CDC/IDSA COVID-19 Clinician Call Q&A

COVID-19 and Thrombosis

July 25, 2020

1. **What should be minimal duration of anticoagulant for severe COVID pneumonia patients who recovers completely? We are seeking MI and Strokes after recovery from COVID 19.**

   Assuming the patient does not have a known or suspected thrombosis, the minimal duration of anticoagulation is until the patient is well enough to be discharged from the hospital. However, as your question implies, there are studies planned to understand the benefits and risks of post-discharge anticoagulation. (Dr. Cuker)

2. **What should we do on discharge? Should COVID patients be discharged on Lovenox or a DOAC and if so for what duration.**

   We do not yet know whether the benefits of post-discharge thromboprophylaxis outweigh the risks and how best to select patients for post-discharge prophylaxis. Studies to address this question are planned. In the meantime, in my institution, we are considering rivaroxaban 10 mg daily as per the MARINER trial for patients who meet MARINER criteria for thrombotic risk and who we do not consider to be at high bleeding risk. (Dr. Cuker)

3. **Is there any data on prophylactic anticoagulation for non-hospitalized patients?**

   At the University of Florida, they have post-discharge guidelines that might partially answer your question, but this applies to patients discharged after being sick enough for admission. (Answered on the call)

   I am not aware of any recommendations for non-hospitalized patients. To my knowledge, there are no data on the baseline risk of thrombosis or on the benefits/harms of anticoagulation or antiplatelet therapy in non-hospitalized COVID patients. Studies are planned. (Dr. Cuker)

   NIH will be starting a trial as part of ACTIV-IV to address this question. I would consider using prophylactic dose in patients who are covid-19 positive with other strong risk for VTE such as homozygous factor V Leiden or similar increased risks. (Dr. Connors)

4. **Do COVID-19 patients who are receiving various forms of anticoagulation for other prior conditions have less morbid events than those who were not on prior anticoagulation? And Who do you think should be done for patients already on agents such as Eliquis or Coumadin?**

   In most circles, they will continue the current medication or switch to a heparin product at the therapeutic dose. There is an algorithm at the university of Florida to that effect. I hope this helps. (Answered on the call)

   Published data to date do not show a protective effect of being on prior anticoagulation. However, these data are difficult to interpret because patients on prior anticoagulation represent an inherently high-risk group. (Dr. Cuker)

5. **Any specific recommendation for hematologic patients with COVID-19?**

I'm not sure I understand the question. In general, patients with chronic hematologic disorders should be treated similarly to other patients. There may be exceptions depending on the specific condition. (Dr. Cuker)

Patients that are immunocompromised or on treatment that could suppress immune response to covid-19 should take extra care not to get exposed. Would consider holding treatments if possible, in an area actively surging until prevalence of covid-19 lower in the local population. (Dr. Connors)

6. **Can you start more aggressive anticoagulation early on and then pull back?**

   Yes. This would be a reasonable thing to do if the patient was bleeding. It could also be reasonable if the patient was felt to be substantially improved and therefore at lower thrombotic risk. But just as there is uncertainty in the optimal intensity of anticoagulation in acutely ill and critically ill COVID patients, so too is there uncertainty on whether to reduce the intensity of anticoagulation when there is a change in illness severity. (Dr. Cuker)

7. **What do you think about increase anticoagulation with worsens hypoxemia? like: enoxaparin 0,5mg/kg for all in hospital, if worse hypoxemia enoxaparin 0,5mg/kg 2xday, if worse or UCI enoxaparin 1mg/kg 2 x day**

   Because autopsy studies suggest that pulmonary microthrombi are a part of COVID lung disease and because anticoagulation could plausibly prevent or ameliorate this complication, using oxygen status as a variable in determining intensity of anticoagulation is reasonable to consider. However, we do not yet have good evidence on the benefits and harms of this approach. (Dr. Cuker)

8. **What about severity of illness, critical care status? ARDS, DD, BMI?**

   These have all been shown to be risk factors for thrombosis and other adverse outcomes in COVID patients. That said, we do not yet have evidence on whether the presence or absence of any of these factors should guide anticoagulation management. In my institution, we generally recommend prophylactic-intensity anticoagulation for acutely ill patients on the wards and we recommend intermediate-intensity prophylaxis for critically ill patients in the ICU. (Dr. Cuker)

9. **Can we depend on inflammatory condition to decide which patient needs high dose ?**

   No, at least not yet. There is evidence that increased inflammation is associated with an increased risk of thrombosis. However, evidence on whether using markers of inflammation to guide anticoagulation is beneficial is currently lacking. (Dr. Cuker)

10. **Who do you think should be done for patients already on agents such as Eliquis or Coumadin?**

    If a patient has a pre-existing indication for anticoagulation and does not have a contraindication (like active bleeding), they should be kept on anticoagulation during their COVID illness. Sometimes they can remain on their home medication. However, depending on severity of illness, kidney and liver function, clinical stability, etc., it may be necessary to transition some patients to a shorter-acting parenteral agent. (Dr. Cuker)

11. **Please don't forget the children who do get sick with COVID and are hospitalized. Any recommendations for children, especially those under 12 years old where we have very low VTE? And, for children under 12.**

    I am an adult hematologist and do not have expertise in the care of children with COVID. I would defer to a pediatric hematologist to address this important question. (Dr. Cuker)

12. **Do you use prophylaxis in patient with no severe disease, but may have risk factor like previous thrombotic events?**

    In general, I do not recommend prophylaxis in patients who are well enough to avoid hospitalization. However, if the patient has a strong risk factor for thrombosis such as prior VTE or recent major surgery, I consider prophylaxis on a case-by-case basis. (Dr. Cuker)

13. **Limited preclinical data suggests that unfractionated Heparin may directly bind the spike protein… would that push you to use heparin rather than other heparin derivative**s

    No. I am aware of the preclinical data and think they are interesting. There are also preclinical data suggesting an antiviral effect of anti-FXa agents. That said, I would not choose one anticoagulant over another based on preclinical data, which may not apply in the clinical setting. (Dr. Cuker)

14. **If patient already in anticoagulants for other reasons what your reaction**

    Please see my response to question #10. (Dr. Cuker)

15. **At our institution, we have used TEG to guide therapy. We have found profoundly pro-thrombotic state despite standard prophylaxis dosing. I personally think it is irresponsible to argue for "standard" therapy when we know that patients have pulmonary arteriolar thrombosis, DVT and PEs. Hematologic society recommendations are sadly behind and far too conservative given the crisis we are facing.**

    Agreed. The risk of bleeding on higher intensity ppx is so low, don't really see the downside. (Answered on call).

    There are differing opinions currently as was highlighted in the debate. Autopsy series also show hemorrhage in the lung in addition to microthrombosis. Some institutions are eager to participate in the clinical trials, some will not participate because higher dose anticoagulation is their current treatment, and some will not participate because they had patients with bleeding complications and will not consider higher doses of anticoagulation. There have been situations with COVID that empiric treatment was used only to find out that it was not useful or potentially harmful (e.g. high dose hydroxychloroquine). Clinicians must take care of patients while research is done with evaluating the available evidence. (Dr. Kreuziger)

16. **What do you think about the use of Argatroban on nephrotic patients with associated COVID19?**

    Argatroban can be used in patients with renal insufficiency and would be recommended in patients with concern for heparin induced thrombocytopenia. In the US, it is much more expensive and thus low molecular weight heparin or unfractionated heparin are used more often. (Dr. Kreuziger)

17. **In patients who have COVID-19 diagnosis but have no criteria for hospitalization, is the use if anticoagulation recommended? if the answer is yes, what would be recommended in these cases and at what dose?**

    See answer to #3. (Dr. Kreuziger)

18. **There are studies suggesting that s1 protein could bind to enoxaparin and this could preserve the viral load. Any comments about this?**

    There are some interesting data about binding of S1 to heparin or enoxaparin inducing a conformational change. We await further in vivo data. Additional analysis of large datasets of infected patients may give additional insights also. (Dr. Kreuziger)

19. **How about the mechanism? Is there something qualitatively (or molecularly) different about COVID-19 compared to severe influenza or other critically ill patients.**

    Studies are ongoing. A recent comparison of lung autopsies from patients with SARS-CoV-2 and H1N1 influenza showed SARS-CoV-2 infection caused more significant endothelial damage. https://www.nejm.org/doi/full/10.1056/NEJMoa2015432 (Dr. Kreuziger)

20. **Given the incidence of bleeding with higher doses of AC, would you consider using Antithrombin plus standard dose AC, to decrease the bleeding risk?**

    Antithrombin deficiency has not been seen frequently in patients with COVID-19. Checking antithrombin activity could be considered if heparin resistance occurs or another anticoagulant could be used. (Dr. Kreuziger)

21. **Are patients in the anticoagulant trials allowed to receive convalescent plasma?**

    The studies with the ACTIV IV network and the RAPID COVID COAG trial allow enrollment in other studies including use of convalescent plasma or antiviral therapy. (Dr. Kreuziger)

22. **Can you please talk about mechanism leading to this high risk of VTE?**

    All inflammatory conditions lead to an increased risk of VTE and SARS-CoV-2 infection causes severe inflammation. (Dr. Kreuziger)

23. **Given the literature for use of a higher dose (0.5mg/kg once daily) for obese patients, with obesity as clearly an adverse prognostic factor for increased COVID-19 mortality, and as >50% of our standard population are obese, why is weight based dosing not receiving more attention in guideline recommendations?**

    Designing anticoagulation trials for COVID-19 highlighted the difference in practice regarding dosing in obesity. There are pharmacokinetic studies and cohort trials of higher doses of anticoagulation in obese patients. No randomized trial data is available. Many institutions do dose adjustment for obesity. (Dr. Kreuziger)

24. **Would you recommend suspending treatment with estrogenic oral contraceptives in a patient with mild COVID 19 due to the increased thrombotic risk?**

    No. The changes in the coagulation system associated with estrogen therapy last for 6 weeks. Stopping oral contraceptive therapy could increase menstrual bleeding and potentially lead to pregnancy, which is a much higher risk for VTE. (Dr. Kreuziger)

25. **Recommendations in pregnancy**?

    Several guidance statements are present including ACOG (https://www.acog.org/en/Topics/COVID-19), SMFM (https://www.smfm.org/covidclinical), and NIH COVID 19 guideline panel (https://www.covid19treatmentguidelines.nih.gov/special-populations/pregnancy-and-post-delivery/) (Dr. Kreuziger)

26. **Recommendations in children?**

    Guidance for children including discussion of the Multisystem Inflammatory Syndrome is noted in the NIH COVID-19 guidelines (https://www.covid19treatmentguidelines.nih.gov/special-populations/children/) (Dr. Kreuziger)

27. **Is there any data preferring one anticoagulant over the other? Any idea about heparin resistance? Duration of anticoagulation after discharge?**

The preference for one anticoagulant over another is based on exposure to patients for administration. Low-molecular weight heparin can be given once a day for prophylaxis and twice a day for treatment. Heparin resistance occurs in other inflammatory conditions and would be another reason to prefer LMWH. Patients with thrombosis should be treated for 3 months of anticoagulation after discharge. See question for #2. If extended duration of anticoagulation is used, recommend FDA approved regimens. (Dr. Kreuziger)

28. **Can you discuss the role of Megakaryocytes outside of bone marrow (e.g. Heart, lungs, peripheral blood) in Thrombotic disease of COVID-19?**

    First these need to be confirmed as megas as dendritic cells also mark for the CD markers used in these studies, it is not clear that these are prothrombotic but may reflect significant inflammation. (Dr. Connors)

29. **Could finding megakaryocytes reflect early release of an immature form because of consumption of platelets?**

    Less likely because we don't see this in ITP, however cytokine driven migration is possible (Dr. Connors)

30. **What about risk of VTE/stroke post COVID infection?**

    When the inflammation resolves the risk si significantly lower. Studies are looking at this question. It could be higher than expected if patients are discharged early to make space in the hospital. (Dr. Connors)

31. **Effect of convalescent plasma?**

    Please ask Infectious Diseases expert. (Dr. Connors)

32. **What about anticoagulation on discharge in patients who were on prophylactic or intermediate dose anticoagulation?**

    See answer to #3.

33. **While I agree that we need RCTs to guide therapy, it is woefully inadequate to recommend standard therapy when we can use TEG and/or monitoring of anti-Xa levels to guide therapy. While we wait for RCTs, patients are dying.**

    See answer to #15

34. **Any comment about correlation between progressive hypoxia as result of pulmonary microvascular thrombosis that may support increased AC dose in wards?**

    Excellent question and is being studied in RAPID-COVID trial

35. **What about cross immunity from community acquired human coronaviruses e.g. HCoV-229E, HcoV-NL63? HcoV-OC43? HCoV-HKu1?**

    Please ask an Infectious Diseases expert. (Dr. Connors)

36. **There are in adults any syndrome like MIS-C with DD increase?**

    Yes absolutely, cytokine storm systemic inflammatory response syndrome. The more severe the inflammatory reaction the higher the D-dimer in general. (Dr. Connors)

37. **If ICU patient on Aspirin or other antiplatelet agents. Would you give intermediate dose anticoagulant?**

    For VTE prophylaxis? Yes, but this is not fully endorsed and there are no data. we are running a trial out of the TIMI group looking at this question--high vs low dose heparin plus/minus clopidogrel. (Dr. Connors)

38. **Is any advantage for patients that take ASA if they get infected with SARS-Cov2?**

    Not that we know of, but we are planning a trial through NIH ACTIV-IV platform. If the patient has a low bleeding risk but could tolerate asa you could consider this. (Dr. Connors)

39. **What is in the "risk assessment" that you do for patients with prior VTE & COVID?**

    Some people are suggesting the IMPROVE-D score as used for post discharged medically ill patients, basically age, obesity, past VTE, etc and D-dimer level. (Dr. Connors)

40. **Is there a greater risk for clotting among individuals with clotting disorders (e.g., FVL) when infected with CV19?**

    This is an excellent question. There might be but there are no data. for someone with FVL and past hx of VTE who gets COVID-19 I would strongly consider using VTE prophylaxis. (Dr. Connors)