

Guidance for the procurement of COVID-19 convalescent plasma: differences between high- and low-middle-income countries

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Vox Sanguinis

Abstract

Background and objectives COVID-19 convalescent plasma (CCP) has been used, predominantly in high-income countries (HICs) to treat COVID-19; available data suggest the safety and efficacy of use. We sought to develop guidance for procurement and use of CCP, particularly in low- and middle-income countries (LMICs) for which data are lacking.

Materials and methods A multidisciplinary, geographically representative group of individuals with expertise spanning transfusion medicine, infectious diseases and haematology was tasked with the development of a guidance document for CCP, drawing on expert opinion, survey of group members and review of available evidence. Three subgroups (i.e. donor, product and patient) were established based on self-identified expertise and interest. Here, the donor and product-related challenges are summarized and contrasted between HICs and LMICs with a view to guide related practices.

Results The challenges to advance CCP therapy are different between HICs and LMICs. Early challenges in HICs related to recruitment and qualification of sufficient donors to meet the growing demand. Antibody testing also posed a specific obstacle given lack of standardization, variable performance of the assays in use and uncertain interpretation of results. In LMICs, an extant transfusion deficit, suboptimal models of donor recruitment (e.g. reliance on replacement and paid donors), limited laboratory capacity for pre-donation qualification and operational considerations could impede wide adoption.

Conclusion There has been wide-scale adoption of CCP in many HICs, which could increase if clinical trials show efficacy of use. By contrast, LMICs, having received little attention, require locally applicable strategies for adoption of CCP.

Key words: COVID-19, SARS-CoV-2, COVID-19 serotherapy, blood transfusion, blood donors.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has spurred a modern pandemic. Passive antibody administration through transfusion of plasma collected from donors who have recovered from COVID-19 has emerged as a promising therapy for the treatment of COVID-19 [1]. This stems from early reports from China where favourable outcomes were observed following administration of convalescent plasma to patients with severe and/or life-threatening COVID-19 [2–4]. Convalescent plasma is not a novel therapeutic approach: it has been used for over a century to treat a variety of infectious diseases, including other coronaviruses (e.g. severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]) [5–9]. The efficacy data supporting early use of convalescent plasma to treat COVID-19 were limited and largely gleaned from small, uncontrolled

case series whereby interpretation of the data was complicated by the presence of concurrent therapies and severity of illness [2, 3, 10]. More recent data both from a matched controlled study and a randomized clinical trial suggest benefit of CCP, even in the setting of severe COVID-19 [11, 12]. At least one study does question its value whereby the mortality was not observed to be significantly different between recipients of CCP and that of controls [13]. However, adverse events have been few to date, suggesting that the risk is comparable to that of non-immune plasma [10, 14]. Rigorously controlled studies – including clinical trials – are already underway and should provide the necessary means to guide practice, definitively [1]. Until those data become available, convalescent plasma is one of only a few available options to contend with COVID-19, providing a stopgap ahead of the possible development of targeted treatment (e.g. direct acting antivirals, plasma-derived SARS-CoV-2 hyperimmune immunoglobulins, monoclonal antibodies,) and/or

preventive strategies (e.g. vaccines). There could also be scope where CCP could be used as a longer-term treatment option, particularly in low- and middle-income countries (LMICs) where resource constraints could bar access to novel treatments, even once available.

We sought to describe the challenges to the convalescent plasma workflow, which span donor identification, recruitment, collections, blood product processing and distribution with an ultimate view to addressing patient needs. Further, while attention to the pandemic has largely focused on high-income countries, it is important to note that the COVID-19 disease burden extends to LMICs that lack comparable resources to contend with the pandemic. This includes to the procurement of convalescent plasma; specifically, the challenges of scaling up this intervention are likely to be affected by the local environment and associated resource constraints. LMICs suffer from a host of systemic challenges that impact their ability to contend both with the health crisis at large and adoption of COVID-19 convalescent plasma (CCP) [15]. This requires careful consideration if to devise solutions that are locally or regionally applicable.

Materials and methods

The International Society of Blood Transfusion (ISBT) established a working group (WG) to develop a guidance document pertaining to the use of CCP as a treatment for COVID-19. The WG comprises 41 members with expertise spanning transfusion medicine, infectious diseases, adult and paediatric haematology. Many of the invitees were members of other ISBT Working Parties (WPs) including clinical transfusion, global blood safety hemovigilance and transfusion-transmitted infectious diseases; most of the invitees were actively engaged in CCP initiatives. In addition to ISBT, members were also aligned with AABB (formerly American Association of Blood Banks) and the Asian Pacific Blood Network. The members represent the Americas, Europe, Africa, Asia and Australia. Three subgroups were established based on interest and expertise related to the donor, product and patient. A series of questions pertaining to each domain was devised and addressed by the subgroups (April to May 2020), based on the best available evidence. Donor- and product-related content was combined into a single document. The content of the guidance document was informed both by expert opinion and a survey, which was administered to members of the ISBT Convalescent Plasma Working Group. In selected cases where there was insufficient geographic representation within the group, the survey was shared with outside members of ISBT. Discussion points were cross-referenced drawing on available evidence at the time (e.g. pre-print and published peer-reviewed data),

coupled with government institutional (e.g. European Commission, US Food and Drug Administration) or professional society guidelines. The approach was primarily descriptive yet the findings were used to guide practice through anticipation of potential challenges, particularly in LMICs.

The content areas that are summarized here include donor selection criteria for CCP collection, pre-donation qualification of CCP donors (including antibody testing) and operational considerations pertaining to collection, storage and distribution of CCP. A separate paper that focuses on clinical use of CCP and related concerns has been prepared.

Donor eligibility

All donors require evidence of COVID-19, either by a molecular test for SARS-CoV-2 (i.e. typically undertaken during active infection), or the presence of antibodies against SARS-CoV-2 (following resolution of symptoms resolution) [16]. It is recommended that blood collectors review documentation of infection rather than rely on verbal account alone. In some countries, a history of symptoms consistent with COVID-19 may also be permissible in lieu of laboratory testing [17] (Table 1).

Donors need to have recovered (i.e. be free of symptoms) at time of donation. Definition of 'recovery' is somewhat variable (Table 1). A minimum of 14 days following resolution of symptoms is consistently applied across countries [18]. However, countries differ in regard to their requirements for repeat negative testing for SARS-CoV-2. Between 14 and 28 days, some countries require a negative molecular test (e.g. of nasopharyngeal swab) before allowing donation. This requirement was largely informed by the perceived risk to collections staff rather than concern of transfusion transmission of SARS-CoV-2 (RNA-aemia is rare in the absence of symptoms) [19]. Nonetheless, some countries maintain stringent requirements for repeat testing, in some cases requiring paired negative tests (e.g. throat and nasopharyngeal swabs [NP] 24 h apart) to confirm viral clearance [20]. The requirement for negative testing has been questioned given limited capacity to perform tests coupled with challenges surrounding the interpretation of those results. Specifically, a high proportion of individuals are still positive for RNA on repeat NP swabs following resolution of symptoms. RNA positivity does not necessarily correlate with infectivity, further confusing the determination of donor suitability. By 28 days after being symptom-free, most countries allow for donation even in the absence of repeat negative testing.

It is important to note that donors of CCP are still required to satisfy all eligibility criteria for community

Table 1 Risks, challenges and potential strategies pertaining to determination of donor eligibility, recruitment and qualification for CCP donation.

Donor considerations	Approach	Challenges
Donor awareness	Education/awareness about the process of becoming a blood donor (and thus a CCP donor)	<p>A high proportion of convalescent plasma donors are expected to be first-time donors</p> <ul style="list-style-type: none"> • Low familiarity with eligibility criteria and donation process • First-time donors are high risk for transfusion-transmitted infections and higher risk for donation related adverse events than repeat donors <p>Donors of CCP need to satisfy same eligibility criteria as community blood donors</p> <ul style="list-style-type: none"> • Attestation from a licensed physician as an accepted donor is needed in some settings • In case of a deferral: need to properly communicate reason for deferral/ ineligibility including test results, for example infectious disease results.
Donor eligibility	Standardization of donor eligibility criteria	<p>Lack of uniformity in donor eligibility criteria with respect to:</p> <ul style="list-style-type: none"> • Ascertainment of diagnosis <i>Molecular testing</i> at time of symptomatic disease vs. <i>Evidence of antibodies</i> against SARS-CoV-2 following resolution vs. <i>Symptoms</i> consistent with COVID-19 in absence of testing • Time since resolution of symptoms to be eligible to donate (e.g. 14 days vs. 28 days) • Requirement for negative SARS-CoV-2 testing prior to donation <p>The criteria for eligibility are continually evolving as more information is known</p> <ul style="list-style-type: none"> • Lack of consensus
	<ul style="list-style-type: none"> • Medical Director use discretion to qualify donors • Relaxing of selected eligibility criteria e.g. donation frequency 	<ul style="list-style-type: none"> • Need to preserve donor safety and comply with national/local regulations
Donor identification	<ul style="list-style-type: none"> • Self-identification • Hospital-based referral • Mining electronic medical records and patient registries 	<ul style="list-style-type: none"> • Donor education: A high proportion of those who self-identify will not qualify <i>Variable reliability of self-referrals</i> • Motivation of donors may alter information to secure early donation to aid a friend/family member in need; anticipated/promised reimbursement • Recall: timing of symptom resolution • Test-seeking to confirm immune status • Individuals may not be able to provide documentation attesting to confirmed infection • Some donors may not have internet access or be internet savvy • Donors may be wary of telemarketers and are unwilling to answer phone calls or and scheduling online • Same donor may be associated with multiple hospitals/blood centres
Donor recruitment	<ul style="list-style-type: none"> • Community and hospital outreach • Social media • Professional websites • Formal news outlets • Reflex patient notification following positive test • Health departments 	<ul style="list-style-type: none"> • Lockdown policies restrict access to eligible individuals • Donors may not be adept with technology, limiting uptake of websites and online applications • Donors may be contacted by multiple organizations • Motivators for and deterrents against blood donation not well studied in LMICs • Electronic medical records and patient registries not widely available in LMICs

Table 1 (Continued)

Donor considerations	Approach	Challenges
Pre-donation qualification	<ul style="list-style-type: none"> Pre-donation screening and administration of donor history questionnaire 	<p>CCP donors need to meet all the same eligibility criteria as community blood donors</p> <ul style="list-style-type: none"> Individuals who satisfy criteria for CCP donation may be deferred for unrelated reasons, for example travel and MSM
	Gender and parity-based screening	<p>Depending on country/blood establishment policy, parous females may be deferred from blood donation as part of TRALI mitigation</p> <ul style="list-style-type: none"> In some countries, parous females may be subject to HLA antibody screening
Compensation/reimbursement	Donor compensation	<p>Policies regarding compensation vary widely by country</p> <p>Expectation of replacement and/or paid donation is common in low and low-middle-income countries.</p> <ul style="list-style-type: none"> Confers risk of TTIs Limited reimbursement for travel and small gifts that cannot be monetized may be permissible in some high-income countries Donors may be allotted special bonus points/blood centre non-monetary currency for CCP donation COVID antibody testing may motivate incentivize donation Active recruitment of donors at paid plasma collection sites to support hyperimmune globulin and vaccine development could result in competition between community blood centres and dedicated plasma collection sites for eligible donors
	Community organizers	<ul style="list-style-type: none"> Community organizers may expect compensation for identification/referral of potential donors. The ISBT Code of Ethics does not support compensating community organizers for identifying/referring potential donors, outside of traditional compensation mechanisms for the appropriate reimbursement of tests performed
Donor Privacy	Informed consent	<p>Loss of privacy and confidentiality</p> <ul style="list-style-type: none"> Balancing respect for privacy and confidentiality with need to access donor medical records to identify eligible donors for CCP Data sharing via email or other electronic means between referring hospitals and health agencies with donor centre Unintended release of private material (e.g. donor pictures, videos and clinical stories/histories) on social media without consent.
Donor safety	Procedural risks	<ul style="list-style-type: none"> First-time donors are higher risk of donation-associated adverse events than repeat donors, for example vasovagal reactions Risk and complications from the venipuncture and apheresis procedure, for example hypocalcemia during apheresis Some donors may be more comfortable with a whole blood donation versus apheresis procedure
	Repeat donations	<ul style="list-style-type: none"> Adverse effect on immunity following repeated donations has NOT been shown
	Psychological duress to donors	<p>Donors may feel obligated to donate</p> <p>Societal pressure/expectation.</p> <ul style="list-style-type: none"> May discourage admission of high-risk behaviour impacting risk of TTIs Risk of repeated quarantine A high proportion of individuals have positive PCR tests from nose or throat swabs 14–27 days post-symptom resolution conferring risk of quarantine until PCR negative The interpretation of persistent PCR-positive test result is unclear, that is whether testing represents active infection (live virus)

CCP, COVID-19 convalescent plasma; ISBT, International Society of Blood Transfusion; LMICs: low- and middle-income countries; MSM, men who have sex with men; PCR, polymerase chain reaction; TTI, transfusion-transmitted infections; TRALI, transfusion-related acute lung injury.

blood donation [18]. Those requirements are intended to preserve donor safety while protecting against risk of transfusion transmissible infections (TTIs). This needs to be integrated into pre-donation qualification to avoid deferral at time of donation despite having satisfied eligibility criteria to serve as a CCP donor. Some criteria for community blood donation have been relaxed with the advent of COVID-19 crisis, including the deferral period following travel, minimum haemoglobin levels, and deferrals pertaining to variant Jacob–Creutzfeldt disease (vCJD) and men who have sex with men (MSM) [21].

The donor eligibility criteria for CCP vary widely by country or even by institution within a given country (Table 2). A determination of donor eligibility is a formidable challenge in LMICs. Capacity for SARS-CoV-2 testing is low in LMICs, even for acutely symptomatic patients. This is ascribed to limited laboratory infrastructure, availability of testing kits and technical expertise, all of which are necessary to execute large scale molecular testing and surveillance. Without testing, the pool of eligible CCP donors remains uncertain. At time of writing, most LMICs report less than 10 000 cases of COVID-19 with most reporting tens to hundreds of cases, questioning whether there is as yet a critical mass of tested individuals and – broadly – whether the burden of COVID-19 is being severely underestimated [22].

Donor recruitment

A variety of approaches have been used successfully to recruit donors for the international CCP initiative. Both formal (e.g. news outlets) and social media have raised public awareness about COVID-19 and the potential efficacy of CCP. This has helped to spur self-identification, whereby recovered patients have been volunteering to donate. There are also parallel active recruitment efforts by blood centres and hospitals, through identification of patients either during admission or testing. Both testing sites and community public health surveillance initiatives can also be used effectively to identify potential donors. For example, recruitment materials can be shared with those who test positive for SARS-CoV-2.

At time of recruitment, information about CCP is provided to prospective donors including the eligibility for donation, the intended application of use (e.g. investigational vs. compassionate use), method of collection and the donation process itself. Many – if not most – CCP donors are expected to be first-time donors and will be unfamiliar with the donation process. First-time donor status introduces considerations of risk: first-time donors are higher risk of TTIs and donation-associated adverse events than repeat donors [23–27]. Repeat donation selects for healthier individuals as criteria for donation (e.g. notably

the absence of social and medical risk factors for infections) need to be met at each donation. Donor status is a notable concern in LMICs: while robust infectious marker screening in HICs and residual risk of TTIs is low, this is not universally the case in LMICs where high incidence and prevalence of TTIs, near exclusive reliance on antibody testing and suboptimal quality systems contribute to risk of TTIs. In short, the theoretical benefits from CCP need to be weighed against the real risks of TTIs. Given the relaxation of some temporary deferral periods during the pandemic, there may be additional risk that has not yet been quantified. Pre-donation qualification and donor informed consent are routine safeguards required to ensure privacy and confidentiality of donors.

There are additional considerations that are specific to CCP. First, given that CCP is still of largely unproven efficacy, some countries have only allowed recruitment of donors for CCP as part of approved clinical trials (e.g. Italy and South Africa). The latter are planned or already underway to evaluate efficacy. Second, given parallel efforts to produce hyperimmune globulin, there is potential competition for eligible donors for convalescent donors, particularly given the ability to compensate donors at plasma collection centres in some countries (e.g. USA). By contrast, community blood centres – at least in most high-income countries – are bound by stringent regulations that limit or preclude financial compensation. Instead, only gifts that are unable to be monetized or reimbursement for travel are allowed.

There is enormous heterogeneity among LMICs with respect to capacity for donor mobilization, collections and distribution [28, 29]. Indeed, some LMICs are able to sustain their blood supplies using voluntary non-remunerated donors (VNRBDs), exclusively. Nonetheless, donor eligibility and mobilization is likely to be a major challenge in the majority of LMICs. Independent of COVID-19, there is an unmet need for blood products in LMICs [30]. In large part, this stems from a low proportion of the eligible population that donate. Recruitment of voluntary non-remunerated donors (VNRBDs) is complex and relatively expensive in LMICs. Ideally, recruitment of VNRBDs is guided by local or regional knowledge of the motivators for and barriers against donation. Such is largely lacking in LMICs. Instead, there is reliance on replacement (e.g. friends and families of the intended recipient) and/or paid donation in decentralized transfusion services in LMICs. Recruitment in HICs has relied, primarily, on prosocial motivation ('altruism'), whereby donors self-identify as being willing to contribute. It is uncertain to what extent that this approach to recruitment applies to the replacement and paid donation – models and how that might impact the CCP initiative in LMICs. Most of the research to guide donor recruitment

Table 2 Regional variation in criteria for COVID-19 convalescent plasma procurement

Geographical distribution	Country	Definition of diagnosis*	Definition of donor recovery for eligibility						
			At least 14 days since resolution of symptoms without additional testing	14–28 days from resolution of symptoms with negative results for COVID-19 on donated plasma	>28 days post symptom resolution	>28 days post-symptom resolution OR >14 days post negative result of a NAT testing on NP swab	>14 days post symptom resolution and 1 negative results for SARS-CoV-2 PCR or by a molecular diagnostic test from blood	Symptom free for more than 14 days AND 2 negative SARS-CoV-2 PCR tests on 2 different days	Negative result of a NAT testing on NP swab and molecular diagnostic test from blood, performed 14 days after the first test
AMERICAS	United States	✓			✓		✓		
	Canada	✓	✓		✓				
	Brazil	✓					✓		
EUROPE	Italy	✓						✓	✓
	UK	✓			✓				
	Netherlands	✓	✓						
	France	✓	✓						
	Spain	✓						✓	
	Germany	✓				✓			
	Belgium	✓			✓				
Asia	Singapore	✓			✓				
	Hong Kong	✓			✓				
	China	✓						✓	
	Taiwan*****	✓					✓		
	India(fx)	✓			✓			✓	
	UAE	✓			✓			✓	
	Oman	✓			✓			✓	
	Saudi	✓			✓			✓	
Africa	Qatar	✓			✓				✓
	South Africa	✓			✓			✓	
Australia	Nigeria	✓			✓			✓	
	Australia	✓			✓				

Pathogen inactivation is NOT intended for the SARS-CoV-2 inactivation.

(fx) In India: donors who have had COVID diagnosis more than 4 months will be excluded from donation.

*Prior diagnosis of COVID-19 documented by a PCR test at time of infection OR by positive anti-SARS-CoV-2 serology following infection.

**Neutralizing antibody titre >1:80 by AABB). A titre of 1:80 may be considered acceptable if an alternative matched unit is not available (per FDA)

***Cut-off for sero-positivity will be set as the mean value +3 SD of the ELISA signal obtained with SARS-CoV-2 negative plasma (pool of plasma samples collected before 2020) at a 1:100 plasma dilution. NAT will not be used as a criteria to release CP (%%) Every 7 days as permitted by allogeneic donor eligibility criteria. Maximum number of donations are limited by the annual limit on volume of donation.

****France: testing has evolved over time: initially a systematic seroneutralization titre (+ an ELISA), more recently a systematic ELISA and seroneutralization titre when ELISA values are within a range of values associated with insufficient negative or positive predictive value a seroneutralization titre >40.

*****Data for Taiwan are based on optimal understanding of the situation as the low number of cases did not justify so far the transfusion of convalescent plasma.

¹Highlights practices for Canadian Blood Services versus Hema-Quebec.

²Performed neutralising antibody titres and now performs Euroimmun tests that equate to a neutralising antibody titre of >1:100.

practices stems from HICs [31]; many of those practices may not be applicable to LMICs, underscoring the need for research that is conducted locally or regionally [32–34]. While more readily accessible and lower cost to recruit replacement and paid donors, these are regarded as higher risk for TTIs [35].

Available recruitment approaches differ between high- and LMICs. For example, social media and formal news outlets could be applied broadly. By contrast, proposed strategies to mine patient records are difficult in LMICs given largely absent electronic medical records and variability in patient registries [34, 36].

Acceptable Cut off for sero-positivity OR SARS-CoV-2 Antibody titres (if applicable)						Accepted interval for Repeat Donation and Total Number of Donations				Gender-Specific Criteria as TRALI mitigation strategy			Pathogen Inactivation
NAT titre >1:160	NAT titre >1:80	NAT titre >1:40	ELISA signal specification only	positive testing for anti-SARS-CoV-2 antibodies	No antibody tests approved currently, samples will be stored for retrospective testing	Every 7 days (%)	Every 2 weeks	Every 4 weeks	min. 2 donation free days between 2 plasmaphereses; max. 60 plasmaphereses per year;	Male donors or female nulliparous donors or negative for HLA antibodies	Male donors or nulliparous female donors	Male Donors Only	
✓	✓**					✓				✓			
	✓		✓			✓				✓		✓	
✓	✓**					✓				✓	✓		✓
✓	✓						✓			✓			✓
		✓		✓****	✓	✓	✓			✓			✓
				✓		✓			✓	✓			(✓)
✓		✓				✓		✓		✓			✓
✓			✓				✓				✓		
		✓			✓			✓			✓		
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					✓	✓					✓	✓	✓
	✓					✓		✓				✓	✓

Pre-donation screening and testing of potential CCP donors

Pre-donation screening is intended to vet potential donors to ensure that they satisfy criteria specific to CCP as well as community donation. Given proximity to illness, some of the pre-donation screening may be undertaken over the phone or electronically (e.g. email). Screening

questions address eligibility (e.g. dates of symptom onset and resolution) and donor health. Depending on the regulatory requirements, there may a need for the donor to provide formal documentation of testing.

In regions/countries where SARS-CoV-2 molecular testing is not routinely performed prior to hospital discharge or de-isolation, a minimum time period is required following resolution of symptoms prior to becoming eligible to donate

CCP and other blood products. Most countries adhere to 14–28 days following resolution of symptoms (Table 2). Longer time periods (e.g. ≥ 28 days) offer dual benefit, ensuring that potential donors are no longer infectious (i.e. affording protection to the collections staff) while also allowing for sufficient time for adequate seroconversion.

Some establishments – albeit a minority – require pre-donation SARS-CoV-2 molecular testing of the blood in addition to negative testing by nasopharyngeal swabs [18, 37].

A central element to pre-donation screening is the demonstration of antibody formation. Not only is this needed to demonstrate recovery, but also the antibodies are postulated to exert efficacy against SARS-CoV-2. Unfortunately, there are multiple challenges pertaining to SARS-CoV-2 antibody testing. At time of writing, there is enormous variability in testing with little standardization to date. This relates to the assays in use, the settings in which they are being deployed (e.g. clinical vs. research laboratories) and what constitutes an acceptable threshold for donation (e.g. optical density, titre, antigenic specificities), particularly given that antibody profiles in the context of CCP treatment have not yet been correlated with clinical outcomes. The immune response in COVID-19 is complex, highly heterogeneous and is as yet not well understood [38, 39]. Neutralizing antibodies have been assumed to be desirable yet titres are variable, particularly in those who with mild to moderate infection [16, 40, 41]. Formal neutralization assays (e.g. plaque reduction neutralization tests [PRNT]) are not amenable to high throughput testing, requiring Biosafety level 3 laboratories and incurring long turnaround times, offering results in 5–7 days of initiation [42]. The assays themselves are also technically demanding accounting for considerable variation in results between laboratories. Therefore, neutralization assays are performed in relatively few laboratories and most institutions do not have ready access to neutralizing assays to determine antibody titres. Even for those that do there is lack of agreement as to what is acceptable. For example, the FDA and European commission recommend that titres are optimally ≥ 160 or ≥ 320 , respectively; however, both regulatory bodies allow for lower titres (e.g. 80) if unable to meet the optimal titres or simply evidence of antibodies using a qualitative serological test [16, 17]. Comparative analyses between the various neutralization tests performed in different laboratories are already underway.

Given the challenges surrounding neutralization assays, most are relying on enzyme immunoassays (i.e. ELISAs) to qualify donors. While increased numbers of assays are becoming available, typically targeting spike protein, receptor-binding domain and nucleocapsid protein [42–44], there is still uncertainty as to which isotype (e.g. IgM vs IgG) and/or subclass (e.g. IgG1 vs IgG2 vs IgG3) of

antibody is most informative. Nonetheless, there appears to be good correlation between spike-binding antibodies as detected by ELISA and neutralization antibodies [44, 45]. Further, there appears to be low cross-reactivity, notably against other coronaviruses [42].

Given the collective uncertainty of interpretation and logistical barriers to antibody testing, some countries have not been prescriptive about testing, instead encouraging retention of samples such that post hoc analysis may be undertaken when testing does become more standardized. This approach will be informative but does little for immediate patient care [16]. Further, there are ethical considerations behind transfusing a blood product of already uncertain efficacy, when one cannot even guarantee that its most basic definition (i.e. the presence of SARS-CoV-2 antibodies) is satisfied or verified. The European Union guidance on CCP collection and transfusion recommends that if the measured neutralizing activity in the collected plasma is considered to be too low for use as COVID-19 CCP, the plasma should be made available for other use (ideally fractionation) [17].

Finally, there are enormous challenges for pre-donation qualification in LMICs given limited laboratory capacity to conduct antibody testing for SARS-CoV-2. Further, in some countries stringent ‘lockdown’ policies that severely restrict travel may discourage or impede potential donors.

Collection facilities

Collection of CCP is no different from other plasma components (Table 3). Therefore, there is no need for a dedicated policy or procedures specific to CCP. The same sites that collected plasma (using whole blood collection or apheresis) prior to COVID-19 would undertake CCP collections. Collection may be undertaken by a centralized blood service (national or regional) or by hospitals that have the necessary expertise and infrastructure to perform collections. All certified blood centres or hospitals must be licensed (i.e. to collect plasma) and need to conform to the appropriate state or national regulatory requirements for blood collections. Those requirements – which are specific to each country – span donor eligibility criteria and donor qualifications for blood donation in general; in addition, there may be requirements that pertain to CCP specifically.

It is prudent to defer mobile collections given the potential infectious risk to collection staff. This pertains to collections for general blood needs as well as CCP. Fixed sites are easier to control from an infectious standpoint particularly given the greater ease of social distancing. By contrast, mobiles (e.g. collection vans) present confined spaces. Nonetheless, if sufficient time has elapsed since an outbreak, dedicated mobile collections could serve as an

Table 3 Summary of collection practices and product characteristics in high- vs low- and middle-income countries

Product characteristics		HICs	LMICs
Collection facility		<ul style="list-style-type: none"> Licensed/accredited sites to collect plasma under the same regulatory framework that preceded COVID-19 <p><i>Fixed sites</i></p> <ul style="list-style-type: none"> Centralized blood service (national or regional) certified by FDA or a competent regulatory agency Licensed hospital-based collection site <p><i>Mobile sites</i></p> <ul style="list-style-type: none"> Not being used given infectious risk to collection staff 	<ul style="list-style-type: none"> Same as HICs Sites need to comply with state or national regulatory requirements for blood collections
Mode of donation	Apheresis	<p><i>Blood centres</i></p> <ul style="list-style-type: none"> Major mechanism for collection; highly efficient If apheresis in use for platelet collections, this can be adapted for plasmapheresis (including CCP) <p><i>Sourced plasma collection sites for fractionation</i></p> <ul style="list-style-type: none"> Potential competition as donors are diverted contribute towards hyperimmune globulin development 	<ul style="list-style-type: none"> Limited access given high cost, availability of apheresis kits and requirement for technical expertise
	Whole blood	<ul style="list-style-type: none"> Has not been a major collection mechanism in HICs to date Longer inter-donation intervals (8-12w) than apheresis collections (once to twice per 7-day period) Minimum haemoglobin requirement applies 	<ul style="list-style-type: none"> Major mechanism for collection; low efficiency but inexpensive Inter-donation interval could be relaxed (e.g. weekly) as long as minimum haemoglobin requirements is met
Donor gender		<ul style="list-style-type: none"> Any female who reports a history of pregnancy should ideally be screened for antibodies against human leucocyte antigen (HLA) and human neutrophil antigens (HNA); this is recommended to mitigate against Transfusion Related Acute Lung Injury (TRALI) Never transfused male donors and female donors who test negative for HLA and HNA antibodies accepted 	<ul style="list-style-type: none"> HLA and HNA antibodies not routinely undertaken given cost and laboratory complexity In absence of testing, only males or nulliparous females recommended as plasma donors.
Volume per component (ml)	Minimum	<ul style="list-style-type: none"> Most units (post-aliquoting for apheresis derived units) are between 200–250 ml Average volume per unit is 200 ml (can be 150 ml). ~200 to 250 ml if derived from whole blood 	<ul style="list-style-type: none"> ~200 to 250 ml if derived from whole blood
	Maximum	<ul style="list-style-type: none"> Apheresis: 600ml–800mL (based on body weight) 200–250 ml if derived from whole blood 	See HICs
	Pooling	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> Data not available

Table 3 (Continued)

Product characteristics		HICs	LMICs
Number of units per collection		<ul style="list-style-type: none"> • Average 3–4 units per collection 	<ul style="list-style-type: none"> • One unit per whole blood collection
Required testing for unit	Standard guidelines	<p>All standard testing requirements for blood donation apply</p> <ul style="list-style-type: none"> • ABO blood group • Red cell antibody screening • TTI testing per local/country requirements, for example HIV, HBV, HCV, T. pallidumHLA (\pmHNA) antibodies (parous females only) 	<p>All standard testing requirements for blood donation apply, for example,</p> <ul style="list-style-type: none"> • ABO blood group • TTI testingNote: testing for TTIs varies by country with respect to • Level of standardization • Assays in use • Testing algorithms • Availability of molecular testing (uncommon for routine donor screening in LMICs) • Quality assurance
	Specific tests	<p>Antibody testing for SARS-CoV-2</p> <ul style="list-style-type: none"> • Approaches vary widely with respect to assays in use and recommendations for titering<i>Testing</i> • Neutralizing antibody titre (n-Ab) or validated immunoassay where the assay has been correlated with n-Ab; • If testing is not readily available, some countries have allowed for banking of sample with post hoc testing when available • Solid-phase ELISA assay against SARS-CoV-2 S, RBP and N proteins are available<i>Titres</i> • Neutralizing antibody titre for SARS-CoV-2 (Range 1:80 to minimum 1:320 and 1:640 in clinical trials) 	<ul style="list-style-type: none"> • Neutralizing Ab testing may not be available • Donor selection may be determined by reactivity in a serologic assay for anti-SARS-CoV-2 antibodies • Recommend banking samples for neutralizing antibody testing • If no testing available, recommend collection from known convalescent individuals without antibody testing
Cellular contamination		<p>Similar to regular FFP unit:</p> <ul style="list-style-type: none"> • $<1 \times 10^6$ WBC • $<50 \times 10^9$ plt/unit • $<1 \times 10^8$ RBC 	See HICs
Pathogen reduction		<ul style="list-style-type: none"> • Licensed and approved technologies are available (e.g. photochemical inactivation) • Not widely adopted • Not mandated for CCP • Recommendation to perform PR if already routine practice; • It is not recommended to implement PR specifically for CCP 	<ul style="list-style-type: none"> • PR not in use in most LMICs likely given high cost and technical complexity of use
Time between collection and freezing		<ul style="list-style-type: none"> • 8–24 h 	<ul style="list-style-type: none"> • 8–24 h

Table 3 (Continued)

Product characteristics		HICs	LMICs
Storage	Liquid	<ul style="list-style-type: none"> • If plans for infusion soon after collection, store at 1–6°C after as allowable by guidelines for maximum of 5 days • If no plans for infusion soon after collection, store at room temperature and freeze at –18°C within 24 h of collection 	<ul style="list-style-type: none"> • 24 h storage at 1–6 C permitted after thaw • For liquid plasma - 1°C and 6°C for up to 40 days.
	Frozen	<ul style="list-style-type: none"> • ≤–18°C within 24 h of collection until administration • Expiration: 1 year at –18°C 	<ul style="list-style-type: none"> • 24 h storage at 1–6 C permitted after thaw • For liquid plasma - 1°C and 6°C for up to 40 days.
Labelling		<ul style="list-style-type: none"> • ISBT-128: ICCBBA has issued a range of description codes for CCP • There is an ISBT128 label specific to CCP • Alternatively, there should be a text label with 'Convalescent Plasma' and/or using tag on CCP units • Special labelling as an investigational product for treatment of COVID-19 may be needed- Note: Integration of the new product codes into existing IT systems may be challenging 	See HICs
Traceability		<ul style="list-style-type: none"> • Full traceability, as per all blood products. • Compliance with national or local regulations 	See HICs
Release		<ul style="list-style-type: none"> • Compassionate use • Research (e.g. clinical trials) • Expanded access programmes (i.e. clinical use with data reporting requirements) CCP testing requirements (e.g. antibodies) vary based on intended use; 	<ul style="list-style-type: none"> • Currently, most CCP administered through clinical trials • Compassionate use is also available
Expiration		<ul style="list-style-type: none"> • Thawed: 5 days for thawed plasma. • 12 months if frozen (same as for standard frozen plasma) 	See HICs
Other products/ derivatives		<p>CCP will likely only serve as a supportive therapy (and not the main therapy) in the future for HICs.</p> <p><i>Hyperimmune gamma globulin</i></p> <ul style="list-style-type: none"> • Alliance of manufacturers has been established to accelerate development of a plasma-derived hyperimmune globulin therapy against COVID-19 • Promise of greater standardization of dosing than CCP • Differences in collection and donor eligibility requirements than CCP; donor who do not meet apheresis plasma donation criteria may still meet criteria for plasma fractionation (e.g. vCJD risk) 	<ul style="list-style-type: none"> • Unknown at time of writing

CCP, COVID-19 convalescent plasma; FFP, fresh frozen plasma; HBV, hepatitis B virus; HCV, hepatitis C virus; HICs, high-income countries; HIV, human immune deficiency virus; HLA, human leucocyte antigen; HNA, human neutrophil antigens; IT, information technology; LICs, low-income countries; n-Ab, neutralizing antibody; PR, pathogen reduction; RBC, red blood cell; T. pallidum, treponema pallidum; TRALI, transfusion-related acute lung injury; TTI, transfusion-transmitted infection; vCJD, variant Creutzfeldt–Jakob disease; WBC, white blood cell count.

efficient means to collect CCP in communities that have been impacted and since recovered from COVID-19.

Blood centre policies are developed around universal precautions. Nonetheless, specific policies and associated measures may be needed to optimize employee safety and/or preserve employees' confidence in their safety. These apply to general blood and CCP collections alike. This may require screening donors and employees (e.g. inquiry about symptoms and signs of COVID-19, obtaining temperatures) prior to entering the collection facility. Social distancing of at least 1.5 m (6 feet) can be accommodated for part of collection process; however, during the confidential donor interview process and collection process, employees and donors will be closer than 1.5 m for some time. Some countries have broadly mandated routine wearing of masks in public, while other have focused on asking phlebotomy staff and CCP donors to wear masks during the collection process. Recommendations regarding the need for personal protection equipment (PPE) use have evolved over the course of the pandemic [46, 47]. Routine use of PPE was not initially recommended; with evidence of transmission of SARS-COV-2 from otherwise asymptomatic individuals, most guidelines, at least in HICs, recommend at least some form of face coverings for donors and blood centre staff. Access to PPE varies greatly but is generally limited, particularly in LMICs, resulting in an increase use of homemade masks, which may be of variable efficacy.

Mode of collection

Plasma collection using apheresis technology is the ideal, offering a highly efficient mechanism to collect large volumes of plasma. A single donor can contribute as many as 3 or 4 units (~600 to 800 ml) of plasma. Apheresis is the major mode of collection in HICs for CCP. Nonetheless, there are barriers to its expanded use, particularly in LMICs including high cost, technical expertise and availability of apheresis kits. Therefore, apheresis is not available in some countries. If apheresis is already in use for routine platelet collections, there are ways to adapt those existing technologies to plasma (including CCP) collection.

For countries that do not have apheresis equipment there is the option to recover plasma from a whole blood collection, whereby the parent product is separated into components (i.e. plasma and red blood cells) after collection. However, whole blood collections to produce CCP raises some concerns in LMICs. First, anaemia is highly prevalent in LMICs, and many potential donors may not meet the minimum haemoglobin threshold for donation [28]. Whole blood donations also confer longer deferral periods (e.g. 8–12 weeks) than plasma. In some

circumstances (e.g. for fractionation), plasma donors are allowed to donate as frequently as twice a week yet adverse effect is rare. Therefore, apheresis optimizes efficiency and frequency of collections [15]. Specific to CCP, obvious potential donors are those who have been acutely ill; given comorbid risk factors for severe disease (e.g. advanced age, cardiorespiratory disease, diabetes e), these individuals may not be ideal candidates for donation given concerns over donor safety. It is important to note that plasma preparation from whole blood collections is not unique to LMICs; in addition, there has been relaxing of the inter-donation intervals whereby whole blood donors could – conceivably – be allowed to donate frequently as long as the donors still meet minimum haemoglobin thresholds. Similarly, status as an LMIC does not bar apheresis as was shown during the 2014 Ebola outbreak in West Africa where logistical barriers were overcome and CCP was collected successfully [48].

Product characteristics

The manufacturing of CCP units is similar to units of either recovered plasma or concurrent/apheresis plasma depending on whether the plasma is derived from a whole blood or apheresis collection, respectively. The volume of the product collected by apheresis may vary, depending on the gender, body weight and height of the donor, as well as the device that is used; in some cases, the collection volume can exceed 800 ml [49]. Following apheresis collection, the CCP follows the same manufacturing process as transfusable apheresis plasma products; it is separated into an appropriate number of products based on the collection volume after which it is typically frozen within 8–24 h of collection. The volume of the units is uniform (but not exact). For example, the minimum volume in the US is ~200 ml (although it can go down to 150 ml); therefore, larger product volumes that are collected using apheresis devices are split into multiple products, each containing at least the minimum designated volume. One needs to pay attention to the maximum volume as many CCP protocols limit the total volume of CCP which can be transfused into a patient. Although many blood centres are performing antibody testing of CCP units, the test results have not been uniformly required as a release criterion for CCP units with a view to compassionate use. By contrast, many research (i.e. clinical trial) protocols require characterization of the CCP (i.e. determination of antibody titres) units prior to use.

Testing

COVID-19 convalescent plasma needs to satisfy the same requirements as community blood donation as are locally

in effect in the country or state of operation. Those testing requirements must be met prior to release of the CCP. Testing is primarily focused on TTIs, ABO isohemagglutinin titres, red cell and HLA antibodies. In some cases, testing for neutrophil antibodies is also undertaken. In most HICs, molecular and/or antibody testing is performed to detect the major TTIs (e.g. HIV, HTLV, hepatitis B and C viruses, syphilis). In many LMICs, TTI testing is more variable, both with respect to the assays, algorithms and quality assurance in use [50, 51]. In countries with high rates of TTIs, quarantine systems or pathogen reduction (PR) of the plasma is recommended but are rarely feasible. However, a quarantine system (i.e. fresh frozen plasma from whole blood being stored until the donor returns and provides a subsequent donation) is logistically challenging especially for CCP. In a few clinical trials, additional tests have been undertaken such as hepatitis E virus (HEV), hepatitis A virus, parvovirus B19, even if these were not tested for routinely prior to COVID-19. Infectious marker screening for these pathogens is typically applied to sourced plasma collections (i.e. for fractionation) [52]. HEV screening of community blood donors is routine in some countries (notably in parts of Western Europe and Japan) given evidence of transmission and risk – albeit rare – of transfusion-associated morbidity [53–55]. In the case of CCP, it is unclear why additional infectious marker testing was adopted specifically; one could speculate that those tests were added out of an abundance of caution [56, 57].

Testing is typically undertaken after collection. To that end, one might consider pre-donation testing, particularly in the event that apheresis is being used given the high cost of the collection kits. HLA antibody testing is routinely employed as a mitigation measure against transfusion related acute lung injury (TRALI) in mostly HICs. Pre-donation HLA antibody testing may be worthwhile in parous females given that up a third of women who report having been previously pregnant have HLA antibodies [58]. In countries where HLA and HNA antibody testing is prohibitive, eligibility to donate CCP may be restricted to males and nulliparous females.

Unlike other blood components (e.g. red blood cells, platelets and cryoprecipitate), quality indices are not typically required for plasma; this is currently the case for CCP units. For situations where antibody testing is not readily available, collection of a retention tube for later qualification of the transfused CCP is recommended.

Labelling

In general, it is recommended that labels and coding adhere to ISBT-128 standards. All units of CCP should be labelled specifically as COVID CP or Blood (Ref 11 and

'Recommendations for Investigational COVID-19 Convalescent Plasma | FDA; 1 May 2020'). For ISBT-128 users, there are a range of product codes that have been generated by the international standards organization which is responsible for the management and development of the ISBT 128 Standard (ICCBBA). Additional requirements are country specific. For example, in the USA, all CCP must also include following statement, 'Caution: New Drug--Limited by Federal (or United States) law to investigational use'. Challenges specific to CCP pertain to integration of the new product codes into existing IT systems. However, the base label is the same as regular plasma for transfusion.

Storage

It is recommended to freeze the plasma at -20°C or preferably colder within 24 h of the end of the collection. Plasma should be stored frozen at constant temperature below -20°C until administration. In settings without access to -20°C freezers (e.g. some LMICs), plasma can be frozen at -18°C or colder within 24 h after blood collection. Under specific circumstances when freezing is not available, liquid plasma may be stored between 1°C and 6°C for up to 40 days.

Frozen plasma can be stored for up to 12 months. Longer periods of storage should be shown not to have altered the therapeutic efficacy of CCP. CCP (like other plasma components) must be transfused ideally as soon as possible after thawing, but definitely within five days of thawing.

Pathogen reduction

Pathogen reduction (PR) refers to a variety of emerging technologies (e.g. photochemical inactivation, solvent detergent treatment) that act directly on the blood product, mitigating risk against a range of pathogens rather than a single or a few pathogens (i.e. the case with infectious marker testing). There are already licensed technologies for treatment of plasma that have been shown to be effective against coronaviruses (e.g. SARS, MERS and SARS-CoV-2) [59–61]. Independent of COVID-19, PR offers the ability to contend with emerging and re-emerging pathogens. Nonetheless, the benefit of PR in the context of SARS-CoV-2 is unclear. For one, RNA is rare in the blood of symptomatic individuals with COVID-19 [20]. While it has been detected rarely in asymptomatic (i.e. recovered) individuals, respiratory viruses are not known to be transfusion transmissible, or at least to result in clinical infection if transmitted [19]. This is tempered by the uncertainty surrounding pathogenesis of a novel virus. PR would allay concerns related to viral

transmission from CCP. Pertinent to LMICs, CCP donors are more likely to be first-time donors and thus have a higher risk of TTIs [23, 25–27]. In countries that issue recovered FFP through a quarantine system routinely, PR would address the risk of the major TTIs (e.g. HIV, HBV and HCV) [37, 62], increasing the overall availability of donor CCP [18]. At time of writing, efforts are underway to evaluate the impact of PR on antibody levels, the safety of PR plasma already in use (i.e. in some countries in Europe and North America) and formal evaluation of PR on the SAR-CoV-2 virus.

There are barriers to the wide adoption of PR. Foremost is cost, which may be prohibitive for most LMICs. PR also requires equipment and skilled personnel to perform. Therefore, most countries have elected not to implement PR specifically for CCP.

Limitations

There are several limitations to this guidance document. Foremost, the data are subject to change: we have tried to refrain from being too prescriptive, acknowledging that publication of new findings is occurring rapidly, and may alter the practices as currently written. Donor eligibility and pre-donation qualification criteria are two examples, where there has been significant overhaul since initial proposal. Second, there was under-representation of contributors from LMICs. At time of writing, most of CCP procurement was focused in HICs, notably the United States and Western Europe given the scale of their regional epidemics. Third, the data, particularly those depicted in the tables, are not regionally representative and in some cases may not represent all practices within a given country. There is variation in practice; this document is intended to impart a framework to contextualize one's own CCP programme if already established or to guide adoption of CCP if still being planned. It is not an exhaustive review of all countries' practices.

Conclusion

Following the advent of COVID-19, there has been remarkable scale-up in the collection and distribution of CCP. Observational data – albeit with very low level of evidence – suggest efficacy of CCP and the rates of associated adverse events are few [2, 3, 14]. Further, clinical trials are underway to evaluate the efficacy of use as post-exposure prophylaxis and treatment of COVID-19 in adult and paediatric populations alike. If CCP is shown, definitively, to work there could be an unprecedented demand for CCP both for clinical treatment and for fractionation into hyperimmune immunoglobulins. Pre-emptively and in a relatively short time, blood centres have

responded to the growing demand for CCP. The eligibility criteria and recruitment strategies for CCP donors have been formalized, and collections have increased to the point that unmet need – in selected HICs – is diminishing. Nonetheless, challenges remain particularly with respect to the characterization of units of CCP and if – or how – the antibodies that are being detected, impact clinical outcomes. LMICs have been relatively neglected in the pandemic; this extends to their capacity to procure CCP [63]. There are also ethical questions pertaining to CCP, not least of which is whether it is appropriate to recommend diversion of resources towards an unproven therapy, when the existing resources in most LMICs are already insufficient to ensure a safe and adequate blood supply to meet clinical demand [64]. In the case of COVID-19, there has been a temporary decline in blood collections, potentially exacerbating the transfusion deficit. While the impact is off-set – in part – by the reduced demand for transfusion given cancellation of elective surgeries and a decline in trauma, there are still a host of challenges spanning recruitment to collections. If CCP is to be adopted in LMICs, approaches need to be tailored to local resource constraints.

Conflict of interest

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