COVID-19: Care of the Critically Ill Patient: A Focus on the Management of Acute Respiratory Distress Syndrome and Coagulopathy

Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** other than handwashing and masking, are there any medications that you recommend to boost immunity to prevent COVID?

**Answer:** Unfortunately at this time, no medications have been shown to prevent COVID-19 infection. Hand hygiene and masking remain some of the most important measures in preventing the spread of COVID-19 infection.

**Question:** which anticoagulants are used DOACs or warfarin after COVID discharge?

**Answer:** There is not great prospective data supporting post-discharge VTE prophylaxis in COVID-19. Most clinicians have been using their judgement and identifying those at highest risk for developing VTE at discharge based on comorbidities and other risk factors. Use of the IMPROVE-VTE score, age, and d-dimer levels may assist in identifying those at highest risk for developing VTE. DOACs likely have been utilized the most for post-discharge VTE prophylaxis in this population. Of course, patients requiring full anticoagulation for another indication (AF, PE/DVT, hypercoagulable disorder, mechanical valve, etc.) should remain on full dose anticoagulant if appropriate, and this may include use of warfarin.

**Question:** Amazing presentation! While on my Critical Care APPE rotation, I have seen providers keep COVID-19 patients with ARDS on Nimbex for up to 1 week. What are your thoughts on the use of NMBA continuous infusions beyond 48 hours?

**Answer:** Although the ACURASYS and ROSE trials evaluated use of 48 hours of NMBA in ARDS, there are patients who may require NMBA beyond that time period. When patients with moderate to severe ARDS initiate their own breath on mechanical ventilation, they may inadvertently induce further lung injury by increasing airway pressures and taking large tidal volumes resulting in volutrauma. Generally if we find this occurring after removal of NMBA, the first approach is to increase the level of sedation and analgesia to reduce respiratory drive. However, re-initiation of NMBA may be required for some patients. This has been the case for many COVID-19 ARDS patients. It is very important to make regular attempts to wean NMBA and provide NMBA-free intervals as the patient begins to recover in order to minimize the total time on NMBA as much as possible.
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Question: If a patient is on anticoagulation for AFib (ie. warfarin / doac) do you continue if they are covid positive?

Answer: Generally speaking, yes. As long as the patient does not have a contraindication to anticoagulation that arises during their hospitalization. We may switch patients to enoxaparin or heparin infusion in the ICU setting if there will be planned procedures and the need for a washout period beforehand. Additionally, many of our critically ill COVID-19 patients develop AKI at some point during their ICU stay and this may necessitate selection of an alternative anticoagulant.

Question: Is there any value in trending D-dimers? Do you check a D-dimer prior to discharge to determine anticoagulation recommendations?

Answer: We do trend d-dimers. If there is an abrupt increase in d-dimer paired with worsening symptoms of shortness of breath or reduced oxygenation, the patient may need to be worked up for VTE. Use of the IMPROVE-VTE score, age, and d-dimer levels may assist in identifying those at highest risk for developing VTE at discharge. Initiation of extended out of hospital prophylaxis should be weighed against the patient's risk for developing bleeding complications.

Question: Have you utilized any low dose systemic tPA outside those with PE/DVT to aid in clearance of fibrin deposition in severe covid associated ARDS

Answer: We have not routinely utilized systemic alteplase to aid in clearance of fibrin deposition. We have used systemic and catheter-directed alteplase for lysis of PE or extensive DVT. For patients developing clots in dialysis catheters, we have utilized low dose systemic anticoagulation with heparin or bivalirudin to improve flow and minimize clot formation.

Question: Do you think the difference in outcomes between the Accurasys and Rose trials may have been due to more proning in Acurasys?
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**Answer:** It is possible that increased use of proning in the ACURASYS trial compared to the ROSE trial may have contributed to the differences in outcomes. Additionally, changes in ventilatory strategies and critical care management of ARDS over a nearly 10 year likely contributed as well.

**Presenter:** Lauren A. Igheri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** Was the CoDEX trial in COVID patients as well?

**Answer:** In early January 2020, the DEXA-ARDS study had been published evaluating the use of corticosteroids in non-COVID-19 associated ARDS. Many clinicians utilized this study as the basis for administering corticosteroids in COVID-19 associated moderate to severe ARDS before trials evaluating corticosteroid use in COVID-19 patients were published later in 2020, including: RECOVERY, CoDEX, REMAP-CAP, and CAPE COVID.

**Presenter:** Lauren A. Igheri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** Have you had the opportunity to work with oncology patients who are often thrombocytopenic, if so what do you recommend for them?

**Answer:** In the event we have a thrombocytopenic patient, we generally hold anticoagulation (full or prophylactic doses) when platelet counts are less than 50,000 which is consistent with the American Society of Hematology recommendations.

**Presenter:** Lauren A. Igheri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** Where do DOACs play a role in prophylaxis

**Answer:** Use of the IMPROVE-VTE score, age, and d-dimer levels may assist in identifying those at highest risk for developing VTE. DOACs have been utilized for post-discharge VTE prophylaxis in populations at high risk for developing VTE when the risk for bleeding remains low.

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Question: Do you personally feel like these therapies (dex, etc.) impact the same endpoints seen in trials (vent, hosp LOS).

Answer: Yes, I feel that prone-positioning, NMBA, and dexamethasone in conjunction with good supportive critical care practices have improved outcomes in our patients. Recovery from COVID-19 associated ARDS is slow and arduous at times. It has been rewarding to see some of our patients who had been very sick, on the highest level of mechanical and circulatory support, walk into the ICU to say thank you to our staff for the care provided.

Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

Question: why is is not recommended to combine mechanical prophylaxis with chemical prophylaxis?

Answer: This is an American Society of Hematology recommendation.

Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

Question: I have had some providers tell me that heparin has more "anti-inflammatory properties than LMWH. Therefore heparin is preferred over LMWH.

Answer: I am not familiar with this recommendation to use heparin over LMWH.

Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

Question: Any role of higher pulse dosing of steroids in mechanically ventilated COVID-19 patients, i.e. methylprednisolone 250 mg IV x 3 days?

Answer: To the best of my knowledge, a high-dose pulse regimen of methylprednisolone has not been evaluated in critically ill patients with COVID-19. My practice has been to use steroid regimens from the RECOVERY/CoDEX (and DEXA-ARDS) trials in appropriate patients.

Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

Question: Thoughts on use of tPA for patients with coagulopathy and ARDS?
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**Answer:** We have not routinely utilized systemic alteplase for COVID-19 associated coagulopathy. We have used systemic and catheter-directed alteplase for lysis of PE or extensive DVT. For patients developing clots in dialysis catheters or other access devices, we have utilized low dose systemic anticoagulation with heparin or bivalirudin to improve flow and minimize clot formation.

**Presenter:** Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** Based on recent findings suggesting improved outcomes (shorter ventilator duration) with therapeutic doses of anticoagulation. Should we only reserve therapeutic doses for confirmed VTE?

**Answer:** This answer to this question is forthcoming pending publication of the ACTIV-4 and ATTACC trial data. ACTIV-4 stopped enrolling critically ill patients with (MV, ECMO) because of futility and a signal for increased bleeding. We are not routinely administering therapeutic-dose anticoagulation in our critically patients with COVID-19 unless we have confirmed or highly suspected VTE.

**Presenter:** Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** If you have to convert cisatracurium to rocuronium due to a shortage, do you use a equivalent dosing or retitrate from initial dosing?

**Answer:** Due to the pharmacokinetic differences in rocuronium vs. cisatracurium, less tends to be more with rocuronium. We initiate therapy at infusion rates recommended in the prescribing information and other medication resources. To ensure as smooth a transition as possible, I would bolus rocuronium when changing over from cisatracurium to rocuronium infusion. The nurse should titrate based on train of four or ventilatory synchrony monitoring. Don't be surprised if lower than typically described infusion rates are needed since there tends to be drug accumulation with rocuronium.

**Presenter:** Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** what is your opinion on CHEST recommendation on just doing standard VTE prophylaxis even in the ICU patients?

**Answer:** I am in support of using standard VTE prophylaxis in our critically ill COVID-19 patients. My institution never adopted a "moderate-dose" prophylaxis protocol due to lack of substantial evidence for this practice. Anecdotally, many of our COVID-19 ARDS patients developed bleeding complications later in their stay even on standard dose prophylaxis. Better evidence to answer to this question is forthcoming pending publication of the ACTIV-4 and ATTACC trial data. ACTIV-4 stopped enrolling...
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Critically ill patients with (MV, ECMO) because of futility and a signal for increased bleeding. We are not routinely administering therapeutic-dose anticoagulation in our critically patients with COVID-19 unless we have confirmed or highly suspected VTE.

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Question: For ICU pt's who are admitted for long time, how often you recommend VTE rule out? thanks

Answer: VTE should be on the differential diagnosis when a patient experiences significantly increased oxygen requirements, shortness of breath, or has a sharp rise in d-dimer. Using objective scoring systems such as Wells Criteria to determine the probability of VTE is helpful.

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Question: Can you say anything- clinical things noted in pregnant patients with COVID-19 regarding anticoagulant use or any other class of COVID-19 medications mentioned in your presentation. Such a great presentation by the way and I travelled internationally to

Answer: We have cared for pregnant patients who have developed COVID-19 associated ARDS at my institution. We treated them with the same pharmacological and non-pharmacological strategies as non-pregnant patients. Pregnant patients may require special cushions/padding to safely remain in prone positioning.

Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

Question: What do you recommend if the CRRT machine clots while the patient is on argatroban?

Answer: You may choose to target a higher PTT goal range if patients develop clotting within the CRRT filter. Citrate may be an alternative, but I do not personally have experience using citrate. Additionally, you may chose to run pre-filter replacement fluids to increase blood flow rate across filter and reduce clotting potential.

Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

Question: What are your thoughts about thromboprophylaxis in patients who are treated as outpatients
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Answer: In general thromboprophylaxis is not routinely recommended for outpatient COVID-19 cases. For patients discharged from the hospital, use of the IMPROVE-VTE score, age, and d-dimer levels may assist in identifying those at highest risk for developing VTE at discharge. Initiation of extended out of hospital prophylaxis should be weighed against the patient’s risk for developing bleeding complications.

Question: Can Lovenox 40mg daily be used for post discharge

Answer: For patients discharged from the hospital, use of the IMPROVE-VTE score, age, and d-dimer levels may assist in identifying those at highest risk for developing VTE at discharge. Initiation of extended out of hospital prophylaxis should be weighed against the patient’s risk for developing bleeding complications. While IMPROVE-VTE scores have been utilized to guide DOAC prescribing for extended out of hospital prophylaxis, it is reasonable to consider enoxaparin on a case by case basis if DOACs are not available/covered under insurance.

Question: Are you dosing NMBAs continuous infusion using fixed rate or titratable (weight-based) & adjusting to TOF?

Answer: Although the ACURASYS and ROSE trials evaluated use of 48 hours of NMBA in ARDS at fixed doses (in order to maintain blinding), it is reasonable to titrate NMBA to train of four or ventilator synchrony.

Question: Is Cisatracurium the only NMBA recommended or would we be able to use rocuronium and others?

Answer: Due to the pharmacokinetic differences with cisatracurium compared to rocuronium, cisatracurium is generally preferred in critically ill patients who have altered hepatic and/or renal function. However, with increased drug shortages during the pandemic, contingency medications such as rocuronium or vecuronium may need to be substituted for cisatracurium. Attention to differences in PK/PD should be noted to avoid prolonged paralytic effects after discontinuing rocuronium or vecuronium infusions.
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**Question:** Are you routinely using aspirin with chemical prophylaxis in your patients

**Answer:** No, we are not routinely adding antiplatelet therapy to VTE prophylaxis regimens. This is in line with NIH and American Society of Hematology recommendations.

**Question:** If the literature with steroids and covid favors dexamethasone, do you think it's appropriate to extrapolate those results to methylprednisolone at equivalent dosing?

**Answer:** While the preference should be to utilize dexamethasone since it is the agent showing benefit for moderate-severe COVID-19 associated ARDS, I believe it is reasonable to use equivalent methylprednisolone dosing in the event of dexamethasone shortage.

**Question:** What was the purpose of measuring the pulmonary wedge pressure in the previous ARDS diagnostic criteria?

**Answer:** In prior Berlin ARDS definitions, pulmonary capillary wedge pressure (aka. pulmonary artery occlusion pressure) was utilized to determine if infiltrates on chest radiograph were attributable to cardiogenic shock (high PCWP, high SVR, low CI)

**Question:** Some of our docs are using higher doses than 6mg of dexamethasone in COVID-19 patients who are obese. Have you seen this? And any data to support this practice?

**Answer:** While I am not aware of higher corticosteroid dosing in obesity, the DEXA-ARDS study (non-COVID-19 population) and the CoDEX study (COVID-19 population) utilized a higher dexamethasone dosing strategy (20 mg daily x5 days, followed by 10 mg daily x5 days) than the RECOVERY trial (6 mg daily x10 days). It may be reasonable to utilize this higher dosing strategy in patients with moderate to severe obesity.
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severe ARDS since only ~16 percent of patients in the RECOVERY trial were mechanically ventilated or required ECMO, indicating a less severely ill population.

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**Question:** Your thoughts on ICS use in each stage of C19 infections?

**Answer:** I don’t believe there is robust literature to support use of ICS over systemic corticosteroids in COVID-19 infection. My practice has been to continue ICS in patients taking them prior to admission for another indication (asthma, COPD) prior to admission and give systemic corticosteroids for COVID-19 on top of that.

**Presenter:** Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** If a patient is on a DOAC from home and is admitted for COVID, would you continue the DOAC inpatient or switch to therapeutic Lovenox of UFH?

**Answer:** Patients requiring full anticoagulation for another indication (AF, PE/DVT, hypercoagulable disorder, mechanical valve, etc.) should remain on full dose anticoagulant if appropriate while inpatient. While it is reasonable to keep patients on home DOACs, critically ill patients may require an agent with a shorter half-life in anticipation of procedures. Additionally, acute kidney injury may result in prolonged DOAC effects which is generally undesirable. Therefore, it may be prudent to switch critically ill patients anticoagulation from DOACs to enoxaparin or heparin.

**Presenter:** Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** have you seen apixaban being used for post discharge thromboprophylaxis, especially in patients with poor renal function?

**Answer:** There is not great prospective data supporting post-discharge VTE prophylaxis in COVID-19. Most clinicians have been using their judgement and identifying those at highest risk for developing VTE at discharge based on comorbidities and other risk factors. Use of the IMPROVE-VTE score, age, and d-dimer levels may assist in identifying those at highest risk for developing VTE. DOACs likely have been utilized the most for post-discharge VTE prophylaxis in this population. Renal function should be considered when selecting an agent. Apixaban likely has the broadest acceptable renal function range compared to other DOACs.
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Presenter: Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

Question: Is there any recommendations for pulse dose corticosteroids in management of COVID19?

Answer: To the best of my knowledge, a high-dose pulse regimen of methylprednisolone has not been evaluated in critically ill patients with COVID-19. My practice has been to use steroid regimens from the RECOVERY/CoDEX (and DEXA-ARDS) trials in appropriate patients.

Question: Percentage of COVID 19 patients with ARDS who progress to fibrotic lung disease?

Answer: I don't believe this has been fully characterized at this time.

Question: Seen surfactant used in Covid patients with ARDS?

Answer: I am not familiar with surfactant literature, but I do know this is a therapeutic modality being developed/studied in COVID-19 ARDS.

Question: Suggest anti Xa monitoring in Covid 19 patient on enoxaparin?

Answer: There are no strong recommendations to support routine anti-Xa monitoring in COVID-19 patients treated with enoxaparin. I would consider using the same monitoring strategies as in non-COVID-19 patients: full dose anticoagulation in obesity, pregnancy, renal dysfunction.

Question: Using corticosteroids in ARDS patient with influenza and Covid-19 patient with ARDS?
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Answer: This is certainly a challenging patient population. It is important to obtain a thorough history and try to decipher the time course for both COVID-19 and influenza. You may discover the patient was COVID-19 positive weeks ago and retested positive on the current admission. In this case, the benefit of corticosteroid administration may be outweighed by the potential harm with administering corticosteroids in a newly diagnosed influenza infection.

Question: Is there benefit in using dexamethasone past 10 days

Answer: I do not believe there is adequate literature demonstrating a benefit of prolonged administration of dexamethasone (beyond 10 days) in COVID-19 associated ARDS.

Question: do we do use tinzaparin ?

Answer: I am not aware of studies evaluating the use of tinzaparin in COVID-19 disease, but it would be reasonable to substitute this agent in place of enoxaparin if this is your formulary LMWH.

Question: Would you recommend corticosteroids in patients with COVID-19 and influenza co-infection?

Answer: This is certainly a challenging patient population. It is important to obtain a thorough history and try to decipher the time course for both COVID-19 and influenza. You may discover the patient was COVID-19 positive weeks ago and retested positive on the current admission. In this case, the benefit of corticosteroid administration may be outweighed by the potential harm with administering corticosteroids in a newly diagnosed influenza infection.

Question: What is the recommended prophylactic dosing for anticoagulation in morbidly obese patients who are mechanically ventilated with Covid-19 without confirmed VTE
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**Answer:** I do not believe there are adequate literature to characterize the "best" prophylactic anticoagulation strategy in obese patients with COVID-19 disease, but it would be reasonable to use similar VTE prophylaxis dose adjustments (e.g. enoxaparin 40 mg twice daily for BMI >35 or 40) as in non-COVID-19 patients.

**Presenter:** Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** Is there any recommendation for the use of antiplatelet therapy in COVID-19 patients?

**Answer:** The NIH and American Society of Hematology do not recommend use of antiplatelet agents alone or in combination with LMWH/heparin for VTE prophylaxis in COVID-19 patients.

**Presenter:** Lauren A. Igneri, Pharm.D., BCPS, BCCCP, Clinical Pharmacy Specialist, Critical Care, Cooper University Healthcare, Camden, NJ

**Question:** What are your thoughts on steroids in patients with influenza and COVID co-infection?

**Answer:** This is certainly a challenging patient population. It is important to obtain a thorough history and try to decipher the time course for both COVID-19 and influenza. You may discover the patient was COVID-19 positive weeks ago and retested positive on the current admission. In this case, the benefit of corticosteroid administration may be outweighed by the potential harm with administering corticosteroids in a newly diagnosed influenza infection.

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**Question:** Can you clarify the use of steroid regimen based on PaO2/FiO2 and hemodynamic status? Use hydrocortisone in shock, higher-dose dex in severe ARDS?

**Answer:** The DEXA-ARDS study (non-COVID-19 population) and the CoDEX study (COVID-19 population) utilized a higher dexamethasone dosing strategy (20 mg daily x5 days, followed by 10 mg daily x5 days) than the RECOVERY trial (6 mg daily x10 days). It may be reasonable to utilize this higher dosing strategy in patients with moderate to severe ARDS (PaO2/FiO2 <150) since only ~16 percent of patients in the RECOVERY trial were mechanically ventilated or required ECMO, indicating a less severely ill population. Hydrocortisone may be preferred in patients with COVID-19 experiencing ARDS with hemodynamic instability (shock) as evidenced by improved outcomes in the REMAP-CAP study.
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Question: one issue our facility is experiencing is COVID patients being on long-term abx due to possible bacterial co-infection despite negative cultures with physicians hesitant to de-escalate/discontinue. can you speak more about your experience dealing with abx

Answer: We have utilized procalcitonin (initial and repeated levels for trending) to assist with early de-escalation of antimicrobial therapy. This has generally allowed us to discontinue antibiotics within the first 24-48h of hospital admission provided the patient is not in septic shock.

Question: How do you convert from a D dimer level to FEU?

Answer: 1.0 mcg/mL FEU is equivalent to 0.5 mcg/mL d-dimer unit.

Question: How do you manage patients with an elevated aPTT prior to starting therapeutic anticoagulation in COVID-19 patients??

Answer: This is certainly a challenge. You may chose to use an alternative monitoring strategy such as unfractionated heparin levels. There may be a role for thromboelastography if that is available at your institution. Hematology specialists should be consulted to provide guidance on a case by case basis and identify concomitant coagulopathies.