

GUIDE FOR HEART FAILURE TRANSFUSION MEDICINE SUPPORT
(Coagulation-based Hemotherapy) – Rev 12/16/2014
University of Texas-Medical School in Houston

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Main Focus of Coagulation-based Hemotherapy (CBH):

- (a) Intra-operative coagulation monitor of all LVAD/BiVAD/OHT/TAH cases or any cardiac surgery cases with significantly high risks for immediate transfusion if needed
- (b) Consultation for unexpected acute bleeding during any cardiac surgeries or in post-op period
- (c) Consultation for any significant coagulopathy or risk of coagulopathy

The general description of CBH service by University of Texas-Houston Medical School, Department of Pathology and Laboratory Medicine is outlined in references [117-133]. The information in this guide contains many clinical protocols, most of which are for background information for CBH trainees in dealing with patients and not carried out by CBH service. Protocols used by CBH service in routine practices are emphasized in the associated texts.

I. LVAD Cases-Preoperative and Operative

-Information on LVAD case (name / MRN and date/time of surgery) is notified to the hemotherapy pathologist on service by the LVAD coordinator (either verbally or by e-mail). The pathologist will notify Blood Bank if that has not been done already.

-Pathologist to review patient's history prior to surgery: medications (anticoagulants, anti-platelet meds) and date of discontinuation prior to surgery (see Appendix C), renal disease, liver disease, pre-op coagulation results. Pre-op tests typically include: PT/PTT, Fibrinogen, platelet aggregation study, CBC, Cr/BUN, Liver Function Test panel, T/S, and all other appropriate admission tests (ordered by admitting physician). If pre-op coagulation tests show abnormal results, further test ordering with interpretation by Pathology and communication with LVAD team would be needed. Examples of further coagulation tests include: PT/PTT mixing study, Thrombin Time, Anti-Xa, specific factor assays and inhibitors, lupus anticoagulant, etc. Platelet aggregation study data are typically available in AM before surgery without full interpretation. The special coag lab (713-704-1693) can be contacted for preliminary results.

-Patients with HIT antibody may need urgent TPE prior to surgery so that UFH can be used in CPB (Appendix D9).

-If a current T/S result is not available, a STAT sample needs to be sent to Blood Bank (pink-top tube, alternately a purple-top tube). A type and screen specimen is good for 3 days. It is good until 12midnight on the third day. Note that the date of collection is day 0. For example, if a specimen is collected on Monday red blood cells cross-matched using that specimen may be transfused until midnight on Thursday.

-Since many patients have a long-term treatment history, check to see if the patient has RBC antibodies, crossmatch compatibility, transfusion history, Rh status (potential to receive Rh-positive platelets), as well as indications to receive special blood products, such as Hgb S-neg, fresh blood components, Rh/K-matched, washed, etc. If the patient requires special components, pay close attention while in the OR to the product usage and inform the blood bank as soon as possible for additional needs.

-If a current T/S result is not available and blood components are urgently needed: ask the nurse to collect sample immediately (in pink-top tube), put a special yellow tag on the request (indicating urgent situation) and tube it immediately to the central lab for T/C. The yellow tag protocol has been available for some time in MHH but not well utilized. Request with yellow

tags will be processed manually and immediately by blood bank. Sending request to HVI lab also delays the order since HVI lab does not do T/C and will divert the sample to central lab which takes more time.

-For LVAD cases, Blood Bank typically cross-matches 10 RBC, 10 FFP, 6 pheresis plts. For patients with antibodies against RBC antigens, 20 RBCs will be cross-matched. For re-do (resternotomy) and patients on anticoagulation or anti-platelet medication case (other than UFH and ASA, respectively), 20 RBC, 20 FFP, 8 pheresis plts will be prepared. Initial set of blood components to be brought to OR at the start of surgery include: 10 RBC, 10 FFP, 2 pheresis plts (all in iced igloo except platelets). Once half of the blood components has been transfused, an additional set will be ordered by OR physicians and brought to OR if further transfusion is anticipated. The second set of blood components can be brought in less than 10 minutes. Platelets can also be held in HVI Blood Bank until just prior to off-pump time.

-Pathologist to give 3 sets of collection tubes to anesthesia before surgery starts. Each set in a bag including 2 blue-top (labeled 1 and 2), 2 Greiner Bio-One (labeled 3 and 4, to be half-filled), and 1 purple-top (labeled 5). They are to be drawn in sequence from 1 through 5 due to strict collection sequence requirement. 18 gage needle would be best to inject sample to tubes. Two 10 cc syringes would be adequate to get enough blood for 5 tubes (or one 10 cc syringe for 3 tubes in selected cases). Note that Greiner tube cannot be the first drawn tube and the tube proceeding to the Greiner tube cannot be a purple-top.

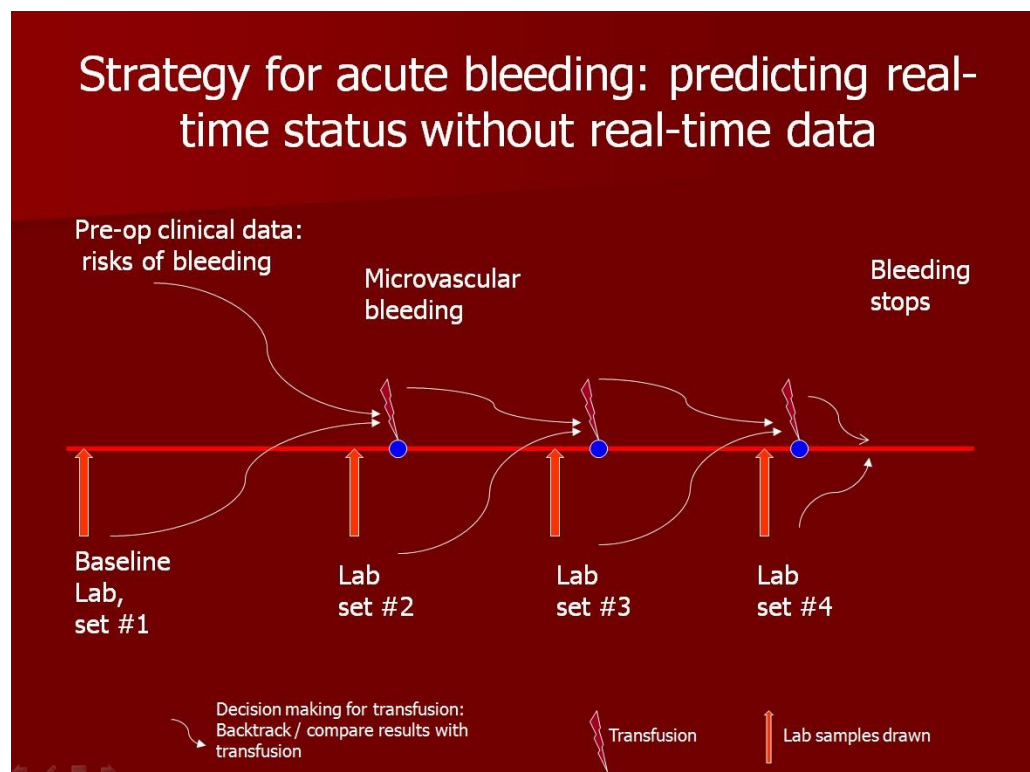
-Tests in HVI Lab include: TEG, hTEG (TEG with heparinase), CBC, DIC screen (PT/PTT/Fibrinogen/TT/ D-Dimer), VFN-P (VerifyNow-P2Y12 for patients on Plavix, called "Plavix Effect Platelet" in EMR), or VFN-A (VerifyNow-ASA for patient on ASA, called "Aspirin Effect Platelet" in EMR). AT needs to be sent STAT to central coag lab since it is not available in HVI lab (low demand). When we need AT during surgery, the sample can be picked up by a technologist from central lab to do it. If the case is scheduled before hand, it is best to do the test the day before surgery. Refer to Table 1 for suggested sets of tests to be used for each phase of surgery. Rapidly-changing clinical situation may dictate different sets of tests based on Pathologist's judgment.

-After induction of anesthesia, anesthesia physician helps to collect blood (1st set) for baseline tests to be done in HVI lab. The tubes should have patient label and initials of drawing personnel. OR courier will get samples from OR to HVI lab. Pathologists/residents may also take samples directly from Anesthesia for processing if needed. HVI lab will log in receiving time for each sample, run tests, call results to OR or give it to pathologist on-site (technologists can release results later). TEG is to run 10 min after blood collection, VerifyNow-P 15 mins, VFN-A 30 mins. TEG/hTEG results are read as soon as R is available. Note that baseline tests may not be needed if patient is stable and all pre-op lab tests are already available. Patient's body temperature is typically let "drifted down" with CPB, but not put into hypothermic state (defined as body core temperature <28 degree C or 82.4 degree F).

-The second set of tests is at rewarming/after hemoconcentration (just prior to off-pump). Samples can be drawn from the CPB pump line since this would be more convenient for this set. This set is the most critical since its results dictate what components (and how many units) to transfuse to patient after off-pump. Heparin causes PT to be slightly more prolonged but its value can still be used to base FFP transfusion on. Patients often develop microvascular bleeding after CPB with various abnormalities in coagulation parameters (see Appendix O).

-The third set of tests is right after off-pump (10 mins after protamine for heparin reversal) and before any blood components are given. This off-pump set may be skipped if the patient is at low risk for bleeding, no evidence of microvascular bleeding during surgery, and intra-operative test results have been stable. However, if patient develops bleeding during off-pump, samples would need to be drawn immediately.

Fig. 1 Strategy for management of acute bleeding



-Pathologists will be in HVI Lab/OR vicinity to select appropriate lab tests (order tests on HVI test order form, see Fig. 3) and review lab results with recommendations for transfusion as needed. Communication with anesthesia can be in person in OR or on phone (704-0811). Pathologists also assure that appropriate blood components are available in OR by predicting blood usage based on lab results, especially important for platelets and cryoprecipitate. Note that thawing cryo before use takes about 15-20 mins. Cryo needs to be kept at room temperature.

-Notify the anesthesiology attending physician (NOT other clinicians) in the OR for any modification/deviation made from the standard practice that may have a potential to compromise the patient's care in urgent situation, such as switching RBC from Rh negative to Rh positive, switching from the crossmatched-compatible units to emergent uncrossmatched units. The potential complications should be notified and management strategy should also be given as well.

-If consultation is requested when patient is already in OR with bleeding (emergency surgery or unexpected coagulopathy in a planned surgery), follow the following steps: (a) Obtain clinical information from OR team and EMR, knowing how many and type of blood components that

have been and being transfused, (b) Establish a new baseline for coag results, then (c) manage coagulopathy using available data.

-If only CBC with platelet and DIC panel are needed for certain blood draw, use only 1 blue top and 1 purple top instead of having to use all tubes in the Ziploc package.

Table 1. Minimum sets of tests for each phase of surgery

	TEG	h-TEG	CBC	DIC screen (PT/PTT/Fib/TT/D-Dimer)	PT/Fib	AT	VFN-A (if pt on ASA)	VFN-P (if pt on Plavix)
1. After anesthesia induction			X	X		*	***	***
2. Just prior to off-pump		**	X		X			
3. After off-pump	**		X	X				
4. As needed for prolonged bleeding	**		X	X				

* In case of heparin resistance; ** optional; ***not needed if preop platelet aggregation test has been done

- Since patient needs to be hypocoagulable during CPB, transfusion of blood components while patient on-pump and without bleeding is typically not necessary unless certain coagulation parameter is critical (for example, Plt < 20 k). One exception is RBCs which are transfused throughout CPB to keep Hgb to the range 8-10 (around 10 just before off-pump). Perfusionists monitor Hgb with POC instruments in the OR and transfuse RBCs through the pump circuit (typically 4-5 units in a non-complicated case). Occasionally, CV surgeons may ask for FFP to be given through CPB circuit if there is significant microvascular bleeding during surgery.

-Transfusion after heparin reversal (with sign of microvascular bleeding) can be based on the most recent lab results (just prior to off-pump). Adjustment to therapy can be made when off-pump lab results are available later.

-If there is microvascular bleeding after heparin reversal (after surgical bleeding has been ruled out), use the following transfusion algorithm for recommendations (also see details in Appendix A1):

1. Use more protamine to neutralize excess heparin:

If (PTT > 45) and (TT>25) -> protamine (50 mg/70 kg BW)

2. Platelet transfusion for quantitative or qualitative platelet defect (after excluding primary fibrinolysis):

If (Plt < 100k) or (MA < 45 and EPL<15 and LY30<8) or (VFN-P < 210 PRU) or (VFN-A < 550 ARU) -> Plt transfusion

3. FFP transfusion for clotting factor deficiency:

If (hTEG-R > 10) -> FFP transfusion

If (20 < PT) or (45 < PTT) -> FFP transfusion (consider PCC after significant FFP transfusion)

4. Cryo for fibrinogen deficiency and chronic renal failure:

If (150< Fibrinogen < 200) or (20 < Alpha < 45 with normal MA) -> FFP transfusion

If (Fibrinogen < 150) or (Alpha < 20 with normal MA) -> Cryo transfusion

If patient has chronic renal failure (uremia with BUN of at least 45), and active bleeding with normal coag results-> Cryo transfusion

5. Use Tranexamic acid for primary fibrinolysis (after excluding secondary fibrinolysis):

If (EPL>15% or LY30 > 8%) and (MA < 50 or CI < 1.0) -> Tranexamic acid

If (Fibrinogen < 150) and (D-Dimer > 10) -> Tranexamic acid

6. FFP transfusion for significant AT deficiency causing heparin resistance:

If (AT 35- 50%) -> FFP transfusion

If (AT <35%)-> AT Concentrate

7. Hgb needs to be at least at 10 immediately post-op (off-pump); also compensate for dilution due to FFP and platelet transfusions

8. Artifacts due to protamine overdose for off-pump panel only:

If (hTEG-R >20 and h-Alpha < 20 and h-MA < 35)

-> consider artifacts due to protamine overdose if patient is not bleeding

-Repeat test panel about 30 mins to 1 hour after treatment for subsequent review and recommendation. Make sure that samples are drawn prior to any subsequent transfusion to establish adequate baseline for adjustment of treatment later (see Fig. 1).

-In emergency bleeding (off-pump) without adequate laboratory data -> start with 2 units of apheresis platelets first. Review off-pump results later and adjust treatment.

9. For bleeding not responding to treatment -> consider rFVIIa (15 µg/kg BW, or 1 vial of 1 mg for 70 kg BW) with the following constraints:

- If (EPL>15% or Ly30 > 8%) and (MA > 70 or CI >3.0)-> rFVIIa is contraindicated (DIC with secondary fibrinolysis)
- If (Fibrinogen < 200) or (Alpha < 45 with normal MA) -> Cryo transfusion then give rFVIIa (through different lines)

Consult with surgery and anesthesia to assure that everyone agrees on the use of rFVIIa before calling Pharmacy at 704-0623. Be sure to document this consensus in consultation note. Note that up to 3 initial rFVIIa doses, each of 15mcg/kg (rounded to nearest 1mg vial) for LVAD cases do not require approval for OR use. Further request would need approval from Dr. M. Escobar or designees (to be contacted by Pharmacy).

- Patient's hemostasis needs to be followed up after surgery for at least 24 hours after surgery. Acute post-op bleeding, if occurs, is typically within 4-6 hours after surgery. Therefore, close monitor of patient's parameters would be critical during that period, especially for high-risk patients (such as patients who bleed excessively during surgery, those on CPB more than 2.5 hours, etc.). Parameters to follow include: DIC panel, CBC with plt, amount of chest tube output. Risk of post-op bleeding may be predicted using intra-operative coag results (see Appendix I, and Fig. 8). If significant bleeding persists, follow the workup steps outlined in section II ("Post-operative") to manage the patient. Decisions for transfusion need to be discussed and coordinated with patient's attending.

-Other detailed information for activities in OR are documented in the following documents

(a) Perfusionist notes: including pump time (on, off, total time), clamp time (on, off, total time).

This hand-written note is inserted in "OR" folder of patient chart

(b) Anesthesia note: including blood component transfusion units (under "Fluids"). This hand-written note is inserted in "OR" folder of patient chart

(c) Nursing post-operative note: including OR time (in/out), surgery time (begin/stop), names of surgeons, anesthesiologists. This note is in EMR under "Clinical notes"

Heartware LVAD or "HVAD"

A more recent "off-pump" LVAD implantation technique using a smaller LVAD, Heartware LVAD or "HVAD", using centrifugal pump as contrast to axial pump in HeartMate II. Heartware is placed close to the heart, in the pericardial sac. Sternotomy (or thoracotomy) is with smaller size and patients are on IV heparin with targeted ACT around 300 sec (PTT around 160 sec) with no CPB used. Lower dose of heparin is used (1 mg/kg or 100 U/kg) compared to that used in HeartMate II (3mg/kg or 300 U/kg). The procedure often takes only about 2 hrs, typically less than 500 cc blood loss, and patients need very few blood units. Pathologists will get baseline testing and stand by; with the intention that if patient needs to be on pump (or develops microvascular bleeding) the regular protocol would need to be followed. Success of off-pump HVAD is patient-dependent and has to be tried in OR to see if this technique is feasible. Severe heart failure patient may not tolerate cardiac manipulation and the surgeon will have to revert to the regular on-pump technique. All the perfusionists stand by in the OR just in case that happens. Note that Heartware is only FDA-approved for bridge-to-transplant (BTT) but not for destination therapy (DT) as of 2014. HeartMate II has been approved for both purposes.

Total Artificial Heart (TAH) or Syncardia™

For TAH cases CBH activities are similar to those for LVAD cases. Some emergent TAH implantation case may be initiated in OR without being previously scheduled, and pathologists may be notified when the case is in progress. In post-op period, antiplatelet medications and anticoagulants are of significant importance (see Appendix D.8 for details).

II. Post-operative bleeding

Patients who undergo CV surgeries may have high risks of post-op bleeding due to the following factors: long pump time due to complicated surgeries, redo (resternotomy due to previous CV surgery), renal disease, liver disease, residual anticoagulant/antiplatelet medications, obesity (risk of heparin rebound), and massive transfusion in surgery causing RV failure. Cardiac tamponade due to bleeding in thoracic cavity can impair cardiac function (including TAH with compression of pulmonary vessels) and the resulting stasis can lead to increasing chest tube output.

Mortality of acute blood loss requiring massive transfusion is high. Severe coagulopathy is associated with a less favorable outcome that is statistically significant when late mortality is included. This late mortality was almost always caused by multiorgan failure secondary to prolonged hypotension and hypoperfusion of major organs at the time of the acute event. The aetiology of coagulopathy is probably multifactorial. As any episode progresses, dilutional effects are difficult to differentiate from those associated with disseminated intravascular coagulation (DIC) [90]. DIC may be triggered by hypoperfusion-induced tissue hypoxia or endotoxin release from either necrotic tissues or transfused products. The fact that many patients involved in massive transfusion incidents develop severe coagulopathy may reflect not only the underlying aetiology and the severity of the haemorrhage, but also a failure to adequately replace coagulation factors. **Our key strategy for treatment for massive hemorrhage: timely blood component transfusion to normalize coag parameters using real-time STAT lab data for rapid transfusion.**

In the post-operative period in the cardiovascular intensive care setting (HVI 8th floor or 5th floor), a standard post-op order by surgeon would look like this: MD to nurse order: if output from one CT > 150 mL, send for CBC and platelet count, DIC screen, call cardiologists, surgeon, and hemotherapy. When there is significant microvascular bleeding (defined as 150-200 cc/hr or more from chest tube drain for several hours without obvious clinical evidence of surgical bleeding), the patient's attending (cardiologist, or surgeon) would request for hemotherapy consultation via the blood bank (713-704-3640), or call the hemotherapy pathologist directly. If the request is received by Blood Bank, technologists would obtain the contact information from the requesting clinicians. The pathologists on call (for hemotherapy consultation) will be notified. The pathologist will obtain clinical information from this contact. The ICU nurse who takes care of the patient can be contacted through the charge nurse (8th floor: 713-704-1077; 5th floor: 713-704-3160) for information on the most recent coag results, most recent transfusion, and current transfusion. Further detailed clinical information is also available from EMR. Transfusion is delegated to Hemotherapy Service, and the pathologist will order blood components as dictated by the laboratory results and clinical findings. Cases with significant bleeding typically need on-site presence of pathologists. Issues related to transfusion need to be discussed with the patient's attending (surgeon in the immediate perioperative period, or cardiologist otherwise). Igloos containing blood components left over from surgery are typically taken to patient's ICU room for potential use. Check with patient's nurse to see if there are enough units to transfuse, otherwise order more from HVI Blood Bank.

For significant bleeding without baseline:

- Order STAT baseline CBC & Plt count, DIC panel
- Start transfusion with RBC, FFP, and plt using the table below based on blood loss
- When results are available (in about 30 min), adjust transfusion component type/dose

-If CT output is significant, the following rules-of-thumb can be used to replace blood loss: for every 500 cc of CT output, give 1 RBC, 0.5 FFP, and 0.2 Platelet (using 1/0.5/1 ratio, i.e. 1 RBC/0.5 FFP/1 random-donor Plt, with rounding)

Blood Loss (CT output), cc	RBC (units)	FFP (units)	Plt (apheresis units)	Total blood component volume**, cc
500	1			300
1,000	2	1		850
1,500	3	1		1,150
2,000	4	2	1	2,000

** 1 RBC 300 cc, 1 FFP 250 cc, 1 Plt 300 cc

For example 2,000 cc blood loss would need 4 RBCs, 2 FFP and 1 Plt for replacement. Any further correction for coagulopathy would require additional blood components (more plts for thrombocytopenia, for example). A new baseline set off lab results would be useful for this purpose.

- Additional sets of tests may need to be ordered to evaluate treatment.
- Hct can also be done in patient's room by the nurse with Gem Premier Instrument which also runs blood gases.
- Order all labs STAT for patients in HVI pavilion in order for tests to run in HVI laboratory. Routine orders are routed to central lab which takes much longer.
- Once coagulation parameters have been almost restored, acute bleeding should subside. If bleeding continues or gets worse in this situation, consider anatomical etiology (surgical bleeding such as due to anastomosis leakage) and discuss with CV surgeons. CV surgeons are typically informed by patient's nurse in significant bleeding situation and usually stand by for possible emergency re-operation. Even if bleeding is caused by a surgical source, normalizing coagulation parameters is helpful to prepare patient for emergently exploratory open-chest surgery.
- For bleeding patients with elevated INR, after transfusion of multiple FFP units (typically defined as 4 or more), if INR still elevated (with adequate platelet count/function and fibrinogen) [94], instead of transfusing more FFP, use KCentra to avoid volume overload. Refer to Appendix A3 for details.
- If CT output is more than 1,000 cc/hr, and not alleviated after significant transfusion, rFVIIa would be considered. Be aware of complications due to the use of rFVIIa and its limitation in patients' outcome [90], also 11% rate of thrombotic complications. Refer to Appendix A3 for details.
- Once bleeding has improved (less than 150 cc/hr with decreasing trend), usually no further treatment would be needed. Another set of lab tests can be ordered in 2 hours with instructions for patient's nurse to call pathologists if bleeding worsens or lab results are critical.
- Less than 150 cc/hr is the targeted level for acute bleeding. Chest tubes can be removed once drain is less than 30-50 cc/hr. Anticoagulant then can be started.
- Without acute bleeding in post-op period, the following are typical threshold for transfusion: Hgb <8, Fibrinogen < 150, Plt < 50 k. Standing orders for transfusion can be ordered to direct transfusion (see Appendix P.3 for patients who are transfusion-dependent)..
- Hemotherapy consult is also requested for acute bleeding in non-post-op patients, typically on HVI 5th floor or 8th floor.

On rare occasions of massive bleeding cases, the hemotherapy pathologists may facilitate timely management by:

- Immediately get 2 blue-tops and 1 purple-top of samples from the nurse, put on patient labels with initials, and take them to HVI lab to order coag tests using the HVI lab order sheet (Figure 3).
- Using available lab results to order blood components on the Blood Bank Pickup slip (green slip, see Fig. 2) with patient's label and patient's arm band red sticker (or written number of the red sticker on the Pickup slip). Blood components can be taken immediately to patient's room for transfusion. Order blood transfusion in EMR.

Fig. 2 Blood Bank Pickup slip

MEMORIAL HERMANN
Blood Bank Pick-up
Blood Bank and Transfusion Service
Memorial Hermann Hospital
Houston, Texas

Pt. Location (Floor/Room #): _____ Ext: _____

Component	Number
Red Blood Cells	_____
Whole Blood	_____
Fresh Frozen Plasma	_____
Platelet Dose	_____
Cryoprecipitate Dose	_____
Rh Immune Globulin	_____
Autologous/Designated	Yes / No
Dialysis/Surg. at Bedside	Yes / No

REQUIRED INFORMATION:
Pneumatic Tube Station #: _____

Person Requesting/Picking Up Blood:
(Please Print) _____

EMERGENCY RELEASE
In consideration of the critical condition of this patient, I request the immediate release of blood/blood components for transfusion without compatibility testing.

PHYSICIAN OR PERSON AUTHORIZED BY PHYSICIAN
Signature Required for Emergency Release/Notify Blood Bank Immediately

431822 3/08

To obtain arm band number on PathNet: go to Blood Bank icon “Patient product inquiry”, enter MRN, click “previous result”, type in “RAB#” then use the most recent arm band number corresponding to most recent T/S results.

To help facilitate checking out blood components from HVI Blood Bank:

- First person reads: patient name, MRN, arm band number from green pickup slip
- Second person matches these (patient name, MRN, arm band number) to those on a slip assigned to each blood unit; then matches blood unit number and expiration date on this slip to blood unit number and expiration date on each blood unit’s attached label.
- Both people sign with initials on a blood release form to be kept in Blood Bank

To help facilitate checking blood components before transfusion (at bedside):

- First person reads: patient name, MRN, arm band number from patient’s arm band
- Second person matches these (patient name, MRN, arm band number) to those on a slip assigned to each blood unit; then matches blood unit number and expiration date on this slip to blood unit number and expiration date on each blood unit’s attached label.
- Both people sign with initials on the left side of the Blood Bank slip.

-To facilitate fast TAT for tests done in central lab (if STAT test is not available in HVI Lab): order tests in EMR or use HVI test order form (Fig. 3), bring samples to the central lab, give the samples to Triage personnel in Specimen Control who will print out an accession number label to put on the tubes and give them to technologists in appropriate testing area.

-Consideration for central venous pressure (CVP) in transfusion: CVP is a good approximation of right atrial pressure, which is a major determinant of right ventricular end diastolic volume. CVP is used as a surrogate for preload. Normal values are 5-10 cm H₂O. Transfusion would

cause volume overload if $CVP > 20$. Transfusion would need to be coordinated with patient's cardiologist in this case. CVP can be decreased by HD (blood volume taken out if patient is on CVVHD, provided that MAP can be kept >60), or giving patient Bumex (diuretic, goal $CVP < 14$), or adjusting vacuum pressure in LVAD/BiVAD (patients on assist devices). Goals are typically set for $<11-13, 15, \text{ or } 20$ depending on cardiac status.

- Consideration for mean arterial pressure (MAP) in transfusion: MAP is the average arterial pressure during a single cardiac cycle. A MAP that is greater than 60 mm Hg is enough to sustain the organs of the average person. MAP is normally between 70 to 110 mm Hg. Note that in post-op period, surgeons may order RBCs (together with FFP and plts to avoid dilutional effect) to keep MAP at desired level. Such transfusions would need to be factored into transfusion to correct coagulopathy. Goals are typically set for MAP >55 or 60 , depending on cardiac status.

Fig. 3 HVI Lab Test Order Form

ROUTINE		TIMED		SPECIMEN COLLECTION		PROVIDE			
PRIORITY		STAT		Date: _____	Time: _____	PATIENT LOCATION AND CONTACT INFORMATION			
Collector/Nurse ID: _____		Ordering Physician - First and Last name		UPIN # _____		ORDERING PHYSICIAN'S INFORMATION			
PANELS				ALPHABETICAL LISTING		MICROBIOLOGY			
<input type="checkbox"/> Acute Hepatitis Panel <input type="checkbox"/> Basic Metabolic Panel <input type="checkbox"/> Comprehensive Metabolic Panel <input type="checkbox"/> Electrolyte Panel <input type="checkbox"/> Hepatic Function Panel <input type="checkbox"/> Lipid Panel <input type="checkbox"/> Renal Function Panel <input type="checkbox"/> ICU SHOCK PANEL - TMC <input type="checkbox"/> DIC SCREEN <input type="checkbox"/> ABG				<input type="checkbox"/> Albumin <input type="checkbox"/> Amylase <input type="checkbox"/> Anion Gap <input type="checkbox"/> BUN <input type="checkbox"/> Calcium, total <input type="checkbox"/> CBC w/Plt & Platelet <input type="checkbox"/> CBC w/Platelet, No Diff <input type="checkbox"/> Cortisol <input type="checkbox"/> Creatinine Serum <input type="checkbox"/> CRP, High Sens. <input type="checkbox"/> D-Dimer, Quant. <input type="checkbox"/> Digoxin <input type="checkbox"/> Dilantin / Phenytoin <input type="checkbox"/> Fentanyl <input type="checkbox"/> Fibrinogen <input type="checkbox"/> FSP <input type="checkbox"/> Gase <input type="checkbox"/> GGT <input type="checkbox"/> Glucose <input type="checkbox"/> HCG Beta <input type="checkbox"/> Hgb A1C <input type="checkbox"/> Hemoglobin / Hematocrit <input type="checkbox"/> Hepatitis B Surface Antigen <input type="checkbox"/> HIV Antibody (HIV-1/2)		<input type="checkbox"/> Iron <input type="checkbox"/> Iron & TIBC <input type="checkbox"/> Lactic Acid <input type="checkbox"/> LDH <input type="checkbox"/> Lipase <input type="checkbox"/> Magnesium <input type="checkbox"/> Phosphorus <input type="checkbox"/> Potassium <input type="checkbox"/> Pre-Albumin <input type="checkbox"/> Pro-BNP <input type="checkbox"/> Protein, Total <input type="checkbox"/> PT / INR <input type="checkbox"/> PTT <input type="checkbox"/> Reticulocyte Count <input type="checkbox"/> SOLUBLE FIBRIN MONOMER <input type="checkbox"/> T3 Uptake <input type="checkbox"/> T3 (Total) <input type="checkbox"/> T4 (Thyroxine) <input type="checkbox"/> T4 Free <input type="checkbox"/> Thrombin Time <input type="checkbox"/> TSH <input type="checkbox"/> Vancomycin level		Specimen Source Required: <input type="checkbox"/> _____ CULTURE: <input type="checkbox"/> _____ BLOOD BANK TESTS: <input type="checkbox"/> ABC & RH <input type="checkbox"/> Antibody Screen <input type="checkbox"/> Direct Antiglobulin Test <input type="checkbox"/> Ili Immune Globulin Workup OTHER: <input type="checkbox"/> _____	
URINE TESTS				DOWNTIME BARCODE LABEL (LAB USE ONLY)		VAD CASE			
<input type="checkbox"/> Creatinine / Protein Ratio-random <input type="checkbox"/> Urinalysis, dipstick <input type="checkbox"/> Urinalysis w/Reflex - Microscopic <input type="checkbox"/> Urinalysis, complete <input type="checkbox"/> Urinalysis w/Reflex to Culture				<input type="checkbox"/> CBC/PLT - WITHOUT DIFF <input type="checkbox"/> DIC SCREEN _____ AT3 <input type="checkbox"/> THROMBIN TIME _____ Fibrinogen <input type="checkbox"/> F.S. MONOMER _____ PT / PTT <input type="checkbox"/> TEG _____ TEG w/ HEPARINASE <input type="checkbox"/> VERIFYNow - ASPIRIN <input type="checkbox"/> VERIFYNow - PLAVIX		<input type="checkbox"/> Iron <input type="checkbox"/> Iron & TIBC <input type="checkbox"/> Lactic Acid <input type="checkbox"/> LDH <input type="checkbox"/> Lipase <input type="checkbox"/> Magnesium <input type="checkbox"/> Phosphorus <input type="checkbox"/> Potassium <input type="checkbox"/> Pre-Albumin <input type="checkbox"/> Pro-BNP <input type="checkbox"/> Protein, Total <input type="checkbox"/> PT / INR <input type="checkbox"/> PTT <input type="checkbox"/> Reticulocyte Count <input type="checkbox"/> SOLUBLE FIBRIN MONOMER <input type="checkbox"/> T3 Uptake <input type="checkbox"/> T3 (Total) <input type="checkbox"/> T4 (Thyroxine) <input type="checkbox"/> T4 Free <input type="checkbox"/> Thrombin Time <input type="checkbox"/> TSH <input type="checkbox"/> Vancomycin level			

III. Heart Transplant Cases-Preoperative and Operative

- Updated list of patients on heart transplant waiting list (United Network for Organ Sharing or UNOS) is sent by e-mail to all hemotherapy pathologists by the Heart Transplant Service coordinator. Information includes patient's transplant priority status, CMV status, and HLA typing (including PRA).
- When a donor heart is available, the Heart Transplant Service coordinator will contact Blood Bank at 704-3640 which in turn pages the Hemotherapy pathologist on-call. Often the coordinator would notify the hemotherapy pathologist directly. When Blood Bank notifies the pathologist of a heart transplant, ask the Blood Bank technologist for the cell phone number of the OHT co-ordinator. The pathologist on-call can contact the co-ordinator and ask him/her when the donor heart has left the harvesting site (this would be an ideal time to come in), also on any update (delay, etc.). Around scheduled surgery time, HVI OR front desk (704-0807) can also be contacted to see whether patient has been in OR yet. The HVI OR front desk typically gives very reliable/accurate timing of the process.
- Pathologists to review patient's history: medications (anticoagulants, anti-platelet meds), renal disease, liver disease, pre-op coagulation results, etc. If coagulation tests show abnormal results, further test ordering with interpretation by Pathology and communication with Heart Transplant team would be needed. Examples of further coagulation tests include: PT/PTT mixing study, Thrombin Time, Anti-Xa, etc. Patients with HIT antibody may need urgent TPE prior to surgery so that UFH can be used in CPB (Appendix D9).
- Patient is typically already in-house (HVI-5th floor or HVI-8th floor). Some may be called to come in for transplant. Admission lab tests, HLA testing (for cross-match with donor, to be done in UT Tissue Typing Lab), blood components (T&C) are ordered by admitting cardiologists.
- Pathologists will be notified by Blood bank of unexpected problems such as (a) blood sample for blood bank workup not received timely for cross-match, (b) unexpected allo-antibodies that may significantly impact getting cross-matched compatible RBC units in a timely manner.
- Result of visualization in donor OR (the recovery surgeon evaluates adequacy of donor heart) is announced. If it is not suitable for transplantation, the transplant is cancelled and every group is informed. If it is suitable, the donor heart is harvested and the recipient is taken to MHH OR. In the donor OR, the process proceeds with cross-clamp (clamping of the vessels going to donor heart), transport of donor heart to MHH OR for transplantation. The time constraint is a maximum of 4 hours between cross-clamping and anastomosis time (connection of the donor heart to recipient's vessels).
- Blood and a lymph node from the donor will also be transported to MHH for HLA cross-match (between donor's and recipient's samples), see Appendix K2 for more details on HLA testing
- For Heart Transplant cases, Blood Bank typically cross-matches 10 RBC, 10 FFP, 4 pheresis or 20 random-donor plts. For redo or patients on anticoagulant/anti-platelet medications, Blood Bank will cross-match 20 RBC, 20 FFP, 8 pheresis or 40 random-donor plts.
- Hemotherapy support is essentially the same as that for LVAD cases (see section I).
- CMV status of patient dictates selection of cellular blood components for transfusion based on the following guidelines:
 - (a) CMV negative patients will receive leukocyte-reduced cellular blood products prior to transplant if transfusion is requested.

(b) During and post transplant surgery CMV-negative cellular blood components will be provided if the patient and the donor are CMV negative, the information is made known to Blood Bank personnel and CMV negative blood products are available.

(c) Leukocyte-reduced cellular blood products will be provided during and post transplant surgery if the donor's CMV status is unknown at the time of transplant.

-“Virtual cross-match” between donor HLA typing and recipient's serum may be done before surgery to predict potential rejection. However, results for the more diagnostic cross-match is not available after surgery. Transplant rejection, diagnosed by cardiac biopsy and a positive cross-match, and may require plasmapheresis/photopheresis, together with other immunosuppressant. For treatment of heart transplant rejection, refer to Appendices K, K2, K3 and L for details.

- Prior to surgery, if the recipient's panel reactive antibody (PRA) is significantly high, plasmapheresis and other treatments may be needed to reduce allosensitization before heart transplant (see Appendix K)

-Since OR schedule for a heart transplant case is unpredictable, patients on transplant waiting list need to have T/S done every 3 days to detect unexpected RBC antibodies which may create problems in blood component procurement at the time of transplantation.

IV. Off-site Hemotherapy Consultation

For simple consultations (such as help to run and interpret coagulation tests for patients in OR or on floors), on-site presence of pathologists may not be needed. The patient's attending (cardiologist, anesthesiologist, or surgeon) would request for hemotherapy consultation via the blood bank (713-704-3640), or HVI Lab (713-704-4371/4374). The pathologists on call (for hemotherapy consultation) will be notified of the consultation and requesting physician. The pathologist will obtain clinical information from this contact.

For patients on floors, the ICU nurse who takes care of the patient can be contacted through the charge nurse (8th floor: 713-704-1077; 5th floor: 713-704-3160) for information on the most recent coag results, most recent transfusion, and current transfusion. Further detailed clinical information is also available from EMR. The pathologist will verbally order STAT laboratory studies through the ICU nurse. Further communication with the requesting physician will be resumed with available lab results for patient management.

For patients in OR, technologists in HVI lab can be asked to bring appropriate tubes to OR for blood collection by anesthesia. Tests can be verbally ordered to the HVI technologists. Further communication with the requesting physician will be resumed with available lab results for patient management (704-0811 for Anesthesia in OR #1).

If there is uncertainty about whether onsite presence of the hemotherapy pathologist is needed, ask the requesting physician directly for a direct answer.

V. Intraoperative Consult for non-LVAD, non-OHT Cases:

For non-LVAD and non-OHT cases with significant risks (for example patients with multiple valve repair/replacement, patient on Plavix), pathologists may be consulted to preop and monitor patients in OR. A scaled-down monitor can be performed with only one set of lab tests (after hemoconcentration). Other sets may be ordered depending on clinical situation. Other activities

are similar to those for LVAD and OHT cases. Only intraoperative note is needed for EMR. Followup note is only needed for significant post-op bleeding.

In some CV surgery cases, ECMO is inserted first and started, followed by off-pump procedure (such as ACB, RVAD). In this case, transfusion is managed by anesthesia. Hemotherapy can stand by for any acute events. Only baseline tests may be needed. Transfusion is typically based on blood loss without other coagulopathy associated with CPB pump. Blood components are typically based on the following: Hct (Gem Premier) -> RBCs needed; FFPs= RBCs, Plts =RBCs/6.

VI. Post-operative anticoagulants and antiplatelet medications

Post-operative anticoagulants and antiplatelet medications are typically initiated by Cardiology team after adequate hemostasis has been achieved. See Appendixes D through G3.

Exception are the following:

- Antiplatelet medications which are to be ordered and monitored for Total Artificial Heart patients (Appendix D8).
- If hemotherapy is consulted to manage difficult anticoagulant problems (for example Appendix P1 & P6 & P8).

Note that many surgery patients may still have the chest open due to coagulopathy. Patients typically have sternal closure on POD #1. In such cases, antiplatelet medications can still be resumed on POD #1 but anticoagulants should be on hold until after sternal closure with adequate hemostasis.

VII. Consults on pre-operative anticoagulants and antiplatelet medications

For consults on pre-operative anticoagulants (such as Pradaxa) and antiplatelet medications (such as Plavix, Prasugrel), appropriate lab tests and consultation note are need to clear patients for surgery. No follow-up notes are needed once patients have been cleared for surgery. CBH service will be on standby (available) for unexpected coagulopathy in surgery. If patients need to have emergent surgery despite residual effect of medications, intraoperative follow-up would be needed for management of coagulopathy.

APPENDIX A1: DETAILS OF TRANSFUSION ALGORITHM WITH TEG DATA

[Approximate doses of blood components are based on expected response for a patient with average body weight (70 kg), see Appendix B.3. Final recommended dose should be based on degree of bleeding and also adjusted for body weight].

- [1] If (PTT > 45) and (TT>25) -> protamine (50 mg/70 kg BW)
- [2] If (50< Plt < 100k) -> 1-2 single-donor apheresis unit (plt ↑30-60)
- If (Plt < 50k) -> 2-3 single-donor apheresis unit (plt ↑60-90)

OR

- If (35<MA < 45) and (EPL <15) and (LY30 <8) -> 1-2 single-donor apheresis unit (plt ↑30-60)
- If (MA < 35) and (EPL <15) and (LY30 <8) -> 2-3 single-donor apheresis unit (plt ↑60-90)

OR

- If (130 PRU < VFN-P < 210 PRU) -> 1-2 single-donor apheresis unit (plt ↑30-60)
 If (VFN-P < 130 PRU) -> 2-3 single-donor apheresis unit (plt ↑60-90)

OR

- If (350 < VFN-A < 550) -> 1-2 single-donor apheresis unit (plt ↑30-60)
 If (VFN-A < 350) -> 2-3 single-donor apheresis unit (plt ↑60-90)
- [3] If (10 < hTEG-R < 15) -> 1-2 unit FFP (clotting factors ↑5-10%)
 If (15 < hTEG-R) -> 2-4 unit FFP (clotting factors ↑10-20%)
- If (20 < PT < 25) or (45 < PTT < 50) -> 1-2 FFP
 If (25 < PT) or (50 < PTT) -> 2-4 FFP (consider PCC after significant FFP transfusion; if PT > 25 -> 2 FFPs and PCC)
 [Notes: 1.5 x mean of ref range for PT and PTT are 20 and 44, respectively]
- [4] If (150 < Fibrinogen < 200) or (20 < Alpha < 45 with normal MA) -> 1-2 FFPs (fib ↑15-30)
 If (Fibrinogen < 150) or (Alpha < 20 with normal MA) -> 1 dose of Cryo (fib ↑90)
 If patient has chronic renal failure (uremia with BUN of at least 45), and active bleeding with normal coag results -> 1 dose of Cryo
- [5] If (EPL > 15% or Ly30 > 8%) and (MA < 50 or CI < 1.0) -> Tranexamic acid, INJ, 1,000 mg/10 mL over 10 mins
 If (Fibrinogen < 150) and (D-Dimer > 10) -> Tranexamic acid, INJ, 1,000 mg/10 mL
- [6] If patient is Heparin resistant: If (ATIII 35- 50%) -> 1-2 FFP
 If (ATIII < 35) -> ATIII concentrate (see Appendix B6 for dosing)
- [7] If (Hgb < 10) immediately off-pump -> RBC transfusion to increase Hgb to 10.0 (1 RBC to increase Hgb by 1.0). To correct Hgb for dilutional effect by FFP and platelets, add at least 1 RBC to every 2 FFP. To correct for dilutional effect by plasma in platelet units, add at least 1 RBC to every 1 apheresis platelet. Only correction of Hgb up to 10 is needed.
- [8] For off-pump panel only: If (hTEG-R > 20 and h-Alpha < 20 and h-MA < 35) -> consider artifacts due to protamine overdose if patient is not bleeding (otherwise consider other suggested treatments in the list)

-In emergency bleeding (off-pump) without available laboratory results -> start with 2 units of apheresis platelets first. Review off-pump results later to adjust treatment.

[9] For bleeding not responding to treatment -> consider rFVIIa (15 µg/kg BW) with the following constraints:

If (EPL > 15%) and (MA > 70 or CI > 3.0) -> rFVIIa is contraindicated (DIC with secondary fibrinolysis)

If (LY30 > 8%) and (MA > 70 or CI > 3.0) -> rFVIIa is contraindicated (DIC with secondary fibrinolysis)

If (Fibrinogen < 200) or (Alpha < 45 with normal MA) -> 1 dose Cryo (fib ↑90) then give rFVIIa (through different lines to avoid clotting). Fibrinogen needs to be > 200 for FVIIa to work.

If patient is acidotic, pH should be corrected to around 7.35 if time permits since acidosis can markedly decrease activity of rFVIIa [39].

APPENDIX A2: DETAILS OF TRANSFUSION ALGORITHM WITHOUT TEG DATA

Since TEG testing takes about 1 hour to finish and other tests in the panel take less than 30 minutes, many urgent cases would have to rely on results other than TEG. Also certain cases do not have TEG data available. The following algorithm offers this alternative. Since secondary fibrinolysis cannot be detected without TEG and early DIC with secondary fibrinolysis is typically not associated with bleeding, a caution is noted for tranexamic acid to be used only with active bleeding. Of course rFVIIa is used only in active bleeding.

[Approximate doses of blood components are based on expected response for a patient with average body weight (70 kg), see Appendix B.3. Final recommended dose should be based on degree of bleeding and also adjusted for body weight].

- [1] If (PTT > 45) and (TT > 25) -> protamine (50 mg/70 kg BW)
- [2] If (50 < Plt < 100k) -> 1-2 single-donor apheresis unit (plt ↑30-60)
If (Plt < 50k) -> 2-3 single-donor apheresis unit (plt ↑60-90)
- OR
- If (130 PRU < VFN-P < 210 PRU) -> 1-2 single-donor apheresis unit (plt ↑30-60)
If (VFN-P < 130 PRU) -> 2-3 single-donor apheresis unit (plt ↑60-90)
- OR
- If (350 < VFN-A < 550) -> 1-2 single-donor apheresis unit (plt ↑30-60)
If (VFN-A < 350) -> 2-3 single-donor apheresis unit (plt ↑60-90)
- [3] If (20 < PT < 25) or (45 < PTT < 50) -> 1-2 FFP
If (25 < PT) or (50 < PTT) -> 2-4 FFP (consider PCC after significant FFP transfusion; if PT > 25 -> 2 FFPs and PCC)
[Notes: 1.5 x mean of ref range for PT and PTT are 20 and 44, respectively]
- [4] If (150 < Fibrinogen < 200) -> 1-2 FFPs (fib ↑15-30)
If (Fibrinogen < 150) -> 1 dose of Cryo (fib ↑90)
If patient has chronic renal failure (uremia with BUN of at least 45), and active bleeding with normal coag results -> 1 dose of Cryo
- [5] If (Fibrinogen < 150) and (D-Dimer > 10) and active bleeding
-> Tranexamic acid, INJ, 1,000 mg/10 mL
- [6] If patient is Heparin resistant and:
If (ATIII 35- 50%) -> 1-2 FFP
If (ATIII < 35) -> ATIII concentrate (see Appendix B6 for dosing)
- [7] If (Hgb < 10) immediately off-pump -> RBC transfusion to increase Hgb to 10.0 (1 RBC to increase Hgb by 1.0). To correct Hgb for dilutional effect by FFP and platelets, add at least 1 RBC to every 2 FFP. To correct for dilutional effect by plasma in platelet units, add at least 1 RBC to every 1 apheresis platelet. Only correction of Hgb up to 10 is needed.
-In emergency bleeding (off-pump) without available laboratory results -> start with 2 units of apheresis platelets first. Review off-pump results later to adjust treatment.
- [8] For bleeding not responding to treatment -> consider rFVIIa (15 µg/kg BW) with the following constraints:
If (Fibrinogen < 200) -> 1 dose Cryo (fib ↑90) then give rFVIIa (through different lines to avoid clotting). Fibrinogen needs to be >200 for FVIIa to work.
If patient is acidotic, pH should be corrected to around 7.35 if time permits since acidosis can markedly decrease activity of rFVIIa [39].

APPENDIX A3: CRITERIA FOR USING PCC AND FVIIa IN MASSIVE BLEEDING

PCC

-For bleeding patients (intraoperative and postoperative) with elevated INR, after transfusion of multiple units of FFP (typically 4 or more), if INR still elevated (with adequate platelet count/function and fibrinogen) [94], instead of transfusing more FFP -> use KCentra to avoid volume overload

-For bleeding patient with elevated INR, and right heart failure (high central venous pressure, CVP/ fluid overload) who could not tolerate large volume transfusion, use KCentra to avoid volume overload.

-PCC may need to be alerted to HVI Pharmacy prior to surgery. If patient has anticipated significant need for transfusion due to: (a) Platelet dysfunction (uremia with BUN of at least 45, antiplatelet medications, etc), (b) Severe liver disease, or (c) Significant RBC transfusion on CPB in OR [6 or more], call pharmacy to get pre-approval for PCC. PCC can be delivered to OR by courier in 15 minutes.

-Details for using PCC is found in Appendix C2

rFVIIa

rFVIIa may be considered for intractable intraoperative and postoperative bleeding [95-97]. In postoperative situation, if CT output is more than 1,000 cc/hr, and not alleviated with blood product transfusion and PCC, rFVIIa would be considered. Of course, surgeons would also be in stand-by for possible emergency re-operation with surgical bleeding (microvascular bleeding is ruled out with adequate coagulation laboratory results after transfusion). Be aware of complications (11% risk of thrombosis) due to the use of rFVIIa and its limitation in patients' outcome [90].

-Criteria for the use of recombinant FVIIa are [90]:

- (1) Severe ongoing hemorrhage, despite optimum conventional pharmacological and blood product support.
- (2) No foreseeable immediate surgical correction of bleeding.

-Details for using rFVIIa is found in Appendix C2

APPENDIX B: MISCELLANEOUS INFORMATION

1. Responsible parties for hemotherapy:

-Attending: 2 hemotherapy attendings on this service;

Day service: 8am-5pm (M-F)

Night service: 5pm-8am (M-F), also all day Sat and Sun.

Blood Bank (contact number 713-704-3640) has updated list of hemotherapy attending schedule. For critical patients (with significant bleeding, for example), the attending on day service needs to give pager numbers of day and night attendings to the patient's nurses by "MD to Nurse Order".

-CP resident: (a) daytime: an assigned CP resident on hemotherapy from Monday through Friday, (b) off-hours/weekend: no residents

-Handoff briefing can be conducted verbally or by e-mail by attendings prior to the starting time of day or night coverage everyday.

2. The following parameters do not affect therapy in acute bleeding (considered adequate hemostasis):

100 < Plt < 133
 45 < MA < 50
 200 < Fib < 230
 45 < Alpha < 53
 (14.7 < PT < 20.0)
 (35.8 < PTT < 45.0)

3. Blood components nomenclature/ effect on coag parameters on a patient with 70 kg BW [69] and administration rate [109]:

1 dose of cryo = 10 units (fib ↑50-100), 150 ml, typically come in 2 half-doses (5 units each)
 1 jumbo FFP = 2 single FFP (clotting factors ↑ 15-20%, fib ↑30), 500 cc
 (Dose of FFP at 10-20 ml/kg can raise most coagulation factors levels in a non-bleeding patient by 25-50% [138])
 1 apheresis plt = 5-6 random-donor plt (plt ↑30) , 200-400 ml
 1 RBC: 350 mL (200 mL apheresis unit), 1 unit for 1 gm increase in Hgb

Administration rates for blood products [109]

Red cells

- Must be started within 30 minutes of receiving product
- Except in emergency situations infusion time is 1½ hours – 4 hours.

Fresh frozen plasma

- Must be started within 30 minutes of receiving product
- Infusion time is 30 minutes per bag.

Cryoprecipitate

- Must be commenced as soon as possible.
- Infusion time is STAT

Platelets

- Must be commenced as soon as possible after receiving product
- Maximum infusion time is 30 minutes.

4. Typical blood component order for non-LVAD cases:

6 FFP, 6 RBC, 6 plt

4 FFP, 4 RBC, 4 plt

5. When fibrinogen level is available for a stable (non-bleeding) patient, use this formula to increase fibrinogen level to 100 mg/dL with cryo:

Units of Cryo = (100 – fibrinogen) x 40 x BW (kg)/25,000

Note that guidelines for the management of active bleeding now indicate that the trigger level for supplementing fibrinogen should be 1.5 to 2.0 g per liter rather than 1.0 g per liter [92].

6. Dosing AT (Thrombate), used for a very low ATIII level (less than 35% which may cause heparin resistance):

Dose (IU) = (desired level – baseline level) x BW (kg)/1.4

Work with Anesthesia to infuse AT prior to heparinization in CPB

Note that a targeted range of ACT > 400 sec with UFH is used during CPB (typically 450-480 s); if ACT value much lower than 400 sec is seen after standard dose of UFH (300 u/kg or 3 mg/kg) heparin resistance is typically the cause. This may be seen in patients with ongoing heparin IV or congenital AT deficiency (rare). Heparin doses in excess of 700 u/kg may not prolong ACT adequately in this case. In mild-moderate heparin resistance, additional heparin (up to 3 times the normal dose) may be attempted before FFP or AT concentrate is considered

7. Important PT/INR thresholds to achieve

Indications	PT	INR
To prepare for typical CV surgery	<18	<1.5
To prepare for CV surgery, patients with high risk of thrombosis	<23	<2.0
ECMO patients with bleeding	<23	<2.0
ECMO patients without bleeding	<27	<2.5

8. To correct Hgb for dilutional effect on Hgb in significant FFP and plt transfusion:

For 1 FFP units, patient needs 1 RBC units (at least 0.5 RBC units)

For 1 apheresis platelet unit, patient needs 1 RBCs.

[Number of RBC for Hgb correction = 0.5 x FFP + apheresis plts]

For massive transfusion, use

(1:1:1) ratio: (6 FFP, 6 RBC, 6 random-donor plts or 1 pheresis plt), or

(1/0.5/1) ratio: (1 RBC/0.5 FFP/1 random-donor Plt or 0.2 pheresis plt), with rounding

9. Minimum platelet count when patient is on pump/off-pump:

-When patient is still on pump, platelet count needs to be kept above 20k. If platelet count is already above 20k and patient still bleeds, transfuse with platelets.

-When patient is off-pump with microvascular bleeding, transfuse with platelets to keep platelet count above 100k [73]

10. Quantitative D-Dimer (based on immunoturbidimetric method) may not be accurate (up to 15% discrepancy) if patient has marked hemolysis. Semi-quantitative FSP may be used instead if needed.

11. Targeted ACT with heparin reversal using protamine: anesthesia typically uses protamine to reverse heparin after cardiopulmonary bypass with targeted ACT of less than 130 sec (or within 10% of pre CPB ACT).

Note that 1 mg of protamine is used to neutralize 1 mg (100 u) UFH. For a 70 kg BW (which requires 21,000 u of UFH with 300 u/kg dosage), it is about 210 mg protamine. Note that some anesthesiologists may use 1.3 mg of protamine to neutralize 1 mg of UFH (273 mg protamine for 70 kg BW).

For high dose of heparin in CPB (300-400 IU/kg), the half-life of heparin is 126 min +/- 24 min [63]. Plasma heparin concentration is 3-4 IU/mL. Hypothermia delays heparin elimination [64]. Chronic renal failure also prolongs the elimination of heparin [65]. However, liver disease has no effect on heparin elimination [66].

At the end of CPB, patients may have adequate hemostasis with normal ACT after heparin neutralization, but develop bleeding several hours later with prolonged clotting time. This phenomenon, known as heparin rebound [67, 68], results from delayed release of heparin which is previously sequestered in tissues (especially in adipose tissue in obese patients) into the circulation. In this case, additional protamine is given to neutralize heparin.

Note that a prolonged ACT may be seen in patients without residual heparin. It may be due to other etiologies (hemodilution, coagulation factor depletion, thrombocytopenia, platelet dysfunction, hypothermia, even excess protamine) [71]. Therefore, more sensitive tests (PTT and TT) should be used to assess residual heparin that may benefit from additional protamine.

For patients not in OR with bleeding, having prolonged PTT/TT due to heparin, then heparin correction can be started with 25 mg protamine sulfate IV which would neutralize 2,500 U of UFH (25x100); then monitor PTT/TT for further dose if needed (PTT/TT should be normalized readily, within 10-15 mins, with quick neutralization of heparin by protamine sulfate). Protamine needed to be infused at least over 10 mins. Faster rate may cause hypotension or anaphylactoid reaction. If patient's MAP is low, infusion over 30 min with close monitor of MAP is needed.

12. Falsely elevated LY30: may occasionally be seen with kaolin as activator in TEG for citrated blood [51]. Other lab data, such as normal D-Dimer, FSP, and fibrinogen may be assessed to rule out actual fibrinolysis.

13. Tranexamic acid for hyperfibrinolysis:

- Hyperfibrinolysis may accompany cardiac surgery using CPB, in patients with liver disease [91], resulting in microvascular bleeding [74]. Clinical suspicion should be high in cases in which bleeding continues despite hemostatic replacement therapy, platelet levels are relatively conserved but fibrinogen levels are disproportionately low, and D-Dimer levels are disproportionately high for DIC in stage II. TEG-Ly30, which may help differentiate fibrinolytic activation from coagulation factor deficiency, is not very sensitive, since it detects only the most marked changes [93].

- Tranexamic acid is used to inhibit hyperfibrinolysis. It is currently used in HVI OR, 10 times more potent than Amicar (EACA)

-Contraindicated in patients with evidence of DIC in stage I (hypercoagulation state with secondary fibrinolysis) since the fibrinolytic system is required to ensure the dissolution of the widespread fibrin [72, 91].

14. TEG testing in HVI Lab vs. Central Coag Lab:

-HVI Lab: TEG or hTEG will be performed as ordered

-Central Lab:

a. TEG is performed as ordered.

b. If hTEG is ordered, TEG will be performed first.

If TEG-R >10, hTEG will also be performed. TEG and hTEG are reported

If TEG-R <10, hTEG is cancelled. Only TEG is performed and reported.

Note that results for hTEG are indicated by suffix "2", for example, R-TIME2, ANGLE2, etc.

15. Falsely elevated plasma free hemoglobin

Specimen for plasma free hemoglobin must be collected in light green top (PST gel separation tube with lithium heparin as an anticoagulant) tube to avoid any falsely elevated plasma free hemoglobin due to post collection in-vitro hemolysis.

16. Platelet dysfunction in uremia

Almost all patients with uremia, the clinical syndrome of advanced renal failure, have a bleeding Diathesis [139]. This predisposition becomes especially problematic when these patients undergo invasive procedures such as surgery, biopsy, or catheter placement. Moreover, many of the clinical presentations of uremic bleeding involve life-threatening conditions including pericardial tamponade, intracranial bleeding, and gastrointestinal bleeding. In hemodynamically unstable patients with uremia, the massive occult bleeding that can occur in these conditions is particularly troubling and should remain a central concern in the evaluation of such patients. When the blood urea nitrogen level is greater than 60 mg/dL or the serum creatinine level is greater than 6.7 mg/dL, bleeding time is significantly prolonged [140]. Bleeding time is currently not considered a reliable test with high incidence of false-positivity and false-negativity. Platelet aggregation study may show decrease in platelet response to various reagents but the threshold for bleeding risk has not been established. Without established criteria, we use an empirical threshold of BUN greater than 45 for cryoprecipitate transfusion in a bleeding patient.

17. Useful phone numbers and unit locations

OR room #1 (HVI, 7th floor): 704-0801 (nurse), 704-0811 (anesthesia)

HVI OR Front Desk: 704-0807

HVI Lab (HVI, 7th floor): 704-4371

HVI Blood Bank (HVI, 7th floor): 704-4374

CVICU charge nurse (HVI, 8th floor): 704-1077

CCU charge nurse (HVI, 5th floor): 704-3160

HVI Pharmacy: 704-0623

Blood Bank: 704-3640

Heart transplant co-coordinator on call: typically uses individual cell phone, a phone number for general info is at 704-4300

HLA Laboratory: 713-500-7380

**For full list of contacts including cell phones (individuals involved in Advanced Heart Failure, including surgeons, anesthesiologists, cardiologist, pathologists, pharmacist, etc.), refer to file "Contact Numbers.xls" in N drive (N:\Clinical\LVAD OHT\)

Room designations in HVI bldg floors:

4th floor: CCU, CIMU

5th floor: HVI

7th floor: HVI-OR

8th floor: CVICU, CVIMU

OR Schedule for LVAD/OHT service (OR 1/OR 2):

Case information can be obtained from:

-BB (704-3640): MTs can access OR Control Tracking in Care4 to obtain OR schedule, typically finalized by 9 pm the day before surgery

-HVI OR Front Desk (704-0807)

APPENDIX C: LISTS OF ANTICOAGULANTS & ANTI-THROMBOTIC MEDICATIONS

Table 2. Common medications before CV surgery [4, 50]

Medication	Effect	Admin	Time to be discontinued prior to surgery	Counter agents if not discontinued adequately prior to CV surgery
Warfarin	Vit-K antagonist	oral	4-7 days	Vitamin K 1-10 mg (oral 24 hrs or more before surgery; IV 6-24 hrs; FFP-less than 6 hrs). See details following this Table
Unfractionated heparin	AT inhibition	IV	4-6 hours	Protamine: 1 mg per 100 U (1 mg)
LMWH	Indirect FXa inhibition	IV	24 hours	Protamine: 1 mg per 100 anti-Xa units of LMWH (only 66% neutralized)
Clopidogrel	ADP-P2Y12 inhibition	oral	5 days	None (platelets during or after surgery)
Ticagrelor (Brilinta)	ADP-P2Y12 inhibition	oral	Less than 5 days	None (platelets during or after surgery)
Prasugrel	ADP-P2Y12 inhibition	oral	7 days [87]	None (platelets during or after surgery)
Abciximab (ReoPro)	GP-IIb-IIIa inhibition	IV	24-48 hours [112, 115]	None (platelets during or after surgery)
Eptifibatide (Integrilin)	GP-IIb-IIIa inhibition	IV	4-6 hours [115]	None (platelets during or after surgery)
ASA	Cyclooxygenase inhibition	oral	No discontinuation	None (platelets during or after surgery)
Dabigatran (Pradaxa)	Direct thrombin inhibition	oral	-Normal or mild impairment (CrCl > 50 mL/min): 3 days -Moderate impairment (CrCl 30-50 mL/min): 4-5 days	Dialysis, FVIIa (not well validated) [41], PCC- See Appendix C2
Bivalirudin (Angiomax)	Direct thrombin inhibition	IV	2 hours	Dialysis, PCC, FVIIa (not well validated) [33]
Rivaroxaban	Direct FXa inhibition	oral	-Normal-moderate impairment (CrCl >30 mL/min): 3 days -Severe impairment (CrCl 15-29.9 mL/min): 4 days	PCC- See Appendix C2
Apixaban	Direct FXa inhibition	oral	Normal or mild impairment (CrCl > 50 mL/min):3 days -Moderate impairment (CrCl 30-50 mL/min):4 days	PCC- See Appendix C2

Bivalirudin (Angiomax):

PTT returns to normal approximately 1 hr after discontinuation of the drug (in therapeutic dose). It is safe to discontinue the medication 2 hours prior to surgery in patients with normal renal function. Angiomax significantly prolongs TEG-R and slightly decreases TEG-Alpha. Dialysis, and FVIIa have been used to reverse Angiomax in bleeding patients [33].

Reversal of Dabigatran:

Dabigatran does not have antidote but dialysis does remove this agent (60% removal over 2-3 hours). FVIIa at low dose (30 µg/kg) has been suggested [41], but not well validated. A normal Thrombin Time indicates that Dabigatran is no longer effective. A normal PTT indicates low level of Dabigatran (most of the drug has been cleared). See Appendix C2 with details of using PCC for reversal.

Reversal of rivaroxaban (Xarelto®) or apixaban [76-81]:

-PCC may be used for severe bleeding associated with use of direct oral Xa inhibitors (eg. Rivaroxaban, Apixaban) requiring a reversal agent. Dialysis is not useful to clear Rivaroxaban or Apixaban. PCC may be useful for bleeding associated with these medications. KCentra (four-factor PCC) is the agent that is currently available at MHH-TMC.

-Anti-Xa level (for LMWH) can be ordered to approximately measure activity of Rivaroxaban or Apixaban. However, no thresholds for bleeding risk have been established.

-A normal PT indicates that Rivaroxaban is at low level (most of the drug has been cleared). PT/PTT are not useful to assess Apixaban level.

-INR may not be the appropriate guide the dosing if the patient is taking Xa inhibitor.

-If PT/PTT are more prolonged in patients taking rivaroxaban or apixaban, mixing study is needed. Depending on results of mixing study, further testing to rule out inhibitor (lupus anticoagulant) or factor deficiency (factor assays) would be needed prior to surgery.

-See Appendix C2 with details of using PCC for reversal.

Reversal of Warfarin:

Goal is for INR < 1.5.

For 24 hours or more before surgery: 2.5 -5.0 mg oral Vit K

For 6-24 hours: 2.5-5.0 mg Vit K by IV

For less than 6 hours: FFP 10 mL/kg (typically 2 FFPs)

-However, for patient with high risk of thrombosis requiring warfarin before surgery (patients with LVAD, total artificial heart, mechanical heart valve, prior stroke, intracardiac thrombus, or cardioembolic events, among others), it is important that the INR before the procedure could be higher but not be suprathreshold. INR can be kept at approximately 2.0 by the time of the procedure [87] (Appendix D.4).

- PCC is reserved for selected cases (bleeding patients with poor tolerance for volume overload).

- See Appendix C2 with details of using PCC for reversal in emergent conditions.

-KCentra for rapid reversal for Coumadin prior to emergent surgery in patients who cannot tolerate volume overload:

-PCC may be used for reversal of warfarin anticoagulation immediately prior to emergent CV surgeries including heart transplant, total artificial heart and left ventricular assist devices.

-For OHT, dose to be mixed and administered only after visualization confirmed by harvesting surgeons. Reversal too soon would require patient to be on heparin and hence would take longer to achieve therapeutic INR with Coumadin later.

-Note that KCentra contains heparin, hence it is contraindicated in patients with heparin-induced thrombocytopenia (HIT). It can only be infused during surgery with appropriate measures (plasma pheresis prior to surgery, heparin neutralization after off-pump).

Table 3. MANAGEMENT OF SUPRA-THERAPEUTIC INR (not for pre-op)

INR	Symptoms	Recommendations
target range < INR < 5	No significant bleeding	Lower or omit dose, resume therapy at a lower dose when INR therapeutic. Monitor INR more frequently.
5 < INR < 9	No significant bleeding	Omit next 1-2 doses and monitor INR. Resume at a lower dose when INR in target range. Consider Vitamin K 1-2.5 mg orally, particularly if at increased risk of bleeding
9 < INR	No significant bleeding	Hold Warfarin. Consider Vitamin K 1, 2.5, 5, or 10 mg orally, particularly if at increased risk of bleeding. With Vitamin K 5-10 mg, expect INR to be reduced substantially by 24-48 hours. Monitor more frequently. Resume therapy at lower dose when INR therapeutic.
Any INR elevation	Significant bleeding	-Hold Warfarin. -Give Vitamin K by slow IV infusion (10 mg IV/NS 50 mL over 30 mins), -Supplemented with fresh frozen plasma or PCC: For INR 2-3.99 -> 10 mL/kg (typ. 2 FFP); also consider PCC, 25 u/kg For INR 4-5.99 -> 15 mL/kg (typ. 4 FFP); PCC is preferred, 35 u/kg For INR ≥ 6 -> 20 mL/kg (typ. 6 FFP); PCC is preferred, 50 u/kg -PCC required for pts with poor tolerance to volume loading (Appendix C2) - Recombinant factor VIIa may be considered as last resort (10-15 micrograms/kg) rounded to the nearest mg, IVP over 2 mins.

Table 4. Platelet Function Testing Results for Patients on ASA and/or ADP P2Y12 Inhibitors: Typical Results for Therapeutic Ranges

Medication	Platelet Aggregation	VFN
ASA only	AA (5 mg/cL) < 15%	VFN-ASA < 550 ARU
	ADP (2.5 uM/mL) 20-50%	VFN-P > 210 PRU
	ADP (50 uM/mL) > 60%	
P2Y12 Inhibitor only	AA (5 mg/cL) > 60%	VFN-ASA > 550 ARU
	ADP (2.5 uM/mL) < 40%	VFN-P < 210 PRU
	ADP (50 uM/mL) < 50%	
ASA and P2Y12 Inhibitor	AA (5 mg/cL) < 15%	VFN-ASA < 550 ARU
	ADP (2.5 uM/mL) < 40%	VFN-P < 210 PRU
	ADP (50 uM/mL) < 50%	

Note:

1. Platelet aggregation with ADP is affected by many conditions besides effect of ASA and ADP P2Y12 inhibitors. The patient's results need to be interpreted with this caveat.

2. Factors causing inaccurate results (or no reading) by VFN:

(a) Severe anemia, severe thrombocytopenia, Greiner tube filled below or above half-way level, no discard sample prior to Greiner sample, a purple-top tube is filled before Greiner tube, Greiner tube not hand-carried to lab. If a test result is unexpectedly low, repeat testing assuring that all technical artifacts are prevented.

(b) Patients who have been treated with Glycoprotein IIb/IIIa inhibitor drugs should not be tested for 14 days after discontinuation of drug administration for abciximab (ReoPro) and up to 48 hours for eptifibatid (Integrilin) and tirofiban (Aggrastat). The recovery time varies among individuals and is longer for patients with renal dysfunction. VerifyNow P2Y12 testing with residual effect of these meds will give error signal or will give falsely-low level. Use Platelet Function Screen with ADP to evaluate platelet function instead (see parts 3 and 4 below)

3. Platelet Function Screen with ADP (abbreviated platelet aggregation study with only ADP, 2 concentrations 2.5 and 50 uM/mL) can be ordered STAT with TAT about 1 hour during day shift (7 am-3 pm) if needed. Hemotherapy pathologist needs to call special coagulation laboratory (713-704-1693) to alert the testing technologist about the request. The samples (3 blue-top tubes) should be hand-carried to the special coagulation laboratory for adequate TAT.

4. Platelet aggregation in patients who have been treated with Glycoprotein IIb/IIIa inhibitor drugs typically shows flat lines similar to those of Glanzmann thrombasthenia. Platelet Function Screen with ADP (rather than VFN-Plavix) should be used to evaluate platelet function. Response to 50 uM/mL ADP typically returns to normal within 48 hours for ReoPro [112] and 6 hours for Integrilin [115]. The recovery time is longer for patients with renal dysfunction.

APPENDIX C2: CRITERIA FOR USING PCC AND rFVIIa [82-85, 104]

This protocol has been approved by CV Pharmacy and Dr M Escobar. Please note Kcentra® and NovoSeven® (rFVIIa) orders will not be delayed. However, all orders are reviewed by a clinical pharmacist specialist for appropriateness prior to preparation. You may receive a call regarding its use if there are concerns.

- This protocol is not intended for patients receiving Argatroban, Bivalirudin, Enoxaparin, and Fondaparinux.
- The use of KCentra and rFVIIa in surgery has to be communicated to and agreed by CV surgeons and anesthesiologists before it can be used in each case. It should be used with laboratory results together with finding of microvascular bleeding.

Labs for All Coagulopathic Patients

- Order CBC (without differential) and platelet count, TEG
- Order DIC panel.
 - DIC panel consists of PT/PTT/D-Dimer/Thrombin time/Fibrinogen

Coagulopathy in Patients Actively Bleeding or Requiring Emergent Reversal for a Procedure on Warfarin

- Step 1: Administer vitamin K 10 mg IV/NS 50 ml over 30 minutes STAT.
 - Onset of action = 4 – 8 hours and peak effect = 12 – 14 hours.

- Administer regardless of what was reported to be given at outside facility.
- Vitamin K will assist in sustaining the effects of Kcentra®
- Step 2: Kcentra®
 - Must be ordered by an attending.
 - Dosing (Use maximum weight of 100 kg if patient > 100 kg)
 - If INR 2 – 3.99 = Give 25 units per kg.
 - If INR 4 – 5.99 = Give 35 units per kg.
 - If INR \geq 6 Give 50 units per kg.
 - Pharmacy will round downward to the nearest vial.
 - Use is restricted to a single dose. Repeat doses do not improve efficacy and increases risk for thromboembolic complications. Hematology consult required if more than 1 dose is needed.
 - Obtain PT/INR/PTT prior to initiating Kcentra® and 2 hours after administration.
- Notes regarding Kcentra® dosing administration
 - Each 500 unit vial contains 400 – 620 units factor IX. Pharmacy will enter the exact dose provide in factor IX units for billing purposes.
 - Kcentra® should be infused through a separate infusion line.
 - It is administered by IV infusion at a maximum 210 units/minute

Coagulopathy in Patients Actively Bleeding or Requiring Emergent Reversal for a Procedure on other Oral Anticoagulants

For off-label use in immediate reversal of Rivaroxaban (Xarelto®), Apixaban (Eliquis®) or Dabigatran (Pradaxa®)

- Dabigatran patients: additional removal with hemodialysis is recommended. Approximately 50% of Dabigatran may be removed after 2 hours of hemodialysis.
- Check a TEG (not Rapid TEG). If R-time is normal, Kcentra® is not required.
- First line: Kcentra®
 - Must be ordered by an attending.
 - Dose = 35 units per kg and is restricted to a single dose. (Use maximum weight of 100 kg if patient > 100 kg)
 - Maximum cumulative dose = 50 units/kg per day.
 - Use is restricted to a single dose. Repeat doses do not improve efficacy and increases risk for thromboembolic complications. Hematology consult required if more than 1 dose is needed.
 - Vial sizes may vary. Pharmacy will round downward to the nearest vial size.
 - Obtain PT/INR/PTT/TEG prior to initiating Kcentra® and 2 hours after administration.

Coagulopathy in Patients NOT on Warfarin or New Oral Anticoagulants AND Patient is Actively Bleeding

- If PTT > 45 and TT > 25 and patient has received heparin within previous 24 hours, administer protamine 50mg/70kg BW
- Maintain fibrinogen > 200 mg/dL in patients actively bleeding.

- Replace fibrinogen 150-200 mg/dL with 2 units FFP. If fibrinogen < 150 mg/dl administer 1 dose of cryoprecipitate.
- Check fibrinogen level 2 hours after cryoprecipitate. If fibrinogen < 150 mg/dL administer 1 additional dose of cryoprecipitate.
- If PT or PTT is prolonged and fibrinogen > 200 mg/dL administer FFP; do not administer cryoprecipitate.
 - 20 < PT < 25 give 2 units of FFP
 - 25 < PT give 4 units of FFP
 - If patients significantly volume overloaded may consider Kcentra 25units/kg x 1 dose to limit the volume requirements associated with FFP infusions.
- Maintain platelets > 100,000/mm³.
 - Replace platelet 50-100,000/ mm³ with 2 single-donor apheresis units
 - Replace platelet <50,000/mm³ with 3 single-donor apheresis units
 - If VerifyNow for aspirin (Aspirin Effect Platelet) or clopidogrel (Plavix effect platelet) demonstrate significant platelet inhibition may give 2-3 single-donor apheresis units
- Check CBC and DIC panel every 8 hours x 24 hours, then daily.
- If above measures have been completed and patient is actively bleeding consider rFVIIa 15 micrograms/kg (rounded to the nearest vial size) IV push over 2 minutes x 1.
 - For rFVIIa to be most efficacious ensure pH ~ 7.4 and body temperature > 36⁰ C.
- Check CBC and DIC panel 1 hour after rFVIIa.
- Calculate DIC score daily.

OHT surgery for patients who are on Coumadin

-KCentra is used to reverse Coumadin right after announcement of a good visualization of donor heart.

-Dosing (Use maximum weight of 100 kg if patient > 100 kg)

If INR 1.5 – 3.99 : Give 25 units per kg.

If INR 4 – 5.99 : Give 35 units per kg.

-No more KCentra should be used after this dose.

-Note that Vit K (5-10 mg) also needs to be given to prevent Coumadin rebound after effect of KCentra /FFP has weaned off in the post-op period. Another dose of Vit K (5-10 mg) will also be considered 10-12 hours later.

-CV Pharmacist needs to be contacted for STAT delivery of Kcentra to OR which takes 10-15 minutes.

-For patients with history of positive HIT test: Kcentra which contains a small amount of heparin should not presents a problem if used right after good visualization (OHT surgery) since these patients are typically well covered with measures such as plasmapheresis and they are exposed to high dose of heparin on CPB which is neutralized with protamine after off-pump.

OHT surgery for patients who are on not on Coumadin

-Routine measures to d/c other anticoagulants should be followed prior to surgery. If PT at off-pump is >25 sec, 2 FFPs will be transfused and followed by Kcentra (25 u/kg). No more KCentra should be used after this dose. If PT at off-pump is < 25 sec, only 2 FFPs at the most would be attempted at first. Note that PT prior to off-pump (hemoconcentration/warming phase) is approximately 3 sec more prolonged than PT at off-pump due to UFH effect. If PT prior to off-pump > 28 sec, PT at off-pump is likely to be >25 sec.

LVAD surgery for patients on Coumadin

-KCentra is used to reverse Coumadin prior to surgery.
 -Dosing (Use maximum weight of 100 kg if patient > 100 kg)
 If INR 1.5 – 3.99 : Give 25 units per kg.
 If INR 4 – 5.99 : Give 35 units per kg.
 -No more KCentra should be used after this dose.
 -Note that Vit K (5-10 mg) also needs to be given to prevent Coumadin rebound after effect of KCentra /FFP has weaned off in the post-op period. Another dose of Vit K (5-10 mg) will also be considered 10-12 hours later.
 -Note that Vit K should not be used for LVAD exchange (typically for LVAD thrombosis) since patient will need to be on Coumadin soon afterwards.

LVAD surgery for patients not on Coumadin

-If PT at off-pump is >25 sec, 2 FFPs will be transfused and followed by Kcentra (25 u/kg). - Only one dose of KCentra can be used.
 -If PT at off-pump is < 25 sec, only 2 FFPs at the most would be attempted at first.

Approval of Factor VIIa or Kcentra® Orders

-Kcentra® or NovoSeven® (rVIIa) must be approved by Heart Failure Cardiology attending physician if patient is in the ICU. May be ordered by Clinical Pathology consulted to manage transfusions and coagulopathy.
-The first dose of Kcentra® or rVIIa does not have to be approved by Dr. Miguel Escobar or a clinical pharmacist specialist if the protocol is being followed. All subsequent doses require approval.

Use with Caution

-In the past 6 months: Ischemic stroke (clinical or imaging evidence), myocardial infarction (clinical or EKG evidence), or venous thromboembolism.
 -Patients 65 years or older.

Contraindications to Use of Recombinant Factor VIIa or Kcentra®

Consult Dr. Miguel Escobar or Kenneth Chong for approval of rFVIIa or Kcentra® if the patient has one of the following contraindications.
 -Suspected DIC (per labs) if the patient is coagulopathic or end stage liver disease.
 -Kcentra® contains heparin. Do not use in patients with active HIT
 -Acute myocardial infarction (MI), acute septicemia, acute crush injury, acute peripheral arterial occlusion, acute thrombotic stroke, acute DVT/PE (within 3 months), or high risk thrombophilia.

- Lupus anticoagulant/anticardiolipin antibodies.
- Protein C, Protein S, or Antithrombin deficiency.
- Homozygous factor V Leiden.
- Double Heterozygous (Factor V Leiden/ Factor II G20210A Prothrombin mutation).
- Pregnancy.
- In past 30 days: history of TIA, angina pectoris, or limb claudication.
- Known or suspected allergy to the drug.

Contact Information

- Miguel Escobar, MD: 281-622-9887; pager 713-764-0073
- Phillip Weeks, Pharm.D.: 409-720-7604
- Adam Sieg, Pharm.D. 605-890-0218
- Kenneth Chong, Pharm.D.: 281-910-8006

APPENDIX D: TYPICAL ANTICOAGULANT AND ANTIPLATELET PROTOCOLS

1.LVAD

Patients with continuous-flow devices require anticoagulation and antiplatelet agents to attenuate the risk of thromboembolic events.

-Various anticoagulant protocols have been developed since the HM II Pivotal Trial [107]. At MHH-TMC, patients are typically put on ASA 81 mg qd to 325 mg qd, UFH for a target range of 60-80 sec, warfarin to achieve INR 2.5-3.5. Heparin discontinuation after overlap with warfarin and achievement of the target INR for 2 to 3 consecutive days.

-ASA can be typically started on POD#2 unless CT output is high.

-When chest tube drainage reached <50 mL/hr and no evidence of bleeding: removal of chest tubes, intravenous heparin may be started on POD#1.

-At MHH-TMC CV surgeon typically start patient on fixed heparin dose. Typical orders:

(a)MD to Nurse Order, Misc: start heparin at xxxx at 200u/hr fixed dose. Check PTT q6hr; Notify MD: If PTT is > 60.

(b)MD to Nurse Order, Misc: Heparin Infusion not intended to achieve therapeutic PTT > 60

(c)MD to Nurse Order, Misc: No Heparin Loading Dose.

Fixed dose is then slowly increased (for example, to 400 u/hr on POD#2, then 800 u/hr on POD#3). Once patient is doing well without bleeding with initial starting dose, on POD#3 order is placed for "Heparin Weight Based Atrial Fibrillation and Stroke Prevention Orders MPP" [therapeutic PTT 60-80 sec, no loading dose].

Typical order:

CDM Heparin Weight Based Atrial Fibrillation and Stroke Prevention Orders: 10/27/14 8:49:00,
1

MD to Nurse Order, Misc: 10/27/14 8:49:00, Repeat PTT in 6 hours following any dose change.
Notify MD: 10/27/14 8:49:00, Temp > If PTT is less < 30 seconds or => 91seconds call
physician immediately

MD to Nurse Order, Misc: 10/27/14 8:49:00, Once therapeutic range is maintained for THREE consecutive PTT readings (60-80 seconds) decrease PTT draws to once daily while patient is on heparin.

MD to Nurse Order, Misc: 10/27/14 8:49:00, Document heparin doses administered and rate changes.

MD to Nurse Order, Misc: 10/27/14 8:49:00, No heparin loading dose or bolus unless specifically ordered by physician

-If clots develop in LVAD patient, cardiologists prefer to use Bivalirudin (rather than UFH) as anticoagulant. LDH and free Hgb may be significantly elevated with clot in LVAD. Clot may lead to LVAD failure, manifested by insignificant increase in LV ejection with increase in speed (in rpm) or power (in watts). This would require LVAD exchange. LVAD exchange surgery is typically short (with CPB time <30 mins). However, lab tests prior to off-pump still need to be followed since platelet count may decrease significantly.

2 TandemHeart System

The TandemHeart System requires that the patient be anticoagulated. It is recommended that the ACT should be 400 seconds for insertion of the device in the catheterization lab or operating room. The ACT should be > 200 seconds during the support period. If ACT is unavailable, aPTT can be used. During support, aPTT should be maintained between 55 and 75 seconds. (MHH-TMC protocol). The TandemHeart System will deliver 900 units/hr at the recommended dosage of 90 units/cc of heparin (10 cc/hr) to the patient through the infusate system of the pump. Additional heparin may be required to be administered peripherally to maintain proper anticoagulation levels.

UFH MPP for TandemHeart

Heparin 45,000 unit / NS 500 mL *TandemHeart LVAD* 45,000 unit
 500 mL, Rate: 900 unit/hr, Route: INJ, Dosing Weight 50 kg, Total Volume: 500 mL, Start date: 11/03/14 3:41:00, Duration: 30 day, Stop date: 12/03/14 3:40:00
 Order Comment: DO NOT USE THESE INSTRUCTIONS FOR ADJUSTMENTS WHILE PATIENT ON SYSTEMIC HEPARIN
 If PTT < 55 sec: Continue current concentration of device heparin and initiate systemic heparin at 2 unit/kg/hr; recheck PTT in 2 hr
 If PTT 55-75 sec: Therapeutic - no change
 If PTT 76-90 sec: Switch device heparin to 25,000 units in NS 500 ml at 500 unit/hr (10 ml/hr) and initiate systemic heparin at 2 unit/kg/hr; recheck PTT in 2 hr
 If PTT 91-110 sec: Switch device heparin to 25,000 units in NS 500 ml at 500 unit/hr (10 ml/hr); recheck PTT in 2 hr
 If PTT >110 sec: Switch device heparin to NS at 10 ml/hr; recheck PTT in 1 hr

For patients with low body weight (for example 50 kg) UFH rate at 900 u/hr may cause PTT to be in supratherapeutic range. In that case, the Tandem heparin device is set to run NS and patient is put on weight-based UFH MPP, for example Infusion Protocol for Heparin Weight-based Atrial fibrillation and Stroke Prevention MPP (Therapeutic PTT of 60-80 sec), see Appendix G1.

Prior to cardiovascular surgery heparin is only stopped when patient is ready to leave ICU room for OR. Typically actual surgery does not start until 2-3 hours later. Patient may still have prolonged PTT but this does not present risks to patient.

3. Intra-aortic balloon pump (IABP)

The existing data suggest that it is safe to omit heparinization when using IABP counter-pulsation [15]. The decision to heparinize should be weighed in the context of other indications or contraindications rather than being an automatic response to the use of IABP.

Most cardiologists including those at MHH-TMC prefer to use Heparin gtt with targeted range for PTT 60-80 sec. Prior to cardiovascular surgery heparin is only stopped when patient is ready to leave ICU room for OR. Typically actual surgery does not start until 2-3 hours later. Patient may still have prolonged PTT but this does not present risks to patient.

4. Schedule of bridging anticoagulant therapies for surgery

1. Stop Warfarin 5 days before surgery.
2. Monitor INR closely pre-and post-procedure to time bridging therapy.
3. Begin UFH when INR falls below 2.0. Increase UFH dose to achieve PTT therapeutic range.
4. If the INR remains elevated (>2.0) 1-2 days before surgery, administer Vitamin K 1-2 mg PO. If patient will have surgery in less than 6 hours, give Vitamin K 2.5 mg IV.
5. Stop UFH 4 hours before surgery.
6. For low bleeding risk surgery, resume UFH after 24 hours, when hemostasis is secured.
7. For major or high bleeding risk surgery, delay the resumption of therapeutic-dose UFH for 48-72 hours, or give low-dose UFH, considering bleeding risk and adequacy of postoperative hemostasis for each patient individually.
7. Start Warfarin at appropriate time and continue until INR is at least 2.0 or 2.5 before discontinuing UFH.

For anticoagulant in patient with high risk of thrombosis (patients with LVAD, total artificial heart, mechanical heart valve, prior stroke, intracardiac thrombus, or cardioembolic events, among others), it can present difficult anticoagulant management problem due to risks of thrombosis vs. risk of bleeding before and during surgery. Patients may need to be on Warfarin until surgery [87]. The INR value at which the risk of bleeding increases is unknown, it is assumed to be elevated when the INR is more than 2.0 [88,89]. For patient with high risk of thrombosis requiring warfarin before surgery, it is important that the INR before the procedure not be suprathreshold. INR can be kept at approximately 2.0 by the time of the procedure [87].

5. Post CABG

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy [16] made the following recommendations for the prevention of saphenous vein graft occlusion following coronary artery bypass grafting (CABG):

- Aspirin (75 mg to 162 mg per day) treatment for indefinite period of time for all patients with coronary artery disease.
- Postoperative aspirin (75 mg to 162 mg/day) starting 6 hours after CABG procedure preferred over preoperative aspirin.

- Addition of dipyridamole to aspirin therapy NOT recommended in patients undergoing CABG
- For coronary artery disease patients undergoing CABG who are allergic to aspirin: Clopidogrel 300 mg loading dose 6 hours postoperatively followed by 75 mg/day,
- Clopidogrel (75 mg/day) in addition to aspirin for 9 to 12 months following procedure, in patients undergoing CABG for non-ST-segment elevation acute coronary syndrome.

Aspirin is recommended for all patients after CABG within 24 hours with adequate hemostasis. It is not recommended to give aspirin to patients after CABG if they're already on warfarin (for patients with history of chronic A. fib, for example). There's no evidence that it improves graft patency for sure and it certainly increases the risk for bleeding. On the other hand, there is evidence that the addition of aspirin to warfarin in patients with mechanical valves results in a further decrease in thromboembolic complications after mechanical valve replacement [Appendix D.11]. There is no evidence yet that says we should give clopidogrel to all of patients after CABG.

6. PERCUTANEOUS CORONARY INTERVENTION

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy made the following recommendations for patients undergoing percutaneous coronary intervention (PCI):

- Aspirin pretreatment (75 mg to 325 mg), followed by aspirin 75 mg to 162 mg per day for long term treatment after PCI.
- Lower doses of aspirin (75 to 100 mg/day) for long term treatment in patients receiving other antithrombotic/anticoagulant agents, such as clopidogrel or warfarin.
- In patients who have undergone stent placement, combination therapy with aspirin and thienopyridine derivative (clopidogrel) preferred over systemic anticoagulation therapy.
- Clopidogrel (75 mg/day) in addition to aspirin for at least 9 to 12 months after PCI. Note that patients who undergo CABG shortly after PCI only need ASA after surgery (except for those with non-STEMI, see Appendix D.5)
- For patients with low atherosclerotic risk (e.g., isolated coronary lesion), clopidogrel for at least 2 weeks after bare metal stent placement, for 2 to 3 months after placement of a sirolimus-eluting stent, and after 6 months after placement of paclitaxel-eluting stent.
- GP IIb-IIIa antagonist such as abciximab or eptifibatide for all patients undergoing PCI, particularly those undergoing primary PCI or those with refractory unstable angina or other high-risk features.
- Abciximab administered as 0.25 mg/kg bolus followed by 12 hour infusion at rate of 10 micrograms per minute.
- Eptifibatide administered as double bolus (each 180 micrograms per kilogram, 10 minutes apart) followed by 18 hour infusion of 2 micrograms per kilogram per minute.
- Tirofiban NOT recommended as alternative to abciximab.
- For patients with non-ST-segment elevation myocardial infarction/unstable angina. (NSTEMI/UA) rated moderate-to-high risk based on Thrombolysis in Myocardial Infarction (TIMI) score, upstream use of GP IIb-IIIa antagonist (eptifibatide or tirofiban) started as soon as possible prior to PCI.
- In NSTEMI/UA patients with elevated troponin level, start abciximab within 24 hours prior to PCI.

-Patients not receiving a GP IIb-IIIa inhibitor, weight-adjusted heparin bolus of 60 to 100 IU/kg should be administered in doses to produce an activated clotting time (ACT) of 250 secs to 350 secs.

-For uncomplicated PCI, routine post-procedural heparin infusion is NOT recommended.

-For patients who do not receive GP IIb-IIIa antagonist, bivalirudin (0.75 mg/kg bolus followed by infusion of 1.75 mg/kg per hour for duration of PCI) preferred over heparin during PCI.

-Routine warfarin or other vitamin K antagonists NOT recommended after PCI in patients with no other indication for systemic anticoagulation therapy.

7.ECMO

Although the ECMO circuit has an anticoagulant lining, low-dose heparin is usually administered to prevent clot formation. The lowest effective level of anticoagulation is not known and heparin may be avoided altogether if the risks of heparin therapy are considered excessive. Some patients with severe hemorrhage have safely undergone several days of ECMO without any systemic anticoagulation at all, although in this situation it would be advisable to avoid prolonged periods of low ECMO flow rates (less than 2 lpm).

For V-A ECMO following cardiopulmonary bypass, excessive bleeding due to coagulopathy is managed as usual. A note of caution about the use of rFVIIa in patients on ECMO- it has been associated with acute generalized intravascular thrombosis.

Following cardiac surgery, heparin is commenced when chest tube drainage is <100 ml/hr for 2-3 hours, the patient is normothermic and coagulation parameters are acceptable. Heparin should ideally be commenced within 24 hours postoperatively and this is usually possible within 12 hours. The dose is titrated to maintain an ACT of 150-180 sec, which should be measured q 2 hr until it reaches a stable level. Heparin resistance is usually due to ATIII deficiency; this may be treated with fresh frozen plasma or ATIII concentrate. Tranexamic acid may be infused whilst on ECMO to treat hyperfibrinolysis.

For V-V ECMO, heparin infusion is commenced at 12u/kg/hr once the post cannulation Kaolin ACT has fallen below 200s. Kaolin ACT should be measured q 2 hr for the first 24 hrs and heparin infusion adjusted as per the list below. The target Kaolin ACT in patients with platelets > 80,000 is 150-180 sec. The target should be decreased if the patients have a tendency towards bleeding. Anticoagulation in patients with marked thrombocytopenia (plt <20k) should be discussed with the ICU physician, in general heparin may be ceased in these patients. In most instances thrombocytopenia prolongs the ACT, hence this may still be a suitable monitor of anticoagulation in mild to moderate thrombocytopenia.

ACT	Response
< 130	Bolus 1,000 u and increase infusion 200 u/hr
130 – 150	Increase infusion 100 u/hr
150-180	No change

180-200	Decrease infusion 100 u/hr
200-250	Decrease infusion 200 u/hr
> 250	Cease infusion for 1 hr. Check ACT hourly and recommence when ACT <200s at 300u/hr less than the original rate

After 24 hours the aPTT is used to monitor anticoagulation (target range of 55-75 seconds). aPTT and ACT should be checked q 6 hr and heparin dose adjusted to the APTT as per the hospital protocol. Platelets are continuously consumed because of the exposure to the foreign surface and the sheer force. As a result, platelet counts should also be monitored frequently. Fibrinogen and D-Dimer should be checked daily. If patient develops DIC with hypocoagulopathy, ECMO is operated without anticoagulant. Severe DIC should be alleviated with blood components (RBC, FFP, Cry, plt); see Appendix P.3. During transfusion, ACT is monitored very closely by ECMO perfusionists and heparin may be added if needed to prevent clot.

For HIT patients, direct thrombin inhibitor bivalirudin is given [37] with a bolus of 0.5 mg/kg followed by a continuous infusion of 0.5 mg/kg/h. Using this protocol, ACT values ranged from 180 to 220 seconds can be achieved.

8. Total Artificial Heart (SynCardia)-Anticoagulation and antiplatelet therapy (based on [75] and U. of Arizona protocol, with modifications)

Note that hemotherapy is requested to be involved in post-op antiplatelet therapy due to its complicated nature. Anticoagulant/antiplatelet therapy is ideally started after chest closure/washout, typically on POD #1, but could be delayed further if needed. Assistance with medication orders can be obtained through Dr P. Weeks (Pharmacy, 704-0623). Pathologist will order antiplatelet medications, platelet aggregation study. Recommendation for heparin/coumadin will be given to primary team. We have been requested by the Heart Failure Service to follow up TAH patients daily until discharge or transplantation due to complicated coagulation problems in these patients. The main goal during followup is to make sure that antiplatelet medications and anticoagulants are in therapeutic ranges to avoid bleeding or thrombosis.

Post-operative period (immediate); When CT < 100 mL/hr x 2 hrs and platelet count > 50k

- Hemotherapy is responsible for starting and monitoring antiplatelet medications.
- Dipyridamole (Persantine) is started at 100 mg PO or NG every 8 hours (75 mg for patients with BW less than 70 kg).
- Start ASA at 81 mg PO or NG per day. ASA may be put on hold if post-op bleeding has been significant.
- Pentoxifylline (Trental) 200 mg is started PO or NG (Oral Suspension) every 8 hours (400 mg if fibrinogen increased above normal). Pentoxifylline oral solution may be compounded by Pharmacy for feeding tube administration if patient is intubated and cannot swallow medications (Non-formulary Pentoxifylline 20 mg/mL, oral suspension, 200 mg NG TID).
- Dipyridamole and ASA doses need to be adjusted based on Platelet aggregation. Platelet aggregation is to be performed twice a week (Monday and Thursday). The first one is done 2

days after starting the medications. The goal is to obtain decrease in aggregation (<40%) with the following: arachidonic acid (2 concentrations), ADP (at 2.5 uM/mL only), Epinephrine (2 concentrations). If aggregation with collagen is decreased (<20%), too much dipyridamole or ASA is being given; daily dosages of one or both are decreased to prevent bleeding.

-Maximum Dipyridamole dosage is 400 mg q8h. Maximum ASA dosage is 325 mg qd.

-If platelet count drops (<50k) requiring transfusion or if patient develops acute bleeding, antiplatelet medications may need to be temporarily stopped or decreased to minimal doses (depending the degree of bleeding) until problems resolve.

-After antiplatelet medications are in therapeutic range with 2 platelet aggregation studies, testing can be stopped to conserve blood.

-Antiplatelet Medications for TAH with thrombocytopenia:

(a) If Plt count <50k, platelet aggregation is not to be performed (results will be abnormal due to low count, patients at risk for bleeding). Keep ASA, Persantine at minimal doses.

(b) If Plt count 50-100: use normal control with similar plt count to adjust medications. If control % aggregation is normal at such plt count, use TAH protocol with the platelet aggregation %. If control % is low, patient's results are expected to be also abnormal, keep antiplatelet medications at minimal doses.

(c) If Plt count >100: perform platelet aggregation as usual to adjust medications.

Post-operative (chest tubes pulled); When CT < 30 mL/hr x 4 hrs

-Heparin is typically ordered and monitored by CV Surgery/Cardiology team in a manner similar to that for LVAD (Appendix D1) with additional use of TEG results as needed.

-Optional use of TEG data: adjustment for heparin should prevent hypercoagulation (to achieve normocoaguability, i.e. CI <3.0). Note that TEG typically shows high MA even with adequate anti-platelet medications by platelet aggregation study. The overall goal is to keep CI <3

-If patient develops acute bleeding on heparin, heparin infusion needs to be stopped until bleeding resolves.

-Duration: Heparin is given for 2 weeks, and then (based on clinical status) may be converted to Coumadin to keep INR 2.5-3.5 for 2-3 consecutive days, then IV Heparin is stopped (see Appendix D12 for Coumadin protocol). If patient is fed through NG tube, this may interfere with absorption of Coumadin if also given through NG tube [113, 114]. It is important to flush the feeding tube following Coumadin to minimize interaction with the tube.

-TT is typically normal or only slightly prolonged even when patient is on heparin with therapeutic range for PTT.

Transfusion threshold (non-bleeding patients)

-Hgb < 7.0

-Plt < 50,000

Daily labs:

-CBC, DIC panel, LDH/haptoglobin, AT III

9. Cardiopulmonary Bypass Anticoagulation with UFH for patient with HIT [30, 32, 36] Strategies for choosing peri-operative anticoagulation in patients with a recent history of heparin-induced thrombocytopenia awaiting CPB

The main objective of this protocol is the use of plasmapheresis for patients with subacute HIT (i.e., those patients with recent HIT in whom the platelet count has recovered but in whom anti-PF4/heparin Ig antibodies (HPF4) remain detectable with or without a positive HIPA. Patients with a history of subacute HIT who require CPB have been successfully anticoagulated with a brief course of unfractionated heparin without complications. This approach is based on the theory that a secondary immune response after re-exposure to heparin is unlikely to occur until at least 3 days later. Thus, a brief exposure to heparin during CPB should not immediately elicit HIT antibodies. Furthermore, because heparin is rapidly cleared after the procedure with protamine neutralization, even if antibodies appeared a few days later, they would not be thrombogenic in the absence of heparin.

For patients with existing HPF4 antibody, plasmapheresis has been reported as a rescue therapy to effectively remove the antibody, thus to decrease the risk of thrombotic complications during heparin re-exposure. There are some general concepts. First, a direct relationship has been noted between anti-HPF4 concentrations measured by either ELISA values or by percentage release of radioactive serotonin via the serotonin release assay and the propensity to develop thrombotic complications. Second, other antibody-mediated diseases improve with plasmapheresis, such as thrombotic thrombocytopenic purpura and myasthenia gravis, generally start to respond when antibody levels are still detectable but reduced by 60-80%, which theoretically can be achieved from one plasmapheresis with 1-1.5 plasma volume. Third, normalization of the platelet count has been accomplished after a series of three apheresis procedures of 3 liter plasma exchanges each from most of the cases reported in the literature. There was also a significant decrease in the heparin-induced platelet aggregation between pre- and post-apheresis patient serum samples from those studies. We use the following strategy to manage patients with history of HIT:

(a) Patients with a history of HIT and a negative HPF4 screen just before surgery can safely be given heparin during CPB.

For patients with circulating anti-HPF4 and no evidence of active HIT (platelet count already recovered), heparin-induced platelet aggregation (HIPA), a functional test for HPF4 antibody, should be performed.

(b) If anti-HPF4 is borderline positive ($OD \leq 0.6$) and HIPA is negative, patient can safely be given heparin during CPB. Check HPF4 daily for 3 days after surgery.

(c) If anti-HPF4 is positive ($OD > 0.6$) and HIPA is negative, patients may still have risk for intraoperative or postoperative thrombotic complications, especially those with high titers of circulating antibodies shown by HPF4. In this case, plasma exchange (plasmapheresis) can significantly decrease the antibody titer and associated risks. Plasma exchange is performed with fresh-frozen plasma replacement using a 1.0 to 1.5 plasma volume exchange (approximately 2,000–4,000 mL based on patient's height, weight, gender, and hematocrit). The timing of

plasmapheresis is dependent on the available time span before surgery. Ideally, TPE is performed daily (typically for 3 consecutive days before surgery), but if necessary can be performed just prior to CPB (such as heart transplant and emergent LVAD). Check HPF4 before and after each TPE. Post-operatively, use alternative anticoagulants if the patient needs (1st choice: bivalirudin, 2nd choice: lepirudin). Check HPF4 daily with clinical follow-up for 4 days after surgery.

(d) If patient had positive anti-HPF4 (OD > 0.6), positive HIPA:

-Option1: perform plasmapheresis daily with 1 to 1.5 plasma volume with FFP daily (typically for 3 consecutive days prior to surgery). Check HPF4 and HIPA before and after each TPE.

Perform one TPE immediately prior to and one TPE immediately after surgery on the day of surgery. Use UFH during the CPB and reverse with Protamine after surgery. Post-operatively, use alternative anticoagulants if the patient needs (1st choice: bivalirudin, 2nd choice: lepirudin). Check HPF4 and HIPA daily with clinical follow-up for 4 days after surgery.

-Option 2: use alternative anticoagulants in surgery (1st choice: bivalirudin, 2nd choice: lepirudin)

HPF4 (Heparin-associated Ab by ELISA)	Functional assay (heparin-induced platelet aggregation or HIPA)**	Strategy
a.Neg	-	Use UFH for CPB.
b.Borderline positive (OD≤0.6)	Neg	Use UFH for CPB.
c.Pos (OD >0.6)	Neg	TPE daily prior to surgery, use UFH for CPB and use alternative anticoagulants post surgery.
d.Pos (OD >0.6)	Pos	Option 1: TPE daily prior to surgery. <u>One TPE immediately prior to and one TPE immediately after surgery on the day of surgery.</u> Option 2: use alternative anticoagulants in surgery (1 st choice: bivalirudin, 2 nd choice: lepirudin).

Legend:

- not tested;

** Serotonin Release Assay (SRA) result, if available, can be used in place of HIPA

NOTES:

- Some patients with CV surgery may not be exposed to UFH during surgery (for example, patients with RVAD placement may be kept on ECMO with standard dose of Angiomax). Communication with surgery team is important to avoid unnecessary plasmapheresis.

- Patients with history of HIT waiting for surgery should have HPF4 done twice a week (Mon, Thurs) to monitor the antibody. If HPF4 is positive, order HIPA or SRA testing.

- Additional apheresis procedure(s) may be performed if post-operative clinical signs/symptoms are suggestive of HIT in the setting of acute drop in platelet count, and signs of thrombotic complications. 5% Albumin may be used as plasma replacement beyond the 48 hours of surgery and the patient doesn't have bleeding. Perform plasmapheresis daily with 1 to 1.5 plasma volume daily (typically for 3 consecutive days). Check HPF4 and HIPA before and after each TPE. Rising in platelet count is a typical finding in recovery.

- Of course the decision to proceed with plasma exchange and UFH has to be agreed by the Heart Failure team (including surgery, cardiology, and anesthesia) for individual case. Both approaches (pre-operative and post-operative) would need close co-ordination by all groups for optimal timing of pheresis.

- HPF4 is batched twice daily on weekdays (M-F) and once on Sat or Sun at Southwest Core Lab (effective 11/17/2014); cut-off receiving time is 9 am and 4 pm M-F and noon on Sat/Sun (receiving time at South West). Test results should be available 3-4 hours after cut-off times. For specific requests, please call to Southwest Hematology/Coagulation # 713-456-5418. HIPA assay is done at TMC Lab in morning shift. If the testing needs to be done during the weekend, arrange with Hematology lab manager to have special coag technologists available.

-HIT antibody by Serotonin release assay (SRA): can be sent to Quests or Wisconsin Laboratory (preferable). TAT of 24 hours may be achieved by taking sample directly to Send-out Section (Kathleen) and with phone follow-up the next day.

- If patient develop marked thrombocytopenia in the post-op period, days after exposure to UFH in surgery, and currently with no clinical evidence of thrombosis, platelets may be transfused since heparin is not in patient's circulation to cause thrombotic complications.

-The IgG-specific ELISA was associated with greater specificity (93.5% vs. 89.4%), but lower sensitivity (95.8% vs. 98.1%) than the polyspecific ELISA [99]. This is attributed to the notion that activation of platelets by HIT antibodies is primarily due to the IgG subclass [100]. The IgG-specific ELISA yields fewer false positive results than the polyspecific ELISA, but at the expense of missing a small proportion of patients with true HIT who are captured by the polyspecific assay [99]. The polyspecific ELISA is used at MHH Lab.

Sensitivity and Specificity of HIT Tests [101]

Assay category	Mechanism	Examples	Sensitivity	Specificity	Comments
Immunologic	Detects antibodies against PF4/heparin, regardless of their capacity to activate platelets	1. Polyspecific ELISA 2. IgG specific ELISA	>95%	50–89%	OD of ELISA result correlates with clinical probability of HIT and odds of a positive functional assay
Functional	Detects antibodies that induce heparin-dependent platelet activation	1. SRA 2. HIPA	90–98%	90–95%	Not widely available; requires referral to a reference laboratory

PF4, platelet factor 4; OD, optical density; SRA, serotonin release assay; HIPA, heparin-induced platelet activation assay.

HIT test results can also be combined with other clinical and laboratory results for a more accurate diagnosis of HIT as seen in the following table [135]:

Estimating the Pretest Probability of HIT: The “Four T’s”			
	Points (0, 1, or 2 for Each of 4 Categories: Maximum Possible Score = 8)		
	2	1	0
Pretest probability score: 6–8 indicates high; 4–5, intermediate; and 0–3, low.			
*First day of immunizing heparin exposure considered day 0.			
Thrombocytopenia	>50% Platelet fall to nadir ≥ 20	30–50% Platelet fall, or nadir 10–19	<30% Platelet fall, or nadir <10
Timing* of onset of platelet fall (or other sequelae of HIT)	Days 5–10, or \leq day 1 with recent heparin (past 30 days)	>Day 10 or timing unclear; or <day 1 with recent heparin (past 31–100 days)	<Day 4 (no recent heparin)
Thrombosis or other sequelae	Proven new thrombosis; skin necrosis; or acute systemic reaction after intravenous UFH bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proven)	None
Other cause(s) of platelet fall	None evident	Possible	

10. Cardiopulmonary Bypass Anticoagulation with Bivalirubin (Angiomax) for patient with HIT [102]

- Angiomax dose: 1mg/kg (BW) bolus, followed by 2.5 mg/kg /hr. If ACT <400, give another bolus 0.5 mg/kg, followed by 5 mg/kg/hr and monitor ACT
- For patients with normal renal function, $T^{1/2} = 25$ min. Angiomax clearance is reduced 80% in dialysis-dependent patients ($T^{1/2}$ increases up to about 3.5 hr)
- During CPB, ACT is kept in the range [400 – 500], TEG-R [20-25], INR ~8, PTT ~180
- 2 hours after the end of Angiomax infusion, expect ACT <270, PTT <100, INR<2.4
- Clearance of Angiomax can be confirmed with a normal Thrombin Time (< 21 sec)
- If patient is bleeding actively due to Angiomax, FFP, cryo, and rFVIIa (last resort) can be attempted together with renal dialysis [33]. Platelets can also be used if there are qualitative or quantitative platelet defects.
- Note that the use of Angiomax in CPB has been known to be associated with severe bleeding complications in some cases.

11. Anticoagulation Following Bioprosthetic Valve Implantation

A variety of combinations (antiplatelet only, warfarin only, or both) have been seen for AVR, MVR, and AVR+MVR [42]

Table II: Discharge antithrombotic therapies by valve type and presence of thromboembolic risk factors.*†

Patient group/ antithrombotic therapy	Overall	AVR	MVR	AVR + MVR
Total patients (n)	320	285	28	7
Antiplatelet only (%)‡	58.8	61.8	35.7	28.6
Warfarin only (%)	10.9	9.1	32.1	0.0
Both (%)	25.6	24.6	28.6	57.1
None (%)	4.7	4.6	3.6	14.3
Patients with risk factors (n)§	197	173	20	4
Antiplatelet only (%)‡	48.7	51.5	35.0	0.0
Warfarin only (%)	15.7	13.9	35.0	0.0
Both (%)	33.5	32.4	30.0	100.0
None (%)	2.0	2.3	0.0	0.0
Patients without risk factors (n)§	123	112	8	3
Antiplatelet only (%)‡	74.8	77.7	37.5	66.7
Warfarin only (%)	3.3	1.8	25.0	0.0
Both (%)	13.0	12.5	25.0	0.0
None (%)	8.9	8.0	12.5	33.3

*Excluding patients with preoperative indications for warfarin (n = 37) or warfarin contraindications (n = 16), or patients who died prior to hospital discharge (n = 15).

†The AHA/ACC guidelines give a Class I recommendation for lifetime warfarin (INR 2.0-3.0) plus aspirin (75-100 mg daily) for all BVR patients with thromboembolic risk factors including atrial fibrillation, prior thromboembolism, left ventricular dysfunction (EF <30%), and the presence of a hypercoagulable state. Additionally, the AHA/ACC guidelines give a Class I recommendation for aspirin (75-100 mg) and a Class IIa recommendation for warfarin therapy (INR 2.0-3.0 x 3 months) in those without risk factors.

‡Antiplatelet medications include aspirin, clopidogrel, dipyridamole.

§Thromboembolic risk factors include atrial fibrillation, prior thromboembolism, left ventricular dysfunction (EF <30%), and hypercoagulable state.

AVR: Aortic valve replacement; MVR: Mitral valve replacement.

12. Warfarin Dosing [6,70]

The warfarin dose that is required is variable and dependent on a number of patient-specific and environmental factors. Evaluate patient to determine warfarin sensitivity and use guidelines below for initial dosing.

a. Initial Warfarin Dosing Guidelines

Day	INR	Warfarin High Sensitivity*	Warfarin Moderate Sensitivity**	Warfarin Low Sensitivity***
Day 1	Baseline INR	2 – 5 mg	5 mg	7.5 mg
Day 2	< 1.5	2 – 5 mg	5 mg	5 – 7.5 mg
	1.5 – 1.9	2 mg	2.5 mg	2.5 – 5 mg
	2 – 2.5	1 – 2 mg	1- 2.5 mg	1 -2.5 mg
	>2.5	none	None	None
Continue below for all patients				
Day 3	< 1.5			5 – 10 mg
	1.5 – 1.9			2.5 mg – 5 mg
	2 – 2.5			0 – 2.5 mg
	2.6 - 3			0 – 2.5 mg
	>3			NONE

Day 4	< 1.5 1.5 – 1.9 2 – 3 >3	10 mg 5 – 7.5 mg 2.5 – 5 mg 0 – 2.5 mg
Day 5	< 1.5 1.5 – 1.9 2 – 3 >3	10 mg 5 – 7.5 mg 2.5 – 5 mg 0 – 2.5 mg
Day 6	< 1.5 1.5 – 1.9 2 – 3 >3	7.5 – 12.5 mg 5 – 10 mg 2.5 – 5 mg 0 – 2.5 mg
Day 7	Make adjustment based on total weekly dose (increase or decrease) by 5-20% depending on current INR and target INR	
*High warfarin sensitivity		**Moderate warfarin sensitivity
Baseline INR > 1.5, Age > 65, Significant hepatic disease, Decompensated CHF, Malnourished, Malabsorption syndrome/ chronic diarrhea, Cancer, Hypoalbuminemia (<2), Thyrotoxicosis, Genetic polymorphism of CYP450 2C9		Baseline INR 1.2 – 1.5, Age 50-65, Concurrent CYP-450 enzyme inhibitor
		***Low warfarin sensitivity
		Baseline INR < 1.2, Age < 50, and no other risk factors

b. Maintenance Warfarin Dosing Guidelines

For Target INR 2.0 – 3.0
INR < 2.0 Increase Weekly dose by 10-15%
INR 2.0 – 3.0 No Change
INR 3.1 – 3.5 Decrease Weekly dose by 5-15%
INR 3.6 – 4.0 Hold 0 -1 dose; then decrease weekly dose by 10-15%
INR >4.0 Hold dose until INR therapeutic; assess bleeding risk, +/-Vitamin K administration; decrease weekly dose by 10-20%

For Target INR 2.5 – 3.5
INR < 2.5 Increase Weekly dose by 10-15%
INR 2.5 – 3.5 No Change
INR 3.6 – 4.0 Decrease Weekly dose by 5-15%
INR 4.1 – 5.0 Hold 0 -1 dose; then decrease weekly dose by 10-15%
INR > 5.0 Hold dose until INR therapeutic; assess bleeding risk, +/-Vitamin K administration;; decrease weekly dose by 10-20%

Notes:

- a. Baseline INR is recommended prior to initiating warfarin therapy to assess sensitivity.
- b. An INR within the last 48 hours is acceptable as a current baseline INR.
- c. Patients shall be carefully monitored with each dose and adjustments in dose are required based on INR values.
- d. With initial dosing, the INR will usually increase within 24- 36 hours.
- e. Daily INR should be obtained in hospitalized patients being initiated on warfarin until INR is within the desired therapeutic range, then INR can be evaluated twice weekly.

APPENDIX E: PT / INR Therapeutic range

INR	PT (sec)	Therapeutic intensity range
<1.5	<18.3	-
1.5-2.0	18.3-22.7	Low
2.0-3.0	22.7-31.0	Moderate
2.5-3.5	27.0-34.9	High
3.0-4.0	31.0-38.6	Very high
5.0	45.8	Critical value
10.0	77.7	Upper reportable limit

Mean x	1.5	2.0	2.5	3.0
PT	19.8	26.4	33.0	39.6

APPENDIX F: PTT / UFH Anti-Xa Therapeutic range

UFH Anti-Xa (IU/mL)	PTT (sec)
0.1	40
0.3	57
0.7	92

Mean x	1.5	2.0	2.5	3.0
PTT	44.0	58.7	73.4	88.0

-For patients with lupus anticoagulant, PTT is not suitable to monitor UFH since patient's baseline PTT is prolonged with no risk of bleeding. The standard of care is using Anti Xa-UFH (available at MHH-TMC).

-In general elevated levels of hemoglobin, bilirubin, or lipids (results from hemolysed, icteric, or lipemic specimens) may interfere with the chromogenic assay for anti Xa and yield spurious decrease in the measured level [110,111]. The spurious levels result from Free Hgb >1.5 g/l, direct bili >342 uMol/l, indirect bili > 236 uMol/l, and Triglyceride >8 mMol/l. More often, the result would not be available when the interference substances exceed the thresholds and an error message is given.

-PTT on the Stago instruments at MHH-TMC is a clot-based test (mechanically measures the clot) and is not affected by elevated levels of hemoglobin, bilirubin, or lipids.

-For patients without lupus anticoagulant and without factor deficiencies, Anti Xa-UFH is also appropriate to monitor UFH. Anti Xa-UFH and PTT would be well correlated.

-For patients with clotting factor deficiency (including liver disease patients and vitamin K deficiency), it presents a problem since pushing UFH dose to a therapeutic Anti Xa-UFH level can cause bleeding [98, 105]. The reason is that a therapeutic level of Anti Xa-UFH would be suprathreshold for patients with underlying coagulation factor deficiency. Anti Xa-UFH level just measures the UFH level in the plasma, nothing else. PTT, on the other hand, is a global test that takes into account effect of UFH and any factor deficiency. For patients in LVAD/OHT service, many have liver problems and are at risk for bleeding using Anti Xa-UFH to dose UFH. PTT would be in the suprathreshold range in such cases.

-Since the Anti Xa-UFH reagent at MHH-TMC (Stago reagent) does not contain AT and uses patient's AT for the reaction, a low AT level (<60%) would underestimate the Heparin concentration. However, the Anti Xa-UFH level in this case reflects the effective level of heparin (comparable to PTT which is sub-therapeutic with risk for clotting). In this case we have to try to bring it higher (either with more UFH infusion or giving FFP / AT concentrates if AT is too low).

-Typical therapeutic range for Lepirudin and Argatroban: 1.5-2.0 x mean of PTT ref range (i.e. 44-58.7 sec)

APPENDIX G1: Typical Infusion Protocol for Heparin Weight-based Atrial fibrillation and Stroke Prevention MPP (Therapeutic PTT of 60-80 sec)

heparin additive 25,000 unit [6 unit/kg/hr] + Premix Diluent Dextrose 5% 500 mL

500 mL, Rate: 9.89 mL/hr, Infuse over: 50.6 hr, Route: IV, Dosing Weight 82.4 kg, Total Volume: 500 mL, Start date: 09/03/14 7:28:00, Duration: 30 day, Stop date: 10/03/14 7:27:00

Order Comment: Heparin Dosing Weight = 82.4 kg
Calculate infusion rate using Heparin Dosing Weight (located in Anticoagulant Flow Record)
Draw PTT every 6 Hours or daily as indicated

PTT < 30 sec	INCREASE rate by 3 units/kg/hr (Heparin Dosing Weight) Notify Physician STAT Draw PTT in 6 hours
PTT= 30 - 45 sec	INCREASE rate by 2 units/kg/hr (Heparin Dosing Weight) Draw PTT in 6 hours
PTT= 46 - 59 sec	INCREASE rate by 1 units/kg/hr (Heparin Dosing Weight) Draw PTT in 6 hours
PTT= 60 - 80 sec	Therapeutic Redraw PTT in 6 hours to confirm PTT daily if 3 consecutive therapeutic PTT values
PTT= 81 - 90 sec	DECREASE rate by 1 units/kg/hr (Heparin Dosing Weight) Draw PTT in 6 hours
PTT= 91 - 99 sec	Hold Infusion for = 30 min DECREASE rate by 2 units/kg/hr (Heparin Dosing Weight) Notify Physician STAT Draw PTT in 6 hours
PTT > 99 sec	Hold Infusion for = 60 min DECREASE rate by 3 units/kg/hr (Heparin Dosing Weight) Notify Physician STAT Draw PTT in 6 hours

Notes:

- Starting dose typically at 4-6 u/kg/hr. Also see Appendix D2 for starting UFH after surgery.
- Some patient may be at risk for both bleeding and thrombosis manifested with recent episodes of both, a modified anticoagulant MPP may be needed. See Appendix P6 for more details.

APPENDIX G2: Typical Bivalirudin Infusion Adjustment for patients with HIT (Therapeutic PTT of 60-80 sec)

bivalirudin 100 mg + Sodium Chloride 0.9% IV 100 mL

100 mL, Rate: Start at 0.05 mg/kg/hr, Route: IV, Dosing Weight 94.7 kg, Total Volume: 100, Start date: 08/11/14 17:01:00, Duration: 30 day, Stop date: 09/10/14 17:00:00
Order Comment: 1 mg / mL conc.

For Renal Dysfunction (CrCl < 45ml/min Or Hemodialysis/CVVHD). Draw PTT q4 hours until within therapeutic range and 4 hours following any rate change. After TWO CONSECUTIVE PTT values in therapeutic range, decrease PTT draws to q12 hrs while on a direct thrombin inhibitor.

If PTT < 60 seconds, increase Bivalirudin rate by 20%;
If PTT 60 to 80 seconds, No Therapeutic change;
If PTT 81 to 90 seconds, reduce Bivalirudin rate by 25%;
If PTT 91 to 105 seconds, reduce Bivalirudin rate by 50%;
If PTT > 105 seconds, hold Bivalirudin for 1 hour and reduce rate by 50%.
If PTT > 200. Hold Bivalirudin for 2 hours then check stat PTT. Resume dosing per protocol with repeat PTT. 1 mg / mL conc.

- Infusion rate in the range 0.00x mg/kg/hr does not prolong PTT to any noticeable degree. Only rate in the range 0.0x mg/kg/hr and above does.
- Note that Bivalirudin also slightly prolongs PT (~18 sec)
- Some patient may be at risk for both bleeding and thrombosis manifested with recent episodes of both, a modified anticoagulant MPP may be needed. See Appendix P6 for more details.
- Dilute Thrombin Time (DTT) would be useful to monitor Angiomax in patients with lupus anticoagulant [106]. PTT is not suitable to monitor Angiomax since these patients' baseline PTT is prolonged with no risk of bleeding.
- For patients without lupus anticoagulant and without factor deficiencies, DTT is also appropriate to monitor Angiomax. PTT and DTT would be well correlated.
- For patients with clotting factor deficiency (including liver disease patients or vitamin K deficiency), it presents a problem since pushing Angiomax dose to a therapeutic DTT can cause bleeding. The reason is that a therapeutic level of DTT would be suprathreshold for patients with underlying coagulation factor deficiency. DTT only measures the Thrombin Time in diluted sample and it does not show any deficiency above Thrombin in the coagulation cascade.

PTT, on the other hand, is a global test that takes into account effect of Angiomax and any factor deficiency in the common and intrinsic pathways. For patients in LVAD/OHT service, many have liver problems and are at risk for bleeding using DTT to monitor / dose Angiomax. PTT would be in the supratherapeutic range in such cases.

-To order DTT, use “MD to Nurse” order. The sample will be sent to Texas Methodist Hospital Laboratory for testing. The following are therapeutic range for various direct thrombin inhibitors:

Bivalirudin (Angiomax): 60-100 seconds.

Dabigatran (Pradaxa): 55-110 seconds.

Argatroban: 50-90 seconds.

APPENDIX G3: Anticoagulant for HIT: Bivalirudin and transition to Coumadin

[43,44,45]

According to the recommendation of American College of Chest Physicians Evidence-Based Clinical Practice Guidelines:

-For patients with HIT, a nonheparin anticoagulant (such as Bivalirudin) should be started. It is recommended against the use of vitamin-K antagonist (Coumadin) therapy until after the platelet count has substantially recovered (i.e., usually to at least 150 K).

-Coumadin therapy should be started with low, maintenance doses (e.g. 2.5 mg to 5 mg), rather than higher initial dose.

-Bivalirudin should be continued after the platelet count has reached a stable plateau and INR has reached the intended target range, after a minimum overlap of at least 5 days.

APPENDIX G4: Anticoagulant with Bivalirudin for suspected HIT:

-For highly suspected HIT (such as significant drop in platelet count without other obvious etiologies, recent exposure to UFH such as in CPB, either currently on UFH or not), Bival gtt MPP for HIT is ordered with PTT target range of 50-80s; monitor for signs of bleeding on this regimen; avoid all heparins, including heparin flushes, fractionated heparin until HIT-Ab ELISA results is available.

-If HIT-Ab ELISA is positive or patient has clinical signs of thrombosis, continue bivalirudin until platelet count reaches 150k, at which point slow coumadin bridge with 5 day overlap could be initiated for 1-2 months of anticoagulant therapy for HIT (see appendix G3).

-A very low platelet count (<15k) is associated with high risk of bleeding. Platelet transfusion can be considered with patient not currently on heparin and not having signs of thrombosis.

-For patients with a need for DVT prophylaxis and having drop in platelet count with associated concern for HIT, DVT prophylaxis can be started with Bival at a fixed low rate (for example, 0.005 mg/kg/hr). Another option for DVT prophylaxis is suspected HIT is fondaparinux 2.5 mg/day subcutaneously. If HIT Ab-ELISA is negative, prophylaxis can be switched to UFH sq. If HIT Ab-ELISA is positive or patient has clinical signs of thrombosis, Bival gtt MPP for HIT is ordered with PTT target range of 50-80s.

-Note that delayed-onset HIT may occur days or even a few weeks after UFH exposure. This syndrome is associated with high-titer HIT antibodies that activate platelets even in the absence of pharmacologic heparin [136].

APPENDIX H: Clinically Important Thresholds for VerifyNow P2Y12 Test

- High risk of bleeding with surgery: <208 PRU [35]
- Acceptable risk of bleeding with surgery: >208 PRU [35]
- High risk of thrombosis after stent placement: > 230 PRU (resistance to P2Y12 inhibitors) [34]
- Low risk of thrombosis after stent placement: < 208 PRU (therapeutic range) [34]

APPENDIX I: USEFUL FILES FOR HEMOTHERAPY SERVICE USING DELL ULTRABOOKS

Dell Ultrabook can be checked out by the hemotherapy faculty from Lenora Trujillo (UT Administrator Assistant, 713.500.5306), and hemotherapy resident from Rhonda Hobbs (MHH Blood Bank, 713-704-3640).

The following instructions are for the Dell Ultrabooks used as a mobile platform for Hemotherapy. However, the general information is also applicable to desktop PCs and other laptops.

1. Using the Dell Ultrabook:

Log in the Dell with the provided user name/pwd for each Ultrabook.

Click on the Wireless icon on the lower right task bar to select wireless network

At UT: select UTHSC network, log in with your UT account

At MHH-TMC: select MHH guest network, open a web page (for example, yahoo.com), click "OK" for web use agreement

At home or other locations: use any wired/ wireless network available

Open Internet Explorer browser. A homepage for Coagulation-based Hemotherapy will appear (<http://hemepathreview.com>; item 14. Coagulation-based hemotherapy). Links for the following items are found:

- Files for Hemotherapy Guide (this file)
- Data sheets (Excel files) for intra-operative follow-up
- MHH-EMR (MHH Physician Link) login

The guide and Data sheets are updated regularly to incorporate any recent changes. The Data sheet for operative period (Operative-Datasheet.xls, see Figs 4-6) allows for direct test result entry and automatic display of suggested blood component (in the lower panel of the Excel file). Decision-support modules are embedded into the Excel file where the user would enter in laboratory results into the data fields and through 45 embedded algorithms (Appendix A, Table 7, Table 8), recommendations of units and type of transfusion products will automatically be populated under the "Summary of Suggestions" section in the Excel file. Note that the recommended transfusions are anticipated for off-pump phase and not for on-pump period. You can download this Excel file to your Dell to enter patient demographics and lab data. The Dell hard drive was encrypted and is secured for patient data. The Data sheets should be saved in "C:\Current Case" folder and the file name to be changed to reflect patient name and date of consult. Lab data in data sheets are to be copied/pasted from the excel files to the EMR notes (consultation and follow-up notes). For acute bleeding scenario other than OR case, use the appropriate data entry fields in the operative template (off-pump and after)

2. To get access to the departmental secure N drive when using the UTHSC network or MHH network:

Map N drive as following: Start->Computer->Map network drive->

Drive: N

Folder: \\129.106.153.1\Pathology\Clinical\LVAD OHT

Log in with your UT account (user: uthouston\xxxx, pwd:xxxx)

After completion of each case, enter patient's demographics in the file "Case Logbook.xls" in this folder. Patient's Data sheets are to be kept under sub-folder "/CBH patients/". These archived data files can be used for future clinical research, presentation, etc. In N drive one can also find other useful reference files (sample consultation notes, TEG, coagulopathy, medications, updates on coagulation tests, etc.).

3. To get access to the departmental secure N drive when using other networks (outside UTHSC network and outside MHH network), use VPN (UT virtual private network):

Log in <http://govpn.uth.tmc.edu> with UT account (Aventail software download and installation is needed for first use, under Admin account)

Map N drive as following: Start->Computer->Map network drive->

Drive: N

Folder: \\129.106.153.1\Pathology\Clinical\LVAD OHT

(Select option to log in using different credentials, user: uthouston\xxxx where xxxx is your UT user name)

4. Neural Network to predict risk of post-operative bleeding (after LVAD/OHT surgery):

-Prediction of significant post-op bleeding offers effective close monitor of patients and prepare for blood components. One can use Neural Networks (artificial neural networks, also connectionist systems) for this purpose: prediction of blood components used during and within 48 hours of LVAD or OHT surgery.

-Neural networks: parallel distributed systems or adaptive systems, they are composed by a series of interconnected processing elements that operate in parallel. Neural networks lack centralized control in the classical sense, since all the interconnected processing elements change or "adapt" simultaneously with the flow of information and adaptive rules. Neural networks can model highly non-linear systems in which the relationship among the variables is unknown or very complex. The network is trained using a set of input-output pairs. For each example in the training set, the network receives an input and produces an actual output. After each trial, the network compares the actual with the desired output and corrects any difference by slightly adjusting all the weights in the network until the output produced is similar enough to the desired output, or the network cannot improve its performance any further.

-Instruction for using Neural Network to predict risk of perioperative and post-op bleeding (see also Fig. 8): the Neural Network software JustNN and data file ("LVAD+OHT-Cases-5-Inputs.tvq" in C:/Current Cases/) are already installed in the Dell Ultrabooks. On other computers, do the following

Download and install software JustNN at

<http://www.justnn.com/>

Download the trained Neural Network data file

<http://www.uth.tmc.edu/pathology/hematopathology/CBH/LVAD+OHT-Cases-5-Inputs.tvq>

Open program JustNN, open data file, click on "Query" in task bar, Select "Add query", double-click on the first input field, enter result, repeat for the remaining 4 inputs (Fig. 8).

The predicted bleeding risk will be shown in the right column: L(low: $N \leq 13.5$), I(intermediate, $N=14-22$), or H(high, $N \geq 22.5$) where N is the total number of units transfused in 48 hours.

5. To create customized CBH Patient List in EMR for easy retrieval:

-A Hemotherapy List has been created with the following steps:

Go to "Patient List"

List maintenance/ New/ Custom/ xxxx (name of custom list "Hemotherapy List")/Next/Finish/

-This list can be shared with all faculty and residents in CBH team:

Go to "Patient List"

Click on the wrench icon

Click on "Hemotherapy List"

Move (->) to active lists

To add patients to list: "Add Patient", enter MRN

The CBH team coming on service the following week will have the list automatically in EMR when they come on service. This would help make the hand off process easier. Additional information on patients can be sent securely by UT-Email using the recent security features (Compose the message, then click the permissions icon and select the "Encrypt").

Fig. 4 Data entry (Pre-op)

	A	B	C	D	E	F	G	H
1	HEMOTHERAPY DATA SHEET							
2								Ver 7/29/2013
3	Consult Type:	LVAD	Pathologist:	Nguyen, Andy				
4	Timing:	operative	Path resident:	Mauzo, Shakuntala				
5	Location:	OR #1	Cardiologist:	Kar, Biswajit				
6	Date:	xx/xx/xxxx	Surgeon:	Gregoric, Igor				
7	Patient: xxxx	MRN: xxxx	Anesthesiologist:	Shahen, Ali				
8								
9	Medications:	Heparin for Tandem Heart						
10	Med stopped on:	4 hrs prior to surgery						
11								
12	LFT results:	Normal	Preop Lab values					
13			Hgb:	8.4	Plt Agg:			
14	Renal function results:	Cr 0.8, BUN 9	Plt:	167	Conc	High	Low	
15	Chronic renal failure?	no	PT/PTT:	14.8/55	AA:			
16			Fib:		ADP:			
17	Coagulation Risk:	intermediate	ATIII:		Coll:			
18					EPI:			
19					Rist:			

Fig. 5 Operative test results / suggested treatment

	A	B	C	D	E	F	G	H	I
21								Flag:	HIGH
22					[optional]				LOW
23	Event		#1	#2	#3	#4	#5		
24	Phase		Baseline	before off-pump	Off-pump	Bleeding	Bleeding		
25	Time		9:30	11:45	13:40	15:20	16:50		
26	R	[5-10] min	xxxx	xxxx					
27	h-R	[5-10] min		5.8					
28	h-Alpha	[53-72] degree		67					
29	h-MA	[50-70] mm		64.4					
30	h-EPL	[0-15] %		0					
31	h-Ly30	[0-8] %		0					
32	h-CI	[-3.0-3.0]		0.7					
33	Hgb	[12-18] g/dL	7.9	8.1	6.7	8.5	10.1		
34	Plt	[133-450]x10 ³ /μL	167	91	55	153	127		
35	PT	[12-14.7] sec	14.7	22.9	28.4	20.6	21.1		
36	PTT	[22.9-35.8] sec	33.1	xxxx	210	48.7	43.1		
37	Fib	[230-510] mg/dL	513	261	186	342	273		
38	TT	[15.0-21.2] sec	19	xxxx	110	18.9	17.1		
39	D-Dimer	[0-0.66] μg/mL FEU	0.81		0.81	0.95	0.86		
40	ATIII	[77-140] %	82	xxxx	xxxx	xxxx	xxxx		
41	VerifyNow-ASA (#1 only)	[target:>550 ARU]	597	597	597	597	597		
42	VerifyNow-P2Y12 (#1 or	[target:>210 PRU]	374	374	374	374	374		

	A	B	C	D	E	F	G
43							
44	Suggestion Summary: I	FFPs (single units)	0	2	4	2	2
45	II	Cryo (dose)	0	0	0	0	0
46	III	Plts (apheresis units)	0	2	2	0	0
47	IV	RBCs (units):	2	5	7	3	1
48	V	Tranexamic acid (gm):	0	0	0	0	0
49	VI	Protamine (mg):	xxxx	xxxx	50	0	0
50	VII	ALERT for use of FVIIa:	---	---	---	---	---
51	VIII	ALERT for AT conc:	---				
52	IX	ALERT for Protamine Overdose:			---	---	---

Note:

1. Only baseline VFN-ASA (for patient on ASA) and VFN-P (for patient on P2Y12 inhibitor) is needed. This baseline value will automatically be carried over to subsequent phases of surgeries for platelet assessment purpose.
2. Presence of heparin (seen with prolonged PTT and TT) is taken into account so that FFP will not be considered for prolonged PTT (baseline or off-pump).
3. The suggested blood components and dosage are based on algorithm (Appendix A). Clinical judgment is critical for final transfusion decision based on clinical situation.
4. The suggested transfusion is most applicable for off-pump phase when most patients will exhibit some degree of bleeding. For suggested transfusion shown in other phases (baseline, hemoconcentration), transfusion is typically not needed. The suggestions just need to be kept in mind for later management.

Fig. 6 Details of rational for suggested treatment (see Tables 7 and 8 for details)

	B	C	D	E	F	G
55	Basis for Suggested Tx:					
56	Hgb <10	2	2	3	2	0
57	h-R: 10-15	0	0	0	0	0
58	h-R: 15-20	0	0	0	0	0
59	h-R: >20	0	0	0	0	0
60	Fib: 150-200	0	0	2	0	0
61	Fib < 150	0	0	0	0	0
62	h-Alpha: 20-45,h-MA>50	0	0	0	0	0
63	h-Alpha < 20,h-MA>50	0	0	0	0	0
64	PT: 20-25	0	2	0	2	2
65	PT>25	0	0	4	0	0
66	PTT: 45-50	0	xxxx	0	2	0
67	PTT>50	0	xxxx	0	0	0
68	PTT>45, TT>25	xxxx	xxxx	hep effec	xxxx	xxxx
69	ATIII: 35-50	0				
70	ATIII <35	---				
71	Plt: 50-100	0	2	2	0	0
72	Plt <50	0	0	0	0	0
73	h-MA: 35-45,h-EPL<15,h-Ly30<8	0	0	0	0	0
74	h-MA <35,h-EPL<15,h-Ly30<8	0	0	0	0	0
75	VFN-P: 130-210	0	0	0	0	0
76	VFN-P <130	0	0	0	0	0
77	VFN-A: 350-550	0	0	0	0	0
78	VFN-A <350	0	0	0	0	0
79	h-EPL >15, h-MA<50	0	0	0	0	0
80	h-EPL >15, h-CI<1	0	0	0	0	0
81	h-LY30 >8, h-MA<50	0	0	0	0	0
82	h-LY30 >8,h-CI<1	0	0	0	0	0
83	D-Dimer > 10, Fib < 150	0	0	0	0	0
84	PTT > 45, TT > 25	xxxx	xxxx	50	0	0
85	h-EPL >15, h-MA>70	0	0	0	0	0
86	h-EPL >15, h-CI>3	0	0	0	0	0
87	h-LY30 >8, h-MA>70	0	0	0	0	0
88	h-LY30 >8,h-CI>3	0	0	0	0	0
89	h-TEG-R: 20, h-Alpha<20, h-MA<35	xxxx	xxxx	---	---	---
90	Pos Hx of CRF (uremia)	0	0	0	0	0

Table 7. Level-1 algorithms derive transfusion needs based on specific sets of laboratory tests.

	Algorithm	Representative Excel Formula (see Excel file cell location for coag test)
1-RBCs for anemia	If Hgb <10 → RBC transfusion to increase Hgb to 10.0 (1 RBC increased Hgb by 1.0)	=IF(C33=0,"0",IF(C33>=10,"0",ROUND(10-C33,0)))
2-FFPs for low clotting factors	If h-R: 10-15 → 2 units of FFP	=IF(AND(C27<=15, C27>10),"2","0")
3-FFPs for low clotting factors	If h-R: 15-20 → 4 units of FFP	=IF(AND(C27<=20, C27>15),"4","0")
4-FFPs for low clotting factors	If h-R: >20 → 6 units of FFP	=IF(C27>20,"6","0")
5-FFPs for low fibrinogen	If Fib: 150-200 → 2 units of FFP	=IF(AND(C37<=200, C37>150),"2","0")
6-Cryo for very low fibrinogen	If Fib < 150 → 1 dose of cryoprecipitate	=IF(AND(C37>0,C37<=150),"1","0")
7-FFPs for low fibrinogen	If h-Alpha: 20-45, h-MA>50 → 2 units of FFP	=IF(AND(C28<=45, C28>20, C29>50),"2","0")
8-Cryo for very low fibrinogen	If h-Alpha < 20,h-MA>50 → 1 dose of cryoprecipitate	=IF(AND(C28<=20, C28>0,C29>50),"1","0")
9-FFPs for low clotting factors	If PT: 20-25 → 2 units of FFP	=IF(AND(C35>20,C35<=25),"2","0")
10-FFPs for low clotting factors	If PT>25 → 4 units of FFP	=IF(C35>25, "4","0")
11-FFPs for low clotting factors	If PTT: 45-50 → 2 units of FFP (however if due to heparin effect in algorithm 13, then disregard value), not applicable for on-pump time	=IF(C68="hep effect","0",(IF(AND(C36>45,C36<=50),"2","0")))
12-FFPs for low clotting factors	If PTT>50 → 4 units of FFP (however if due to heparin effect in algorithm 13, then disregard value), not applicable to on-pump time	=IF(C68="hep effect","0",(IF(C36>50,"4","0")))
13-No FFP due to heparin effect	If PTT>45, TT>25 → due to heparin effect	=IF(AND(C36>45,C38>25), "hep effect", "xxxx")
14-FFPs for low ATIII	If ATIII: 35-50 → 2 units FFP, applicable to baseline only	=IF(AND(C40<=50, C40>=35),"2","0")

15-ATIII Conc for very low ATIII	If ATIII < 35 → ATIII concentrate, applicable to baseline only	=IF(AND(C40>0,C40<35),"AT Conc","---")
16-Apheresis Plts for low platelets	If Plt: 50-100 → 2 apheresis units of platelets	=IF(AND(C34 > 50,C34<=100),"2","0")
17-Apheresis Plts for low platelets	If Plt <50 → 3 apheresis units of platelets	=IF(AND(C34>0,C34 <=50),"3","0")
18-Apheresis Plts for low platelets	If h-MA: 35-45,h-EPL<15,h-Ly30<8 → 2 apheresis units of platelets	=IF(AND(C29<=45, C29>35, C30<=15,C30>0,C31<=8,C31>0),"2","0")
19-Apheresis Plts for low platelets	If h-MA <35,h-EPL<15,h-Ly30<8 → 3 apheresis units of platelets	=IF(AND(C29>0, C29<=35, C30>0,C30<=15,C31>0,C31<=8),"3","0")
20-Apheresis Plts for ADP inhibition	If VFN-P: 130-210 → 2 apheresis units of platelets	=IF(AND(C42<=210, C42>130),"2","0")
21-Apheresis Plts for ADP inhibition	If VFN-P <130 → 3 apheresis units of platelets	=IF(AND(C42>0,C42<=130),"3","0")
22-Apheresis Plts for AA inhibition	If VFN-A: 350-550 → 2 apheresis units of platelets	=IF(AND(C41<=550, C41>350),"2","0")
23-Apheresis Plts for AA inhibition	If VFN-A <350 → 3 apheresis units of platelets	=IF(AND(C41>0,C41<=350),"3","0")
24- Tranexamic acid for primary fibrinolysis	If h-EPL >15, h-MA<50 → 1gram of Tranexamic acid	=IF(AND(C30>15,C29<=50,C29>0),"5","0")
25-Tranexamic acid for primary fibrinolysis	If h-EPL >15, h-CI<1 → 1gram of Tranexamic acid	=IF(AND(C30>15,C32<=1),"5","0")
26- Tranexamic acid for primary fibrinolysis	If h-LY30 >8, h-MA<50 → 1gram of Tranexamic acid	=IF(AND(C31>8,C29<=50,C29>0),"5","0")
27- Tranexamic acid for primary	If h-LY30 >8,h-CI<1 → 1gram of Tranexamic acid	=IF(AND(C31>8,C32<=1),"5","0")

fibrinolysis		
28- Tranexamic acid for primary fibrinolysis	If D-Dimer > 10, Fib < 150 → 1gram of Tranexamic acid	=IF(AND(C39>10,C37<=150,C37>0),"5","0")
29-Protamine for excess heparin	If PTT>45, TT>25 → 50 mg of protamine (only off pump and after)	=IF(AND(E36>45,E38>25),"50","0")
30-Secondary fibrinolysis, no FVIIa!	If h-EPL >15, h-MA>70 → no FVIIa	=IF(AND(C30>15,C29>70),"No FVIIa!","0")
31-Secondary fibrinolysis, no FVIIa!	If h-EPL >15, h-CI>3 → no FVIIa	=IF(AND(C30>15,C32>3),"No FVIIa!","0")
32-Secondary fibrinolysis, no FVIIa!	If h-LY30 >8, h-MA>70 → no FVIIa	=IF(AND(C31>8,C29>70),"No FVIIa!","0")
33.Secondary fibrinolysis, no FVIIa!	If h-LY30 >8,h-CI>3 → no FVIIa	=IF(AND(C31>8,C32>3),"No FVIIa!","0")
34-Possible Protamine Overdose	If h-TEG-R>20, h-Alpha<20, h-MA<35 (only off pump and after, no bleeding seen) → Yes to possible protamine overdose	=IF(AND(F27>20, F28>0, F28<=20, F29>0, F29<=35), "YES!!", "---")
35-Cryo for chronic renal failure	Pos Hx of CRF (uremia)	=IF(B15="yes","1","0")
36. Only baseline VFN's needed	If baseline VFN exists, carry over to subsequent phases	D41=IF(C41>0, C41, "xxxx")

Table 8. Level-2 algorithms combine results from Level-1 algorithms (Table 7) for final transfusion suggestions

	Summary of components	Rules to combine algorithm steps	Representative Excel Formula (see Excel file cell location for coag test)
1	FFPs (single units)	Maximum value from algorithm 2-5,7,9-12,14	=MAX(INT(C57),INT(C58),INT(C59),INT(C60),INT(C62), INT(C64),INT(C65),INT(C66),INT(C67),INT(C69))
2	Cryo (dose)	Maximum value from algorithm 6,8,35	=MAX(INT(C61),INT(C63),INT(C90))
3	Plts (apheresis units)	Maximum value from algorithm 16-23	=MAX(INT(C71),INT(C72),INT(C73),INT(C74),INT(C75), INT(C76),INT(C77), INT(C78))
4	RBCs (units):	-RBCs to increase Hgb to 10: A -RBCs to correct Hgb for FFP: B=0.5 x FFPs -RBCs to correct Hgb for plts: C=Plts -If Hgb-(A+B)>10 no RBCs needed -Otherwise, RBCs=A+B+C	=IF(C33-0.5*C44-C46>10,"0",C56 + 0.5*C44 + C46)
5	Tranexamic acid (gm):	Maximum value from algorithm 24-28	=MAX(INT(C79),INT(C80),INT(C81),INT(C82),INT(C83))
6	Protamine (mg):	Value from algorithm 29	=E84
7	ALERT for use of FVIIa:	Any pos value from algorithm 30-33	=IF(AND(C85="0", C86="0",C87="0",C88="0"),"--", "No FVIIa!")
8	ALERT for AT conc:	Value from algorithm 15	=C70
9	ALERT for Protamine Overdose:	Value from algorithm 34	=E89

Fig. 8 Using the trained Artificial Neural Network to predict risk of perioperative bleeding in a new case

Add query, enter test results Predicted outcome (last column)

	R	CI	Plt. Count	PT	D-Dimer	RISK
1.0	7.5000	-3.1000	80.0000	24.0000	3.0900	I
2.0	7.9000	-4.2000	70.0000	29.7000	1.4400	H
3.0	5.1000	?	133.0000	36.8000	?	I
4.0	8.5000	-3.1000	68.0000	23.5000	0.3700	L
5.0	6.1000	0.6000	80.0000	22.0000	8.1600	I
6.0	7.3000	1.9000	219.0000	?	2.2200	L
7.0	8.8000	-14.5000	29.0000	36.1000	4.0600	H
8.0	9.7000	0.7000	55.0000	28.4000	0.9500	H
9.0	8.7000	-1.6000	45.0000	22.8000	17.0500	I
10.0	6.2000	5.3000	191.0000	18.3000	1.2700	L
11.0	6.4000	1.9000	136.0000	20.8000	2.5100	L
12.0	?	?	126.0000	16.3000	2.2300	L
13.0	5.9000	1.5000	143.0000	22.1000	2.2500	L
14.0	9.2000	-1.7000	64.0000	26.3000	0.0600	H
15.0	4.9000	3.6000	63.0000	18.8000	0.0200	I
16.0	7.0000	-0.9000	132.0000	21.3000	0.0100	L
17.0	5.8000	1.3000	181.0000	15.7000	0.4600	L
18.0	4.7000	1.3000	69.0000	22.6000	2.1400	I
19.0	4.6000	0.9000	77.0000	28.0000	1.0200	I
20.0	5.2000	1.4000	177.0000	19.7000	1.9100	L
21.0	6.9000	-1.8000	81.0000	22.0000	1.0900	H
1.0	7.6000	-0.6000	85.0000	22.7000	1.4400	L
2.0	6.2000	-0.8000	65.0000	23.0000	14.8300	I
3.0	4.7000	1.2000	112.0000	20.8000	13.5100	H
4.0	5.6000	-0.1000	88.0000	22.4000	2.1800	H
5.0	8.9000	?	229.0000	19.2000	3.6600	L
6.0	11.1000	?	103.0000	21.7000	?	L
7.0	7.9000	?	72.0000	23.8000	2.1500	L
8.0	5.3000	1.5000	152.0000	23.3000	0.0600	L
9.0	3.1000	?	51.0000	19.2000	3.0000	I
10.0	8.0000	-3.2000	64.0000	24.9000	1.6500	L
11.0	4.1000	0.2000	101.0000	18.2000	2.3700	I
12.0	4.2000	-1.9000	54.0000	23.4000	3.7100	L
13.0	5.1000	2.5000	135.0000	22.7000	0.6800	L
14.0	6.1000	1.7000	110.0000	18.5000	3.1300	I
15.0	15.8000	?	132.0000	25.9000	?	I
16.0	9.4000	?	43.0000	19.9000	0.5300	I
17.0	9.0000	0.0000	151.0000	24.1000	1.7000	L
18.0	8.3000	?	94.0000	22.7000	0.9300	L

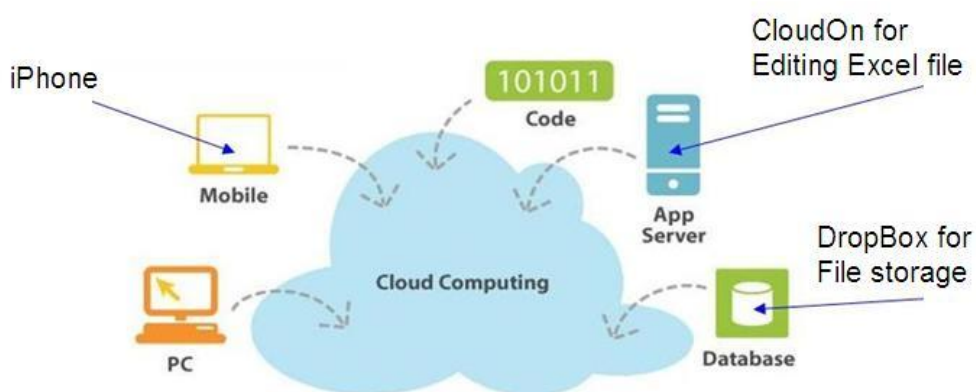
RISK OF BLEEDING	L:	<=13.5
(Total number of units transfused in 48 hours)	I:	14-22
	H:	>=22.5

APPENDIX I2: CBH Operative Datasheet using iPhone

1. CloudOn platform

An iPhone (or iPad) app called "CloudOn" can be set up and connected to DropBox (see Fig. 9). CloudOn allows for running CBH Datasheets (MS Excel files) on an iPhone. The updated Excel file is saved in DropBox. The Datasheet can be used to track lab results during surgery, also to get transfusion recommendations based on CBH transfusion criteria. Finally it can be included in EMR note for CBH service. No patient's demographics (full name, MRN) should be entered in the Excel file since DropBox is not a secure storage space. Use only pt's initials and date of surgery for demographics.

Fig. 9 CloudOn Mobile platform



2. Installing CloudOn on iPhone

- Go to iTunes site, download the free "CloudOn" app using one's iTunes account
- Log in existing hemotherapy account
(ask the CBH attending for user and password)

3. Using CloudOn on iPhone

- Open CloudOn; select DropBox (Fig 10). Screen will show a list of i-Operative-Datasheets (Fig 11). Select one of them; make sure that the file has not been used before (if it was, just select another file)
- Enter data for the case (Fig 12); file will be saved by clicking file icon at upper right corner; to view transfusion recommendations scroll to lower part of screen (Fig 13)
- File can be e-mail to self (or to others) by clicking the right arrow icon at upper right corner (Fig 14). This file then can be opened in one's e-mail account and be copied/pasted to EMR note.
- Screenshot image of file can be taken (press Home button and Power button at the same time). Image will be saved in Photo folder and can be sent by messaging as image attachment.
- CBH guide is also available in DropBox and can be reviewed on iPhone (Fig 15)
- Note that only one user can access files in this hemotherapy account at any given time. To let others get access to the files, exit the CloudOn app by double-clicking Home button and swipe out the CloudOn app.

Fig. 10 Select DropBox on CloudOn site

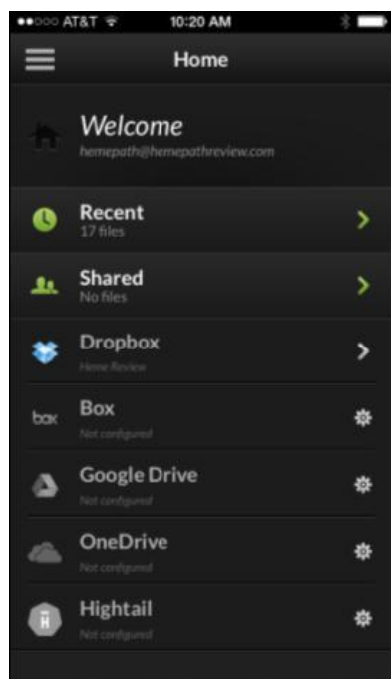


Fig. 11 Select one i-Operative Datasheet from the list

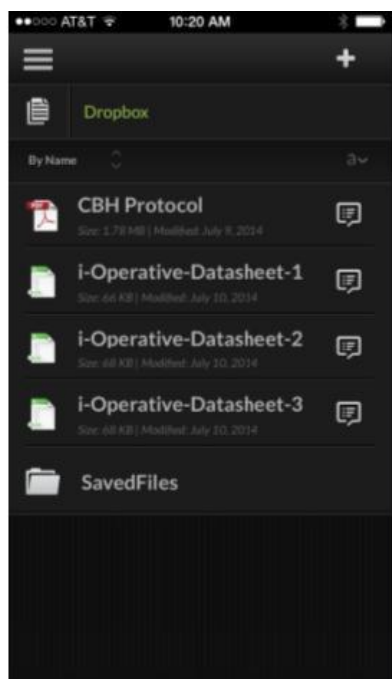


Fig. 12 Data entry

	A	C	D	E	F	G
1	CBH DATA SHEET-iPhone Version 7/12/14					
2	RF? y/n:	n	Pt:	DE	Date:	7/1/14
3	Phase	#1 Basils	#2 Roum	#3 Off-yone	#4 Bleeding	
4	Time					
5	R	xxxx	xxxx			
6	h-R		5			
7	h-Alpha		20			
8	h-MA		40			
9	h-EPL		4			
10	h-ly30		4			
11	h-CI		1			
12	Hgb	12	9			
13	Pit	230	40			
14	PT	12	22			
15	PTT	32	xxxx			
16	Fib	320	110			
17	TT	20	xxxx			
18	D-Dimer 0.5					
19	ATIII	80	xxxx	xxxx	xxxx	
20	VFN-A		xxxx	xxxx	xxxx	(#1)
21	VFN-P		xxxx	xxxx	xxxx	(#1)

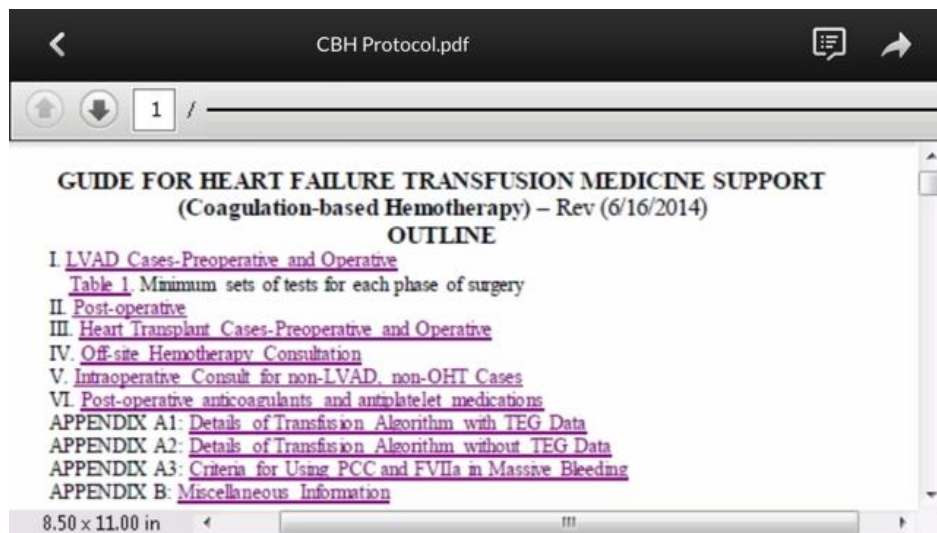
Fig. 13 Transfusion recommendation

	A	C	D	E	F	G
18	D-Dimer 0.5					
19	ATIII	80	xxxx	xxxx	xxxx	
20	VFN-A		xxxx	xxxx	xxxx	(#1)
21	VFN-P		xxxx	xxxx	xxxx	(#1)
22						
23	FFPs	0	2	0	0	single
24	Cryo	0	1	0	0	dose
25	Plts	0	3	0	0	dose
26	RBCs	0	5	0	0	
27	Trnx A	0	0	0	0	gm
28	Prota	xxxx	xxxx	0	0	mg
29	I-FVIIa	-	-	-	-	
30	I-AT con	-	xxxx	xxxx	xxxx	
32						
33						
82						
83						
84						
85						
86						

Fig. 14 Sending the Datasheet by e-mail



Fig. 15 Reviewing the CBH guide



APPENDIX J: EMR Notes and CPT Codes for billing

- For LVAD cases with advanced notice (at least one-day in advance), hemotherapy notes include: consultation, intra-operative followup, and (POD #1) follow-up with sign-off. If patient has persistent coagulopathy/bleeding, additional notes on subsequent days would be needed.
- For emergency LVAD cases without advanced notice and OHT cases, hemotherapy notes include: consultation (also including intra-operative information), and (POD #1) follow-up with sign-off. If patient has persistent coagulopathy/bleeding, additional notes on subsequent days would be needed.
- For others (non LVAD/OHT surgeries, acute bleeding, etc.), hemotherapy notes include: consultation (also may include intra-operative information for surgery), and (POD #1) follow-up with sign-off. If patient has persistent coagulopathy/bleeding, additional notes on subsequent days would be needed.
- We have been requested by the Heart Failure Service to follow up TAH patients daily until discharge or transplantation due to complicated coagulation problems in these patients. It takes minimal effort to check EMR for acute event, to follow coag results and to write a followup note.
- For CPT code, use 99222 (50 minutes) or 99223 (70 minutes) for the initial consultation (with Consultation Note), 99222 for most straightforward cases and reserve 99223 for more complex cases with very complicated workup and intervention. 99223 is also for emergent consultation that includes intraoperative follow-up. 99221 (30 minutes) is sometimes used for very simple consultation.
- 99231-3 (15 minutes) for each subsequent day we follow the patient (with Follow-up Note) with a very straightforward follow-up; i.e. no/minor bleeding, minor management changes, etc.
- 99232-3 (25 minutes) for each subsequent day we follow the patient (with Follow-up Note) with complications, i.e. intra-operative or post-op follow-up requiring to go back to check on the patient multiple times during the day for multiple lab checks, interventions, etc. 99233 (35 minutes) is sometimes used for very complicated follow-up.
- Consultation note (CPT code 99222 or CPT 99223) must include 10 components in Review of Systems and 8 components in Physical Examination. Alternately, the following has to be stated in the consult note:
 - (a)“I have spent at least 50 minutes (or 70 minutes) on the patient’s evaluation and management; more than 50% of the time involves counseling and coordination of care” (write a short description of the work involved), or
 - (b)“The 10 point review of systems performed with pertinent positives and negatives as per HPI”.
- For prolonged service, description of activities with timing have to be included in clinical notes. CPT code 99356 is used for the first additional hour and 99357 for each additionally subsequent ½ hour.
- EMR notes have to be signed in 48 hours of the provided service.

To prepare for billing:

- Print out patient’s Demographics sheet from EMR
- Write in the lower right corner case information (sample):
 - Hemotherapy
 - Consultation CPT 99222 (7/12/2015)
 - Follow-up CPT 99232-3 (7/13/2015)

Pathologist: John Doe, MD; signature
 -Leave the form in Peggy Bell's UT mail box for McKesson/Traci Allen billing (Peggy's office: MSB 2.020, phone 500-5404)

APPENDIX K: TYPICAL DESENSITIZATION AND TREATMENT OF ANTIBODY-MEDIATED HEART TRANSPLANT REJECTION WITH PLASMA APHERESIS

Table 5 Examples of Desensitization Therapies [30]

Therapy	Dose	Frequency
Plasmapheresis	(A, F) 1.5 volume exchanges	(A) 5 consecutive days (B) 5 times, every other day (c) 2-3 times/week until transplant (D) 5 times, every other day, every 2-4 weeks
Intravenous immunoglobulin (IV Ig)	(A, B) 2g/kg IV divided over 2 days (C) 2-3 g/kg IV divided over 4 days (D) 0.1 mg/kg IV (E) 100 mg/kg IV (F) 20 g (of 10% IV Ig) (G) 150 g (of 10% IV Ig) divided over 3 rounds	(A) Every 2-4 weeks (D) Every 2-4 weeks (E) Every 4 weeks (G) Every 4 weeks
Rituximab	(A) 1g IV (C, E) 375 mg/m ² (G) 500 mg	(A) Weekly x 4 (C) x 2 doses (E) Weekly x 4 (G) Every 2 weeks

(A) UCLA; (B) Stanford University; (C) University of Maryland; (D) University of Toronto; (E) University of Wisconsin; (F) Loyola University Chicago; (G) University of Berlin.

Table 6 Examples of Therapies for Antibody-Mediated Rejection [31]

Therapeutic modality	Dose	Frequency	Duration
Plasmapheresis	1-2 plasma volume exchanges	-Daily -Every other day -3 times per week -Once weekly	3-5 days 1-2 weeks 1-4 weeks 2-4 weeks
IV immunoglobulin	100 – 1000 mg/kg	1–3 times per week, often given after each plasmapheresis	1-4 weeks
Rituximab	375 mg/m ²	Once weekly	1-4 weeks

APPENDIX K2: HLA Testing for OHT

-For OHT, HLA class I (A, B, C, E) and class II (DP, DQ, DR) are considered clinically important.

-For pre-transplant testing, recipient has testing for ABO-Rh, HLA typing (class I, class II), anti HLA in the form of panel reactive antibody (PRA) which indicates the degree of HLA antibody reactivity to the general population (a high number for PRA, for example 100% indicates difficulty to find compatible donor). These data are entered into UNOS's database. The donor's data (ABO-RH, HLA typing) are also entered into UNOS's database to match appropriate recipients for OHT.

-On the day of OHT, blood and a lymph node from the donor will also be transported to MHH for HLA cross-match (between donor's cells and recipient's serum). Even though this cross-match is the gold standard to determine compatibility, timing of OHT does not allow for cross-match results to be available prior to OHT. Instead, a virtual cross-match would be done prior to OHT; i.e. comparing recipient's HLA antibodies to donor's HLA antigens to predict results of the actual cross-match.

-For post-transplant testing, donor-specific antibody (DSA) in recipient's plasma is followed to monitor recipient's reaction to the graft.

-DSA is measured in mean fluorescence intensity (MFI). Following are the ranges associated with risk of rejection:

High risk: > 8,500 MFI

Moderate risk: 3,000-8,499 MFI

Low risk: 1,000-2,999 MFI

Very low risk: 500-999 MFI

-Note that DSA measurement is based on Luminex beads which have a high degree of false positivity. The use of MFI ranges (instead of just an MFI) value alleviates this problem but not completely. MFI levels need to be correlated with clinical information and also cardiac biopsy. Positivity for C4d in cardiac tissue capillary is associated with antibody-mediated rejection.

-Blood transfusion can increase HLA antibody levels, causing OHT rejection and requiring treatment. For this reason, transfusion for OHT candidates and OHT patients needs to be minimized whenever possible. For example, Hgb threshold for RBC transfusion can be set as low as 6.0 if the patient is hemodynamically stable.

APPENDIX K3: Antibody Mediated Rejection (AMR) and Acute Cellular Rejection (ACR)

Cardiac AMR and ACR are diagnosed with endomyocardial biopsy, together with HLA testing and clinical information. The following criteria for AMR and ACR are endorsed by the International Society of Heart and Lung Transplant (ISHLT) [137]

The 2013 ISHLT Working Formulation for Pathologic Diagnosis of Cardiac Antibody-Mediated Rejection		
Grade	Definition	Substrates
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both absent
pAMR1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are absent
pAMR1 (I+)	Immunopathologic AMR alone	Histologic findings are absent and immunopathologic findings are present
pAMR2	Pathologic AMR	Histologic and immunopathologic findings are both present
pAMR3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema with immunopathologic findings are present.

pAMR: pathologic AMR

Immunopathologic: positivity for C4d in cardiac tissue capillary

ISHLT-2004 Acute Cellular Rejection Grading Scheme

Grade	Histopathologic findings
0R, none	None
1R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
2R, moderate	Two or more foci of infiltrate with associated myocyte damage
3R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis

From Stewart et al JHLT, 2005

-Mixed rejection (AMR and ACR): most transplant pathologists recognize that biopsies with the histopathologic and/or immunophenotypic findings of AMR also have a component of ACR. In

most cases the ACR is low grade (Grade 1R). Less commonly, however, higher grade of ACR such as 2R or 3R are encountered in association with AMR.

Incorporating pathologic AMR diagnosis into the clinical picture

The 2013 ISHLT defines biopsy-based pathologic AMR, but this is only one factor in the clinical diagnosis and treatment of AMR. The presence of DSA, imaging and hemodynamic assessments of graft function, and other signs and symptoms of graft failure must all be considered by the clinical team. This integration is fundamental for patient management but challenging and remains open to debate between centers. One of the primary controversies revolves around treating patients with "asymptomatic/subclinical" AMR. In these patients with normally functioning grafts, the risk of intensifying immune suppression (further predisposing to infections and neoplasms) must be weighed against the potential benefit of preventing later cardiac allograft vasculopathy (CAV) and other complications.

An online survey of 184 ISHLT members showed greatest agreement for treating AMR with graft dysfunction regardless of pathologic AMR severity. Most centers also would treat AMR if DSA was present, with or without graft dysfunction and with any degree of pathologic AMR severity. In the absence of both graft dysfunction and DSA, pAMR1 would be treated by 30% of respondents, pAMR2 by 50% of respondents, and pAMR3 by 70% of respondents.

Treatment of cardiac transplant rejection [31]:

-AMR: treatment with plasmapheresis x 5 (3 daily ones followed by 2 more every other day) with IVIg, anti-thymocyte antibodies, and Rituximab. Refractory AMR is treated with more plasmaphereses.

-ACR: treatment is typically considered for ACR 2R and 3R with immunosuppressants (steroids, antithymocyte globulin). Refractory ACR is treated with photopheresis.

APPENDIX L: THERAKOS™ Photopheresis for solid organ transplant [52-59]

A therapy originally designed to reduce the skin symptoms associated with cutaneous T-cell lymphoma (CTCL), an immune related lymphoma. THERAKOS™ Photopheresis has also been used to treat: graft-versus-host disease (GVHD) that can occur after bone marrow transplantation; and to treat rejection that can occur after some solid organ transplant (SOT) operations. Extracorporeal photopheresis has been used to help treat patients with heart, lung, kidney and liver transplant rejection. Published studies in adults have been carried out to assess the ability of ECP to help prevent or treat organ rejection in heart transplant patients. The therapy involves the intravenous (IV) collection of blood from the body and the treatment of that blood, first with a medication called methoxsalen (psoralen, UVADEX®), then with ultraviolet-A (UVA) light, after which the blood is returned to the body. THERAKOS™ Photopheresis is also known as extracorporeal photopheresis (ECP), photoimmune therapy, and immune cell therapy. In many patients, THERAKOS™ Photopheresis has very positive effects, although not all

patients will respond. In the case of SOT rejection, successful treatment with photopheresis can reduce or reverse rejection and symptoms of rejection in some organs. One other effect of successful photopheresis therapy in GVHD and SOT rejection is that patients may be able to take lower doses of steroids and other immunosuppressive medication. As with any medical treatment, it is difficult to predict the type and extent of response patient will have.

The side effects of THERAKOS™ Photopheresis are listed below:

- Sensitivity to sunlight for 24 hours (avoid sunlight, wear UVA-protective glasses, and wear sunscreen with an SPF (sun protection factor) of at least 15
- Fatigue, itchiness, fever, redness
- Risk of infection due to needle puncture
- Drop in blood pressure

There is no standard schedule for extracorporeal photopheresis, and reported schedules vary by the organ type. However, most reported cardiac and lung schedules initiate therapy with 2 consecutive days of extracorporeal photopheresis weekly for 1 month, followed by biweekly therapy on 2 successive days for months 2 and 3, then monthly on 2 consecutive days for months 4–6. Two consecutive procedures are called a session. The total number of procedures is therefore 24 (or 12 sessions)

APPENDIX M: Acquired von Willebrand Syndrome (AVWS) in LVAD patients [47-49, 61]

-Patients with LVAD implantation have a high risk of major bleeding, particularly GI bleeding, during the support time and at the time of heart transplant. AVWS occurs in many patients on continuous-flow assist devices and appears to be a significant contributor to the observed bleeding. It has been determined that increased prevalence of bleeding with continuous-flow devices is not explained by excessive anticoagulation therapy. Bleeding during LVAD support is particularly frequent in older patients and, unless prevented, may constitute a major limitation of this bridging therapy.

-AVWS is often incidentally suspected in an LVAD patient with a decrease in aggregation with high concentration of Ristocetin in platelet aggregation study. AVWS then needs to be ruled out with vWD panel (F VIII, vWF:Ag, vWF:RCo), and vWF multimer.

-All anticoagulation medications are discontinued during the bleeding episode and until hemodynamic stability is achieved. The bleeding site is identified and corrected, if possible.

-Patients with AVWS have abnormal vWF multimer (decrease in large multimer) but F VIII, vWF:Ag, vWF:RCo are typically not decreased. For rare cases with bleeding due to AVWS and vWF:RCo \leq 45%: treatment can be started with Humate-P

Loading dose: 30-60 IU/kg (start with 30 IU/kg)

Maintenance dose: 20-40 IU/kg q 12-48 hrs (start with 20 IU/kg q 24 hrs)

Daily lab: vWD panel with targeted trough (before next dose) of vWF:RCo \geq 45%

Prophylactic treatment for non-bleeding: target vWF:Rco \geq 30%

- After stabilization of hemoglobin levels, anticoagulation treatment is resumed on an individual patient basis considering the extent of bleeding, the patient's age, and the risk of thrombosis. The majority of patients are restarted on warfarin and aspirin.

Notes:

1. Criteria to diagnose AVWS:
 $vWF:RCo / vWF:Ag < 0.8 \rightarrow AVWS$
 Note that vWF:RCo can be normal, vWF:Ag can be normal or even increased
 Large vWF multimer is decreased (long TAT makes this test less useful for clinical management)
2. vWD panel is performed at MHH-TMC lab (M-F). vWF multimer is sent to Wisconsin Blood Center Lab (TAT 7-10 days)
3. A high percentage of (elderly) LVAD patients would also have MGUS, exacerbating the AVWS with this combination. MGUS can be ruled out with serum protein immunofixation (bypassing serum protein electrophoresis which may yield a false-negative result).
4. Dosing for concentrate infusion Humate-P (in IU):
 $0.5 \times (\text{desired } vWF:RCo \text{ level in } \% - \text{baseline } vWF:RCo \text{ level in } \%) \times \text{BW in kg}$
 Humate-P is expected to be cleared more rapidly than that used for vWD due to existing condition, however it is still the best treatment for acute bleeding. Besides LVAD, AVWS can be seen in: aortic stenosis, VSD/ASD, ECMO, mitral valve regurgitation, myeloproliferative neoplasms, monoclonal gammopathy, and autoimmune disorders.
6. For new diagnosis of AWS, always notify Dr. Sriram Nathan to discuss about treatment for patients. Clinical Hematology may also need to be requested by cardiologists for followup.
7. AWS may also be seen in patients with aortic valve stenosis. AV repair typically alleviates the clinical complications.
8. For heart failure patients on anti-platelet medications and also with uremia: platelet aggregation results may be similar to those of AWS patients (decreased aggregation with all reagents). Without adequate time for full workup prior to surgery, cryoprecipitate would be useful for microvascular bleeding during and after surgery since cryoprecipitate helps with both conditions.

APPENDIX N: TYPICAL ORDERS

- FFP product order: 09/13/12 0:38:00, Stat, ONCE, 2, day, # Units 2, To give, 9/13/12
- PRBC: 07/12/12 22:23:00, Stat, ONCE, 1, day, # Units 1, To give, 7/12/12
- Platelet product order: 07/12/12 22:23:00, Stat, ONCE, 1, day, # Units 6, To give, 7/12/12
- MD to Nurse Order, Misc: 07/12/12 15:25:00, please re-start persantine at 100mg q8H when CT output is $< 100\text{ml}/\text{h} \times 2\text{hrs}$.
- MD to Nurse Order, Misc: 07/12/12 15:21:00, please page Dr. Xxxx @ xxx-xxx-xxxx for the following reasons. 1. CT output $> 100\text{ml}/\text{hr}$ or $< 30\text{ cc}/\text{hr} \times 4\text{ hrs}$. 2. Hct $< 22\text{g}/\text{dl}$ 3. Plt count $< 50,000$ 4. INR > 2.0
- MD to Nurse Order, Misc: 07/29/12 9:27:00, Please transfuse platelets if Platelet count is less than 50,000. Please transfuse RBC, if hemoglobin less than 8. Please Transfuse cryo, if fibrinogen less than 100.
- MD to Nurse Order, Misc: 08/08/12' 12:43:00, 1. Please continue to check CBC and DIC panel Q12 hours. 2. Please page Dr. Xxxx xxx-xxx-xxxx if chest tube output increases more than 100 cc/hr, if the chest tube output decreases to less than 30 cc/hr x 4 hours
- MD to Nurse Order, Misc: 07/15/12 6:05:00, Please contact Dr. Xxxx (xxx-xxx-xxxx) when CT output is less than 50 cc/hr x 4 hours.

- MD to Nurse Order, Misc: 07/12/12 15:41:00, Please increase the heparin to 1200 units/ hr and re-check the PTT in 4 hours. Thank you.
- MD to Nurse Order, Misc: 08/08/12 21:41:00, Increase Heparin gtt to 700 Units per hour and recheck PTT with AM labs
- Dipyridamole: 75 mg, 1 tab, Route: NG, Drug form: TAB, Q8H, kg, Start date: 07/15/12 16:00:00, Stop date: 08/15/12 8:00:00
- Dipyridamole: 100 mg, 2 tab, Route: NG, Drug form: TAB, Q8H, kg, Start date: 07/15/12 16:00:00, Duration: 30 day, Stop date: 08/15/12 8:00:00
- Pentoxifylline Oral Suspension 20 mg/ml, 200 mg, 10 mL, Drug form: MISC, Route: NG, Q8H, 09/10/12 12:00:00, Duration: 30 day, Stop date: 10/10/12 8:00:00
- Platelet Function Studies: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- Platelet Aggregation: 07/15/12 11:00:00, Stat, ONCE
- Antithrombin III Functional Assay: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- LDH: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- Haptoglobin: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- CBC w/ Diff and Platelet: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- CBC (no diff): 07/15/12 10:00:00, Routine, Start At and Q6H, 4, day
- BMP: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- Liver Function Panel: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- Plasma Hemoglobin: 08/08/12 6:00:00, Timed Study, Q-Tu and Th, 4, week
- Prealbumin: 08/08/12 6:00:00, Timed Study, Q-Tu and Th, 4, week
- DIC Screen: 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- Thromboelastograph: 07/15/12 11:16:00, Stat, ONCE, 1, day
- TEG (Heparinase): 07/15/12 11:00:00, Routine, ONCE
- TEG (Heparinase): 08/08/12 6:00:00, Timed Study, Early AM, 30, day
- Thrombate (AT III concentrate): 3,294 unit, Route: IV, Drug form: INJ, ONCE, Start date: 07/15/12 15:23:00, Stop date: 07/15/12 15:23:00
- DIC Screen: 07/15/12 6:05:00, Routine, Start At and Q6H, 4, day
- PRBC: 08/20/12 19:27:00, Stat, ONCE, 1, day, # Units 10, Surgery, 8/20/12
- Platelet product order: 08/20/12 19:27:00, Stat, ONCE, 1, day, # Units 10, Surgery, 8/20/12
- FFP product order: 08/20/12 19:27:00, Stat, ONCE, 1, day, # Units 10, Surgery, 8/20/12
- PT and PTT: 08/20/12 19:19:00, Stat, ONCE
- Fibrinogen: 08/20/12 19:19:00, Stat, ONCE, 1, day
- D-Dimer: 08/20/12 19:19:00, Stat, ONCE, 1, day
- Hemoglobin and Hematocrit: 08/08/12 19:29:00, Stat, ONCE, 1, day
- Amicar I.V.: Loading dose: 5 g during the first hour, followed by 1 g/hour IV for 3 hours
- Coagulation factor VIIa 1,000 micrograms, route IVP, drug form: PDR/INJ, once
- Protamine (sulfate) 50 mg IV/10 minutes
- Heparin 25,000 units in D5W Premix (titrate) 25000 unit: 25,000 unit, 500 mL, Rate: Titrate as Directed or per Protocol, Dosing Weight 95, kg, Route: IV, Total Volume: 500, Start date: 08/12/12 18:27:00, Duration: 30 day, Stop date: 9/12/12 18:26:00, Replace Every: 24 hr
- Vitamin K 2.5 mg PO
- Heparin 25,000 unit (Heparin – infusion (ACS Protocol) heparin 25,000 units in D5W 500 mL Premix 25,000 unit) 25,000 unit Start at 13 units/kg/hr – adjust per ACS protocol

- Bivalirudin 250 mg + Sodium Chloride 0.9% IV 250 mL (bivalirudin 250 mg in NS 250 mL (for HIT) 250 mg + Sodium Chloride 0.9% IV 250 mL) 250 mg Please use Direct Thromb Inhibitor MPP

-MD to Nurse Order, Misc: 03/05/13 22:59:00, If CT output > 200 ml/hr please draw CBC w/o diff, DIC screen, TEG. Notify Hemotherapy, Surgeon, & Cardiologist.

-Notify MD: 07/23/13 5:20:00, If bleeding > 150 ml/hr in ONE chest tube, notify results to Pathologist on call via Blood bank. Notify cardiologist and surgeon.

-Tranexamic acid, INJ, 1,000 mg/10 mL over 10 mins

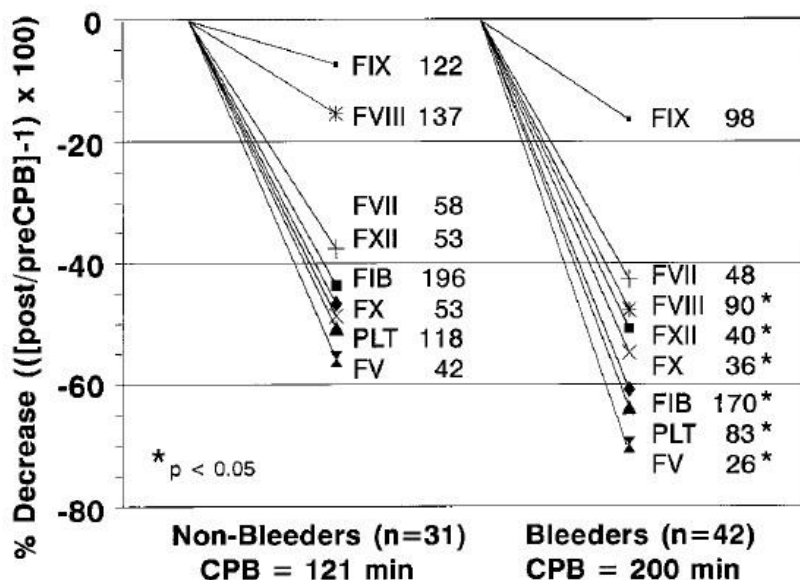
-Warfarin: 5 mg, 1 tab, Route: PO, Drug form: TAB, Q5PM, Dosing Weight 79, kg, Start date: 08/22/13 17:00:00, Duration: 1 doses or times, Stop date: 08/22/13 17:00:00

-Vitamin K1 + Sodium Chloride 0.9% IV 50 mL: 5 mg, 0.5 mL, Route: IVPB, STAT, ONCE, Dosing Weight 104, kg, Priority: Routine, Start date: 09/02/13 7:00:00, Duration: 1 doses or times, Stop date: 09/02/13 7:00:00

-Iron sucrose + Sodium Chloride 0.9% IV 240 mL (Venofer + Sodium Chloride 0.9% IV 240 mL) 200 mg IVPB Daily 500 ml/hr [for patient with iron deficiency and intolerance to oral iron]

-MD to Nurse order: if CT <100 cc in 3 hours, call cardiologist for anticoagulant therapy

APPENDIX O: Effects of CPB on coagulation results [28]



Relationship between hemostatic changes in platelets and coagulation factors with CPB and excessive microvascular bleeding (MVB).

Percent decreases were compared in patients without MVB (nonbleeders) who averaged 2 h in CPB as compared with patients with excessive MVB who averaged >3 h in CPB. Percent decreases were calculated by pre-CPB and post-CPB values in the following equation: $[(\text{post-CPB}/\text{pre-CPB}) - 1] \times 100$. Average absolute values for hemostatic variables are also indicated. Coagulation factors V, VII, VIII, IX, X, and XII are expressed as % activity, fibrinogen concentration is expressed as $\text{mg/L} \times 10^{-1}$, and platelet count is expressed in $1000/\mu\text{L}$. *, $P < 0.05$.

APPENDIX P: Difficult problems in coagulopathy management

1. Anticoagulant for patients with thrombotic complications and hypocoagulopathy without active bleeding

Occasionally, difficulty in anticoagulant management may be encountered for patients who need to be started on anticoagulant for thrombotic complications (such as showing loss of arterial pulse) and having existing hypocoagulopathy (prolonged PT/PTT, etc.). If patients do not have active bleeding, start anticoagulant (Angiomax) with low dose 0.005 mg/kg/hr. UFH should be avoided due to possible HIT causing thrombosis. Note that infusion rate in the range 0.00x mg/kg/hr does not prolong PTT to any noticeable degree. Only rate in the range 0.0x mg/kg/hr and above does. If INR is significantly prolonged (INR>2.5), typically seen in liver failure, transfuse with FFP to decrease INR (down to around 2.0) to prevent bleeding before slowly increase the bivalirudin dose to a therapeutic PTT. FFP transfusion and bivalirudin dose adjustment need to be co-ordinated together.

2. HLA Antibody workup for refractory thrombocytopenia due to HLA alloantibodies

-For patients with refractory thrombocytopenia proven with lack of response to platelet transfusion, workup for HLA alloantibodies may be initiated with Blood Bank consultation. With consensus by Blood Bank attending, the following steps may be followed to facilitate a speedy workup.

-Obtain 1 red-top tube from patient, send to Central Lab (specimen control) for HLA antibody panel, give clinical history in down-time request sheet (refractory thrombocytopenia, not responding to platelet transfusion), specify that sample to be sent to UT HLA Laboratory (713-500-7380). Optional HLA typing can also be ordered with 1 yellow-top tube. Order in EMR is through MD to Nurse Order.

-In case of emergency, call HLA Lab and talk to Dr Ling (713-500-7380) directly. Result may be available on the same day or the next day.

-For platelets, the most important data are antibodies against HLA-A, HLA-B (class 1). Titer (MFI) against these indicates how strong the antibodies are. A high PRA (in percentage) indicates increasing difficulty in getting compatible platelets. The report shows an antibody table with MFI (titer) against HLA-A and HLA-B loci. Details are given regarding unacceptable donor and acceptable donor for platelet transfusion. However, even those with MFI>500, some immune suppression measures are suggested with the platelet transfusion such as high-dose IV steroid, IV IG and Rituximab.

-Bring the hard-copy report from HLA Lab (UT-MSBS Bldg 6.282, Orange section) to Blood Bank manager. She will send this to AABB with request for number of platelet units (example, 1 dose each day). AABB is to send compatible platelets to Gulf Coast Blood Center to be distributed to MHH-TMC)

3. Management of transfusion-dependent patients on LVAD/BiVAD/ECMO

Critically-ill patients may become transfusion-dependent. A typical case is a patient comes in with cardiogenic shock, intubated, s/p ECMO, shocked liver, AKI, on CRRT, coagulopathy with DIC requiring multiple blood transfusions. Another typical scenario is a patient with LVAD and RVAD, shocked liver, and renal failure.

-For patients on ECMO, correct hypocoagulopathy with the following transfusion thresholds

- 1) Plt < 50,000 -> Plt transfusion
- 2) Hgb < 8 -> RBC transfusion
- 3) INR > 2.5 -> FFP transfusion
- 4) Fibrinogen < 150 -> FFP or Cryo transfusion

-If patient is not bleeding, heparin should be used for ECMO with therapeutic goal of PTT: 55-75. If INR is prolonged, use low-dose heparin. ASA does not need to be discontinued. Other antiplatelet medications (typically ADP- P2Y12 inhibitors) need to be discontinued on ECMO.

-If patient has thrombosis and no acute bleeding, bivalirudin is a better choice (dose for regular ACS protocol). Dose is adjusted using MHH protocol with therapeutic PTT 50-80 sec. If patient has prolonged baseline PT/PTT, start with low dose bivalirudin at 0.02 mg/kg/hr. Dose can be decreased much lower (for example 0.005 mg/kg/hr) with specific order for no titration as needed to prevent excessively prolonged PTT, especially for renal patients. Patient needs bivalirudin to inhibit thrombin in ongoing thrombosis. If INR is significantly prolonged (INR>2.5), typically seen in liver failure, transfuse with FFP to decrease INR (down to around 2.0) before slowly increase the bivalirudin dose. FFP transfusion and bivalirudin dose adjustment need to be co-ordinated together. Platelet count needs to be kept > 50k. FFP or Cryo transfusion for Fibrinogen < 150.

-If patient is bleeding (with or without thrombosis), no anticoagulant is used, especially if INR is already elevated. FFP is required if INR is significantly prolonged (>2.0, or PT >23 sec). The targeted INR is ≤ 2.0 . Antiplatelet medications (ASA) should be discontinued. Platelet count needs to be kept > 60. Once patient has stopped bleeding, Angiomax can be started at low dose to keep PTT not significantly prolonged (0.005 mg/kg/hr, with no titration). Angiomax can later be scaled up to regular protocol with titration to keep PTT in therapeutic range when bleeding completely resolves. FFP transfusion and bivalirudin dose adjustment need to be co-ordinated together.

-CBC with Plt and DIC screen q 2-4hrs

-For significant thrombocytopenia (platelet count <20k), even without bleeding antiplatelet medications need to be on hold until platelet count recovers. Anticoagulation in patients with marked thrombocytopenia (plt <20k) may be temporarily ceased in these patients to prevent bleeding.

For patients who are critically ill with on-going coagulopathy, standing order for lab testing and transfusion would simplify the process. For example,

(a) For a non-bleeding patient:

MD to Nurse Order: (1) CBC without differential, Platelet Count, DIC screen every 4 hours, (2) Transfusion with RBC if Hgb <8.0, FFP if INR > 2.5, Platelets if Plt count < 50k. Call hemotherapy pathologist on call before transfusion.

(b) For a bleeding patient:

MD to Nurse Order: (1) CBC without differential, Platelet Count, DIC screen every 2 hours, (2) Transfusion with RBC if Hgb <8.0, FFP if INR > 2.0, Platelets if Plt count < 60k. Call hemotherapy pathologist on call before transfusion.

Talk to the ICU nurse about this standing order and give her/him your pager for contact. The nurse will call the hemotherapy pathologist when there is a need to transfuse and will order the tests/transfusions, document the notification in EMR. Typically, RBCs are used most often, followed by Platelets, and next by FFPs. RBCs can be transfused through the ECMO line. Other blood components have to be transfused directly to patient.

If PTT is not responding to heparin, check ATIII level. If ATIII is very low, use FFP or ATIII concentrate. No need to check ATIII level if PTT responds to heparin.

4. Thrombophilia workup

Patients with significant clinical findings of thrombophilia need further investigation with the following laboratory tests: FV Leiden, FII mutation, LA, ACA, PC, PS, AT, homocysteine, and HIT (with supporting clinical and laboratory findings). If any of these tests is positive, clinical hematology consult should be suggested to the Heart Failure team. Note that level of Protein C and Protein S would be decreased with Warfarin. UFH and Direct Thrombin Inhibitors may yield false-positive result for lupus anticoagulant.

5. Blood oozing from cannula site

Patients may have blood oozing from cannula sites (for example ECMO site). Sometimes this may be caused by leakage of connectors close to incision site. Dry the area and look for source of oozing. If connector leaks are found, surgery needs to be called to replace the connectors. Otherwise, check CBC/DIC panel to see if blood products are needed to correct coagulopathy. Anticoagulant infusion rate may be decreased if needed. If coagulation parameters are not significantly abnormal, surgery needs to be called.

6. Modifying anticoagulant MPP for patient with risk of both bleeding and thrombosis

Some patient may be at risk for both bleeding and thrombosis manifested with recent episodes of both, a modified anticoagulant MPP may be needed. For example, a modified Bival MPP due to new PE event in a patient with bleeding risk [therapeutic PTT 50-65 rather than 50-80]. Let's say that patient currently on Bival 0.01 mg/kg/hr with PTT 47 sec. We will change Bival rate to 0.015 mg/kg/hr to keep PTT above 50 then start using the new modified MPP (created with assistance from CV Pharmacist).

Orders:

- Bivalirudin 250 mg in NS 250 mL (for HIT) 250 mg + Sodium Chloride 0.9% IV 250 mL: 250 mg, Rate: Start at 0.015 mg/kg/hr, Dosing Weight 88, kg, Route: IV, Total Volume: 250, Start Date: 04/29/14 15:28:00, Duration: 30 day, Stop date: 05/29/14 15:27:00, Replace Every: 24 hr
- MD to Nurse: Notify MD of ANY bleeding.
- Modified Bival MPP (to be coordinated with HVI Pharmacy to put in EMR):

bivalirudin 250 mg in NS 250 mL (for HIT) 250 mg + Sodium Chloride 0.9% IV 250 mL

250 mg, Rate: Start at 0.015 mg/kg/hr, Dosing Weight 88, kg, Route: IV, Total Volume: 250, Start Date: 04/29/14 15:28:00, Duration: 30 day, Stop date: 05/29/14 15:27:00, Replace Every: 24 hr

Order Comment: For Renal Dysfunction (CrCl < 45ml/min Or Hemodialysis/CVVHD). Draw PTT q4 hours until within therapeutic range and 4 hours following any rate change. After TWO CONSECUTIVE PTT values in therapeutic range, decrease PTT draws to q12 hrs while on a direct thrombin inhibitor.

If PTT < 50 seconds, increase Bivalirudin rate by 20%;

If PTT 50 to 65 seconds, No Therapeutic change;

If PTT 65 to 80 seconds, reduce Bivalirudin rate by 25%;

If PTT 81 to 105 seconds, reduce Bivalirudin rate by 50%;

If PTT > 105 seconds, hold Bivalirudin for 1 hour and reduce rate by 50%.

If PTT > 200. Hold Bivalirudin for 2 hours then check stat PTT. Resume dosing per protocol with repeat PTT. 1 mg / mL conc.

Similarly for UFH infusion: if patient has not been started on UFH, select an infusion rate, increase infusion rate slowly (by 200 u/hr) to get PTT into the desired therapeutic range, then start a modified MPP. For example, we have a patient who needs to be started on UFH with a modified therapeutic range of 50-65 sec (instead of the standard 60-80 sec). A typical starting infusion rate would be 200 u/hr, PTT to be done 4-6 hrs after starting. If PTT is less than 50 sec, infusion rate would be increased to 400 u/hr and another PTT done 4-6 hours after. If PTT is still less than 50 sec, infusion rate would be increased to 600 u/hr and another PTT done 4-6 hours after. Whenever PTT is between 50-65 sec, a modified MPP can be started. This process is similar to that described in Appendix D1 (post-op heparin for LVAD) except that infusion rate is changed every 4-6 hours to get into PTT therapeutic range faster. If a modified MPP cannot be implemented immediately, monitor PTT with appropriate infusion adjustment similar to that in standard MPP but with a different therapeutic range for PTT (Appendix G1).

Typical orders:

MD to Nurse Order, Misc: 11/06/12 06:42:00, start Heparin at 200 u/hr; check PTT in 4 hours; please page Dr xxxx at xxxx if PTT is > 65 sec or PTT <50 sec

-[PTT came back at 37 sec]

MD to Nurse Order, Misc: 11/06/12 11:12:00, increase Heparin to 400 u/hr; check PTT in 4 hours; please page Dr xxxx at xxxx if PTT is > 65 sec or PTT <50 sec

-[PTT came back at 45 sec]

MD to Nurse Order, Misc: 11/06/12 16:22:00, increase Heparin to 600 u/hr; check PTT in 4 hours; please page Dr xxxx at xxxx if PTT is > 65 sec or PTT <50 sec

-[PTT came back at 61 sec, in therapeutic range]

MD to Nurse Order, Misc: 11/06/12 21:40:00, PTT q4 hours x2

-[PTT came back at 58 sec, and 60 sec, now we have 3 consecutive PTT's in therapeutic range]
MD to Nurse Order, Misc: 11/07/12 07:21:00, PTT every 12 hours

7. Management of HIT in bleeding patients

Management of HIT may be problematic in bleeding patients (such as intracranial bleeding). It has been demonstrated that plasma exchange is a useful alternative to anticoagulant (Bivalirudin) in such clinical presentation [108]. Plasma exchange (1 plasma volume with FFP) can remove the PF4/heparin complexes, thus preventing on-going thrombosis and allowing platelet recovery. This deters any further bleeding complications allowing for implementation of appropriate anticoagulation. The effects of HIT antibodies and risk for prothrombotic complications can be significantly reduced after two procedures with no further evidence of HIT after 4 procedures.

8. Monitor anticoagulant in a patient with lupus anticoagulant and severe liver disease

PTT is prolonged due to combined effect of underlying liver dysfunction, lupus anticoagulant, and anticoagulant such as Angiomax. Lupus anticoagulant is likely to cause a prolonged baseline PTT. However, alternate testing (dilute thrombin time) is not useful with underlying liver disease. PTT is the best option to monitor Angiomax dosing and try to maintain PTT at the high end of therapeutic range to compensate for the prolongation of baseline PTT due to lupus anticoagulant. A modified anticoagulant MPP may be needed. For example, a modified Bival MPP with therapeutic PTT 60-90 rather than 50-80.

9. Therapeutic plasma exchange for severe sepsis with compromised hemodynamic status

Several case series and small randomized controlled trials suggest that therapeutic plasma exchange (TPE) improves coagulation, hemodynamics and possibly survival in severe sepsis [114]. The exact role of TPE in modern sepsis therapy remains unclear. However, TPE might be able to ameliorate DIC and septic cardiomyopathy in selected patients. Rescue TPE should be instituted on the basis of team decision for individual cases.

10. Modifying anticoagulant MPP for patients with severe thrombophilia despite therapeutic PTT for UFH

For patients on UFH with severe thrombosis despite having therapeutic PTT, a modified anticoagulant MPP may be needed. For example, a modified UFH MPP due to repeated thrombotic events would use a therapeutic range PTT of [70-100] rather than [55-75]. Modification of MPP is similar that that described in section 6 of this appendix.

11. Transfusion support for DIC

Consumption coagulopathy in DIC presents a challenge for management [116]. In patients with bleeding, or in immediate post-op period with abnormal coagulation parameters, transfusion is needed to control hemostasis. However, in patients without bleeding or not in immediate post-op period prophylactic transfusion is not indicated except for very critical coagulation parameters that predispose patients to spontaneous bleeding, i.e. platelet count <15-20 k, INR > 3.0-3.5, Fibrinogen < 100. Antifibrinolytic agents are needed for primary fibrinolysis but are contraindicated in secondary fibrinolysis (early phase of DIC).

Diagnosis of DIC can be more accurately obtained with the scoring system by The International Society for Thrombosis and Haemostasis (ISTH) [134] in the following table:

Table II. ISTH Diagnostic Scoring System for DIC.

Scoring system for overt DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?

If yes: proceed

If no: do not use this algorithm

Order global coagulation tests (PT, platelet count, fibrinogen, fibrin related marker)

Score the test results

- Platelet count ($>100 \times 10^9/l = 0$, $<100 \times 10^9/l = 1$, $<50 \times 10^9/l = 2$)
- Elevated fibrin marker (e.g. D-dimer, fibrin degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT ($<3 s = 0$, >3 but $<6 s = 1$, $>6 s = 2$)
- Fibrinogen level ($>1 g/l = 0$, $<1 g/l = 1$)

Calculate score:

≥ 5 compatible with overt DIC: repeat score daily

< 5 suggestive for non-overt DIC: repeat next 1–2 d

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