Hemodialysis patients make long-lived antibodies against SARSCOV-2 that may be associated with reduced reinfection

Banham, Gemma; Godlee, Alexandra; Faustini, Sian; Cunningham, Adam; Richter, Alex; Harper, Lorraine; Backhouse, Claire; Casey, Anna; Dunbar, Lynsey; Emmanuel, Beena; Fahy, Megan; Moss, Paul; Nightingale, Peter; Ratcliffe, Liz; Stringer, Stephanie

DOI:
10.1681/ASN.2021020188

Haemodialysis patients make long-lived antibodies against SARS-CoV-2 that may be associated with reduced re-infection

Dr Gemma D Banham MRCP PhD [1, 5*], Dr Alexandra Godlee BM BCh PhD [2, 5*], Dr Sian E Faustini PhD [3], Prof Adam F Cunningham PhD [3], Prof Alex Richter FRCPath MD [3, 5], Prof Lorraine Harper PhD FRCP [4, 5] on behalf of the COVID-HD Birmingham Study Group[#]

1. Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham
2. Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham
3. Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham
4. Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham
5. University Hospitals Birmingham NHS Foundation Trust

*contributed equally

The COVID-HD Birmingham Study Group authors are Claire Backhouse, Anna Casey, Lynsey Dunbar, Beena Emmanuel, Megan Fahy, Paul Moss, Peter Nightingale, Liz Ratcliffe, Stephanie Stringer, and Matthew Tabinor.

Running title: SARS-CoV-2 Ab and re-infection in HD

Manuscript word count: 800

Corresponding authors:

1. Dr Gemma D Banham. Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT. UK
   gemma.banham@nhs.net

2. Professor Lorraine Harper. Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham. B15 2TT. UK
   l.harper@bham.ac.uk

Key words: COVID-19, SARS-CoV-2, Antibody, Haemodialysis

A definitive version was subsequently published in The Journal of the American Society of Nephrology. September 2021, 32 (9) 2140-2142 (Published online August 31, 2021)

DOI: https://doi.org/10.1681/ASN.2021020188

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections have disproportionately affected patients receiving in-centre haemodialysis. In England, 11.3% of in-centre haemodialysis patients were reportedly infected by COVID-19, with a 23% fatality rate (1) - 45 times greater than in non-haemodialysis, age-matched populations (2). Nevertheless, little is known about antibody responses induced by infection and whether these associate with protection.

We report a single-centre observational cohort study of 990 haemodialysis patients, performed between 10th March 2020 and 9th January 2021. We measured the longevity of serological responses to SARS-CoV-2 infection and the risk of re-infection. Participants were recruited from the in-centre haemodialysis population at University of Birmingham Hospitals NHS Foundation Trust. SARS-CoV-2 infection waves were defined as first wave, March-July 2020 and second wave October 2020-January 2021. Antibodies (combined IgG, IgA and IgM (IgGAM)) against SARS-CoV-2 spike glycoprotein were examined by ELISA in surplus serum from routine clinical samples taken during the first wave (3). We modelled antibody responses longitudinally using generalised estimating equations, allowing for sampling variation between individuals (Supplement). Frequency of PCR-confirmed SARS-CoV-2 infection during the second wave was analysed according to antibody status.

Clinical data and SARS-CoV-2 infection status were collated from electronic medical records. SARS-CoV-2 infection onset-date was defined as date symptoms started or positive PCR test, whichever was earlier. In patients testing antibody positive without a history of SARS-CoV-2 infection, predicted onset-date was defined as the date 50% of symptomatic patients had developed SARS-CoV-2 within their haemodialysis unit.

Anti-spike SARS-CoV-2 antibodies were detected in 25.9% (256/990) of patients from the first wave of COVID-19 with 54.7% seroconverting without a history of infection (140/256) (Table 1). Fifteen patients with PCR-confirmed COVID-19 had no evidence of an antibody response. Six of these 15 patients died after testing SARS-CoV-2 PCR+ (median 4 days, range 1-5 days) and six patients had no samples after 14 days following PCR+ test. Excluding these 12 patients with insufficient samples for analysis, 96% (82/85) of patients PCR+ for SARS-CoV-2 generated an antibody response.

We investigated whether antibodies generated against SARS-CoV-2 persist in patients receiving haemodialysis. 174 patients provided additional samples after testing positive; of these 132 (75.9%) remained antibody-positive at last sample (median duration 124 days following infection, interquartile range 95-210). Modelling of our data showed that the predicted mean IgGAM anti-spike response remained positive beyond 200 days following infection but declined over time (Figure 1). Those with symptomatic disease had higher predicted mean IgGAM responses than asymptomatic individuals (p=0.004).

During the second wave, patients were screened routinely for infection. Ninety PCR+ cases were identified in 937 at-risk haemodialysis patients - 11.4% (80/700) of patients without pre-existing antibodies but only 4.2% (10/237) of those with pre-existing antibodies (risk ratio 0.37 95% CI 0.19-0.70, p=0.001), with no differences in the proportion of patients who were symptomatic, hospitalised or who died, according to antibody status (Table 1). Eight of the 10 patients with antibodies detected in the first wave, who tested PCR+ during the second wave, had antibody ratios lower than the predicted mean for the cohort (range 65-192 days between last IgGAM and PCR+ tests) (Figure 1).

In this haemodialysis cohort, antibody responses to the SARS-CoV-2 spike protein are maintained, as in other cohorts (4, 5) and may be associated with a reduced frequency of re-infection. Those with lower levels of antibodies appear to be at greater risk of re-infection. Our analysis is limited to quantification of antibody responses; assessment of the neutralising capacity of these antibodies and associated T cell responses is required to conclude that the immune response is protective against re-infection.

We confirmed SARS-CoV-2 infection in 4.2% (10/237) of haemodialysis patients with pre-existing antibodies whereas in healthcare workers only 2 asymptomatic infections were detected amongst 1265 antibody positive participants (6). The different infection rate is, perhaps, unsurprising given the significant immunosuppression associated with haemodialysis (7), differences in testing frequency, the age disparity between the studied groups, and potential differences in symptom expression but this requires further investigation.

This is a large haemodialysis cohort, however the analysis does have limitations. We were unable to collect samples from most patients who died early in the pandemic who may not have developed a robust antibody response. Due to our sampling strategy, we were unable to describe the maturation of the immune response comprehensively for an individual from time of infection, however we used generalised estimating equations to allow for this. Early sampling was biased towards those with symptoms and we may have missed individuals showing short-lived responses whilst asymptomatic.

In conclusion, haemodialysis patients who survive SARS-CoV-2 infection generate an antibody response which is well maintained and appears to be associated with a reduced frequency of re-infection. Given that patients with lower responses may be at increased risk

of re-infection, the capacity of anti-vaccine antibody responses to protect haemodialysis patients should be closely monitored to determine efficacy.

Ethical Approval:

Ethical approval granted by the North West-Preston Research Committee (ref 20/NW/0240 IRAS Project ID: 282164) for the NIHR UPH Coronavirus Immunological Analysis (CIA) study.

Funding:

Funding for reagents was provided by a grant from the Queen Elizabeth Hospital Birmingham Charity, (Grant / Award Number: 16-3-046)

Author Contributions:

GDB, AFC, AR and LH designed the study. GDB and AG were involved in data collection and analysis. SEF and AR performed experiments. GDB and AG prepared figures. GDB, AG, AFC, AR, and LH drafted and revised the paper; all authors approved the final version of the manuscript.

Additional Contributions:

We thank Dr Anna L Casey, Liz Ratcliffe (Department of Pathology, University Hospitals Birmingham NHS Foundation Trust) for sample collection; Claire Backhouse, Beena Emmanuel, Lynsey A Dunbar (Clinical Immunology Service, University of Birmingham) for processing samples; Dr Matthew Tabinor and Dr Megan Fahy (University Hospitals Birmingham NHS Foundation Trust) for assistance with data collection; Dr Peter Nightingale (University Hospitals Birmingham NHS Foundation Trust) for providing statistical oversight; Prof Paul Moss (Institute of Immunology and Immunotherapy, University of Birmingham and University Hospitals Birmingham NHS Foundation Trust), the Chief Investigator of the CIA

Study, for arranging ethical approval and for his input in study design and Dr Stephanie Stringer (University Hospitals Birmingham NHS Foundation Trust), the clinical lead for the haemodialysis service, for coordinating the COVID-19 response. None of these individuals received compensation for their contribution.

We would like to thank the Department of Pathology, University Hospitals Birmingham NHS Foundation Trust and the Clinical Immunology Service, University of Birmingham for processing samples together with the medical teams and dialysis nurses who cared for these patients.

Disclosures:

The authors have nothing to disclose.

References:

1. The Renal Association B, UK: UK Renal Registry (2020) COVID-19 surveillance report for renal centres in the UK: A summary of the first wave of the pandemic – March to August 2020. . 2020

2. Savino M, Casula A, Santhakumaran S, Pitcher D, Wong E, Magadi W, et al.: Sociodemographic features and mortality of individuals on haemodialysis treatment who test positive for SARS-CoV-2: A UK Renal Registry data analysis. *PLoS One,* 15**:** e0241263, 2020 10.1371/journal.pone.0241263

3. Cook AM, Faustini SE, Williams LJ, Cunningham AF, Drayson MT, Shields AM, et al.: Validation of a combined ELISA to detect IgG, IgA and IgM antibody responses to SARS-CoV-2 in mild or moderate non-hospitalised patients. *J Immunol Methods,* 494**:** 113046, 2021 10.1016/j.jim.2021.113046

4. Wajnberg A, Amanat F, Firpo A, Altman DR, Bailey MJ, Mansour M, et al.: Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. *Science,* 370**:** 1227-1230, 2020 10.1126/science.abd7728

5. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al.: Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*, 2021 10.1126/science.abf4063

6. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, et al.: Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. *N Engl J Med*, 2020 10.1056/NEJMoa2034545

7. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al.: Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol,* 3**:** 1526-1533, 2008

Table 1: Comparing outcome, co-morbidity and demographic variables dependent on detection of SARS-CoV-2 antibodies.

	All n = 990	AB- n=734	AB+ n=256	p value
Male (%)	579 (58.5)	447 (60.9)	132 (51.6)	**0.009**
Female (%)	411 (41.5)	287 (39.1)	124 (48.4)	
Ethnicity (%)				**0.006**
White	481 (48.6)	381 (51.9)	100 (39.1)	
Asian	296 (29.9)	201 (27.4)	95 (37.1)	
Black	142 (14.3)	100 (13.6)	42 (16.4)	
Other	35 (3.5)	24 (3.3)	11 (4.3)	
Unknown	36 (3.6)	28 (3.8)	8 (3.1)	
Age: years (IQR)	65 (54-75)	64 (54-75)	67 (55-75)	0.482
IMD: decile (IQR)	2 (1-5)	2 (1-5)	2 (1-4)	0.096
BMI: kg/m^2 (IQR)	27 (23-32)	27 (23-31)	27 (24-32)	0.228
CCI (IQR)	7 (5-8)	7 (5-8)	7 (6-8)	**0.024**
DM (%)	418 (42.2)	288 (39.2)	130 (50.8)	**0.001**
Immunosuppression medication (%)	155 (15.7)	120 (16.3)	35 (13.7)	0.310
Symptoms reported (%)	227 (22.9)	111 (15.1)	116 (45.3)	**0.000**
Hospitalised (%)	128 (12.9)	57 (7.8)	71 (27.7)	**0.000**
Died (%)	93 (9.4)	66 (9.0)	27 (10.5)	0.463
Alive at the start of the second wave		**n=700**	**n=237**	
PCR+ during second wave (%)		80 (11.4)	10 (4.2)	**0.001**
Immunosuppression medication (%)		8 (10.0)	1 (10.0)	1.000
Symptoms reported (%)		57 (71.3)	5 (50.0)	0.171
Hospitalised (%)		34 (42.5)	4 (40.0)	0.880
Died (%)		10 (12.5)	2 (20.0)	0.511

Antibody status determined during the first wave. P values from Chi-squared tests for categorical data and Wilcoxon rank-sum tests for continuous data where medians and interquartile ranges (IQR) are displayed. Current use of immunosuppression medication or intravenous agent within a year of the start of the first wave. Symptoms reported compatible with SARS-CoV-2 infection. Death by 9th January 2021. PCR positivity during the second wave is reported as a percentage of those patients alive at the beginning of the second wave, with associated presence immunosuppression, symptoms, hospitalisation and

death reported as a percentage of those who are PCR positive. AB- SARS-CoV-2 anti-spike IgGAM seronegative; AB+ SARS-CoV-2 anti-spike IgGAM seropositive; IMD Index of Multiple Deprivation 2019; BMI Body Mass Index. CCI Charlson Comorbidity Index. DM diabetes mellitus.

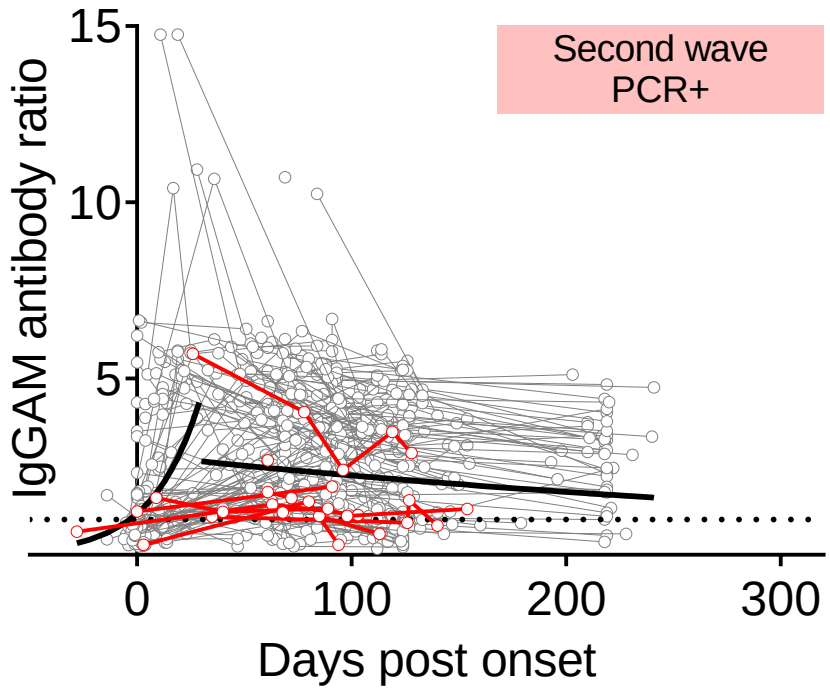

Figure 1: The serological response to SARS-CoV-2 and the risk of re-infection

Grey and red lines represent individual antibody ratios over time for patients who were antibody positive during the first wave and alive at the start of the second wave. Patients testing PCR positive during the second wave (red lines). Patients who do not test PCR positive during the second wave (grey lines). The predicted mean IgGAM serological response for the cohort (solid black lines). The threshold for antibody positivity is represented by a dotted line.