OPEN LETTER

Animal derived antibodies should be considered alongside convalescent human plasma to deliver treatments for COVID-19

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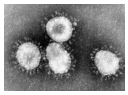
v1 **First published:** N/A, **N/A**: N/A N/A
Latest published: N/A, **N/A**: N/A N/A

Abstract

Published data on the first 5,000 coronavirus patients to receive plasma shows promise in the United States. However, delivering convalescent plasma therapies in low- and even middle-income countries is both difficult and costly. Here we discuss the advantages and disadvantages of antisera raised in animals that may allow poorer countries to control the devastating effects of COVID-19.

Keywords

Covid19, therapy, plasma, hyper-immune sera, antibodies



This article is included in the Coronavirus (COVID-19) collection.

Open Peer Review

Reviewer Status *AWAITING PEER REVIEW*

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Author roles: Ainsworth S: Conceptualization, Writing – Review & Editing; **Menzies S**: Conceptualization, Writing – Review & Editing; **Pleass RJ**: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by Wellcome [208938].
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Ainsworth S, Menzies S and Pleass RJ. **Animal derived antibodies should be considered alongside convalescent human plasma to deliver treatments for COVID-19** Wellcome Open Research , : https://doi.org/

First published: N/A, **N/A**: N/A N/A

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In a recent editorial published March 27th, Roback and Guarner discuss the possibilities and challenges of using human convalescent plasma to treat Covid-19[1,2]. Although we wholeheartedly agree with their conclusions, they fail to consider the complementary merits of using larger domesticated animals to generate similar clinical benefits, that avoid the considerable regulatory and logistical hurdles arising from the use of human donors.

While showing recent clinical promise and near immediate availability[1,2], human convalescent plasma is expensive and time consuming to process due to the need to screen for human pathogens and requires the identification of donors with high neutralising anti-SARS-CoV-2 titres. At the time of writing a routine diagnostic to detect hyper-immune individuals is still not routinely available, while generating large amounts of product to satiate current clinical demand may not even be possible, as manufacturers with the skills to make enriched antisera to scale will still need capacity to generate other plasma therapies for equally pressing diseases, e.g. IVIg for the routine treatment of neurological disease.

In lower middle- and low-income countries (LMICs and LICs), plasma products are expensive and often scarce, due to lack of import from higher-income countries, insufficient local supply of plasma, and lack of infrastructure to establish plasma manufacturing capacity[3]. These factors contribute to the poor availability of human convalescent plasma in LMICs and LICs where deaths from COVID-19 are likely to be very substantial indeed[4]. While human convalescent sera may not be readily available in outbreak situations, antisera of animal origin containing high titres of neutralising antibody can be produced in 2-4 months. Animal-origin purified IgG and IgG fragment preparations are still routinely used as antivenoms[5], and even though immunization of horses with inactivated Ebola virus (EBOV) failed to yield effective therapeutic antisera, equine hyperimmune sera produced using EBOV virus-like particles conferred protection against lethal challenge in rodents[6]. That antisera generated in horses can potently neutralise SARS-CoV-2 *in vitro* has also recently been observed[7].

Until a reliable vaccine or therapeutic intervention becomes available, for LMICs and LICs, we therefore advocate immunisation of larger animals, e.g. horses and sheep, such as is already the standard to generate antivenoms, anti-toxins, and anti-rabies therapeutics for human use. The polyclonal nature of antisera raised in animals makes it particularly suited to neutralising multiple antigens, toxins and enzymes that in humans bitten by snakes cause coagulopathies that are also observed in COVID-19 patients[8,9]. The animal approach is still used today in the treatment of diphtheria, a potentially fatal respiratory disease caused by a toxin-producing bacterium *Corynebacterium diphtheriae*. The method, which harvests antibody-rich serum after injecting the diphtheria toxin into horses may appear antiquated, but it nonetheless saves lives[10].

Furthermore, as equine and ovine hyper-immune serums are already licensed therapies routinely used throughout the world, including Europe and North America, we suggest there would be less of a requirement for time-consuming phase 1 safety testing, as there is already a reasonable, although clearly not perfect, safety profile for animal derived immune sera administered through the *i.v.* route to critically sick patients[11,12]. A recent publication that domesticated cats are highly susceptible to SARS-CoV-2 may also favour approaches to develop antisera in animals for their protection and treatment[13].

Although animal derived immunoglobulins provide effective treatments for the aforementioned indications, consideration must be given to the safety of such therapeutics. Intravenous administration of animal derived immunoglobulins is associated with the development of early and delayed (5 – 14 days post administration) adverse reactions, known as serum sickness. The incidence of adverse reactions to animal immunoglobulins shows great variation between products (from 3% to 88%) and is heavily influenced by quality of manufacturing processes and physicochemical properties of immunoglobulins. Early adverse reactions are often mild (typically, pruritis, urticaria, mild gastrointestinal disturbances), but can on occasion lead to life-threatening anaphylaxis. Serum sickness also occurs with intravenously administered human immunoglobulins[14]; and is typically a mild condition that only becomes clinically life-threatening when doses of immunoglobulins are administered on multiple occasions, at high dosages, or over prolonged periods of time[14]. During a one-off infusion, early adverse reactions and subsequent serum sickness can be carefully monitored and pharmacologically controlled[15]. Nevertheless, these routinely manageable early and delayed reactions may be a risk worth taking over the alternative currently unmanageable and, unfortunately, frequently fatal severe SARS-CoV-2 infection.

The recent excitement and potential usefulness of convalescent hyper-immune IgG must however be tempered by observations that anti-SARS-CoV-1 antibodies can contribute to severe acute lung injury[16]. This has been shown to occur through productive engagement of FcγRs expressed by alveolar macrophages that induce cytokine storms leading to Acute Respiratory Distress Syndrome (ARDS[16]). Animal derived IgG most likely do not optimally engage functional *in vivo* responses from human FcγRs and may yet turn out to be superior to human convalescent IgG for the short-term treatment of patients with ARDS.

Mitigation of adverse reactions can also be controlled during product development. For example, enzymatic cleavage of neutralising IgG into $F(ab')_2$, or removal of N-linked glycans from the Fc, are tried and tested approaches to limit interactions with human immune receptors that may give rise to the observed adverse events associated with injected antibodies[17,18]. Other options currently being investigated include using cattle transgenic for human immunoglobulin genes and glycosylation humanised pigs, but scaling-up manufacture from the limited animals available (difficult to breed) from single for profit companies

would appear insurmountable in the short term to satisfy escalating demand in LICs and LMICs.

Although the use of animals in medicine has fallen out of favour with the general public, the scale of the current crisis requires a multi-pronged approach that will inevitably involve the holistic and complementary use of animals to control SARS-CoV-2 and future emerging viruses that affect both humans and the animals they live with.

Data availability

No data is associated with this article.

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