Techniques and applications of perioperative therapeutic plasma exchange

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Purpose of review
Therapeutic plasma exchange (TPE) is a useful adjunct in the management of antibody-mediated disorders. The indications for TPE now include the perioperative setting. This review updates the anesthesiologist on the relevant clinical indications and precautions of plasma exchange.

Recent findings
Although still considered experimental, TPE for heparin-induced thrombocytopenia for urgent cardiac surgery is the most promising recent advance.

Summary
Plasmapheresis, or TPE, removes monoclonal antibodies, immune complexes and paraproteins. The utility of TPE in the perioperative period has recently become more apparent. Antibody-mediated disorders are associated with postoperative morbidity and mortality and are treated with TPE. Indications for TPE for cardiac surgery include heparin-induced thrombocytopenia, thrombotic thrombocytopenia purpura and antiphospholipid syndrome. Other indications for perioperative TPE are typically related to immunomodulation during solid-organ transplant. Immunomodulation, primarily with immunosuppressive medications and TPE, of a previously allosensitized recipient pretransplant increases the likelihood of a successful match. TPE is also useful in the management of intentional and inadvertent ABO incompatible recipients and is essential in the treatment of hyperacute rejection. TPE will likely be more utilized in the future and understanding the essentials of the procedure will facilitate the perioperative management of antibody-mediated disorders.

Keywords
critical care, plasmapheresis, therapeutic plasma exchange, thoracic surgery

INTRODUCTION
Plasmapheresis or therapeutic plasma exchange (TPE) is a technically demanding, semiautomated procedure typically performed by a hematologist led service employing specialized nurses or technicians trained to program and manage the device, the fluid replacement regimen and monitor for complications. Central venous access is usually obtained by the primary team, using a large-bore, dual-lumen catheter similar to those used for continuous veno-venous hemofiltration or dialysis. Alternatively for intraoperative TPE, blood can be drawn and returned directly via the cardiopulmonary bypass (CPB) circuit, which is ideal if vascular access is limited or hemodynamic instability is present.

TPE effectively removes monoclonal antibodies, auto or alloantibodies, immune complexes and paraproteins. Apheresis technology uses a computerized process to pump blood from the patient, fractionate it into cellular and plasmatic layers by centrifugation, separate and remove the target layer or component and return the remaining fractions to the patient along with a volume replacement fluid. TPE involves the targeted removal of the circulating plasma; other modalities include cytapheresis that removes excess cellular components, usually without volume replacement, but this discussion is limited to TPE only. A recent, more detailed review and discussion of TPE techniques such as immunabsorption can be found in the Journal of Clinical Apheresis [1].

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Complications arise from placement of the central line [2], hypotension on exposure to the extracorporeal circuit, potential hypovolemia and hypocalcemia from the citrate used to anticoagulate the circuit and present in the plasma used as replacement fluid [3]. Co-infusion of 2 g of intravenous calcium chloride during a TPE procedure will maintain a stable ionized calcium level. Of note, albumin is commonly used as a replacement fluid but we must ensure that allogeneic plasma is given in the perioperative period in order to avoid hemodilution of clotting factors and subsequent increased bleeding risk.

In principle, TPE attempts to remove the patient’s plasma fraction and replace it with allogeneic ‘normal’ plasma, ideally free from pathogenic antibodies. Continual allogeneic plasma replacement is necessary to avoid hypovolemia, but dilutes the pathogenic/patient plasma, leading to exponentially decreasing removal efficiency, as shown in Fig. 1. Most antibody mediated disease can be linked to antibody titer, although how complete the removal of antibodies needs to be for treatment or prevention purposes has not been clearly determined. Antibody removal can be driven by titers if available and ranges known; for example less than 0.4 optical density on a heparin-induced thrombocytopenia (HIT) ELISA or less than 10% on a panel reactive antibody screen ought to prevent disease progression but a true ‘threshold titer’ is unknown. Typically, however, treatments are more empiric and driven by disease severity or established protocols if used for the prevention of disease. Treatment frequencies are illustrated in Fig. 3 and Table 1. Figures 2 and 3 demonstrate that an increased number of treatments are required to clear IgG antibodies [e.g. antihuman leukocyte antigens (anti-HLA)] compared with IgM (e.g. anti-ABO), as the large interstitial fluid compartment acts as a reservoir for IgG antibodies circulating in the plasma. This large volume compartment must also be depleted of IgG to maintain low plasma titers.

THERAPEUTIC PLASMA EXCHANGE IN CARDIOTHORACIC SURGERY

Perioperative TPE has demonstrated utility as a treatment for antibody mediated, immunologic-based diseases. These include HIT, thrombotic thrombocytopenia purpura, the antiphospholipid syndrome and acute humoral (antibody-mediated) organ rejection. The most developed indication is for the prevention and treatment of humoral transplant rejection and prior Left Ventricular Assist Device recipients or redo transplantation presents an especially high risk of alloimmunization; therefore, TPE use is increasing.
who are treated with heparin for cardiac catheterization or surgery. These antibodies may be found in 22% of patients postcatheterization and 50% of those post CPB [5]. Despite the high frequency of antibody formation, clinical evidence of HIT presents much less commonly. In an observational study of 1722 patients, Piednoir et al. [6] found 63 (3.6%) suspected cases and only 24 (1.4%) confirmed cases. The development of HIT greatly increases the risk of thrombosis (odds ratio 37) and thrombotic events occurred in over 50% of patients diagnosed with HIT [7].

![Figure 2](image2.png)

**Figure 2.** Antibody clearance is isotype dependent. IgM is limited to the intravascular space, whereas IgG is distributed throughout the extracellular fluid compartment. This allows titres to rebound after treatment due to slow redistribution from the extracellular fluid. De-novo antibody production causes titres to rebound for all isotypes; hence, concurrent immunosuppression is required in addition to TPE.

![Figure 3](image3.png)

**Figure 3.** Number of treatments required for antibody clearance. One TPE treatment exchanging 1.5 circulating plasma volumes will remove approximately 75% of antibodies. With IgM molecules being limited to the 3 liters circulating volume, one treatment will maintain this level, assuming antibody production is low. For IgG, however, multiple treatments are required to attain the same level of depletion in the entire extracellular fluid compartment throughout which IgG is distributed. Targeting a lower titre may be clinically indicated in which case further treatments will be necessary.
The use of the direct thrombin inhibitor bivalirudin is the current recommendation by the American College of Chest Physicians (ACCP) for anticoagulation during urgent cardiac surgery in patients diagnosed with HIT [8**]. Although hirudin, lepirudin, argatroban, danaparoid, fondaparinux, aniodc and the combination of heparin with an antiplatelet agent such as epoprostenol, iloprost or tirofiban have been used for this indication, the use of bivalirudin is uniquely supported by two prospective studies [9,10]. These strategies are limited by the lack of specific reversal agents and the concern for significant postoperative bleeding remains [11,12] with a reoperation rate of 6% reported in cases anticoagulated with bivalirudin [10]. The ACCP also recommends delaying nonurgent cardiac surgery, if possible, to permit resolution of HIT and clearance of the antibodies. HIT antibody titres spontaneously decline within 50–80 days, in which case heparin is the preferred anticoagulant for these newly seronegative patients with a recent history of HIT [13,14]. Patients with a history of HIT and persistent antibodies, however, should receive nonheparin anticoagulants unless the antibodies have been identified as nonplatelet activating antibodies [8**].

Despite these recommendations, the patient may be considered an unacceptably high risk for perioperative bleeding with the use of irreversible heparin alternatives. In addition, more complex surgery and the use of hypothermia was avoided in prospective studies of bivalirudin and the clotting of stagnating blood in vein grafts, the venous reservoir and the thoracic cavity have all been reported, presenting technical reasons for bivalirudin anticoagulation to be avoided. In these circumstances, it is desirable to have the option to use standard heparin anticoagulation and the use of perioperative TPE may permit this. By removing the HIT antibodies and converting the patient to a seronegative status, the use of heparin now complies with ACCP guidelines.

In a retrospective review of 11 urgent, complex cardiac surgery patients, Welsby et al. [15] reported that a single intraoperative TPE treatment reduced antibody titers by 50–84%, rendering titers seronegative in most patients. The procedure was performed in the operating room and well tolerated with no adverse events attributable to heparin use or HIT. Preoperative TPE has also been successfully utilized to permit heparin use in a patient requiring urgent left ventricular assist device insertion, again without thrombotic complication [16], despite only partial clearance of the HIT antibodies. Jaben et al. [17] reported two additional cases of successful TPE with heparin anticoagulation in the setting of acute HIT and urgently indicated surgery. Other, older case reports also support this strategy of TPE and heparin re-exposure without complication [18–20]. Important details to be discussed with the TPE team include the volume of exchange proposed, the need for plasma rather than albumin replacement/return fluid and the timing and tolerability of the procedure for each individual patient. In the setting of high dose heparinization for CPB, acute intraoperative thrombosis in patients with HIT has not been reported, possibly because the ratio of heparin to antibody alters antibody/antigen binding properties [21]. Therefore, intraoperative TPE can be delayed until the initiation of CPB in hemodynamically unstable patients; the procedure still removes HIT antibody for the more vulnerable postoperative period when thrombosis is more typically encountered. When performing TPE during CPB, it is imperative to realize that heparin is also removed with the patient’s plasma fraction requiring replacement during the procedure to maintain adequate anticoagulation. For a 2000 ml exchange, for example approximately 8000–10 000 units of heparin will be needed. Heparin re-exposure without complication [18–20]. Important details to be discussed with the TPE team include the volume of exchange proposed, the need for plasma rather than albumin replacement/return fluid and the timing and tolerability of the procedure for each individual patient. In the setting of high dose heparinization for CPB, acute intraoperative thrombosis in patients with HIT has not been reported, possibly because the ratio of heparin to antibody alters antibody/antigen binding properties [21]. Therefore, intraoperative TPE can be delayed until the initiation of CPB in hemodynamically unstable patients; the procedure still removes HIT antibody for the more vulnerable postoperative period when thrombosis is more typically encountered. When performing TPE during CPB, it is imperative to realize that heparin is also removed with the patient’s plasma fraction requiring replacement during the procedure to maintain adequate anticoagulation. For a 2000 ml exchange, for example approximately 8000–10 000 units of heparin will be needed and the ACT closely monitored.

In summary, perioperative plasmapheresis and heparin re-exposure, either prior to or during surgery, appears to be a well tolerated alternative to the nonheparin anticoagulants when they are considered clinically contraindicated.

### OTHER THROMBOTIC INDICATIONS

Thrombotic thrombocytopenic purpura (TTP) is a microvascular occlusive disease traditionally characterized by the pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic disease...
abnormalities, fever and renal failure, although a clinical diagnosis of TTP may be made with the presence of thrombocytopenia, schistocytosis and significantly elevated lactate dehydrogenase (LDH). Pathological inhibition of ADAMTS-13, a metalloprotease responsible for cleaving the hemostatically most active, high molecular weight von Willebrand Factor multimers, promotes a prothrombotic state predisposing to microvascular thrombosis [22]. The most common inhibitor is an acquired anti-ADAMTS-13 autoantibody. These patients demonstrate less than 5–10% of normal enzyme activity during acute episodes of TTP and are typically treated with TPE to clear the autoantibody and excess high molecular weight von Willebrand Factor multimers and immunosuppression to inhibit autoantibody production and re-synthesis and plasma replacement therapy to normalize factor levels [23] although other mechanisms may also exist [24].

Postoperative TTP is a rare cause of thrombocytopenia after cardiac surgery [25]. A distinguishing feature between postoperative TTP and HIT is the presence of microangiopathic hemolysis and elevated serum LDH. In a retrospective analysis of 535 patients undergoing coronary artery bypass grafting (CABG), with and without concomitant procedures, 45 patients were identified as thrombocytopenic and five of those patients did not demonstrate recovery with conventional therapy [26]. All patients demonstrated reduced collagen-binding affinity assay for degraded vWF consistent with diminished ADAMTS-13 activity but, despite aggressive TPE, 3/5 (60%) of patients died. No patient demonstrated pathological ADAMTS-13 antibodies, supporting a nonimmune mediated decrease of ADAMTS-13 activity. Decreased ADAMTS-13 activity is commonly seen after CABG with a 50% decrement seen in both on-pump and off-pump operations, [27] although the exact mechanism is unclear.

Cardiac surgery in patients with the Anti-Phospholipid Syndrome (APS) is associated with significant risk of thrombosis, bleeding and mortality. Dornan reported the case of a 31-year old woman who developed catastrophic APS 5 days postpartum. Two years postpartum, severe mitral regurgitation due to Anti-Cardiolipin Syndrome/APS, required valve replacement and was complicated by acute postoperative biventricular failure [28]. Extracorporeal membrane oxygenation was needed until a total of six plasma exchanges resulted in recovery of myocardial performance.

**Transplantation**

Evaluation of a patient for solid-organ transplantation includes an assessment of the degree of allosensitization. That is, the patient’s serum is evaluated for circulating antibodies against human leukocyte antigens (HLA). This can be assessed by a variety of laboratory techniques and is typically reported as panel reactive antibody (PRA) levels. The United Network for Organ Sharing (UNOS) allocation system utilizes a calculated PRA or CPRA that incorporates the abundance of each specific HLA molecule in the UNOS donor pool [29]. For most solid organ transplants, a CPRA > 10% is considered elevated. It is important to note that the institution determines the strength of unacceptable antibodies and some level of donor/recipient incompatibility (e.g. weak antibody titers) may be tolerated [30]. The CPRA then represents the likelihood that a potential donor in UNOS will be incompatible. For most solid organ transplantation, a CPRA > 10% is considered elevated.

Treating patients that have preformed antibodies to HLA molecules with immunosuppression and including TPE in the perioperative management plan is an attractive option. The best evidence of successful desensitization comes from live-donor renal transplantation, [31] though lowering the PRA pretransplant also appears to improve outcomes with other solid organ transplantation [32–34,35].

As shown in Figs. 2 and 3, antibody isotype modifies clearance efficiency; as many pathologic anti-HLA antibodies are of the IgG subtype, multiple treatments are included in an extensive schedule requiring central venous access for up to a week. As detailed in Table 2, TPE is also a component of management strategies to treat established rejection episodes.

**Management Strategies for ABO Incompatible Transplant Recipients**

ABO blood group antigens also play an important role in solid-organ transplantation. As a rule, patients develop specific antibodies to absent blood group antigens at a young age. That is, patients that are blood group A will have preformed antibodies to blood group B (anti-B), which would seem to prohibit ABO-incompatible solid-organ transplantation. However, due to a scarcity of donor organs, especially in patients with blood group O (and therefore preformed antibodies to blood groups A and B), ABO-incompatible solid-organ transplantation is performed. Specifically, this practice is adopted in living donor renal transplantation, liver transplantation, and heart transplantation in children. This practice is rarely performed in adult lung or adult heart transplantation, mainly due to the lack of a bailout strategy for patients that experience hyperacute rejection and the relative
abundance of ABO compatible organs in this population. TPE is essential to reduce the rate of hyperacute rejection in ABO incompatible transplantation.

This fact was demonstrated in early case reports of successful ABO-incompatible solid-organ transplantation. For example, in the early 1980s a patient with blood group O inadvertently received a kidney transplant from a donor with blood group A. The patient was successfully managed with plasma exchange therapy and had no signs of hyperacute rejection [36]. The current use of TPE and timing of this therapy (preoperative or intraoperative) is dependent on a number of factors, namely treatment center preferences, preoperative strength of blood group anti-A and anti-B antibodies, and the specific blood group antigen [37,38]. That is to say, blood group A antigens actually have various

<table>
<thead>
<tr>
<th>Types of rejection</th>
<th>Manifestation</th>
<th>Treatment options</th>
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<tbody>
<tr>
<td>Hyperacute</td>
<td>Onset is minutes to hours after transplantation. Occurs with recipient presensitization to donor antigens, typically ABO or HLA. Characterized by graft dysfunction with histologic and immunopathologic evidence of infiltrating neutrophils, edema, capillary damage and antibody deposition and complement activation.</td>
<td>Initiate treatment immediately, including in operating room</td>
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<tr>
<td>Treatment strategies are broad and target circulating antibodies, B cells and T cells</td>
<td>High-dose IV corticosteroids</td>
<td>TPE</td>
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<tr>
<td>IVIG</td>
<td>Cytoytic therapy (e.g. ATG)</td>
<td>IV calcineurin inhibitors (e.g. tacrolimus)</td>
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<tr>
<td>Acute Antibody Mediated</td>
<td>Onset can be at any time after transplantation. Characterized by capillary damage and evidence of antibody deposition and complement activation (e.g. positive C4d staining in capillaries). There can also be serologic evidence of donor-specific antibodies.</td>
<td>Can be refractory to standard therapy</td>
</tr>
<tr>
<td>Treatment options:</td>
<td>High-dose IV corticosteroids</td>
<td>TPE</td>
</tr>
<tr>
<td>IVIG</td>
<td>Cytoytic therapy (e.g. ATG)</td>
<td>Alter baseline immunosuppression</td>
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<tr>
<td>Chronic Antibody Mediated</td>
<td>Onset is months to years after transplantation. Characterized by intimal thickening of arteries. In cardiac allografts this leads to a specific form of coronary vasculopathy. In renal allografts, a similar process occurs and can also see an associated glomerulopathy.</td>
<td>Chronic antibody mediated rejection can occur without overt clinical symptoms and treatment for this condition is under investigation</td>
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<td>Symptomatic forms are typically treated similar to acute antibody mediated rejection (see above)</td>
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<tr>
<td>Acute and Chronic Cellular</td>
<td>Onset for acute is days to year after transplantation, chronic is months to years. Characterized by graft dysfunction and disorder is related to T-cell activity against the allograft. Biopsies typically show an inflammatory infiltrate (typically lymphocytes) with various degrees of parenchymal damage.</td>
<td>Corticosteroids are cornerstone of therapy</td>
</tr>
<tr>
<td>Treatment options for asymptomatic chronic rejection are under investigation</td>
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ATG, antithymocyte globulin; C4d, complement component 4d; HLA, human leukocyte antigens; IV, intravenous; IVIG, intravenous immunoglobulin, TPE, therapeutic plasma exchange. TPE is a cornerstone for acute antibody mediated and hyperacute (presumed antibody mediated) rejection episodes and contributes to a multimodal approach to remove antibodies then suppress antibody formation while simultaneously dampening both innate and adaptive immune responses to the threatened organ.
subtypes: A₁, A₂, etc, and each is associated with variable amounts of A antigen and, therefore, success with ABO-incompatible solid-organ transplantation. The specifics of this are beyond the scope of this review but it is worth highlighting that no randomized controlled trials have been performed to evaluate these protocols. Examples of TPE protocols utilized at our center are detailed in Table 1. Similar TPE and immunosuppression schedules are followed for the treatment of hyperacute rejection due to HLA incompatibility and the planned regimen for the prevention of rejection in the setting of a highly HLA alloimmunized recipient. These regimens are often modified, as the IgM ABO antibodies are easier to clear than IgG anti-HLA antibodies.

**CONCLUSION**

TPE has historically been used as rescue therapy for antibody-mediated disease processes [44] and, although few randomized studies exist, prospective study is increasingly positive [45]. The treatment of TTP and antibody-mediated rejection [46] remain the most common perioperative applications of TPE, although in the critical care setting, its use in the management of autoimmune diseases [47,48], neurological conditions [3*], burns [50] and poisoning [51] may be increasingly encountered. Certainly, the increasing complexity of transplantation practices in terms of prior alloimmunization (following multiple transfusions and/or Left Ventricular Assist Device bridge to transplantation), retransplantation and intentional ABO-incompatible transplantation will require perioperative physicians to be familiar with TPE.

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**Conflicts of interest**

I.J.W. is the PI for an Investigator Initiated Trial of High-yield Plateletpheresis during Cardiac Surgery sponsored by Terumo BCT, who also manufacture a plasmapheresis device.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as: & of special interest & of outstanding interest


**THROMBOTIC THROMBOCYTOPENIC PURPURA AFTER TRANSPLANT**

Calcineurin inhibitors are a ubiquitous immunosuppressive therapy for patients with a solid-organ transplant. An important side-effect of both cyclosporine and tacrolimus (FK506) is an association with TTP [39]. TPE was found to be superior to plasma infusion in a clinical trial many years ago [40]. However, patients with drug-associated TTP were not the focus of this trial. In fact, therapies for patients for calcineurin-associated TTP are largely unstudied. General recommendations are to stop the offending drug immediately, institute TPE and use an alternative immunosuppressant [41,42]. The TPE schedule used will be similar to that outlined in Table 1 but without the use of intravenous immunoglobulin and up to 7 days of therapy to effectively clear IgG antibodies. Remission is common and mixed isotype, high titre IgA or IgG antibodies are associated with remission; close surveillance follow-up is essential [43].


40. The expert guidelines for evidence-based application of TPE, albeit with minimal emphasis on the perioperative period.


44. A well-constructed meta-analysis describes the national application of TPE for one of the best studied indications.