The ChAdOx1 nCoV-19 vaccine has been associated with increased risk of thrombosis. Understanding of the management of these rare events is evolving, and currently recommended treatments include human normal immunoglobulin and nonheparin anticoagulation such as direct oral anticoagulants. Our report describes three consecutive patients presenting to a London teaching hospital with vaccine-induced thrombotic thrombocytopenia (VITT), also referred to as vaccine-induced prothrombotic immune thrombocytopenia. The patients ranged in age from 40 to 54 years and two had no known previous medical comorbidities. Two patients had cerebral venous sinus thrombosis and one had a deep vein thrombosis. Two were treated with anticoagulation, one with oral rivaroxaban and the other with an intravenous argotrabran infusion that was later converted to oral apixaban. One patient received three doses of human normal immunoglobulin and 5 days of therapeutic plasma exchange. This case series may be used to improve understanding of the clinical course and management of VITT.

KEYWORDS
anticoagulants, drug utilisation, evidence-based medicine, vaccines, virology
What is already known about this subject

- Vaccination with the ChAdOx1 nCoV-19 vaccine has been associated with pathological thrombosis, including cerebral venous sinus thrombosis.
- Strategies to treat these rare events are being investigated and include the use of nonheparin anticoagulation and human normal immunoglobulin.
- Treatment guidelines are still evolving.

What this study adds

- Our study describes the presentation, management and clinical course of three consecutive cases of vaccine-induced prothrombotic immune thrombocytopenia (VITT) following the ChAdOx1 nCoV-19 vaccine.
- The cases included both cerebral venous sinus thrombosis and deep vein thrombosis, and management varied between patients.
- On presentation all patients had low platelet count, raised D-dimer measurement and were anti-PF4-antibody positive.
- These observations may be used to gain insight into the pathophysiology and optimal management of VITT.
identified on ultrasonography (Figure 2). She had no known risk factors for deep vein thrombosis. She was managed in ambulatory care with oral rivaroxaban, prescribed initially for at least 3 months (since extended to 6 months following review in the haematology outpatient clinic). After her initial management with anticoagulation she had a magnetic resonance imaging (MRI) scan and venogram of her head, which were both normal.

Patient 3: This 40-year-old woman had the ChAdOx1 nCoV-19 vaccine on 25 May 2021 (day 0). She had no comorbidities and was not on any prior medication. On day 2, she developed headache. On day 14, she presented to hospital with headache and seizures. The initial platelet count was $45 \times 10^9/L$ and D-dimer was >6000 ng/mL. Acute superior sagittal and cortical vein thrombosis was identified on CT venography (Figure 3). In the emergency department, levetiracetam 2.8 g IV was administered for seizure management. Cryoprecipitate (2 pools), methylprednisolone (1 g IV) and human normal immunoglobulin (70 g IV, 1 g/kg, based on initially estimated body weight 70 kg) were administered on admission for clinically suspected VITT.

She was admitted to the neurointensive care unit for continued observation and management. There was evidence of further seizure

**FIGURE 1** Admission CT head, patient 1

**FIGURE 2** Imaging from patient 2. A, Doppler ultrasound image showing a longitudinal section through the right popliteal vein, with no blood flow demonstrated. B, Transverse section showing echogenic material in the vein

**FIGURE 3** Imaging from patient 3. (A) A coronal section from the admission CT venogram, with a filling defect (“empty delta sign”) seen in the superior sagittal sinus (black arrow). An axial section from the unenhanced CT scan performed approximately 6 hours later (B) shows venous haemorrhage in the left frontal lobe (white arrow), with marked mass effect
activity and continued fluctuation of her consciousness level. Anti-epileptic treatment was intensified with the addition of sodium valproate 1.2 g twice daily. A second CT scan of her head demonstrated left intra-cerebral haemorrhage related to the venous thrombosis, with significant mass effect (Figure 3). A bifrontal decompressive craniectomy was performed and an intracranial pressure transducer was inserted. Cryoprecipitate and platelets were administered intraoperatively, targeting a fibrinogen concentration of >1.5 g/L and platelet count of >100 × 10^9/L, respectively. Due to the aggressive disease course, therapeutic plasma exchange was started postoperatively. An approximately equal ratio of human albumin solution 5% and human plasma (Octapas) was used as replacement fluid. This was repeated daily for five sessions. Following this, a second dose of human normal immunoglobulin was administered (70 g IV, 1 g/kg). Argatroban was started 24 hours post-operatively for anticoagulation. It was infused intravenously at a rate of 0.6–1 μg/kg/min, titrated to achieve a target activated partial thromboplastin time ratio of 1.5.

After 17 days of invasive ventilation, she was extubated. On day 36 she was deemed to be sufficiently stable for the argatroban infusion to be switched to apixaban 5 mg orally 12-hourly. She was subsequently transferred to the stroke unit on day 40. A third dose of human normal immunoglobulin was administered on day 44 (50 g IV, based on an accurate body weight), completing two effective doses with an interval of approximately 3 weeks, as it was considered that the first dose would have been removed by plasma exchange and anti-PF4 antibodies remained detectable. She was transferred to her local hospital for continued rehabilitation on day 52. At this time, she had severe left hemiparesis, and receptive and expressive dysphasia, and required seizure prophylaxis with sodium valproate 1.2 g twice daily and levitaracetam 1.5 g twice daily.

### 3.2 Investigations

Patients 1 and 3 had D-dimer levels >6000 ng/mL on admission, with the D-dimer of patient 2 initially recorded as 4205 ng/mL. The D-dimer values were higher in patients 1 and 3, both of whom experienced cerebral venous thrombosis, whilst patient 2 had a deep vein thrombosis. All patients had positive testing for anti-PF4 (Table 1).

| Patient | Anti-PF4 testing on admission (normal <0.400) | Blood film comments from admission |
|---------|-----------------------------------------------|----------------------------------|
| 1       | 2.16                                          | Genuine marked thrombocytopenia with few large platelet clumps noted. Toxic vacuolation on some neutrophils and mild left-shifted neutrophils to band form and reactive lymphocytes. No blast and red cell fragments noted. |
| 2       | 2.84                                          | Platelets appear reduced on blood film. Occasional large forms seen. |
| 3       | 1.88                                          | Genuine thrombocytopenia confirmed. No platelet clumps/fibrin strands seen. No red blood cell fragments. Normal white blood cell morphology noted. |
All patients had thrombocytopenia at baseline, confirmed on blood film microscopy (Table 1). In patient 1, who died shortly after admission, the baseline platelet count was $8 \times 10^9/L$. In patient 2, the platelet count was initially $90 \times 10^9/L$. The platelet counts of patient 3, in relation to relevant therapeutic interventions, are presented in Figure 4.

4 | DISCUSSION

Our case series adds to the growing body of literature discussing VITT. Early studies observed cases occurring primarily in women under 40 years of age. Our series describes VITT affecting two women and one man, somewhat older than the initial cases reported elsewhere. Whilst it was supposed that there may be a link between age and risk of VITT, this was not supported by a recent analysis performed by Public Health England that reviewed all the cases of VITT reported up to 26 May 2021. At this time 348 suspected cases of VITT had been reported to the MHRA. The vaccine-related blood clots were not strongly linked to sex, and it was felt that the female preponderance in the earlier cohorts may have been due to a higher vaccine uptake in women at that time.

Our patients all presented within 3 weeks of vaccination and typically reported initial symptoms within 1 week of vaccination. This is in keeping with a recent study in the United States where patients presented with VITT 1–2 weeks post vaccination. In an analysis of cases reported to the MHRA up to 26 May 2021, all cases of VITT occurred after the first dose of the vaccine and there were no reported cases after the second dose. The implications of this are uncertain, as people affected by VITT after a first dose are unlikely to be re-challenged with a second dose. However, since the initial data was gathered by the MHRA, there have been data to support that risk of VITT after a second dose of the vaccine may not be any greater than that observed in the general unvaccinated population.

The patients in our series received different treatments related to the nature and timing of their presentations. Two of the patients presented with bleeding associated with thrombosis. Patient 1 had major intracranial haemorrhage and died, patient 3 had a bleed after VITT diagnosis that resulted in major disability. Therefore, it is diagnostically important to be aware of patients presenting with bleeding post vaccination and consider VITT in these cases, rather than just in cases of thrombosis. Since anticoagulation is a core management strategy in VITT, this presents a difficult risk-benefit decision and further research is needed to determine optimal management.

Patient 3 had the longest duration of hospital stay, requiring three IVIG infusions and plasma exchange. This management is consistent with the rapid guidance from the Expert Haematology Panel which states repeated IVIG can be considered in cases of VITT, and that patients should be followed up after discharge and given further IVIG in the case of recurrently falling platelet counts or a rising D-dimer. Our patient had no relapse of these features but was given a repeat dose of IVIG due to the severity of her initial presentation and the persistence of anti-PF4 antibodies. The guidance also suggests that in cases refractory to IVIG, rituximab (a monoclonal antibody that targets CD20 protein on B cells) can be considered. Our patient also had five sessions of plasma exchange, and a recent study indicated that in patients not responsive to IVIG, plasma exchange was effective in treating vaccine-induced thromboses. Interestingly, IVIG was not offered in the management of patient 2. Whilst her presentation was less severe than the other cases, guidelines suggest that IVIG could have been considered to help reduce any disease progression. Despite the lack of IVIG her clinical course has remained good and she has had no further events of thrombosis.

Similar to other reports from the United States and Europe, all our patients had positive tests for heparin-induced thrombocytopenia antibodies and no historical exposure to heparin. The pathogenesis of vaccine induction of these antibodies is unclear, but it has been observed that VITT is almost exclusively associated with SARS-CoV-2 vaccines that use an adenovirus vector: ChAdOx1 nCoV-19 (platformed on a replication-deficient chimpanzee adenovirus, Oxford/AstraZeneca) and Ad26.COV2.S (replication-deficient human adenovirus 26, Janssen). The Sputnik V vaccine (Gamaleya Research Institute) also uses an adenoviral vector and has not had any reported cases of VITT that we could identify. Another vaccine using the adenoviral vector is the Ad5-nCOV (CanSino Biological Inc/Beijing Institute of Biotechnology), which has not yet been linked to pathological thrombosis. No increased risk of thrombosis has yet been reported with the use of the mRNA-platformed vaccines; however, these have been associated with rare reports of immune thrombocytopenia.

Acute thrombocytopenia has also previously been noted in animal trials with adenovirus vectored vaccines. Case reports have similarly linked systemic adenovirus infection to a thrombotic thrombocytopenic picture. Possible mechanisms for this include the development of antibodies against PF4 and direct interaction between the adenoviral vector and platelets. A recent report has found that the antibodies of patients with VITT bind to PF4 within the heparin-binding site.

COVID-19 is itself a prothrombotic disease and thrombocytopenia is also frequently observed, with several putative explanations. Therefore, another potential mechanism is cross-reactivity of the anti-SARS-Cov2 spike protein antibodies with PF4. However, this does not explain the apparent difference in rate of VITT between different vaccine platforms, which all employ the SARS-CoV-2 spike protein as the antigenic target.

Our case series has several limitations. There are only three patients, so broad inferences about ongoing management strategies cannot be made. Patient 1 was transferred from a district hospital, and investigation results prior to the transfer were not available to us. Additionally, some laboratory investigations were not performed in all patients. We collected data retrospectively, and some relevant information was not available. Despite these limitations, this series adds to the collective body of evidence on the presentation, clinical course and management of this rare condition.

5 | CONCLUSION

In our three VITT cases, one patient died, one was managed in ambulatory care and the third is recovering in hospital, with life-changing
neurological impairment. Where immunomodulatory treatments (immunoglobulin and therapeutic plasma exchange) were employed in one case, this was followed by an improvement in platelet count. Likewise, use of nonheparin anticoagulants in two cases was followed by amelioration of the prothrombotic process. This aligns with reports from other centres. Through sharing of experiences of this rare complication, understanding and management can be optimised.

ETHICS APPROVAL
St George’s Hospital audit registration number AUDI001000.

PATIENT CONSENT
Signed consent from the patient or their next-of-kin was obtained for anonymised data to be published in this report.

ACKNOWLEDGEMENTS
No funding was received for this work.

COMPETING INTERESTS
D.G. is employed part-time by Novo Nordisk outside of the submitted work.

AUTHOR CONTRIBUTION
D.G. and I.W. contributed to the conception and design of the work. I.W. collected data from patient records, which was independently reviewed by D.G. I.W., D.S., A.W.H. and D.G. drafted the manuscript. All authors interpreted the data, critically revised the manuscript and provided final approval of the version to be submitted.

DATA AVAILABILITY STATEMENT
Anonymised data is available on reasonable request to the corresponding author.

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How to cite this article: Watts I, Smith D, Mounter S, Baker EH, Hitchings AW, Gill D. A case series of vaccine-induced thrombotic thrombocytopenia in a London teaching hospital. Br J Clin Pharmacol. 2022;88(4):1935-1941. doi:10.1111/bcp.15116