I was asked to give a talk on how to identify and treat important coagulopathies. This talk will probably be a review for a lot of you. It might be an important review since medicine is becoming so fragmented what I find is that many people that do primarily medical oncology have forgotten some of the basics of bleeding disorders and often I get involved at that point. I don’t do too much oncology anymore, so what I find is that I spend a great deal of my time on the hematology consult service and very, very often I’m asked to see patients for unexplained bleeding. So the objective of this talk are to discuss the pertinent clinical aspects of bleeding, to review the hematological disorders causing bleeding such as coagulation factor disorders and platelet disorders, to review the approach to acquired bleeding disorders especially particularly those involved in liver disease and kidney disease, how to treat and perhaps recognize and treat people that have Warfarin induced bleeding, the recommendations for these interventions are changing as we speak, and now we have these new novel oral anticoagulants that are becoming available and there is more in the pipeline that will become available very shortly. And at least where I am at the present time I see many, many patients who are treated with these new oral anticoagulants that have very significant bleeding disorders associated with them. And finally if I have time I want to try to go over just shortly how you interpret the laboratory evaluation for these patients.

So begin with, some basic stuff, the clinical features of bleeding disorders. If you have a platelet disorder you tend to have bleeding at the site of the skin, mucocutaneous membranes, you tend to have petechiae. There is an exception to that and that is drug-induced platelet dysfunction tends not to cause petechiae, petechiae are characteristic of people that have thrombocytopenia, so if someone is on aspirin and they are bleeding and they don’t have petechiae that doesn’t mean they don’t have
platelet dysfunction from their aspirin. They tend to get ecchymoses, if so it’s due to the confluence of petechiae and they tend to be very small, the bleeding tends to be immediate because the primary platelet plug is inadequate and is dissolved very rapidly. Surgically related trauma, bleeding is usually very, very mild with a platelet dysfunction and the reason for that is when you go in and macerate tissue and traumatize tissue the way surgeons do then what happens is there is a lot of thromboplastin that’s released and a lot of local thrombin is formed so that tends to overcome the thrombocytopenia or defect with a platelet dysfunction.

On the other hand people that have coagulation factor disorders tend to have deep muscle bleeds, joint bleeds, particularly those that have congenital factor deficiencies, factor 9, factor 8 deficiencies. People that have acquired disorders in coagulation tend not to have joint bleeding, that’s a very important thing to discern between the patients. I would say perhaps 3 to 4 time a year on the hematology consult service over at Presby and Montefiore we see patients that come into the hospital that have some sort of surgery done and they are 70, 80 years old and it turns out that this, you know if they are males that they very frequently have a factor 8 deficiency, so they have hemophilia that’s just never been diagnosed before, it’s been very, very mild and they’ve never had a problem that has caused them to bleed. This is something that’s very, very important because the assumption is that if you live to be 60 or 70 or 80 and you haven’t been into the hospital for bleeding that you can’t have one of these disorders and you can. The other thing is the assumption is that you don’t have a family history that you can’t have one of these disorders, but the reality of the matter as the literature would indicate that the individual when they present with bleeding with a factor 8 deficiency as an example that there is a 25% chance that that’s the first proband, that that’s the first person in their family to
have it as a spontaneous mutation. The other characteristic of a coagulation disorder obviously is the bleeding tends to be delayed, so these are people that go to surgery, they do real well and then you know a day later, or hours after the surgery they begin to ooze someplace.

So this is an example of what we mean by petechiae, these are you know obviously lesions that don’t blanch because they are not vascular in nature, they are due to small hemorrhages due to a thrombocytopenia in this case. Sometimes you can see this with vasculitis. If so they are almost always palpable, all you have to do is put your hand across the skin and if you feel little bumps then what you are probably talking about is a vasculitis rather than an actual petechial bleed of some sort. These lesions here are beginning to connect together so they are sort of forming small purpura.

This is an example of hemarthrosis which is characteristic of a person who has factor 8, or factor 9 deficiency, that is hemophilia A or hemophilia B. It is not characteristic of a person that has an acquired factor 8 or factor 9 deficiency. The person who has an acquired factor 8 or factor 9 deficiency almost never develops a hemarthrosis. These tend to occur, just primary factor 8, acquired factor 8 by the way. These primarily occur in women who are pregnant and women that undergo surgery and people that receive – receive antibiotics that’s the cephalosporins or perhaps aminoglycosides. They are generally caused by an antibody and pretty characteristically these people present with something that looks like this, and that is where they have these very, very diffuse ecchymoses sort of all over their body. It tends to occur in places where they have needle punctures or trauma, sometimes their entire body can be blue. You know it’s – there is a patient I saw a couple of years ago that was bitten by a cat and 70 year old lady, and she came to the hospital
looked like a blue man syndrome, you know everything was blue all over. She hemorrhaged everywhere and she had a factor 8 inhibitor. So that’s kind of important because these are clinical signs that can help you if you are dealing with people that have these kind of disorders.

So the coagulation factor disorders that we commonly see, those that are hereditary are hemophilia A and B, that is factor 8 and factor 9 deficiency, people that have Von Willebrand’s disease. Von Willebrand’s disease is the most common hereditary bleeding disorder in the world. It’s very, very common among Caucasians, less common among African Americans and less common still among people of Eastern Asian extraction. Practically everything else you can think of that’s hereditary is very, very rare and probably the next thing you would think about would be a factor 11 deficiency seem primarily in people of Jewish extraction or perhaps people from the Middle East. There is a small pocket of people in South America that have a higher incidence of having factor 11 deficiency. Acquired bleeding disorders include those from liver disease, kidney disease, vitamin K deficiency or Warfarin overdose; other anticoagulant overdose and obviously disseminated intravascular coagulation and if I have enough time I’ll try to go over some of these with you.

Hemophilia A and B are in terms of their presentation are very, very similar. These people tend to get these joint bleeds that I’ve talked to you about. If they have trauma to their muscle they may have intramuscular bleeds, sometimes they get retroperitoneal bleeds. They tend to have a prolonged PTT although that isn’t necessary to make the diagnosis. That’s very important to understand that because one of the things that I see pretty frequently is the people that come in bleeding and their PTT is normal and the question is you know what are they bleeding from? And oh, by the way, they
cannot possibly have hemophilia, that’s absolutely not true. Hemophilia can be mind, it can be severe as indicated here and if you have a mild form of hemophilia the PTT can be absolutely normal. In order for longer PTT in most laboratories your factor, coagulation factor level that you are measuring needs to be around 25% and that’s about where you start bleeding. And you can have spontaneous bleeding at that level. Complications of this include the hemarthrosis that I have mentioned, the hematomata that I mentioned, these people can develop severe urinary tract bleeding, they can bleed into their brains, they can go into shock, you know etc, etc.

The urinary tract bleeding is kind of interesting because in the urinary tract there is a high concentration of urokinase so invasion of the urinary tract, any kind of a surgical approach to that can predispose these people to significant bleeding. This is also true for people that have Von Willebrand’s disease. So in that’s sort of a setting it’s important to have someone who knows something about this to be involved because there are some interventions that could be used to prevent complications during the surgical procedure or after.

The treatment of hemophilia A is basically the replacement of the factor 8, okay. There is lots of products that are available to do this on the market, they are of different purities, some are plasma derived, some are recombinant. The advantage of the recombinant products is that you have less of a chance of developing inhibitor due to your transfusion. The other advantage to it is that the survival of the recombinant product tends to be more predictable than that of a plasma derived product. Most hemophilia centers in this modern day age use recombinant products. I used to direct the hemophilia program when I was at Ohio State. At that time it was the second largest hemophilia program in the
country and it was about the time that the AIDS crisis hit and now it’s one of the – not one of the biggest. Primary because of AIDS, and at that time we were using plasma derived products, now we just use the recombinant derived products unless otherwise contraindicated.

It’s very important to understand that most of – that really all of the recombinant derived products are pure factor 8, they have no Von Willebrand’s factor in them at all. Factor 8, the factor 8 molecule is a combination of factor 8 procoagulant which causes the blood to clot and its carrier molecule which is called Von Willebrand’s protein or Von Willebrand’s factor. So therefore if you have a person that has a prolonged PTT who is bleeding who has a low factor 8 it’s very important to know whether that patient has hemophilia or they have Von Willebrand’s disease. If they are a female it’s unlikely that they are going to have hemophilia, correct? It’s a sex linked disease. On the other hand, there are females that are carriers of hemophilia. That does not occur very often but I do see them on occasion. So it’s very, very important to know whether you are dealing with Von Willebrand’s disease or hemophilia regardless of the gender of the patient.

If you give a person who has Von Willebrand’s disease a recombinant form of factor 8 which contains no Von Willebrand’s factor then you’ve done them no favors. They simply don’t respond to it. Okay? If you give a person with hemophilia something that contains a lot of Von Willebrand’s factor and heaven forbid you give them too much what will happen is they will have thrombosis. The reason for that is the Von Willebrand’s protein serves as a bridge between platelets and platelets in the endothelial surface and causes microthrombi in both veins and arterials. And there is evidence
that with high levels of Von Willebrand’s factor you’ll have major clotting. This has been in the past a black box warning in those factor 8 products that contain Von Willebrand’s factor.

Treatment of hemophilia B is primarily to use purified factor 9 or a nonactivated PCC. For most of us this would be alpha 9 or maybe Profilnine, a nonactivated PCC contains factors 2, 7, 9 and 10 with a trace amount of factor 7. During the production of these products these factors can become activated and as a result of that patients treated with this have a predisposition to thrombosis so it’s very, very important to know that if you are dealing with somebody that has a factor 9 deficiency number one that the diagnosis is secure, and that usually requires you know a hematologist to be involved in that to know how to interpret the results of the blood samples. But also it means that you have to be very careful because some of these PCCs contain heparin, Profilnine does not, but most of the rest of them do. The reason they contain heparin is to prevent the activation of the coagulation factors that those products are manufactured, and every now and then we’ll see a person that requires this sort of therapy that has a history of HIT, Heparin Induced Thrombocytopenia in the past and to expose those people to PCC containing heparin could easily kill them. Okay, so these are things that are very important to know. Now granted these are not common disorders but they are common in the sense that they have to be considered when a person presents.

Another thing that I see every now and then is that when people are treated for these disorders, especially by non-hematologists, what tends to happen is you know they are on a surgical service or some general medicine service someplace and what will happen is some resident will order someone to get you know factor 8 and they stop bleeding and then they just stop. I see this all the time, and
I’ll talk about it in a minute when I talk about DIC. And then they start bleeding again. And the reason for that is because what happens when you replace factor 8 you have to give it repetitively in a timed sequence in order to maintain factor 8 levels to a level that will protect the patient from bleeding and allow the primary hemostatic plug to form followed by the thrombin induced fibrin clot that would be more firm and protect the person from bleeding and allow fibrosis to take place and wound healing to take place.

Treatment of hemophilia A, I don’t want to go into this in any detail because the reality of the matter is under most circumstances people will panic and get a hematology consult anyways, but the point with this slide is that the therapy for hemophilia A sort of depends upon the severity of the disease and the clinical presentation. It’s important to understand that often they require not only coagulation factor replacement but they may require the addition of epsilon aminocaproic acid or trans-Cinnamic acid which blocks the fibrinolytic pathway and enhances the effect of the factor 8 replacement.

DDAVP is a drug that’s commonly used, I see it used all the time in the intensive care unit for just about everybody that’s bleeding and I see it used a lot preoperatively for patients who somebody thinks they are going to bleed. And in point of fact DDAVP is a drug that is very effective for people who have mild hemophilia. The thing about DDAVP and where I see it used I think inappropriately a lot is that DDAVP is basically completely ineffective in a person with a platelet count that’s less than 100,000. DDAVP is used pretty frequently in older people that go to surgery, if you have back surgery or something like that and the problem with DDAVP is with age you get
renal impairment and with age your risk of developing hyponatremia and seizures from DDAVP increases. Therefore to use it inappropriately particularly in an older patient seems to me to be wrought with great problems. I had a patient last year that was a little bit older I gave DDAVP to for another reason and she developed seizures and hyponatremia and just about died from it. She had renal impairment that I that I ignored. So it’s something you have to be considered.

The other thing to consider is that hemophilia B as I said is treated with PCCs or factor 9, the distribution of factor 8 and factor 9 are a little bit different. Factor 8 has the capacity to diffuse into the intravascular space, factor 9 doesn’t, okay, or I should say that’s the other way around, factor 9 and factor 8 doesn’t. And so what happens is that when you treat a person with factor 9 deficiency you have to give a higher dose of replacement than you do with factor 8. And that’s another mistake that I see people making every now and then. It’s an important thing to consider.

Complications of therapy for these two disorders include well they include the formation of the antibodies. Okay, these are alloantibodies and they are due to the transfusion that patients have. This is different than the autoantibodies that you get with acquired hemophilia. This occurs in about 10 to 15% of people with hemophilia A and less with hemophilia B. That’s because the factor 8 molecule is more complex than the factor 9 molecule and has more mutations involved in it so there is a higher risk of developing alloantibody in that setting. The other thing obviously is you can get viral infections with recombinant products. That risk is much less but nevertheless it’s there. These people do have a higher frequency of developing hepatitis B, hepatitis C and the subsequent complications associated with it.
Acquired hemophilia A, which is the most common inhibitor that we see is an autoantibody against factor 8. It’s incidence is age related, if you are real young it’s unlikely you are going to have it; if you are older you are more likely to have it, significantly more likely to have it. Nevertheless it’s relatively rare. We tend to see some of these cases because you know we have – it’s a referral center and it’s an enriched population. Pretty typically these people have soft tissue bleeding in their skin as I illustrated earlier, only less than 5% develop hemarthrosis, so that’s an important differential indicator of what a person may be bleeding from. It’s very frequently idiopathic, it can be associated with autoimmune processes such as systemic lupus, erythematosus, you know rheumatoid arthritis etc. It can be seen in malignancy, it can be seen in pregnancy, it can be seen in people having different sorts of drugs and it can just plain be idiopathic. The important thing about this is that the antibody is what we refer to as a type II inhibitor, that’s differentiated from so-called type I inhibitor. A type I indicator is indicated in this slide here, it is an inhibitor in which all the factor 8 activity disappears as the inhibitor becomes more active. That’s the type of an inhibitor you see in patients who have inhibitors that are associated with factor 8 or factor 9 deficiencies, hemophilia A or hemophilia B. Those are alloantibodies primarily although they may not necessarily be that. These people when they have these antibodies tend to bleed like crazy, okay, whereas people that have type II autoantibodies associated with acquired hemophilia tend to have antibodies which don’t completely inhibit factor 8 activity. So although the inhibitor is there they tend not to bleed quite as bad as a person with hemophilia A does. And as a consequence of that the inhibitor activity can be immediately overcome by the infusion of excessive amounts of factor 8.
So in years past that was an approach that we used, somebody came in with an acquired inhibitor we gave them you know lots of factor 8, massive amounts of factor 8 and they got better for a little while. The problem is that these inhibitors can be divided into those that are high responding inhibitors and low responding inhibitors. High responding inhibitors are by definition the patient who you give factor 8 to, or factor 9 and what happens next is although you control their immediate bleeding a week later or two weeks later they start bleeding even worse and they are titers are even higher. Okay? I just saw a patient like that just last week as a matter of fact. The patient came in with – he was a hemophiliac, came in with factor 8 inhibitor, he was seen a couple of weeks before, his inhibitor was treated with a drug called FIBA, factor 8 inhibitor bypassing activity which contains a small amount of factor 8. He came back again I guess it was 2 weeks later and his inhibitor titer was twice as high as it was before with intraperitoneal bleeding.

So anyways the treatment of these type of inhibitors depends upon really what the inhibitor level is and this is measured by what’s called a Bethesda unit. If the Bethesda unit is low, less than 5, these people might do well just with factor 8 or perhaps even with DDAVP. If the inhibitor is very, very high then they need something to bypass that inhibitor and that could be FIBA with the proviso that you might make ti worse over time, or in this more modern day and age it would be activated factor 7. You can eradicate these inhibitors by giving patients Cyclophosphamide or some other sort of immunosuppressive drug such as Mycophenolate or Rituxan or Imuran and steroids and acutely IVIG can be effective. Unlike the inhibitor associated with factor 8 and factor 9 deficiencies immune tolerance therapy is not effective. So you can’t eradicate the inhibitor by taking these people and exposing the low doses of factor 8 continuously like you can with hemophilia.
Von Willebrand’s disease, well okay so Von Willebrand’s factors synthesize in the endothelium and some evidence indicates also in the megakaryocytes. It forms very large multimers that circulate, it’s a carrier protein for factor 8C which is factor 8 procoagulant, and it anchors platelets to each other and to the subendothelium and the subendothelial matrix, so it’s extremely important in the formation of that primary hemostatic plug. It’s an autosomal dominant disease, rarely successive, it’s recessive and its incidence is 1/10,000 so it’s actually more common than people might think. The clinical features of it depending upon the severity of the disease is primarily mucocutaneous bleeding.

The definition of Von Willebrand’s disease from a laboratory standpoint has changed over the years. Okay, now at this point in history – it may change next week – is that to make the diagnosis of Von Willebrand’s disease you need a ristocetin cofactor activity of less than 30. Above that we would refer to that as somebody with a low Von Willebrand’s factor. In the past we would have referred to that patient has having mild type 1 Von Willebrand’s disease.

This is the classification for Von Willebrand’s disease, there is three main types. Type 1 is a partial quantitative deficiency, depending on how low the Von Willebrand’s factor is you might consider that to be someone with a low Von Willebrand’s ristocetin cofactor activity. And there is type 3 in which you have a complete deficiency. People that have type 3 Von Willebrand’s disease present as if they have hemophilia, okay, and this is why it’s important to be able to tell the difference. Type 2 is a qualitative deficiency, that is the Von Willebrand’s protein itself is abnormal and that can be
divided into type 2A in which you have increased lysis or removal of some of the Von Willebrand’s multimers, that’s segments of the Von Willebrand’s protein that are preferentially moved from circulation. A type 2B, in which patients can present with thrombocytopenia particularly if they are pregnant or receiving some sort of replacement therapy with fresh frozen plasma, perhaps cryoprecipitate, and maybe complicated by the presence of thrombosis with DDAVP therapy, okay. So in people that have type 2B Von Willebrand’s disease intervention with DDAVP is relatively contraindicated. There is also type 2N called N for Normandy. Type 2 Normandy Von Willebrand’s disease is a disease in which there is decreased binding of the factor 8 procoagulant to the Von Willebrand’s protein. So in this setting these people present just exactly like they have hemophilia, okay. And this may account for a fair number of women who are diagnosed as having hemophilia A. That is to say they actually have type 2N Von Willebrand’s disease and the laboratory at the local institution isn’t sophisticated enough to discern the difference. Type 2M Von Willebrand’s disease is where the Von Willebrand’s protein doesn’t adhere to its receptors on the platelet surface.

So this slide shows you the multimeric analysis of Von Willebrand’s protein. N stands for normal and the other things are the different types of Von Willebrand’s disease, some of which I’ve mentioned. And what you do is you pass this through an SDS polyacrylamide gel and under an electrical field and then you stain it for the multimers. The multimers migrate according to their molecular weight. So if you have a type 2B Von Willebrand’s disease as designated by 2B on the slide here, then in that setting you lose your large and sometimes your intermediate molecular weight multimers. If you have type 1 the multimers remain intact. That’s how we tell the difference.
The other way that we can tell the difference is by platelet aggregations. If you aggregate platelets to ristocetin with type 1 or type 2A Von Willebrand’s disease what you would expect is a decreased response to ristocetin. Why? Well there is no Von Willebrand’s protein for ristocetin to interact with. On the other hand if you have a type 2B Von Willebrand’s disease type 2B Von Willebrand’s disease is characterized by an abnormal Von Willebrand’s protein that sticks too much to the platelet surface and therefore if you expose those platelets to this thing that causes platelets to agglutinate, this antibiotic called ristocetin then what happens is you end up with platelet intravascular platelet aggregation, okay? And you become more sensitive to ristocetin than you should be, okay? So that’s the other way that you tell the difference. So the workup for a patient for Von Willebrand’s disease is a look at factor 8 procoagulant activity, Von Willebrand’s antigen activity or ristocetin cofactor activity and you do platelet aggregations and a multimeric analysis, all right?

So there is this thing called acquired Von Willebrand’s disease that we see on occasion, okay. The classic presentation of this is so-called Heyde syndrome, that’s a person that’s had you know aortic valve problem, a PDA that’s patent, something like that. We can see this in people on LVADs and on occasion you’ll see these in people with hemodialysis. And sometimes you’ll see it in people with an autoimmune process, in fact that’s the most common presentation. So the autoimmune type of acquired Von Willebrand’s disease the presentation is generally around the age of 62, these people have mucocutaneous you know bleeding. I’ve listed there some of the causes for this. The lymphoproliferative process, mechanism is largely unknown but some of these people have an autoantibody. And others, particularly if they have plasma cells present and they have multiple
myeloma, they actually get adherence of the Von Willebrand’s protein to either amyloid fibrils or to the circulating protein itself. There is evidence that they even adhere to plasma cells.

In people that have these cardiovascular disorders in which they have patent PDAs in the aortic valves and things like that what tends to happen is that the Von Willebrand’s protein binds to the surface of the endothelial cells or to the aortic valve or whatever is abnormal and under high pressure the Von Willebrand’s protein stretches out and when it stretches out it becomes susceptible to lysis by its enzyme that normally breaks down Von Willebrand’s disease to smaller multimers, that’s called ADAMTS-13.. And as a consequence to that you get this acquired Von Willebrand’s syndrome.

In general acquired Von Willebrand’s syndrome is type 1 or type 2A, rarely type 2B and a characteristic of it is that under normal circumstances a signal protein which is a portion of the Von Willebrand’s protein that is removed as the protein matures and is released from the endothelium remains high or normal in levels, but the mature Von Willebrand’s protein is consumed and disappears from the plasma. That’s a characteristic of acquired Von Willebrand’s disease and that’s how you make the diagnosis with the exception of people that had both thyroidism with acquired Von Willebrand’s disease in which these levels are actually decreased due to decreased production rather than increased clearance. So this is a slide that just sort of tells you about what Von Willebrand’s propeptide is. This is something that we look at – I look at it pretty frequently actually to tell you the truth. And it’s very, very useful in that regard to try to discern whether you are dealing with an acquired Von Willebrand’s disease or a hereditary disorder of some sort.
Here is a slide which demonstrates a type of hereditary Von Willebrand’s disease called type 1 Vicenza, another name for it is type 1C. It’s called type 1C because it’s characterized by increased clearance of Von Willebrand’s protein and this little graph shows you the relationship between the ratio of the Von Willebrand’s propeptide and the Von Willebrand’s antigen which is just another, it’s a protein measurement for Von Willebrand’s ristocetin cofactor activity. As you can see with type 1C or Vicenza the ratio is increased and with no mutation present it’s normal, okay. So that’s how we use it.

Another thing that can be done is that you can treat these people and see when the Von Willebrand’s protein disappears. Okay, so the treatment for DDAVP type 1 or type 1 and some type 2As is to use DDAVP .3 mg/kg. And what I do when I first make this diagnosis is I give these people a DDAVP challenge, I expose them to DDAVP and then I measure the disappearance of some segment of the factor 8 molecule. I use ristocetin cofactor activity or Von Willebrand’s factory activity. And I see how long it lasts in the plasma. Normally it should be there for 8 to 12 hours, if it disappears in 4 hours then you are talking about somebody that has a type 1C Von Willebrand’s disease. This is important because what tends to happen is that these people require therapy with a drug called Humate P rather than DDAVP. People that have type 2B Von Willebrand’s disease DDAVP is contraindicated or at least relatively contraindicated because you can make the disease worse, type M and type N and type 3 it doesn’t work at all. Humate P is a factor 8 concentrate which has a predictable amount of Von Willebrand’s protein in it and it is the treatment of choice in the United States for people that have Von Willebrand’s disease that cannot be treated with DDAVP, it’s just
that simple. There is other products that are available, Alphanate and Co 8 HP are available in the United States, however the amount of Von Willebrand’s protein varies from batch to batch, it’s not entirely predictable and for most of us we don’t use it.

The previous treatment of choice for Von Willebrand’s disease has been cryoprecipitate, I’m sure somebody has seen somebody treated with this recently or sometime in the past. It’s no longer considered to be the you know the state of the art mainly because there is really no real way to, to purify cryoprecipitate and eliminate the (inaudible) risk. Now there are products that are available but they are hard to get. Plus cryoprecipitate contains a lot of fibrinogen in it and other things which the patient may not need exposure to. Epsilon aminocaproic acid is useful particularly if people are having dental procedures done or urological procedures where there is a lot of urokinase that’s produced due to trauma. IVIG has been used along with Rituximab to treat patients who have acquired Von Willebrand’s Syndrome related to antibody production.

Disseminated intravascular coagulation is a very common problem that we see in patients who have malignancy. For some reason, I don’t know quite why, but for some reason people seem to equate disseminated intravascular coagulation with an excessive risk of bleeding and the reality of the matter is most people with DIC thrombose, they don’t bleed, they die from renal failure. And if you investigate almost everybody that has disseminated malignancy with the you know very sensitive tests they will have evidence of activated coagulation and they will have evidence of DIC. This is something that I don’t think a lot of people appreciate or take advantage of.
The characteristic of DIC is that you have an increased consumption of fibrinogen and you have increased consumption of platelets, those two things together, okay. That’s—many, many years ago I used to run a coagulation laboratory where I used to do this routinely, I would measure fibrinogen and platelet disappearance in patients and this was absolutely uniform. I should also say that this is absolutely uniform with people that have end stage liver disease also. They have chronic DIC. And there is no way of escaping it, it’s there. Now commonly DIC is associated with sepsis, trauma, malignancy, usually you know disseminated malignancy, obstetrical complications, you know the great catastrophes that pregnant women have, vascular disorders like rheumatoid arthritis, systemic lupus, erythematosus, generalized atherosclerosis, aortic aneurisms, very common, reactions to drugs, toxins, etc, etc., you can read this yourself.

Another characteristic of DIC is that everybody consumes antithrombin and fibrinogen, everybody consumes antithrombin and fibrinogen protein C, everybody does, okay. So a characteristic of this is that they have low antithrombin levels and they have low protein C levels. If those levels get low enough they can get purpura fulminans and necrose off their tips of toe, the tip of their penis, their breast, you know their nose, ears, etc., etc. And that’s a bit of a tragedy because this is absolutely reversible and preventable. So if you have somebody has a disseminated malignancy and they have a low protein C or antithrombin the very first thing I think about is they have a chronic DIC process. Now both of those things are made in the liver so you know if they have disseminated liver disease it may be a little bit more complex in that, but in general that’s what I think about.
So the treatment of DIC is number one is treat the underlying disorders to replace what’s missing, okay, and you replace what’s missing primarily by giving fresh frozen plasma. Oh I know someone is going to tell me that to get fresh frozen plasma is going to make DIC worse, you know because this still appears in some textbooks. That’s absolutely not true. Fresh frozen plasma gives back to the patient those inhibitors, the four reactions of coagulation that they are consuming, it gives back to them protein C, protein S and antithrombin. And I’ll tell you almost weekly I see these people in the ICU, someone gave them fresh frozen plasma and their ProTime PTT got better and then they just died, okay. And that’s a mistake because what you have to do is you have to give these people fresh frozen plasma around the clock, either by continuous infusion or intermittently, but you have to give it around the clock until their underlying disease is controlled or until you are convinced it’s safe to stop it and try them off the replacement. It’s very, very effective. Cryoprecipitate is indicated in those people that have hypofibrinogenemia. And you can also replace the factor 8 with it if you need to.

If you have real low levels of protein C there is a product out there called C Protein, it’s an inactivated protein C that’s available if you can get it and you can raise your protein C levels from undetectable to 100% in a single dose. And there is now data that would indicate that in those people that are antithrombin deficient that giving them antithrombin concentrates is highly effective for the discontinuation of the DIC process. Heparin is not used very much as you probably expect since you can bleed from it, but I do use it and it is effective. But it’s a temporary measure and it is wrought with some danger as you might expect.
Platelet disorders are – well they can be due to abnormal distribution of platelets, that is you know splenomegaly, something like that. You can get a dilutional effect in which the platelet count appears to be low and you can get increased destruction due to TTP, DIC, hemolytic uremic syndrome, etc., etc., ITP. You can qualitative platelet effects that are inherited or acquired. Acquired are due to medications, chronic renal disease, cardiopulmonary bypass surgery exhaust platelets and those platelets will not function immediately after that surgery plus you typically develop with any kind of invasive surgery, intraabdominal surgery, thoracic surgery pretty typically you develop postoperative thrombocytopenia, day 2 to day 3 recovery day 7 to day 10, super recovery day 10 to day 13 or 14 and then the platelet count returns to normal. The reason that’s important is because we are often asked to see patients with a suspected HIP, we go – you know have some sort of vascular surgery or thoracic surgery done, their platelet count drops a couple of days after surgery and somebody says they have to have – you know someone gets a HIP panel and the HIP panel is a little abnormal but the reality of the matter is it’s almost always postoperative thrombocytopenia and requires no intervention except maybe replacement of platelets if the person is bleeding.

Thrombocytopenia can be idiopathic, it can be drug induced, it can be due to lymphoproliferative disorders, sarcoidosis, DIC and microangiopathic hemolytic anemia, okay. What’s important about this is in people that have TTP and HUS thrombocytopenia tends not to cause bleeding. In fact it almost never causes bleeding. In fact if you have bleeding, if you have bruises it’s almost never TTP or HUS, so that’s an important clinical finding. That’s a very, very important clinical finding. Platelet counts can drop to 5,000, 6,000, 7,000 and they just will not bleed. You can invade them,
you can do all kinds of things to them and they just will not bleed, all right, and that’s because the platelets are hyperaggregable.

HIT, much the same thing. These people do not throw petechiae, they do not bleed, all right. It’s important to remember that there is this thing called pseudo HIT. Pseudo HIT is a person who has malignancy that you’ve got on, I don’t know, some sort of Heparin as a prophylactic or something and what happens is they begin to get blood clots everywhere and their platelet count is low because they have chronic DIC, okay, and you get a HIP panel on them and the HIP panel is a little abnormal and everybody says they have HIP. Oh no, no, no, that’s what is – that’s what pseudo HIT is. Okay, that’s a person that has malignancy associated chronic DIC, okay and that’s a very bad (inaudible) finding.

And then of course you have ITP. Okay, this little graph here sort of tells you what the risk of bleeding with thrombocytopenia is for most patients, those patients without HIT or TTP or HUS. And what can be seen here is your risk of bleeding doesn’t really increase until you are around 20,000. In a normal person who has no fever, has no DIC that risk doesn’t really increase significantly until it gets down around 10,000, okay. So for the most part in people that are not bleeding with low platelet counts this is not a panic situation, these people tend to do pretty well and you have time to think about what’s doing it, you know what’s causing it. Work them up, etc, etc.

Okay, so immune thrombocytopenia in adults we are talking about chronic thrombocytopenia, it tends to occur more in females than males, it’s relatively unusual. The platelet counts are usually less
than 50,000 but they can be just about anything and it’s a disease that is very difficult to cure. It is a complication of people that have solid malignancies, there is a higher frequency in people with malignancies than not. It can be considered to be primary, that is idiopathic or secondary to something else and there is some classifications that I’ve indicated here: new, severe, chronic, etc, etc. I’m not so sure they are that important. There is a morbidity and mortality associated with it, however that morbidity and mortality is associated with me, it’s the treatment that we do. Okay these people tend to die from infections due to you know steroid intervention, etc, etc. For that reason we don’t really recommend that people with ITP particularly be treated unless there is a reason to do it, okay. And that usual reason to do it is when the platelet count begins to drop to that, you know that dangerous level, 20,000 or perhaps 30,000 just to be safe.

So the evaluation for ITP, it’s listed here. I’m not going to go over it in any great detail because I’m running out of time but the point I want to make here is that I see an awful lot of antiplatelet antibodies being ordered, okay, so if you do antiplatelet antibodies, particularly those that are glycoprotein specific, glycoprotein 2B 3A, 9 you know specific antibodies to specific glycoproteins on the platelet surface the positive predictive value is only 80%, okay so I don’t recommend that you get it at all because I don’t think they are helpful. If you are looking at platelet associated antibodies the positive predictive value is even less, it’s about 50%. So I don’t see any value in getting them, there is data that would indicate that if you are thrombocytopenic due to chemotherapy, if you are thrombocytopenic due to something else other than ITP that you can identify you have about a 40 to 50% chance of having positive platelet associating antibodies. If you have ITP you have about 20 to 30% chance of not having detectable antibodies therefore you know why would you do them, okay?
So the management of ITP steroids, IVIG, there is this thing called anti–IV antiD, RhoGAM which is highly effective, low volume, complication with it is hemolysis in some patients and other things to suppress the immune system, mainly Rituximab.

Kidney disease and coagulopathies, okay, so the important thing about this is that you can get coagulopathies with kidney disease, particularly platelet dysfunction with only minor increases in your serum creatinine, especially if you are diabetic. Your serum creatinine goes up to 1.5 you’ll get platelet dysfunction, in fact it would be almost everybody. So when you see somebody in the intensive care unit or you are taking care of somebody with renal impairment that’s one of the things you have to think about is that these people may have a bleeding disorder due to their kidney dysfunction. And what’s the treatment for it? The treatment for it is that if they are anemic you transfuse them, you keep their hemoglobin up above 10, that’s the treatment of choice. It’s not dialysis, you know, well it’s dialysis if you need to I guess for the kidney disease, but it’s you don’t treat the bleeding by dialysis, you treat them by transfusing them. You don’t give them DDAVP, well you do if they don’t respond to transfusion because that’s the second treatment of choice. And you don’t give them cryoprecipitate, cryoprecipitate is ineffective in that setting, okay. And oh by the way you don’t give them platelet transfusions either, okay, because the minute you transfuse the platelets they become abnormal themselves. So that doesn’t work either. So you transfuse them and the reason for that is because when blood passes through you know a tube, particulate matters and a fluid goes through a tube what happens is that the particles with a large mass centralized in the flow and the particles with a little bit of mass are out in the distal portion of the flow. So that if you are anemic the platelets retract centrally and if you transfuse them they are forced distally in the flow,
okay. So you increase the opportunity for the platelets to interact with whatever defect there is in the endothelium and by the way bleeding is never really spontaneous, is it? It’s always associated with a defect someplace. Always. All right, so if you increase the probability of the platelets interacting with some defect in the endothelium you are going to protect that patient from bleeding, you do that by giving them transfusions. All right?

In liver disease, okay, the thing about liver – people that have chronic liver disease is that they are predisposed to both bleeding and thrombosis, your risk of a venous thrombotic event outside of the portal vein is four times greater than you know age adjusted same age group okay. If you include the portal vein it’s much higher than that. All right? Unfortunately these people have defects that predispose them to thrombosis and bleeding and it’s pretty damn hard to tell what they are going to do, okay. Almost everybody has chronic DIC, in fact in my experience everybody has chronic DIC. It depends on how hard you look for it. Okay, if you measure fibrinogen and platelet survivals everybody has it. If you look at things that tell you that they have increased thrombin generation, F1 and 2 fragments as an example, or fibrin peptide A and B levels everybody has it, okay. So in that sort of a setting sometimes it’s difficult to know what to do but in general you know unless there is a contraindication all of these people should be on some sort of prophylactic anticoagulation of some sort, at least when they are hospitalized anyways and not ambulatory, all right?

So how do you manage these sort of things? Well first of all if you have prolonged ProTime PTT everybody gets vitamin K. It’s automatic. Okay, but you are going to say they have liver disease, vitamin K doesn’t work in liver disease. Oh but it does because lack of biliary salts in the GI tract
due to biliary obstruction or liver disease or whatever will decrease vitamin K absorption. All right, so you give them vitamin K. Okay what about fresh frozen plasma, do you give that? Well no you don’t give that because you can’t, you can’t correct the ProTime PTT with it, or if you did it would be a temporary correction, all right? And you don’t want to expose these people to you know volume overload, etc, etc. they are already volume overloaded if they have chronic liver disease anyways.

But if they have low fibrinogen you give them cryoprecipitate or this drug called Rheostat which is a purified form of fibrinogen. It’s not recombinant but it’s you know virally purified and it’s pure fibrinogen. You give them packed red cell transfusions and that helps restore their platelet function because people with liver disease also get platelet dysfunction, it’s not as common as with renal disease but it’s there and sometimes it’s hard to know. And plus these people tend to have thrombocytopenia. They have thrombocytopenia because they have big spleens or they have thrombocytopenia because they have chronic DIC, or they have thrombocytopenia because thrombopoietin which is made in the liver is reduced, okay. So if you give them platelet transfusions they may nor may not work, okay. So in this sort of a setting DDAVP might work, but you have to replace the platelets first. The treatment of choice in this setting is to give cryoprecipitate. Okay?

Vitamin K deficiency, I’m going to be done here in a second. I was supported to have more time than this. So but I want to get through with this part of it because this is kind of new and I want to make sure everybody knows this. So in vitamin K deficiency the treatment of choice is not to give people fresh frozen plasma, okay, because I’m still seeing this in our emergency rooms and stuff
still. The treatment of choice for vitamin K, for vitamin K deficiency due to Warfarin is number one if their INR is 5 and they are not bleeding you just stop the Warfarin, okay? You might want to give them vitamin K but usually you just stop the Warfarin. If you are in a setting where a person is bleeding, okay, and they have a prolonged INR then the treatment of choice if you want to correct that INR within a half hour is to give them a 4 pack of PCC. There is only one in the United States, they call it Kcentra okay. That’s important because if you give them fresh frozen plasma on the average to correct the PTT down to – the INR down to 1.5 it takes on the average about 9 hours. If you have someone that’s actively bleeding that’s the wrong thing to do, right? I mean you want to correct them immediately. Of course you want to give them vitamin K too. The amount of Kcentra you give is based upon what the INR is, okay.

As I said earlier, some of these PCCs contain Heparin, Kcentra is one that does, so that if you have somebody that has a history of HIT then you want to use this drug called Profilnine. It’s a PCC that has a very small amount of factor 7 in it, so you have to add activated factor 7, small doses of 1 mg at the max and these people get better within a half hour. That’s the treatment of choice. And that should be available you know in everybody’s emergency room.

Okay, well anyways let me go through – finish this up. There is one other thing I just want to say, I’m not going to get through all this junk. But there is one other thing I want to say – so we have these new oral anticoagulants out there, okay, and I’m seeing a lot of people that are coming in the hospital bleeding from this stuff. They are all old, they all have renal failure and the drugs have all been used inappropriately. If the drugs are used appropriately the risk of bleeding is no different
than with Warfarin. They are very, very safe drugs if used appropriately. But my God when they bleed they you know they bleed.

So the question is what do you do? And what I see constantly being done is people coming to the emergency room or they are on some service someplace and they are bleeding from Xarelto or Dabigatran or something like that. And they are given fresh frozen plasma, fresh frozen plasma around the clock you know. These are very potent anticoagulants, they increase your level, they inhibit the factor 10A or thrombin depending on which drug you use by a thousand-fold. Okay so giving people fresh frozen plasma isn’t going to do anything, it doesn’t help them in any way or form except for you know run the risk of volume overload.

If you have Dabigatran, Dabigatran is 30% protein bound, so the treatment of choice for Dabigatran toxicity is to remove the Dabigatran. It’s to immediately hemodialyze them. If you need immediate reversal of bleeding you know it’s just absolutely acute and you just can’t wait to hemodialyze somebody then you give them activated factor 7.

If you have somebody that’s on Apixaban or Xarelto these are anti-10A inhibitors, and those people present with a prolonged ProTime. You don’t give them fresh frozen plasma, it’s ineffective, it doesn’t work. I see that all the time. What you do in that setting well I guess the reality of the matter is I don’t know what you do in that setting, all right? You can’t hemodialyze them because it’s 90% protein bound. Right now as the data presently exists it looks like the treatment of choice in that setting is to give a 4 factor PCC, is to give them Kcentra, 50 u/kg as fast as you can give it. And
if that doesn’t work then the next treatment of choice would be to give them FIBA, alright? It’s not to give them fresh frozen plasma.