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COVID-19 GUIDANCE DOCUMENT

Perioperative Coronavirus Vaccination—Timing and Implications: A Guidance Document

HelenMari Merritt-Genore, DO, Rainer Moosdorf, MD, PhD, Erin Gillaspie, MD, MPH, Sylvain Lother, MD, Daniel Engelman, MD, Shahnur Ahmed, BS, Frank A. Baciewicz, MD, Michael C. Grant, MD, Rita Milewski, MD, Kelly Cawcutt, MD, J. Awori Hayanga, MD, Subhasis Chatterjee, MD, and Rakesh C. Arora, MD, on behalf of The Society of Thoracic Surgeons Workforce on Critical Care

Methodist Physicians Clinic, Omaha, Nebraska; Department for Cardiovascular Surgery, Phillips University, Marburg, Germany; Department of Thoracic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee; Division of Critical Care and Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada; Heart and Vascular Program, Baystate Health and University of Massachusetts Medical School–Baystate, Springfield, Massachusetts; School of Medicine, Wayne State University School of Medicine, Detroit, Michigan; Department of Surgery, Wayne State University, Detroit, Michigan; Division of Cardiac Anesthesia, Surgical Critical Care and Acute Care Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland; Division of Cardiac Surgery, Yale University, New Haven, Connecticut; Division of Infectious Diseases & Pulmonary and Critical Care Medicine, University of Nebraska Medical Center, Omaha, Nebraska; Department of Cardiovascular and Thoracic Surgery, West Virginia University School of Medicine, Morgantown, West Virginia; Division of General and Cardiothoracic Surgery, Michael E DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas; Department of Surgery, Section of Cardiac Surgery, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

ABSTRACT

EXECUTIVE SUMMARY Cardiothoracic surgical patients are at risk of increased coronavirus disease severity. Several important factors influence the administration of the coronavirus disease vaccine in the perioperative period. This guidance statement outlines current information regarding vaccine types, summarizes recommendations regarding appropriate timing of administration, and provides information regarding side effects in the perioperative period for cardiac and thoracic surgical patients.

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The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19) pandemic and has presented novel clinical challenges that must be navigated using current best evidence and clinical judgment. The approval of the first vaccinations in late 2020 provided a general sense of hope but raised questions regarding the optimal timing of vaccination relative to major cardiac and thoracic surgeries.

Patients who require cardiothoracic surgery are at risk for adverse outcomes from COVID-19, as underlying cardiovascular disease and oncologic processes have each been identified as independent predictors of increased mortality.[1-3] Comorbidities such as hypertension, diabetes, chronic lung conditions, and chronic kidney disease have also been recognized to increase COVID-19 severity.[4-8] The risk of thromboembolic events for patients undergoing surgery for malignant disease is significantly elevated and may be further exacerbated by concomitant COVID-19 infection.[9,10] Additionally respiratory complications may slow the recovery of the cardiothoracic patient. The incidence of respiratory

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Address correspondence to Dr Merritt-Genore, Methodist Physicians Clinic, 1120 N 103rd Plaza, Ste 210, Omaha, NE 68114; email: helenmari.merritt@gmail.com.

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complications ranges from 4% to 8% for patients undergoing coronary bypass and as high as 20% to 45% after esophagectomy.[9,11] Systemic inflammatory response syndrome is a typical sequela of both extracorporeal circulation and the hyperimmune reaction during the critical phase of COVID-19 infection. These responses show similar patterns, as recently demonstrated by an upregulation of neutrophil extracellular traps, and may synergistically increase the effect and foster an increase in hypercoagulative status.[12,13] The potential for hospitalized patients to acquire COVID-19 through nosocomial spread poses further risk.[14,15] In a recent study of 71 patients undergoing transcatheter valve replacement, 2 patients acquired COVID-19 from an unknown source soon after the intervention, both of which led to death within 2 weeks after discharge.[16] Perioperative COVID-19 may thus be associated with prolonged postsurgical recovery, increased perioperative complications, increased length of stay, and increased mortality.[17,18] Measures to reduce COVID-19 infection in patients requiring cardiothoracic interventions should be implemented at all phases of care to improve outcomes.

As of the first week of July 2021 in the United States approximately 58% of adults and 47% of the population for a total of 158 million people have been vaccinated according to the Centers for Disease Control and Prevention (CDC).[19] Vaccination has proven highly effective at reducing COVID-19 transmission, and acquired immunity reduces infection severity, risk of hospitalization, and risk of death for those who are infected with the virus.[20-25] As mutations and variation in the original viral strain become more prevalent, vaccination dosing and potentially modification for protection may be required.[26]

The COVIDSurg Collaborative has advocated for the prioritization of surgical patients over the general population to facilitate the reinstitution of elective surgery globally and also to prevent COVID-19-related deaths in patients undergoing major surgery.[27] Various surgical societies have developed recommendations to guide perioperative vaccination. The recent American College of Cardiology statement on cardiovascular disease considerations for COVID-19 vaccine prioritization[28] identified patients with nonrate-controlled atrial fibrillation, with an implantable cardioverter defibrillator or on antiarrhythmics to suppress ventricular arrhythmias, with obstructive coronary artery disease, and with heart failure as higher risk for adverse outcomes with COVID-19.[28-30]

At the time of the drafting of this document no formal guidelines existed regarding the timing of vaccine doses in relation to major cardiothoracic surgical procedures. To determine the optimal timing in cardiothoracic surgery patients, representatives from critical care, adult cardiac and thoracic surgery, and infectious disease subspecialities have collaborated to provide a guidance statement based on currently available data. As with other guidance documents, it is acknowledged that much of the impact, risks, and long-term sequelae of the pandemic and of the vaccinations themselves remain largely unknown. Finally although misinformation exists in some communities regarding COVID-19 vaccines, this document offers the cardiothoracic surgical readership a guide regarding the relevant basics of vaccines to counsel patients and inform their practice.

GENERAL VACCINE INFORMATION

As of early June 2021 there were 102 vaccines in phase I to III trials and 185 under investigation in preclinical studies, whereas 3 COVID-19 vaccines had received US Food and Drug Administration Emergency Use Approval.[21-25,31] One additional vaccine is currently in use in Europe, Canada, Asia, and Latin America, and its US Emergency Use Approval application is currently being prepared.[31] Table 1 provides details regarding each vaccine type and sequence of vaccination. The COVID-19 messenger RNA (mRNA) vaccines (ie, Moderna and Pfizer-BioNTech) contain mRNA surrounded by lipid nanoparticles. These mRNA sequences are delivered to host cells where they are transcribed into proteins akin to those on the surface of the COVID-19 virus, triggering a host immune response.[25] Based on clinical trial data a second dose of vaccination is recommended 21 to 28 days after the first dose for both Pfizer-BioNTech and

TABLE 1 Comparison of Coronavirus Disease 2019 Vaccines[21-25]

	Method of Action	Efficacy 2 Weeks After First Dose(%)	Efficacy After Second Vaccination(%)	Notes
Moderna	Messenger RNA	80	94	Second dose at 4-6 weeks
Pfizer	Messenger RNA	80	95	Second dose at 3-6 weeks
Johnson & Johnson	Viral vector vaccine	66	One dose	
Astra-Zeneca[a]	Viral vector vaccine	64	70[b]	Second dose between 4 and 12 weeks

[a]Not presently available in the United States; [b]Depends on dosage.

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Moderna vaccines, respectively, and is accompanied by a robust immune response (Table 1).[21-25] COVID-19 viral vector vaccines (ie, Johnson & Johnson/Janssen and Oxford/Astra-Zeneca) use a modified version of adenovirus, which expresses a stabilized spike protein on its surface but is incapable of replicating. These viral proteins are recognized by host cells, which induce an immune response. The Johnson & Johnson vaccine is administered as a single dose, whereas the Astra-Zeneca vaccine requires 2 doses for full efficacy, with the second dose given between 4 and 12 weeks after the first.[22] Similar to the Astra-Zeneca vaccine, the Johnson & Johnson vaccine was temporarily paused because of reports of thrombotic events. However after investigation the US Food and Drug Administration and CDC both recommended resumption of its administration.[32-33]

Most side effects occur within 7 days of vaccine administration and are mild to moderate in severity (Figure 1).[21-25] Maximum efficacy was achieved at 2 weeks after the final vaccine dose.

Because of concern over supply shortages, adverse effects, variant mutations, and booster necessity, combination or "mixed" vaccine series from different manufacturers have been considered and used in some scenarios. Although antibody levels seem to be similar to homogenous vaccination, concerns have been raised regarding an increase in adverse effects.[34,35] The CDC presently does not support mixed-product series, because efficacy and safety has not been fully evaluated.[36] Further trials are ongoing in this realm.

GUIDANCE DEFINITIONS

Although high-quality data directly addressing vaccination in the perioperative period for cardiothoracic patients are scarce, the following recommendations are based on the best available evidence, including data from current and prior disease outbreaks and consensus opinion from experts. It is important to note that standard-grade recommendations were not used because of data limitations and the nature of the changing landscape in this realm. The guidance statements thus fall into 3 modified categories as follows:

- *Recommended:* The intervention is beneficial (strong recommendation) *or* the intervention is a best practice statement.
- *Not recommended:* The intervention is not beneficial *or* may be harmful.
- *Consider:* The intervention may be beneficial in selected patients (conditional recommendation) *or* exercise caution when considering this intervention.

VACCINATION BEFORE EMERGENT OR URGENT SURGERY

It is *not recommended* to delay emergency surgery based on vaccination status.

VACCINATION BEFORE ELECTIVE SURGERY

1. We *recommend* that patients complete a full vaccination series as early as possible before any

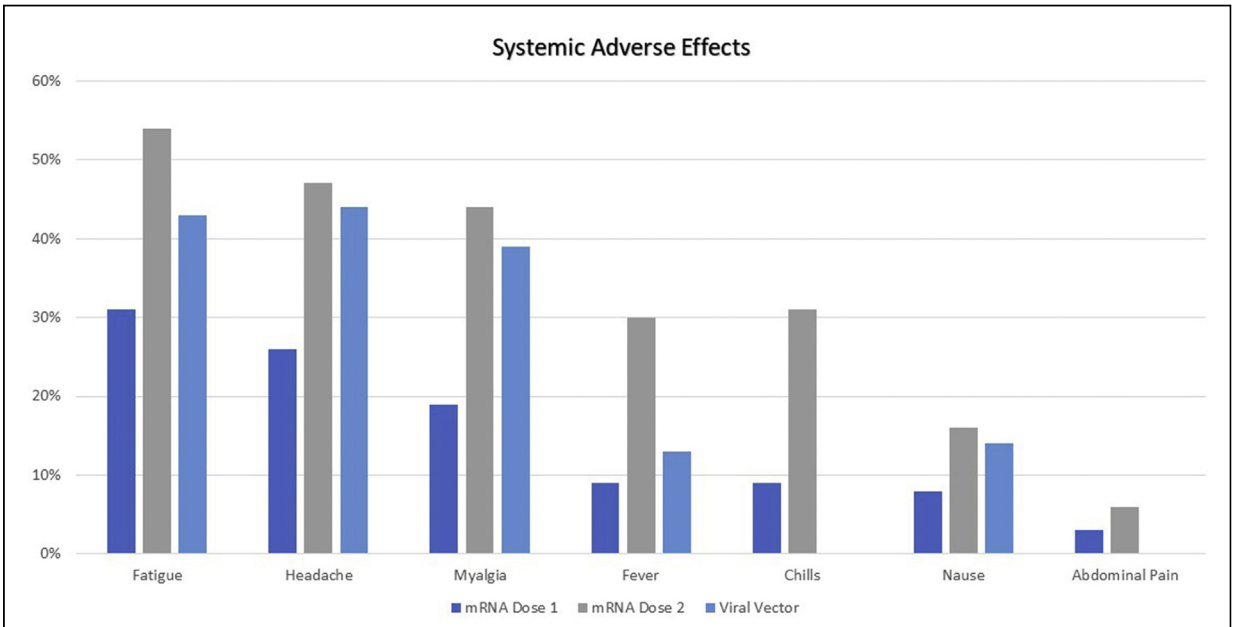

FIGURE 1 Incidence of common systemic adverse effects after messenger RNA (mRNA) and viral vector coronavirus disease 2019 vaccination.[21-25,44] The first and second dose of mRNA vaccines are separated to illustrate differing incidences of reactogenicity.

elective surgical procedure that is not time sensitive. Clinical trials demonstrate maximum efficacy against COVID-19 occurs at least 2 weeks after complete vaccination.

2. For elective surgeries that are time-sensitive and cannot afford the completion of a vaccination series, a single dose of vaccine as early as possible before surgery *should be considered*. Data demonstrate protection from infection beginning 14 days after the first dose.
3. Administering COVID-19 vaccines within a few days before surgery is *not recommended* because patients are unlikely to benefit immunologically, may have side effects mimicking infection, and side effects may be significant in some cases and affect postoperative recovery.
4. Shared decision-making between providers and patients and documentation of informed consent regarding choice to receive or refuse vaccination *is recommended* for all patients before nonemergent surgery.

SUPPORTING DATA. The suspension or delay of elective cases during the pandemic creates negative effects on health outcomes.[37,38] Efforts should continue to ensure the performance of safe and prompt surgery, regardless of vaccine status. However data support global vaccine prioritization for patients scheduled for elective surgery. The COVIDSurg Collaborative evaluated the number of patients needed to be vaccinated preoperatively to prevent 1 COVID-19-related death in 1 year. They enrolled 141,582 patients across 1667 hospitals in 116 countries and concluded that vaccination for elective surgery could prevent 56,687 COVID-19-related deaths.[27]

TIMING OF VACCINATION. Although completion of both vaccine doses (mRNA) is most effective and is recommended, evidence shows that a single dose of vaccine is protective against "wild-type" COVID-19 to varying degrees and that immunity will typically begin to develop approximately 10 to 14 days after the initial dose of mRNA and viral vector vaccines (Figure 1).[21-24] Therefore if a vaccine is administered only a few days before surgery, patients are unlikely to reap the benefits in the immediate perioperative period. In general the earlier the vaccine can be given preoperatively, the greater the protection.[27]

Reactogenicity refers to the subset of reactions that occur around the time of vaccination and represent a physical manifestation of the inflammatory response to vaccination.[39] Physicians should ensure vaccination reactogenicity has resolved and that any adverse event risk is minimal before proceeding with elective cases. Much of the data for these recommendations stems from childhood vaccine research. Pediatric guidelines suggest a 7-day wait time in children (in nonpandemic situations) after administering an inactive vaccine and up to 3 weeks after receiving a live attenuated viral vaccine (ie, measles, mumps, rubella, or polio vaccination).[40] The Vaccination Commission of the German Robert Koch Institute (comparable with the US CDC) published recommendations in 2016 stating that inactivated viral vaccines may be given up to 3 days before surgery, whereas live vaccines should not be given within 14 days of an elective intervention.[41]

At this time research is ongoing to have a complete understanding of the safety of administering mRNA and viral vector COVID-19 vaccines in the perioperative setting. None of the currently available vaccines is a live or attenuated vaccine, thus making it difficult to directly extrapolate guidelines. Current, recent, or upcoming surgery is not technically a contraindication to vaccination, but certain factors might lead a provider to consider these as a precaution.[42,43]

VACCINATION AFTER SURGERY

1. We *recommend* shared decision-making (between all providers and the patient) to develop a personalized plan for future vaccination after cardiothoracic surgery.
2. In general we *recommend* that patients recover from *immediate major surgery and/or postoperative complications* before vaccination. The rationales for this are to allow a robust immune response to vaccination and to avoid a setback or confounding symptoms where there is potential overlap of vaccine adverse responses and manifestations of postoperative complications.

SUPPORTING DATA. Resolution of the acute phase of recovery may be confirmed by several criteria including no persistent systemic inflammatory response, unremarkable wound healing, liberation from respiratory support, and undergoing a typical convalescence without active medical problems that may interfere with the vaccination effect or mimic side effects. Vaccination is thus not recommended for patients still in an intensive care unit or ward with active, acute medical problems; however being in a skilled nursing facility is not a contraindication for vaccination. The convalescent time is not considered to be concrete and varies by individual patient and by procedure. For example after an esophagectomy patients have a median length of stay of 13 days with 25% of patients requiring discharge to institutional care facilities postoperatively and an 18.2% readmission rate.[44] This is in distinction to data from patients undergoing coronary bypass surgery, which suggests a more variable percentage of discharge to skilled nursing facilities based on age (ie, 15% in ages

65-69 and 56% in patients >85 years old) and a median length of stay at the facility of 10.6 days.[45,46]

Although vaccines themselves do not cause active infection, uncertainty may arise between similarities in adverse effects versus postoperative infections or complications (fever, fatigue, myalgia) or even confusion with COVID-19 illness itself. Between 50% and 70% of patients receiving the mRNA vaccines developed some form of systemic reaction within 0 to 7 days of vaccination, with the second dose producing more systemic effects and the elderly population reporting more adverse effects.[47] After the first vaccination the most common systemic symptoms were fatigue, headache, and myalgia (incidence ranging between 19% and 31%). The second mRNA vaccination may manifest a higher reactogenicity with fatigue, headache, fever, chills, and myalgias all common and ranging between 25% to 54% in incidence. Specifically fever and chills occurred at 30% after the second vaccination.[48] Systemic adverse effects were also noted at similar incidences after viral vector vaccination.[25] Vaccination in the acute postoperative period may cause diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination or superimposing adverse effects of the vaccine on the underlying illness.

For instance in an esophagectomy patient fever and malaise may indicate an anastomotic leak (present in between 6% and 11% of patients).[9] Likewise sternotomy patients may develop postoperative pneumonia or a deep sternal wound infection. In addition to creating a bit of a clinical conundrum, there is substantial cost and increased length of stay associated with the workup of postoperative fever.[48,49]

As a counterpoint to the issue of investigating a fever of unknown origin, timing of vaccination as it relates to the benefit to the patient and community as a whole of viral infection spread will also need to be factored. At time of writing there is still a lack of clarity from the World Health Organization and CDC on appropriate recommendations in this regard. As such individual institutions and heathcare system are relegated to determine this cost and risk-to-benefit ratio within the context of local COVID-19 burden. Prior vaccination initiatives for hospitalized patients (but not specifically cardiothoracic patients) for immunity against other illnesses (ie, influenza) have been successful. Data suggest that up to 70% of patients who were vaccinated during hospitalization demonstrate successful immune response (seroconversion and/or 4-fold or greater increase in antibodies to at least 1 influenza strain)[50] without increased risk of fever, evaluation for fever, outpatient visits, or readmission within 7 days. This seems to suggest an adequate immune response to vaccination without an increased risk of reactogenicity complicating the clinical picture. The influenza vaccination is also well studied and has been well established regarding safety profile, whereas the COVID-19 vaccination was only recently developed and approved for emergency usage[21-25]; however given the differences between the influenza and COVID-19 vaccines, these data must be interpreted and applied cautiously. The influenza vaccine is typically an inactivated viral vaccine or live attenuated vaccine and represents a different mechanism of action to the current COVID-19 vaccines (mRNA and viral vector).[47] Reactogenicity, specifically fever, occurs less frequently after the influenza vaccine versus the COVID-19 vaccine (1%-3% vs 9%-30%).[47-51] For all these reasons shared decision-making is suggested for vaccination timing postoperatively, considering each patient's observed and expected postoperative course and short- and long-term risks and benefits.

SPLIT PREOPERATIVE AND POSTOPERATIVE DOSING

We *recommend* that all doses should be administered as close to the recommended interval as possible. However the second dose may be administered safely up to 42 days after the first dose when a delay is inevitable.

SUPPORTING DATA. The CDC COVID-19 Vaccine Task Force recommends that all doses should be administered as close to this interval as possible. However the second dose may be administered up to 42 days after the first dose when a delay cannot be avoided.[52] Regarding patients who undergo surgery between the first and second dose of an mRNA cycle, the CDC acknowledges a grace period for administration of the second vaccine dose. Pfizer-BioNTech recommends the second vaccination occurs between 21 days and 6 weeks, whereas Moderna guidelines suggest between 28 days and 6 weeks is safe.[52]

KNOWN PRIOR COVID-19 INFECTION

1. We *recommend* that surgery should be delayed if possible during the period that a patient may be infectious.
2. Vaccination is *recommended* for patients with prior COVID-19 infection.

SUPPORTING DATA. The timing of elective surgery after recovery from COVID-19 uses both symptom- and severity-based categories and ranges from 2 weeks for an asymptomatic patient to up to 12 weeks for patients who required care in the intensive care unit.[50] Further preoperative studies may be recommended to evaluate the patient's cardiopulmonary function, coagulation status, markers of inflammation, and nutritional status after COVID-19 illness, and if the patient experienced critical illness or prolonged symptoms, then consideration of surgical delays should incorporate the

trajectory of the patient's recovery and the presence of new risk operative risk factors.[53]

Seroreversion and length of natural immunity appears to be related to the severity of illness, with a more robust antibody presence in patients who were most ill, whereas up to 5% to 10% of individuals do not develop IgG antibodies after known infection.[54-58] Infection with SARS-CoV-2 produces antibodies against specific antigens that target the nucleocapsid protein and the spike protein's S1 subunit and receptor binding domains. Antibody testing against nucleocapsid, spike, or receptor binding domains indicates a prior exposure to SARS-CoV-2. The CDC presently recommends vaccination for all persons with prior COVID-19 illness, because natural immunity seems to be more variable than protection from vaccination.[52] Complex understanding of antibodies and identification of best testing are rapidly expanding and will be of interest in future guidance documents. Patients should wait at least 14 days after COVID-19 diagnosis and for complete resolution of their illness before getting their first vaccine dose.

It is important to note that patients who have previously been infected with COVID-19 seem to have higher systemic reactogenicity after the first vaccination (headache, fever, chills, muscle pain, etc) than seronegative patients.[55] Furthermore investigation is ongoing as to whether a single dose of vaccination is sufficient in patients with prior COVID-19 infection, with present guidelines endorsing standard vaccination with recommended doses.

Because of associated comorbidities, monoclonal antibodies may have been administered to cardiothoracic surgery patients at the time of COVID-19 illness. If patients received these therapies a period of 90 days should pass before vaccination based on CDC recommendations.[52] This is primarily to ensure that a robust immune response is achieved from the vaccine administration.

SPECIFIC POPULATIONS

For patients who are to have thymectomy, have had thymectomy, or otherwise have impairment of T-cell function (transplant recipients), response to the COVID-19 vaccine may be diminished.[59,60] The CDC guidelines *recommend* vaccination of immunocompromised individuals despite uncertain efficacy of immunity compared with the general population.[61] Preoperative antibody testing in specific populations may be obtained to determine immunity and to plan for appropriate postoperative management.[62] Convalescent plasma therapy has been well tolerated in this population and should be considered a treatment option if these patients develop a clinical course of COVID-19 after surgery.[63-66] Finally, given the distinctive nature of pulmonary and cardiac transplant patients, the group defers to specific transplant societal recommendations regarding vaccination in these populations.

VACCINE-INDUCED IMMUNE THROMBOCYTOPENIA AND THROMBOSIS

Vaccine-induced immune thrombocytopenia (VITT) is a unique complication that is more prevalent with the viral vector as opposed to the mRNA vaccines. Considering important implications in the postoperative phase of cardiothoracic surgery, VITT is further expanded here. The etiology is understood to be like heparin-induced thrombocytopenia and leads to arterial and venous thrombosis.

Cerebral sinus vein thrombosis is another even more rare but serious complication occurring mainly but not exclusively in younger female patients between 10 and 16 days after vaccination.[32] Cases were associated with thrombocytopenia and platelet-activating antibodies against platelet factor 4, similar to heparin-induced thrombocytopenia and thrombosis. One proposed mechanism involves "soluble spike protein variants," which can occur when a segment of introduced DNA from a viral vector is not transcribed optimally into the cell nucleus and is subsequently spliced into shorter protein variants, which are released as soluble spike protein variants.[67] The soluble spike protein variants may bind to the endothelial angiotensin-converting enzyme receptors, like the SARS-CoV-2 virus itself, and may thus mimic the endothelitis with prothrombotic effects, including a neutrophil extracellular traps reaction of neutrophils as part of the inflammatory process.

Specials flow patterns in some major veins like the non-unidirectional flow in the cerebral sinus vein may contribute further. A possible role of an endothelitis-like syndrome during cardiothoracic surgery should be considered as intervals for vaccination and surgery are determined.[67] Proposed therapy consists of high-dose intravenous immune globulins for at least 2 days and consideration of nonheparin anticoagulants (direct and indirect Xa inhibitors, direct thrombin inhibitors), weighing of course the risks and benefits of bleeding, particularly in cases of cerebral sinus vein thromboses.[68] A comprehensive understanding of VITT as it relates to surgery (and specifically cardiothoracic surgery) is currently incomplete, with further data to guide care anticipated over time. Presently if surgery is required close to vaccine administration, the authors *recommend* attention should be given to the type of vaccine the patient received.

COMMENT

Patients undergoing major surgery suffer worse outcomes if infected with COVD-19 in the postoperative

period. Even a single dose of vaccination provides increased protection against severe COVID-19 infection and mortality in the perioperative period. Recommendations are sparse to help guide decisions regarding the timing of vaccination dosing in the perioperative period. In general patients should be vaccinated as far in advance as possible for elective cases to maximize protection from the vaccination. Although vaccination status should not factor into emergent or unavoidable surgical interventions, anticipating reactogenicity may be helpful. Patients in the acute phase of recovery from major cardiothoracic surgery may delay vaccination briefly to allow for a full immune response to the vaccine and to avoid clinical confusion with common systemic symptoms after vaccination. As providers decide between vaccines during the perioperative period, consideration should be given to potential complications (including VITT) and to dosing details, including the need to coordinate follow-up appointments for a second vaccine administration. The guidelines for vaccination timing now permit up to 6 weeks between a first and second dose of mRNA vaccines.

Patients with prior COVID-19 illness should still be vaccinated and may experience more reactogenicity after the initial dose of vaccine. Recently new variants of SARS-CoV-2 have appeared, and protection against all strains from vaccination is presently undetermined. As stated above and pertinent here as well, providers deciding between vaccines during the perioperative period should consider potential complications, dosing details, and the need to coordinate follow-up appointments for second vaccine administration. Shared decision-making between providers and patients and awareness of the variants, regional conditions, and infectious rates may guide the determination of vaccination type and timing.

The strength of the recommendations within this article are modified because of data limitations, and it is important to note that the guidance statements were formed based on existing information at the time of development. The authors acknowledge that new data are continually emerging regarding the COVID-19 pandemic and proffer this guidance document based on best current available knowledge.

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