# COVID-19 infection in patients with severe aplastic anaemia

The coronavirus disease 2019 (COVID-19) pandemic has caused concern among physicians caring for immunosuppressed patients. Aplastic anaemia (AA) is a rare life-threatening bone marrow failure disorder that presents with severe pancytopenia and a hypocellular marrow.[1] Patients with severe disease are at increased risk of infection due to neutropenia and immunosuppressive therapy (IST), particularly if the absolute neutrophil count (ANC) is <200/μl. Additionally, standard IST regimens for AA include anti-thymocyte globulin (ATG), high-dose corticosteroids, and cyclosporine (CsA), which suppress T-cell function and can lead to viral reactivation, particularly of herpesviruses. Preceding viral infection as an initial trigger of AA or of disease relapse is possible as viruses can lead to immune destabilisation. Many viruses are known to cause transient cytopenias, but sustained marrow aplasia has mainly been associated with parvovirus.[2,3]

Questions regarding AA in the COVID-19 era include: (i) Do patients with AA have a higher susceptibility to COVID-19? (ii) If infected, do patients with AA suffer more severe disease? And (iii) Can newly diagnosed patients with severe AA (SAA) safely receive IST? Because AA is rare, the literature is currently limited to case reports that show varying severities of infection with different treatments and outcomes.[4,5] In another chronic haematological condition, sickle cell disease (SCD), patients have been found to experience a mild infectious course but are at risk of having acute SCD-related complications.[6,7] In the present case series, we report the clinical outcomes of five patients with SAA who developed COVID-19 infection.

The median (range) age of the patients with SAA at the time of COVID-19 diagnosis was 32 (21–61) years. Four patients had a previous diagnosis of SAA while unique patient number (UPN)-4 was diagnosed with SAA and COVID-19 simultaneously. Patients received standard IST and eltrombopag (EPAG) on clinical protocols NCT01623167 or NCT04304820. By 6 months, three had achieved haematological response and one (UPN-2) was a non-responder. Of the responders, one patient (UPN-1) had relapsed, was treated with a second round of IST (alemtuzumab and, later, EPAG), and regained response. UPN-2, who had not responded to first-line IST, required two additional therapies and had stable blood counts (Table I).

UPN-1 had mild symptoms at COVID-19 diagnosis and recovered after 3 days of symptomatic outpatient management. He presented 1 month later with new onset right shoulder and back pain and was diagnosed with herpes zoster reactivation. UPN-2, a 61-year-old overweight former smoker, had fever, upper respiratory tract symptoms, and pneumonia on imaging. Mild hypoxia not requiring oxygen occurred, which improved with outpatient dexamethasone treatment. UPN-3, a young male with extensive cardiovascular history, was tested for COVID-19 due to precipitous drop in ANC on routine blood monitoring for SAA and was found to be positive. He was admitted briefly for monitoring and treated with granulocyte-colony stimulating factor (G-CSF) with improvement in ANC. UPN-4 presented with severe pancytopenia and was diagnosed with asymptomatic COVID-19 infection and SAA simultaneously. Administration of horse-ATG (h-ATG) was delayed for 3 months until a negative COVID-19 polymerase chain reaction (PCR) test was obtained, but he was started on CsA and EPAG soon after SAA diagnosis. However, he experienced recurrent ileitis and small bowel obstruction necessitating surgical resection. Non-specific pathology showed only inflammation, and a diagnosis of post-COVID-19 immune colitis was made. UPN-5 had mild symptoms of COVID-19 and had recovered fully with symptomatic treatment at home.

At last follow-up, all patients had recovered completely from the infection (Table I). Four patients (UPN-1, -2, -3, and -4) received antibody tests and were found to have severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) immunoglobulin G (IgG) spike protein-positive antibodies at 24, 3, 8, and 35 weeks after their COVID-19 infections respectively. UPN-4 had achieved a complete response to IST treatment and remains on low-dose CsA. The other four patients with previously successfully treated SAA retained their baseline blood counts (Fig 1) and continued on their respective ongoing treatment (Table I).

In our present cohort of patients with SAA the clinical spectrum of COVID-19 infection was consistent with age and other comorbidities.[8] Common symptoms included fever, cough and headache. The oldest subject (aged 55 years) had worse respiratory illness requiring steroids. No patients required COVID-19 infection-directed therapies or had interruption of ongoing immunosuppression. One patient (UPN-4) diagnosed with simultaneous SAA and COVID-19 infection was treated with early initiation of oral therapy, low dose CsA/EPAG, while h-ATG, a more potent immunosuppressant, was delayed until COVID-19 PCR was negative. This treatment strategy did not impact SAA outcome.

The risk of relapse is highest for patients within 2–4 years of their initial IST treatment, in particular when haematological recovery is partial.[9] In four patients with stable blood

First published online 29 April 2021
doi: 10.1111/bjh.17415

**Table I.** Characteristics and outcomes of patients with severe aplastic anaemia (SAA) and coronavirus disease 2019 (COVID-19).

| | Patient | | | | |
|---|---|---|---|---|---|
| Variable | UPN-1 | UPN-2 | UPN-3 | UPN-4 | UPN-5 |
| Severity of SAA | VSAA | SAA | VSAA | SAA | SAA |
| Age at SAA dx, years | 24 | 55 | 35 | 21 | 24 |
| Sex | Male | Female | Male | Male | Female |
| Pulmonary history | Fungal infection (treated) | No | No | No | No |
| Cardiovascular history | No | No | Hypertension familial aortic aneurysm | No | No |
| Smoking history | None | Former | Former | None | None |
| BMI, kg/m$^2$ | 24·3 | 26·7 | 26·37 | 24·4 | 26·8 |
| 1st treatment | h-ATG, CsA, EPAG | h-ATG, CsA, EPAG | h-ATG, CsA, EPAG | h-ATG, CsA, EPAG | h-ATG, CsA, EPAG |
| Response at 6 months | CR | NR | PR | CR | PR |
| Relapse | Yes | NA | No | No | No |
| 2nd treatment | Alemtuzumab | CsA | – | – | – |
| 3rd treatment | EPAG | EPAG | – | – | – |
| At COVID-19 diagnosis | | | | | |
| Age, years | 27 | 61 | 36 | 21 | 32 |
| Time from SAA dx to COVID-19 infection, months | 29 | 61 | 9 | 0 | 99 |
| SAA status | PR | PR | PR | NA | PR |
| Ongoing treatment for SAA | EPAG 150 mg daily | EPAG 150 mg daily | CsA 225 mg daily | NA | None |
| Fever | Yes | Yes | No | Yes | No |
| Respiratory symptoms | Dry cough | Cough, rhinorrhoea | None | None | None |
| Altered smell/taste | No | No | No | No | Yes |
| Other symptoms | Headache | None | None | None | Headache, fatigue |
| Pneumonia | No | Yes | No | No | No |
| Hospitalisation | No | No | Yes | No | No |
| Outcome | Full recovery | Full recovery | Full recovery | Full recovery | Full recovery |
| SARS-CoV-2 antibody (IgG) | Yes | Yes | Yes | Yes | NA |
| Post-COVID-19 complications | Herpes zoster | – | | Recurrent ileitis and perforation s/p small bowel resection | – |
| SAA status post-COVID-19 | No change from baseline | No change from baseline | Transient decline in neutrophils | NA | No change from baseline |

VSAA was defined as an ANC of <200/μl. CR was defined as absolute ANC of >1000/μl, platelet count of ≥100 000/μl, haemoglobin ≥100 g/l. PR was defined as blood counts no longer meeting the standard 'Camitta' criteria – ANC of ≥500/μl, platelet count of ≥20 000/μl, absolute reticulocyte count of ≥60 000/μl. Relapse was assessed on patients with response at 6 months and defined as decline in blood counts after successful treatment with immunosuppressive therapy. COVID-19 was diagnosed by real-time quantitative polymerase chain reaction of nasopharyngeal swabs. ANC, absolute neutrophil count; BMI, body mass index; CR, complete response; CsA, cyclosporine; dx, diagnosis; EPAG, eltrombopag; h-ATG, horse anti-thymocyte globulin; IgG, immunoglobulin G; NA, not applicable; NR, no response; PR, partial response; (V)SAA, (very) severe aplastic anaemia; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Published 2021. This article is a U.S. Government work and is in the public domain in the USA.
*British Journal of Haematology*, 2021, **193**, 902–905

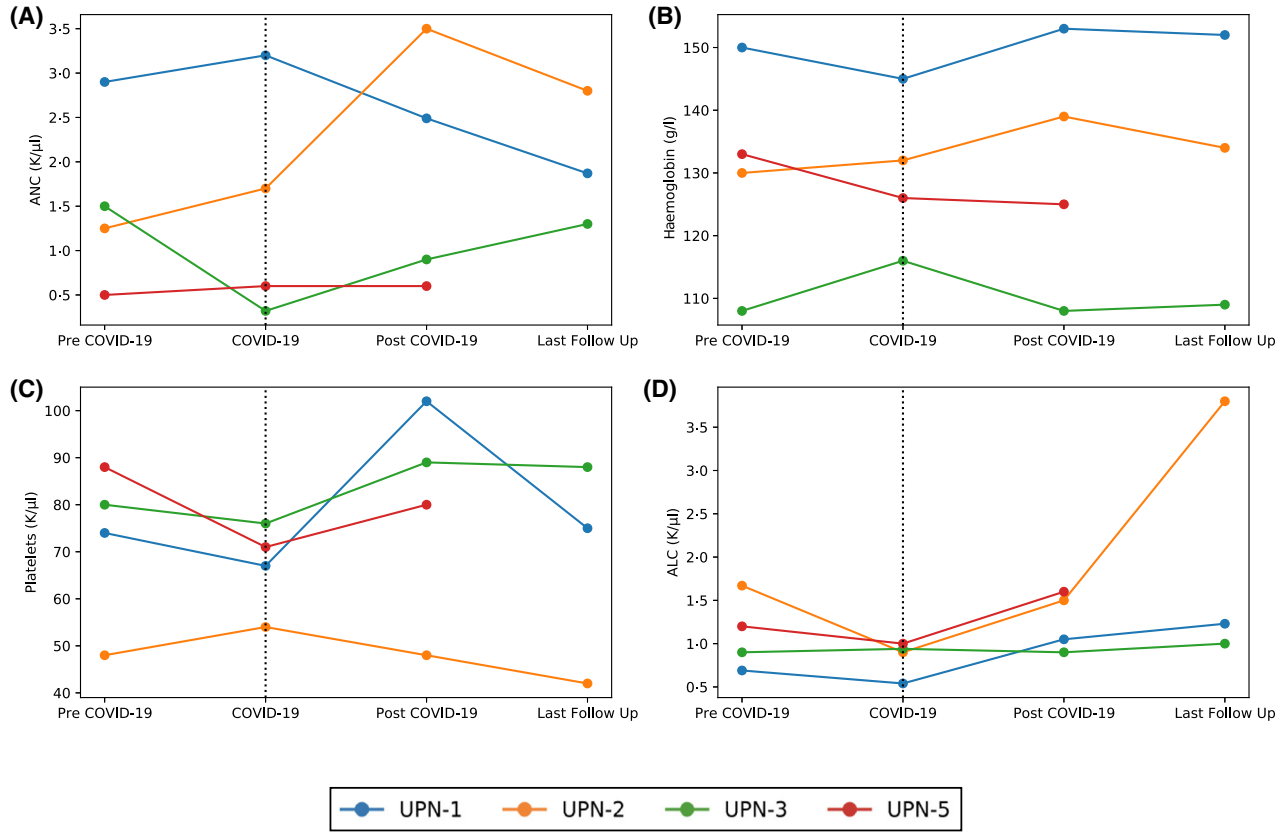


**Fig 1.** Peripheral blood counts in four subjects with coronavirus disease 2019 (COVID-19) infection and history of severe aplastic anaemia (SAA) at time points before, during, and after the infection. The last laboratory follow-up from the time of COVID-19 infection varied in the four patients: unique patient number (UPN)-1 (27 weeks), UPN-2 (3 weeks), UPN-3 (8 weeks), and UPN-5 (7 weeks). The last follow-up to assess recovery and complications was the same as laboratory follow-up for UPN-1 and UPN-3 but UPN-2 was 5 weeks and UPN-5 was 12 weeks. (A) Absolute neutrophil count (ANC), (B) haemoglobin, (C) platelets and (D) absolute lymphocyte count (ALC). [Colour figure can be viewed at wileyonlinelibrary.com

counts with or without ongoing CsA or EPAG, blood counts were unaffected during and after COVID-19 infection. UPN-3 had a dramatic decrease in ANC with infection that required temporary G-CSF administration. No patient met the criteria for relapse of SAA. Close monitoring of full blood counts continues for all patients. Absolute lymphocyte counts were noted to decrease slightly in three of four patients but returned to previous levels weeks later.

Two patients had post-viral complications. UPN-1 had uncomplicated herpes zoster at 1 month after COVID-19 infection, concurrent with PCR positivity for SARS-CoV-2, a reported complication.[10] In UPN-4, recurrent ileitis commenced shortly after COVID-19, each time responsive to glucocorticoids. The temporal relationship to recent COVID-19 infection, absence of family history of inflammatory bowel disease, and histology showing only inflammation, suggested the ileitis to represent a post-viral autoimmune process. Although ileitis has not been reported previously, other autoimmune diseases such as inflammatory myopathy[11] and paediatric inflammatory multisystem syndrome[12] have been identified in patients after COVID-19 infection.

In summary, we report the largest case series to date of patients with SAA and COVID-19 infection. In younger patients and without major comorbidities from all stages of SAA disease course, COVID-19 infection was self-limiting. COVID-19 did not result in SAA relapse but these results cannot be generalised to patients who may have more severe COVID-19 manifestations due to other underlying comorbidities.[13] The timing of relapse post viral infection is not established therefore longer follow-up may lead to better knowledge. In patients with concurrent SAA and COVID-19 infection, continuation or initiation of CsA and/or EPAG during SARS-CoV-2 infection does not appear to complicate infectious course.

## Acknowledgements

The authors would like to thank the patients and families who participated in these studies. Support for this trial was provided by the Intramural Research Programme of the National Heart, Lung and Blood Institute (NHLBI) as well as GlaxoSmithKline and Novartis, the manufacturers of EPAG, who also supplied the study drug.

## Author contributions

Casey Paton and Liza Mathews performed research, analysed results, and wrote the paper; Bhavisha A. Patel and Emma M. Groarke designed the research, performed research, analysed results, provided clinical care and wrote the paper; Olga Rios and Jennifer Lotter provided clinical care; Neal S. Young performed research, provided clinical care and edited the paper.

## Conflict of interest

Neal S. Young has a co-operative research and development agreement (CRADA) with Novartis that provides research funding. Novartis reviewed the manuscript prior to submission. All other authors have no conflicts of interest to declare.

## Data sharing

Patient data will not be shared with other researchers to protect confidentiality.

**Casey Paton**
**Liza Mathews**
**Emma M. Groarke**
**Olga Rios**
**Jennifer Lotter**
**Bhavisha A. Patel**
**Neal S. Young**
*Hematology Branch, National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda, MD, USA.*
*E-mail: bhavisha.patel@nih.gov*

**Clinicaltrials.gov identifier:** NCT01623167.

*Casey Paton and Liza Mathews contributed equally to this manuscript.

First published online 01 XXXX 2021
doi: 10.1111/bjh.17415

## References

1. Young NS. Aplastic anemia. *N Engl J Med*. 2018;**379**:1643–56.
2. Young NS, Brown KE. Parvovirus B19. *N Engl J Med*. 2004;**350**:586–97.
3. Mende M, Sockel K. Parvovirus B19 Infection. *N Engl J Med*. 2018;**379**:2361.
4. Wang Y, Lu X, Chen T, Wang J. Lessons from a patient with severe aplastic anemia complicated with COVID-19. *Asian J Surg*. 2021;**44**:386–8.
5. Akcabelen YM, Koca Yozgat A, Parlakay AN, Yarali N. COVID-19 in a child with severe aplastic anemia. *Pediatr Blood Cancer*. 2020;**67**:e28443.
6. Menapace LA, Thein SL. COVID-19 and sickle cell disease. *Haematologica*. 2020;**105**:2501–4.
7. Subarna C, Giselle P-P, Fester I, Virginia T, Charlotte G, David R, et al. COVID-19 in patients with sickle cell disease - a case series from a UK Tertiary Hospital. *Haematologica*. 2020;**105**:2691–3.
8. Stawicki SP, Jeanmonod R, Miller AC, Paladino L, Gaieski DF, Yaffee AQ, et al. The 2019–2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: a Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper. *J Glob Infect Dis*. 2020;**12**:47–93.
9. Scheinberg P, Young NS. How I treat acquired aplastic anemia. *Blood*. 2012;**120**:1185–96.
10. Tammaro A, Adebanjo GA, Parisella FR, Pezzuto A, Rello J. Cutaneous manifestations in COVID-19: the experiences of Barcelona and Rome. *J Eur Acad Dermatol Venereol*. 2020;**34**:e306–7.
11. Dalakas MC. Inflammatory myopathies: update on diagnosis, pathogenesis and therapies, and COVID-19-related implications. *Acta Myol*. 2020;**39**:289–301.
12. Schvartz A, Belot A, Kone-Paut I. Pediatric inflammatory multisystem syndrome and rheumatic diseases during SARS-CoV-2 pandemic. *Front Pediatr*. 2020;**8**:605807.
13. Keiffer G, French Z, Wilde L, Filicko-O'Hara J, Gergis U, Binder AF. Case report: tocilizumab for the treatment of SARS-CoV-2 infection in a patient with aplastic anemia. *Front Oncol*. 2020;**10**:562625.