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Convalescent Plasma Treatment in a Pandemic: An Historical Perspective

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Abstract

The scientific concept behind the use of blood serum from a convalescent patient who had recovered from an infectious disease to treat another patient ill with the same malady arose in Germany in the early 1890s in the context of pneumonia. In the succeeding decade, the approach was extended to other contagious diseases by investigators in Europe and the US but the evidence from case studies was unconvincing and it was largely abandoned.

Interest in convalescent serum was renewed in the 1910s and it was attempted during an epidemic of poliomyelitis in the US. This work presaged its application in treating patients who developed the deadly bronchopneumonia associated with the influenza pandemic of 1918, especially at US naval hospitals. Such therapy was rarely used in the UK but convalescent serum and other immune blood products were introduced to prevent and attenuate measles infections in children during biennial epidemics of the disease in London during the 1930s.

In recent decades convalescent plasma has been used to treat pandemic influenza and viral infections causing acute respiratory distress syndrome but most trials were uncontrolled or underpowered so that the true value of the therapy was not established satisfactorily. The recent pandemic of coronavirus disease 2019 represented a substantial opportunity to test convalescent plasma therapy in randomised controlled trials. The disappointing outcomes to date reflect more than a century of experience which demonstrated that this empirical treatment, however rational and attractive in principle, is difficult to make work in practice.

Keywords

Convalescent, serum, plasma, pandemic, COVID-19, coronavirus

Introduction

The World Health Organisation (WHO) first became aware of a cluster of cases of a viral pneumonia with unknown cause in Wuhan, People's Republic of China on 31 December 2019. By March 2020, coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic.[1]

As early as January 2020 collections were made in China of plasma from patients with COVID-19 who had recovered; this so-called convalescent plasma (CP) was then used to treat patients critically ill with the disease.[2] The rationale for CP as a potential therapy was explained by authors from Chongqing Medical University who reviewed clinical trials, meta-analyses and recommendations relevant to earlier outbreaks of infectious disease and concluded: 'Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events'.[3]

This paper reviews the origins of the idea that preparations such as CP, which are derived from the blood of patients who have recovered from a particular infectious disease, can be used as specific therapy for patients who are sick with that same disease. The subsequent history and development of this therapeutic concept is traced through a series of relevant examples, notably the 1918 influenza-pneumonia pandemic in the US and recurrent epidemics of measles in the UK during the 1930s. The difficulties encountered and the lessons learned help put in perspective current attempts to deploy CP and demonstrate its effectiveness during the COVID-19 pandemic.

Origin of serum therapy

The rationale for CP therapy drew upon on the seminal experimental work of Emil Behring (1854-1917) and Shibasaburo Kitasato (1852-1931) at Berlin's Institute of Hygiene where Robert Koch (1843-1910) was Director. In 1890 they showed that by repeatedly inoculating an animal with a bacterial toxin they induced it to develop an immunity to the pathogenic effects of the toxin. The animal's blood serum, the cell-free liquid part remaining when the blood had been allowed to clot, carried antitoxic properties able to neutralise the toxin. Moreover, they showed that this antitoxic immunity could be transferred to a susceptible animal by injecting it with serum taken from an animal rendered immune to the toxin.[4]

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[1] World Health Organisation. Listing of WHO's response to COVID-19. 2020; published online, 29 June. www.who.int/news/item/29-06-2020-covidtimeline/ (accessed 28 Feb 2022).

[2] Shen C, Zhaoqin-Wang, Zhao F, Yang Y, Li J, Yuan J, *et al*. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *Journal of the American Medical Association*. 2020; 323: 1582-1589.

[3] Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infectious Diseases.* 2020; 20: 398-400.

[4] Behring E, Kitasato, S. Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. *Deutsche medizinische Wochenschrift*. 1890; 16: 1113-1114.

The potential of 'antitoxins' made by inoculating animals with either diphtheria or tetanus toxin for the cure and prevention of the respective diseases was immediately recognised and the concept broadened to treat other bacterial infections using anti-bacterial sera. Serum therapy was the only specific treatment available in the decades before the advent of antimicrobial chemotherapy and antibiotics.[5] The production of antitoxins and antisera in horses was a complicated process involving careful preparation of bacterial broths, repeated inoculations according to set schedules to boost specific immunity, and subsequent processing of the serum to ensure a safe product of guaranteed potency.[6]

In his private laboratory in Berlin in 1891, Paul Ehrlich (1854-1915) investigated the development of immunity in animals injected with the plant toxins ricin and abrin and drew attention to the coincidence between the development of immunity and the onset of healing:

> The most striking finding, which surprised me the greatest, is the sudden, I would say, critical emergence of immunity on the sixth day. One is instinctively led to suppose that the critical drop in fever in so many diseases, which, as in pneumonia and measles, often occurs at the end of the first week, can be attributed to a similar process, a critical onset of immunity.[7]

Ehrlich's speculation provided the rationale for the treatment of infectious diseases with convalescent serum (CS): the infecting bacterium made a specific toxin exerting pathogenic effects to which the body produced a specific antitoxin that neutralised the toxin so that fever relented and the patient recovered. Post-crisis the serum of convalescent patients would therefore be expected to contain antitoxins instrumental in fighting the disease to which Ehrlich gave the generic name 'antibodies'.[8]

Convalescent serum therapy of pneumonia

At about the same time, Georg Klemperer (1865-1946) and Felix Klemperer (1866-1932), at the 1st Medical Clinic of the Charité Hospital in Berlin under Ernst von Leyden (1832-1910), carried out studies of immunisation in relation to pneumonia. In rabbit experiments, they believed that the pneumococcus produced a 'pneumotoxin' to which the animal responded by making a neutralising anti-pneumotoxin. Serum taken from an immune rabbit protected naïve rabbits against pneumococcal infection. In addition, a subcutaneous (sc) injection of a small amount of immune rabbit serum given to

[5] Wawrzynczak EJ. The advent of serotherapy in Britain tracked by *The Extra Pharmacopoeia*, 1895-1920. *Pharmaceutical Historian*. 2019; 49: 33-46.
[6] Wawrzynczak EJ. Lifesaving serum from horses: the Lister Institute of Preventive Medicine, tetanus antitoxin, and World War I. *Veterinary History*. 2019; 20: 28-52.
[7] Ehrlich P. Experimentelle Untersuchungen über Immunität. I. Ueber Ricin. *Deutsche medizinische Wochenschrift*. 1891; 17: 976-979.
[8] Ehrlich P. Experimentelle Untersuchungen über Immunität. II. Ueber Abrin. *Deutsche medizinische Wochenschrift*. 1891; 17: 1218-1219.

pneumonia patients caused a significant drop in temperature in all cases but not in patients with a different infection.[9]

The Klemperer brothers referenced the earlier papers of Behring and Kitasato and that of Ehrlich as well as similar work on immunity to pneumonia and its treatment in animals by contemporary German researchers.[10] They were clear that their work represented preliminary experiments aimed at guiding future studies of the healing power of the serum of immunised animals in patients with pneumonia. However, they also showed that serum taken from patients recently recovered from pneumonia worked in their rabbit model of the disease, providing suggestive evidence of the potential value of CS treatment.

Clinical use of CS was reported at a meeting of the Association for Scientific Medicine held in Königsberg, Prussia on 11 January 1892 when Ernst Neisser (1863-1942) described his work with Ludwig Lichtheim (1845-1928), Professor of Medicine at the University of Königsberg. After reviewing the discovery of antitoxins and early studies of immunity in pneumonia he detailed experiments confirming the Klemperers' work which stimulated Lichtheim to conduct therapeutic experiments in patients with a potentially curative serum:

> Obtaining such [therapeutic serum] from rabbits to inject into humans was certainly not safe given the known harmful effects of the serum of foreign species; on the other hand, within the serum of the person who had critically survived a pneumonia, had become 'critically immune' according to Ehrlich, the same healing principle had to be presumed as in rabbit serum.

The first subject was injected into the arm vein with a large quantity of serum obtained from a patient recovering two days after a pneumonic crisis. The treated patient whose temperature dropped at once recovered and in turn provided CS which was injected into another patient with pneumococcal infection.[11]

Clinical studies of CS in patients with pneumonia were not confined to Germany. In 1892, multiple authors published papers in several European countries, which were referred to in the report of a case from the US.[12] Positive outcomes followed injection in 30 cases, although some recoveries might have occurred by crisis before the usual time. The American authors still felt the results suggested that: 'in the blood of persons or animals, after an attack of pneumonia, there exists a substance antidotal to pneumonia'. However, having treated further cases using one or more sc injections in various doses, the same authors expressed 'most distinct disappointment' at the

[9] Klemperer G, Klemperer F. Versuche über Immunisirung und Heilung bei der Pneumokokkeninfection. *Berliner klinische Wochenschrift*. 1891; 28: 833-835 & 869-875.
[10] Emmerich R, Fowitsky A. Die kunstliche Erzeugung von Immunität gegen krupose Pneumonie und die Heilung dieser Krankheit. *Münchener medizinische Wochenschrift*. 1891; 38: 554-558.
[11] Neisser E. Ueber Heilversuche bei der Pneumonie. *Deutsche medizinische Wochenschrift*. 1892; 18: 593-594.
[12] Hughes WE, Carter WS. A case of pneumonia treated by transfusion of blood from a convalescent case. *Therapeutic Gazette*. 1892; 16: 668-673.

'irregular results' obtained and suggested 'important factors' other than anti-pneumotoxin were involved in producing crisis and immunity.[13]

The first decade of convalescent serum therapy

The German-language literature suggests that the concept of CS therapy arose in Germany although it is difficult to pinpoint a single originator. Over the next decade, it was tried by several practitioners at various locations against a variety of diseases believed to have an infectious cause, principally typhoid fever, scarlet fever and measles (Table 1). The practice quickly spread to other parts of Europe and beyond but failed to become mainstream medicine and the number of case studies published declined. The reasons for this loss of interest may be glimpsed from a contemporary critique.

The author of a German overview of immunity research noted that authors repeatedly claimed a favourable influence on the course of disease when the numbers of cases treated were too small to allow proper assessment of the method. He questioned the rationale of the treatment because making effective animal sera required the repeated injection of increasing doses of toxins or bacteria to generate immunity which was quite different to the spontaneous healing of natural infections. Lastly, he complained that the application of the method was made difficult or impossible by the challenge of obtaining CS in sufficient quantity.[14]

Two specialist monographs by British authors were dismissive of using serum derived from convalescents. One concluded: 'Obviously such a procedure could have but a very limited application, even if of any value, which is extremely doubtful'.[15] The other was unimpressed by von Leyden's case studies in scarlet fever: 'These experiments are of theoretical rather than practical interest, as it is not to be expected that such a remedy could become generally used'. He added: 'Convalescents from a disease could not be expected to sacrifice a portion of their blood for the benefit of other patients – at all events, not in this country'.[16]

The potential risks of administering CS did not seem of particular concern. In the production of antitoxic serum horses were tested with tuberculin and mallein to ensure they were free from tuberculosis (TB) and glanders respectively.[17] Injecting such preparations usually resulted in few complications apart from rashes, swelling and pain in the joints and pyrexia, which also occurred with normal horse serum because of its foreign origin.[18] By this time, the arm-to-arm method of vaccinating against smallpox,

[13] Hughes WE, Carter WS. The injection in pneumonia and typhoid fever of serum from convalescents. *Therapeutic Gazette*. 1894; 18: 365-371.
[14] Dieudonné A. *Immunität, Schutzimpfung und Serumtherapie: Zussamenfassende Uebersicht über die Immunitätslehre*. Leipzig: Verlag von Johann Ambrosius Barth; 1905, p.198.
[15] Hewlett RT. *Serum Therapy, Bacterial Therapeutics and Vaccines*. London: Churchill; 1903, p.190.
[16] Bosanquet WC. *Serums, Vaccines and Toxines in Treatment and Diagnosis*. London: Cassell; 1904, p.228.
[17] Hewlett, *Serum Therapy*, 1903 (Note 15), p.37-38.
[18] Hewlett, *Serum Therapy*, 1903 (Note 15), p.67-72.

which was believed to risk the transfer of syphilis from one person to another, had been substituted by glycerinated calf-lymph.[19]

Year	Author(s)	Location	Disease(s)
1892	Neisser [20]	Königsberg	pneumonia
1892	Stern [21]	Breslau	typhoid fever
1893	Hammerschlag [22]	Wien	typhoid fever
1896	Pollak [23]	Prag	typhoid fever
	Weisbecker [24]	Gerden, Oberhessen	measles
	Weiss [25]	Wien	rheumatoid arthritis
1897	Huber, Blumenthal [26]	Berlin	scarlet fever, measles, pneumonia, erysipelas
	Weisbecker [27]	Gerden, Oberhessen	typhoid fever, scarlet fever, pneumonia
1901	Kühn, Suckstorff [28]	Rostock	typhoid fever
1902	von Leyden [29]	Berlin	scarlet fever

Table 1. A decade of publications on convalescent serum therapy in principal German-language medical journals, 1892-1902.

[19] Bosanquet. *Serums, Vaccines and Toxines*, 1904 (Note 16), p.137-138.
[20] Neisser, Ueber Heilversuche, 1892 (Note 11).
[21] Stern R. Ueber Immunität gegen Abdominaltyphus. *Deutsche medicinische Wochenschrift.* 1892; 18: 827-830.
[22] Hammerschlag A. Ein Betrag zur Serumtherapie. *Deutsche medicinische Wochenschrift.* 1893; 19: 711-712.
[23] Pollak G. Ueber die Behandlung des Typhus abdominalis mit Blutserum von Typhus-Rekonvaleszenten. *Zeitschrift für Heilkunde*. 1896; 17: 449-464.
[24] Weisbecker. Heilserum gegen Masern. *Zeitschrift für klinische Medizin*. 1896; 30: 312-316.
[25] Weiss J. Die Wirkung von Seruminjektionen auf den Gelenkrheumatismus. *Centralblatt für innere Medicin*. 1896; 17: 417-421.
[26] Huber O, Blumenthal F. Ueber die antitoxische und therapeutische Wirkung des menschlichen Blutes nach überstandenen Infectionskrankheiten (Scharlach, Masern, Pneumonie und Erysipel. *Berliner klinische Wochenschrift*. 1897; 34: 671-675.
[27] Weisbecker. Heilserum gegen Typhus, Scharlach, Pneumonie. *Zeitschrift für klinische Medizin*. 1897; 32: 188-206.
[28] Kühn A, Suckstorff A. Beitrag zur Statistik, Pathologie und Therapie des Abdominaltyphus. *Deutsches Archiv für klinische Medizin*. 1901; 71: 324-369.
[29] von Leyden E. Die Behandlung des Scharlachs mit Reconvalescentenserum. *Deutsches Archiv für klinische Medizin*. 1902; 73: 616-631.

In this context, it is notable that Albert Neisser (1855-1916), Professor of Dermatology and Venereology at the University of Breslau (modern-day Wrocław, Poland), conducted ill-conceived and unsuccessful therapy experiments in 1892-93 in which he gave patients with syphilis intravenous (iv) infusions of serum from donors with tertiary syphilis. The 1898 publication of this work and especially cases of serum injections in young prostitutes brought Neisser public opprobrium, professional criticism, disciplinary measures, a formal reprimand and a substantial fine for not seeking the informed consent of his patients.[30]

Revival of interest in serum therapy in the US

After a hiatus of some ten years, there was renewed interest in CS in Europe and especially in the US. In severe cases of scarlet fever treated on or before the fourth day of the disease, a marked amelioration of general symptoms occurred after iv injection of large doses of CS obtained from two or more donors in the third or fourth week of convalescing. Favourable results were also claimed after administration of serum from smallpox convalescents to patients with severe or haemorrhagic smallpox if injections were made early in the disease. By this time, serum was routinely tested by the Wassermann reaction to exclude donors with syphilis, mixed and cultured to ensure sterility, and kept on ice in ampoules with phenol added as preservative.[31]

Some researchers infused *normal* human serum which appeared to be of value in patients with scarlet fever who developed sepsis. An alternative approach involved intramuscular (im) injections of fresh human *blood*, convalescent or normal, mixed with sodium citrate to inhibit clotting. By the mid-1910s blood transfusion was being used widely for treating haemorrhage, certain anaemias and haemophilia. Also used were normal human serum and normal *horse* serum available commercially. Serum from *placental* blood was used for toxicoses of pregnancy. Clinicians further explored the value of administering a patient's own serum, an 'autoserum', to treat disease and 'salvarsanised' autoserum was tried for syphilis of the brain.[32]

An important centre developing therapeutic sera was the Rockefeller Institute for Medical Research in New York. Its Director, Simon Flexner (1863-1946), developed a horse serum broadly active against the meningococcus responsible for epidemics of cerebrospinal fever. In a large series of cases, the serum gave a marked reduction in overall mortality compared with historical cases; survival was favoured by early and intensive serum therapy via intrathecal injection.[33]

The outbreak of World War One exacerbated an ongoing epidemic of cerebrospinal fever in Europe and stimulated military demand for anti-meningococcal serum. The

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[30] Benedek TG. "Case Neisser": experimental design, the beginnings of immunology, and informed consent. *Perspectives in Biology and Medicine*. 2014; 57: 249-267.

[31] Kolmer JA. *A Practical Text-Book of Infection, Immunity and Specific Therapy*. Philadelphia: WB Saunders Company; 1915, p.775-776.

[32] Kolmer JA. *A Practical Text-Book of Infection, Immunity and Specific Therapy*, Second Edition. Philadelphia: WB Saunders Company; 1917, p.825-843.

[33] Flexner S. The results of the serum treatment in thirteen hundred cases of epidemic meningitis. *Journal of Experimental Medicine*. 1913; 17: 553-576.

Rockefeller Institute supplied Flexner's serum directly to the Royal Navy.[34] In the UK, the Lister Institute of Preventive Medicine supplied the Royal Army Medical Corps with its anti-meningococcal serum and developed type-specific sera against each of the main strains of meningococcus distinguishable by serum tests.[35]

A leading cause of death in the US was lobar pneumonia. Rufus Cole (1872-1966), Director of the Rockefeller University Hospital in New York, and his colleagues discovered that the pneumococcus causing the disease occurred in multiple serologically defined strains. Horse serum raised against the Type I pneumococcus, when given early and in large amounts by repeated infusions, was effective at combating the disease in patients infected by the corresponding strain and in reducing mortality among this group of patients. The antiserum was used during epidemics in US Army camps.[36]

During 1916, an epidemic of acute anterior poliomyelitis broke out in the US. Through the work of Flexner and others the disease was known to be caused by virus which induced an immunity in the serum of monkeys and humans.[37] Since the virus could not be cultured it was not possible to raise a horse serum. However, as the virus had never been detected in the blood, several workers at the Rockefeller Institute and elsewhere, obtained serum from recently recovered patients and used both intraspinal and iv or im injections of CS in large amounts to treat patients soon after diagnosis to arrest onset of paralysis.[38]

Pandemic influenza-pneumonia and the US Navy

On 28 August 1918, a severe and rapidly spreading epidemic of influenza in the US was recognised first at the US Naval Hospital, Chelsea, Massachusetts (Figure 1). Part of the global pandemic of so called 'Spanish flu' the disease was often more severe than typical flu, was associated with more frequent and serious complications and extraordinarily contagious, attacking many of the hospital staff. In five to ten percent of affected patients the disease developed into a massive and highly fatal bronchopneumonia. The case fatality rate of the earliest patients with influenza-pneumonia reached as high as 60 or 70 percent.[39]

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[34] Wawrzynczak EJ. The Royal Navy's response to an epidemic of cerebrospinal fever during World War One. *Topics in the History of Medicine*. 2021; 1: 39-69.

[35] Wawrzynczak EJ. Treatment of military cases of cerebrospinal fever during WWI: the concerted efforts of the RAMC, MRC and Lister Institute to make serum therapy work. *BMJ Military Health*. 2020; 166: 347-351.

[36] Avery OT, Chickering HT, Cole R, Dochez AR. *Acute Lobar Pneumonia: Prevention and Serum Treatment* (Monograph No. 7). New York: Rockefeller Institute for Medical Research, 1917.

[37] Flexner S, Lewis PA. Experimental poliomyelitis in monkeys: active immunization and passive serum protection. *Journal of the American Medical Association*. 1910; 54: 1780-1782.

[38] Amoss HL, Chesney AM. A report on the serum treatment of twenty-six cases of epidemic poliomyelitis. *Journal of Experimental Medicine*. 1917; 25: 581-608.

[39] Keegan JJ. The prevailing pandemic of influenza. *Journal of the American Medical Association*. 1918; 71: 1051-1055.

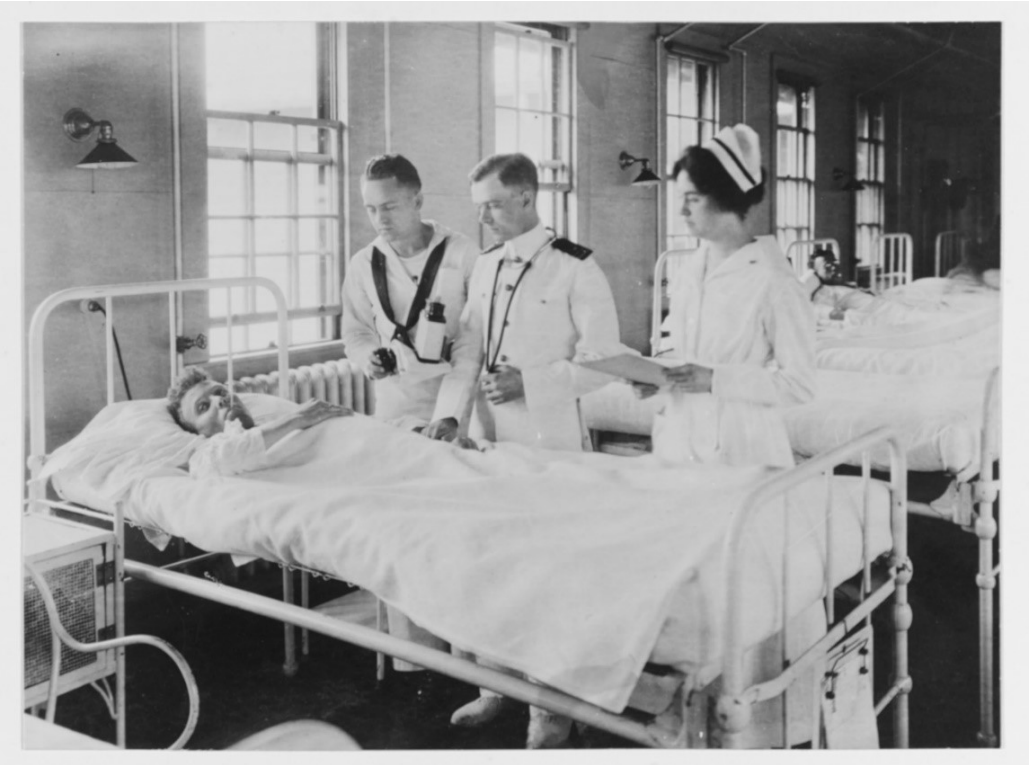

Figure 1. US Naval Hospital, Chelsea, Massachusetts. Surgeon, nurse and corpsman examine a patient in Ward 6, Group I, 2 June 1919. US Naval History and Heritage Command, Photograph # NH 42355.

At the end of September, the *Journal of the American Medical Association* noted: 'Few physicians will attempt to treat the condition with any special reference to its bacteriologic cause'.[40] No specific treatment was available because of much uncertainty about the role of the so-called influenza bacillus. Without a confirmed causative agent to use for immunising animals it was not possible to make a therapeutic serum; the only option was to use blood from convalescent patients which quite probably contained antibodies for the presumed agent responsible.[41] Doubt remained about what caused influenza and what role various bacteria might play in the development of secondary pneumonia.[42] [43] [44]

Lieutenant William R Redden (1881-1952), a Boston doctor recently graduated from Harvard Medical School who enlisted in the Medical Corps of the US Naval

[40] Anon. The epidemic of influenza. *Journal of the American Medical Association*. 1918; 71: 1063-1064.
[41] Anon. Epidemic influenza. *Journal of the American Medical Association*. 1918; 71: 1136-1137.
[42] Anon. The influenza outbreak. *Journal of the American Medical Association*. 1918; 71: 1138.
[43] Anon. Quarantine and isolation in influenza. *Journal of the American Medical Association*. 1918; 71: 1220.
[44] Anon. The present epidemic of influenza. *Journal of the American Medical Association*. 1918; 71: 1223.

Reserve in January 1918, was assigned to the Naval Hospital, Chelsea.[45] He had spent some time at the Rockefeller Institute and was familiar with the serum therapy of pneumonia.[46] Based on CS treatment during the polio epidemic, Redden suggested the use of serum from convalescent influenza-pneumonia patients to his superior Lieutenant-Commander Lee W McGuire (1883-1959). A preliminary report published in October described the beneficial results of treatment in 37 cases but noted that some donor serum appeared inactive.[47] Later, donor serum was pooled to avoid this problem.[48]

The initial results appeared promising but further trial was required because the severity of the disease appeared to be waning.[49] A second paper, published in March 1919, reported results for all cases treated at the Naval Hospital. Patients received one or more iv doses of CS at intervals of 8-16 hours. Three injections sufficed in most patients and one third needed only a single injection. Most were treated within four days of diagnosis and more than half within 48 hours. Of 151 patients, more than half of whom had been received during a recrudescence of the epidemic when the severity of the disease resembled that at its start, there were only six deaths and few complications.[50] In developing this convalescent influenza-pneumonia serum McGuire and Redden were awarded the Navy Cross for distinguished service.[51]

The experience of CS therapy at different naval hospitals varied but most observers were satisfied that treatment was beneficial, although complicating pneumococcal or streptococcal pneumonia proved fatal in several cases.[52] At hospitals where there was a ready supply of convalescent patients willing to act as donors, patients with influenza who could be closely observed for signs of incipient pneumonia, and the necessary laboratory and clinical support to hand it was feasible to give the prompt and intensive treatment that had proved most successful in treating various infectious diseases at the hands of the Rockefeller researchers.

At a meeting of the Massachusetts Medical Society held on 3 June 1919 Redden reported on an additional 100 patients treated in private practice with CS obtained from civilian donors. Mortality was four times higher than in the naval hospital, but most

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[45] Mead FS (ed). *Harvard's Military Record in the World War*. Boston, Massachusetts: Harvard Alumni Association, 1921, p. 789.

[46] Redden WR. Development of specific serum therapy in pneumonia. *United States Naval Medical Bulletin*. 1919; 13: 35-43.

[47] McGuire LW, Redden WR. Treatment of influenza pneumonia by the use of convalescent human serum: preliminary report. *Journal of the American Medical Association*. 1918; 71: 1311-1312.

[48] McGuire LW, Redden WR. Discontinuance of compatibility test in serum treatment. *Journal of the American Medical Association*. 1918; 71: 1765.

[49] Anon. Serums and vaccines in influenza. *Journal of the American Medical Association*. 1918; 71: 1408.

[50] McGuire LW, Redden WR. Treatment of influenza pneumonia by the use of convalescent human serum: second report. *Journal of the American Medical Association*. 1919; 72: 709-713.

[51] Naval History and Heritage Command. Influenza of 1918 (Spanish Flu) and the US Navy. 2015; published online, 6 April. www.history.navy.mil/research/library/online-reading-room/title-list-alphabetically/i/influenza/influenza-of-1918-spanish-flu-and-the-us-navy.html/ (accessed 28 Feb 2022).

[52] Navy Department Bureau of Medicine and Surgery. *Annual Report of the Surgeon General, U.S. Navy. Fiscal Year 1919.* Washington: Government Printing Office; 1919, p.448-449.

patients were seen two to five days later. Patients donated blood gladly and considered it an honour to help. He concluded that the work of investigators at other US naval, military and civilian hospitals using citrated whole blood, citrated plasma or serum from convalescents, with or without pooling, substantiated his belief in the value of convalescent therapy.[53]

In the published account of the discussion after the meeting, however, two Boston doctors raised concerns. The first brought up the great variation in mortality from bronchopneumonia reported at different locations during the pandemic and cautioned against judging the value of serum treatment without a control group of untreated cases. The second had conducted a small study in which comparable cases were matched, one treated with CS, the other untreated, with no apparent difference in outcome. Redden reiterated the need to treat early in the disease and stressed the value of clinical experience:

> I have no intention of criticising either of the speakers, but I still think that my position of having treated 250 cases is different from that of the individual who has treated only 30, whether they are controlled or uncontrolled. The controlled cases on the outside have been favorable for those who used serum.

He noted that his critics, whatever their concerns, admitted they would opt to have serum treatment if unlucky enough to come down with the disease.

Measles epidemics and the London County Council

The use of convalescent blood products received little attention in the UK with a few brief reports giving scant details of patients treated during the influenza pandemic.[54] [55] [56] In the early 1920s the US and Europe saw continued investigations of the treatment and prophylaxis of diseases including measles for which there were no reliable and effective animal sera.[57] An Italian doctor is claimed to be the first to use CS to confer passive protection in the case of measles in 1907.[58] This was followed by work in the US, Germany and France.[59]

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[53] Redden WR. Treatment of influenza-pneumonia by use of convalescent human serum. *Boston Medical and Surgical Journal*. 1919; 181: 688-692.
[54] Huff-Hewitt WE. Human serum in influenza. *British Medical Journal*. 1919; 1(3045): 575.
[55] Carlyle PM. Injection of whole blood in influenza. *British Medical Journal*. 1919; 1(3048): 698.
[56] McIntosh J. Studies in the aetiology of epidemic influenza. In: *Medical Research Council, Special Report Series. No. 63.* London: HMSO; 1922, p.5-46.
[57] Kolmer JA. *A Practical Text-Book of Infection, Immunity and Specific Therapy*, Third Edition. Philadelphia: WB Saunders Company; 1923, p.874, 875, 899-901.
[58] Marson P, Cozza A, De Silvestro G. The true historical origin of convalescent plasma therapy. *Transfusion and Apheresis Science*. 2020; 59: 102847. Published online, 11 June. www.trasci.com/article/S1473-0502(20)30150-6/fulltext (accessed 28 Feb 2022).
[59] Parish HJ. *A History of Immunization*. Edinburgh: E&S Livingstone; 1965, p.285-289.

Serum prophylaxis was introduced to the UK in 1925 by William SC Copeman (1900-1970) who had experience of its use in measles at the Faculty of Medicine of the University of Paris and so was able to make detailed recommendations.[60] [61] The disease was widespread and so highly contagious that it infected practically all children. It had high mortality in the youngest, being the number one killer among infectious diseases among the under-fives, especially those subject to poverty and overcrowding. Typically, serum was collected from a donor, an adult or child over ten years of age, a week after complete defervescence.

Importantly, CS could be used at different times to achieve different outcomes. In a child infected for fewer than six days, im injection of CS established short-term passive immunity. This was generally used to defer an attack of measles in infants who were under three years of age, weakened by other diseases, or in hospital. The later in the incubation period the patient received CS the larger the dose required. The serum of adults who had previously had measles at any period of their life could also be used but higher doses were required to compensate for diminished potency. In urgent cases a parent's or relation's blood, citrated or non-citrated, could be injected in two to four times the amount. (Table 2).

Time of injection	Outcome
Before the 6th day	*Sero-prevention* – passive immunity lasting about a month
6th to 9th day	*Sero-attenuation* – active immunity established
10th day	Local inhibition of eruption – no general immunity established
After eruption	*Sero-therapy* – no constant effect observed
Normal subject	*Sero-vaccination* – injection of serum plus blood from an early case of measles

Table 2. Passive and active immunity resulting from different modes of serum therapy. After Copeman, On some recently developed methods, 1925 (Note 60).

If injection of CS was delayed until the second half of the incubation period, the attack of measles could not be blocked but the disease was turned into a mild form that imparted to the child a long-lasting active immunity. This mode of use was indicated where a healthy subject more than two to three years old had been infected with measles for the first time. It was judged better to allow the modified disease, which lacked the risk of common complications including bronchopneumonia and otitis media, to induce active immunity rather than repeatedly renewing the patient's passive immunity using serum. After the tenth day, attenuation could no longer be reliably achieved (Figure 2).

[60] Copeman WSC. On some recently developed methods for measles prophylaxis. *Journal of Hygiene*. 1925; 24: 427-441.

[61] Copeman WSC. The prophylaxis of measles with a suggested scheme for dealing with epidemics. *Proceedings of the Royal Society of Medicine*. 1927: 20; 1609-1620.

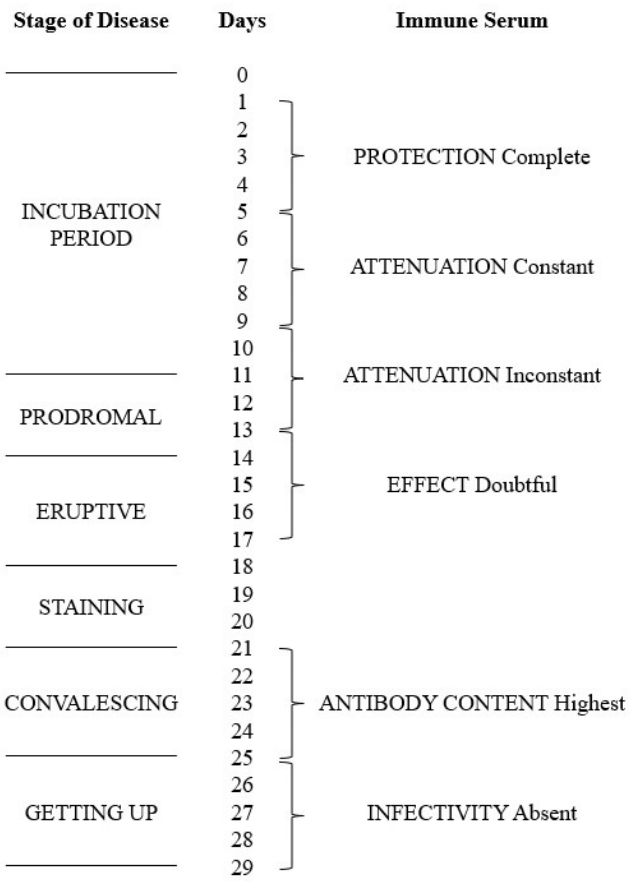

Figure 2. Synoptic chart showing the typical course of measles. Adapted from Brincker, The control of measles, 1938 (Note 62).

In 1927, convalescent serum began to be used in private practice and in a few hospitals. Measles epidemics peaked in London on a regular two-year cycle; the 1929-30 outbreak was the first in which measles CS was used on a large scale at fever hospitals of the Metropolitan Asylums Board. It proved very useful in preventing children from contracting the disease after known exposure on a hospital ward. But supplies of such CS were insufficient and limited to the infectious disease hospitals because most convalescents were small children from whom blood was not easily obtained and few adults suffered from the disease.[62]

In 1930, London County Council took over responsibility for the fever hospitals and began serum preparation on a large scale. The demand for immune serum was directly related to the prevalence of measles. As a result, CS was usually unavailable when most needed at the start of an epidemic and then available in large amounts at its end when scarcely required. In subsequent epidemics young healthy volunteers, including nursing staff and medical students, acted as a source of adult serum. The amounts of serum were still insufficient and so appeals were made to the public to act as serum donors in exchange for modest remuneration. [63]

[62] Brincker JAH. The control of measles. *Lancet*. 1936; 1(5863): 103-107.
[63] Gunn W. The serum prophylaxis of measles. *Proceedings of the Royal Society of Medicine*. 1938: 31; 828-840.

By the late 1930s, as well as small amounts of CS, public health authorities of major cities and towns kept bulk stocks of adult serum prepared in their own laboratories or with help from makers of biological products, for example the Wellcome Research Physiological Laboratories, for the use of hospitals, children's homes and residential schools. Another option, based on evidence that antibodies passed from mother to child, was a preparation extracted from human placenta such as Lederle's 'Immune Globulin'. For all approaches, a major drawback was the lack of a method to assay the potency of the anti-measles antibodies in each batch.[64]

In the 1935-36 epidemic, the protection rate of all three approaches exceeded 70 percent in children injected prophylactically but there was no comparison group since all known contacts in whom an attack was potentially dangerous were given immune serum. Serum-attenuated cases showed significantly reduced rates of attack and complication compared with control subjects from whom serum had been withheld and disease ensued.[65] In schools, attenuation rather than prevention was the principal aim.[66] In the home, community doctors gave parents' whole blood to child contacts in the family to modify an attack and mitigate complications.[67]

During the decade, CS was also used to treat patients with scarlet fever, diverse streptococcal infections, mumps, chickenpox and whooping cough, and limited studies were undertaken in a wide range of other infectious diseases.[68] Continued studies of CS in children infected with polio failed to give convincing findings and the approach was discredited by the late 1930s. Such studies used sera of unknown potency, administered in varying dosages and routes at different stages of the disease, and often lacked controls. Since it was widely accepted that human serum was harmless, however, enthusiasts continued to believe its administration was beneficial.[69] As a knowledgeable observer in the UK commented in 1933:

> Therapeutic enthusiasm is notoriously proof against hard facts, and we may therefore expect this treatment to be continued by those who already believe in it. But something will have been gained if the lessons and disappointments of the past lead to the more scientific planning and administration of this mode of treatment in the future.[70]

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[64] Gunn W. Measles. *Lancet*. 1938; 1(5979): 795-799.

[65] Gunn W, Russell WT. A review of the measles epidemic 1935-36 including references to treatment and the preparation and use of immune measles sera. In: London County Council. *Measles: Report of the Medical Officer of Health and School Medical Officer on the Measles Epidemic, 1935-36*. London: London County Council; 1938, p.19-46.

[66] Hobson FG. Measles: the conduct of a school epidemic. *British Medical Journal*. 1938; 2(4046): 171-175.

[67] Culbert TD. Parental whole blood in the prophylaxis of measles. *British Medical Journal*. 1938; 2(4056): 705.

[68] Levinson SO, Wolf AM. Human serum: its application in medicine. *Medical Clinics of North America*. 1941; 25: 219-243.

[69] Paul JR. *A History of Poliomyelitis*. New Haven: Yale University Press; 1971, p.190-199.

[70] Walshe FMR. A paper on poliomyelitis. *British Medical Journal*. 1933; 2(3808): 1197-1200.

Scientific developments and new disease threats

Therapy of infectious diseases with immune animal sera was gradually abandoned after the 1930s. The approach had narrow specificity, suffered from batch variability, was difficult to administer, had allergic side-effects, and was expensive whereas antimicrobial chemotherapy was broadly active, more consistent, easy to administer, less toxic and cheaper. Use of animal antibodies became restricted largely to antitoxins, antivenoms and certain antiviral products.[71]

In the 1940s new methods to fractionate proteins present in blood plasma enabled the use of im injections of human antibody, or immunoglobulin (Ig), made by pooling plasma from multiple donors previously exposed to common infectious diseases. Such purified products were used to prevent and treat measles, rubella and hepatitis A. Preparations of so-called 'intravenous immunoglobulin' (IVIg) allowed increased dosing. Potency improved with 'hyperimmune' products derived from the plasma of donors with a high level or titre of specific antiviral antibodies. More recently engineered human 'monoclonal antibodies' have emerged as a viable option.[72]

Since the 1950s the world has faced repeated threats from emerging viral diseases for which specific treatments did not exist at the time of outbreak and CS therapy was tried, including several viral respiratory infections: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and different strains of influenza. The prospect of a global influenza pandemic, especially one associated with the high mortality of the Spanish flu pandemic, brought convalescent blood products back into focus.[73]

A meta-analysis of eight clinical trials published in the US during the Spanish flu pandemic of 1918 concluded that patients who received convalescent blood products may have experienced a clinically important reduction in the risk for death and that early therapy was superior to late treatment. However, the few studies had many methodological limitations: the size of most trials was small, treated patients often had more severe illness, the treatment regimens were not standardised, and none was a blinded, randomised or placebo-controlled trial.[74]

During the SARS outbreak of 2002-2003 the rapid spread and subsequent control of the disease precluded controlled trials of treatment. A systematic review carried out at the request of the WHO found seven studies of CS or IVIg to be inconclusive because of confounding effects including patient comorbidities, the stage of illness and the co-administration of other treatments. Collection of clinical information was not

[71] Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. *Clinical Infectious Diseases*. 1995; 21: 150-161.

[72] Marasco WA, Sui J. The growth and potential of human antiviral monoclonal antibody therapeutics. *Nature Biotechnology*. 2007; 25: 1421-1434.

[73] Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. Hark back: passive immunotherapy for influenza and other serious infections. *Critical Care Medicine*. 2010; 38(4 Suppl): e66-e73.

[74] Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Annals of Internal Medicine*. 2006; 145; 599-609.

standardised which limited the interpretation of these retrospective studies. The authors concluded:

> We suggest that, in the event of a future outbreak of SARS-CoV or another novel agent, attempts be made to develop treatment protocols and to collect and contribute information for a standardized minimum dataset that could facilitate analysis of treatment outcomes among different settings. As observational studies pose problems of interpretation, the need is great for good-quality randomised trials, despite the difficulties in organising such trials.[75]

A later meta-analysis of 32 studies of convalescent blood products for Spanish influenza A (H1N1), SARS-CoV, avian influenza A H5N1, and the 2009 'swine flu' pandemic influenza A (H1N1) showed a statistically significant reduction in the pooled odds of mortality after treatment compared with placebo or no treatment, with larger effects if treatment started soon after symptom onset but the studies were commonly of low or very low quality, lacked control groups, and were at risk of bias.[76] Subsequently, the efficacy of CP in patients with MERS could not be evaluated because of the limited number of cases.[77]

Early enthusiasm for CP during the COVID-19 pandemic

In the SARS and MERS outbreaks it had been shown that CP contained virus-neutralising antibodies. Early in 2020, once the scale of the COVID-19 pandemic was appreciated, it was evident that antiviral CP would become available in the quantities required to treat large numbers of patients when enough had recovered from the disease to act as potential donors. CP could be obtained by the standard procedure of collection by apheresis at blood banks or hospitals and transfused into patients using conventional practice.[78] [79]

To some investigators it was a stopgap measure for emergency use that could be quickly deployed to treat individuals with early symptoms of the disease and protect those exposed to infection such as healthcare workers, the elderly and other vulnerable

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[75] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Medicine*. 2006; 9: e343.

[76] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F-M, Lim WS, *et al*. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *Journal of Infectious Diseases*. 2015; 211: 80-90.

[77] Ko J-H, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, *et al*. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antiviral Therapy*. 2018; 23: 617-622.

[78] Bloch EM, Shoham S, Casadevell A, Sachais BS, Shaz B, Winters JL, *et al*. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *Journal of Clinical Investigation*. 2020; 130: 2757-2765.

[79] Malani AN, Sherbeck JP, Malani PN. Convalescent plasma and COVID-19. *Journal of the American Medical Association.* 2020; 324: 524.

groups before suitable drugs and vaccines had been developed.[80] For others it was an opportunity to execute high quality, prospective, randomised trials that compared CP and well-defined control groups so as to categorically establish whether the approach worked in the clinic or not.[81]

The Cochrane Library launched a 'living review' of clinical trials. Its first report in May 2020 included eight completed studies of CP comprising a total of 32 participants but these were not randomised or controlled, patients received other treatments, and some had underlying health problems. Forty-eight ongoing trials were identified, including one with hyperimmune Ig, of which 22 were randomised.[82]

The earliest published studies had been small uncontrolled case series. The first randomised trial in patients with severe illness or life-threatening disease from Wuhan, China showed evidence of antiviral activity and some clinical improvement in less sick patients but did not reach statistical significance because the outbreak had been swiftly suppressed and only 100 or so patients, about half the number intended, had been recruited.[83]

Concerns were raised about treatment studies using research strategies that were easy to implement but unlikely to yield unambiguous results, trials investigating similar hypotheses and risking duplication of effort, and reports being rushed to preprint servers before peer review. It was argued that the crisis brought on by the pandemic was no reason to make exceptions to the high standards of research because of clinicians' urgency to produce results, care for patients or exercise autonomy.[84]

In April 2020 the US Food and Drug Administration (FDA) had already initiated an Expanded Access Protocol and nationwide programme together with the Mayo Clinic and the blood banking community to give patients access to CP, primarily to assess the safety profile of treatment. Analysis of 20,000 treated patients showed a low incidence of transfusion-related serious adverse events and the vast majority of thromboembolic or thrombotic events and cardiac events were judged unrelated to plasma perfusion.[85] [86]

Although the multicentre, open-label programme at registered sites enrolled about 100,000 patients in hospitals and acute care facilities overall, data suitable for analysis

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[80] Casadevall A, Pirofski L. The convalescent sera option for containing COVID-19. *Journal of Clinical Investigation*. 2020; 130: 1545-1548.

[81] Sullivan HC, Roback JD. Convalescent plasma: therapeutic hope or hopeless strategy in the SARS-CoV-2 pandemic. *Transfusion Medicine Reviews*. 2020; 34: 145-150.

[82] Valk SJ, Piechotta V, Chai KL, Doree C, Monsef I, Wood EM, *et al*. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database of Systematic Reviews*. 2020; 5: CD013600.

[83] Casadevall A, Joyner MJ, Pirofski L-A. A randomized trial of convalescent plasma for COVID-19 – potentially hopeful signals. *Journal of the American Medical Association.* 2020; 324: 455-457.

[84] London AJ, Kimmelman J. Against pandemic research exceptionalism. *Science*. 2020; 368: 476-477.

[85] Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruna KA, Klassen SA, *et al*. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *Journal of Clinical Investigation*. 2020; 130: 4791-4797.

[86] Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, *et al*. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clinic Proceedings*. 2020; 95: 1888-1897.

were available from only about 35,000 transfused patients. A retrospective analysis suggested clinical and mortality benefits when high-titre CP was used within three days of diagnosis.[87] Subsequent analysis of about 3,000 of the patients led to similar conclusions but only if they had not received mechanical ventilation before transfusion.[88]

Largely based on these analyses the FDA issued an Emergency Use Authorization (EUA) in August 2020, widening access to all adults in the US. Experts criticised the move since it threatened to undermine the recruitment of patients for randomised control trials (RCTs).[89] The charge that non-randomised studies risked engendering false confidence and might impede the advance of clinical knowledge offered by well-designed RCTs had already been articulated.[90] For some the authorisation was premature and a missed opportunity.[91]

The FDA's action in granting an EUA for CP, as for hydroxychloroquine, raised concern that decision-making had been unduly influenced by political pressure since no randomised trial had established efficacy.[92] At the same time, the FDA continued to encourage properly conducted RCTs and the National Institutes of Health reiterated guidelines that appropriate RCTs were required to determine that CP was effective and safe for the treatment of patients with COVID-19.[93]

Optimism for CP dampened as multiple trials report

In April 2020, NHS Blood and Transplant had announced the launch of a major programme to collect CP to support an ongoing clinical trial programme.[94] REMAP-CAP (Randomised, Embedded, Multifactorial, Adaptive Platform – Community-Acquired Pneumonia) enrolled critically ill patients with confirmed COVID-19 for CP therapy. In January 2021 a data safety review of this international multicentre trial

[87] Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, *et al*. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv.* 2020; published online, 12 August. www.medrxiv.org/content/10.1101/2020.08.12.20169359v1/ (accessed 28 Feb 2022).

[88] Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, *et al*. Convalescent plasma antibody levels and the risk of death from Covid-19. *New England Journal of Medicine*. 2021; 384: 1015-1027.

[89] Ledford H. US widens access to Covid-19 plasma – despite lack of data. *Nature*. 2020; 584: 505.

[90] Califf RM, Hernandez AF, Landray M. Weighing the benefits and risks of proliferating observational treatment assessments. *Journal of the American Medical Association.* 2020; 324: 625-626.

[91] Estcourt LJ, Roberts DJ. Convalescent plasma for covid-19. *BMJ*. 2020; 370: m3516.

[92] Kupferschmidt K, Cohen J. In plasma OK, critics see politics, not science. *Science*. 2020; 369: 1038-1039.

[93] Baden LR, Solomon CG, Greene MF, D'Agostino RB, Harrington D. The FDA and the importance of trust. *New England Journal of Medicine*. 2020; 383: e148.

[94] NHS Blood and Transplant. Major COVID-19 convalescent plasma programme announced. 2020; published online, 25 April. www.nhsbt.nhs.uk/news/major-covid-19-convalescent-plasma-programme-announced/ (accessed 28 Feb 2022).

flagged that CP intervention had hit a pre-specified statistical threshold for futility and recruitment was stopped.[95] The investigators concluded CP had a low likelihood of improving organ support-free days in these patients.[96]

A second trial, RECOVERY (Randomised Evaluation of COVid-19 thERapY) was then established at short notice to test a range of potential treatments for patients hospitalised with COVID-19. This randomised, controlled, open-label platform trial being carried out at over 175 NHS hospitals in the UK randomly assigned patients to four potential therapies and used a simple 28-day mortality endpoint. The trial's innovative design enabled the important demonstration that low-dose dexamethasone significantly reduced deaths by one-third in ventilated patients.[97]

The RECOVERY trial allocated more than 11,500 patients to receive either usual care or usual care plus high-titre CP, making it the largest randomised trial of CP therapy in patients hospitalised with COVID-19. In January 2021 an interim review of safety and efficacy data brought this arm of the trial to a halt.[98] Compared with usual care alone, the addition of high-titre CP did not improve survival or other prespecified clinical outcomes and there was no significant evidence of material benefit or hazard in any patient subgroup.[99]

Although various evaluations of CP were conducted during the COVID-19 pandemic, RECOVERY demonstrated that it was possible to take advantage of the integrated healthcare system of the UK to rapidly generate high-quality evidence within the context of routine patient care. It was one of a portfolio of government-funded national platform treatment trials testing candidate treatments selected by a newly assembled UK COVID-19 Therapeutics Advisory Panel.[100] [101]

In February 2021 the FDA restricted its authorisation to the use of high-titre COVID-19 CP for the treatment of hospitalised patients early in the disease course and for hospitalised patients with impaired immunity unable to produce an adequate

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[95] REMAP-CAP. Convalescent Plasma for COVID-19. 2021; published online, 16 January. www.remapcap.org/covid19publications/convalescent-plasma-for-covid-19/ (accessed 28 Feb 2022).

[96] Writing Committee for the REMAP-CAP Investigators. Effect of Convalescent Plasma on Organ Support-Free days in Critically Ill Patients with COVID-19. *Journal of the American Medical Association*. 2021; 326: 1690-1702.

[97] Normand ST. The RECOVERY Platform. *New England Journal of Medicine*. 2021; 384: 757-758.

[98] RECOVERY Trial. RECOVERY trial closes recruitment to convalescent plasma treatment of patients hospitalised with COVID-19. 2021; published online, 15 January. www.recoverytrial.net/ (accessed 28 Feb 2022).

[99] RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet*. 2021: 397: 2049-2059.

[100] Pessoa-Amorim G, Campbell M, Fletcher L, Horby P, Landray M, Mafham M, *et al*. Making trials part of good clinical care: lessons from the RECOVERY trial. *Future Healthcare Journal*. 2021; 8: e243-250.

[101] Chinnery PF, Bonnet M, Cave A, Hofer MP, Lamb A, McConkey GA, *et al*. Choosing drugs for UK COVID-19 treatment trials. *Nature Reviews Drug Discovery*. 2022; 21: 81-82.

antibody response.[102] Patients with innate or acquired immunosuppression represented a population at special risk of persistent SARS-CoV-2 infection and there was evidence suggesting a mortality benefit and clinical improvement following CP transfusion that warranted further investigation.[103]

An update of the Cochrane living review in May 2021 included thirteen studies of CP of which twelve were RCTs including more than 40,000 patients treated mainly in hospitals and in countries around the world. In patients with moderate to severe COVID-19, CP made no difference to deaths from any cause up to 28 days after treatment compared with placebo or standard care and did not improve or worsen the patients' condition. Up to this date, only one RCT had tested CP in individuals with a confirmed diagnosis of milder COVID-19.[104]

In this trial conducted in Argentina, 160 older patients with symptomatic infection who tested virus-positive were transported to trial hospitals and administered CP or placebo within 72 hours of the onset of symptoms. High-titre CP therapy reduced the risk of developing severe respiratory disease by half relative to placebo.[105] However, a larger RCT in outpatients presenting to the emergency department within seven days after symptom onset reported no significant difference in disease progression between CP and placebo groups.[106]

In December 2021, the WHO updated its 'living guideline' for the use of therapeutics in the treatment of COVID-19. It recommended CP should not be used in patients with severe or critical COVID-19 except in the context of a clinical trial. It also strongly recommended against CP in patients with non-severe COVID-19 given the low baseline risk of mortality, mechanical ventilation and hospitalisation in non-severe illness, the feasibility challenges in CP administration, and the potential harm from transfusion risks.[107]

During the two years of the COVID-19 pandemic, in addition to the many clinical trials that recruited too few subjects or lacked control groups, there had also been a proliferation of systematic reviews of the limited data available.[108] These served to

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[102] Food and Drug Administration. FDA in brief: FDA updates Emergency Use Authorization for COVID-19 convalescent plasma to reflect new data. 2021; published online, 4 February. www.fda.gov/ (accessed 28 Feb 2022).

[103] Senefeld JW, Klassen SA, Ford SK, Senese KA, Wiggins CC, Bostrom BC, *et al*. Use of convalescent plasma in COVID-19 patients with immunosuppression. *Transfusion*. 2021; 61: 2503-2511.

[104] Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, *et al*. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews*. 2021; 5: CD013600.

[105] Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, *et al*. Early high-titre plasma therapy to prevent severe Covid-19 in older adults. *New England Journal of Medicine*. 2021; 384: 610-618.

[106] Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, *et al*. Early convalescent plasma for high-risk outpatients with Covid-19. *New England Journal of Medicine*. 2021; 385: 1951-1960.

[107] WHO. *Therapeutics and COVID-19: living guideline*. 2022; published online, 14 January. www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1/ (accessed 28 Feb 2022).

[108] Pearson H. How Covid broke the evidence pipeline. *Nature*. 2021; 593: 182-185.

highlight a high degree of heterogeneity in disease severity among patients, timing of CP administration, dose of CP given, titre of anti-SARS-CoV-2 antibodies in CP, level of antiviral antibodies developed by the recipient, and measures used to evaluate outcomes.[109]

Conclusion

The idea of using the serum of convalescent patients for the therapy of infectious diseases, which originated as a speculative hypothesis in Germany in the early 1890s, spread quickly but was soon found wanting. Conclusions from the earliest studies were undermined by low numbers of cases, observer bias, and questions about the potency of donor serum, concerns that have recurred repeatedly since.

Experience showed that it was necessary to use good quality serum, intervene early after infection and treat intensively to achieve the best clinical outcomes. Satisfying these criteria in practice was difficult except in specialised hospital settings and in the case of patients suffering from well-characterised infectious diseases. Even then, the sometimes-marginal advantages of convalescent therapy were difficult to prove because trials were uncontrolled.

Studies in viral outbreaks causing acute respiratory distress, from Spanish flu to MERS, have failed to establish rigorously the value of CS or CP therapy. Factors including the novelty of the diseases, restricted numbers of patients and quick resolution of outbreaks have conspired to make such trials difficult but the need for properly conducted RCTs has been emphasised repeatedly. COVID-19 became the first substantial opportunity to put CP therapy to a proper test given prior knowledge of coronavirus diseases and the scale of the pandemic.

The initial response to the COVID-19 pandemic understandably focused on the most seriously ill patients in hospital. However, history suggests this group was unlikely to have been an easy target given the time elapsed between infection and treatment. Perhaps unsurprisingly, RCTs have confirmed that CP therapy is not effective overall in treating COVID-19 patients who are critically ill or have been hospitalised with moderate to severe disease. The results of trials in patients with COVID-19 at an earlier stage have been equivocal to date.

It remains to be seen whether hospitalised patients could benefit from CP therapy if they lack antibodies neutralising SARS-CoV-2 because they have failed to mount an adequate immune response. Another group which might benefit includes individuals with asymptomatic infection or mild symptoms at high risk of disease progression who have not responded to vaccine or cannot do so because they are immune suppressed. Experience suggests that post-exposure prophylaxis could be effective if administered at the right stage of infection.

However, COVID-19 is a complex disease in which immune dysregulation is an important component of the pathophysiology, especially in patients with severe disease. Antiviral agents, including antiviral drugs as well as CP, have a clear opportunity to play

[109] Menichetti F, Falcone M, Tiseo G. Management of COVID patients with convalescent plasma: Do we have the final word? *European Journal of Internal Medicine*. 2022; 95: 13-16.

a role in the early stages of the disease but agents modulating the host immune response appear to be especially relevant in the later stages. Identifying the therapeutic window within which CP or other passive antiviral therapies can be expected to work is therefore crucial.[110]

At the start of the pandemic, CP had the advantage that it was available relatively quickly and relatively cheaply anywhere that plasma could be produced from recovered patients, but there was also great variability in the amount of antiviral antibody in the products prepared for injection. Two years later, CP faces competition from hyperimmune Ig and monoclonal antibodies, which have been manufactured with greater consistency, although these products are both more difficult to prepare and more costly.[111]

As the pandemic evolved, SARS-CoV-2 variants emerged which escaped neutralisation by highly specific therapeutic monoclonal antibodies. In principle, the antibody content of CP taken from recently recovered patients would adapt to new variants and remain relevant for treatment. As an alternative, however, some developing countries are trialling hyperimmune antibodies derived from horses immunised with SARS-CoV-2 antigens as a broad coverage, low cost, scalable treatment for COVID-19.[112]

The application of CP therapy for COVID-19 has posed something of a conundrum. As a short-term measure, CP can be deployed early in a pandemic when there are no alternatives but it is unlikely to work well in patients who have advanced disease. Conversely, if used at an earlier stage of infection, CP might successfully prevent or attenuate disease but its long-term use is more difficult to justify in the face of other viable options, especially vaccines and targeted antivirals.

The medical imperative to save lives suggests that CP will play a role in future pandemics. However, the apparent simplicity of this empirical remedy fails to reflect the underlying complexity of immunity in natural infection and early enthusiasm has repeatedly turned to disillusion as the well-meaning endeavours of doctors failed to generate objective clinical data to prove the treatment's worth. The experience of COVID-19 has further underlined the need for broad collaboration on the design, conduct and co-ordination of RCTs in future pandemics.[113]

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[110] Van de Veerdonk FL, Giamarellos-Bourboulis E, Pickkers P, Derde L, Leavis H, van Crevel R, *et al*. A guide to immunotherapy for COVID-19. *Nature Medicine*. 2022; 28: 39-50.

[111] Estcourt LJ. Passive immune therapies: another tool against COVID-19. *Hematology: American Society of Hematology Education Program (2021)*. 2021(1): 628-641.

[112] Moreira-Soto A, Arguedas M, Brenes H, Buján W, Corrales-Aguilar E, Diaz C, *et al*. High efficacy of therapeutic equine hyperimmune antibodies against SARS-CoV-2 variants of concern. *Frontiers in Medicine*. 2021; 8: 735853.

[113] Note added in proof. For further commentary on the uncertain value of convalescent plasma for COVID-19 and the need for pre-pandemic planning of trials see: Estcourt L, Callum J. Convalescent plasma for Covid-19 – making sense of the inconsistencies. *New England Journal of Medicine*. 2022; 386: 1753-1754.

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