I. Tocilizumab – 8 mg/kg IVPB x1 (max 100kg)
   a. Recombinant IL-6 receptor antagonist
      i. Initially used because severe COVID-19 was described early as a “cytokine storm” which caused very high levels of inflammatory markers (including CRP, ESR, & IL-6)
   b. Initial tocilizumab studies were retrospective in nature, low statistical power, heterogeneous patient population, and low frequency of concomitant use of corticosteroids
   c. COVACTA – Hospitalized patients with severe COVID-19 PNA
      1. All spectrums of supplemental oxygen:
         a. 1/3 on NC, 1/3 on NIV/HFNC, 1/3 MV
      2. Median time from symptom onset to randomization: 11 days
      3. Only ~50% received corticosteroids, no one received remdesivir
      4. Primary endpoint: Clinical status after 28 days (no difference)
         a. Tocilizumab patients had a shorter time to discharge and in the ICU with no mortality difference
   d. EMPACTA – Hospitalized patients with severe COVID-19 PNA
      i. Excluded patients on non-invasive and mechanical ventilation (pre-intubation trial)
         1. 64% receiving supplemental oxygen
         2. Focused on high-risk minority patient populations
         3. Median time from symptom onset to randomization: 8 days
         4. 80% received corticosteroids and ~50% received remdesivir
      ii. Primary endpoint: mechanical ventilation or death at 28d (12% v. 19.3% p = 0.04)
         1. No difference in 28-day all-cause mortality
   e. REMAP-CAP – Critically ill patients with COVID-19 PNA receiving CV/respiratory support
      i. Key exclusions: >24 hrs since ICU admission, immunosuppressed, ALT >5x ULN
      ii. 88% of patients received corticosteroids
      iii. Primary outcome: respiratory and cardiovascular organ support-free days
         1. Tocilizumab improved primary outcome (Median 10 days v. 0 days placebo)
         2. Improved 21-day mortality (28% v. 36%)
      iv. Highest benefit seen in those with elevated inflammatory markers (e.g. CRP)
   f. RECOVERY (Pre-print release)
      i. Hospitalized patients with suspected/confirmed COVID-19 with evidence of progression (receiving supplemental oxygen and CRP ≥ 75 mg/L)
      ii. Randomized up to 21 days after main RECOVERY trial (dexamethasone) randomization
      iii. 45% NC, 41% NIV, and 14% receiving MV
iv. 82% of patients receiving corticosteroids
v. Largest study to date including over 4000 patients
vi. Improved 28-d mortality with tocilizumab (29% v. 33%)
   1. Reduced risk of mechanical ventilation
g. Ultimate role for tocilizumab
   i. Hospitalized patients who have rapidly progressing COVID-19 pneumonia
   ii. Consider looking at inflammatory markers, may be a more patient-specific decision
   iii. Use tocilizumab in combination with corticosteroids
   iv. Don’t know the effects of a second dose, specifically with adverse events
   v. Avoid in those who are significant immunocompromised or with a serious bacterial co-infection as it can cause immunosuppression
      1. Consider avoiding use in those with transaminitis due to unknown effects

II. Corticosteroids
a. COVID-19 patients requiring supplemental oxygen should receive corticosteroids
   i. Greatest benefit in those mechanically ventilated
   ii. Some question of harm in those patients on room air
   iii. RECOVERY trial authors didn’t describe the type of supplemental oxygen patients were receiving, do certain subgroups benefit more than others?
b. Most common dexamethasone dosing regimens for COVID-19
   i. 6mg q24 x10 days: RECOVERY trial
   ii. 20mg q24 x5 days then 10mg q24h x5 days: CoDEX/DEXA-ARDS trials
c. Should try to use evidence-based dosing regimens rather than modifying to avoid ADE such as hyperglycemia
   i. In the DEXA-ARDS trial, no difference in hyperglycemia between treatment groups
   ii. In CoDEX, no difference in insulin administration between groups
d. Consider extending the corticosteroid treatment course in those who have decompensate while receiving their treatment (maybe a 14-day course instead of 10)
e. More unknown what to do for patients who have already completed their treatment course
   i. Likely a more patient-specific decision, recognizing there is limited data to support
   ii. Question if something else is going on (cryptogenic organizing PNA, VTE, etc)

III. Anticoagulation in COVID-19
a. First reports from China described the abnormal coagulation labs in COVID-19 patients
   i. Prolonged PT & aPTT, elevated D-dimer, IL-6, ESR, and CRP
   ii. 2020 Lancet article described a higher risk of death (18 times!) in COVID-19 patients with D-dimer levels >1000 mcg/mL
b. Then published research described increased rates of arterial and venous thrombosis
c. NEJM article compared autopsy findings from COVID-19 compared to H1N1
COVID-19 was more associated with diffuse alveolar hemorrhage and widespread thrombosis/microthrombi.

VTE prophylaxis was then recommended as standard of care in COVID-19 patients worldwide.

Due to concern of higher VTE risk in COVID-19 patients, despite VTE prophylaxis, some countries (including the US) started using intermediate intensive VTE prophylaxis.

- The practice changes were based on anecdotal reports without robust data.

In Nov 2020, UK NICE (National Institute for Health and Care Excellence) COVID-19 Guidelines suggested intermediate dose anticoagulation should be considered in patients receiving advanced respiratory support.

JACC state-of-the-art review recommended VTE prophylaxis with LMWH and suggested continuing prophylaxis post-hospital discharge up to as long as 45 days.

- This statement was extracted from information in other critically ill states with no COVID-19 specific data.

Observational reports described reduced mortality in COVID-19 patients receiving therapeutic anticoagulation.

In Dec 2020, NIH ACTIV-4a trial (comparing VTE prophylaxis v. treatment) stopped enrolling critically ill patients due to the potential for harm identified by the independent oversight board.

- Multi-platform research study including patients from the ATTACC, ACTIV-4a, and REMAP-CAP data sets.
  1. Includes a mix of both ICU/non-ICU patients and LMWH/UFH as treatments.
  2. Treatment regimens varied between studies, even with the same agents.
     - Some even received intermediate anticoagulation despite the trial evaluating therapeutic v. prophylactic anticoagulation.

- Primary outcome: 21-day organ support-free days (advanced CV/respiratory support).
  1. ICU mortality: Therapeutic anticoagulation 35.3% v. 32.6% in usual care.
  2. ICU major bleeding: Therapeutic anticoagulation 3.7% v. 1.8% in usual care.
      - Met the pre-specified futility marker and paused ICU patient enrollment.
  3. Therapeutic anticoagulation reduced mortality, (5.7 v. 7.7%) and improved organ-support free days in non-ICU patients.

- Convalescent plasma:
  - Data is not overwhelming to support widespread use.

- Remdesivir
  - No major role to initiate in critically ill patients.
  - Consider completing the treatment course if started prior to intubation.
VI. Take-home points
   a. Don’t forget basic principles of critical care (e.g. FASTHUGS-BID)
   b. Be sure to closely read the literature (peer-reviewed but especially pre-print)
   c. Collaborate with colleagues inside and outside your institution