**Academic Half Day – Coagulation/Anticoagulation**

**Facilitator Guide**

Agenda:

1:10 – 1:20 pm Theory Burst

1:20 – 2:15 pm Small Groups: Case 1

2:15 – 2:30 pm Questions with the Expert

2:30 – 2:40 pm Break

2:40 – 3:20 pm Small Groups: Cases 2 & 3

3:20 – 3:30 pm Questions with the Expert

**While waiting for theory burst, how much of the coagulation cascade can you remember? Draw what you remember.**

**Case #1**

**Mrs. Deevee Tea is a 60 yo Female pmh CAD and NSTEMI s/p PCI DES mLAD 3 months ago comes to clinic with 1 week of right swollen, painful leg. You are initially concerned for cellulitis, but her doppler demonstrates an acute proximal DVT. You call her to tell her the news and need to gather a bit more history now that you’ve found the DVT.**

1. **What are a few major history points you want to know when assessing a DVT?**

* Location:
  + proximal vs distal: a proximal DVT is one that is located in the popliteal, femoral, or iliac veins. Distal is anything beyond this.
  + In general, we treat all proximal DVTs, but distal DVTs is much more nuanced. Treatment for distal DVTs depends on symptoms, risk of bleeding, and risk of embolization. If you decide not to treat a distal DVT, most experts recommend serial dopplers to monitor for progression.
* Provoking factors:
  + Hospitalization, Surgery, Estrogen, pregnancy, prolonged immobilization, Cancer, active IBD, obesity, nephrotic syndrome, trauma with long bone fractures, Viral infections (COVID), Smoking
    - ~50% of all VTE diagnosed were during or within 3 months of hospitalization/surgical procedure
    - If no DVT ppx is used, general surgery patients have about 15-30% risk of VTE. Orthopedic patient after hip surgery risk is ~60%.
* Other comorbidities:
  + Renal failure, cirrhosis, mechanical valves, thrombocytopenia, strokes, DM, alcohol use, frequent falls, miscarriages
  + These comorbidities are important as they help you estimate bleeding risk and also treatment choices. For example, DOACs are not safe in Child-Pugh class C. Alcohol can increase your bleeding risk via liver disease, thrombocytopenia, and lower fibrinogen levels.
* Other medications – DAPT. DOACs can also interact with amio, -azoles, rifampin, and phenytoin.
* Prior history of clots or bleeding – important for estimating risk of recurrent VTE.
* FH of clots or bleeding – may point you towards a particular inherited thrombophilia.
* Prior miscarriages

**She states that she has never had a DVT before – nor has anyone in her family. Her newly diagnosed DVT is in the right femoral vein, is causing some associated pain and swelling in her leg. Aside from her hospitalization a few months ago, she cannot identify any provoking factors. She never received any femoral central venous access during her NSTEMI a few months ago. Her only past medical history is CAD/NSTEMI, and she has never been pregnant. Her medications include aspirin, clopidogrel, atorvastatin, carvedilol, and valsartan.**

1. **What agent would you like to treat with? For how long would you like to treat her?**

* Provoked vs unprovoked: this case is intentionally borderline. She was hospitalized 3 months ago, so you could call it provoked. However, after a surgical procedure and hospitalization, assuming the patient is back to baseline, VTE risk significantly improves after ~6 weeks and is at population baseline ~3 months.
  + We will call this one unprovoked for today.
* Agent selection: for most patients, rivaroxaban or apixaban is recommended due to their ease of use. Alternative regimens include LMWH + warfarin (would need to bridge due to risk of hypercoagulable state initially) or LMWH + dabigatran (requires a 5-10 day bridge as this is how the initial trials were performed).
  + Let’s be honest, most the time we’re choosing rivaroxaban or apixaban.
* Duration: this is actually more nuanced discussion as well depending on if the VTE was provoked vs unprovoked, risk of bleeding and risk of recurrent VTE.
  + In general, we treat provoked DVTs for 3 months if the provoking factor is resolved...think short term immobilization or surgical procedure.
  + We treat first unprovoked DVT for a minimum of 3 months and can extend AC out to 6-12 months.
  + If the VTE was a symptomatic PE, having recurrent DVTs, or the provoking factor cannot be removed (think active cancer, IBD, or prolonged immobilization), the patient may deserve prolonged/lifelong AC.

1. **What should you do with her DAPT?**

* Since she is 3 months out, most would likely stop the aspirin and continue her clopidogrel and start apixaban.
* Twelve months after her PCI, two options: 1) switch the clopidogrel to aspirin and continue apixaban or 2) stop clopidogrel and continue monotherapy DOAC (this is based on the AFIRE trial)

1. **You are calling this an unprovoked DVT, so you decide to start treating with apixaban. The patient is tolerating the therapy well and asks you if she should be tested for hypercoagulability disorders. What patient populations should or should not be tested for hypercoagulability disorders?** ***Try to answer the question and then review tables 2 and 3 in the appendix.***

* Most of the time, hypercoagulable workups do not change management.
* Additionally, experts frequently do not recommend testing *asymptomatic family members.* Studies have shown that even when an inherited disorder is not identified, a FH of thrombosis remains an independent risk factor for VTE in the future.
  + Sometimes, hypercoagulable workups may influence family decisions, perioperative anticoagulation, avoidance of hormonal contraception, or some reversible treatments (ie PNH, MPNs, etc).
* Consider *only* in certain circumstances:
  + thrombosis at unusual sites
  + recurrent idiopathic thrombosis
  + age <50 with unprovoked thrombosis
  + Clear family history in one or more first degree relatives
  + Warfarin-induced skin necrosis -> Protein C/S deficiency
* Should NOT test in anyone on anticoagulation or with acute thrombosis.
  + The AC and acute thrombus can change the levels of many of the things we would be testing for.

1. **If you did decide to order a hypercoagulable workup (not saying you should...), what tests would you order? *Try to answer the question and then review tables 4 and 5 in the appendix.***

* First off, would probably not consider ordering any hypercoagulable workup on this patient as it was her first unprovoked VTE (or even weakly provoked).
  + Not sure how this changes given her recent arterial thrombus (NSTEMI) as well - maybe a question for the expert??
* For this patient, you might consider testing her for Factor V Leiden, prothrombin gene mutation, Beta-2-glycoprotein antibodies (for APLS) and anticardiolipin antibodies (for APLS). As these tests are genetic tests or antibodies they do not change in acute thrombus or on anticoagulation.
* Other tests to consider (*but not order*) would include protein C, protein S, antithrombin, lupus anticoagulant (for APLS). All of these tests would change on anticoagulation and with acute thrombus.
* If clotting at unusual sites like splanchnic or cerebral veins, may consider testing for myeloproliferative neoplasms or PNH.

1. **The patient also read online that blood clots can be a sign of cancer and a side effect of medications. She asks if she should be tested for cancer? Are there any medications that she should avoid?**

* Medications:
  + In general, it would be reasonable to try to avoid the below medication classes. If she were to have a strong indication for one of the below medications with minimal alternatives, you should have risks vs benefits discussion with the patient, understanding that the absolute increase in risk is pretty small.
    - OCPs – also think about transdermal contraceptives (Xulane) and hormonal replacement therapy. HRT is about a twofold increase risk. Risk is increased if also smoking.
    - Tamoxifen
    - VEGF inhibitors like Bevacizumab
    - Steroids – 1.2-2x increased risk.
* Cancer:
  + The most common malignancies associated with VTE are pancreatic cancer, GBM, gastric, ovarian, and myeloproliferative neoplasms.
  + Approximately 20% of patients with symptomatic DVT have a known diagnosis of active malignancy.
  + Interestingly, thromboembolism can precede the diagnosis of malignancy.
  + Routine evaluation for occult malignancy in unselected patients with VTE is NOT warranted.
    - 2018 meta-analysis of four RCTs demonstrated no mortality benefit with extensive screening strategies vs age-appropriate screening – however, cancer was detected at earlier stages in the extensive stage group.

**Case 1 Continued**

**She is now on apixaban. One week later, you are working in the ED, when she presents with hematemesis, melena, hypotension, and altered mental status.**

1. **Spacing back to GIB AHD – How many pharmacologic therapies and non-pharmacologic interventions can you remember to start ordering?**

|  |  |
| --- | --- |
| **Pharmacologic** | **Non-pharmacologic** |
| IV PPI BID | Two large bore IVs |
| Ceftriaxone for SBP ppx (if cirrhotic) | Type and screen/Coags/serial Hgb |
| Octreotide for variceal hemorrhage (if cirrhotic) | Consent for blood |
| Adequate resuscitation/bolus IVF | Consider airway protection |
| Transfuse pRBC for Hgb <7 | GI consult/EGD |

1. **Unfortunately, she is too confused to answer any of your history questions and med-rec. Is there an objective way to monitor her coagulopathy?**

* For patients on DOACs, INR or PTT are not reliable. You should NOT be using these tests to assess her coagulopathy.

1. Anti-Xa levels:
   * Anti-Xa is a functional assay performed by adding patient plasma to reagent factor Xa and measuring the activity of factor Xa using an artificial factor Xa substrate.
   * Can be used to monitor UFH, LMWH, or Factor Xa inhibitors. However, it is critically important that the assay be calibrated to the specific drug. *At this time, UC’s lab is not calibrated to monitor DOAC levels, and thus should not be used to monitor DOACs*.
   * There are two Anti-Xa levels in Epic, so be sure you are ordering the correct one!
     + Anti-Xa for DOACs is a send-out lab and takes about 2 weeks to return, so not helpful in acute trauma. Could consider sending this out when patients are on CYP inducers (ie carbamazepine or rifampin).
     + Anti-Xa unfractionated heparin – helpful for monitoring someone’s heparin if they have a chronically prolonged PTT (maybe like with lupus anticoagulant).
     + Anti-Xa LMW Heparin – can be used to monitor levels at extremes of body weight or pregnancy. There is data to suggest that BMI >40, therapeutic LMWH is 0.8 mg/kg BID rather than the typical 1 mg/kg BID. This has to do with the distribution of body water vs adipose tissue.
     + *Please refer to number 6 in the appendix to see the Epic order.*
2. TEGs are a really fun discussion. It is a type of viscoelastic test performed on whole blood that is able to assess the full hemostatic process including platelet activation, clot formation, and clot lysis.
   * Physical properties of the clot are measured by use of a cylindrical cup that oscillates. As the clot forms, the torque of the rotating cup is transmitted to a pin and the degree of the pin rotation is converted into an electrical signal.

* TEGs have largely been validated in trauma, cardiac surgery, and perioperative management of liver transplants. *The use in general Hematology practice remains uncertain.* 
  + In general, very fascinating test, but probably should not use them unless you are preparing liver transplants for the OR or in an ICU setting.
* *Please see the interpretation graph in the appendix (number 7).*

1. **Are there any reversal agents for the following anticoagulants?**

* Apixaban/Rivaroxaban: Andexanet alfa – suggested only for life threatening bleeding (ie intracranial bleeds, severe GIB) in addition to antifibrinolytic therapy (tranexamic acid). VERY EXPENSIVE! 4-factor PCC is reasonable alternative if andexanet alpha not available.
* Dabigatran: idarucizumab – different medication, but otherwise, similar indications/cost to above.
* Warfarin: vitamin K and PCC. Vitamin K takes a bit longer (cheaper), but PCC provides the vitamin K-dependent factors immediately.
* Heparin: protamine. Causes vasodilation, which frequently causes transient, mild-moderate hypotension. Other side effects include IgE-mediated anaphylaxis with mast cell degranulation. It can also cause pulmonary vasoconstriction.

1. **Would you consider placing an IVC filter in the patient? Why or why not?**

* In general, IVC filters are NOT recommended for acute DVT.
* When they are used, they are used in patients who have a contraindication to AC therapy (ie recent surgery, hemorrhagic stroke, active bleeding).
* Retrospective and observational data in patients with recurrent PEs show significantly decreased PE, but no change in mortality.
* If you do place an IVC filter, it is very important that it be removed when feasible. If they are left in longterm, this foreign material can be prothrombotic and propagates clots itself (such irony!)

**Case 2**

**Paul-Wong Patty is a 60 yo female who is currently in the PACU for an elective hip replacement. Preop coags were sent and they found a prolonged PTT. You are on the Hematology consult team, and the Anesthesiologist asks you what to do next.**

1. **What history would you like to obtain from this patient? As you ask history questions, explain why you asked that history question.**

* No prior bleeding events (no heavy menses or mucosal bleeding) -> hemophilia or other factor deficiency
* No prior clots -> Antiphopholipid syndrome
* No other medications -> Anticoagulation and ortivancin can prolong PTT
* Normal diet, no alcohol use -> vitamin K deficiency
* No prior bowel resections or IBD -> vitamin K deficiency
* No miscarriages, but has never been pregnant -> Antiphospholipid syndrome
* No FH bleeding -> Hemophilia or other factor deficiency
* No known liver disease -> Cirrhosis
* Clinically stable (ie not in florid sepsis) -> DIC

1. **Do you have a way of thinking through prolonged coags? *Think through it, and then refer to number 1 in the appendix.***

* The first step is identifying if the prolongation is PTT only, both PTT/INR, or INR only.
* Isolated prolonged PTT:
  + VIII – it can be a factor deficiency due to congenital (Hemophilia A) or an acquired inhibitor. It can also be von Willebrand Disease since vWF binds VIII in the blood (vWD can have either a normal or prolonged PTT).
  + IX - congenital (Hemophilia B) or acquired
  + XI – congenital (Hemophilia C) or acquired – this does not typically cause much bleeding. It is also NOT X-linked.
  + Antiphosopholipid syndrome – clinical context is key here! Are they bleedy or clotty? Any autoimmune history? Miscarriages?
* Elevated PTT and INR:
  + Think about meds (heparin, warfarin), liver disease and DIC (refer to next question for more info).
* Elevated INR only:
  + VII: early vitamin K def and factor VII deficiency.

1. **Compare and contrast coags, factor levels, and platelets in liver disease vs DIC. How can you distinguish between them?**

* Low fibrinogen, low factor VII, low factor IX, prolonged INR/PTT, and thrombocytopenia are common in both liver disease and DIC.
* Clinical context is very important; however you can also obtain a *factor VIII level*. Factor VIII is made in the endothelial cells, so will be normal/high in cirrhosis. However, in DIC, factor VIII will be low as it is consumed.

1. **In this patient with a prolonged PTT, what workup would you like to obtain?**

* Again, it depends on the clinical context.
* First, repeat the test 😊
* Other workup that may be reasonable to obtain:
  + Mixing study
  + Lupus anticoagulant
  + Factor VIII, IX, and XI
  + If family history of vWD or mucosal bleeding, could consider testing for vWD
    - Workup for vWD is probably more at the subspecialty level, but could be an interesting question for the expert.

1. **Could this be a new diagnosis of hemophilia? Why or why not?**

* X linked disease: since hemophilia is X-linked, it much more prevalent in male populations
* Age: it is unlikely that this patient grew to the age of 60 without known hemophilia, but sometimes mild Hemophilia A/B (levels 5-40%) or Hemophilia C can be discovered in adult age.
* So answer: Probably not, but could *maybe* be hemophilia C (ie factor XI def), as it causes less clinical bleeding and is not X-linked.

1. **How do you perform and interpret a mixing study?**

* A mixing study is performed by measuring the clotting time after a patient’s plasma is mixed with normal plasma (at varying dilutions).
* If the mixing study corrects, you are dealing with factor(s) deficiency. This is because when you added the normal plasma, you were also giving factor a deficient recipient. If it corrects, then you start ordering factors to find which one the patient is deficient in.
* If the mixing study does not correct: you are dealing with a factor inhibitor. Most antibodies with not be sufficiently diluted by 1:1 mixes.

1. **This patient’s mixing study does not correct. Also, her lupus anticoagulant just resulted which is significantly elevated. What do you think is going on? How do you make the diagnosis of antiphospholipid syndrome? *Think through it then refer to number 8 in the appendix.***

* The lupus anticoagulant is preventing the mixing study to correct. This is because the antibody responsible for the lupus anticoagulant is still present in the plasma. It can correct if you add excess phospholipid.
* Definite APLS diagnosis requires 1 clinical criteria and 1 laboratory criteria.
* *Please review the chart in the appendix (number 8)*
* For this patient: Not enough to make the diagnosis. No clinical criteria, and her laboratory criteria need to be repeated in 12 weeks.

**Case 3**

**You are working in the CVICU, taking care of Mr. Lo Platite. He is a complex 60 yo M pmh NICM EF 15% s/p Bi-V ICD, atrial fibrillation, CKD, COPD who has been hospitalized for 5 days for a heart failure exacerbation, and he has multiple previous hospitalizations in the last one month. Since admission, his medications have included sacubitril-valsartan, carvedilol, spironolactone, furosemide, and a heparin drip. You bring up on rounds that you’ve noticed that his platelets have been downtrending. When he came in his platelets were at 350, and now they are only at 80.**

1. **What is your differential for thrombocytopenia? What additional workup could you consider?**

* There is a broad differential for thrombocytopenia including
  + Pseudothrombocytopenia (platelet clumping)
  + Destruction (MAHAs, autoimmune, mechanical destruction from devices)
  + Decreased production from primary BM problem (malignant, infectious, nutritional, sepsis)
  + Sequestration from the spleen
* For this case, try to get your groups to start considering the diagnosis of HIT if they are not already considering (destruction category).
* Possible workup to consider would include a smear, hemolysis labs, viral studies, assessing for splenomegaly, and possibly LE dopplers looking for DVT.

1. **Your workup is largely negative, except that now you have found an acute, proximal lower extremity DVT. How does this change your ddx? What score could you use to assess the risk of this presumed diagnosis?**

* HIT results from autoantibody to endogenous platelet factor 4 in complex with heparin. This activates the platelets leading to venous and arterial thrombosis.
* You can use the 4T Score. Please calculate this with your groups. His 4T score is 8 points, which creates ~50-64% chance of having HIT.
  + 2 points for platelet drop > 50% AND platelet nadir > 20
  + 2 points for platelet fall <1 day with prior heparin exposure within 30 days
  + 2 points for new thrombosis
  + 2 points for no other cause of thrombocytopenia apparent.

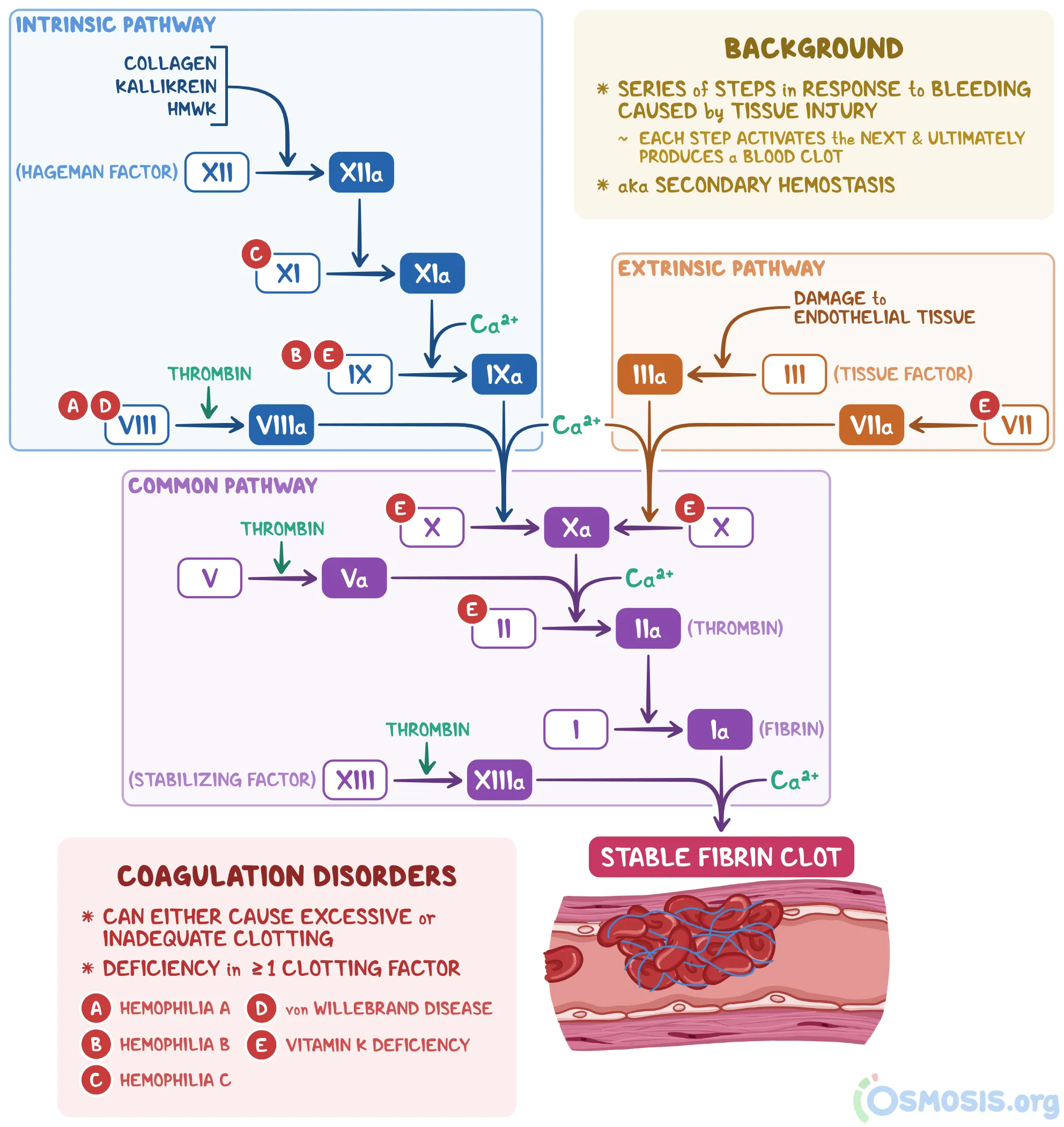
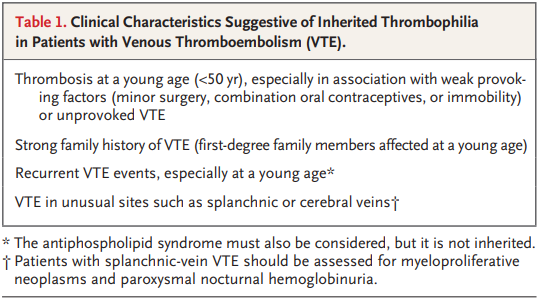
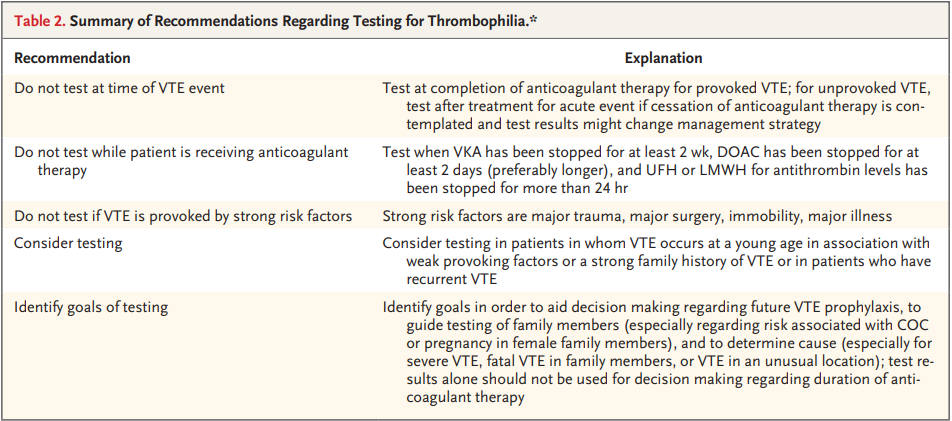
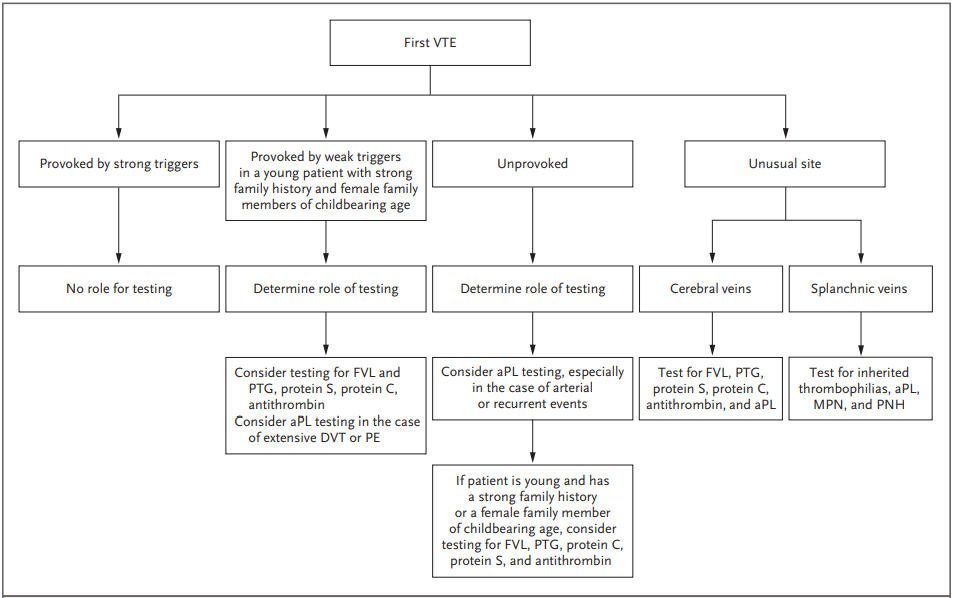
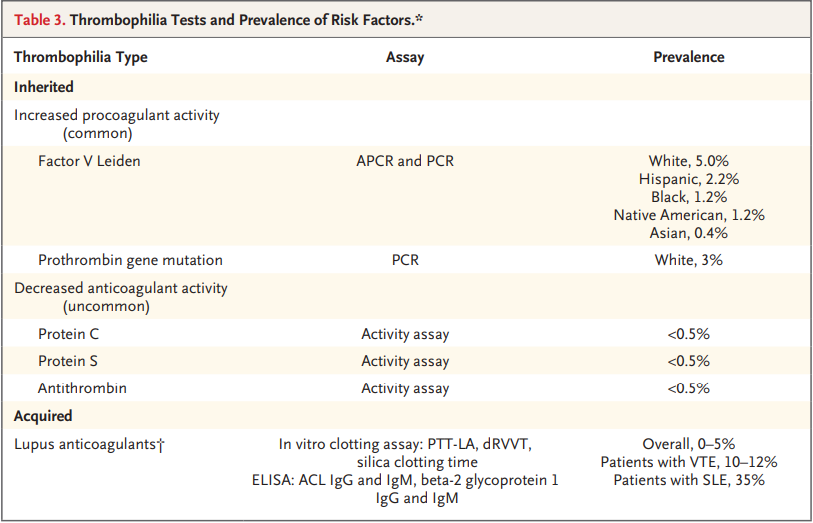
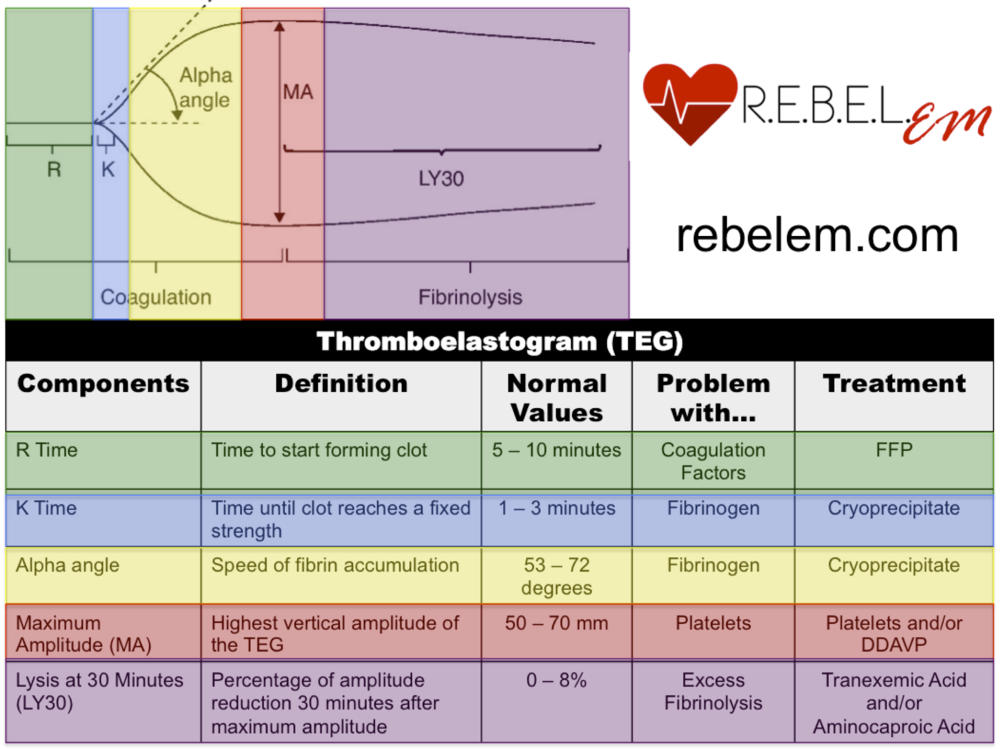
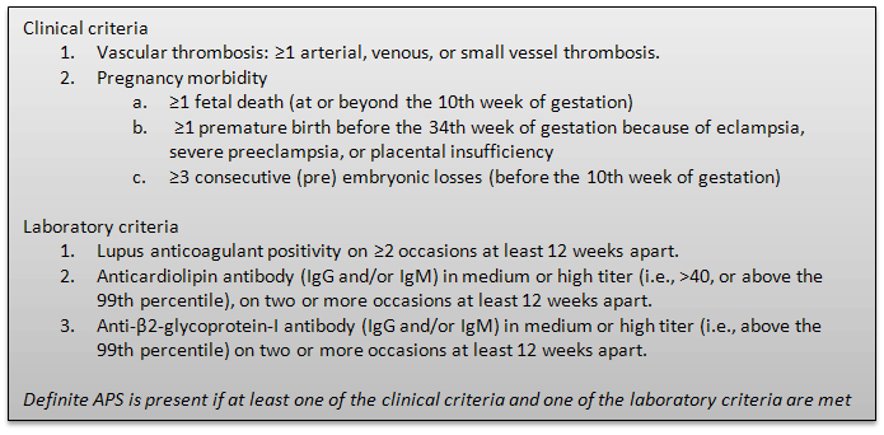
1. **What additional workup would you like to confirm your presumed diagnosis?**

* Given his high 4T score, we would make the presumptive diagnosis of HIT, pending the results of the antibody testing.
* HIT antibody testing can be down in two ways: 1) immunoassays and 2) functional assays.
  + Immunoassays (ELISA) are fast, widely available, and easy to interpret. They measure if the antibody is present, BUT CANNOT tell if they functionally activate platelets. Thus, they have a higher false positive rate as they might detect antibodies that are NOT clinically significant.
  + Functional assays (serotonin release assay) assess if an antibody activates platelets and thus causes clinical HIT. Thus, they are more specific and will have fewer false positives. However, these are more resource intensive and usually send out tests.
    - Be careful with patients taking ticagrelor. This interferes with the functional assay creating false negatives.
* Thus, we should workup HIT as follows:
  + Low 4T score: no lab workup, and no change in heparin products.
  + Intermediate or high 4T score: STOP heparin AND test immunoassay.
    - Immunoassay very low: HIT is usually ruled out.
    - Intermediate 4T and HIGH immunoassay: HIT confirmed
    - High 4T and intermediate immunoassay: HIT confirmed
    - Intermediate 4T and intermediate immunoassay: **obtain functional assay.**

1. **This patient’s immunoassay returns elevated. How would you like to manage this patient moving forward? *Talk about it as a group then look at number 9 in the appendix.***

* It is important to STOP all heparin containing products BEFORE the immunoassay comes back if the 4T score is intermediate/high.
* Must stop all heparin products: This obviously includes heparin drips, LMWH, but also includes heparin flushes, heparin-bonded catheters, heparin-containing transfusions (such as prothrombin complex concentrates), and some TPN products. Be sure to tell their nephrologists if the patient is receiving hemodialysis (will need to run heparin-free HD)
  + We should avoid heparin containing products lifelong – put this in the EMR and discuss this with the patient.
* Anticoagulation: We will start non-heparin anticoagulation immediately. This is usually an Argatroban drip, but could also be a DOAC.
* Duration: If no thrombus has occurred, they should continue anticoagulation for four weeks. Since our patient has a DVT, they should continue anticoagulation (probably DOAC, but could be warfarin as long as the bridge is not heparin) for 3 months.
* The thrombocytopenia will resolve within about 7 days of stopping heparin.

**Appendix**:

1. 
2. 
3. 
4. 
5. 
6. 
7. 
8. 
9. 