Hark back: Passive immunotherapy for influenza and other serious infections

Thomas C. Luke, MD, MTMH; Arturo Casadevall, MD, PhD; Stanley J. Watowich; Stephen L. Hoffman, MD, DTMH; John H. Beigel, MD; Timothy H. Burgess, MD, MPH

The world is experiencing a pandemic of swine-origin influenza virus H1N1. The ability to use SOIV H1N1 vaccines as a public health tool has been described as a “race against time.” Oseltamivir and related drugs are being used in an effort to reduce morbidity and mortality, but their efficacy for treating severe influenza is suboptimal, and possible widespread emergence of oseltamivir-resistant mutants is a concern. Another approach for prevention and treatment of serious influenza is infusion of hyperimmune plasma. The United States has thousands of licensed blood product collection centers that produce millions of liters of plasma licensed by the Food and Drug Administration on an annual basis for the treatment of serious conditions. Immunotherapy using infusion of convalescent plasma (or hyperimmune intravenous immunoglobulin) has been reported to be an effective treatment for severe influenza and other virulent pathogens in animal models and humans. Plasma obtained from those that have recovered or were early recipients of vaccine offers a resource for production of an immediately available and potentially effective therapy at the local, state, and national level. Past, current, and future uses of immunotherapy and current advisory body recommendations for this approach are presented. (Crit Care Med 2010; 38[Suppl.]:S000–S000)

Key Words: influenza; passive; immunotherapy; convalescent; plasma; serum; immunoglobulin; antibody

The world is experiencing a pandemic of swine-origin influenza virus (SOIV) H1N1. The ability to use SOIV H1N1 vaccines as a public health tool has been described as a “race against time” (1). Epidemiologic data suggest that pregnant women, children younger than 4 yrs, and younger adults may be at higher risk for severe disease (2), and segments of the susceptible population will become ill before they can be immunized (2). The final impact of the SOIV H1N1 pandemic cannot be predicted but local, state, national, and global health and political bodies are preparing for a surge of cases that may place severe strains on healthcare and social systems. Some governments responded to the ongoing threat of H5N1 influenza by creating antiviral, antibiotic, and other medical product stockpiles and developed pandemic response plans that may help to alleviate the severity of this pandemic.

Initial testing of the SOIV H1N1 virus found it susceptible to neuraminidase inhibitors (oseltamivir and zanamivir) and resistant to adamantanes (amantadine and rimantadine) (3). Reports of oseltamivir-resistant mutants, although not unexpected, are nonetheless concerning (4–7). During the 2007 to 2008 influenza season, seasonal H1N1 rapidly developed resistance to oseltamivir, increasing from 12.3% to 98.5% of the samples tested (8, 9). Should a similar pattern of rapid resistance to oseltamivir emerge for SOIV H1N1, satisfactory treatment options will be limited and supportive care will be the only option for most.

One potential therapeutic option is passive immunotherapy with plasma from convalescent patients or hyperimmune intravenous immunoglobulin (hIVIG) containing polyclonal antibodies obtained from recovered patients or recipients of effective vaccine. This approach is not without precedent; human-derived and animal-derived convalescent serum, plasma, and hIVIG were the standard of care for treatment of many pathogen-mediated and toxin-mediated diseases before the advent of “modern” pharmaceuticals in the 1950s (10–12). Historical evidence suggests that this approach might have efficacy for treating influenza. During the Spanish influenza pandemic, investigators reported that convalescent blood products were highly effective in the treatment of influenza pneumonia and what is now known as acute respiratory distress syndrome (13–36).

A recent meta-analysis of these historical studies concluded that patients with Spanish influenza pneumonia who received influenza-convalescent human blood products may have experienced a clinically significant reduction in mortality (37). The authors suggested that convalescent plasma or hIVIG in the modern era could be a timely, effective, and widely available treatment during an H5N1 pandemic (or other infectious dis-
ease for which no good treatment exists) and that well-designed clinical trials should be conducted. Further support for this hypothesis comes from human studies conducted in the Soviet Union that reported that convalescent serum products and hIVIG were efficacious in the prevention or treatment of influenza and influenza pneumonia (38–42), and from animal studies (43–50) using various types of passive immunotherapies. Successful treatment of a pulmonary H1N1 infection in severe combined immunodeficiency mice with hemagglutinin-specific antibodies with very low virus-neutralizing activity in vitro (51) and in H5N1-infected mice with equine-derived H5N1 Fab fragments (52, 53) provides evidence that passive immunotherapy is beneficial in a model of severe disease for immunologically competent and incompetent hosts.

We present an overview of the modern process for producing large volumes of plasma, historical and current uses of passive immunotherapy to treat infectious agents, a description of advisory body recommendations, and efforts to collect convalescent SARS-CoV-2 plasma for use in a clinical trial.

**Modern Production of Plasma**

The production and transport of licensed blood products in the United States are regulated by the Food and Drug Administration (54). Blood products are obtained in blood donor centers and source plasma centers. Blood donor centers typically rely on volunteers or directed donors who give blood products after a defined screening process and informed consent to insure the safety of both donors and the nation’s blood supply. Directed donors provide blood products for personal use or a specific person/purpose. Blood donor centers typically produce fresh-frozen plasma (FFP) that is suitable for patient infusion or that can be used to produce intravenous immunoglobulin (IVIG). Source plasma centers produce frozen plasma, typically from paid donors, for the manufacture of IVIG products. Frozen plasma is not licensed for direct infusion into patients.

Plasma is obtained by two primary methods: automated apheresis or fractionation. The maximum volume of FFP or frozen plasma (Table 1) obtained by automated apheresis has been established by the Food and Drug Administration (55). Automated apheresis can be performed in an individual once or twice within a 7-day period; this equates to a potential volume of 625-1250 to 800-1600 mL per week. The volume of FFP derived from fractionation of 500 mL of whole blood is approximately 250 mL (56). The frequency of whole blood donation is once every 8 weeks (56 days) (57).

Before the 1950s, the collection, transport, and transfusion of blood products using glass containers and nonstandardized consumables made the process logistically and clinically challenging. The introduction of plastic equipment and bags by Walter and Murphy (58, 59) radically simplified the process. As a result, the United States (and other nations) have developed a sizeable national infrastructure and workforce devoted to the production of blood products. The American Association of Blood Banks accredits approximately 1200 blood banks, transfusion centers, and blood centers (60). The American Red Cross has established 34 blood services regions with multiple blood collection centers in the United States (61). The America’s Blood Centers network has >600 member centers in 45 states (62). The Plasma Protein Therapeutics Association reports that 335 source plasma centers were located in the United States in 2007. It is estimated that 14.6 million liters of frozen plasma and FFP are produced annually (63) and that 4 million units of FFP are annually transfused in the United States, with a similar number in Europe (64–65). This infrastructure could produce a clinically significant volume of convalescent plasma obtained from recovered patients or from early vaccine recipients for treating severe influenza, antiviral-resistant influenza, or new or emerging infectious disease.

**Historical Use of Convalescent Serum and Hyperimmune Immunoglobulin**

Serum therapy was the only modality available for the treatment of infectious diseases until the introduction of sulfonamides. It was launched by the discovery of Behring and Kitasato that administering immune sera could protect a host against bacterial toxins. Use of serum therapy diminished dramatically in the 1940s with the introduction of penicillin and other antibiotics. The abandonment of serum therapy was the result of the toxicity associated with animal-derived serum, the difficulty of making an early specific diagnosis, and the technical limitations of collecting and administering serum in that era. However, serum therapy retained a niche in the treatment of venomous bites and eventually returned in the 1960s in the form of specific immune globulins for a variety of conditions.

In general, animal sera were used to treat diseases if animals could be infected or immunized to yield high-titer sera in large volumes. In contrast, for diseases that affected only humans and when animal immunization was not practical (such as viral diseases), the serum was usually of human origin. To overcome the collection, cold-storage, transportation, and immunoassay limitations of that era, the “lyophile” process was developed and involved drying pooled hyperimmune serum in a vacuum (66). The powder was solubilized in distilled water and several milliliters were administered intramuscularly. Lyophilized sera were available for the prophylaxis and/or therapy of conditions such as scarlet fever, measles, mumps, chickenpox, erysipelas, German measles, and acute hemolytic streptococcal infections (66). Although the majority of historical studies were not conducted by current standards, the results are valuable if considered within the limitations of the data.

**Use of Human Convalescent Sera Against Bacterial Diseases**

In general, most bacterial diseases such as pneumococcal pneumonia and meningococcal meningitis were treated with immune sera derived from animal sources (11, 12, 67). Animal sera were preferred because large amounts of sera could be recovered from animals and the material could be standardized in laboratory tests. Nevertheless, it was recognized that human sera had bactericidal activity in the form of complement, and several studies attempted to obtain better results through the use of convalescent sera or fresh serum in combination with an animal-derived specific antisera. Human se-

<table>
<thead>
<tr>
<th>Donor Weight (Weight)</th>
<th>Plasma Volume (Weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110–149 lb</td>
<td>625 mL (640 g)</td>
</tr>
<tr>
<td>150–174 lb</td>
<td>750 mL (770 g)</td>
</tr>
<tr>
<td>&gt;175 lb</td>
<td>800 mL (820 g)</td>
</tr>
</tbody>
</table>

Human convalescent serum was also used for the treatment of scarlet fever. Birkhaug (71) reported the use of 15–85 mL of pooled human convalescent sera obtained 3–5 wks after defervescence of 37 patients during the first 7 days of disease. Although this was not a controlled study, the author noted improvement in most patients, particularly when the serum was administered early in the course of disease. Another bacterial disease treated with human antibody preparations was whooping cough. Administration of “hyperimmune antibacterial pertussis human serum” was considered to have significant value for the treatment and prophylaxis of contacts (72). Another preparation, known as “lyophile hyperimmune serum,” was derived from young boys who had a history of pertussis (73). This preparation was used as late as the 1940s and was reported to be effective in children with and without the addition of sulfonamides (73), but double-blind, controlled studies of pertussis treatment with hIVIG decades later revealed no therapeutic benefit (74).

**Human Convalescent Sera Against Viral Disease.** Human convalescent sera have been used to treat and prevent measles, mumps, polio, Spanish flu, vaccination, and varicella, among others. A review of the use of convalescent sera published in 1943 (75) concluded that measles and mumps convalescent sera were effective for the prevention of disease when administered to exposed individuals who were at risk for disease. During a measles epidemic in Baltimore in the winter of 1942, convalescent serum was fractionated to generate fractions enriched in antibodies and used with high efficacy to prevent disease (76). The majority of treated individuals were children who received from 2–5 mL of fractionated convalescent serum by intramuscular injection (76). Varicella convalescent serum was considered of questionable value, but controlled clinical trials conducted in the 1970s found that zoster immune plasma from convalescing adults was highly effective in preventing postexposure varicella in immunosuppressed children (77).

The efficacy of poliomyelitis convalescent therapy was uncertain, especially if administered once the disease had manifested; nevertheless, volumes in the range of 100 to 200 mL delivered intravenously were used in treatment. The relative ineffectiveness of this therapy may have been a result of inadequate amounts of antibody. One study showed that the amount of neutralizing antibodies in poliomyelitis convalescent sera was highly variable and suggested that better results might be obtained using selected sera with high neutralizing titers to polio virus (78).

Published studies from the Spanish flu H1N1 pandemic reported that transfusion of influenza convalescent human blood products (whole blood, plasma, or serum) reduced morbidity and mortality in patients with influenza complicated by pneumonia. Luke et al (37) conducted a meta-analysis of eight studies involving 1703 patients to determine the impact on mortality and other factors. The typical volume of plasma or serum administered was 125–250 mL on one to two occasions (range, 1–7), and the agent was usually obtained from the donor 7–60 days after symptoms had resolved. The overall crude case-fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls (Fig. 1). The range of absolute risk differences in mortality between the treatment and control groups was 8% to 26% (pooled risk difference, 21% [95% confidence interval, 13% to 27%]). The overall crude case-fatality rate was 19% (28 of 148) among patients who received early treatment after <4 days of pneumonia complications) and 59% (49 of 83) among patients who received late treatment (after >4 days of pneumonia complications) (Fig. 2). The range of absolute risk differences in mortality between the early treatment group and the late treatment

---

**Figure 1.** Absolute risk difference of serotherapy vs. control. Absolute risk difference in mortality for each study, with 95% confidence intervals and the pooled estimate obtained using a random-effects model. The results were statistically significant, favoring treatment with serotherapy ($z = 7.1, p < .001$).

**Figure 2.** Absolute risk difference in early vs. late serotherapy. Absolute risk difference in mortality for each study, with 95% confidence intervals and the pooled estimate obtained using a random-effects model. The results were statistically significant, favoring treatment with serotherapy ($z = 6.73, p < .001$).
group was 26% to 50% (pooled risk difference, 41%; 95% confidence interval, 29% to 54%). The authors concluded that controlled trials are needed to establish the efficacy of this approach for H5N1 and other influenza strains.

Modern Use of Convalescent Plasma, Serum, and IVIG

The use of convalescent human plasma/serum/IVIG to treat viral infectious diseases in modern medicine is limited, and few randomized, clinical trials have been conducted. Reasons for this development include the development of highly effective vaccines that drastically reduced the number of cases of many infectious diseases; the development of chemotherapeutics and other medical interventions that have, or are perceived to have, a wider utility against pathogens; and a research focus to develop monoclonal antibodies to treat specific pathogens. However, convalescent plasma or hIVIG has been attempted when other therapies were unavailable.

Argentine hemorrhagic fever—caused by Junin virus, a member of the arenaviruses—is the only infectious disease in which convalescent plasma is, to our knowledge, the standard of care. Enria et al (79) recently published a review describing the history, preclinical development, clinical trials, and current status of Argentina’s National Program for the treatment of Argentine hemorrhagic fever. This program was established after conclusive results of a double-blind, placebo-controlled study demonstrated that patients treated with 500 mL of convalescent plasma intravenously within 8 days of onset of symptoms had a case-fatality rate of 1.1% compared to 16.5% for those treated with nonconvalescent plasma. The treatment volume was later standardized by the development of a formula that included the titer of neutralizing antibodies in each unit of convalescent plasma and the patient’s body weight as variables (79).

Chinese investigators treated a previously healthy 31-year-old man with H5N1 influenza–pneumonia using convalescent H5N1 plasma 11 days after symptoms first began (80). The plasma was obtained from an individual who had recovered from H5N1 16 months previously. Three 200-mL transfusions of convalescent plasma (neutralizing antibody titer 1:80) were administered over 24 hrs. After the first transfusion, the patient’s viral load was reduced by a factor of approximately 12 (from 1.68 × 10^10 to 1.42 × 10^9 copies/mL) during the first 8 hrs and was undetectable within 32 hrs. Concurrently with plasma administration, the patient was also receiving oseltamivir as the standard of care. The patient made a full recovery and was discharged.

Convalescent plasma and hIVIG were used in hospitals in Southeast Asia to treat severe acute respiratory syndrome often as a “rescue” treatment for patients with a deteriorating clinical course despite other treatments (81–85). All reports were retrospective studies, and different passive immunotherapy products were used in conjunction with steroids, ribavirin, interferon-alpha, and other treatments. Reported outcome measures varied and included death, time to discharge, the development of acute respiratory distress syndrome, and the need for ventilation. Although the authors indicated that passive immunotherapy was beneficial in reducing morbidity and mortality rates, a systematic review categorized the studies as inconclusive because of the confounding effects of varying co-treatments (some possibly harmful), comorbidities, and other factors among the studies (86). The authors suggested that controlled trials for this approach are needed to establish the efficacy of this approach for severe acute respiratory syndrome.

Use of convalescent human immunodeficiency virus plasma to treat patients with acquired immunodeficiency syndrome and human immunodeficiency virus was assessed in multiple clinical trials. The treatment course lasted 1–4 yrs with frequent infusions of high-titer plasma at intervals of every 2–4 wks with 250–500 mL of plasma (87–91). No patient had human immunodeficiency virus infection cured, but investigators reported a halt or delay in the progression of disease or in the number of acquired immunodeficiency syndrome-related complex conditions during the study period. The intensity of the treatment regimen, the lack of viral clearance by convalescent plasma, and the development of highly active antiretroviral therapy products severely limited the utility of this approach for treating human immunodeficiency virus.

Convalescent plasma has been used in the treatment of Lassa fever and Ebola virus with mixed results (92, 93). According to Jahrling et al (92, 93), optimal convalescent plasma containing neutralizing antibodies to specific strains of Lassa fever develops several months after recovery, with only a minority of patients having high titers. Therefore, treatment plasma should be obtained from the same geographical region (strain-specific) and pretested for neutralization titer (92). The usefulness of convalescent plasma in the treatment of Ebola virus is questionable after well-controlled primate studies, regardless of anecdotal reports of human effectiveness (93).

A number of other viral diseases have been treated with hIVIG and IVIG with variable results. Red blood cell aplasia caused by parvovirus B19 infection is the only recognized viral infection in which treatment with IVIG may eradicate infection (94, 95). However, there is considerable evidence that passive immunotherapy may beneficially modify the natural history of viral diseases. These are summarized here.

Cytomegalovirus. Cytomegalovirus–enriched immune globulin preparations have shown benefit when used in combination with ganciclovir in the treatment of cytomegalovirus pneumonia. This immune globulin preparation is also utilized in the treatment of ganciclovir-resistant cytomegalovirus infections (96).

Respiratory Syncytial Virus. In adult bone marrow transplantation patients with respiratory syncytial virus pneumonia, combination therapy using aerosolized ribavirin and standard IVIG (500 mg/kg every other day for 12 days) resulted in a 22% mortality rate, compared to a historical mortality rate of 70% (97). In pediatric bone marrow transplantation patients with respiratory syncytial virus pneumonia, those treated with combination aerosolized ribavirin and respiratory syncytial virus antibody-enriched IVIG had a 9.1% mortality rate, compared with the historical rate of 50% to 70% in patients administered ribavirin alone (98).

Vaccinia Virus. Certain complications of vaccination with the vaccinia virus (smallpox vaccine) have been treated with vaccinia immune globulin, including generalized vaccinia, eczema vaccinatum, and progressive vaccinia. Although no controlled trials of efficacy have been reported, anecdotal experience suggests that vaccinia immune globulins for these conditions are beneficial and are now considered the standard of care (99).

Hepatitis A. Persons who recently have been exposed to hepatitis A and who have not been previously vaccinated against the disease are recommended to...
receive standard IVIG as postexposure prophylaxis. This recommendation is based on data that showed IVIG, when administered within 2 wks after an exposure, is >85% effective in preventing hepatitis A (100, 101). IVIG also can attenuate the clinical expression of hepatitis A infection when administered later in the incubation period (101). Standard IVIG is used because it contains sufficient anti-hepatitis A antibodies (100).

Hepatitis B. For patients with hepatitis B and cirrhosis undergoing orthotopic liver transplantation, hepatitis B high-titer immunoglobulin G is administered preoperatively and postoperatively to prevent reinfection. This has been shown to be 50% to 85% effective in preventing recurrence of hepatitis B in the transplanted liver (102). This result may be improved with the concurrent use of the antiviral lamivudine (103).

Rabies. Rabies high-titer immunoglobulin G is the standard recommended therapy after exposure (104).

Ebola Virus. A hyperimmune serum derived from goats was developed by Russian researchers. It was reportedly tested in human clinical trials for biological safety and reactivity, and it was immediately and successfully administered to four researchers suspected of becoming infected with Ebola virus during their experimental work (105).

Advisory Body Recommendations and SOIV H1N1 Convalescent Plasma Collection Efforts

The Defense Health Board convened a meeting of national and international experts in February 2008 to evaluate the potential of convalescent plasma. The Defense Health Board is a Federal Advisory Committee to the Secretary of Defense that provides independent scientific recommendations on matters relating to operational programs, health policy development, health research programs, and requirements for the treatment and prevention of disease and injury (106). Participants included representatives from the World Health Organization, the Department of Health and Human Services, the Department of Homeland Security, the Centers for Disease Control, the National Institutes of Health, the Food and Drug Administration, the Center for Biologics Evaluation and Research, the Plasma Protein Therapeutics Association, nonprofit blood donor centers, and clinical care experts. The Defense Health Board recommended that convalescent plasma therapy guidelines should be developed as part of the national pandemic influenza plan and as an alternate treatment for novel, natural, or human-made bioterrorism agents in future research and practice (107).

In July 2009, the World Health Organization Blood Regulators Network issued “Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Pandemic Influenza Planning” (108). The Blood Regulators Network wrote that “convalescent plasma might play a role in the urgent response to pandemic influenza in settings where vaccination and/or effective antiviral chemotherapy is lacking.” The group emphasized the need for well-designed clinical trials and the need to coordinate with the plasma production industry so that large-scale production could be accomplished if warranted.

Clinical researchers and blood product donor specialists at the National Institute of Allergy and Infectious Diseases, the Naval Medical Research Center, and other institutions are collaborating to address these recommendations. A clinical study (Clinical Trial ID NCT00984451) has been developed to collect plasma that has high titers of anti-influenza novel H1N1 antibodies (109). The plasma will be obtained from individuals who have recovered from the SOIV H1N1 virus or who have been vaccinated. This study is in progress.

CONCLUSION

In the past 30 yrs, the world has experienced three significant pandemics of new viral pathogens—human immunodeficiency virus, severe acute respiratory syndrome, and SOIV influenza—for which effective and timely quantities of vaccines and/or therapeutics did not exist at the start of the pandemic. The threat of H5N1 or other virulent influenza strains that can explode globally has not diminished. The United States also has experienced the initiating salvo of biowarfare in the form of anthrax attacks with the threat of other viral, bacterial, or toxin agents looming. Researchers, regulatory bodies, industry, and governments responded to the threat of H5N1 influenza and other pathogens by creating oseltamivir and antibiotic stockpiles, maximizing current vaccine production processes, formulating response plans, and developing investigational therapeutics and vaccines, efforts that may make a difference during this SOIV pandemic. However, resistant mutants to existing chemotherapeutics can arise naturally with disturbing speed or potentially by directed design.

Convalescent plasma obtained from those who have recovered or were early recipients of vaccine offers an opportunity to produce an immediately available and potentially effective prophylactic or therapy at the local, state, and national levels for new and emerging diseases. The United States already produces millions of liters of plasma on an annual basis, and the existing infrastructure and personnel could be prepared a priori to produce a potentially therapeutic product. Convalescent plasma is not a panacea and will not be effective for all pathogens. However, for some pathogens—such as Argentine hemorrhagic fever, which can be effectively treated with 500 mL of convalescent plasma—it could be a standard-of-care therapy and produced in clinical population-relevant volumes.

A potentially complete model for such a national program exists for anthrax. Human convalescent plasma obtained from individuals receiving anthrax vaccine adsorbed is effective in the prevention and treatment of anthrax in animal models, and hyperimmune serum was successful in the treatment of human cutaneous anthrax (110–112). A national effort to collect and administer convalescent plasma in real time, or to establish repositories of plasma product for future events (in the form of high titer FFP or lyophilized plasma), could result in an economic and available therapeutic adjunct for anthrax prophylaxis or treatment in large populations (112; Casadevall, Hoffman, and Luke, personal communication). This should be achievable given the several hundred thousands of U.S. military and first responders who are being, or have been, vaccinated against anthrax. The concept also has potential application to epidemics of seasonal and pandemic influenza. Potential donors include the millions who become ill before the delivery of vaccine and the millions of healthcare workers and other groups who have a designated priority for vaccination in accordance with the Health and Human Services Pandemic Influenza Plan (113).

REFERENCES

2. Advisory Committee on Immunization Practices: Use of Influenza A (H1N1) 2009


40. Zhukova EA: [Character of the therapeutic action of different schemes of administra- tion of donor anti-influenza gamma-globulin to influenza patients]. Tr Inst Im Pastera 1985; 63:47–51


43. Sweet C, Bird RA, Jakeman K, et al: Production of passive immunity in neonatal ferrets following maternal vaccination with killed influenza A virus vaccines. Immunology 1987; 60:83–89


59. Walter CW: Invention and development of the blood bag. Vox Sang 1984; 47:318-324


111. Lucchesi PF, Gildersleeve N: The treatment of anthrax. JAMA 1941; 14:1506–1508
