COVID-19 Disease Management Discussion

Brief overview of spectrum of COVID-19 disease:

Most patients have mild disease (81%).
  Up to 30% of these are asymptomatic
Approximately 14% develop more severe disease defined requiring hospitalization and O2 support.
Approx 5% develop need for ICU level care. (Likely lower now as care improves).
ICU mortality appears to be in the 33-62% range.
  Data is a bit limited because many early case series still included many patients who were not yet discharged from the ICU or hospital.
Overall case fatality rate is likely on range of 0.5%. Still in study.

ICU cases:
ARDS picture can develop leading to ICU for Acute hypoxic respiratory failure
  -Pathophysiology picture may be severe vasculitis / inflammatory storm
  -Septic physiology can develop including need for vasopressor therapy
  -ARF can develop including need for CRRT  (inflammatory storm / vasculitis?)
  -Cardiac toxicity (atrial and ventricular arrhythmias) can develop
    Often may have been related to iatrogenic causes  (are we seeing less now?)
      -Hydroxychloroquine
      -Azithromycin
  -Barotrauma can occur, but is less common than in other etiologies of ARDS

Predictors of poor outcome:

Age >60  (and subsequently increasing risk >70 and >80).
Increasing number of co-morbidities
Higher SOFA score at presentation
Elevated D-Dimer

Summary page of all COVID published literature:
https://www.ncbi.nlm.nih.gov/research/coronavirus/?utm_source=The%20Scope&utm_campaign=941e5e9b7e-Weekly_Scope_Jan_12_2018_COPY_01&utm_medium=email&utm_term=0_809ad7d22b-941e5e9b7e-90115317
Management of a patient with suspected / confirmed COVID-19 requiring inpatient care (hypoxia / resp distress needing oxygen therapy, +/- ARF)

Follow recommendations for infection prevention by obtaining rapid turn-around COVID-19 NP PCR testing in ER setting, appropriate segregation of COVID-19 positive inpatients (CCU at St. Alphonsus currently) and compliant donning / doffing of PPE by healthcare workers. Use of the healthcare team to their full scope of practice can lower the number of healthcare workers in direct contact with the patient. Communication via phones / video can allow two providers to make care decisions with only one in the room. Appropriate placement of IV pumps and ventilator control panels can decrease frequency of nursing, RT and providers entering and exiting the room.

Obtain the following labs / imaging studies:

CBC, CMP, Lactate, CRP, ESR, PT, PTT, D-Dimer, Fibrinogen, BNP, Troponin, Procalcitonin, +/- Ferritin

Obtain ABG if significant O2 need or respiratory distress
Obtain CXR
Obtain EKG.

Consider CTPA if clinical picture / labs make VTE event more likely.

Collect infectious disease testing
   Viral nasopharyngeal swab for COVID-19 PCR
   Influenza test (in season)
   Blood cultures if meeting criteria for severe pneumonia or sepsis
   Urine antigens (strep pneumo / legionella) if severe pneumonia or sepsis
   Sputum culture if severe pneumonia or sepsis

Routinely consider ID and pulmonary consultation so that all three services can work together on cases. This may be beneficial in guiding development of evidence based care protocols.
**Antibiotics:**

In most cases, treat patient for typical bacterial pneumonia.
- Ceftriaxone + doxycycline if milder case.
- Consider Zosyn + vancomycin or equivalent if sepsis criteria met.
- Most COVID-19 cases have a normal to mildly elevated lactate.
  A high lactate should raise concern for a bacterial infection.
- Decisions on abx narrowing / cessation should be based on clinical course and laboratory data trend.

**Oxygenation:**

**Give Supplemental O2 to achieve O2 sat >90%.** Reasonable to aim for O2 sat >93% in stabilization process. Then can lower target to 90%. Severe COVID-19 cases will usually require high oxygen concentrations. Follow the guideline table embedded within the ARDSnet protocol to balance FIO2 and PEEP to achieve target O2 sat. Target saturation may be lowered to high 80s in some cases to balance risks of high PEEP (>20) and high FIO2 levels (>0.8).

**High flow O2 and Non-invasive ventilation (BiPAP / CPAP) can aerosolize SARS-CoV-2.** It is reasonable to use these oxygen delivery strategies to avoid mechanical ventilation and potentially improve lung recruitment through easier patient position changes. A HEPA filter can be used on the flow tubing of the NIV equipment to lower the risk of exposure to aerosolized SARS-CoV-2.

Expect oxygenation to be a worsening problem. Significant intrapulmonary ventilation-perfusion mismatch and subsequent shunting is present and the moderately sick patient at admission will have a high likelihood of needing escalating pulmonary support. **Mechanical ventilation can be needed and should be managed via an ARDSnet (low tidal volume) focused protocol.** The intubation process is high risk to the provider and should be done by the available provider with the highest skill set in intubation and with full PPE (ideally including a plexiglass box) and using RSI protocol.

**In combination with ARDSnet driven ventilator use, prone ventilation should be considered for 12-16 hours a day.** This requires careful nursing team management especially around the position changes to avoid ETT dislodgement.
In most hospitals, ‘prone teams’ are organized to make the changes in the early morning and late afternoon. Prone positioning is often used overnight and supine in the day. Pressure wound avoidance strategies can minimize risks in both supine and prone positions. See data on prone ventilation in Mechanical Ventilation in ARDS section in lower part of this document.

**Sedation**

In mechanically vented patients, moderate sedation will usually be required to control anxiety and help better achieve vent goals. Options include: Versed + fentanyl. Propofol. Dexmedetomidine (Precedex).

**Neuromuscular blockade:**

Neuromuscular blockade is not standardly recommended in ARDS. One ARDS trial did show benefit (not COVID-19). Subsequent trials in ARDS (not COVID-19) have not shown benefit over sedation alone. However, neuromuscular blockade is typically used while the patient is in prone position. Neuromuscular blockade is also used for ventilator dyssynchrony that prevents attainment of tidal volume goals or when refractory hypoxemia or hypercapnia occur.

**ECMO:**

Extra-corporeal membrane oxygenation (ECMO) can be considered. Data is limited on use in COVID-19. It is technically challenging and only certain tertiary centers can do. Some early data out of China did not show great benefit.

**Intravenous Fluids:**

**Be judicious with IVF.**

Use maintenance fluids if no shock.
If shock, give 250-500 ml bolus of LR or NS in first 15-30 minutes.
Watch for volume overload carefully.
Continue to give 250-500 ml boluses to reach perfusion targets.
Perfusion target is MAP >65, UO >0.5 ml/kg/hr, improving HR if tachycardic, improving extremity perfusion if poor, improving mentation if encephalopathy exists and improving lactate levels.
If hypotension persists despite antibiotics and IVF, then vasopressors need to be initiated. Norepinephrine is a usual first line consideration. Vasopressin would be an appropriate add on agent if goal of MAP >65 is not achieved. Neosynephrine and epinephrine would be other agents to consider. In refractory shock, it is reasonable to add hydrocortisone 50 mg IV q 6 hrs to cover for relative adrenal insufficiency.

**Remdesivir** is an antiviral agent. The MOA is via inhibition of an RNA dependent RNA polymerase. Remdesivir was studied via a randomized, double-blind multicenter trial (ACTT-1) in hospitalized patients with COVID-19. There were 60 study sites including 45 in the US and the trial reported on 1059 patients (538 Remdesivir, 521 placebo). Enrolled patients had lung findings of pneumonia or O2 sats <94% or were requiring mechanical ventilation or ECMO. Remdesivir was dosed at 200 mg IV on day 1 and 100 mg IV on day 2-10. Faster clinical improvement was seen in the Remdesivir group versus placebo (11 versus 15 days). The rate ratio for recovery was 1.32; 95% CI 1.12 to 1.55. p<0.001. Recovery was defined as being off O2 and not having ongoing active inpatient medical care. Mortality at 14 days was non-significantly improved at Remdesivir 7.1% versus placebo 11.9%. The hazard ratio for death was 0.70; 95% CI, 0.47-1.04. Adverse events were seen more in the placebo than in the Remdesivir groups. This was 14 day data to unmasking of the study to publish these results. We will likely see 28 day data in the near future. It will be interesting to see if mortality data shows statistical improvement. Of note, this study excluded patients with significant liver dysfunction (hepatocellular enzymes >5x ULN) and patients with renal dysfunction. Renal function cutoff was not published although no patients on CRRT were included. This is a limitation of the study as many COVID-19 patients have ARF. We are unsure of whether these patients will benefit from Remdesivir.


It is reasonable to use Remdesivir 200 mg IV on day 1 and 100 mg IV on day 2-10 in hospitalized COVID-19 patients who have normal renal function.
**Famotidine**
Binds to protease that is integral to viral replication.

Observational study at Columbia University in New York City. 1620 inpatients (not intubated) of which 84 were on famotidine within 24 hours of admission. Home use of famotidine was documented in 15% of those on famotidine in the hospital and 1% of those not on famotidine. The risk for intubation or death was lower in the cohort on famotidine versus not on famotidine. HR 0.42, 95% CI 0.21-0.85. This seemed to be largely driven by a lower risk of death. Use of a PPI was not associated with a reduced risk of intubation or death. In 784 inpatients without COVID-19, there was no benefit for famotidine on risk of intubation or death. Plasma ferritin levels dropped in famotidine users versus non-users (708 versus 846, p 0.003). This may indicate that famotidine reduced viral replication and therefore lowered inflammation / cytokine storm.

*Reasonable to consider famotidine 20 mg IV / PO q 12 hrs for COVID-19 inpatients.*

*Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Study. Feedberg et al. Gastroenterology. ePublished 14 May 2020.*

**Zinc**
Impairs replication of certain viruses by inhibiting RNA dependent RNA polymerase. No data on benefit in COVID-19. Some mild improvements seen in some studies with other coronavirus induced URIs.

*Reasonable to start on inpatients who can take PO. 220 mg PO q day*

**Vitamin C**
No data on COVID-19 treatment. No clear data on benefit when added acutely for coronaviruses.

No clear recommendation.
Ivermectin:

Theoretically may interrupt viral protein entry into nucleus of cell. No data on COVID-19. Some studies raise question of whether adequate levels to inhibit viral entry can be achieved in human cells.

Not indicated.

Lopinavir / Ritonavir (Kaletra)

Lopinavir / Ritonavir did not show benefit in a 199 person trial in Wuhan. (Published in NEJM on 3/19/20).

This drug is no longer in use for COVID-19.

Anti-inflammatory Medications:

Actemra (Tocilizumab) is an IL-6 blocker. It is used to shut down the inflammatory storm associated with COVID-19 as T lymphocytes and macrophages are activated and release IL-6. As a pulmonary capillary vasculitis is probably a big part of the pathology of the disease, there is hope that this medication will show benefit. The data we have is based on a retrospective study of 21 hospitalized patients with COVID-19 in China. Patients received Tocilizumab 400 mg IV x 1 after 7 days of total inpatient care. Of note, lopinavir / ritonavir and methylprednisone were also given to these patients. 15 of the 20 patients had decreased O2 need. CT chest improved in 19 of 20 patients. Lymphocyte counts normalized in 10 of 19 patients. CRP decreased in 16 of 19 patients. There were no serious adverse drug events. 20 of 20 patients lived to an average discharge at 15 days. There was no comparison group. Of the 21 patients, 3 received a second dose of Actemra within 12 hours.

Effective treatment of severe COVID-19 patients with tocilizumab. Xiaoling Xu et al. PNAS 19 May 2020

Actemra is fairly readily available in the United States. Typical dosing in the US has been 200 mg IV x 1.
IDSA recommends using in context with a clinical trial.
For a hospitalized patient with a CRP > 10 mg/dl, this could be considered but data is weak. Another consideration would be Anakinra below.

Anakinra (Kineret)

Anakinra inhibits IL-1 receptors to interrupt the inflammatory storm associated with COVID-19. A retrospective cohort study performed in Milan in March 2020, Italy looked at the ability of Anakinra to improve outcomes hospitalized COVID-19 patients with moderate-severe ARDS on non-invasive ventilation and with hyperinflammation (CRP > 100 mg/l and/or Ferritin > 900 ng/ml). High dose Anakinra (5 mg/kg IV q 12 hrs) was given to 29 patients, low dose Anakinra (100 mg SC q 12 hours) was given to 7 patients and usual care (plaquenil + Kaletra + no steroids) was given to 16 patients. Low dose Anakinra showed no benefit on inflammatory markers or clinical course at 7 days and was stopped. The high dose Anakinra group showed reduction in CRP and improvement in oxygen needs at 21 days in 21 of 29 patients (72%). Five patients (17%) were on mechanical ventilation and three patients (10%) died. In the usual care group at 21 days, 8 of 16 patients (50%) showed improvement in oxygen need. One patient (6%) was on a mechanical ventilator and seven patients (44%) died. At 21 days, survival was 90% in the high dose Anakinra group and 50% in the usual care group. Dosing of high dose Anakinra was continued until CRP decreased by >75% and P/F ratio >200 for at least 2 days. Upon discontinuation, low dose Anakinra was given for 3 days.


An alternative to Actemra, giving Anakinra may benefit patients with extreme inflammation. We will need to watch for more data on this. Cost and availability may limit this. We had access to Actemra in New Jersey, not Anakinra.

Hydroxychloroquine (Plaquenil)

Hydroxychloroquine was used extensively in the January to April 2020 time frame. Dose was 400 mg PO bid x 1 day, then 200 mg PO bid x 4 more days. There was a
case series from France in February–March that looked at 36 patients. Disease course was shorter for patients on hydroxychloroquine or hydroxychloroquine + azithromycin versus control. This was not a randomized trial however. Prior data on SARS in China showed that hydroxychloroquine was helpful. Every trial since then has shown no improvement and increased risks.

At this point, use of hydroxychloroquine is not recommended.

Corticosteroids:

Corticosteroid use is confusing. Corticosteroids are not routinely recommended by IDSA outside of a controlled trial. However, many sites in the US are using them based on some data out of China.

In China, using solumedrol 40 mg/day or equivalent was not associated with delayed SARS-CoV-2 viral clearance. Patients were about 7 days into illness in this trial. This contrasts to early use (<5 days since onset of disease) of corticosteroids in SARS which led to delayed viral clearance.


A retrospective review of 46 patients admitted with COVID-19 pneumonia looked at steroid versus no steroid use. 26 patients received 1-2 mg/kg of solumedrol for 5-7 days. 20 patients did not receive steroids. Patients treated with steroid defervesced faster than other patients and had more rapid improvement in oxygenation and radiographic findings. Patients treated with methylprednisolone were weaned off oxygen earlier (median of 8 days vs. 14 days, $p<0.001$).


In a retrospective review of 201 patients admitted in Wuhan, China with COVID-19 pneumonia, use of solumedrol had a positive effect on mortality in those who developed ARDS. Treated patients had a 46% mortality (23 of 50 died) versus
untreated patients with a 62% mortality (21 of 34 died). The administration of methylprednisolone appears to have reduced the risk of death in patients with ARDS (HR, 0.38; 95% CI, 0.20-0.72; P = .003)


Actual practices have varied greatly in regards to steroids. A case series out of Seattle, WA looking at 105 patients admitted to UW hospitals showed that only 3% were treated with the addition of corticosteroids. Of note, 11% of patients were on corticosteroids at baseline.

*Buckner et al, Clinical Infectious Disease, 2020 May 22  e-published ahead of print*

Meanwhile in a series out of Vancouver, BC ICU settings, 24% of 117 admitted patients were treated with corticosteroids.

*Mitra et al, CMAJ 27 May 2020 e-published*

**Summary**

There is no commonly accepted evidence based answer to guide corticosteroid use in hospitalized COVID-19 patients. It is reasonable to use solumedrol 40 mg / day in inpatients with elevated inflammatory markers (CRP being the mainstay, consider if >10 mg/dl). As inflammatory markers are often elevated in COVID-19 patients, this means corticosteroids will often be a consideration well before full-blown ARDS and need for critical care. In my personal experience (J Glass in New Jersey), 37 of 39 admits had an elevated CRP. We used solumedrol in many of them.

As noted above, hydrocortisone can be added for refractory shock if steroids were not used up to that point.

**Convalescent Plasma**

MOA is via passive immunity through a transfusion from a person who been recovered from COVID-19 (asymptomatic x 10 days, Ab titer >1:1000).
Case series of 5 ICU pts with mechanical ventilation who were give 400 ml of convalescent plasma day 10-22 s/p admission. Fever improved in all pts. 3 of 5 extubated and discharged. 2 still intubated.

Second study with 10 ICU pts. Pts received 200 ml convalescent serum 10-20 days s/p symptom onset. All improved.

FDA / Mayo clinic trial (multicenter) ongoing in the US to give a better picture of risks / benefits. 5000 ICU hospitalized pts (66% ICU). Multicenter US. Convalescent serum 250-500 ml x 1. Safety check reported. 36 serious reactions within 4 hours of transfusion -- Includes 15 deaths, 7 volume overload events, 11 TRALI events, 3 allergic reactions. The 7 day mortality was 15%. Trial ongoing – awaiting outcomes.

Convalescent serum 200 – 500 ml IV x 1 is being studied currently. IDSA recommends use in context of a clinical trial. Hospitalized COVID-19 pts. Reasonable to give for patients who can be enrolled in this trial.

Anticoagulation:

Therapeutic anticoagulation may be one of the key treatment maneuvers for severe COVID-19 infection.

Patients with COVID-19 infection have a profoundly altered coagulation picture leading to a hypercoagulable state.

A descriptive study from China of hospitalized COVID-19 pneumonia patients treated in January 2020 showed that survivors had significantly better coagulation profiles than non-survivors. The study included 183 patients (85 F / 98 M). Mean age 54 and 41% had co-morbidities. At end of study, 78 (43%) were discharged, 21 (12%) had died and the rest were still hospitalized. D-Dimer (normal range <0.5 ug/ml) was higher in non-survivors versus survivors.

Survivors 0.66 (0.38 – 1.50) versus Non-survivors 2.12 (0.77-5.27) (p<0.001).

VTE events are common in these patients.

In one study from the Netherlands, 184 ICU patients with severe COVID-19 infection were studied. At the time of the descriptive study, 23 (13%) had died, 22 (12%) had been discharged alive and 139 (76%) were still in the ICU. All patients had received standard dose thromboprophylaxis at least. The authors didn’t clarify how many received therapeutic anticoagulation, but the tone of the paper was that most were on prophylactic dosing. 31% of patients had a PE, DVT, MI, ischemic stroke or arterial embolization event. 27% of the events were VTEs and 3.7% were arterial clotting complications. Of the 28 VTE events, 25 were Pulmonary Emboli. Overall, this paper brings up the concern that prophylactic anticoagulation was not enough.


All patients in four ICUs in France between 3/3 – 3/31/20 were assessed. This included 150 patients (122 male, mean age 63). There were 64 thrombotic events in the 150 patients. Pulmonary emboli occurred more than DVT. 28 of 29 patients on CRRT had circuit clotting. 3 clotting events of the centrifugal pump on ECMO occurred. 95% of patients with clots had elevated D-Dimer and fibrinogen. No DIC was seen. vWF activity was increased. Lupus anticoagulant was seen in 50/57 (87.7%) of patients tested. In a comparison of COVID-19 ARDS patients versus non-COVID-19 ARDS patients, the risk of thrombotic complications was higher (11.7% vs 2.1%, p <0.008). Anticoagulation was recommended per ISTH guideline. (see below).


Interim guidance came out from the International Society for Thrombosis and Hemostasis on prophylactic anticoagulation in severe COVID-19 infections in April 2020. The recommendation was for prophylactic heparin. US Authors responded with concern that prophylactic anticoagulation is not enough. There is a hypercoaguable subtype DIC associated with COVID-19 that drives organ failure. This will not respond to therapeutic heparin dosing. Full
anticoagulation with a heparin gtt or therapeutic lovenox is required. One reason for this is that fibrinogen levels are often very high. Sometimes >700 mg/dl. This renders the patient resistant to lower (prophylactic) doses of heparin. Once fibrinogen >900 mg/dl, there is a risk of thrombosis from this. Additionally, the concomitant presence of ARF in many patients limits lovenox dosing. The authors end up recommending an unfractionated heparin gtt as the ideal strategy. It is reasonable to follow anti-Xa levels to assure anticoagulation. It is reasonable to consider salvage tPA in critically ill patients, but guidance on this is not out.


Coagulation abnormalities include prolonged aPTT and elevated D-Dimer levels. Determining whether the prolonged aPTT is due to a clotting factor deficiency, an inhibitor of a specific coagulation factor or a non-specific inhibitor was the goal of a study published in the NEJM in early May. A total of 216 COVID-19 hospitalized patients with severe disease had blood work done. Of these 44 (20%) had a prolonged aPTT. Of these 35 patients were further investigated. Median age 57. 66% male. Two patients had confirmed or suspected VTE events. No clinically significant bleeding or arterial thrombosis was seen. No patients had factor 8 or 9 deficiency. Mild factor 11 deficiency was seen (clinically likely unimportant). About 50% of patients had factor 12 deficiency. Lupus anticoagulant was found 91% (31 of 34) patients tested. All 31 patients had a prolonged aPTT with a 50:50 mix.


An observational study from inpatients at Beth Israel Hospital in NYC was e-published in the Journal of the American College of Cardiology in early May. The study followed inpatients with COVID-19 between 3/14/20 – 4/11/20. Therapeutic anticoagulation was provided to 786 patients of the 2773. The mean hospital stay was 5 days. The mean time to anticoagulation initiation was 2 days. The in-house mortality was 22.5% for those anticoagulated versus 22.8% without anticoagulation. The mean survival was 21 days versus 14 days. LDH, Ferritin, CRP and D-Dimer levels were higher in those anticoagulated. In a subset of 395
patients admitted to the ICU, the mortality on anticoagulation was 29.1% (mean survival 21 days) versus 62.7% (mean survival 9 days). There was no difference in inflammatory markers in those anticoagulated versus not. Major bleeding risk (transfusion or code for significant bleed) was higher in anticoagulated patients (3.0% versus 1.9%). There were no clear guidelines determining which patients were being placed on anticoagulation. There was no blinding. This is purely observational.


Due to the high VTE rates in COVID-19, it is reasonable to place inpatients on an unfractionated heparin gtt if the D-Dimer is elevated >3000 ug/l. An alternative to a heparin gtt is therapeutic lovenox if renal function is normal. Consideration should be given to continuing anticoagulation for 3 months post-discharge. Eliquis 5 mg PO bid would be one strategy.

ACEI or ARB:
Current recommendation is that these agents should be continued if the patient is taking chronically. These classes of medication lead to ACE receptor 2 up-regulation in the pulmonary bed. This is the portal of entry for COVID-19 so this led to some early concerns about use. But they also may block viral entry through their effects. And they help control co-morbidities that put the patient at more risk with COVID-19. The balance of these effects was initially unclear. Early case series are showing that populations that do worse in terms of mortality are older patients with co-morbidities that include ACEI / ARB treatment. However, stopping these meds has not been shown to improve the course of disease. At this point, continue the med unless concern - ARF or hyperkalemia.

NSAIDs
May confirm a risk of poorer outcome in a small case series from France. COVID-19 is often associated with renal injury. NSAIDs should be avoided to lower the overall risk to the kidneys in the acute phase of COVID-19.

Other medications
Pay attention to effective treatment of co-morbidities that may affect clinical care. COPD, CAD, DM, HTN, Atrial fibrillation, etc.
Resource – Diagnostic Criteria for Acute Respiratory Distress Syndrome (ARDS)

ARDS first described in 1967

ARDS Criteria developed in 1994 (American European Consensus Conference)

A. Acute onset of hypoxemia defined by partial pressure of oxygen / fraction of inspired oxygen (PaO2 / FIO2 ratio or P/F ratio) of <200 WITH
B. New bilateral infiltrates on chest imaging AND
C. Not attributable to heart failure as defined by pulmonary capillary wedge pressure (PCWP) as measured by a Swan-Ganz catheter) of not more than 18 mm Hg (Or absence of suspected LA hypertension / cardiogenic pulmonary edema if PCWP was not available).

Criteria refined in 2012 (Berlin Criteria)
   (European Society of Intensive Care Medicine)
Three categories of ARDS
   Mild: P/F ratio of 200-299  (formerly called acute lung injury)
   Moderate: P/F ratio of 100-199
   Severe: P/F ratio <100

‘Acute’ onset is now defined as onset of bilateral infiltrates within 7 days of exposure to an ARDS risk factor or worsening respiratory symptoms.

Pulmonary infiltrates criteria more broad now
   Bilateral infiltrates on CXR or CT chest

Don’t need a PCWP. Use echocardiography to define cardiac function.
You can have coexistent HF with ARDS, but the infiltrates can’t be solely from HF.

PEEP must be 5 cm H2O or higher on the mechanical ventilator or non-invasive ventilation in the ‘mild’ category.

Research is ongoing into biomarkers that may help identify ARDS.
Resource – ARDSNet Ventilation Protocol
Ventilator Management: ARDS Net Protocol:

Weight(kg): Predicted body weight (PBW)

Male 50+2.3(ht in inches-60)            Female 45.5+2.3(ht in inches-60)

Vent Mode: AC

Tidal Volume (Vt): Start 8 ml/kg PBW instead of usual range of 8-10 ml/kg that we start with in non-ARDS
Reduce Vt to 7 ml/kg and then 6 ml/kg over 1-3 hours

Respiratory rate: <35/min to match baseline minute ventilation. So start matched to patients RR rate

Vt adjustment then needs to happen to minimize barotrauma:

Pplat goal: <30 cm H2O (Pplat = Plateau pressure)
Check inspiratory Pplat with a 0.5 sec pause at least every 4 hours & after every change in PEEP or Vt.

If Pplat>30 then decrease Vt by 1 ml/kg steps until Vt is 5 ml/kg (or if necessary 4 ml/kg).
If Pplat<25 and Vt<6 ml/kg increase Vt by 1 ml/kg steps until Plat>25 or Vt=6 ml/kg

If breath stacking (auto peep) or severe dyspnea occurs, Vt may be increased to 7 or 8 ml/kg if Pplat<30

Oxygenation:
Goal is PaO2 55-80 or SpO2 88-95
Use below combination of FIO2 and PEEP to achieve goal

FIO2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
PEEP 5 5-8 8-10 10 10-14 14 14-18 18-22

PEEP should be applied beginning with the minimum value for a given FIO2

This ratio of FIO2 and PEEP tries to balance oxygen toxicity and PEEP effects on cardiac output.

pH Goal=7.30-7.45
If pH =7.15-7.30
Increase set rate until pH>7.30 or PaCO2<25 (max rate =35)
If set rate=35 and pH is still <7.30 then consider giving NaHCO3 via IV route

If pH<7.15
Increase rate to 35. If set rate =35 and pH<7.15 then consider NaHCO3.
If NaHCO3 doesn’t correct, increase Vt in 1 ml/kg increments until pH >7.15.
Pplat target (<30) may have to be exceeded.

If pH>7.45
Decrease vent rate if possible.

I:E ratio=1:1 - 1:3
Adjust flow rate and inspiratory flow wave form to achieve this goal.

Weaning trial:
Perform daily if patient meets all criteria below:
1. FIO2<=0.4 and PEEP<=8
   (Values should be same or better than prior day)
2. Pt taking spontaneous breaths (turn down set rate and see)
3. Systolic bp>=90 without concomitant pressor use
Resource – Mechanical ventilation modalities for ARDS

Low Tidal Volume Ventilation
This is the main modality used for ARDS. See protocol above (ARDSnet)

Why does low tidal volume ventilation have benefit over standard ventilation?
  Reduced barotrauma (application of high pressures to the lung resulting in injury)
  Reduced volutrauma (avoiding high tidal volumes which cause stretch injuries)
  Improved hemodynamics (BP and organ perfusion) as a result of:
    less over-distention of the lung and improved venous return to the heart

Downside of low tidal volume ventilation: can result in collapse of lung parenchyma
So we find the right balance of breath volume (Vt) and airway pressures (PpI).

Prone Ventilation
Has been used in ARDS.
Study in 2013 looked at 16 hrs of prone positioning a day versus standard positioning in severe ARDS.
Started prone ventilation 12-24 hours after stabilization but no longer than 36 hours after intubation.
Inclusion criteria: P/F <150, FIO2 > 0.6, PEEP 5 or greater and on ARDSnet protocol
28 day mortality benefit of prone positioning was found (16% versus 32.8%)
90 day mortality benefit persisted.
No complications in prone group versus usual care (no skin breakdown differences).
One limitation: This study was done at centers with substantial experience in prone ventilation.

Why does prone ventilation help?
  Improved lung ventilation perfusion matching
  Improved R ventricular dysfunction
  Recruitment of lower lobe atelectatic lung units (reduced compression of lung units in prone)
  Decreased intrapulmonary shunting
  Improved maintenance of open lung units, thus limiting ventilator induced lung injury
  Improved secretion clearance

Neuromuscular Blockade
Has been studied in ARDS and has improved mortality at 90 days was seen in one study.
Subsequent study did not show this.
Currently not recommended as primary approach.
See above ‘Management’ section for times to consider.

High frequency oscillatory ventilation
Very frequent, small breaths did not help ARDS outcomes.
Mechanical ventilation without maintenance of open lung units has the potential to exacerbate lung
injury as a result of opening and closing of lung units – called ‘atelectrauma’.
Resource – Radiographic Finding of COVID-19


This study looked at CT chest – initial modality that was used in China in January / February 2020.

Figure 1a: An axial CT image obtained without intravenous contrast in a 36-year-old male (Panel A) shows bilateral ground-glass opacities in the upper lobes with a rounded morphology (arrows). An axial CT image obtained in a 44-year-old male (Panel B) shows larger groundglass opacities in the bilateral lower lobes with a rounded morphology (arrows). An axial CT image obtained in a 65-year-old female (Panel C) shows bilateral ground-glass and consolidative opacities with a striking peripheral distribution.
Figure 2: An axial CT image obtained without intravenous contrast in a 56-year-old female shows ground-glass opacities with a rounded morphology (arrows) in the right middle and lower lobes. The left lung was normal.

Figure 3: An axial CT image obtained without intravenous contrast in a 42-year-old male in the “late” time group (10 days from symptom onset to this CT) shows bilateral consolidative opacities, with a striking peripheral distribution in the right lower lobe (solid arrows), and with a rounded morphology in the left lower lobe (dashed arrow).
Figure 5a: An axial CT image obtained without intravenous contrast in a 43 year old female (Panel A) shows a “crazy-paving” pattern as manifested by right lower lobe ground-glass opacification with interlobular septal thickening (arrows) with intralobular lines. An axial CT image obtained in a 22-year old-female (Panel B) shows an area of faint ground-glass opacification in the left upper lobe with a ring of denser consolidation (arrow, “reverse halo” sign).

Time course of Chest CT findings:
Comparing CXR and CT Chest:


Fig. 1. Representative chest radiographic (A) and CT images (B, C) of COVID-19 pneumonia manifesting as confluent mixed ground-glass opacities and consolidation on CT. A. Anteroposterior chest radiograph shows multifocal patchy peripheral consolidations in bilateral lungs, except for left upper lung zone. B, C. Coronal and axial chest CT images show confluent mixed ground-glass opacities and consolidative lesions in peripheral bilateral lungs. Discrete patchy consolidation (arrowheads) is noted in left upper lobe. On axial CT image (C), confluent lesions are mainly distributed in peripheral lung along bronchovascular bundles. Most of lesions spare juxtapleural area, and minor proportion of lesions touch pleura. Lesions contain multiple air-bronchograms, and air-bronchogram in superior segment of right lower lobe is distorted (arrows). COVID-19 = Coronavirus disease 2019, CT = computed tomography
Fig. 2. Representative chest radiographic (A) and CT images (B, C) of COVID-19 pneumonia manifesting as confluent pure ground-glass opacities on CT. 

**A.** Baseline anteroposterior chest radiograph shows patchy ground-glass opacities in right upper and lower lung zones and patchy consolidation in left middle to lower lung zones. Several calcified granulomas are incidentally noted in left upper lung zone.

**B, C.** Baseline axial and coronal chest CT images show confluent pure ground-glass opacities involving both lungs. Most of confluent and patchy ground-glass opacities about pleura and fissure in peripheral lung. A few calcified granulomas are incidentally noted in left upper lobe.
Fig. 3. Representative chest radiographic (A) and CT images (B) of COVID-19 pneumonia manifesting as single nodular lesion. 
A. Anteroposterior chest radiograph shows single nodular consolidation (arrows) in left lower lung zone. B. Coronal chest CT image taken on same day shows 2.3-cm ill-defined nodular lesion with reversed halo sign with thick rim in left lower lobe, abutting adjacent pleura.