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EDUCATIONAL FORUM

AstraZeneca vaccine induced immune thrombotic thrombocytopenia (VITT)

In mid-March, the use of the AstraZeneca vaccine was paused or halted in many European countries due to 30 reported cases of venous thrombosis occurring shortly after vaccination. This was followed by the CDC recommending a pause in the administration of the Johnson & Johnson vaccine last week due to reports of six similar cases. What was unusual about these cases was that they were most often in women under age 55, were associated with severe thrombocytopenia, and involved relatively rare sites of thrombosis, including cerebral venous sinus thrombosis (CVST) and splanchnic venous thrombosis of the gut. As of April 9, there have been 222 cases reported in Europe (169 CVST and 53 splanchnic vein thromboses). Additionally, the UK has reported 79 cases with 44 cases of CVST and the remainder described as "other clots."

The most detailed data we have on this syndrome comes from two studies published in the April 9 edition of the *New England Journal of Medicine*, one from Germany and another from Norway.[1,2] The two case-series are strikingly similar, and the data and observations have therefore been combined. In total, 16 patients were studied in detail. All patients presented with thrombosis associated with thrombocytopenia from 4–16 days following their first dose of the AstraZeneca vaccine. The age range was from 22–54 years of age, 11 were women and two were men. Thirteen patients had cerebral venous thrombosis (CVST), four had splanchnic vein thrombosis (one of whom also had CVST), and several had additional clots elsewhere. Two of the patients had underlying autoimmune disease with one having a history of anti-phospholipid antibodies. Nine of the patients died.

Nine patients had extensive serologic analyses. Platelet counts were in the 10,000–30,000 per cmm range in most patients, with only one patient having a level of 107,000 per cmm. D-dimer levels were strikingly elevated in all patients, often above the upper limit of the laboratory range. Because clinically this syndrome mimicked heparin induced thrombocytopenia (HIT), patients were tested for the platelet activating antibodies seen in HIT. All nine tested patients had strongly reactive platelet activating antibody assays showing binding to platelet factor 4 (PF4). This is similar to the pattern seen in HIT, where in that syndrome, antibodies that bind PF4 are triggered by low doses of heparin. Sera from 22 of 24 patients with suspected VITT (including many of the above patients), also showed high levels of platelet activation with the addition of PF4.

In summary, the clinical picture of moderate-to-severe thrombocytopenia and thrombotic complications at unusual sites beginning approximately one to two weeks after vaccination with the AstraZeneca vaccine closely resembles severe HIT. HIT is a well-recognized prothrombotic disorder caused by heparin induced platelet-activating antibodies, also directed at PF4. In recent years, it has been recognized that triggers other than heparin can rarely cause a HIT-like disorder. These triggers include certain polyanionic drugs such as pentosan, infections (viral and bacterial), or knee replacement surgery. If VITT is suspected, the PF4-heparin antibody test can be used to confirm the diagnosis, and if confirmed, treatment should follow the same algorithm used for patients with HIT.

The above two studies, by providing a link between thrombosis and the immune system, strengthen the view that vaccination may have triggered the syndrome. Although several theories have been offered, the exact mechanism that drives the formation of the antibodies remains undefined. Estimates of the frequency of the syndrome are hampered by differences in the accuracy of the reporting of vaccine induced complications. The European Medicine Agency, using its available data in 9.2 million vaccinated individuals, has suggested a frequency of 1:210,000 shots. However, using data from Germany, which has one of the most accurate reporting systems, suggests a frequency as high as 1:100,000 shots.

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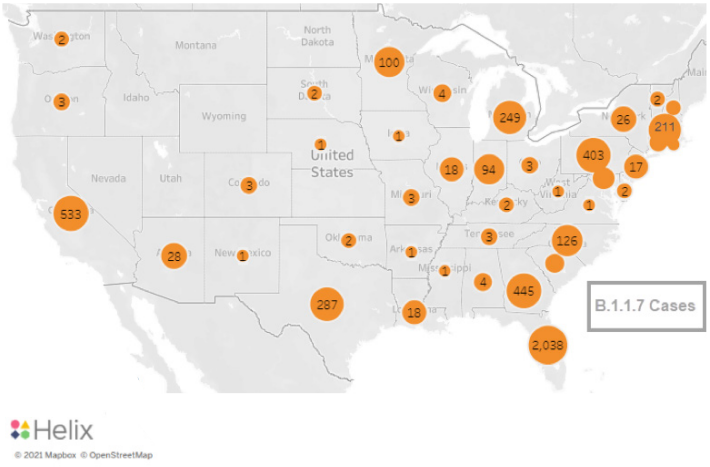
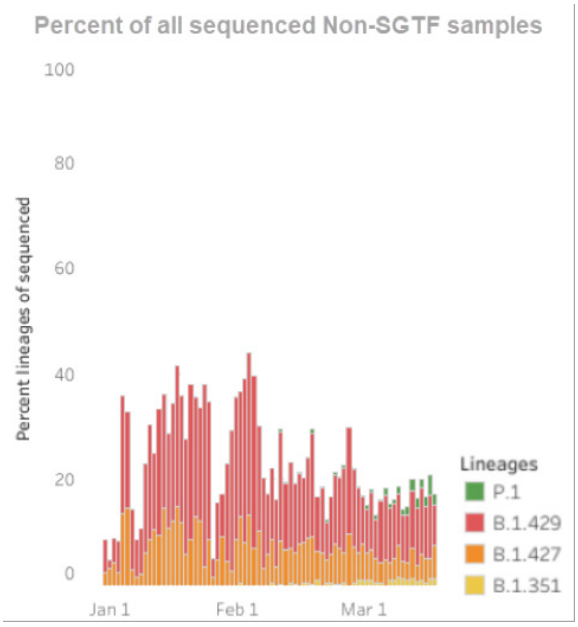
The available data to date suggests that the frequency of VITT might be lower with the Johnson & Johnson vaccine, in the range of 1 per million shots. The AstraZeneca and Sputnik V vaccines share similarities in that they are both non-replicating viral vector DNA vaccines using SARS-Co-V-2 spike protein DNA inserted into the same chimpanzee adenovirus. The Sputnik V vaccine also combines this with a different chimpanzee adenovirus for the second dose. The J&J vaccine uses a similar technology, but the viral vector is a human based adenovirus. No cases have been reported with the Sputnik V vaccine. There have been about 40 cases of "immune thrombocytopenia" with the mRNA vaccines from Pfizer and Moderna, and one thrombotic death from the Pfizer vaccine.[3]

In terms of how this will affect vaccine hesitancy, perhaps the most important information we can share with our patients is the following: although the mechanisms causing VITT are likely to be different, we nonetheless understand that COVID-19 is itself a prothrombotic disease. In a preprint study published this week, U.S. investigators, using a large EHR data base, looked at the rate of CVST two weeks after the onset of COVID-19 and compared it to the rate two weeks following vaccination. In over 513,000 infected patients, the rate was 39 per million patients. In over 489,000 patients who had been vaccinated with either the Pfizer or Moderna mRNA vaccines, the rate was 4.1 per million (two cases observed). Similarly, the European Medicines Agency has estimated that the risk of cerebral venous thrombosis after the AstraZeneca vaccine at 5.0 per million people. Approximately 30% of the CVST cases that occurred in COVID-19 in the US study were in patients under the age of 30. Splanchnic vein thrombosis was also observed at a rate ten-fold higher in the infected cohort compared to the vaccinated cohort. It thus appears that the rate of CVST and splanchnic vein thrombosis are approximately ten-fold higher from COVID-19 compared to the rate from COVID-19 vaccination.[4]

Update on the variants of concern (VOC)

The available VOC data on transmissibility, virulence, and resistance to vaccine and mAb were detailed in the prior edition of the COVID Forum. Compared to two weeks ago, the daily COVID-19 case rate has increased almost 20% and is now back up to ~65,000. The death rate has not increased in parallel, likely due to the high level of vaccination in the elderly population. In contrast to the last surge, at least for now, cases are concentrated in smaller geographic areas such as Michigan and metro New York city. The B.1.1.7 variant, however, is now present in most regions of the US. Helix, one of the lab companies contracted to monitor the prevalence of the different VOCs is reporting that 59% of tests are now positive for B.1.1.7. Next in frequency, as noted on the below chart, are the two California VOCs formerly known as CAL.20 and now known as B.1.427/B.1.429. The South Africa B.1.351 variant is next in frequency but remains at a stable low level. Of significant concern is the increase in the Brazil P.1 variant that notably forced the closure of the Whistler Ski Resort near Vancouver last week and continues to be responsible for the high case rates in Brazil, including among those who were initially infected with the wild strain COVID-19 last spring. Although P.1 continues to have an overall low prevalence, it is increasing over the past several weeks. Because the increase in transmissibility of the P.1 variant relative to B.1.1.7 variant is not known, it is difficult to predict whether the increased prevalence of B.1.1.7 will eventually outpace and therefore extinguish the P.1 variant. This is significant as P.1 contains the E484K mutation which confers resistance to convalescent and vaccine induced antibody, whereas the B.1.1.7 strain does not contain this mutation and therefore vaccine sensitivity is maintained.[5]





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Pfizer mRNA vaccine efficacy against B.1.351 strain

There has been ongoing concern that vaccines may have reduced efficacy against emerging strains of SARS-CoV-2. SARS-CoV-2, as is characteristic of other coronaviruses, is frequently mutating. Most mutations are disadvantageous; some provide a survival advantage. Any mutation that allowed SARS-CoV-2 to evade host immunity would confer survival advantage. Such mutations could also reduce or eliminate vaccine efficacy. Pfizer announced early results of a phase III trial of its existing vaccine, BNT 162b2. The results of vaccine administration to 800 persons in South Africa where B.1.351 is the predominant strain showed a vaccine efficacy of 100%. Nine patients in the placebo group contracted COVID-19 vs. none in the vaccine arm. Importantly, the small number of persons in the trial to date resulted in wide confidence intervals with the lower bound at 53.5%. Further analysis of the phase II trial that began last summer confirmed that the Pfizer vaccine was very effective at preventing severe disease and death (Table 1). These encouraging results confirm speculation that despite lower neutralizing antibodies observed against the B.1.351 in vaccine recipients, vaccine efficacy largely remains intact.[6]

Table 1: Vaccine efficacy

Trial group	Vaccine efficacy (%) (95% CI) (Seven days post second dose)		
	Symptomatic illness	Severe illness (CDC definition)	Severe Illness (FDA definition)
All trial participants	91.3 (98–93.2)	100 (88–100)	95.3 (71–99.9)
US trial participants	92.6 (90.1-94.5)	NR	NR

Pfizer reports successful vaccine trial among children 12 to 15 years of age

Results from a phase III clinical trial for the Pfizer COVID-19 vaccine in children 12–15 years of age were recently summarized. Comparing 1,131 individuals who received the vaccine to 1,129 who received placebo, the vaccinated cohort had zero new COVID-19 cases, while the placebo cohort developed 18 new cases. The vaccine elicited a robust antibody response, and the adverse events were similar to those observed among individuals 16–21 years of age.[7]

Pfizer reports plans to submit amendments to the FDA and other regulating institutions around the world for emergency authorization in this age group, with the hope of vaccinating children before the beginning of the next school year. The study results will be submitted for peer-review publication in the coming months. A vaccine trial in children 6 months to 11 years of age is currently underway.

Is herd immunity an achievable goal?

The following is abstracted from an article in Nature[8] which details, for a variety of reasons, why herd immunity may not be achieved. When we think of herd immunity, our minds go to polio, smallpox, and measles, which while not extinct, are rare in most parts of the world and certainly no longer epidemic. Initially, it was presumed that when the combined rate of prior infection plus vaccination reached the theoretical 60–70% range, viral transmission would drop markedly, and the pandemic would wind down. The three factors which could combine to prevent this from happening are:

- Lack of widespread vaccination worldwide
- Waning immunity to COVID-19 over time
- The combination of two important characteristics of the variants: They have a higher Ro and therefore increased transmissibility and they are resistant to convalescent and vaccine induced antibodies.

The second surge in Manaus has provided evidence that prior immunity would not be the major contribution to herd immunity. Only eight months after the spring surge which resulted in about 66% of the population becoming seropositive,[9] a new surge is now underway with many of those now suffering their second bout of COVID-19. There are two likely reasons for this high reinfection rate and we do not yet have the data to know the relative contribution of each. The first is the eight-month time span between the two surges which is about the time immunity is waning from infection with seasonal coronaviruses. The second is the emergence of the P.1 variant with its increased Ro and resistance to convalescent antibody.

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Since both the population at risk after initial infection will increase over time and variants may continue to emerge with higher Ro(s) and resistance to vaccine induced antibodies, herd immunity may become a moving target which might not be achievable. Fortunately, as noted below, our vaccines so far are proving to be effective against the VOCs to which they've been tested. Rather than herd immunity, we may find ourselves with a controlled endemic infection similar to influenza with the need for periodic immunizations, the timing of which will depend on the length of vaccine-induced immunity and the frequency with which vaccine resistant variants emerge.

Neurologic and psychiatric disorders are common six months following COVID-19

To determine neurologic and psychiatric sequelae from COVID-19, a retrospective time-to-event analysis was conducted using data from the TriNetX electronic health records network, comprising over 81 million patients.[10] All live patients, 10 years of age or older, who had an index event from January 20, 2020 to December 13, 2020 were included. Index events included intracranial hemorrhage, ischemic stroke, parkinsonism, Guillain-Barre, nerve disorders (including nerve root and plexus disorders), myoneural junction disease or other muscle disease, encephalitis, dementia, psychosis, mood or anxiety disorder, substance use disorder, and insomnia. Patients diagnosed with COVID-19 were compared to patients diagnosed with influenza and, more broadly, to patients diagnosed with any respiratory tract infection during the study period.

The COVID-19 cohort consisted of 236,379 patients. Within six months following diagnosis, 33.6% had at least one index event, and that event represented a new diagnosis in 12.8%. The incidence was higher among patients admitted for intensive care: 46.4% overall and 25.8% new diagnoses.

Compared to the cohort with influenza, all index events were statistically more common for the COVID-19 group except parkinsonism and Guillain-Barre syndrome. When compared to the cohort with any respiratory tract infection other than COVID-19, all index events were statistically more common among patients with COVID-19.

Neurologic and psychiatric sequelae are generally more common with COVID-19 than with influenza and other respiratory infections. The below chart highlights the risk of neurological and psychiatric sequela in outpatients with COVID-19 compared to patients with influenza and other respiratory infections. Since many of the index events were not new, this study methodology may also reflect that patients with chronic neurologic and psychiatric conditions are more likely to receive medical attention and need intensive care with COVID-19. Unfortunately, the contributions of social isolation, job and financial insecurity, family strain, and increased worry related to a global pandemic could not be evaluated from this study methodology.

	COVID-19 *vs* influenza in patients without hospitalisation (N=96 803)*		COVID-19 *vs* other RTI in patients without hospitalisation (N=183 731)*	
	HR (95% CI)	p value	HR (95% CI)	p value
Intracranial haemorrhage (any)	1·87 (1·25–2·78)	0·0013	1·38 (1·11–1·73)	0·0034
Intracranial haemorrhage (first)	1·66 (0·88–3·14)	0·082	1·63 (1·11–2·40)	0·010
Ischaemic stroke (any)	1·80 (1·54–2·10)	<0·0001	1·61 (1·45–1·78)	<0·0001
Ischaemic stroke (first)	1·71 (1·26–2·33)	0·0003	1·69 (1·38–2·08)	<0·0001
Parkinsonism	2·22 (0·98–5·06)	0·028	1·20 (0·73–1·96)	0·42
Guillain-Barré syndrome	0·90 (0·44–1·84)	0·99	1·44 (0·85–2·45)	0·10
Nerve, nerve root, or plexus disorders	1·69 (1·53–1·88)	<0·0001	1·23 (1·15–1·33)	<0·0001
Myoneural junction or muscle disease	3·46 (2·11–5·67)	<0·0001	2·69 (1·91–3·79)	<0·0001
Encephalitis	1·77 (0·86–3·66)	0·095	2·29 (1·28–4·10)	0·0046
Dementia	1·88 (1·27–2·77)	0·0008	1·95 (1·55–2·45)	<0·0001
Mood, anxiety, or psychotic disorder (any)	1·49 (1·45–1·54)	<0·0001	1·18 (1·15–1·21)	<0·0001
Mood, anxiety, or psychotic disorder (first)	1·85 (1·72–1·99)	<0·0001	1·40 (1·32–1·48)	<0·0001
Mood disorder (any)	1·49 (1·43–1·55)	<0·0001	1·22 (1·19–1·26)	<0·0001
Mood disorder (first)	1·78 (1·61–1·96)	<0·0001	1·37 (1·27–1·47)	<0·0001
Anxiety disorder (any)	1·48 (1·43–1·54)	<0·0001	1·16 (1·13–1·19)	<0·0001
Anxiety disorder (first)	1·80 (1·67–1·94)	<0·0001	1·37 (1·30–1·45)	<0·0001
Psychotic disorder (any)	1·93 (1·63–2·28)	<0·0001	1·44 (1·27–1·62)	<0·0001
Psychotic disorder (first)	2·27 (1·56–3·30)	<0·0001	1·49 (1·15–1·93)	0·0016
Substance use disorder (any)	1·26 (1·19–1·33)	<0·0001	1·11 (1·07–1·17)	<0·0001
Substance use disorder (first)	1·21 (1·05–1·38)	0·0054	0·89 (0·81–0·97)	0·013
Insomnia (any)	1·52 (1·42–1·63)	<0·0001	1·18 (1·12–1·24)	<0·0001
Insomnia (first)	2·06 (1·82–2·33)	<0·0001	1·51 (1·38–1·66)	<0·0001
Any outcome	1·47 (1·44–1·51)	<0·0001	1·16 (1·14–1·17)	<0·0001
Any first outcome	1·83 (1·71–1·96)	<0·0001	1·28 (1·23–1·33)	<0·0001

Details on cohort characteristics are presented in the appendix (pp 37–40). HR=hazard ratio. RTI=respiratory tract infection. *Matched cohorts.

Table 4: **HRs for the major outcomes in patients without hospitalisation after COVID-19 compared with those after influenza or other RTIs**

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Is fomite transmission a concern? This is a respiratory virus after all …

Experience is growing with COVID-19 allowing a more complete understanding of how this virus is most efficiently transferred between people. The CDC has recently summarized the evidence indicating that respiratory transmission is clearly the most important method of person to person spread.[11] Quantitative microbial risk assessment (QMRA) studies have been conducted to understand and characterize the relative risk of SARS-CoV-2 fomite transmission and evaluate the need for and effectiveness of prevention measures to reduce risk. Findings of these studies suggest that the risk of SARS-CoV-2 infection via the fomite transmission route is low, and generally less than 1 in 10,000, which means that each contact with a contaminated surface has less than a 1 in 10,000 chance of causing an infection. This emphasizes the importance of masking as the most important adjunct to vaccination in pandemic control.[12] This observation is critically important in setting policy. A recent review emphasizes several important features: i. Real world studies have detected only low levels of viral RNA in the environment rarely isolating viable virus, ii. Strong epidemiologic evidence supports respiratory transmission as the dominant route of infection, iii. Ventilation and proximity are the most important factors influencing transmission efficiency.[13] SARS-CoV-2 has been isolated from stool, semen, and blood yet to date there have been no documented cases of fecal-oral, sexual or blood born transmission. There has been speculation of rare fecal aerosol transmission.[14] Efforts to control spread should focus on the interventions preventing the transmission or respiratory droplets; particularly wearing of well-fitting masks.

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He served as Chief Medical Officer from 1995 to 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for OptumCare. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.