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# Therapeutic plasma exchange (TPE) as a plausible rescue therapy in severe vaccine-induced immune thrombotic thrombocytopenia

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ABSTRACT

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is associated with high titers of immunoglobulin G class antibodies directed against the cationic platelet chemokine platelet factor 4 (PF4). These antibodies activate platelets via FcγIIa receptors. VITT closely resembles heparin-induced thrombocytopenia. Inflammation and tissue trauma substantially increase the risk for forming pathogenic PF4 antibodies. We therefore propose the use of therapeutic plasma exchange as rescue therapy in VITT to deplete antibodies plus factors promoting inflammation such as excess cytokines in the circulation as well as extracellular vesicles derived from activated platelets.

Schultz et al. have reported on five patients suffering from thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 Vaccination [1]. Similar side effects have also been reported by others and were also found with other vaccines [2–4].

In the Schultz report, they found that the patients had high levels of antibodies against platelets approximately 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine. All patients had high levels of antibodies to platelet factor 4 (PF4) -polyanion complexes. Since the findings were not related to prior administration of heparin, the authors proposed that the reactions represented a rare vaccine-related disorder that strongly resembles heparin-induced thrombocytopenia (HIT), which they referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT) [1].

Similarly, Greinacher et al. assessed the clinical and laboratory features of eleven patients in whom thrombosis or thrombocytopenia developed after vaccination; of these, six died [4]. All had platelet-activating antibodies against PF4 and moderate to severe concomitant thrombocytopenia, however, in agreement with the study by Schultz et al., none of them had received heparin before the onset of symptoms, leading the authors to suggest that interactions between components of the vaccine, specifically free DNA, and PF4 could be a possible trigger of these PF4-reactive antibodies.

Scully et al. also reported on the occurence of anti-PF4 antibodies, unrelated to the use of heparin therapy, in a mostly young, generally healthy cohort of 23 patients presenting with acute atypical thrombosis following vaccination with ChAdOx1 nCov-19 [5]. On the basis of the pathophysiological features observed, they recommended that platelet transfusions should be avoided in these patients due to the risk of progression of thrombotic symptoms.

Anti-platelet antibodies are known to occur in a number of diseases associated with thrombosis, including standard heparin-induced thrombocytopenia, patients with the lupus anticoagulant who thrombose (CD 36) [6], and in aTTP where patients have antibodies not only to the enzyme ADAMTS13 but also to CD 36, a well-known platelet activator [7]. According to the ASFA guidelines, apheresis is an established therapy for aTTP based on a randomized trial that showed significant benefit of plasma exchange over just using replacement with plasma [8]. Indeed, much of the pathophysiology of VITT is remarkably similar to that of aTTP.

This suggests that removal of antibodies in VITT may be of benefit. Plasma exchange allows not only the removal of anti-PF4 antibodies and immune complexes and the replacement of factors consumed during the process of thrombosis, but also depletes factors supporting inflammation, including excess inflammatory cytokines in the circulation. As

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**Table 1**
Adverse events during plasma exchange (TPE) of patients with various diagnoses (ICD-10 codes in brackets) performed either with a) centrifuge technique (10,428 procedures) or with b) filtration technique (123 procedures). Adverse events were graded as mild (no medication necessary), moderate (supportive medication used) and severe (interruption of the procedure due to side effects.

| Diagnosis | Patients | Total procedures | Adverse events | | | |
|---|---|---|---|---|---|---|
| | N | N | Mild | Moderate | Severe | Total % |
| **TPE-centrifuge:** | | | | | | |
| Sepsis (A39.0−48.5) | 141 | 576 | 0,7 | 0,5 | 0,0 | 1,2 |
| DIC (D65) | 35 | 154 | 0,0 | 1,3 | 0,0 | 1,3 |
| Coagulopathy (D68.6−68.8) | 42 | 351 | 0,6 | 1,1 | 0,3 | 2,0 |
| ITP (D69.3) | 41 | 429 | 0,7 | 1,4 | 0,0 | 2,1 |
| TTP (M31.1) | 762 | 8831 | 1,0 | 3,1 | 0,4 | 4,5 |
| Covid-19 | 12 | 87 | 1,1 | 1,1 | 0,0 | 2,3 |
| **TPE-filtration:** | | | | | | |
| Sepsis (A39.0−48.5) | 2 | 3 | 0 | 0 | 0 | 0 |
| DIC (D65) | 1 | 3 | 0 | 0 | 0 | 0 |
| Coagulopathy (D68.6−68.8) | 2 | 13 | 0 | 0 | 0 | 0 |
| ITP (D69.3) | 3 | 7 | 0 | 0 | 0 | 0 |
| TTP (M31.1) | 14 | 97 | 2,1 | 9,3 | 1,0 | 12,4 |

concurrent inflammation has been proposed as one of the major risk factors for the formation of anti-PF4 antibodies [9], the depletion of inflammatory mediators by TPE might provide additional benefit in VITT patients by reducing the inflammatory co-stimulus. In addition, TPE depletes extracellular vesicles (EVs) which are mainly derived from activated platelets. While detailed studies in this respect are still missing, platelet-derived EVs are likely to contribute to VITT in many regards. They expose PF4 providing a large surface for the binding of anti-PF4 antibodies, as known from the pathogenesis of classical HIT. Moreover, EVs support thrombosis by their exposure of phosphatidylserine (PS) [10,11] and it has been shown that PS exposed on EVs can act as a ligand for platelet CD36 and thereby promote platelet activation [12]. In support of this concept, Xie et al. have recently reported on a case of VITT who recovered after receiving TPE [13].

Based on our experience in treating patients with MODS with TPE [14] we recommend that TPE be performed with a centrifugal device and using citrate as the anticoagulant. TPE removes not only antibodies, but also numerous inflammatory substances that are present in the plasma. The replacement fluid should be 1:1 with plasma from healthy donors [14,15]. While the procedure itself lowers the platelets to some extent this will recover once the antibodies are removed since the consumption will decrease and production prevail.

To counteract eventual hypotension when initiating apheresis, an initial infusion of 200 mL of albumin solution (50 g/L) can be used and the dose of inotropic drugs should be adjusted. At least daily procedures are recommended until the consumptive coagulopathy -DIC is reversed.

When considering TPE as a therapy, there may be some hesitation due to concern over the risk of side effects. Table 1 shows data from the World Apheresis Association registry on adverse events in various diagnoses related to the present problem. Overall, more than 129, 000 therapeutic apheresis procedures have been registered. Of these, only one possible death due to therapy was reported in an 80 year old man severely ill with TTP who died from a myocardial infarction during the procedure: adverse events that cause interruption of the procedure were present in 0.3 % of the TPEs [16].

Based on the pathophysiology of the VITT and its relative similarity to other disorders, particularly aTTP in which antibodies are associated with thrombosis, we suggest that antibody removal by plasma exchange along with appropriate immunosuppression should be considered as a therapeutic approach.

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