

Lessons learned in the collection of convalescent plasma during the COVID-19 pandemic

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Background The lack of definitive treatment or preventative options for COVID-19 led many clinicians early on to consider convalescent plasma (CCP) as potentially therapeutic. Regulators, blood centres and hospitals worldwide worked quickly to get CCP to the bedside. Although response was admirable, several areas have been identified to help improve future pandemic management.

Materials and methods A multidisciplinary, multinational subgroup from the ISBT Working Group on COVID-19 was tasked with drafting a manuscript that describes the lessons learned pertaining to procurement and administration of CCP, derived from a comprehensive questionnaire within the subgroup.

Results While each country's responses and preparedness for the pandemic varied, there were shared challenges, spanning supply chain disruptions, staffing, impact of social distancing on the collection of regular blood and CCP products,

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and the availability of screening and confirmatory SARS-CoV-2 testing for donors and patients. The lack of a general framework to organize data gathering across clinical trials and the desire to provide a potentially life-saving therapeutic through compassionate use hampered the collection of much-needed safety and outcome data worldwide. Communication across all stakeholders was identified as being central to reducing confusion.

Conclusion The need for flexibility and adaptability remains paramount when dealing with a pandemic. As the world approaches the first anniversary of the COVID-19 pandemic with rising rates worldwide and over 115 million cases and 2.55 million deaths, respectively, it is important to reflect on how to better prepare for future pandemics as we continue to combat the current one.

Key words: blood collection, blood component production, blood donation testing, blood safety, plasma, transfusion medicine.

Introduction

Throughout human history, mankind has struggled with and died from many pandemics. Various organizations, including the World Health Organization (WHO), have developed guides to help inform national and international pandemic preparedness [1]. Echoes of past epidemics, including the flu pandemic of 1918, are seen today as the world struggles with this new pandemic, while waiting for a vaccine and a cure. The lack of definitive treatment or preventative options for coronavirus disease 2019 (COVID-19) led many early on to consider COVID-19 convalescent plasma (CCP) as potentially therapeutic. Convalescent plasma (CP) had been used for over a century on a smaller scale to treat a variety of infections (airborne, droplet or vectorially transmitted), including SARS-CoV and MERS-CoV. However, the COVID-19 pandemic marked the first time where CP was deployed on a massive scale. Blood centres navigated the obstacles successfully to bring CCP to patients, collecting CCP even as regulators scrambled to provide a regulatory framework for the collection, manufacturing, labelling, transfusion and reimbursement, and while scientists tried to address fundamental questions relating to the immunopathogenesis and testing for a novel virus, with the main goal of providing patients an effective and validated new therapy.

COVID-19 highlighted many areas for improvement in pandemic management from the perspective of supply and demand of both traditional blood products as well as provision of novel therapeutics. The challenges (and concomitant lessons) span from donor qualification, to supply chain maintenance, staffing and safety and to the testing and labelling of products. The current success is largely due to the flexibility and open communication between donor centres, hospitals, governmental

administrators and regulators throughout the pandemic as new information required ongoing development and refinement of policies and practices. For many countries, coordination of the response has been lacking or ineffective contributing to disjointed efforts, hoarding of supplies and public confusion. In others, coordinated messaging facilitated donor education, encouraging testing and donation.

Materials and methods

The International Society of Blood Transfusion (ISBT) established a Working Group (WG) with members from all 6 WHO regions, to address existing practices and provide recommendations on the collection and use of CCP. A subgroup was assigned to draft a manuscript to document the lessons learned pertaining to CCP with a view to offer guidance for future pandemics. This manuscript was drafted as a companion to earlier publications on procurement and clinical use of CCP by the same group [2, 3].

Clinical trials, compassionate use and support from regulators

Consider convalescent plasma is still considered an investigational therapy, and in many countries, its use is restricted to research (clinical trials). While not unique to CCP, regulators actively encourage clinical trials for unproven therapies to provide strong evidence of efficacy [4–6]. By contrast, compassionate use treatment and observational studies may facilitate access, but result in slower scientific yield. The pandemic highlighted the ethical challenge of reconciling compassionate and research use of an investigational product. Compassionate use, by diverting patients eligible for inclusion in clinical trials,

impeded trials and slowed quality data gathering. The counterpoint is how to defer treatment in favour of research when an investigational product has already been shown to be safe, exhibits some signals of efficacy, and where a viable alternative to treatment is not available [7]. Understandably, the lack of treatment options for COVID-19 drove early enthusiasm for CCP and pressure for easy access. In countries where both clinical trials and compassionate use were allowed, trial enrolment was hampered by ease of acquiring CCP through compassionate use which bypassed the risk of a patient being randomized to a non-CCP arm. In future epidemics, clinicians, researchers, ethicists and policymakers will likely continue to struggle balancing access to a promising therapeutic (the need of the one) with gathering quality data through trials that restrict access (the needs of the many).

Health authorities and clinicians should work together during pandemics to accelerate authorization of clinical trials, especially for therapies like CP whose parent component, plasma, is well-known to medicine and has a well-understood safety profile. Clinical trials require a major investment in time and resources, which is especially true during a global health crisis. Infection is often waning by the time trials get underway using existing authorization processes, leaving studies underpowered to test their primary outcomes, as evidenced by the 2014–2016 West African Ebola outbreak [8] and SARS-CoV-2 pandemic [9]. Too many trials may prove to be as detrimental as too few, tying resources to studies that are unlikely to achieve targeted outcomes, while fewer protocols across many collaborating sites might otherwise have succeeded.

Failure to determine whether CP can be an effective early phase therapeutic during pandemics would be a lost opportunity, impacting future pandemics [10]. A proposal for future pandemic management is to authorize a group of internationally recognized experts, key regulators and related professional organizations to oversee an emergency pandemic clinical trial protocol. This protocol would – ideally – be developed ahead of the next global health crisis, thus enabling rapid, harmonized deployment across multiple sites and countries. Such a protocol would serve to standardize key questions that need to be addressed, along with the data collection structure to follow. This would encourage investigators to coordinate trials more effectively, allowing rapid execution of large, multi-site trials, and help standardize the collection of key data elements spanning infectivity and recovery, treatment and testing, safety, dosing and overall efficacy of potential therapeutics.

Ongoing involvement of regulatory authorities would be paramount. All key stakeholders, including

biotechnology companies, blood suppliers, researchers, healthcare providers and international peers, would attend frequent joint meetings with their respective regulatory agencies to allow for quick, conclusive and prompt actions. The framework must also include the provision for allocation of national budgets to help early funding.

The pandemic has already spurred innovative approaches to data gathering. These include pairing of trials that were initiated independently of each other to accelerate enrolment goals or pooling of data where independent enrolment was suboptimal, such as the ‘COMPILE’ study to pool data from ongoing and discontinued RCTs pertaining to CCP [11], and analysis from several countries using Bayesian statistical methodologies to determine the effect of CCP on clinical status as the primary outcome, including the effect of various covariates. Similarly, some efforts have been made to coordinate international clinical trials, including the REMAP CAP study [12] of CCP efficacy in critically ill patients and the involvement of hospitals in the US and Brazil in the Canada-led CONCOR-1 trial [13] in moderately ill patients treated within 24 h of hospital admission. Other ongoing, multinational studies are underway. The expectation is that more uniform data gathered globally will enable better answers that will ultimately drive improved patient outcomes.

Donor centre logistical challenges

SARS-CoV-2 highlighted areas for improvement in supply chain management both of traditional blood products as well as novel therapeutics. Blood centres, already struggling with low blood inventories and declining community interest in donation, embraced the challenges to establishing a new blood product line with unique (and often dynamic) donor qualification and product labelling requirements.

CCP competes for the same limited resources as blood components and products derived from plasma fractionation, impacting the supply of all. Donor centres rely on a ‘just in time’ delivery model for many consumables (e.g. personal protective equipment – PPE, bags and test tubes), so are susceptible to supply chain disruptions (shipment delays); increased utilization of supplies; and increased demand for supplies not routinely used in pre-pandemic operations.

Blood centres must be considered as part of the critical infrastructure, taking active part in coordination efforts, especially at local levels. Clear and frequent communication is essential. They must be able to communicate critical changes in their supplies and availability of all blood products including CP to governmental organizers and hear how hospitals will be adjusting their service levels that might impact blood inventory requirements.

Managing frontline staff exposure and use of personal protection equipment (PPE)

Frontline workers not only faced potential exposure to COVID-19 in their personal lives, but also increased occupational risk of exposure given interactions with each other and the public (donors). Adequate staffing was especially challenging during peak infectivity as staff become infected, are quarantined following exposure and miss work to care for affected family members or due to fear of becoming infected. Feelings of stress, fatigue, depression and helplessness are common for all staff throughout the pandemic, especially when given new tasks, extra shifts or redeployed. It is important for staff to feel heard, protected and provided frequent, active communications about any changes.

In most countries, the lack of a stable supply of PPE was an ongoing challenge even as guidance on their usage changed. The use of hand sanitizer, masks and other PPE was ultimately adopted everywhere. However, the lack of adequate supplies forced many to make their own supplies and/or repurpose single-use PPE, particularly in low- and middle-income countries (LMICs) where challenges in finding sufficient PPE to protect staff (let alone the public) were common, adding to staff and donor stress. Referenced policies should be created to provide staff with the most up-to-date information on any PPE workarounds, including how to make, clean or how long to reuse them.

Collection space limits, access to apheresis equipment and CCP donor room management

Social distancing forced the modification of the collection environment, reducing significantly collection capacity, as fewer whole blood beds and apheresis machines could be placed within a given area to guarantee at least 2 metres (6 feet) between donors. Mobile drives were severely limited as businesses closed, restricted outside access or adopted remote workforce policies. Plasma collection was especially challenging for LMICs as whole blood was the primary mechanism to collect both regular plasma and CCP and without or with limited apheresis equipment, collecting sufficient plasma and CCP from the limited donor pool was difficult.

Additional spacing was not necessary for CCP collection, although donors and staff occasionally expressed concern about having potentially infectious 'recovered patients' present. This was especially true initially when data were lacking on the kinetics of infection. In response, some centres allocated separate rooms or collected CCP outside standard working hours.

Recruiting CP donors

Donor recruitment during a pandemic is challenging. Studies on what motivates convalescent individuals to donate CP are limited. Most likely they give out of altruism, as relief or gratitude for surviving, as a directed donation for a loved one, or for knowledge about their immunity. Multiple pathways must be deployed to identify and maximally recruit CP donors. Hospitals, clinics, clinicians, testing laboratories, government officials and public health departments are valuable partners. Recovered patients should be encouraged to donate several times, especially at the beginning to help bolster the inventory. If CP donors donate more frequently or have modified suitability criteria (e.g. lower haemoglobin requirements), additional medical oversight will be needed to ensure donor safety.

In exchange for recruiting donors, partners may insist that some or all collections be dedicated to a specific hospital, physician's group, geographic location, research protocol and/or patient or patient group. While a great source of donors, this adds much complexity and stress. The overall management follows the high-touch model of a specialized donation programme rather than the lower-touch model of traditional allogeneic blood donation. To scale collections and maximize resources, blood centres need to apply as many routine blood collection policies as possible. The high-touch model, however, likely will be critical early on.

While Healthcare and public health authorities work to recruit donors, it is important to maintain safeguards to prevent unauthorized access to or improper use of protected information. Maintaining donor trust and attention to donor safety and privacy concerns is key to convincing the community to become regular CP donors. Weeks of negotiation might be needed before recruitment begins, with the development of additional questionnaires, policies, and talking points. Workflows should be created to identify which parts of the recruitment process are handled by which blood centre staff versus any potential recruiting partners. A standardized check list of pre-requisite information and approved testing is helpful. Once qualified, the recruitment team must have the infrastructure and flexibility to work around donor's schedules and ability to travel to minimize delays.

As soon as reliable patient testing is available, recruitment should focus to recovered individuals with documented presence of the infectious agent positive, such as the nasopharyngeal swab real-time polymerase chain reaction (RT-PCR) test for COVID-19. Consistent and ongoing education and messaging about the need to donate across all media platforms is needed to drive

donors to self-recruit directly with the blood centre to further increase the inventory. In the end, unique solutions may be needed to optimize local opportunities and demands.

Media partners and pressures

It is important to utilize all media platforms in recruiting donors: social media, messaging applications, billboards, national papers, news programmes and radio/TV. Each is uniquely positioned to reach different groups. National promotions with coordinated messaging can be very effective particularly with use of national leaders and prominent persons as spokespersons. A clear message however is not always a nuanced message. CCP was often touted as a 'cure' despite the lack of peer-reviewed evidence, increasing general demand for CCP even as clinical trials were struggling to enrol patients.

Donor/product qualification

COVID-19 is not considered transfusion-transmitted [14]; however, CCP must follow all the national requirements to prevent infection common for all blood products. During future pandemics, where transmission mechanisms might be unknown, pathogen reduction should be considered [15].

The definition of what constitutes clinical recovery and, consequently, CP donor acceptance will evolve as new tests and data become available. International societies/organizations (ISBT, AABB, WHO), scientists, publishers and the media are important in rapidly disseminating and releasing policies and research results. For example, over the course of the first few months of the pandemic, WHO simplified the criteria for discharge from isolation for COVID-19 [16] and acknowledged that residual cough or loss of taste/smell could linger while still waiting for results on residual live viral shedding, roughly 20 days (range 6–59) [17–19] and after 28 days [20] for SARS-CoV-2, respectively. Antigen-based rapid diagnostic tests, while faster, cheaper and easier to perform than RT-PCR, are frequently less sensitive. Saliva sampling for RT-PCR may be attractive alternatives to nasopharyngeal swabs for respiratory viruses, although are not without limitations [21].

The US FDA currently recommends a nAb titre $\geq 1:160$ and $\geq 1:80$ for CCP as optimal and acceptable for use, respectively, although it is still unclear which antibody specificities provide the best neutralizing potential, what minimal titre levels are optimal, how long nAbs titres in donors remain at therapeutic levels, and which surrogate assays provide the best answers to these questions. Testing with live viruses – viral neutralization tests (VNT) or

plaque reduction neutralization tests (PRNT) – remains the gold standard to detect and measure nAbs. However, they require sophisticated containment facilities, highly trained personnel, are time-consuming (4–7 days), produce live pathogenic virus and not available in many parts of the world.

Another potential solution uses pseudotyped lentiviruses (lentivector plasmids) [22], which are extensively modified to reduce pathogenicity and express a luciferase reporter gene for easy detection. The method is sensitive, reproducible, faster (1–2 days) and requires only a biosafety level 2 laboratory. Several studies have shown good agreement between the various nAb methods [20, 23, 24]; however, no formal standardization exists, limiting result comparisons across platforms.

Ab titres may quickly wane, increase as the immune response matures or remain stable for months [25]. Testing each donation via a quantitative assay as a release test is the only way to provide quality assurance for CP [26] and determining optimal CP dosing. While important for dosing and outcomes analysis, large scale nAb testing as a CP release test is not possible. Other assays must be utilized, such as ELISA- and CLIA-based assays, commonly employed for blood centre testing. Several organizations (ISBT, AABB, BEST, ASCP) are currently working collaboratively to determine correlations. There is a good agreement with some but not all nAb titres and ELISA or CLIA tests [19, 27], with variation depending on antigen source (spike or nucleocapsid antigens). SARS-CoV-2-specific IgG titre $>1:1000$ and $>1:640$ has shown promise in two early trials [28, 29].

Recently, the FDA issued new updates about the emergency use authorization (EUA) to 'limit the authorization to the use of high titre COVID-19 convalescent plasma for the treatment of hospitalized patients early in the disease course and to those hospitalized with impaired humoral immunity and cannot produce an adequate antibody response' defining a number of tests to be used for CCP screening, with a minimum qualification test criteria to be followed [30]. With this new FDA guidance, units with low antibody titres should be reliably identified as soon as possible and either relabelled as frozen plasma or sent for plasma fractionation.

Triaging donors based on symptoms, recovery time and test results

NAbs have a peak detection in severe patients 10–15 days after infection, with higher titres seen in more severe than mild or asymptomatic cases [19]; therefore, recently recovered symptomatic patients confirmed positive via a validated nasopharyngeal RT-PCR are ideal CCP donors, with higher detectable nAb estimates. Donors who are 'presumed

positive' are the next best donors (had symptoms and a strong epidemiologic link). In The Netherlands and South Africa, approximately 40% and 16% of CCP collections, respectively, have no SARS-CoV-2 antibody (Vrieling and Vermeulen, personal communication). Donors who have had no symptoms and who have not had a diagnostic test are least likely to have high titre nAbs and require additional testing with different methodologies for confirmation. These donors have limited usefulness as CP donors (at great expense) unless a significant percentage of the overall community has been infected. The lack of sensitive and specific assays may result in providing products with unknown efficacy, confounding outcomes analysis. It is important to freeze samples until suitable tests are available for retrospective testing.

Qualifying donors and assessing donor suitability

CP donors are more likely to be first time donors, requiring more assurances and education. They should meet the same qualifications as regular plasma donors, including HLA and possibly HNA antibody screening in multiparous women, to ensure the greatest overall safety profile [31]. Exceptions to allogeneic criteria may be necessary especially for early or frequent donors and will require additional policies and medical oversight. Symptoms like increased post-donation fatigue, excessive vasovagal reactions, declining haemoglobin levels and increased bruising may need to be monitored to ensure donor safety.

Managing donor questions about immunity and reinfection

Specific questions about CCP donor safety centre around either the implications of donor testing regarding protection against future infection, or the adverse effect of donation on a donor's immunity. The relative roles of humoral and cellular immunity in protection from recurrence of any infection are largely unknown as is any definitive predictive statement linking antibody titre or specificity with future infection or reinfections.

Recurrence risk is related to host factors, mutations in the virus and therapies that have been received. While COVID-19 persisted in patients with B-cell deficiency-related hypogammaglobulinaemia, despite a robust anti SARS-CoV-2 T-cell response [32], and while high-frequency plasma donation is associated with depletion of a variety of plasma proteins including plasma immunoglobulins [33, 34], there are no current data suggesting an increased infectious risk or other negative health effect relative to short term (2–6 months) increased apheresis donations of any type.

Donors were also afraid donating CP would permanently reduce the level of protective antibodies in their body. Current US and European regulations require periodic determination of IgG level in high-frequency plasma donors to monitor loss, although it is unclear if such testing is needed for CP donors who might donate at higher frequency for a limited number of months. SCANDAT may eventually provide an answer relative to short- and long-term CCP donor health [35], as could haemovigilance programmes. As we understand more about COVID-19, it will help to update a common, readily accessible repository where donors can be directed to answer their questions and concerns.

Inventory management; how to provide units with short supplies?

CP is a limited resource. The blood centre and the transfusion service are ultimately guardians of the blood supply, distributing or issuing components, respectfully, following common principles of patient care, transfusion medicine best practice, distribution guidance by national regulatory agencies and/or dosing regimens by study protocols and peer-reviewed literature. One must always be consistent in 'not treating physician's anxiety but treating patient's needs'.

Some places will triage CP inventory with a limited number of transfusion specialists especially when inventory is low. Others will provide CCP only within the context of a clinical trial or after ethics committee approval to maximize the effectiveness signal and minimize demand. Others – especially where compassionate use is high – will try to ensure as many patients as possible have access to at least one unit of CCP. Each solution has its pros and cons. Concerns about restricting access to minority groups should be considered, regardless of which method is used. Good communication between expert prescribing and BTS physicians is key to developing and updating clinical guidelines and order sets.

Exclusive use of group AB CP for all patients is not possible; therefore, ABO isogroup units should be the first choice for transfusion. When ABO compatible CP is unavailable and transfusion is recommended, consider using units with low titre ABO isoagglutinins (≤ 64 – ≤ 100) or that are 'least incompatible' (i.e. B plasma to an AB patient).

Therapeutic value

The therapeutic efficacy of CP can only be established in well-controlled clinical trials with properly consented patients using products that are well-characterized. Early

reports have shown that very early administration (within 72 h after the onset of symptoms) in high-risk patients reduce significantly the frequency of disease worsening and hospitalization [36], or decrease in mortality when high titre nAb CCP was transfused [37]. Data have also shown that once patients start producing nAbs [38] or developing end organ damage [39], CCP transfusion is not beneficial, and several CCP trials in patients well into their disease course have been stopped for futility. Without widespread access to reliable and correlated testing, data collection on efficacy and dosage will be hampered.

Several clinical trials involve maintaining retention samples from the donor or CCP hoping that analyses of the samples mapped to specific patient outcomes may allow the identification of all therapeutic molecules and their optimal doses, whether it be anti-RBD (receptor binding domain) or nAb titres, cytokines or other immunomodulatory molecules. Preferred Ab classes and epitope specificities promoting antibody-dependent cellular cytotoxicity (ADCC) or other immune defence mechanisms should also be investigated to optimally characterize CP or hyperimmune globulin in the future. Although previous experience with influenza [40] suggests that hyperimmune globulin could eventually provide a more consistent and higher potency therapy compared to CP, the additional manufacturing and qualification required for hyperimmune globulin delays initial availability.

Conclusion

The pandemic is not over, and the response is still evolving. Many questions remain unanswered that must be addressed by the global scientific community,

such as the real therapeutic value of convalescent plasma, the ideal dosage and timing for usage, and whether CP still has a role after hyperimmune globulins or therapeutic monoclonal blends are available. How do the vaccines, CP, or other immune-bolstering therapies alter the native immune response and how do they impact CP donor suitability? As variant strains emerge, will there be a need to characterize wild type versus variant CP?

Some of what we believe now might prove to be incorrect in future. Changes in supply chain management, investment in infrastructure, staff safety and coordination of data gathering to enhance our ability to be flexible and adapt to novel and dangerous new threats, whatever the transmission mechanism might be, are just a few lessons hopefully learned during this pandemic. Preparedness for pandemics outside of pandemic situations must be taken seriously in the future.

Conflict of interests

The authors declare no conflict of interests.

Author contributions

Silvano Wendel and Kevin Land share together the co-authorship, where both had the same dedication to the manuscript.

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