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ANTIBODY THERAPY IN THE TIME OF CORONAVIRUS

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A BRIEF HISTORY OF IMMUNITY

Pathogens have waged an antagonistic war against living creatures, be they plants or animals, since the dawn of time. Early writing from Egypt and China outline cultivation of plants resistant to various diseases.[1] For humans, the Bible says, and it was widely believed, that sickness and disease are the wages of sin (Romans 6:23) and trace back to Adam and Eve's disobedience to God.[2]

In the first century BC, Greek physician Hippocrates was first to propose separating disease from religion writing that disease "has a natural cause . . . like other affections." And that "Men regard its nature and cause as divine from ignorance and wonder".[3]

Since Hippocrates, investigations included why the same pathogen will sicken and even kill one host but not another. Yet it wasn't until 16th century Ming Dynasty pediatrician, Wan Quan, that medicine first tried to prevent a devastating disease by exposing healthy individuals to small doses of a pathogen.[4]

Wan used a process since called variolation (from the Latin name, variola, for smallpox) to immunize against the disease by taking fluid from pustules of an infected individual and rubbing it into superficial scratches made in the skin of a healthy individual in the hope that a mild, but protective infection would result. The scarified patient would develop pustules identical to those from naturally occurring smallpox, but usually had a less severe disease, which also imparted permanent immunity from a future severe case of smallpox. The procedure, which became widely used in Western medicine, was controversial because a few such immunized individuals developed a severe form of smallpox and died.

Although variolation continued for smallpox, it wasn't until the late 18th century England that a "safer" form of active immunization was discovered by Albert Jenner, now known as the "Father of Immunology."[5] After observing that a cowpox infection in humans appeared to protect them against smallpox, Jenner inoculated an eight-year-old boy with cowpox matter from

a blister on the hand of an English milkmaid. After the boy developed and recovered from cowpox, Jenner repeatedly exposed the boy to smallpox material, but the boy never fell ill.

Jenner not only discovered a new method of imparting immunity to a disease through a process he called vaccination (from vacca, the Latin word for cow), but he discovered cross-immunity between forms of pathogens. His method grew in popularity and eventually replaced variolation.

The next major discovery in vaccination occurred nearly 100 years later when in 1885, the French physician, Louis Pasteur, prevented the almost certain death of a nine-year old boy bitten severely by a rabid dog with daily injections of spinal fluid from a rabies-infected rabbit that was treated with formaldehyde, which was known to inactivate the rabies virus.[6] The boy never developed rabies and the "Pasteur Method" became standard treatment for rabies until well into the 20th century.

About the same time Pasteur was developing his methods for vaccination using attenuated viruses, the German researcher Emil von Behring with his associate, Shibasabura Kitasato, showed that serum from animals (horses) immunized against diphtheria to animals suffering from it could cure the infected animals.[7] Behring then used the serum to successfully ward off diphtheria in humans. The potential for treatment for a wide variety of infectious agents was immediately apparent and applied. In 1901 Behring, who was also the first to use the term "antibodies" to describe this "passive" form of immunity, was awarded the very first Nobel Prize in medicine for his discovery.

A German caricature showing Emil von Behring extracting diphtheria antitoxin from a horse through a tap.
Source: The Wellcome Collection, CC BY 4.0

In 1900, Behring's German colleague, Paul Ehrlich, who also worked with diphtheria, proposed the "side-chain theory" of immunity to explain at a chemical level what Behring and his predecessors had discovered.[8] Ehrlich hypothesized that in response to a toxin or other foreign matter called antigens (a term first described by Ehrlich's contemporary, Hungarian researcher Laszlo Detre), cells manufactured and secreted "side chain" chemicals (antibodies) that bind to the foreign antigen, which may be a receptor on a pathogen.

In 1948, Swedish immunologist Astrid Fagraeus described that B lymphocytes were specifically involved in antibody production.[9] By 1957 Australian Frank Burnet and American David Talmage developed the clonal selection theory; that is, that a lymphocyte makes a single specific antibody molecule that is determined before it encounters an antigen.[10]

By 1959 American researcher Gerald Edelman and his British colleague, Rodney Porter, independently published the molecular structure of antibodies, for which they jointly were awarded the Nobel Prize in 1972.[11] This was followed by the invention of monoclonal antibodies in 1975 by German scientist Georges Kohler and his Argentinian colleague Cesar Milstein, ushering in the modern era of antibody research and discovery.[12] Indeed, the subsequent ability

to sequence and construct genetic material brings us to where we are today using synthesized RNA and DNA to construct a whole new class of antibody therapies and vaccines.

USE OF CONVALESCENT PLASMA AND EMERGENCE OF IMMUNOGLOBULIN CONCENTRATES

The history of the continued use of plasma from those recovering from a pathogen (CP) has been well documented by others from its initial use by Behring in diphtheria to use in a wide variety of infections over the last 120 years.[13,14,15]

By the 1940s and 1950s, antibiotics and vaccines began to replace the use of convalescent plasma for treating many infectious disease outbreaks. But during the Korean War thousands of UN troops became infected with Korean hemorrhagic fever, caused by the Hantavirus. With no other treatment available, doctors transfused convalescent plasma to sickened and exposed soldiers saving thousands of lives.[16]

During World War II, Edwin Cohn, a noted protein chemist at Harvard, discovered a way to separate and concentrate various blood proteins, called plasma fractionation, using temperature and alcohol.[17] His concentrates of human albumin were used extensively on wounded soldiers to help stabilize their blood pressure until bleeding could be controlled. Cohn's process, which still goes by his name (i.e., Cohn fractionation), also allowed the separation out of clotting factors as well as immunoglobulins. Cohn's lab also applied the newly developed freeze-drying process to both albumin and later immunoglobulins to allow concentrates to be stored at room temperature and restored for use with sterile water, rather than having to be refrigerated.[18]

The ability to standardize, purify and concentrate plasma proteins, as well as improve storage conditions, spawned a huge growth in pharmaceutical companies getting into the plasma fractionation business. Albumin and immunoglobin preps could also be heat-treated to destroy pathogens.

The massive infection with HIV of individuals with hemophilia A due to contaminated clotting factor concentrates in the 1980s, shook up the plasma fractionation industry with large players such as Armour, Bayer, Baxter and Cutter exiting the markets. That void was largely filled by the fractionators that were traditionally tied to blood collection organizations using excess plasma from whole blood donations. As they grew, these fractionators relied on largely paid donors, most from the US. This includes companies such as BPL (UK), Biotest and Octapharma (both German), CSL Behring (Australia), Grifols (Spain), Kedrion (Italy) and Takeda (Japan).[19]

Today, intravenous gamma globulin, or more properly intravenous immunoglobin G (IVIG), which is 95 percent IgG, the most effective and stable antibody form, is used to treat a growing list of diseases, starting in the early 1950s to help patients with inherited immunodeficiencies.[20] IVIG is approved for use in most countries for multifocal motor neuropathy, chronic lymphocytic lymphoma, chronic inflammatory demyelinating polyneuropathy, Kawasaki disease and idiopathic thrombocytopenic purpura. The number of inflammatory and autoimmune diseases for which IVIG is used "off label" has expanded enormously. These diverse disorders range from blistering skin diseases to transplant rejection, and neurologic diseases.[21] Indeed, the world market for IVIG has been rising at seven to eight percent a year with no ceiling seen for the foreseeable future.[22] Among IVIG products remain a list of so-called hyperimmune immunoglobulins (HIG).

What clearly emerges from a literature review is that, absent of an effective vaccine or other therapy, antibody-rich preparations from convalescent patients do a great job in warding off infections and/or reducing morbidity and mortality, when given prophylactically either in the absence of and often early after exposure to a pathogen. Indeed, the US Centers for Disease Control and Prevention (CDC) recommends early postexposure prophylaxis (PEP) with immune globulin preparations for a variety of exposures to effectively prevent infection with hepatitis A, B and C, influenza, measles, rabies, varicella and others, especially for those at high risk of morbidity and little or no evidence of effective previous vaccination.[23] In cases where a vaccine against the pathogen exists (such as hepatitis A and B), CDC recommends PEP use of the vaccine either with or without the additional use of an antibody prep.

Use of antibody preps have a more mixed result when disease symptoms emerge. For example, studies in the 1920s and 30s using CP in patients with early symptoms of polio but preparalytic, found no statistical differences in mortality to those who did not receive CP.[24] However, lacking any other therapy, and due to the very mixed nature of how polio strikes it victims, the use of CP PEP remained recommended until the 1950s implementation of a vaccine.

More recently, PEP use of CP for Ebola, first in 1976 outbreaks in Central Africa and then between 2014-16 more widely in Western Africa, was the only therapy available.[15] It proved effective in warding off severe disease, but its use in advanced cases was mixed. Indeed, one of the few comparative, but nonrandomized trails of CP in Ebola patients found somewhat lower mortality in the CP group, but the difference was not statistically significant.[25]

COVID19 AND ANTIBODY THERAPIES

Which leads us to use of CP, HIG and monoclonal antibodies in the current pandemic. The first reports of CP use came rapidly as the infection spread across the global. Early publications from epicenters of disease in China and Italy found encouraging outcomes, and countries across the globe began gearing up to collect and distribute products.[26,27]

From experience with the first coronavirus outbreak of SARS-CoV-1in China in 2004-05, we knew convalescent plasma could change the course of the disease in infected patients.[28] We also knew from our 120-year experience with CP that given prophylactically, or even PEP, antibody preps can prevent viral infection or severe morbidity, but there was little data on the two most important questions concerning CP and COVID19: when is it ideally used? And what's the most effective dosing? Other questions arose, such as we knew from Ebola studies that those with mild cases made little antibody: would the same be true for SARS-CoV-2 infection?

In parallel with gearing up for collection of CP around the world, many high-income countries began setting up randomized control trials involving the various antibody preps. Indeed, as of this writing (early January 2021), the site tracking clinical trials (clinicaltrials.gov)

lists over 150 active or recruiting trials of CP with about another handful completed.[29] The site also shows a score or more of COVID HIG trials, and over 70 studies using monoclonal antibodies, including several that were terminated for showing little improvement for patients on ventilators receiving the synthetic antibody preps.[30]

US EXPERIENCE WITH COVID19 CP

The experience of the US with CP for treating COVID19 infections can both be observed as a model, as well as a controversial mess. Even eight months after the first unit of CP was collected under an FDA protocol, there remains confusion as to when and how it should be used (Katz, preprint). The media reports that tens of thousands of monoclonal antibody preps go unused because many hospitals haven't yet figured out how to give them to the outpatients who might benefit most, that is patients with early symptoms and comorbidities, but no severe respiratory symptoms.[31]

As of December 2020, over 250,000 patients had been treated with CP under first FDA's Expanded Access Program (EAP) and since August, under a wider Emergency Use Authorization (EUA).[32] It is worth examining the US COVID19 timeline and CP response to understand what was done well, the controversy surrounding CP use and availability, as well as the current confusion over use of any of the antibody preps.

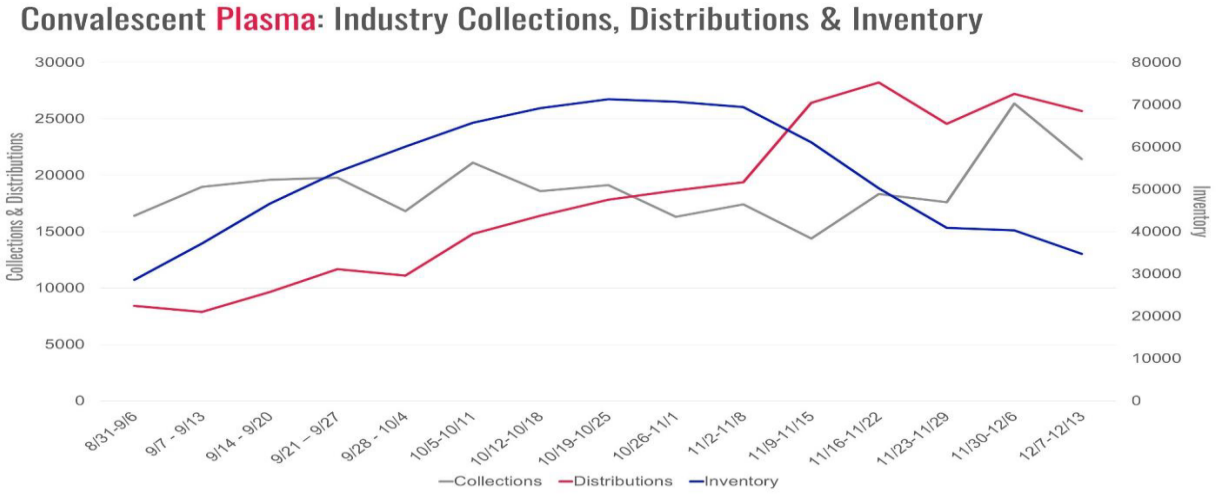

Figure 1. CP collections and distribution since the end of August 2020 showing that until new spikes of COVID19 in the fall inventories of CP had been rising, and while collections have increased following the new spikes, demand has been outstripping CP availability. Source: ABC Newsletter 2020 #43, 11 December 2020

Although rumors of a new contagious and deadly virus in China were circulating as early as November 2019, the first announcement by the World Health Organization of a "Mysterious Coronavirus-Related Pneumonia in Wuhan, China" came on January 9, 2020.[33] Just six days later, a Washington state resident became the first person in the US with confirmed case of COVID19, having just returned from Wuhan.

By the end of February, New York City hospitals were diagnosing scores of residents with COVID19, most with a connection of recent travel to Europe (i.e., Switzerland and Italy), where outbreaks were occurring.[34]

Meanwhile, a debate was raging between and among US public health agencies (i.e., NIH, FDA and CDC) with the regional public health communities about making CP widely available.[35] With hospitalizations and deaths rising, the argument that eventually saw the widespread collection and use of CP in April was that the therapy must be widely available for compassionate use.[36]

Since the 1970s, FDA allowed access to investigational drugs under "compassionate use" waivers to treat patients with serious diseases or conditions for which there are no comparable or satisfactory therapy options available outside of clinical trials.[37] However, this access was case-by-case and it wasn't until 1987 that FDA published regulations for a formal pathway for patients to access such drugs under what it called an Expanded Access Protocol or EAP. Those EAP access regulations were revised in 2009 and again in 2017.

Since 1987, FDA was receiving over 1,000 applications annually for individual patients to use investigational drugs. Never had the regulations been used to make an investigational drug widely used until COVID19. Usually, wider use to a promising investigational drug was made available under an Emergency Use Authorization (EUA), but only after the drug had demonstrated both preliminary safety and efficacy in drug trials.

Since the 1970s, the "gold standard" worldwide for clinical trials has been so-called prospective randomized controlled trials or RCT, whereby an investigational drug is given in a strictly controlled environment to measure its effectiveness against the standard therapy for a disease, or giving about half the patients in the trial a placebo.[38] While many research institutions inside and outside the US were setting up RCTs for CP and other antibody preps, an agreement was struck to make CP widely available under an EAP.

The Mayo Clinic was designated by US Department of Health and Human Services Biomedical Advanced Research and Development Authority (uscovidplasma.org) to oversee data collection by over 2,000 registered US hospitals that between March and the end of August 2020, transfused over 94,000 units of CP among 105,000 patients enrolled in the study. Mayo's lead investigator for CP study has noted at several forums that the EAP was never expected to register over 5,000 patients, much less tens of thousands.[39]

But controversy haunted the EAP and later the EUA for CP. Research institutions conducting RCTs of antibody preps, including CP, as well as other possible treatments were finding that patients or their families were refusing to be randomized if it meant they could not receive CP. This significantly slowed the pace of recruitment of patients in such trials. It also confounded trials when enrolled patients insisted on getting CP even where the trial was investigating a new non-antibody drug.

Other high-income countries either followed the US lead in making CP widely available or insisted on proceeding with RCTs first. Several countries, such as Germany, did both in enrolling patients in RCT of CP while making it available on a compassionate basis where a patient might have no other option.[40]

In August 2020, FDA went the next step to make CP even more widely available through an EUA, which requires no centralized data collection on experience and outcomes except for adverse reactions to CP.[41] It justified going from the EAP to an EUA based on historical use of CP in general and specific use in patients with COVID19 infection in the Mayo EAP.

> "When comparing the 7-day and 28-day survival of hospitalized patients receiving convalescent plasma with lower levels of antibodies (lower titer, ID50 < 250) to those receiving higher levels of antibodies (higher titer, ID50 ≥ 250), there was no significant difference in survival in the overall population of hospitalized patients at Day 7 following the administration of COVID-19 Convalescent Plasma or in those hospitalized patients who were intubated. However, there were statistically significant improvements in survival at Day 7 in [those who were not intubated and] who were treated within ≤ 72 hours of diagnosis.
>
> "In the overall population of 4,330 patients for whom 7-day data were available there was no effect of the administration of COVID-19 Convalescent Plasma across the range of titers administered. However, in the [3,420 patients who were not intubated and who were] treated within 72 hours of diagnosis, there was a dose response of convalescent plasma evident, with higher antibody levels associated with better outcomes (fewer deaths). A similar dose response pattern was observed in the 2,817 patients who remained hospitalized at Day 28."[41]

Many infectious disease specialists were not impressed. The New York Times reported that the head of NIH, Francis Collins, and head of NIH's infectious disease division, Anthony Fauci, both urged FDA not to go to a EUA believing the data from the Mayo trial was "weak" and more data on CP was needed from RTCs to warrant an EUA.[42]

President Donald Trump, who was lagging in his reelection polls due to a perceived weak early response to the pandemic, tweeted that Collins' and Fauci's objections were "politically motivated." So, when FDA went ahead an approved the EUA for CP despite NIH opposition, that decision itself was deemed political. Indeed, both the media and surveys of Americans feared that approval of the "Holy Grail" in this pandemic, that is, the various vaccines in current RCTs would also be politicized.[43]

In reality, results from the Mayo trial with CP mirrored the trials in hospitalized patients with severe COVID19 using the monoclonal antibody preps. In November 2020, after stopping RCTs of three monoclonal antibodies in hospitalized patients with SARS/ARDS, FDA approved

under an EUA Eli Lily's monoclonal antibody prep bamlanivimab, as well as several days later, Regeneron's casirivimab and imdevimab preps, but only for confirmed cases of COVID19 with mild to moderate symptoms, and only for those "who are at high risk for progressing to severe COVID19."[44]

Famously, in early October, President Trump was whisked by helicopter to nearby Walter Reed National Military Medical Center, after showing increasing signs of respiratory distress several days after it was confirmed he acquired the COVID19 virus.[45] While at Walter Reed, the President received the steroid dexamethasone, which had become standard therapy for respiratory distress in COVID19 patients, but he also received, at his own request based on a conversation with the president of Regeneron, a dose of the company's antibody cocktail.[46] Since the drug was still investigational, the FDA authorized the President to receive the cocktail under an individual EAP compassionate use request. It remains unknown whether the President's quick recovery was due to the drugs administered, but he was released only three days after being admitted to Walter Reed.

EMERGING RESULTS FROM RCT ON CP

While several studies, including the EAP Mayo Clinic study, using CP continued to show improvement in hospitalized patients,[47,48] other studies have shown using CP in moderate to severe COVID19 patients have shown no benefit in using the therapy.[49,50] Two most notable studies have emerged from Argentinian medical groups.

The first major RCT published from the Argentinian PlasmAr Study Group in the New England Journal of Medicine in November 2020 in over 300 patients with COVID19 severe pneumonia found, "No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo."[50]

In contrast, a second paper from the Argentinian INFANT-COVID-19 Group published results from a randomized, placebo-controlled trial of CP with high IgG titers against SARS-CoV2 in over 160 elderly subjects within 72 hours of mild COVID19 symptoms. The study

found that 16.2 percent of patients receiving plasma vs. 31.2 percent receiving placebo went on to experience severe respiratory disease.[51] The authors concluded that, "Early administration of high-titer convalescent plasma against SARSCoV2 to mildly ill infected seniors reduced COVID-19 progression." They went on to say that, "This safe, inexpensive, outpatient intervention facilitates access to treatment from industrialized to low- and middle-income countries (LMIC), can decompress demands on hospitals, and may contribute to save lives."

EXPERIENCE IN OTHER COUNTRIES

This author has sat in on multiple conferences including reports from a score or more countries from around the globe. While many countries are taking a conservative approach in awaiting more results from RCTs, others have gotten the message that earlier is better when it comes to administering any antibody prep to COVID19 patients at risk for severe disease. A sampling of "lessons learned" follows.

A brief webinar sponsored by the Pandemic Response Initiative at the University of California San Francisco Institute for Global Health Sciences was held 10 December 2020 (UCSF). Stimulus for this discussion was an agreement between the Bill & Melinda Gates Foundation and Eli Lilly to distribute monoclonals to LMIC. The speakers were a combination of industry, therapy and African public health experts. The main takeaways were as follows:

- A main "benefit" from the global war against the SARSCoV2 virus may be the rapid development (and investments) in what was "fringe" or boutique technologies for development of newish vaccines (e.g., genetic and viral carrier, as opposed to traditional attenuated or viral protein vaccines); monoclonals against specific pathogens (as opposed to more traditional convalescent plasma or hyperimmune globulins); as well as new antiviral drugs developed against lower frequency but devastating outbreaks, such as for Ebola.
- The biotech/pharma industry clearly see long-term benefits from potentially expanding the market and make it more feasible for these high tech and expensive technologies to potentially replace the older ones.

- While supporting older available technologies, high income countries (HIC), like the US, in Europe, Canada, etc., have clearly embraced the newer technologies, especially for vaccines. LMIC, however, will more likely use one of the various viral-based Chinese vaccines that are cheap and easy to produce, and appear to be relatively effective (60- 70%) in warding off infection, although apparently higher (about 90%) in preventing severe morbidity and reducing mortality.
- African health representatives expressed interest in the Gate-Lilly partnership, but expressed high skepticism in several areas. First, these technologies are hugely expensive to produce and require low temp cold chains that exist only in major Sub-Saharan cities. While the pharma companies talk about building factories in African countries to reduce costs, can these new technologies really compete with older ones in low resource countries? Second, will companies really partner with African countries in developing and testing new technologies, or will it be the same old transfer of technology from Europe or the US? And third, while there have been major investments by biotech firms in Africa, most is in South Africa and little with other Sub-Saharan countries' physicians and scientists, home to another 1.3 billion people.

In summary, the seminar unfolded as a "tale of two cities," or more properly, two realities. The new technologies may be the new reality for HICs, but transfer of that tech to LMIC, which haven't even yet fully exploited lower tech solutions, seems daunting at best, or at least highly premature. It is also clear that the monoclonals are finally realistic competition for the plasma industry. It will be years before synthetic antibodies can replace the current drivers of the IVIG market, but clearly that is a biotech focus given the steady and significant annual global growth in the plasma-based products.

Similarly, an Eastern-Mediterranean World Health Organization Regional webinar was organized by the Iranian Blood Transfusion Organization and held 24 November 2020. The main takeaways were as follows:

- While nearly every blood collection organization (BCO) across the globe had disaster plans drafted, the vast majority did not address a pandemic as a possible scenario. In

many cases, BCOs were not included in their government's disaster response plans. Consequently, BCOs had difficulties in getting access to PPE and even regular supplies as supply chains tighten; emergency transportation for staff, donors and blood; and preferential access to news media.

- For most countries, the first few weeks to months of pandemic social restrictions were highly disruptive to maintaining an adequate blood supply; although most (BCOs) have since adjusted.
- Iran reported a 25% initial drop in donations in the February/March period of the outbreak. In Pakistan, some hospital-based BCOs had upwards to a 50% drop. Austria too saw a 50% drop, but were able to reverse the loss quickly by directly contacting regular donors
- BCOs that heavily rely on donor collections at schools/from students, religious establishments, and/or business organizations suffered immediate and the most severe drops in collections, requiring them to shift to fixed site collections. Donor outreach was largely either by contacting regular donors directly or by more general needs messages through the news outlets and social media (mostly through Facebook).
- Staff shortages due to illness exacerbated collection problems.
- Often donors needed reassurance that BCOs were using precautions to protect them from possible transmission from staff and other donors. Celebrities and religious and government officials were used to get out the messages of blood needs to potential donors.
- Blood shortages became alleviated both by special donor recruitment measures, but also by drops in blood use as trauma of all kinds generally lessened during social lockdowns. As hospital beds filled with COVID19 patients, less blood was also being used for elective surgery.
- Countries like Iran and Pakistan, where significant amounts of RBCs go to younger patients with B-thalassemia, reported difficulties in meeting those needs.
- Countries like Pakistan, where BCOs are mostly hospital-based, saw more severe blood shortages where they rely on replacement donors. The bigger BCOs with a significant volunteer donor base had less severe shortages than smaller, more rural hospital-based BCOs. .

- Most countries organized collection of COVID19 CP within four to six weeks after major outbreaks occurred in February or March. Demand for CP continues to be high especially as hospital admissions are spiking again. None of the LMIC were collecting CP to process into HIG because of high demand for the patient use of the plasma.
- Iran reported collecting 11,000 units of CP with constant demand, although no data were shown.
- Saudi Arabia is increasingly giving CP "prophylactically with promising results"; that is, PEP as outpatients with early symptoms after a confirmed diagnosis. Again, no data were reported.
- Saudi Arabia is also treating CP with pathogen inactivation as a "precaution," although they admitted the plasma was unlikely to transmit the coronavirus.
- FDA, and to a lesser extent AABB and WHO, were mentioned as primary sources for pandemic blood donor and CP information.
- Most countries are screening donors either by confirmed diagnosis and/or using an antibody test to both uncover potential CP donors, but also to understand how the virus is spreading among the generally healthier population that donors represent.

In summary, the experiences of many BCOs to the pandemic were similar: lack of adequate preparation; canceled blood drives and scared donors; blood shortages; personnel absences; good response to media outreach; started collecting CP as early as possible; addressing supply chain shortages; etc. This isn't surprising as in this small community within healthcare, everyone talks to each other and copies "best practices."

SUMMARY & DISCUSSION

Had it been plentiful enough and easy to administer, it is likely that CP, along with HIG and the monoclonals had the potential to be an effective prophylaxis to save the lives of thousands of frontline healthcare workers or perhaps made a dent in the over 100,000 lives lost up to December 2020 in the US alone among residents and staff in long-term care facilities.[52,53] Ironically, and in desperation, it has largely been used, especially in the early months, as "rescue

therapy" among the sickest in our hospitals with no significant impact on survival of such patients.

There are plenty of lessons to be learned from this "once in a century pandemic." But that is the problem: we will learn those lessons while the next pandemic may be HIV-like, or Mad Cow Disease-like, or something entirely different. Or maybe it will be another disease where lessons learned from pandemics through history say we need to isolate the most vulnerable and protect everyone else the best we can, including using known solutions like CP, but early and to the most vulnerable.

As the new genetic vaccines roll out, who main job is to make antibodies in the inoculated to ward off infection, one realizes it really is all about antibodies and how best to use them and solicit their production, both in vitro and in vivo. Unlike the "gold standard" measles vaccine, which is over 98 percent effective and imparts permanent immunity, we do not know if the new genetic vaccines using only strands of RNA or DNA will generate any permanent immunity in the B or T cells of our immune system. And will they, like seasonal flu vaccines which impart partial immunity to new strains of influenza viruses, protect against the mutations the SARSCoV2 is undergoing?

We are enamored with these new genetic vaccines because they are potentially safer than traditional vaccines made from attenuated virus. Nearly 45 years later, we still do not know what caused an outbreak of hundreds of cases of Gillian-Barre among the 45 million who received the 1976 swine flu vaccine.[54] This fact coupled with an unfounded hysteria over concerns of a possible link between autism and childhood vaccines drives us to look to high tech solutions to cure and prevent disease, rather than "blood from others."

But it is this search for the next generation of drugs that can also create confusion. FDA was very clear when it halted trials of monoclonals in those with severe COVID19 disease that it was futile to use these drugs in already very ill patients. But with now similar findings in RCTs, FDA has not updated its advice on the use of CP since August, despite growing evidence that the best use of CP, along with HIG and the monoclonals, is at least PEP.

As a final note, I monitor a Facebook group of over 14,000 hospital blood bank workers, mostly in the US but also around the world (Facebook Blood Bank Group). Recently, the question was asked by one member whether CP was being given to "outpatients", meaning those with mild symptoms but potential risk for severe disease. Of 16 responders (a very small sample size), several hospitals reported yes; most said no, that CP was still only given to the sickest in intensive care, to which two responders said that those on ventilators no longer get the plasma at their hospital.

Coupled with the recent Washington Post report cited above where little of the monoclonals are being used at hospitals, it reinforces that the US is both a model and a cautionary tale in this pandemic.[31] Politics, love of new technology and the desire to move quickly to vaccinations, have confused not only the average American, but many healthcare worker as well.

The jury is still out on the best practices in using CP therapeutically. By the time we figure it out, vaccines will be widely distributed and demand will decline, especially when HIG also becomes widely available. The synthetic antibody preps are expensive and so far, difficult to ramp up production. But that should change over time, especially with Gates money behind monoclonal antibody distribution to LMIC.

The lessons learned with COVID-19 are hard ones. We'll be much better prepared next time, unless next time is another 100 years from now when those lessons will have been forgotten or believed to be irrelevant.

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