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Update article

Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow

La plasmathérapie anti-infectieuse : hier, aujourd'hui, demain

O. Garraud [a,b,*], F. Heshmati [c], B. Pozzetto [a,d], F. Lefrere [e], R. Girot [f,g], A. Saillol [h], S. Laperche [b]

[a] *Faculté de médecine de Saint-Étienne, université de Lyon, 42023 Saint-Étienne, France*
[b] *Institut national de la transfusion sanguine, 75015 Paris, France*
[c] *Hôpital Cochin, Assistance publique des Hôpitaux de Paris, 75005 Paris, France*
[d] *Laboratoire des agents infectieux et d'hygiène, CHU de Saint-Étienne, 42055 Saint-Étienne, France*
[e] *Groupe Necker–Enfants malades, Assistance publique des Hôpitaux de Paris, 75015, Paris, France*
[f] *Hôpital Tenon, Assistance publique des Hôpitaux de Paris, 75020 Paris, France*
[g] *Université Pierre-et-Marie-Curie–Paris 6, 75005 Paris, France*
[h] *Centre de transfusion sanguine des armées, 92140 Clamart, France*

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Abstract

Plasma therapy consists in bringing to a patient in need – in general suffering a severe, resistant to current therapy, and even lethal infection – plasma or specific, fractioned, antibodies, along with other immunoglobulins and possibly healing factors that can be obtained from immunized blood donors; donors (voluntary and benevolent) can be either actively immunized individuals or convalescent persons. Plasma therapy has been used since the Spanish flu in 1917–1918, and regularly then when viral epidemics threatened vulnerable populations, the last reported occurrence being the 2013–2015 Ebola virus outbreak in West Africa. The precise action mechanism of plasma therapy is not fully delineated as it may function beyond purified, neutralizing antibodies.

Keywords: Plasma therapy; Convalescent plasma; Neutralizing antibodies; Therapeutic plasma; Infectious disease; Transfusion; Ebolavirus infection

Résumé

La plasmathérapie consiste en l'apport à un patient, en général victime d'une infection sévère, résistante au traitement en cours et potentiellement létale, de plasma thérapeutique ou d'anticorps spécifiques purifiés, mais aussi des immunoglobulines polyréactives et des facteurs de cicatrisation présents dans le plasma des donneurs. Ces donneurs (bénévoles et volontaires) peuvent avoir été préalablement immunisés ou ils ont été infectées mais ils sont alors convalescents. La plasmathérapie a été mise en œuvre dès la grande grippe espagnole de 1917–1918, puis ensuite très régulièrement à chaque occurrence d'épidémie virale menaçante, la dernière en date étant l'épidémie de fièvre Ebola apparue récemment en Afrique de l'Ouest. Les mécanismes d'action précis de la plasmathérapie – au-delà des seuls anticorps neutralisants – sont encore non précisément identifiés.

Mots clés : Plasmathérapie ; Plasma convalescent ; Anticorps neutralisants ; Plasma thérapeutique ; Maladies infectieuses ; Transfusion ; Ebolavirus

1. Concept of passive immunotherapy and history

The concept of passive immunotherapy emerged in the late XIXth century, following the setup of Experimental Medicine. It derived from the earliest works of Ehrlich in Germany and,

* Corresponding author. Faculté de médecine de Saint-Étienne, université de Lyon, 42023 Saint-Étienne, France.
E-mail address: ogarraud@ints.fr (O. Garraud).

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though less directly, of Pasteur in France and Bordet in Belgium, who identified the key factor that "complements" the neutralizing action of antibodies [1].

The principle of serotherapy was established in 1880 when it was shown that immunity against diphtheria, and then tetanus toxins largely relied on antibodies present in blood of animals intentionally immunized with non-lethal doses of toxins, which could be transferred to naïve animals experiencing active infection [2,3].

This has been successfully applied to humans suffering notably from diphtheria, sera from diverse animal species (goats, horses, sheep) being subjected to a flourishing pharma-industry between 1920 and 1940. Such "immune sera" saved numerous lives against the otherwise lethal effects of bacterial toxins, though at the expense of occasional iatrogenic hazards termed in particular the "serum sickness", actually a type III hypersensitivity immune response according to the Gell and Coombs classification of 1963 [4,5].

Once plasma fractionation into plasma derived-therapeutic factors was made available around the 50s, immunoglobulins (Igs) were purified and concentrated from highly immunized donors having fully recovered from past clinical or asymptomatic infection, constituting the so-called hyperimmune immunoglobulin fractions. Human Igs—and particularly specific Igs, but non only—progressively replaced the use of animal sera, especially under the form of intravenous Igs (IVIGs) and they are still in current use, notably for neutralizing the tetanus toxoid toxin, the hepatitis B virus (HBV), the rubella virus, the pertussis toxin and the rabies virus [6].

Besides, there has been accumulating evidence that polyclonal Igs from plasma offered by regular blood donors—under the form of IVIGs—conferred some degree of protection to achieve pathogen elimination or the reduction of pathology in severely infected patients presenting with bacterial sepsis or acute viral infections. IVIG use has even been proposed to help protecting exposed patients and especially children having not yet developed infection, such as with human immunodeficiency virus type 1 (HIV-1) [7,8].

Of important note, on a very regular basis, and for more than 100 years, whole blood or plasma recovered from convalescent patients has been transferred to actively infected individuals, often as last chance or experimental treatments. Transfusion of blood with the purpose of conferring some protection was not current practice in the 1st half of the XXth century [9] but it was performed in experimental protocols, often intended to be compassionate. Indeed, decades after immunotherapy against allergens in hay fever was initiated (1911), Mary Loveless demonstrated that blood from immunized Ragweed sensitive individuals benefited to non-immunized Ragweed sensitive individuals during the hay fever season [3].

These experiences tell a number of important information:

- protection to certain severe infection or disease is transferable by serum, plasma or Igs/Antibodies (Abs)—from bulk to highly purified;
- protective Abs can be obtained and processed from deliberately infected animal hosts or from naturally-infected convalescent humans;
- protective Abs can even be used prophylactically;
- not only specific neutralizing Abs but also polyreactive Igs can confer some degree of protection against infection or disease.

2. Plasma therapy and severe outbreaks

The past and present centuries experienced a number of viral outbreaks evolving as epidemics, along with viral endemic-epidemic situations. Until recently, effective antiviral therapies were either experimental, or hazardous, or unaffordable. The A/H1N1 Spanish flu (1917–1919) killed more people than the First World War ever (between 30 and 50 million people, depending on the estimates). More recently, the SARS coronavirus epidemics (2003), the A/H5N1 flu epidemics (2005–2015), the A/H1N12009p flu epidemics (2009–2010), the recent Ebolavirus epidemics (2013–2015) proved exceedingly lethal and threatened the global health systems, calling for protection measures of non-exposed populations, prophylaxis to exposed but not yet infected populations and experimental therapy of attacked individuals. Each of those situations—including the early Spanish flu—proposed the use of convalescent plasma therapy. Besides, some viral infections are present under the form of locally or regionally restricted epidemics, with a large attack rate within exposed populations but a low expansion capacity. Those epidemics that are particularly severe in general, and often lethal such as viral hemorrhagic fevers (VHFs) [10] and hantavirus infections, were found eligible for convalescent plasma therapy protocols whenever possible: these are Lassa Fever, Argentine Hemorrhagic Fever, Rift Valley Fever, and Sin Nombre and Puumala virus infections, to cite some. Besides, also, some viral infections evolving as endemic-epidemic, emerging or reemerging situations that were major killers, especially in low-income areas, such as measles, HIV/AIDS and rabies [11] were also found to be eligible for plasma therapy. Lately, viral infections that are not particularly lethal compared to some other previously cited ones but that have threaten or still threaten populations, both in the developing and the economically developed world, and against which efficacious antiviral chemotherapy is limited, have been tested for the opportunity to use specific IVIG: these are chikungunya virus infection [12], dengue virus infection, and possibly others such as hepatitis E virus (HEV) infection [13], and also *Trypanosoma cruzi* infection (Chagas disease) [14]; of note, despite experimental attempts, *Plasmodium falciparum* malaria seems to resist plasma therapy or specific Ig benefits.

3. Serum and convalescent plasma therapy: from experimental to large-scale protocols

3.1. Historical reports

Historically, since Roux and Yersin discovered that clinical diphtheria symptomatology was attributable to a toxin (1888), and that Behring and Shibasaburo made anti-diphtheria toxin

serum available (1890), therapies based on hyperimmune sera have been consistently used to treat infected individuals and largely applied until sulfonamides were introduced in year 1930 [1,2]. One of the largest uses was perhaps for treating tetanus toxoid, with animal sera and then—as of the 60s—with specific human Igs. Only two situations still rely on serum animals: botulism and diphtheria. CMV infection, hepatitis A virus (HAV) infection, measles, hepatitis B, rabies, tetanus, pertussis, vaccinia and chicken-pox (varicella) [15] can be fought by human sera [4,6–8]; indeed, plasma fractionation has been made available back to year 1945 and since then, specific Igs can be made available when convalescent blood individuals are eligible for blood or plasma donation. An HAV epidemics was treated back in 1945 by unfractionated Ig treatment, and then specific—fractionated Igs—were used to treat HAV and HBV infections prior to the large-scale campaigns of vaccination. Less specifically or prophylactically, IVIG treatment has been proposed to treat victims of toxic shock syndrome after ingestion of contaminated food in the 60s. Based on evidence obtained from successful use of either non-fractionated or specific Igs in a few viral infections, immune therapies were given occasionally: in 1953 to fight a smallpox outbreak in India, and in many other occasions, and still as has been proposed during the 2013–2015 Ebola crisis [6–8].

3.2. Reported experiences

3.2.1. The Spanish flu (1917–1919)

A fascinating report—actually a meta-analysis of former reports contributed by physicians facing A/H1N1 Spanish flu patients—offers a look-back on serum therapy or whole blood therapy carried out by a variety of practitioners in different countries, with general observations of either mild or distinct improvement after the procedure [16]. This was probably the pioneer experience in plasma—actually serum—therapy performed to face a viral outbreak, with many others after that.

3.2.2. Measles (as of the 30s)

Protection against measles has relied for a long time on plasma therapy and this viral infection offers one of the largest reported experiences [17], with still—or rebound—interest as recently analyzed by a meta-analysis of the Cochrane series (2014) [18].

3.2.3. Arenaviruses (50s to 80s)

The Argentine (Junin virus, JUNV) and Bolivian (Machupo virus, MACV) HFs were described in the 50s and the Lassa virus (LASV) in the early 70s. All can lead to severe hemorrhage and proved to benefit from convalescent plasma therapy protocols, prior to new antiviral drug use. Several mid-80s publications reported in particular experiences with plasma therapy in LASV infection [19–23]. Two important observations were made available at that time: firstly, that only late—as opposed to early—plasma can confer some protection against disease, and secondly, that plasma brings healings factors preventing excess vascular leakage and also procoagulant factors.

3.2.4. Bunyaviruses (mid 80s)

There have been a couple of published experiences of plasma therapy against the Rift Valley fever virus (RFFV) and the Sin Nombre virus (SNV). In the latter case, patients having recovered from another hantavirus, i.e. the cardiopulmonary syndrome (HCPS)-hantavirus, cleared viral load after exposure to SNV and recovered successfully [24,25]. Specific Igs obtained from convalescent individuals showed promises in experimental protection of monkeys infected by the Puumala virus (PUUV) [26]. Next, there is some interest to explore immunotherapy against the Crimean-Congo HF virus, another member of the *Bunyaviridae* family belonging to the *Nairovirus* genus [27].

3.2.5. HIV/AIDS (the 90s)

Several groups on both sides of the Atlantic attempted to infuse heated plasma collected from HIV-1 seropositive symptom-less individuals to AIDS patients. The French group led by Jean-Jacques Lefrère was indeed a pioneer in such compassionate protocol. The outcome was the maintenance over weeks of anti-p24 Abs in transfused patients, and a delay in the appearance of further AIDS symptoms. Information has been made available by those investigators that there were probably factors other than Abs that mattered in the beneficial observed effects [28–31].

3.2.6. Coronaviruses (SARS, 2002–2003)

The human SARS-CoV outbreak has been rapidly faced by convalescent therapy initiatives with reports being made available quite early after the episodes. All released publications claimed that this therapy was followed by a drop of viral load and an improvement of patient symptoms [32–38]. A meta-analysis conducted quite recently concluded in the safety of the procedure and a global decrease in mortality [39]. A look-back study very elegantly provided additional information: compared to antiviral therapies that—for some of them—proved harmful, no blame was posed on convalescent plasma therapy having been performed by means of either unfractionated plasma or purified Igs. Another analysis reports some interest of this therapy with mention to the sustained anti-inflammatory effect which it carries. Those look-back studies and meta-analyses were also driven by the perspective of offering convalescent plasma therapy to treat individuals infected by MERS-CoV, an epidemics that affects presently the Arabic peninsula [40].

3.2.7. Influenza viruses: the recent serious outbreaks

The early years of the XXIst century already faced two serious flu epidemics with new influenzavirus serotypes. The 2005 A/H5N1 infection, which is still ongoing in a few countries such as Egypt, led to occasional convalescent plasma therapy initiatives and preparedness plans interrogate the possibility to propose plasma therapy in the future if this serotype would become pandemic [41–45]. The 2009 A/H1N12009p flu infection led to very severe cases and plasma therapy or hyperimmune Ig therapy has been proposed. Both study reports and meta-analyses or look-back studies show a certain efficacy when applied early (before 5 days after exposure). Experimental studies done with material collected during the outbreak also

conclude that this procedure shows promises to reduce the viral burden and morbidity/mortality [46–53].

3.2.8. Chikungunya virus (2005–2006 and onwards)

An outbreak due to the Chikungunya virus (CHIKV), a member of the *Togaviridae* family, genus *Alphavirus*, was observed in the Indian Ocean as of 2004 in Mayotte and in 2005–2006 in the island of Réunion, where more than one third of the population has been infected, a large number of them being symptomatic and few severely symptomatic. The virus spread in India in 2006 and then in the Caribbean area; it is also present in Southern Europe. Because of its attacks rate and the economical and societal impact, the use of purified specific IgGs was taken into consideration. Specific IVIG, obtained from plasma from convalescent Réunion islanders [12], were used years after in children suffering infection in the French Caribbean Islands. Data are not been made available to the scientific community so far, but there is strong hope in this therapy.

3.2.9. Ebolavirus (2014)

The proof of concept that convalescent plasma is efficient in Ebolavirus (EBV) disease was brought as soon as of 2001 in an experimental model [54]. The intensity of the 2013–2015 outbreak in West-Central Africa has prompted NGOs, WHO, and diverse consortia in the US and Europe to set up protocols for collecting plasma from convalescent individuals, despite uncertainty on the one hand of the viral clearance and on the other hand on the existence and sustainability of protective neutralizing Abs. A general preference has been made for fractionated Igs that can be processed from plasma given by repeated apheresis procedures [55–58]; alternatively, some practitioners insisted on the interest of therapeutic or specific plasma to bring endothelial healing and plasma procoagulant factors [59]. Plans have been made, and IVIGs have supposedly been prepared in order to be further used when new cases are declared [59–61]. One study has reported use of convalescent plasma in addition to an antiviral drug in two patients; both recovered without noticeable sequel (although one of them experienced multi-organ failure and necessitated kidney replacement) [62]. The authors indeed concluded that the role of convalescent plasma vs other support care is difficult to delineate.

4. Concluding remarks: Old or new fashion therapies? Novel serotherapies: protective antibodies and monoclonals?

Is plasma therapy the last chance treatment—a compassionate therapy—or is it a subtle resuscitation tool to care (if not cure) a severely infected patient showing not only organ failure and distress, but often severe hemorrhage? Hundred years of practice have not allowed a precise answer to this question; however, there is one constant observation: plasma therapy and hyperimmune Ig therapy must be applied as early as possible after the onset of infection and/or disease manifestation. Regarding the possible mode of action of this therapy, the technologists tend to favor specific Igs from cracked plasma whereas physiologists recognize the additional effect of healing factors preventing excess vascular leakage and procoagulant or antifibrinolytic factors, with direct potential interest. Obviously, infectious diseases that do not present as HFs will be better counteracted by purified Abs; manufacture of monoclonal Abs are indeed strongly wished in these cases, with the example of HIV, where many attempts have been made over a couple of decades [63]. Another virus which displays a high attack rate and can lead to severe pathology, including HF symptoms as seen with DENV could be in theory eligible for plasma or Ig therapy [64]; however, this viral infection is versatile in eliciting neutralizing Abs and it has been proposed that Abs raised to one serotype may even be facilitating towards some of the other three serotypes. Programs are however aimed at eliciting modified Abs that can be protective; DENV is indeed considered as a serious threat in certain parts of the world, with potential to reach milder or temperate areas as the South of Europe [10,65].

As a final remark, it is important to note that, if plasma therapy—whatever the form of convalescent plasma or purified Abs—, is possible, this is through the generosity of patients who either recovered from infection or have been exposed to it without manifesting symptoms (and with the proven absence of virus persistence). In all cases, there is benevolence and many of us would pledge for that humane quality is not altered by the money of business system and stays in the field of the voluntary non-remunerated system of blood donation [66]. Obviously, one has to make sure that plasma (and purified Igs/Abs) are devoid of remaining virus (and other pathogens) and protocols, by use of pathogen reduction technologies which are now largely available in economically wealthy countries but must be made available as well in developing countries facing viral outbreaks (as has been the case during the Ebola crisis).

Disclosure of interest

The authors declare that they have no competing interest.

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