\*The intent of this product is to be a resource, not a replacement for institutional protocols. Standard 1 of AmSECT’s Standards and Guidelines for Perfusion Practice.1 These Standards and Guidelines may also be superseded by the judgment of the healthcare professional considering the facts and circumstances of the individual case.

**SUBJECT/TITLE: Therapeutic Plasma Exchange (TPE) During Cardiopulmonary Bypass
 (CPB)**

**PURPOSE:**

To provide a guideline and resource for treating highly sensitized anti-HLA antibody donor recipients to decrease the risk of allograft failure via hyperacute or accelerated antibody-mediated rejection (AMR) after reperfusion of the transplanted heart.2

**TARGET POPULATION:**

Highly sensitized patients with naturally occurring anti-ABO antibodies or acquired antibodies to HLA2:

1. Those supported with cardiac assist devices
2. Multiparous women
3. Individuals with a previous allograft transplant
4. Recipients of numerous homologous blood products.

**DEFINITIONS:**

1. Apheresis: a cell processing and cell collection platform utilizing continuous-flow centrifugation and optical detection technology to perform a wide variety of apheresis procedures.
2. TPE during CPB: A process where plasma is removed from the patient’s circulating blood volume via centrifugal fractionation through an apheresis circuit in parallel with the CPB circuit. The remaining components, mostly red blood cells, are returned to the patient with either albumin, plasma, or both.
3. Circulating Blood Volume = CBV (measured in mL)
4. Heart Lung Machine = HLM
5. Panel Reactive Antibody = PRA assay
6. % Plasma Volume Calculation: 1-Hct (%) = plasma volume (%)
7. Plasma Volume Exchange Calculation: (Plasma volume (%) x CBV (mL)) + HLM prime volume (mL)
8. Calculated Total Blood Volume (TBV): TBV (mL) = patient CBV (mL) + HLM prime volume (mL)

**IMPORTANT LIMITATIONS OF THIS DOCUMENT:**

1. In emergency situations, immediate life support measures of whatever appropriate nature come first with attention turning to measures described in this protocol/process as soon as possible and practical.
2. The judgement of the healthcare professional, taking into account all of the patient’s circumstances, should always take precedence over these protocols.
3. This protocol/process encourages high quality patient care but observing it cannot guarantee any specific patient outcome.
4. AmSECT reserves the right, but not the duty, to update this protocol from time to time.
5. Review period: Review as changes occur or per institutional protocol.
6. Original hard copies and computer copies of this protocol are stored under the supervision of the Chief Perfusionist, Department of Cardiovascular Perfusion.
7. Documents relating to patient care standards are developed according to the accepted hospital standards.

 **POLICY:**

1. During any solid organ transplant necessitating full CPB in highly sensitized recipients, plasmapheresis may be necessary.
2. Anti-HLA antibodies are associated with an increased risk of allograft failure and morbidity and mortality.3
3. AMR occurs in up to 18% of heart transplant recipients.3
4. The immediate concern with highly sensitized patients is the potential for hyperacute or accelerated AMR after reperfusion of the transplanted heart. The estimated incidence of patients listed for cardiac transplantation who have positive panel reactive antibody assay (PRA) titers is 11-15%.2
5. AMR can be caused by naturally occurring anti-ABO antibodies or acquired antibodies to Human Leukocyte Antigens (HLA), as measured by PRA.3
6. Coupling plasmapheresis with CPB provides a means to remove cytotoxic antibodies in the PRA positive patient and provides for a high-flow exchange when it would not otherwise be possible in hemodynamically unstable patients.2
7. TPE is used peri-operatively to prevent AMR in pre-sensitized organ transplant recipients by centrifugal fractionation and removal of patient’s plasma and replacement with equal volumes of homologous fresh frozen plasma (FFP).3
8. Plasmapheresis can remove 90% of circulating antibodies.4

**PERFUSION PUMP CONSIDERATIONS: See Procedure**

**APHERESIS PROCEDURE: See Appendix**

**PERFUSION PROCEDURE**

1. Heart Lung Machine Circuit Modifications:
	1. For apheresis circuitry ‘INLET’ connection from CPB circuit: Insert size-appropriate straight connector with luer lock (LL) proximal to the inlet of the hard-shell venous reservoir (HSVR). Note: Place LL facing downward to prevent air entrainment from the venous line into the apheresis circuit. Place a stopcock on LL and turn off to the circuit.
	2. For apheresis circuitry ‘OUTLET’ connection to CPB circuit: Place a stopcock to an available HSVR cardiotomy lured suction port and turn the stopcock off to the HSVR.
2. Notify the plasmapheresis team at least 30 minutes prior to procedure.
3. Prior to initiating bypass/plasmapheresis verify with apheresis clinician:
	1. The total estimated plasmapheresis time (average time is approximately 90 minutes: 60 minutes for neonates and infants, 120 minutes for adults)
	2. The total calculated plasma volume to be removed during plasmapheresis.
4. Initiate CPB in the usual manner.
5. Plasmapheresis will begin at the perfusionist’s instruction after at least 10 minutes of stable, full-flow CPB has been achieved and the post-dilutional Hct has stabilized with current value entered the apheresis device, by:
	1. opening the ‘INLET’ stopcock on the venous HLM line to the apheresis circuit
	2. opening the ‘OUTLET’ stopcock on the HSVR lured port
6. One of the primary concerns and side effects of plasmapheresis during CPB is removal of several drug therapies; including, heparin, anesthetics, steroids, and ionized calcium; therefore, serial activated clotting times (ACT’s), heparin protamine titration (HPT) and arterial blood gases (ABG’s) are run during the entire plasmapheresis period to verify:
	1. Maintenance of adequate systemic heparinization (determined by heparin concentration and/or ACT) according to institutional protocol. Additional heparin boluses may be required during rewarming or ultrafiltration.
		* **See Appendix for additional guidelines for Heparin Dosing**
	2. Adequate ionized calcium levels (maintain > 0.80 mmol/L during bypass)
		* **See Appendix for additional guidelines for Calcium Dosing**
	3. Hematocrit (Hct) values for the apheresis clinician to program into the apheresis device:
		* Note: Accurate Hct values are very important to establish an ‘INTERFACE’ for how the plasmapheresis device separates the plasma from the blood. If the Hct becomes inaccurate during plasmapheresis, RBC’s will spill over into the waste, which would be visible to the technician. For example, a Hct value of 30% is programmed into the apheresis device during the initial setup procedure. This value needs to be changed to the actual post-dilutional Hct of the patient after full CPB is achieved. Hct values should be rechecked within 2 minutes after any PRBC transfusion to program into the apheresis device.
7. While the PRA assay cannot be done on a stat basis to verify an appropriate decrease in circulating cytotoxic antibodies prior to cross clamp removal, the goal is to complete pheresis prior to removal of the cross clamp and reperfusion of the transplanted heart.
8. At the end of the intraoperative plasmapheresis period, request the following from the apheresis clinician:
	1. Return any unused units of FFP to the primary perfusionist for transfusion to the HLM PRN.
	2. Flush the apheresis circuit volume into the HLM before disconnecting from the HLM circuit.
	3. Verify the total apheresis circuit volume (mL) to be flushed into the HLM circuit for adequate Input/Output (I/O) documentation on the perfusion record.

**CLINICAL ASSESSMENT/SCREENING:**

1. None

**RELATED DOCUMENTS:**

1. None

**REFERENCES:**

1. American Society of ExtraCorporeal Technology Standards and Guidelines for Perfusion Practice (May 23, 2017).
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4. Robinson JA, Radvany RM, Mullen MG, et al. Plasmapheresis followed by intravenous immunoglobulin in pre-sensitized patients awaiting thoracic organ transplantation. Therap Apheresis. 1997;1:147-51.
5. Despotis GJ, Summerfield AL, Joist JH, et al. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg. 1994 Dec; 108(6): 1076-82.
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**APPROVED BY:** *(signature of CMO and CNE only required)*

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**APPENDIX**

APHERESIS PROCEDURE:

1. Plasmapheresis has been shown to be efficacious if performed preoperatively as soon as notification of donor acceptance is received:4 A 1.5 plasma volume exchange has been reported as a target exchange for preoperative procedures.4, Larson et al found that that a 3.0 plasma volume exchange during CPB could be performed because of the higher flow rates achieved when connected to the HLM.2
2. Other centers use the following plasma exchange volumes during plasmapheresis on CPB:
	1. Highly sensitized patients receive a 1.5 TBV plasma exchange
	2. Liver pheresis patients receive a 2.0 TBV plasma exchange
	3. ABO incompatible patients receive a 2.5 TBV plasma exchange
3. Citrate anticoagulation is routinely used during plasmapheresis, except in:
	1. Patients with hepatic and renal compromise have limited ability to metabolize and clear citrate, resulting in the potential for citrate toxicity. Each unit of FFP contains 15-18% citrate. Using citrate anticoagulant in addition to the amount of citrate contained in FFP used during plasmapheresis could result in citrate toxicity in these patients.
	2. CPB patients are already systemically anticoagulated with heparin so citrate anticoagulation via the plasmapheresis circuit is unnecessary and would further decrease ionized calcium levels during the plasmapheresis period on CPB.
		1. Since fluid must be connected to the apheresis circuit ‘CITRATE SPIKE’, PlasmalyteTM is substituted when citrate anticoagulation is contraindicated or unnecessary. Systemic heparinization is managed during CPB per established protocol.
	3. Higher plasmapheresis flow rates up to 120-150 mL/min can be achieved when withdrawing directly from the CPB venous line compared to traditional plasmapheresis.2

ANTICOAGULATION MANAGEMENT:

Utilizing the Medtronic HMS system:

The Medtronic Heparin Management System (HMS) Heparin Protamine Titration (HPT)/ACT and blood gases will be run in a serial manner during the entire plasmapheresis period to verify accurate ionized calcium and Hct values for the apheresis team.

* 1. When the HPT/ACT/blood gas is complete, **immediately** treat out-of-range parameters and run the next set of samples during the entire plasmapheresis period.
	2. HPT/ACT values should be kept in normal established ranges during plasmapheresis on CPB (HPT at the Heparin Dose Response projected heparin concentration and ACT > 480 seconds).
	3. Administer additional heparin boluses indicated by the HMS machine when either the HPT or the ACT fall below acceptable levels.
		+ HPT/ACT will decline at a significantly increased rate than usual due to heparin removal from plasmapheresis and ultrafiltration.
		+ The ACT may remain artificially elevated due to cooling, hemodilution and decreased R-value correlation during bypass,5 so the HPT should be followed and closely monitored to maintain adequate anticoagulation.

Without the Medtronic HMS system: If the HMS system is not available to run heparin concentrations, the following anticoagulation protocol can be considered:

1. Systemic heparinization of 500 units/kg
2. Run a heparin infusion of 100 units/kg/hr heparin drip during the entire plasmapheresis period
3. Run serial ACT’s and blood gases during the entire plasmapheresis period to verify accurate ionized calcium and Hct values for the apheresis team. After each ACT and blood gas is completed, immediately treat out-of-range parameters, and run the next set of samples.
4. May need bolus of ~100 units/kg heparin in the CPB circuit during rewarming
5. Ultrafiltration will exacerbate heparin removal during plasmapheresis and should be discontinued during plasmapheresis. Ultrafiltration may be resumed at the end of the plasmapheresis period.

BLOOD GAS AND ELECTROLYTE MANAGEMENT

1. Serial blood gases (Hct and electrolytes) should be run with each HPT/ACT or more often when clinically necessary and share results with the apheresis technician.
	1. Calcium levels will decrease rapidly during the plasmapheresis/cross clamp period, so special attention should be made to maintain protocol calcium levels.
	2. Apheresis IV calcium chloride drip during intraoperative plasmapheresis period:
		1. Calcium supplementation recommendation: have apheresis team maintain ionized calcium levels of 1.0 - 1.1 mmol/L through their circuit by maintaining a standard calcium drip rate. The perfusionist will need to bolus additional PRN calcium into the bypass circuit per normal routine or as described below.
		2. Calcium gluconate Calcium gluconate can exacerbate acidosis, so acidotic patients are supplemented with calcium chloride.
	3. Perfusionist PRN calcium chloride bolus technique: the following calcium supplementation technique is considered off-label use for extracorporeal support. The use of this technique must be authorized by the operating surgeon and utilized following institutional protocol.
		1. Ionized calcium levels typically need to be supplemented 0.1 to 0.2 mmol/L by the perfusionist to maintain levels > 0.8 mmol/L during TPE on CPB. PRN boluses by the perfusionist into the bypass circuit will have a more immediate systemic effect than manipulating the plasmapheresis circuit calcium chloride drip-rates between each serial ABG.
		2. For patients ≤ 35 to 40 kg, 10 mg calcium chloride per kg body weight will increase ionized calcium levels by approximately 0.1mmol/L:
			1. Administer 10mg/kg boluses at a time and
			2. Maintain calcium levels during the plasmapheresis period so you do not need to supplement the calcium concentration > 0.3 mmol/L at any one time.

EXAMPLE: To increase a 5.0 kg child’s ionized calcium level from 1.0 to 1.2 mmol/L, two doses of 50 mg (10 x 5 kg) calcium chloride would be administered, with a repeat ABG verification performed immediately (i.e., serially) during the plasmapheresis period, as described above:

1st dose: 10 mg x 5 kg = 50 mg will increase iCa from 1.0 to approx 1.1 mmol/L

2nd dose: 10 mg x 5 kg = 50 mg will increase iCa from 1.1 to approx 1.2 mmol/L

For patients > 35 to 40 kg, a smaller calcium dose per kg body weight may be sufficient. For these patients, verify ionized calcium levels after each 300-500 mg bolus of calcium chloride.