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A consideration of convalescent plasma and plasma derivatives in the care of Severely-ill patients with COVID-19

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ABSTRACT

The pathogenesis and immunopathological damage of severe forms of COVID-19 resemble acute autoimmune disease sparked by SARS-CoV-2, including an early systemic overproduction of proinflammatory cytokines. Such immunopathological features provide a rationale for the use of passive immunotherapy with convalescent plasma as a source of neutralizing anti-viral antibodies and of anti-inflammatory plasma components. While convalescent plasma therapy is now being evaluated in prospective clinical trials, we further consider the therapeutic potential of human hyper immune globulins, and of heterologous, engineered and monoclonal neutralizing antibodies as anti-viral agents to treat COVID-19. Good medical practice procedures are still needed and is why we also discuss the potential use of polyclonal polyspecific immunoglobulins (IVIG), a therapeutic plasma derivative, with potent anti-inflammatory activity, in severe forms of Covid-19.

1. Introduction

The speed and amount of scientific information on COVID-19 are unprecedented. As hemotherapy makes its way into care for COVID-19 patients [1], this paper focuses on the pathogenic rationale for using whole convalescent plasma, plasma derivatives and anti-SARS-CoV-2 antibodies as pharmaceutical approaches to COVID-19 treatment.

2. Pathogenesis and immunopathology of COVID-19

2.1. Primary target-organ lung

SARS-CoV-2 primarily targets the respiratory tract. Evidence now accumulates that this virus trespasses airways, inducing endotheliitis and targeting the systemic microcirculation [2–4].

The ratio of the angiogenic markers sFlti//PIGF increases by a factor of 5 upon recovery from COVID-19 [5,6], linking SARS-CoV-2 pathogenesis to the renin-angiotensin system in induction of lung disease [7]. The virus uses its Spike (S) protein to hook onto the membrane ACE2 receptor and to hijack airway epithelial cells. When infected the virus expands by replication and cells become targets of either beneficial or destructive cell-mediated cytotoxic host-resistance processes; some individuals overcome the virulent attack, others becoming victims of it. Upon the initial phase of viral replication, cytolysis ensues, manifested by fever and flu-like symptoms, followed, in a minority of infected subjects, by a second phase of worsening respiratory symptoms. Pneumonia and acute respiratory distress syndrome (ARDS) may then develop two to three weeks post-infection, i.e. 5–10 days from the onset of symptoms. A process tentatively called 'viral sepsis' may spark disease mechanisms of COVID-19 with patients ending up with the clinical picture of septic shock [8]. Based on knowledge gained from infections with former SARS coronaviruses, it is likely that this corresponds to the onset of seroconversion and reduction of viral load [9–11].

Poor or delayed viral clearance causes sustained damage of the ACE2 with angiotensin-2 receptor carrying cells being kept back in their reparative capacity [12]. The bystander pathway to infect respiratory lining cells, ciliated and goblet cells, goes through the enzyme transmembrane protease serine 2 (encoded by the TMPRSS2 gene); indeed, blocking this enzyme prevents SARS-CoV-2 infection of human cell cultures *in vitro* [13]. Settled in the upper respiratory tract at the time of infection, an acquired immune response with anti-CoV-2 antibody formation takes place followed, most probably, by the formation of immune complexes, with the virus serving as the antigen (Fig. 1). Specific anti-viral antibodies can be detected within 10 days after the outbreak of disease [14]. The extent of the time lag from initial infection to detecting antibodies begins to be scrutinized; in 149 COVID-19 convalescent

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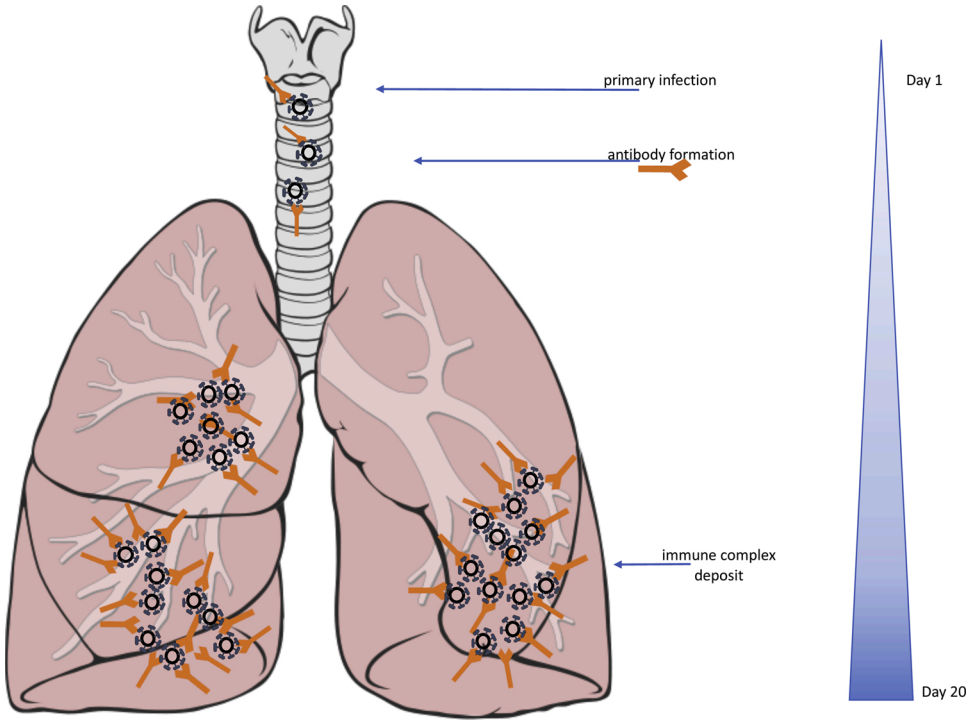

Fig. 1. Pulmonary Immune Complex Trapping. Pulmonary Immune complex damage starts out in the upper airways where the acquired immune system recognizes antigen. Upon descent of SARS-CoV-2 into the pulmonary tissue, local formation or deposition of soluble circulating immune complexes becomes possible. Not sketched: Complement deposition in the parenchyma of lungs, except in the large airways as shown in C57BL/6 mice [28].

individuals, recurring RBD-specific antibodies with potent antiviral activity were found in all individuals tested, suggesting that a vaccine designed to elicit such antibodies may be broadly protective [15,16].

In this study, antibody sequencing revealed clones of RBD-specific memory B cells which expressed similar subspecificities in different convalescing study participants; sub-specificities cannot be excluded to be relevant, i.e. SARS-CoV-2 envelope (E), nucleocapside (N) and RNA-dependent RNA polyerase (RdRp) all of might be associated with clinical manifestations. Indeed, disease course often varies from patient to patient [17] within each of these recent studies a male prevalence in hospitalisations and mortality appear [18]. Whichever relationship between viral antigen and antibody (prozone, equilibrium, postzone) occurs, soluble, circulating immune complexes and, most likely, complement activating immune complexes will form locally i.e. deposited in the vascular–endothelial barrier and the alveolar–epithelial layer, leading to microvascular coagulation, alveolar edema, hemorrhage, and the massive influx of native immune peripheral white blood cells [19]. Compatible with this view for SARS-CoV-2 is the estimated disease incubation time of two to three weeks, enough time for the virus to induce specific anti-SARS-CoV-2 antibodies [20].

At the outset, the literature was affirmative on an ensuing pulmonary fibrosis upon a SARS-CoV-2 attack. More recent studies, predominantly based on autopsy findings [21] pave the way to a deeper understanding of COVID-19 pulmonary disease. The excessive inflammation, induced or not by immune complexes and hypoxia, are good grounds for development of coagulopathy. In addition, antiphospholipid antibodies round up the picture of a virally-induced anti-phospholipid syndrome [22]. Diffuse intravascular coagulopathy (DIC) has been observed to start from a lung-centric coagulopathy and spread systemically [23–25]: It is well known that immune complexes directly induce DIC [26]; pulmonary infections are prone to excessive coagulation [27].

2.2. Systemic consequences - cytokine storm

With such a large organ system as our lungs affected by virulent SARS-CoV-2, a systemic spread to other organ systems, similarly to organ extention from single organ autoimmune diseases, marks the later stages of COVID-19. Loss of balance in the cytokine equilibrium (cytokine storm) initially in lung tissue, goes on to involve the blood and lymp systems whereupon systemic COVID-19 mutiorgan damage will ensue; such organs as kidneys and liver will suffer from reduction of glomerular filtration rate and elevated liver enzymes [22,29]. Mild hematological changes are lymphopenia associated with low platelet counts while most severe forms lead to DIC and thrombosis [22,23,30] Table 1. The macrophage activation syndrome (MAS) [31] or hemophagocytic lymphohistiocytosis (sHLH), anti-phospholipid syndrome and septic shock make the clinical picture multisystemic. A predominant feature of these severe forms of disease are high levels of IL1-beta, IL-6, IL-7 and TNF in

Table 1
Targeted laboratory findings to estimate the extent of systemic viral damage by SARS-CoV-2.*

parameter	unit	normal	medium	Severe
innate WBC	x 10^9 /l	3–8		
lymphocytes	x 10^9 /l	1–3	cytopenia two lineages	cytopenia three lineages
platelets	x 10^9 /l	150–370		
triglycerides	mmol/l	<1.7	1.5–4.0	>4.0
fibrinogen	g/l	1.8–3.5	<2.5	<1.5
ferritin	ng/ml	13–150	2000–6000	>6000
asparate aminotransferase (ALAT syn. GOT)	IU/l	<50	>30	>60
C reactive protein	mg/l	<5.0	>50. 0	>100.0
IL-10	pg/ml	48.8 +/− 5.8	47.0 +/− 5.3	49.7 +/− 12.3
IL-2	pg/ml	10.0	>10	>20
IL-6	pg/ml	61 +/− 10.1	163 +/− 153	517 +/− 796
TNFα	pg/ml	<12.0	>100	>1000 towards 5000
procalcitonin	µg/l	<0.15	>0.5	>2.0
D-Dimer	µg/l	<500	>500	>1000

* values borrowed [34,36,37] & own data (unpublished).

peripheral blood samples, dubbed as a «cytokine storm» [32].

The histopathological consequence of the cytokine storm presents as HLH with, hyaline membranes seen at autopsy in lung tissue [33], reflecting hyperinflammation burdened by hypercytokinemia with multiorgan failure, surmised as viral sepsis by some [8]. The clinically overt sHLH includes unremitting fever, cytopenias, and hyperferritinaemia; and pulmonary disease leading to acute respiratory distresss syndrome (ARDS), indistiguishable from SARS in approximately 50 % of patients.

Seen from the angle of laboratory assays [14]. The most appropriate selection of analytes for COVID-19 staging is not fully established. Next to a large variety of analytes there are many attempts to stage severity of a nosological entity by such assays [34,35]. We here select a series of analytes currently in use at our institution and note that the list is prone to change when better knowledge of COVID-19 emerges.

Proinflammatory cytokines and the chemokines tumour necrosis factor (TNF) α, interleukin 1β (IL-1β), IL-6, granulocyte-colony stimulating factor, interferon gamma-induced protein-10, monocyte chemoattractant protein-1, and macrophage inflammatory proteins 1-α are significantly elevated in COVID-19 patients [38].

A cytokine profile reflects disease severity (Tables 1 and 4). Predictors of fatality from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China, showed elevated ferritin (mean 1297·6 l ng/ml in non-survivors *vs* 614.0 ng/ml in survivors; $p < 0{\cdot}001$) and IL-6 ($p < 0{\cdot}0001$), once again suggesting that mortality might be due to virally driven hyperinflammation [39]. Artificial Intelligence (AI) has also been used as a predictor. In fact, 3 biomarkers are reported to predict outcome, with a 90 % accurracy 10 days in advance when 485 blood samples of patients hospitalized with COVID-19 in Wuhan were assessed. In this study LDH, alone, played a crucial role in distinguishing the vast majority of cases that required immediate medical attention [40]. These are not COVID-19-specific routine lab assays but they may be predictive of a battle against viral sepsis [6,8].

3. Diagnosis of COVID-19 supported by laboratory services taking into account comorbidities and senescence

Much emphasis is currently placed on laboratory diagnosis to detect serum anti-SARS-CoV-2 antibodies, more particularly of the IgM or IgG isotypes. Antibody cloning may be used to spot specific memory B cells expressing related antibodies in different individuals [15]. Anti- RBD IgM titers were found to be negatively correlated with duration of symptoms and timing of sample collection whilst IgG titers were level [15]. In our laboratories, we currently explore the possibility, that some of the signal antibodies don't carry viral antigen in an immune complexed form. The ongoing research efforts and advances in complementary technologies will pave the way to new point of care assays in the coming months [15]

Elderly patients in which immunosenescence takes hold [41,6,42,43] are more susceptible to catching severe COVID-19 hence their classification into a'risk group'. In addition, malnourished, alcoholic and smoke abusing individuals [44] are nefarious victims of impaired resistance against any infectious agents.

A majority of COVID-19 patients are elderly, subjected to immunosenescence and (threatening) chronic obstructive pulmonary disease COPD as a pulmonary senescence marker [45] hence their (mucosal) defense against SARS-CoV-2 is impaired from the very beginning of the infectious attack [46], explaining their classification into the at risk group. In addition, nosological entities, such as cancer, cardiovascular diseases, especially when fostered by arterial hypertension or diabetes mellitus [47], are now well identified to facilitate COVID-19. Currently, in Switzerland, over 50 % of the 605 deaths at the time of this writing (beginning in April 2020) are mainly men >83 years old, having reached the status of delayers [48].

Whereas, in younger, work-force individuals, with an effective immune response, and a strong functional ACE2/AT2 cell population, little or no symptoms occur, the elderly are burdened with ACE2-deficiency and reduction of AT2 cells; this is followed by inflammatory damage set by immune complexes inducing the cytokine storm and hypercoagulation (see coagulation 2.1) [49]. Cardiovascular disease and type 2 diabetes, conditions more frequent in the elderly, pave the way for severe COVID-19.

Table 2
Selection of frequently assessed laboratory tests and their concentrations in the elderly as compared to work-force individuals.*

Elevated in the elderly	Decreased in the elderly
Al kaline phosphatase	Calcium, zinc
Cholesterol	Creatin kinase, eGFR*
Clotting factors VII and XIII	Dehydroepiandrosterone, Testosteron
D-Dimer*	Estrogen
Ferritin*	Growth hormone
Fibrinogen	IGF-1, Interleukin-1*
Postprandial glucose	Phosphor, selenium, thiamin
Parathormone	X-tocopherol (vitamin E)
Interleukin-6*	Vitamins B6 and B12, vitamin C, vitamin D
Noradrenalin	Alanine Aminotransferase
Parathyroid hormone	
Prostate specific antigen	
Triglycerides	
Uric acid	
Glycated Haemoglobin (HbA1c)	

Data taken from [60] and [61].
* Asterix-marked analytes relevant in COVID-19 diagnosis.

Youth, working age, healthy elderly or frail senior persons today: each life stage provides for a different background for disease appearance. On a time line, chronological age (CA) and biological age (BA) often disconnect and nosological entities declare themselves at different BAs.

Apparently not so with COVID-19 epidemiological numbers of which adhere to chronological age. SARS-CoV-2 is a death threat by and large for the elderly [50] none the least because of the deviations of a number of biomarkers in old age (Table 2). Immune failure occurs when adaptive strategies are not developed by the aging T cell system [51,52] and a T cell exhaustion has been reported recently to occur in COVID-19 patients [53].

This is remarkable since other viruses, e.g. measles, which is spread like SARS-CoV-2, do target children, an age group which is increasingly recognised as possible victim of SARS-CoV-2 as well [54] sharing features of Kawasaki Disease [55]. With the current prolongation of life-expectancy the studies into the biological background of human senescene explain the reasons for long life: shortening of telomers. Cell senescence induces interleukin release [48] and identification of senescence-associated β-galactosidase (Saβ-gal) activity in tissues, detectable at pH 6.0, are now accepted to indicate lost senescent cell CD169+macrophages [56], these may constitute a priviledged target for SAR-Co-V-2 [57].

As of April 3rd, 2020, in Switzerland the death rate of 2172 COVID-19 cases > 80 years of age men and women was 14.32 % increasing in the 60–69 yrs age group (1.49 % of 2543 confirmed cases). The 50–59 yrs age decade with 4022 cases had a death rate of 0.32 % diminishing with younger decades to negligible death rates (www.bag.admin.ch, www.bfs.admin.ch) [58,51].

The most frequent comorbidities were arterial hypertension (69 %), cardiovascular disease (55 %) and diabetes mellitus (29 %); prediabetes [59] was not separately considered in this survey (Fig. 2).

4. Therapeutic options

4.1. Pharmacologicals

At present, one may classify the ways to treat COVID-19 (Table 3) as follows:

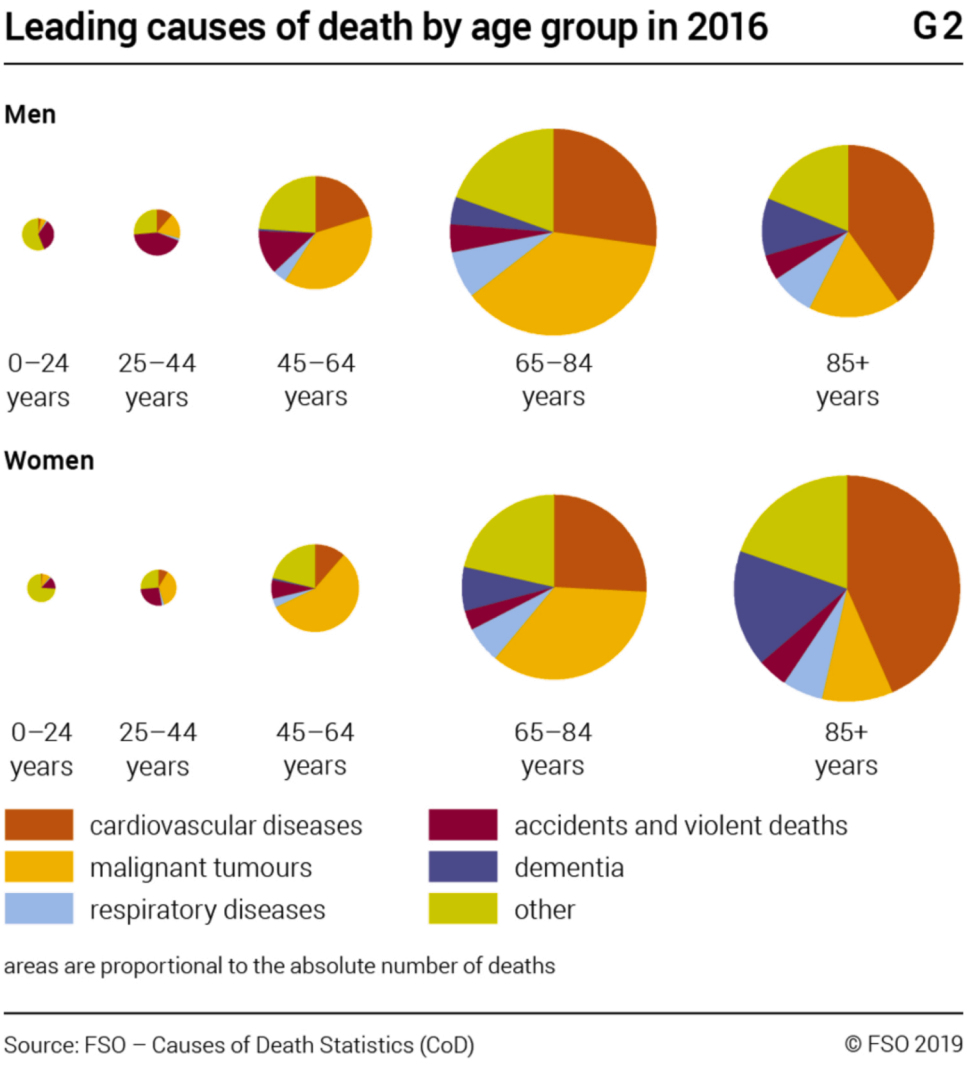

Fig. 2. Comorbidities in Switzerland.
Comorbidities Pie charts of six major disease groups striking the Swiss population at different ages to focus on comorbidity as a basis for risk of death by SARS-CoV-2 infection.
Reproduced, with permission, from the "Leading causes of death by age group" (https://www.bfs.admin.ch/bfs/de/home/statistiken/kataloge-datenbanken/grafiken.assetdetail.262901.html) Please note the regression of malignant tumors in the very old.

(i) Blockage of viral replication, (e.g. remdesivir EIDD-2801)
(ii) Prevention of viral cell entry (e.g. Multiple antibody cocktail, monoclonal antibody candidates, TAK-888)
(iii) Reducing hyperimmune response and ARDS (e.g. Kezvara, Actemra, Remestemcel-L, and Xeljanz)

The approaches in ii and iii have recently been updated elsewhere [62]. This review article from Paris (France), a trendsetting description for a multiple point approach to modulate immune reactions provoked by SARS-CoV-2 is delineated. Accordingly, immunotherapy may either enhance the hosts' own beneficial, as yet insufficient, immune reactions conversely, immunotherapy may suppress detrimental activities of the host's immune system. Several URLs can be consulted for updates among them, www.niaid.nih.gov, and a recent report from France comprehensively asserted the current options, to an extent which extended to the most recent literature including non-peer reviewed reports.

In France (Université de Marseille) drug repurposing with the antimaralial, chloroquine, was promoted by some but rightly put into doubt by others [63,64]. As soon as laboratory medicine succeeded in identifying the COVID-19 cytokine storm, the rationale to attenuate this storm with mAbs directed against cytokines and/or their receptors came into focus, the more so as we are experienced with these drugs in the treatment of autoimmune diseases; as an example, Tocilizumab, which is composed of two monoclonal antibodies inhibiting the cell receptor of

Table 3
Promising/candidate drugs as of 2020 with planned or ongoing clinical trials.

Trade name/ generic name	Clue	Leadership organization	Links
Putative Prevention of SARS-CoV-2 Target Cell Entry			
APN01	Decoy cell receptor	Apeiron Biologics	clinicaltrials.gov
Antibody cocktail	Virus neutralization	Regeneron	VelociSuite^{R}
Monoclonal Ab candidates	Virus neutralization	Vir Biotechnology Biogen WuXi Biologics	wuxibiologics.com
TAK-888	Modified antiviral antibody	Takeda	trialsitenews.com
Dampen Cytokine Deregulation («Storm»)			
Kevzara (sarilumab)	Blocking IL-6	Regeneron Sanofi	VelociSuite^{R}
Actemra (tocilizumab)	Blocking IL-6	Genentech BARDA	gene.com
Remestemcel-L	Lymphoid Stem Cells	Mesoblast NIH	mesoblast.com
Xeljanz (tofacitinib)	Reduce inflammation	Pfizer	xeljanz.com

Go also to: directorsblog.nih.gov.

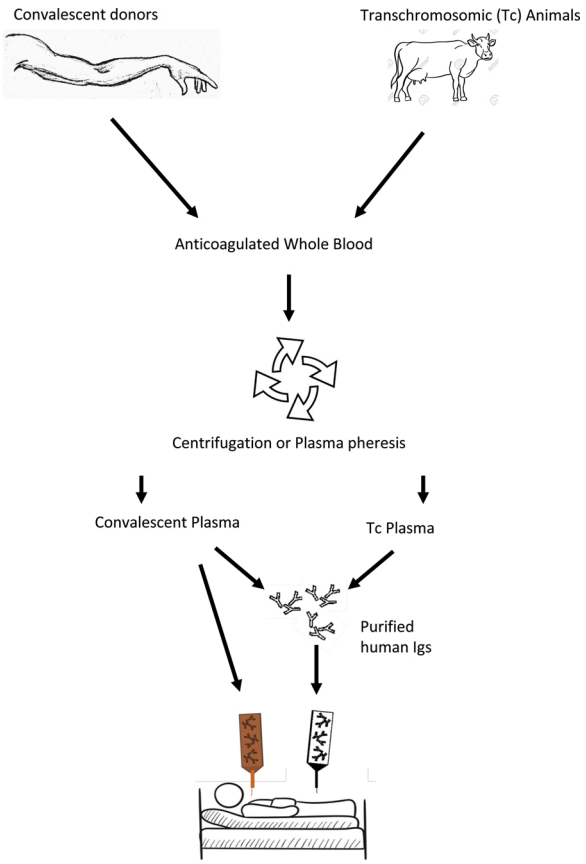

Fig. 3. From convalescence to blood plasma donation and more.
Human or cattle blood, both containing human antibodies, yield plasma which contains anti-SARS-CoV-2 antibodies with the option to separate them from the remainder of plasma proteins.

IL6 is also used in the treatment of rheumatoid arthritis [65].

Successful humoral and/or cellular acquisition of immunity/resistance against SARS-CoV-2 infection is currently explored for humoral and cell-mediated resistance [66]. Genetic engineering involving CRISPR Cas 9 not only allows production of mAbs of ever increasing specificity *in vitro* but also production of human antibodies without human donors (https://sabbiotherapeutics.com) by inserting human artificial chromosomes built by the entire human immunoglobulin gene repertoire, [67] into bovidae (Fig. 3).

4.2. Rationale to engage in convalescent plasma therapy

Convalescent source plasma from recovered COVID-19 patients, and perhaps later with plasma recovered from transgenic (Tc) bovidae as a source for potentially beneficial antibody therapy has been of increasing interest to clinincians caring for COVID-19 patients. No definitive results on benefit leaves therapists ambivalent [6]. The receptor binding domain of SARS-CoV-2 comprises the major targets or epitopes for such antibodies, *i.e.* S1-RBD, S1-NTD and S2 [68].

Upon active vaccination of transchromosomic (Tc) cattle with the plasmid vaccines expressing the MERS-CoV spike protein the animals begin to synthesize potentially MERS-CoV-2 protective antibodies within 2 weeks [69]. These encouraging results, obtained with coronavirus antibodies produced from Tc cattle are bound to be transposed to the SARS-CoV-2 and other Tc techniques using mammalian artificial chromosomes [70,71] (www.cslbehring.com).

Currently, the major reason to transfuse convalescent plasma to COVID-19 patients is to help patients on the basis of the plasma content of protective/therapeutic antibodies [72]. Of course, an antibody directed against ACE-2 would block docking of SARS-CoV-2 to respiratory epithelial cells such that S-Proteins would be prevented from entering the cell: One may be sceptical about the rationale to target the viral spikes with an antibody binding of which to the SARS-CoV-2 could in fact enhance its virulence instead of neutralizing it [72] - ADE: antibody dependent enhancement of virulence [73]. The specificity might be directed at a surface spike protein receptor binding domain (RBD) or an internal nucleoprotein (NP) a distinction originally thought important to complement RT-qPCR for diagnosis but likely to be relevant for the estimation of protective capacity [74]. Recent findings involving sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry and revealed important commonalities between SARS-CoV-2 and SARS-CoV infection thus providing favourable opportunity to antiviral intervention using CPT [13]. When over 200 RBD-specific monoclonal antibodies derived from single B cells of eight SARS-CoV-2 infected individuals were isolated their virus neutralization activity correlated with their competitive capacity with ACE2 for RBD-binding [75]. Findings like these spark interest into candidates for the development of therapy for COVID-19 patients.

Despite the current lack of placebo-controlled studies and lack of knowledge about a protective capacity of either IgM or IgG anti-SARS-CoV-2 antibodies, the clinical observation in many recovered patients, motivates wards to transfuse CPT: A case series reports on critically ill patients successfully treated with CPT has sparked worldwide interest into such an approach [76,77,64]. The right timing of anti-SARS-CoV-2 provision to patients must be adressed: A good time to transfuse CPT depends on the temporal profiles of the viral load and the time it takes to produce antibodies [74]. Thus, patients with symptoms and forming anti-SARS-CoV-2 antibodies had a shorter duration of reactive rRT-PCR oropharyngeal saliva samples and were clinically stable compared to patients without detectable anti-SARS-CoV-2 IgM antibodies [17]. Conversely, antibodies might be blamed for promoting SARS-CoV-2 entry into target cells through oponization of the virus-a process now termed “antibody-dependent enhancement (ADE) [73]. Of course, we know this from anti-D immunisation of RhD negative women of child-bearing age; passive administration of antibodies attenuates the immune response in the long run [77,78]. Hence, such patients may become vulnerable to subsequent infection long after the transfused antibodies have tapered off (half-life of IgG: 21 days).

More recently, an observational study from China suggests clinical efficacy of CPT administered to 10 severe patients [77]. A solid advantage of CPT, which uses proven techniques of blood banking to be produced, is the safety issue: well investigated with unrestricted usage worldwide, transfusion transmitted infectious disease (TTID) marker testing and look back programs, i.e hemovigilance [79,80], fresh frozen plasma (FFP) is a well established stable blood product to treat many diseases, even in the elderly [81]. So far, the search for SARS-CoV-2 in circulating blood has yielded negative results [66] but free SARS-CoV-2 viral RNA was found in the peripheral blood of 15 % of COVID-19 patients labelled RNAaemia (N = 41) (37)). FFP from healthy blood donors is also a volume replacement fluid.

Plasma exchange therapy has now been proposed by some to alleviate the cytokine storm of COVID-19 [82]. Transfusion of FFP by inverting the ABO blood type donor/recipient compatibility scheme of red blood cell concentrate transfusion, conveys to AB-type donors a rare donor status; this remains valid for the care of the elderly who still exhibit significant titers of anti-A and anti-B histobloodgroup antibodies [83]. Furthermore, FFP may cause transfusion associated acute lung injury (TRALI) or transfusion associated circulatory overload (TACO) but medics know this and are testing to avoid them [84]. Blood type A and 0, being the most frequent, we must assume, that AB and A type plasma will soon be out of stock, even with regard to CPT plasma provision. Some short term metrics following transfusion of ABO-compatible CPT revealed only minor serious adverse events in 5000 hospitalized COVID-19 patients [85]. This report suffered from shortcomings in information on provenance and GMP (good

manufacturing practice) of CPT (www.uscovidplasma.org). At Stony Brook Hospital in New York a placebo controlled clinical study with a planned enrollment of up to 500 hospitalized COVID-19 patients is being done (Elliott Bennett-Guerrero, MD). In Switzerland, as of April 2020, the drug agency Swissmedic, has registered efficacy studies for CPT nationwide. The rationale: individuals infected with SARS-CoV-2 (Germany 4th May 2020: 163.400 cases) with no apparent symptoms or recovering from COVID-19, at a first glance might be carriers of protecting factors produced by acquired immunity in their blood plasma. Right now, we dont know if anti-SARS-CoV-2 antibodies are protective against the virus. The spike (S) protein, which mediates entry of SARS-CoV-2 into ACE2 -expressing cells is similar to the HIV-1 envelope glycoprotein and its expression can be impeded with antibodies making it a putative target of a SARS-CoV-2 vaccine [86]. With CPT, only a few randomized trials have been published. 140 children and adults with influenza were randomized to receive CPT with high levels of anti-influenza antibodies or standard FFP with no significant benefit of CPT [87]. At this time it remains unclear whether detection of anti-antiSARS-CoV2 antibodies is identical with humoral immunity. When introduced into the TTID screening for blood donors, and when completed with titrations, those donors who might qualify for preparative plasmapheresis of hyperimmune plasma will be identifiable on a large scale.

The question is: how long would CPT maintain its curative activity?

4.3. Plasma fractionation to make therapy more Specific/Viable or restrictive?

Plasma obtained with remuneration or unpaid from whole blood units or source plasmapheresis is prescribed as fresh frozen plasma (FFP) units. In addition, one may blend the units in large pools to serve as starting material for stable Immunoglobulin-hemoderivatives. The plasma fractionation market was valued at $16,823 M in 2018, and is expected to reach $30,536 M by 2028, likely to grow by 6.1 % from 2019 to 2028. (www.alliedmarketresearch.com)

With viruses for which the protective capacity of anti-virus antibodies is acknowledged, such as against hepatitis B virus or varicella zoster, plasmapheresis of immune donors yields a source to produce anti-viral antibody concentrates, e.g. Dynavax (www.hepb.org), hepatitis B immunoglobulin P, Zoster Immunoglobulin –VF. Enrichment of immunoglobulins in the recovered plasma makes sense since the volume to inject is reduced relative to the active component therein. It is tempting to fractionate the CPT in the same way one applies for preparation of IVIG from large plasma pools of healty donors or transgenic cattle humanised for immunoglobulin synthesis (Fig. 3); the future will tell us [67,88].

To do so, a cautionary note applies: one encounters the risk of separating non-immunoglobulin protective factors, i.e. those which are present in CPT having helped the very COVID-19 recovered donor to overcome her/his cytokine upheaval (cytokine storm). Such proteins as shed IL-receptors, or CRP, a1-antitrypsin, C1 esterase inhibitor, metalloproteinase might be present in CPT in their active state and their putative therapeutic potential would be lost [89].

4.3.1. The challenge of monoclonal antibodies

Numerous monoclonal antibody products will enter clinical trials in the immediate future in order to explore their capacity to limit or modify SARS-CoV-2 infection [90]. A diversity of possible target epitopes on SARS-CoV-2 including NP, S, (https:/iibr.gov.il) is challenging [91]. Protein microarray technology is used to narrow down epitope specificity of antibodies of several isotypes against hundreds of antigens in a high throughput setting [92]. Coronavirus antigen microarray featuring immune-recognition relevant epitopes from SARS-CoV-2 have been explored and the resulting profiles are suitable to select convalescent plasma [93]. Using immunoglobulin specificities found in convalescent plasma as templates and implying their neutralizing capacity towards SARS-CoV-2, a race is now going on to find potent monoclonal antibodies which will prevent the virus from entering target cells, in addition to monoclonal antibodies dampening the cytokine deregulation.

4.3.2. Country-restricted self-sufficiency issues

For the time being, convalescent plasma donation appears to be only indirectly of concern for any Red Cross, Red Crescent or other humanitarian organization to include convalescent plasma in their general recruitment programs for blood donation, but this may change. The approval of products by such agencies as the FDA or compliance with the European Pharmacopoeia requirements is not yet settled but definite registration appliances for anti-SARS-CoV-2 antibody carrying plasma donors might become institutionalized.

As an example, in coordination with the U.S. Food and Drug Administration (FDA), the US Red Cross is seeking people who are fully recovered from COVID-19 to sign up to donate plasma to help current COVID-19 patients. The population is informed that patients who have fully recovered following a COVID-19 diagnosis may have antibodies in their plasma that can help those with serious or immediately life-threatening COVID-19 infections. (www.redcrossblood.org). Other countries are issuing similar slogans. The idea behind it calls to volunteers for nonremunerated donation and care should be given, on ethical backgrounds, that this remains so and that wastage tends to be nil [94,95].

4.4. IVIG therapy to improve COVID-19

With a recent case report from Wuhan (China) on a few severely COVID-19 ill patients apparently cured by IVIG [96], insight into action mechanisms will have to be elucidated to make this possibility rational to the prescribing clinicians: the background for clinical trials on patient victims of this ever expanding pandemic caused by SARS-CoV-2 RNA virus will become more solid as complete applications of plasma exchange and IVIG are now being considered [97]. The temptation is great to go further with IVIG, the more so as commercially available IVIG (Gamunex^{R}-C, Flebogamma^{R} DIF Grifols) contained antibodies cross-reactive with SARS-CoV-2, and middle east respiratory syndrome-CoV [82]. Since every so often with IVIG, administration is used as an added support of primary therapy, often in an off-label context, we need to update the therapeutic mantra actually in use worldwide.

More than forty years have passed since human immunoglobulins were first administered through the i.v. route. The beneficial use of IVIG brightened through 4 decades with prophylactic and therapeutic benefits for a large array of diseases of different immunopathological backgrounds. Clinical studies were slowed down as fear of the risk of exposure to transfusion-transmitted diseases put the breaks on clinical research. This problem was solved in a very sensible way ever since solvent-detergent (S-D) treatment was found to disrupt enveloped viruses and riboflavin/ultraviolet light was used to eliminate microbes [98]. With anti-SARS-CoV-2 antibody-enriched IVIG preparations one must be alert not to go too far with safety requirements given the fact that such preparations might contain traces of SARS-CoV-2 dependent viral RNA [99,100]. Conversely, at the outset, IVIG was studied in younger patients suffering from severe combined immunodeficiency disease (SCID) of (mainly microbial) antigens sufficient for clinical pictures of (SCID) or with acquired antibody deficiency syndrome. IVIG therapy then extended to other diseases, most of them striking adults or even the elderly. Those medics who found new indications were also motivated by the observation of certain individuals without signs of general immunodeficiency but unable to mount a specific immune response to a particular set (mainly microbial) of antigens.

The many therapeutic options currently prescribed around the globe for COVID-19 can be classified in a time frame set by the severity stage of COVID-19. We use here a simple three stage order from proven infection using PCR testing (prodromal) to infected but still mild, to severe, then requiring hospitalization (Table 4).

Table 4
How to best integrate immunotherapy into overall treatment programs of COVID patients*.

Program option	Disease stage		
	prodromal	outbroken	Severe
ventilation	0	0	+
virostatic	+	+	0
Cytokine Balance Improvers	0	0	+
Plasma Exchange			+
IVIG (polyclonal, polyspecific)	0	0	+
Convalescent Plasma	0	+	+
Ig hyperimmune anti-SARS-CoV-2 (cow?)	+	+	0
Monoclonal antibodies	0	+	0

5. Conclusions

The link between immunotherapy targeting immunopathological damage in COVID-19 patients, occasionally resembling autoimmune disease, and therapeutic approaches based on polyclonal polyspecific as well as specific anti-SARS-CoV-2 antibody therapy, seems promising and motivates many research efforts. The classical steps from *in vitro* evidence, animal evidence and human clinical evidence are often bypassed in the treatment of patients occurring in an off-label context. As we attempt to do, in Table 4, immunotherapy ought to be placed into a context of an overall treatment program which, as experience builds up, will turn into cost-efficient benefits for patients.

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