NOTTO Guidelines for Vaccine Induced Thrombotic Thrombocytopenia in Organ Donation and Transplantation

Abstract

From the context of organ donation, COVID-19 vaccine-induced thrombotic thrombocytopenia (VITT) is important as there is an ethical dilemma in utilizing versus discarding organs from potential donors succumbing to VITT. This consensus statement is an attempt by the National Organ and Tissue Transplant Organization (NOTTO) apex technical committees India to formulate the guidelines for deceased organ donation and transplantation in relation to VITT to help in appropriate decision making.VITT is a rare entity, but a meticulous approach should be taken by the Organ Procurement Organization's (OPO) team in screening such cases.All such cases must be strictly notified to the national authorities like NOTTO, as a resource for data collection and ensuring compliance withprotocols in the management of adverse events following immunization. Organs from any patient who developed thrombotic events up to 4 weeks after adenoviral vector-based vaccination should be linked to VITT and investigated appropriately.The viability of the organs must be thoroughly checked by the OPO, and the final decision in relation to organ use should be decided by the expert committee of the OPO team consisting of a virologist, a hematologist, and atreating team. Considering the organ shortage, in case of suspected/confirmed VITT, both clinicians and patients should consider the risk-benefit equationbased on available experience, and an appropriate written informed consent of potential recipients and family members should be obtained before transplantation of organs from suspected or proven VITT donors.

Keywords: *COVID-19, deceased donor, NOTTO, organ donation, transplantation*

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The COVID-19 pandemic has affected humanity globally, leading to significant morbidity and mortality. In addition to preventive measures such astheuse of masks, social distancing, and hand washing, vaccination has proven to be a highly successful strategy for controlling severe COVID-19 infection. Several vaccines using novel technologies have been deployed in large population cohorts in a relatively short period of time with variable efficacy. While vaccination is effective in controlling severe infection as well as the spread of infection, there are reports of adverse effects following vaccination, though infrequent and minor. One such side effect is vaccine-induced thrombotic thrombocytopenia (VITT).

VITT, also termed as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), is a rare syndrome that has been encountered in some individuals who have received adenoviral vector-based vaccines, ChAdOx1 CoV-19 vaccine (Astra Zeneca, University of Oxford, and Serum Institute of India) and Ad26.COV2.S vaccine (Janssen; Johnson & Johnson).[1] Though the incidence of VITT is exceedingly rare, there are, however, high chances of underreporting of such cases as asymptomatic subjects are not routinely subjected to investigations to diagnose VITT. The adverse event following immunization (AEFI) data in India showed that there is a minusculebut definitive risk of thromboembolic events following the administration of Covishield vaccine, with a reporting rate of 0.61 cases/million doses, which is much lower than the 4 cases/million reported by UK's regulator medical and health regulatory authority. Germany has reported 10 events per million doses. There were no potential thromboembolic events reported following the administration of the Covaxin vaccine. Routine platelet count or D-dimer testing following COVID-19 vaccination is not advised.

Risk factors for VITT are unknown. Theetiopathogenesis is not well

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definedbut autoantibodies to platelet factor 4 (PF4) arefound to have a strong association with VITT which acts through antibody-dependent platelet activation, resulting in increased consumption of platelets, leading to thrombosis followed by thrombocytopenia and bleeding manifestation.

Clinical features ofVITT usually develop within 4 weeks after COVID-19 vaccination.[2,3] Thrombosis, most frequently cerebral venous sinus thrombosis, followed by portal venous thrombosis but venous or arterial thrombosis may occur at any site. These are commonly associated with

- Intracranial hemorrhage
- Thrombocytopenia (platelet count of <150 × 10^9/l)
- High levels of D-dimer (usually >4000 μg/L)
- Often associated with low fibrinogen levels
- Positive testing for antibodies to PF4 by an enzyme-linked immunosorbent assay (ELISA).ELISA-based anti-PF4 antibodiesarealmost 100% sensitive while taking optical density >2.0–3.0.Non-ELISA rapid immunoassays for PF4 are neither sensitive nor specific and should not be used. The recommendation for regular PF4 antibody testing in the donor and the recipient may be hampered by the specific availability of this test in hematology laboratories, even in transplant centers, and thus can be donefrom accredited laboratoriesat the regional/state level. There are other causes of thrombocytopenia and/or thrombosis[4] that should be considered, especially in individuals with negative PF4 antibody testing.

From the context of organ donation, VITT is important as there is an ethical dilemma in utilizing versus discarding organs from potential donors succumbing to VITT, as there is a possibility thatorgans derived from patients who have undergone cerebral venous sinus thrombosis following VITT may result in an immune thrombocytopenia triggered by passenger lymphocytes following organ transplant. Organs with a high passenger leukocyte burden (e.g., liver, lung, small intestine, and pancreas) from donors with VITTare more likely to confer an additional risk in the transplant recipient. Organs with low leukocytes burden and tissues, such asblood vessels grafts, bone, tendons, menisci, skin, and cornea/sclera, are not considered to pose a significant risk of passenger lymphocyte syndrome. The UK National Health Service is monitoring 26 patients who received kidney (15), simultaneous pancreas and kidney (1), liver (7), lung (1), islet (1), or heart (1) transplants from confirmed TTS donors for outcomes.

Organs from any patient who developed thrombotic events up to 4 weeksafter adenoviral vector-based vaccination should be considered to be linked to VITT and investigated appropriately.[3] The risk of developing immune-mediated thrombocytopenia and associated complications must be weighed against the benefit of organ transplantation. These organs should be graded as marginal, with a careful explanation of the risks to the recipient, which may be well documented. As these are classified as marginal donors, principles of recipient selection should be based on any marginal donor. These may include patients with rare blood groups, those wait-listed for prolonged periods, high MELD score, acute liver failure, acute on chronic liver failure, hepatic artery thrombosis, or primary non-function following liver transplantation, highly sensitized renal recipient, absence of any access for dialysis, etc.

The organs should be carefully assessed for poor flow during perfusion, which may suggest microthrombosis and may render organs unfit for use. Petechial hemorrhageonthesurface of organs due to low platelet counts does not make anorgan unsuitable.The risk of acquired VITT is the highest in the first 30 days.

Organ transplantation outcome from deceased donors with VITT

The UK experience reported that 10 donors out of 13 consented deceased organ donors with VITT after the first dose of ChAdOx1 nCoV-19 vaccine proceeded to donate 27 allografts in 26 recipients.[5] Many encountered thrombotic complications and also unfavorable graft outcomes, which

raised concerns among organ procurement organizations (OPO) across all parts of the world.There were seven major hematological complications (three bleeds and four venous or arterial allograft thromboses) in six recipients, resulting in the loss of threetransplants within 9 days of transplantation. One recipient died within a day of transplantation from a presumed cardiac event.Early major hematological complications such as thrombosis or clinically significant bleeding, which may result from preexisting hemostatic and endothelial dysfunction in the allograft and possible transmission of pathogenic lymphocytes producing anti-PF4, are the potential risks of transplanting organs from donors with VITT. This raised concerns among OPO across all parts of the world.Nineteenbrain-dead donors with VITT syndrome in the UK have had organs offered for transplantation, but onlynineliver grafts (from eightdonors) with optimal patient and liver graft survival at 3 months follow-up.[6] This signifies skepticism within the transplant community.[2-4] There were 78% (21/27) of total allografts having a satisfactory function at a median follow-up of 19 days.[4] However, there are a few reports[7-9] with favorable outcomes as well.The first Indian study reported successful organ transplantation from an 18-year-old girl who presented with VITT followingthe1stdose of the CovishieldCOVID-19 vaccine (Oxford/AstraZeneca formulation).All four recipients (31-year-old and 22-year-old kidneys recipients, 64-year-old liver recipient, and 26-year-old combined heart and lung recipient) had normal graft function without any thrombotic complication at 16 weeks of transplantation.[8] India crossedthe landmark of100-croreCOVID-19vaccinedoses.[10] In India, the Oxford–Astra-Zeneca vaccine has been one of the major vaccines being used, hence raising an alarm and theoretical concern of encountering more such cases. Transplantation societies across the world have shown concern about VITT and amended their guidelines. In the UK, the rise of VITT cases in the general population led to the formulation of VITT guidelines for solid organ transplantation (SOT).[11] However, the International Society of Heart and Lung Transplantation[12] recommended no specific protocol and insisted on following measures as in the general population. India[13] toohas recently updated its vaccine guidelines for SOTthrough National Organ and Tissue Transplant Organization (NOTTO) and its transplant societies andstated a cautious approach for potential donors with VIIT.

This consensusstatement is an attempt by the NOTTO apex technical committeesto formulateguidelines for organ donation and transplantation in relation to VIIT tohelp in appropriatedecision-making.

Recommendations

General

1. A registry should be set up under NOTTO for monitoring prospective recipients undergoing transplants from VITT donors.
2. The National AEFI committee advisory for diagnosis, treatment, and reporting of thromboembolic events after COVID-19 vaccination should be followed.[2]
3. There are other causes of thrombocytopenia and/or thrombosis that should be considered, especially in individuals with negative PF4 antibody testing.
4. Routine platelet count or D-dimer testing following COVID-19 vaccination is not advised.
5. We suggest not using aspirin before or following vaccination unless there is another indication.
6. Aspirin increases bleeding risk, and there is no evidence it reduces the risk of VITT.
7. At present, there is no evidence to suggest the use of organs from living donors with active VIIT.

Management of donor

1. Ensure adherenceto government guidelines for conducting post-mortem examination, which is now allowed 24 × 7[14,15]
2. VITT is a rare entity, buta meticulous approach should be taken by the OPO team in screening such cases, and all such cases must be strictlynotified to the national authorities as a resource for data collection and ensuring compliance of protocols in the management of AEFI.[16,17]
3. A complete history of vaccination, including type of vaccine andinterval from last dose to occurrence of any such event, should be an integral part of history in all potential donors.
4. A complete physical examination should be done to find out any evidence of vascular thrombosis. Basic hematological tests should be performed to screen any evidence of platelet activation and/or consumption. Any abnormal physical examination or screening tests should be followed with radiological assessment, for detecting the multi-organ impact of VITT in the donor.
5. In case of suspected/confirmed VITT, the decision to proceed for transplant must be assessed by weighing the risk-benefit ratio and informed consent in respect to this condition must be taken.
6. Organs should be assessed for the presence of thrombi (including biopsy if required).
7. The threshold for pre-implantation biopsy must be low.
8. The viability of the organs must be thoroughly checked by the OPO, and the final decision in relation to organ use should be decided by the expert committee of the OPO team consisting ofa virologist, a hematologist, and a treating team.
9. Organ donation should be canceled in the case of severe disseminated intravascular coagulation, and organs should be discarded if thrombi were extensive.
10. Preferably avoid transplanting the organs to the recipients with previous thrombotic complications.
11. Preferably avoid platelet transfusion in VITT donors.

Management of recipient

1. Considering the organ shortage, both clinicians and patients should consider the risk-benefit equationbased on limited experience, and an appropriate written informed consentof potential recipientsand family members should be obtained before transplantation of organs from suspected or proven VITT donors.
2. No change in immunosuppression of the recipient receiving organs from VITT donors is required.Organ transplant recipients of VITT donors should have serial monitoring of thrombotic/hemorrhagic events, hemostasis, and graft dysfunction and undergo regular testing with PF-4 antibodies, platelet counts, D-dimer, fibrinogen, PT-INR, and FDP for early detection of the possibility of transmission. Surveillance of the recipient and reporting of graft dysfunction/thrombo-embolic events should preferably be mandatory.
3. There is no evidence for protocol biopsy in VITT recipients.
4. There are no specific prophylactic therapy recommendations currently. However, prophylactic anticoagulation for the recipient is an individualized decision based on the risk of bleeding.
5. In the case of a thromboembolic event in a recipient, there is no specific management protocol thatis at variance from the general population with VITT. If the recipient is partially vaccinated/unvaccinated, the scheduled dose of vaccine should be avoided.

Suggestions

With the continued global administration of the COVID-19 vaccine, donors with VITT syndrome are likely to continue and more research and longer-term recipient follow-upareneeded to guide the optimal approach for organ transplantation from deceased donors with VITT.All individuals with VITT and thrombosis and even without thrombosis should receive full (therapeutic) dose anticoagulation. We suggest a non-heparin anticoagulant rather than heparin, especially if heparin-induced thrombocytopenia remains in the differential. If the suspicion for VITT is high, anticoagulation should not be delayed while awaiting confirmatory testing.Novel anti-coagulation such asargatrobancanbe used for preserving the viability of organs.For adult patients, the recommended argatroban dose is 2 mcg/kg/min administered as a continuous intravenous infusion.

Monitoring: Obtain baseline aPTT.The activated partial thromboplastin time (aPTT) should also be obtained 2 h after the initiation of therapy and after any change in dosage.Monitor aPTT (target range of 1.5–3 times of initial baseline, not to exceed 100 s).The appropriate duration of anticoagulation is unknown.A reasonable approach for VITT with thrombosis would be to continue anticoagulation for 3months after normalization of the platelet count, as long as no further thrombosis occurs. For VITT without thrombosis, anticoagulation until platelet count recovery and perhaps longer if tolerated (4–6 weeks after platelet count recovery) appears prudent.

Disclaimer

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The COVID-19 pandemic is evolving in a dynamic manner; therefore, this guideline is a live and dynamic document and will be updated as per the evolving situation. This paper is submitted simultaneously in Indian Journal of Nephrology and Indian Journal of Transplantation.

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Conflicts of interest

There are no conflicts of interest.

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