[a]Months since the most recent event, contact, or departure from a geographic area.

TABLE 2

Select randomized controlled trials of COVID-19 convalescent plasma

	Antibody titer threshold	Conclusion
Adults hospitalized with severe COVID-19 pneumonia		
Li et al.[25]	1:640 or greater anti-RBD	No effect on clinical improvement within 28 days
Simonovich et al.[26]	>1:400 anti-spike	No effect on 30 day mortality
Agarwal et al.[27]	None	No effect on progression or mortality at 28 days
RECOVERY group[28]	≥1:100 neutralizing[a]	No effect on 28 day mortality
Adults with early COVID-19 disease		
Libster et al.[29]	>1:1000 anti-spike	0.20–0.81 relative risk reduction for severe respiratory disease

Abbreviations: ELISA, enzyme-linked immunosorbed assay; RBD, receptor binding domain.

[a]IgG ELISA with sample to cutoff ratio of ≥6.0, previously shown to be associated with neutralizing antibody titers ≥1:100.