MCCCN Stand-Up Conference Call
April 9, 2020
Starting at 10:00 AM

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The diagram illustrates the clinical course and management of viral infections, focusing on:

**Stage I (Early Infection):**
- **Clinical Symptoms:** Mild constitutional symptoms, Fever >99.6°F, Dry Cough, diarrhea, headache.
- **Clinical Signs:** Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild).

**Stage II (Pulmonary Phase):**
- **Shortness of Breath:** Hypoxia (PaO2/FiO2 ≤ 300 mmHg).

**Stage III (Hyperinflammation Phase):**
- **ARDS:** SIRS/Shock, Cardiac Failure.
- **Elevated inflammatory markers:** CRP, LDH, IL-6, D-dimer, ferritin, Troponin, NT-proBNP elevation.
- **Potential Therapies:** Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions.
- **Reduce immunosuppression:** Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors.

The diagram also highlights the progression of severity of illness over time and the interplay between the viral response and host inflammatory response phases.
COVID-19 Disease Course

- For hospitalized patients with pneumonia, limited studies suggest the disease course (Wuhan experience and others):
  - ~50% develop hypoxemia by day 8
    - Severe illness and cytokine release syndrome appear to develop mostly within 5–10d after symptom onset in susceptible patients.
    - Markers of severe infection include regular high fevers (>39°C), RR > 30, worsening oxygen requirements (4–6L nasal canula), also elevated IL-6 levels (> 40–100), CRP (>10x normal), ferritin (> 1000), d-dimer (>1).
  - ARDS develops in 17–29%
  - Patients in the ICU require:
    - Non-invasive ventilation (42%)
    - Mechanical ventilation (47%)
    - High-flow O₂ (11%)
    - ECMO (2-5%)
COVID-19 in Washington State

- Critical Illness experience (Washington State)[7]
  - Small patient series (n = 21)
    - Age: 70 (mean)
    - Comorbidities: in 86%
    - Duration of symptoms: 3.5d (mean)
      - Admission to ICU within 24h of hospitalization: 81%
    - Nearly all had radiographic abnormalities at presentation.
      - Leukopenia: in 67%
  - Mechanical ventilation: in 71%
    - ARDS in 100% of those who required mechanical ventilation, most developed within 72h.
    - Most patients were not in shock, but 67% received vasopressors.
    - Cardiomyopathy: developed in 33%
      - Unclear if direct viral effect v. critical illness stress
    - Mortality: 67% (as of publication date)
General schema for respiratory support in patients with COVID-19

Low flow nasal cannula
- Typically set at 1-6 liters/minute.

High flow nasal cannula
- Titrate FiO2 based on patient’s saturation. If FiO2 requirement escalating (e.g., >80%) consider awake pronation or CPAP trial.
- Consider limiting flow rate below ~40 L/min to reduce aerosolization.
- N95 mask & aerosol precautions.

CPAP
- Titrate CPAP up as tolerated (in more severe hypoxemia might target ~15-18 cm).
- Viral filter.
- N95 mask & aerosol precautions.
- (Helmet interface likely ideal if available).

Awake pronation plus {High Flow Nasal Cannula or CPAP}
- If tolerated, awake patient may lie in a prone position (ideally for 12-18 hr/day).
- Limited to cooperative patients. May be useful if access to ventilator is limited.

Invasive mechanical ventilation
- Target tidal volumes of ~6 cc/kg.
- Permissive hypercapnia may be useful to allow for lung-protective settings.
- May use conventional lung-protective ventilation strategies or APRV.

Prone positioning
- Consider for severe hypoxemia (e.g. PaO2/FiO2 < 150) that doesn't respond to ~12-24 hours of invasive ventilation with high mean airway pressure (e.g. high PEEP or APRV).

VV-ECMO
- Indications remain unclear.
- Early discussion with ECMO center or team may be advisable.

The optimal strategy for respiratory support in COVID-19 remains unknown. Patients with more complex respiratory disease (e.g. COPD plus COVID-19) might benefit from BiPAP. Choice of CPAP vs. HFNC may vary depending to resources and patient preference. COVID appears to cause progressive micro-atelectasis, which responds well to CPAP.
Awake Proning? Avoid Intubation?

- Patients treated with HHFNC or CPAP or Non Invasive Ventilation
- Monitor closely in ICU
- If develop clinical signs of excessive inspiratory efforts, tachypnea, anxiety, increased WOB...
- Intubation should be prioritized
COVID-19 + hypoxic vasoconstriction

mechanism to match perfusion to ventilation
constriction of small intrapulmonary arteries in response to alveolar hypoxia
(blood is diverted to better oxygenated lung)
global (e.g. high altitude pulmonary edema - HAPE)
or
focal (e.g. atelectasis, pneumonia)

why might hypoxic vasoconstriction explain COVID-19
“silent hypoxemia”
possible loss of lung perfusion regulation and hyperperfusion of gasless alveoli
Coronavirus Disease 2019 (COVID-19) in Italy

Data as of March 13, 2020

22,512 cases of COVID-19

2,026 cases of COVID-19 among healthcare workers

1,625 deaths

Timeline of COVID-19 symptom onset and diagnosis in 2020

Cases by age range

- 24.0% 0-18 y
- 59.8% 19-50 y
- 12.4% 51-70 y
- 1.2% >70 y
- Median age, 64 y

Cases by sex

- 59.8% Male
- 40.2% Female

Cases by severity

- 24.9% Critical
- 46.1% Severe
- 5.0% Moderate
- 10.6% Unspecified symptoms
- 6.7% Few symptoms

Cases by region/province of diagnosis

Authors: Edward Livingston, MD; Karen Bucher, MA, CMI

Sources: Adapted from the COVID-19 Task Force of the Department of Infectious Diseases and the IT Service Instituto Superiore di Sanità. https://www.iss.it/infografiche

Please cite as: JAMA. Published online March 17, 2020. doi:10.1001/jama.2020.4344

Replying to @PulmCrit @critconcepts

anecdotes don't make science but the guy fared well (GCS 15, no resp distress, sat's ok with 35% O2) so far with CPAP (PEEP 10) and THIS CT scan. @PulmCrit It adds to your idea that those patients benefit hugely from CPAP. @ThinkingCC @iceman_ex

A.S.O. Mauriziano Torino

BrightSpeed

19/03/2020
16:04:38
SE:4
IM:126
When to Intubate?

- Avoid emergent intubations - Protocol
- Frequent clinical re-evaluation in patients on HHFNC or NIV
- Prolonged time to apply PPE
- Increased risk of infection to the person performing the intubation

**HFNC preferred non-invasive strategy**

**Should be performed in negative pressure room. If this is not possible, should be performed behind closed curtains with HEPA filter bed side.**

- FiO2 should always be set at 100%.
- Initial LPM should be set at 20LPM.
- LPM should be titrated up to a maximum of 50LPM as needed in order to achieve an SpO2 >88%.

Requiring 90% - 100% to achieve sat 88-90%

ALL PATIENTS ON NPPV

On NRB w/ 5L NC w/ SpO2 < 85

PRIORITY 1 – Patient’s at HIGH risk for requiring intubation

**Proning** should be encouraged in all patients and may be considered in PRIORITY 1 patients however Physician should be aware that proning appears to induce a non-sustainable improvement in SpO2. Proning should therefore be seen as “buying time” rather than “recruiting.” Regardless of SpO2 improvement, PRIORITY status should not change based on SpO2 improvement during proning.

Consider intubation:
- Hypoxemic patient on maximal non-invasive oxygen with SpO2 <85 – 88% w/ distress. (Presenting typically in the form of anxiety and tachypnea).
- Hypoxemic patient on maximal non-invasive oxygen with sustained SpO2<80%
HYPOXIC $SpO_2<90\%$

- LIKELY OR KNOWN COVID?
  - N: RESUS 1-2
  - Y: RESUS 4

- UNSTABLE / CRASHING?
  - Y: RESUS 4
  - N: NASAL PRONG OXYGEN 4L/MIN + SURGICAL MASK ON PATIENT
    - SENIOR DR REVIEW

RESUS

SIGNIFICANT INCREASED WORK OF BreATHING?

- CLINICAL EVALUATION, CXR, POCUS
- ASSESS PRONING RESPONSIVENESS
- CONSIDER INCREASE $FiO_2$

NECATIVE PRESSURE ROOM

- CLINICAL EVALUATION, CXR, POCUS
- INCREASE $FiO_2$
- ASSESS PRONING RESPONSIVENESS IF TOLERATED
- D/W ICU
- CONSIDER HIGH FLOW NASAL CANNULA WITH SURGICAL MASK OVER CANNULA (STAFF IN FULL PPE / N95)

TYPE L 😞

- Hypoxia partly due to abnormalities in pulmonary blood flow, which may respond to changes in patient positioning. Because the lungs are not severely affected, the patient does not feel as breathless

- PATIENTS MAY PROGRESS TO TYPE H
  - NEED FREQUENT MEDICAL REVIEW

TYPE H 😞

- Significant dyspnoea may represent a more advanced stage of lung injury and greater need for invasive ventilation

- PATIENT ALERT, COOPERATIVE, ABLE TO TURN THEMSELVES
- REMOVE ECG LEADS BEFORE TURNING
- CAUTION WITH IV LINES, IDC, ETC
- DOCUMENT ANY CHANGE IN RR AND $SpO_2$
- PATIENT CAN ALSO TRY LYING ON EITHER SIDE

OXYGEN DELIVERY OPTIONS

- NASAL PRONGS PLUS
- SIMPLE FACEMASK PLUS
- NON-REBREATHER PLUS
Who will develop ARDS with COVID-19?

- 201 patients with confirmed COVID-19
- Median age 51 years (IQR, 43–60 years)
- 63.7% male, and 32.8% had comorbidities.
- 33% required mechanical ventilation, and median time from admission to ARDS was 2 days (IQR, 1–4 days).

- Age ≥65 years, neutrophilia, and organ or coagulation dysfunction were associated with ARDS and death.

- Among those with ARDS, treatment with methylprednisolone was associated with significantly better outcomes: 23 of 50 (46%) methylprednisolone recipients died compared with 21 of 34 (61.8%) nonrecipients (hazard ratio, 0.38).

- Although corticosteroids appeared to be beneficial in this cohort, WHO guidelines do not recommend adjunctive corticosteroids outside of a clinical trial.

COVID-19 - rapidly progressive ARDS

Day 1

Day 2

Day 3
COVID-19 does not lead to “typical” ARDS

• Primary characteristic observed is the dissociation between the relatively well preserved lung mechanics and the severity of hypoxemia.

• In first 16 patients in Italy, the respiratory system compliance of $50.2 \pm 14.3$ ml/cmH2O was associated with shunt fraction of $0.50 \pm 0.11$.

• Such a wide discrepancy is virtually never seen in most forms of ARDS.

• Relatively high compliance indicates well preserved lung gas volume in this patient cohort, in sharp contrast to findings in severe ARDS.

Gattinoni L et al. AJRCCM Articles in Press. Published March 30, 2020 as 10.1164/rccm.202003-0817LE
Hypoxaemia

Dysregulation of Pulmonary perfusion
- Low Elastance
- Low V/Q
- Low recruitability
- Limited “PEEP response”

Phenotype L

Pulmonary Micro-Thrombosis

Pulmonary Oedema Collapse – “ARDS-like”
- High lung Elastance
- Higher Recruitability
- High R→L shunt
- Higher “PEEP response”

Phenotype H
Type L vs. Type H (Severe ARDS)

*High PEEP, Prone, VV-ECMO*

**Type L Phenotype:**
Spontaneous breathing, non-aerated tissue virtually 0. Venturi mask, FiO2 0.8

**Type H Phenotype:**
Mechanical Ventilation, PEEP 5. Non-aerated tissue 54%. Volume control, 7.8 ml/kg TV, RR 20, FiO2 0.7

PaO$_2$/FiO$_2$
- Type L: 95 mmHg
- Type H: 84 mmHg
COVID-19 indicates coronavirus disease 2019; PEEP, positive end-expiratory pressure; \( \text{FiO}_2 \), fraction of inspired oxygen; \( \text{Pao}_2 \), arterial partial pressure of oxygen. Boxplots show the 25th, 50th, and 75th percentiles (box); 10th and 90th percentiles (whiskers); and outlying points (circles).
Severe ARDS (Type H)

- High PEEP, high MAP
- Prone
- Inhaled nitric oxide 10 ppm
- VV-ECMO

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**Overview of ARDS Ventilator Management Strategies**

**1. Basic Lung Protective Ventilation**
   - ARDS Network Ventilation strategy:
     a. Use VCV or PCV, targeting VT 6 ml/kg PBW
     b. Maintain PaO2/FiO2 $>300$
     - Increase PEEP if necessary
     - Consider HFOV if PaO2/FiO2 $<150$
   - If ventilation is not adequate, consider peacemaking

**2. Patient-Ventilator Asynchrony**
   - Consider reflex-activated adjustments (eg, flow rate & pattern, respiratory pause)
   - Assess potential to benefit from pharmacologic agents
   - Consider in patients with severe ARDS and strong respiratory drive (double-triggering)
   - For dose-triggering, consider increasing VT $1$ mL/kg (max $8$ mL/kg), provided PaO2/FiO2 $>200$
   - For flow-aspiration, consider a variable flow pressure breath mode of ventilation
   - Volume-targeted PC (PRVC, Vc, Acflow)
   - Pressure control, pressure support

**Prone Positioning**
   - Consider after initial 13-24 hrs of stabilization
   - Use 18 hours (generally 4 pm to 2 am)
   - Discontinue when:
     - Instability in prone position
     - Supine 0 hrs, PaO2/FiO2 $>150$ in PaO2 $>50$ & PEEP $>10$

**Higher PEEP**
   - For pts with PaO2/FiO2 $<150$, consider higher PEEP table
   - Recruitment maneuvers:
     - For pts with clear chest radiography, negative PaO2 or PaCO2 $>15$
     - Recommend PCO2: 40-20-5 for 1-3 hrs (as tolerated)
     - 5 minute hold after 60 seconds
     - Provider should be at bedside if pressures $>40$ on H2O used

**Neuromuscular Blockade**
   - No benefit of routine use of NMB in moderate/severe ARDS
   - Consider significant neuromuscular impairment and concern for VILI

**Pneumothorax Pressure (PPV) Guided Therapy**
   - Informals of transpulmonary end-inspiratory (Pp-0) and end-expiratory (Pp-PEEP) pressures
   - Requires A/EA ventilation and placement of Pas catheter

**Airway Pressure Release Ventilation (APRV)**
   - Increases Pmean with lower PPas; data outcomes benefit
   - Concern for P-0-0-0 in pts with strong respiratory drive

**Inhaled nitric oxide (INO)**
   - Start at $10$ ppm
   - If responsive (improved oxygenation) or brought in by Survival Flight
     - Maintain $10$ ppm and reduce PaO2 down to $8$, then Straite $0$ down, or consider Vioett or loprostig, per Respiratory care
   - If no response, discuss with team to consider stopping

**High Frequency Oscillatory Ventilation (HFOV)**
   - Absolute contraindications: irreversible pulmonary process/evaluative, but lower survival if at vent $7-10$ days pre-ECMO
   - Extraosseous Membrane Oxygenation ECMO
   - Absolute contraindications: irreversible pulmonary process evaluative, but lower survival if at vent $7-10$ days pre-ECMO
   - Consider if PaO2/PaO2 $<50$ x3 hrs or $<60$ x5 hrs, or $P<7.25$ or $Paco2 >60$ x6 hrs

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**Low PEEP/High FiO2 Protocol**

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Typical response of COVID patient to APRV initiation

**Pre-Intubation**
*FiO2 100%, saturation 85%*

**After stabilization on APRV**
*FiO2 50%, saturation 94%*

Dramatic improvement in oxygenation and chest radiograph (when performed) are seen within 12 hours of APRV initiation. This is generally able to avoid the need for paralysis or proning. In many cases, patients are able to be maintained comfortable and awake on the ventilator, facilitating expedited extubation.
Prone position ventilation for critically ill patients with COVID-19. (A) An intubated patient turned prone; (B) an intubated patient with extracorporeal membrane oxygenation support turned prone. (Photograph by Drs. Haibo Qiu and Chun Pan.)

Mortality of Ventilated COVID-19 Patients

- **Wuhan**: of 37 critically ill Covid-19 patients who required mechanical ventilation, 30 died within a month.
- **Seattle**: only 1 of 7 patients > 70 who were put on a ventilator survived; just 36% of those younger than 70 did.
- **Italy**: JAMA Monday, nearly 90% of 1,300 critically ill patients with Covid-19 were intubated/MV; only 11% received noninvasive ventilation. 25% died in the ICU; 58% were still in the ICU, and 16% had been discharged. Older pts (age ≥ 64 years) had higher mortality (36%) vs. younger (15%).
Disease Course and late “failures”

**Hyperacute:**
severe hypoxaemia and breathlessness leading to immediate intubation;

**Indolent (improving):**
moderate or severe hypoxaemia but only moderate work of breathing.

**Biphasic:** initial indolent course followed – typically after 5 - 7 days – by an acute deterioration with hyper-inflammation, worsening respiratory failure with bilateral infiltrates and consolidation.
Thick Tenacious Secretions in COVID-19

• Can lead to partial endotracheal tube (ETT) occlusion
• Rescue-Cath used to clear ETT
• Balloon catheter with net
• Avoids need for reintubation and ETT exchange
• AGP
Extubation of COVID-19 patient

• NPR
• Preoxygenate
• Full PPE
• SAT/SBT
• Consider higher PEEP in obese
• Extubate to HHFNC 100% FiO2, Flow 30-50 lpm
• Wean FiO2 slowly....
Microvascular thrombosis from severe endothelial dysfunction in COVID-19 pathophysiology: Anticoagulation for critically ill COVID-19 patients

- DIC seems to be a driver of disease severity
- Diagnostic hallmark of COVID-DIC is a rapidly rising D-dimer
- High D-dimer is a strong prognostic factor for poor outcome
- D-dimer > 1 associated with 20-fold increased death rate, Zhou et al
- Pulmonary and organ thrombi have been reported in autopsy findings in COVID-19
Biomarkers in COVID-19

- 191 patients
- Wuhan, China
- Risk factors with poor prognosis:
  - Older age
  - High SOFA score
  - D-dimer > 1 μg/mL

*Lancet 2020; 395: 1054–62*
**HEPARIN?**

- ARDS
- P/F ratio < 200
- Cannot r/o PE
- Too unstable for PE CT
- Systemic anti-coagulation with heparin
Possible approach to empiric anticoagulation in COVID-19

Is D-dimer above ~1,000-2,000 ng/ml?

No

- **DVT prophylactic anticoagulation** (consider higher dose than normal, if D-dimer is moderately elevated).
  - **Follow serial D-dimer** (If D-dimer rises above 1,000-2,000 ng/mL, then re-consider anticoagulation).

Yes


Contraindication to anticoagulation?

No

- Check fibrinogen level and/or thromboelastography (TEG)
  - Normal or hyper-coagulable pattern (nearly always)
    - R-time low or normal on thromboelastography
    - Fibrinogen level is normal or elevated
  - Hypo-coagulable pattern (rare, late-stage)
    - R-time prolonged on thromboelastography
    - Fibrinogen level low

Yes

- **Therapeutic anticoagulation**, e.g.:
  - Normal renal function: therapeutic dose low molecular weight heparin
  - Renal failure: heparin infusion

- Follow fibrinogen level and/or thromboelastography occasionally. Discontinue anticoagulation if evidence of hypo-coagulable pattern.
- For severe hypercoagulability, consider addition of aspirin.

No anticoagulation

The role of anticoagulation remains unknown and highly controversial. This is one general approach which could be reasonable, but treatment decisions should always be individualized.
**Hypercoagulability**
- PT
- APTT
- Fibrinogen
- Activated factor II (FVIIa; functional clotting assay)
- Factor VIII (functional clotting assay)
- Antithrombin (enzymatic anti-FXa assay)
- Coagulation protein C (functional enzymatic assay)
- Coagulation proteins S (free proteins S turbidimetric immunoassay)

**Platelet hyper-reactivity**
- Platelet function analyzer 100/200
- VWF:ag
- VWF RCo activity
- VWF multimers
- VWF collagen binding
- ADAMTS-13 (antigen and activity)

**Anticoagulants**

**Anti-platelet medications**

**Complement overactivation**
- C3, C3a
- C4
- C4a, C5a
- Bb
- Sc5b-9

**Complement inhibitors**

**Fibrinolytics**

**Hypo-fibrinolysis**
- D-dimer (immunoassay)
- Alpha 1 antiplasmin (antigen immunoassay)
- Tissue plasminogen activator (t-PA; antigen immunoassay)
- Inhibitor of tissue plasminogen activator 1 (PAI-1; antigen immunoassay)

**COVID-19-induced coagulopathy**
COVID-19 Treatments

• Vitamin C for ARDS / Sepsis
  • CITRIS-ALI trial
  • Vit C 50 mg/kg q6h x 96 hours
  • Decreased 96-hour mortality 4% vs. 23%
  • Decreased 28-day mortality 29.8% vs. 43.6%

• Antiviral therapy
• Immunotherapy
• Convalescent Plasma
• Placenta-based Stem cell therapy