

US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COVID.S Vaccination, March 2 to April 21, 2021

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IMPORTANCE Cerebral venous sinus thrombosis (CVST) with thrombocytopenia, a rare and serious condition, has been described in Europe following receipt of the ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca), which uses a chimpanzee adenoviral vector. A mechanism similar to autoimmune heparin-induced thrombocytopenia (HIT) has been proposed. In the US, the Ad26.COVID.S COVID-19 vaccine (Janssen/Johnson & Johnson), which uses a human adenoviral vector, received Emergency Use Authorization (EUA) on February 27, 2021. By April 12, 2021, approximately 7 million Ad26.COVID.S vaccine doses had been given in the US, and 6 cases of CVST with thrombocytopenia had been identified among the recipients, resulting in a temporary national pause in vaccination with this product on April 13, 2021.

OBJECTIVE To describe reports of CVST with thrombocytopenia following Ad26.COVID.S vaccine receipt.

DESIGN, SETTING, AND PARTICIPANTS Case series of 12 US patients with CVST and thrombocytopenia following use of Ad26.COVID.S vaccine under EUA reported to the Vaccine Adverse Event Reporting System (VAERS) from March 2 to April 21, 2021 (with follow-up reported through April 21, 2021).

EXPOSURES Receipt of Ad26.COVID.S vaccine.

MAIN OUTCOMES AND MEASURES Clinical course, imaging, laboratory tests, and outcomes after CVST diagnosis obtained from VAERS reports, medical record review, and discussion with clinicians.

RESULTS Patients' ages ranged from 18 to younger than 60 years; all were White women, reported from 11 states. Seven patients had at least 1 CVST risk factor, including obesity (n = 6), hypothyroidism (n = 1), and oral contraceptive use (n = 1); none had documented prior heparin exposure. Time from Ad26.COVID.S vaccination to symptom onset ranged from 6 to 15 days. Eleven patients initially presented with headache; 1 patient initially presented with back pain and later developed headache. Of the 12 patients with CVST, 7 also had intracerebral hemorrhage; 8 had non-CVST thromboses. After diagnosis of CVST, 6 patients initially received heparin treatment. Platelet nadir ranged from $9 \times 10^3/\mu\text{L}$ to $127 \times 10^3/\mu\text{L}$. All 11 patients tested for the heparin-platelet factor 4 HIT antibody by enzyme-linked immunosorbent assay (ELISA) screening had positive results. All patients were hospitalized (10 in an intensive care unit [ICU]). As of April 21, 2021, outcomes were death (n = 3), continued ICU care (n = 3), continued non-ICU hospitalization (n = 2), and discharged home (n = 4).

CONCLUSIONS AND RELEVANCE The initial 12 US cases of CVST with thrombocytopenia after Ad26.COVID.S vaccination represent serious events. This case series may inform clinical guidance as Ad26.COVID.S vaccination resumes in the US as well as investigations into the potential relationship between Ad26.COVID.S vaccine and CVST with thrombocytopenia.

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JAMA. 2021;325(24):2448-2456. doi:10.1001/jama.2021.7517
Published online April 30, 2021.

On February 27, 2021, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the single-dose Janssen/Johnson & Johnson COVID-19 (Ad26.COVS.2.S) vaccine, a replication-incompetent human adenovirus 26 vector vaccine.¹ As of April 12, 2021, approximately 7 million doses of this vaccine had been administered nationwide.^{2,3}

On March 18, 2021, the European Medicines Agency announced findings of a rare thrombosis with thrombocytopenia syndrome (TTS) after receipt of the ChAdOx1 nCoV-19 vaccine (Vaxzevria, Oxford/AstraZeneca), which uses a recombinant replication-deficient chimpanzee adenovirus vector.⁴⁻⁶ Cerebral venous sinus thrombosis (CVST), a rare and serious condition,⁷ was noted in 72% of these initial TTS reports. A mechanism similar to autoimmune heparin-induced thrombocytopenia (HIT),⁸ in which platelet-activating antibodies develop in the absence of heparin exposure, has been proposed to explain the occurrence of CVST with thrombocytopenia after ChAdOx1 nCoV-19 vaccination.⁹⁻¹¹

One case of CVST with thrombocytopenia in a male patient was reported during the phase 3 clinical trial of the Ad26.COVS.2.S vaccine.¹² Six cases of CVST with thrombocytopenia after Ad26.COVS.2.S vaccination were reported through the Vaccine Adverse Event Reporting System (VAERS) to the Centers for Disease Control and Prevention (CDC) and FDA as of April 12, 2021; information about 1 case was published.¹³ On April 13, the CDC and FDA recommended a pause in the use of the Ad26.COVS.2.S vaccine.^{2,14} By April 21, 6 additional cases of CVST with thrombocytopenia and 3 cases of non-CVST TTS following administration of Ad26.COVS.2.S vaccine were reported to VAERS.¹⁵ On April 23, after reviewing data on TTS cases following postauthorization Ad26.COVS.2.S vaccination, CDC's Advisory Committee on Immunization Practices (ACIP) reaffirmed its interim recommendation for use of the Ad26.COVS.2.S vaccine in all persons aged 18 years or older in the US.¹⁶

The aim of this case series was to describe the clinical and laboratory details of the first 12 US post-EUA cases of CVST with thrombocytopenia after Ad26.COVS.2.S vaccination reported to VAERS.

Methods

VAERS is the US passive surveillance (spontaneous reporting) system for adverse events after immunization and is jointly administered by CDC and FDA. This investigation was conducted as part of the routine activities of VAERS and the Clinical Immunization Safety Assessment (CISA) Project.¹⁷ VAERS and CISA clinical consult activities are long-running surveillance programs conducted for public health purposes. CDC does not consider these to be research activities. The activities herein were confirmed to be nonresearch under the Common Rule in accordance with institutional procedures and therefore were not subject to institutional review board requirements. Informed consent was not obtained for this secondary use of existing information (see, eg, 45 CFR §46.102(I)(2), 21 CFR §56; 42 USC §241(d); 5 USC §552a; 44 USC §3501 et seq).

Key Points

Question What were the clinical characteristics of the first US patients reported to have cerebral venous sinus thrombosis (CVST) with thrombocytopenia following receipt of the Ad26.COVS.2.S (Janssen/Johnson & Johnson) COVID-19 vaccine?

Findings In this case series of 12 patients, all were women, younger than 60 years, and had symptom onset ranging from 6 to 15 days after vaccination requiring hospitalization. Of 11 patients with heparin-platelet factor 4 enzyme-linked immunosorbent assay (ELISA) heparin-induced thrombocytopenia (HIT) antibody test results, all were positive. At last follow-up, outcomes were death (n = 3), intensive care unit (ICU) care (n = 3), non-ICU hospitalization (n = 2), and discharge to home (n = 4).

Meaning This case series may inform clinical guidance and investigations into the potential relationship between the Ad26.COVS.2.S vaccine and CVST with thrombocytopenia.

VAERS accepts reports from clinicians, vaccine manufacturers, and the public regardless of clinical severity of the event or determination of causality. Physicians at FDA identified reports received by VAERS describing cases of CVST with thrombocytopenia by manually reviewing all serious reports. CDC and FDA also received notification through direct outreach from clinicians and public health officials; these reports were ultimately also captured in VAERS. In addition, CDC and FDA investigators searched symptom text and performed automated coding searches. US reports of CVST with thrombocytopenia in the VAERS database from March 2 through April 21, 2021, following post-EUA Ad26.COVS.2.S vaccine receipt were included. Confirmation of a diagnosis of CVST with thrombocytopenia, as well as signs, symptoms, diagnostic test results, and outcomes of reported cases, were obtained through medical record review or discussions with treating clinicians. CVST risk factors were defined as described in a review.⁷ Case information was also reviewed with physician investigators from CDC's CISA Project, including specialists in infectious diseases, neurology, and hematology. Cases were also reviewed to determine if they satisfied Brighton Collaboration interim case definition 9.2 for TTS, which includes new-onset thrombocytopenia (platelet count $<150 \times 10^3/\mu\text{L}$) without evidence of platelet clumping, venous or arterial thrombosis, and absence of prior exposure to heparin.¹⁸

To protect patient privacy, age is reported in 2 categories: 18 to 39 years or 40 to 59 years. Race was noted because COVID-19 has been documented to disproportionately affect racial/ethnic minority groups.¹⁹ Race was categorized as White, Black, Asian, or all other races and determined based on medical record review by CDC abstractor or from the reported race on the VAERS report. Data were also collected on Hispanic ethnicity.

Results

Twelve cases of CVST with thrombocytopenia were reported during March 2 to April 21, 2021, after receipt of the Ad26.COVS.2.S vaccine (Table 1), which is administered as a single dose. The last follow-up date for patient outcomes and

Table 1. Demographic Information and Clinical Features of Initial 12 Patients With Cerebral Venous Sinus Thrombosis and Thrombocytopenia Following Emergency Authorization Receipt of Ad26.COVID.5 Vaccine—US, 2021^a

Patient No.	Age, y	CVST risk factor ^b	Time in days		Initial signs/symptoms	Late signs/symptoms	Location of CVST	Intracerebral hemorrhage	Other thromboses diagnosed	Discharge to home ^e
			Vaccination to symptom onset ^c	Vaccination to admission						
1	≥40	Yes	6	11	Headaches, lethargy	Severe headache, left-sided weakness, dry heaving	Right transverse sinus and right sigmoid sinus	Right temporoparietal junction	No	No
2	18-39	No	9	16	Headaches	Severe headache, aphasia	Left transverse sinus, left sigmoid sinus, confluence of sinuses, and straight sinus	Left temporal lobe	Left internal jugular vein thrombosis	Yes
3	18-39	No	8	17	Headaches, fever, vomiting	Left arm weakness, gaze deviation, left neglect, seizure, changes in speech	Superior sagittal sinus, inferior sagittal sinus, straight sinus, cortical veins	Bilateral frontal lobes, right subarachnoid and intraventricular	No	No
4	18-39	Yes	8	16	Headaches, nausea, myalgia, chills, fever	Severe abdominal pain, fever	Right transverse sinus and right sigmoid sinus	No	Portal vein thrombosis and right pulmonary embolus	Yes
5	18-39	Yes	6	18	Chills, dyspnea, fever, headache	Bruising, unilateral leg swelling, loss of consciousness	Right transverse sinus and right sigmoid sinus	No	Bilateral lower extremity DVT, right internal jugular vein thrombosis	No
6	≥40	Yes	13	15	Back pain, bruising, abdominal pain	Headache	Right transverse sinus and straight sinus	Right occipital lobe	Portal vein thrombosis, splenic vein, right hepatic vein, distal superior mesenteric vein, right posterior tibial and peroneal DVT	No
7	18-39	No	15	18	Headache, neck pain, nausea, vomiting, photophobia	NA; worsening of initial symptoms	Superior sagittal sinus, transverse sinuses, straight sinus, possible sigmoid	No	Right internal jugular vein thrombosis	No
8	18-39	No	10	23	Headache	Left lower leg pain and foot swelling	Right transverse sinus, right sigmoid sinus	No	Lower extremity DVT, pulmonary embolus, right internal jugular vein thrombosis	Yes
9	≥40	No	7	11	Headache, cognitive fogging, right arm weakness	Aphasia, seizure	Superior sagittal sinus, bilateral cortical veins	Bilateral frontal lobes	None	No
10	18-39	Yes	7	10	Headache, nausea, vomiting, photophobia	Loss of consciousness, seizure	Superior sagittal, right transverse and sigmoid sinus	Right temporal lobe and left cerebellar hemisphere, subarachnoid	None	No
11	18-39	Yes	11	25	Headache, blurry vision	Neck stiffness, vomiting	Torcula, bilateral transverse sinus, right sigmoid sinus	Right posterior temporal lobe	Bilateral internal jugular vein thromboses	No
12	≥40	Yes	6	13	Headache, petechial rash, neck pain, photophobia, body aches	Dizziness	Left transverse and sigmoid	No	Right pulmonary embolism, left internal jugular vein thrombosis	Yes

Abbreviations: CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; NA, not applicable.

^a Data as of April 21, 2021.

^b CVST risk factors include obesity (n = 6), hypothyroidism (n = 1), and combined oral contraceptive use (n = 1).

^c CDC medical officers used clinical judgment to determine symptom onset date and timing, and there may be differences between other reports.

^d Outcomes for those not discharged home include continued intensive care unit hospitalization (n = 3), non-intensive care hospitalization (n = 2), and death (n = 3).

Box. Clinical Presentations Leading Up to Diagnosis for the Initial 6 Patients With Cerebral Venous Sinus Thrombosis and Thrombocytopenia Following Emergency Authorization Receipt of Ad26.COVID.2.S Vaccine—US, 2021

Case 1 (Age ≥40 y)

- Six days after vaccination, the patient developed lethargy.
- Eight days after vaccination, she started to have a mild headache, which became persistent.
- Eleven days after vaccination, her headache acutely worsened and she developed dry heaving with left-sided weakness.
- She was transported by emergency medical services to the local hospital where her platelet count was $43 \times 10^3/\mu\text{L}$ and CT of the head revealed a large right temporoparietal hemorrhage. During transfer to a higher level of care on the same day, the paramedics noted her right pupil had become dilated and fixed. Upon arrival, CT angiography of the head and neck identified right transverse and sigmoid sinus thromboses.

Case 2 (Age 18-39 y)

- Nine days after vaccination, the patient developed a persistent headache.
- Fifteen days after vaccination, she began to have difficulty speaking.
- Sixteen days after vaccination, she had a severe headache associated with nausea and increased difficulty with speech. In the ED a head CT showed a left temporal lobe hemorrhage and suspected underlying sinus thrombosis. Upon transfer to a tertiary hospital the same day, platelet count was $78 \times 10^3/\mu\text{L}$ and CT venogram identified thromboses in the straight sinus, confluence of sinuses, left transverse sinus, left sigmoid sinus, and left intracranial internal jugular vein.

Case 3 (Age 18-39 y)

- One day after vaccination, the patient developed a transient fever.
- Approximately 8 days after vaccination, she developed a headache and nausea, which also resolved.
- Approximately 11 days after vaccination, headache, nausea, and fever recurred, accompanied by vomiting. For the next 4 days, symptoms continued intermittently.
- Seventeen days after vaccination, she developed a change in affect, vomiting, and change in speech. She was taken to an ED, where left gaze deviation and left-sided weakness were noted and her platelet count was $18 \times 10^3/\mu\text{L}$. She had a seizure in the ED. CT angiogram of the head and neck and magnetic resonance imaging and venogram of the brain revealed a right frontal lobe hemorrhage, possible right subarachnoid hemorrhage, and right superior sagittal sinus vein thrombosis.

Case 4 (Age 18-39 y)

- Eight days after vaccination, the patient developed chills and myalgia.
- Nine days after vaccination, she developed fever (temperature up to 38.0°C) and a severe posterior headache that progressed to the right side of her head. The headache increased in severity over the next 3 days and was associated with nausea and vomiting.
- Twelve days after vaccination, she was evaluated in the ED and discharged with an over-the-counter product containing aspirin, acetaminophen, and caffeine given for treatment of a possible migraine. There was some improvement in her symptoms.
- Fourteen days after vaccination, she developed abdominal pain with severe bloating and maximum temperature of 38.1°C .

(continued)

Box. (continued)

- Sixteen days after vaccination, she returned to the ED for evaluation of her abdominal pain and recurrence of her headache. An ultrasound of the abdomen revealed a portal vein thrombosis. CT angiography of the chest showed a right pulmonary embolism. A magnetic resonance venogram revealed a right transverse and sigmoid sinus thrombosis. She also had a platelet count of $127 \times 10^3/\mu\text{L}$.

Case 5 (Age 18-39 y)

- Shortly after vaccination, the patient developed a single self-limited febrile episode.
- Approximately 6 days after vaccination, she developed fever, rigors, shortness of breath, jaw pain, and headache. Testing at an ED did not identify a specific etiology; she was prescribed azithromycin. Fevers, rigors, and shortness of breath resolved, but headaches associated with visual changes continued.
- Approximately 16 days after vaccination, she developed ecchymoses, periorbital and lower extremity petechiae, bilateral lower extremity pain and right lower extremity swelling, and intermittent shortness of breath. She presented to an outpatient facility for care. An ultrasound revealed a right lower extremity deep vein thrombosis and she was prescribed dabigatran (a direct thrombin inhibitor). No platelet count was recorded.
- Seventeen days after vaccination, she lost consciousness and was transported to the ED; she had a platelet count of $10 \times 10^3/\mu\text{L}$. Magnetic resonance imaging of the brain revealed right transverse sinus venous thrombosis and right internal jugular vein thrombosis.

Case 6 (Age ≥40 y)

- Approximately 13 days after vaccination, the patient developed back pain and malaise. Over the next 2 days, she noticed unexplained right forearm bruising and abdominal pain.
- Fifteen days after vaccination, her platelet count was $13 \times 10^3/\mu\text{L}$ at an outpatient visit and she was referred to the ED, where an ultrasound of the abdomen revealed portal vein thrombosis with mild retroperitoneal, intraperitoneal, and pelvic hemorrhage. Lower extremity ultrasound revealed deep vein thrombosis of the right posterior tibial and peroneal veins.
- Seventeen days after vaccination, she reported a headache in the posterior occipital area and mild nausea; CT of the head showed thrombosis of the right transverse sinus and straight sinus; a few days later, intracranial hemorrhage was noted on CT of the head.

Abbreviations: CT, computed tomography; ED, emergency department.

patient platelet counts was April 21, 2021. There was 1 additional report of a patient hospitalized for COVID-19 pneumonia after Ad26.COVID.2.S vaccination followed by a hospitalization with CVST and pneumonia; because thrombosis is a known complication of COVID-19,¹² this patient is not included in this case series report.

The first 6 cases of CVST and thrombocytopenia that led to the pause in Ad26.COVID.2.S vaccination all occurred in women younger than 60 years; all but 1 initially presented with headache. Initial clinical presentations for these first 6 reported US cases are provided in the **Box**.

Summary of Clinical Case Data and Outcomes of the 12 Cases

Following the identification of the first 6 cases of CVST with thrombocytopenia, an additional 6 cases were identified. Characteristics of these 12 cases are described below. Ten met the

Table 2. Immunologic and Functional HIT Assays

Test	Purpose	Method	Reference range
Heparin-platelet factor 4 (PF4) enzyme-linked immunosorbent assay (ELISA)	Immunologic HIT assay that measures the amount of HIT antibodies directed against PF4 (detects functional and nonfunctional antibodies)	Patient serum is added to a microtiter plate coated with PF4 (or heparin-PF4 complex) Alkaline-phosphatase linked secondary anti-human IgG antibody is added and incubated with the test samples After washing, a colorimetric substrate is added and the optical density of the colored product is measured after a 30-min incubation	Optical density values 0-0.499 (of note, each integer unit increase equals a 10-fold increase in signal intensity)
Serotonin release assay (SRA)	Functional HIT assay that measures serotonin release from dense granules in platelets as a marker for platelet activation in the presence of high and low doses of heparin	Patient serum is added to donor platelets labeled with ¹⁴ C-serotonin in the presence of low (0.1 U/mL) and high (100 U/mL) concentrations of heparin (and in some specialized reference laboratories, buffer control) Platelet activation is determined by the amount of ¹⁴ C-serotonin released into the reaction supernatant	<20% Platelet activation difference between the low and high concentrations of heparin Saline buffer is not generally tested; if performed, there will not be significant serotonin release in buffer for classic HIT
Latex immunoturbidimetric assay (LIA)	Functional immunologic HIT assay that detects the presence of PF4 HIT antibodies based on their ability to competitively inhibit agglutination of HIT-like monoclonal antibodies bound to latex particles	Patient plasma is added to latex particles coated with a HIT-like monoclonal antibody and PF4 molecules conjugated with fluorescent marker With negative plasma (those without HIT antibodies), the latex/monoclonal antibody particles and PF4 molecules agglutinate, which will increase detectable fluorescence Positive plasma will compete with the latex/monoclonal antibody particles leading to less agglutination and lower fluorescence	≥1.0 U/mL
p-Selectin expression assay (PEA)	Functional HIT assay that measures platelet surface p-selectin expression as a marker of platelet activation in the presence and absence of high-dose heparin	Patient serum is incubated with platelets pretreated with PF4 purified from normal donor platelets ± high (100 U/mL) concentration of heparin Platelet activation is determined by measuring the presence of p-selectin (CD62p) by flow cytometry	Percent release with PF4 vs PF4 + high-dose heparin, reported as positive, negative, or borderline

Abbreviation: HIT, heparin-induced thrombocytopenia.

interim (version 9.2) case definition according to the Brighton Collaboration for TTS (2 did not have evidence of review of a peripheral smear to rule out platelet clumping); all had radiographic evidence of CVST satisfying level 1 criteria, indicating the highest level of certainty.

A description of selected tests used in the diagnosis of HIT is included in Table 2.

Of the 12 patients with CVST and thrombocytopenia reported to VAERS as of April 21, 2021, the patients' ages ranged from 18 to younger than 60 years, all were White women, and ethnicity was reported as non-Hispanic for 11 and unknown for 1 (Table 1). Eleven women were younger than 50 years. Reports came from 11 states. The median interval from vaccination to symptom onset was 8 days (range, 6-15 days). The median interval from vaccination to hospitalization was 16 days (range, 10-25 days). Median time from symptom onset to hospitalization was 7 days (range, 2-13 days).

At least 1 risk factor for CVST was identified in 7 patients: obesity (n = 6; body mass index range, 30.9-39.9 [calculated as weight in kilograms divided by height in meters squared]), hypothyroidism (n = 1), and use of combined oral contraceptives (n = 1). None of the patients was pregnant or within 12 weeks postpartum, had prior thrombosis, a personal or family history of thrombophilia, or documented prior exposure to heparin.

In addition to CVST, 7 patients had intracerebral hemorrhage and 8 had non-CVST thromboses (Table 1). Platelet nadirs ranged from $9 \times 10^3/\mu\text{L}$ to $127 \times 10^3/\mu\text{L}$ (Table 3). D-dimer or fibrinogen values were abnormal in all patients. Heparin-platelet factor 4 (PF4) HIT antibody ELISA results were positive in 11 patients; 1 was not tested. Of the 11 patients with positive PF4 HIT antibody ELISA results, func-

tional platelet HIT antibody results were as follows: 1 positive (both serotonin release assay and P-selectin assay); 8 negative (6 serotonin release assay only, 2 both serotonin release assay and latex immunoturbidimetric assay); and 2 without testing reported. Additional thrombophilia testing was conducted in 11 patients and was negative (Table 4), including tests for antiphospholipid antibody syndrome using 1 or more assays (anticardiolipin antibodies, β_2 glycoprotein 1 antibody, and lupus anticoagulant).

One patient reported a history of SARS-CoV-2 infection approximately 4 months prior to vaccination; in that patient, SARS-CoV-2 viral testing and serology was not performed during the admission for CVST. For the other 11 patients, 10 had negative SARS-CoV-2 nucleic acid amplification results during their hospital admission; 1 had a negative SARS-CoV-2 antigen test result. For these 11 patients without a reported history of SARS-CoV-2, serologic testing results were as follows: 4 patients tested negative and 7 were not tested (Table 3).

All patients were hospitalized and 10 were admitted to an intensive care unit (ICU). Six patients initially received heparin for thromboses, all initially admitted to the hospital before public notification of CVST and thrombocytopenia events (April 13, 2021)^{2,14}; all were subsequently changed to a non-heparin anticoagulant. Two patients did not receive anticoagulation. Four patients received nonheparin anticoagulation initially for CVST treatment (argatroban, n = 2; bivalirudin, n = 2). In addition to anticoagulation, 7 patients received intravenous immunoglobulin (IVIG) and 3 of these also received systemic corticosteroids; 4 had platelet transfusions. At the time of the last follow-up, the patient outcomes were death (n = 3), continued ICU care (n = 3), continued non-ICU hospitalization (n = 2), and discharge home (n = 4). Of the 9

Table 3. Results From Hematology and SARS-CoV-2 Testing for Initial 12 Patients With Cerebral Venous Sinus Thrombosis and Thrombocytopenia Following Emergency Authorization Receipt of Ad26.COVID.2.S Vaccine—US, 2021^a

Patient No.	Platelet nadir, $\times 10^3/\mu\text{L}^b$	D-dimer peak, $\mu\text{g}/\text{mL}^b$	Fibrinogen nadir, mg/dL^b	Initial		SARS-CoV-2		Heparin-PF4 ELISA test (optical density) ^{b,c}	Functional platelet assay test results ^c
				INR	aPTT, s	Serology	Viral assay		
1	12	>20.0	93	1.4	31	Not done	Negative (PCR)	Not done	Not done
2	69	1.1	166	1.2	22.3	Nucleocapsid antibody negative	Negative (PCR)	Positive (1.2)	Negative SRA
3	18	8.46	82	1.5	31.1	Not done	Negative (PCR)	Positive (2.7)	Negative SRA
4	127	5.45	240	1.1	31.2	Not done	Negative (PCR)	Positive (3.0)	Negative SRA
5	10	7.05	141	1.1	18.1	Antibody negative ^d	Negative (PCR)	Positive (1.6)	Negative SRA
6	13	112.07	59	1.3	34.5	Spike antibody negative	Negative (PCR)	Positive (3.2)	Negative SRA, negative LIA
7	64	7.84	77	1.2	- ^e	Not done	Not done	Positive (1.4)	Not done
8	90	6.7	239	0.9	28	Not done	Negative (antigen)	Positive (2.3)	Negative SRA
9	15	>4	332	1.1	26.9	Nucleocapsid antibody negative	Negative (PCR)	Positive (2.5)	Negative SRA
10	9	13.47	128	1.2	24.1	Not done	Negative (PCR)	Positive (2.2)	Not done
11	102	41.71	206	1.2	30.2	Not done	Negative (PCR)	Positive (2.6)	Negative SRA, negative LIA
12	20	45.57	149	- ^f	26.4	Not done	Negative (PCR)	Positive (2.1)	Positive SRA and PEA, negative LIA

Abbreviations: aPTT, activated partial thromboplastin time; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; INR, international normalized ratio; LIA, latex immunoturbidimetric assay; PCR, polymerase chain reaction; PEA, P-selectin expression assay; PF4, platelet factor 4; SRA, serotonin release assay.

Conversion factors: To convert platelet counts to cells/ μL , multiply values by 1000.

^a Data are as of April 21, 2021. No patient received heparin prior to the detection of thrombocytopenia.

^b Reference range may vary by laboratory; representative ranges include the following: D-dimer, <0.5 $\mu\text{g}/\text{mL}$; fibrinogen, 200-400 mg/dL ; heparin-PF4

ELISA optical density, 0-0.499 (each integer unit equals a 10-fold increase in signal intensity); platelets, 150-450 $\times 10^3/\mu\text{L}$.

^c See Table 2 for more details.

^d Information was not available to distinguish whether antinucleocapsid or anti-spike SARS-CoV-2 antibodies were assessed.

^e The initial PTT value in this patient was obtained when the patient had already received anticoagulation.

^f The initial INR value in this patient was obtained when the patient had already received anticoagulation.

Table 4. Results of Selected Testing for Hypercoagulable States in Initial 12 Patients With Cerebral Venous Sinus Thrombosis and Thrombocytopenia Following Emergency Authorization Receipt of Ad26.COVID.2.S Vaccine—US, 2021^a

Patient No.	Antiphospholipid antibody testing			Homocysteine level	Antithrombin activity
	Anticardiolipin antibody	β_2 Glycoprotein 1 antibody	Lupus anticoagulant assay		
1	Negative IgM, IgG		dRVVT negative	Normal	
2	Negative IgM, IgG	Negative IgM, IgG	dRVVT negative	Normal	Normal
3	Negative IgM, IgG	Negative IgM, IgG	dRVVT negative		
4	Weak positive IgM (17.9 mg/dL), negative IgG ^b	Weak positive IgM (15.3 mg/dL), negative IgG ^b			Normal
5	Indeterminate IgM (16.0 mg/dL), negative IgG ^c	Negative IgM, IgG	dRVVT negative	Normal	
6	Negative IgM, IgG	Negative IgM, IgG	dRVVT negative		Normal
7	Negative IgM, IgG		dRVVT negative	Normal	Normal
8	Negative IgM, IgG	Negative IgM, IgG	dRVVT 86 (≤ 45 seconds) ^d hex confirmation pending		
9	Negative IgM, IgG	Negative IgM, IgG	dRVVT negative		
10					
11	Negative IgM, IgG	Negative IgM, IgG	RVVT ratio negative		Normal
12	Negative IgM, IgG	Negative IgM, IgG	RVVT ratio negative		Normal

Abbreviations: dRVVT, dilute Russell viper venom time. Blank cells indicate that testing was not found in the medical records.

^a Additional testing performed in at least 1 patient includes for protein C and protein S activity, antinuclear antibodies, flow cytometry for paroxysmal nocturnal hemoglobinuria, serum protein electrophoresis, and heparinase testing; all results were normal. Testing for selected inherited causes of hypercoagulability were negative in all patients where results were available.

^b Reference range: <15.0 mg/dL = negative, 15.0-39.9 mg/dL = weak positive.

^c Reference range in IgM phospholipid (MPL) units: 0-12 = negative, 13-19 = indeterminate, 20-80 = low to moderately positive, and ≥ 81 = high positive.

^d The patient was receiving anticoagulation so the elevated value is not considered abnormal.

patients who were still alive at last follow-up, 6 had a platelet count within normal range ($150 \times 10^3/\mu\text{L}$ to $450 \times 10^3/\mu\text{L}$); all had last known platelet counts higher than $100 \times 10^3/\mu\text{L}$.

Of the patients who died, all had intraparenchymal hemorrhage and evidence of mass effect on initial head CT conducted in the emergency department. Two were obese; none had other CVST risk factors. Median time from admission to death was 1 day (range, 1-2 days). In addition to supportive ICU care, 1 received argatroban and IVIG; the other 2 did not receive anticoagulation or IVIG before dying.

Additional CVST Cases

Since April 21, 2021, 2 additional US reports to VAERS of CVST with thrombocytopenia following administration of Ad26.COVID-19 have been confirmed as of April 25. One is a man younger than 40 years; the other is a woman aged between 40 and 59 years. Investigation is ongoing.

Discussion

This case series describes the first 12 reported cases of CVST with thrombocytopenia following Ad26.COVID-19 vaccination in the US. In many respects, the clinical presentation and laboratory features were similar to those seen in Europe after ChAdOx1 nCoV-19 vaccine, another adenoviral vector COVID-19 vaccine.⁹⁻¹¹

Similar to the initially described European cases of CVST with thrombocytopenia following ChAdOx1 nCoV-19 vaccination, the US cases of this condition also occurred primarily in women younger than 40 years and in patients without diagnosed thrombophilia.⁹⁻¹¹ The European patients had a median platelet nadir count of $19 \times 10^3/\mu\text{L}$ ^{9,10} (US patients were also $19 \times 10^3/\mu\text{L}$), and several had non-CVST large-vessel thrombosis (30% of initially reported CVST cases following ChAdOx1 nCoV-19 vaccination⁹⁻¹¹ vs 75% following Ad26.COVID-19 vaccination).⁹⁻¹¹ In the European cases of CVST with thrombocytopenia following ChAdOx1 nCoV-19 vaccination, 50% of patients died,⁹⁻¹¹ compared with 25% of US patients who had CVST with thrombocytopenia.

Similar to the TTS cases (including CVST) described in Europe following receipt of ChAdOx1 nCoV-19 vaccine, the US cases of CVST with thrombocytopenia also had positive heparin-PF4 HIT antibody ELISA tests in the absence of prior exposure to heparin, as would be seen in autoimmune HIT.⁸ However, in the initial European CVST reports, 88% of patients tested with functional platelet HIT antibody tests had positive results⁹⁻¹¹; in contrast, functional platelet HIT antibody test results were positive in only 1/9 (11%) of the US cases with results available. The heparin-PF4 ELISA detects presence of anti-PF4 antibodies; functional platelet HIT antibody assays determine the extent to which these antibodies activate platelets in the presence of heparin, leading to aggregation.²⁰

Functional platelet HIT antibody assays have higher specificity than the heparin-PF4 ELISA and are typically positive in patients with strongly positive (eg, optical density >1) ELISA tests.²⁰ Because of this, functional platelet HIT antibody assays are generally considered to be the criterion standard test

for verification of classic and autoimmune HIT.²⁰ In contrast, the utility of these functional platelet assays for confirming TTS is unclear. It is possible, given the clinical scenario of these patients, that the negative functional platelet assay results may represent false negatives. Lack of standardization in functional platelet HIT antibody assays may lead to differences in results by different laboratories.^{21,22} For example, in the initial European studies, the functional platelet HIT antibody assays included the use of a saline buffer,⁹⁻¹¹ which is not always included when assessing for classic HIT.⁸ The European studies also did not use the serotonin release assay that was most commonly used in the US cases.⁹⁻¹¹ It may be important to notify testing laboratories that postvaccination TTS is being evaluated, so that testing methods can be adjusted if needed.⁸ Given that the number of CVST with thrombocytopenia cases following Ad26.COVID-19 vaccination in the US is still small, obtaining additional information about functional platelet HIT antibody assay results could help with investigations into the mechanism of CVST and thrombocytopenia following Ad26.COVID-19 vaccination.

The results described in this US investigation suggest that CVST with thrombocytopenia following Ad26.COVID-19 vaccination is a rare syndrome with timing that appears to cluster around 1 to 2 weeks following vaccination. The biological mechanism for this new syndrome of CVST with thrombocytopenia (and other types of TTS) is an active area of investigation globally. The FDA has stated that a causal relationship between Ad26.COVID-19 vaccine and TTS is plausible and has updated its EUA with a warning about rare clotting events after Ad26.COVID-19 vaccination, primarily among women aged 18 to 49 years.²³ The clinical course and laboratory test results suggest that the pathogenesis of TTS may be similar to autoimmune HIT. Autoimmune HIT is thought to be triggered by the formation of antibodies directed against PF4, a constituent of platelet alpha granules released during platelet activation. In contrast to classic HIT in which exogenous heparin triggers antibody formation, in autoimmune HIT, an endogenous polyanion such as polyphosphates and chondroitin sulfate triggers PF4 antibody formation.²⁴

However, while it has been proposed that a component of the ChAdOx1 nCoV-19 vaccine could take the place of heparin or an endogenous polyanion,⁹ the precise mechanism of TTS in relation to COVID-19 vaccination has not yet been established. The Global Advisory Committee on Vaccine Safety (GACS) has stated that a platform-specific mechanism related to adenovirus vector vaccines cannot be excluded.⁵ Although the Ad26.COVID-19 vaccine and ChAdOx1 nCoV-19 vaccine both use an adenoviral vector, the viral vectors are different (human vs chimpanzee).²⁵ CVST and thrombocytopenia following SARS-CoV-2 infection has been reported in at least 2 cases²⁶; HIT testing was not done in these cases. As of April 21, 2021, no reports of CVST with thrombocytopenia following authorized mRNA COVID-19 vaccines had been reported to VAERS and confirmed.

These findings have important clinical and public health implications. CDC has updated its interim clinical considerations for use of authorized COVID-19 vaccines to indicate that women aged 18 to 49 years should be aware of the increased

risk of TTS after receipt of Ad26.COVID.2.S vaccine.²⁷ The preponderance of patients with positive heparin-PF4 ELISA tests supports the recommendations in the CDC's Health Alert Network to avoid heparin when TTS is suspected and to strongly consider anticoagulation with a nonheparin agent.² Clinicians should consult with a hematologist when managing patients with TTS and report such cases to VAERS.^{2,23,27} The American Society of Hematology has posted additional clinical information and resources for clinicians caring for patients with TTS after Ad26.COVID.2.S vaccination.²⁸

With the exception of hematologic findings (thrombocytopenia, extracranial thrombosis), the clinical presentation of the US patients with CVST and thrombocytopenia following Ad26.COVID.2.S vaccination is similar to typical CVST patients.^{7,29} Eleven of the 12 US patients in this series presented initially with headaches; as illustrated by the vignettes of some of the initial 6 US patients with CVST and thrombocytopenia, headaches occurring with CVST may wax and wane and even improve with over-the-counter treatments. A subacute presentation of headache is present in 90% of patients with typical CVST.^{7,29} An advisory released by the American Heart Association on April 15, 2021, describes symptoms including headache that should increase concern for CVST or other thrombosis.³⁰ In the phase 3 study of Ad26.COVID.2.S vaccine, headaches occurred in 44% of patients younger than 60 years in the first week following vaccination; most patients' symptoms appeared within 2 days and resolved within 2 days.¹² In the US cases of CVST with thrombocytopenia following Ad26.COVID.2.S vaccination, symptoms began at least 6

days after vaccination and persisted for at least a week for most. Urgent consultation with a neurologist is prudent when a patient is suspected or confirmed to have CVST. In addition, since the median time from symptom onset to hospitalization was 7 days in the US CVST case series, patient and clinician education might shorten the time to clinical evaluation and therefore treatment. The US patients who died had had features known to be associated with poor outcomes in CVST, notably hemorrhage.³¹

Limitations

This case series has several limitations. First, VAERS is a passive surveillance system, so even with public notification of CVST and thrombocytopenia following Ad26.COVID.2.S vaccination, cases of CVST with thrombocytopenia may be underreported. Second, most data were obtained by retrospective medical record review, and information might not be documented. Third, some laboratory investigations were not performed in all patients.

Conclusions

The initial 12 US cases of CVST with thrombocytopenia after Ad26.COVID.2.S vaccination represent serious events. This case series may inform clinical guidance as Ad26.COVID.2.S vaccination resumes in the US as well as investigations into the potential relationship between Ad26.COVID.2.S vaccine and CVST with thrombocytopenia.

ARTICLE INFORMATION

Accepted for Publication: April 26, 2021.

Published Online: April 30, 2021.
doi:10.1001/jama.2021.7517

Author Contributions: Drs Lale and See had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: See, Lale, Guh, Shimabukuro, Wheeler, Edwards, Creech, Clark, DeStefano, Broder.

Acquisition, analysis, or interpretation of data: See, Su, Lale, Woo, Guh, Shimabukuro, Streiff, Rao, Wheeler, Beavers, Durbin, Miller, Mba-Jonas, Nair, Nguyen, Talaat, Urrutia, Creech, Clark, Broder.

Drafting of the manuscript: See, Lale, Woo, Guh, Rao, Nguyen, Broder.

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Supervision: See, Shimabukuro, Edwards, Nair, Clark, DeStefano, Broder.

Other - neurological expertise: Urrutia.

Other - clinical expertise: Wheeler.

Other - reading all serious reports: Woo.

Conflict of Interest Disclosures: Dr Streiff reported receiving grants from Janssen for the

Cassini clinical trial of rivaroxaban for prevention of cancer-associated thrombosis; personal fees from Janssen for serving on the advisory board for the Cassini trial; from Bayer, Bristol Myers Squibb, and Dispersol for providing consultative advice; from Bayer for CME lectures; and from Pfizer for CME lectures and serving on the advisory board.

Dr Streiff also reported receiving grants from NHLBI for a study on missed doses in VTE prophylaxis, from AHRQ for work on individualized feedback on VTE prophylaxis practices, and from PCORI for research on patient education to improve acceptance of VTE prophylaxis. Dr Durbin reported receiving grants from Pfizer as an investigator for the Pfizer COVID-19 vaccine trial and grants from NIH for serving as the site principal investigator for the AstraZeneca COVID-19 vaccine trial; receiving personal fees from Merck for consultative advice on dengue vaccine development; and serving on the scientific advisory board for Valneva. Dr Edwards reported receiving grants from NIH and providing consultative advice to BioNet and IBM; she also reported serving on data and safety monitoring boards of Pfizer, Moderna, Merck, Sanofi, Roche, X-4 Pharma, and Seqirus. Dr Talaat reported receiving grants from Pfizer for serving as the site principal investigator for the phase 3 adult COVID-19 vaccine study and the phase 1-3 pediatric (under 12) COVID-19 vaccine study, both at Johns Hopkins University; she also reported receiving grants from the NIH-Coronavirus Prevention Network for serving as a co-investigator on the phase 3 AstraZeneca COVID-19 vaccine trial in adults. Dr Urrutia reported receiving grants from Genentech Inc for serving as the site principal

investigator on the TIMELESS trial and his work on the investigator-sponsored OPTIMIST main trial. Dr Creech reported receiving grants from Merck as well as personal fees from Altimmune, Horizon, Karius, Premier, and Astellas for providing consultative advice. No other disclosures were reported.

Funding/Support: This work was supported by the Centers for Disease Control and Prevention (CDC) Clinical Immunization Safety Assessment (CISA) Project contracts 200-2012-53664 to Johns Hopkins University and 200-2012-50430 to Vanderbilt University Medical Center.

Role of the Funder/Sponsor: CDC provided funding to Drs Creech, Durbin, Edwards, Streiff, Talaat, Urrutia, Walker, and Wheeler. CDC, including CDC authors along with non-CDC coauthors, conducted the investigations; performed collection, management, analysis, and interpretation of the data; was involved in preparation, review, and approval of the manuscript; and made the decision to submit the manuscript for publication.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or the Food and Drug Administration (FDA). Mention of a product or company name is for identification purposes only and does not constitute endorsement by the CDC and FDA.

Additional Contributions: We thank the following CDC staff who contributed to this article without compensation aside from their salaries. For data

collection: Kathy Byrd, MD, MPH (CDC COVID-19 Response), Margaret Cortese, MD (CDC COVID-19 Response), Amelia Jazwa, MSPH (CDC COVID-19 Response), Anamika Khatri-Dua, MD (CDC COVID-19 Response), Susan Lukacs, DO, MSPH (CDC COVID-19 Response), Mike McNeil, MD, MPH (CDC COVID-19 Response), Monica Parise, MD (CDC COVID-19 Response), Allan Taylor, MD, MPH (CDC COVID-19 Response). For leadership and support: Denise Cardo, MD (CDC COVID-19 Response). We also thank the following individuals who contributed to this article with funding support through the CISA Project. For programmatic support: Paula Campbell, MS, MPH (Vanderbilt University) and Braxton Hern, BS (Vanderbilt University). For vaccine safety expertise: Elizabeth Barnett, MD (Boston University), Neal Halsey, MD (Johns Hopkins University), Thomas Kickler, MD (Johns Hopkins University), Nicola Klein, MD, PhD (Kaiser Permanente Northern California), Philip LaRussa, MD (Columbia University), Stephen Pelton, MD (Boston University), Elizabeth Schlaudecker, MD, MPH (Cincinnati Children's Hospital Medical Center), Michael Smith, MD, MSCE (Duke University), Mary Staat, MD, MPH (Cincinnati Children's Hospital Medical Center), Melissa Stockwell (Columbia University), Emmanuel "Chip" Walter, MD, MPH (Duke University), and Jennifer Yui, MD, MS (Johns Hopkins University). We also thank the clinical staff who have cared for these patients and who reported these events to VAERS.

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