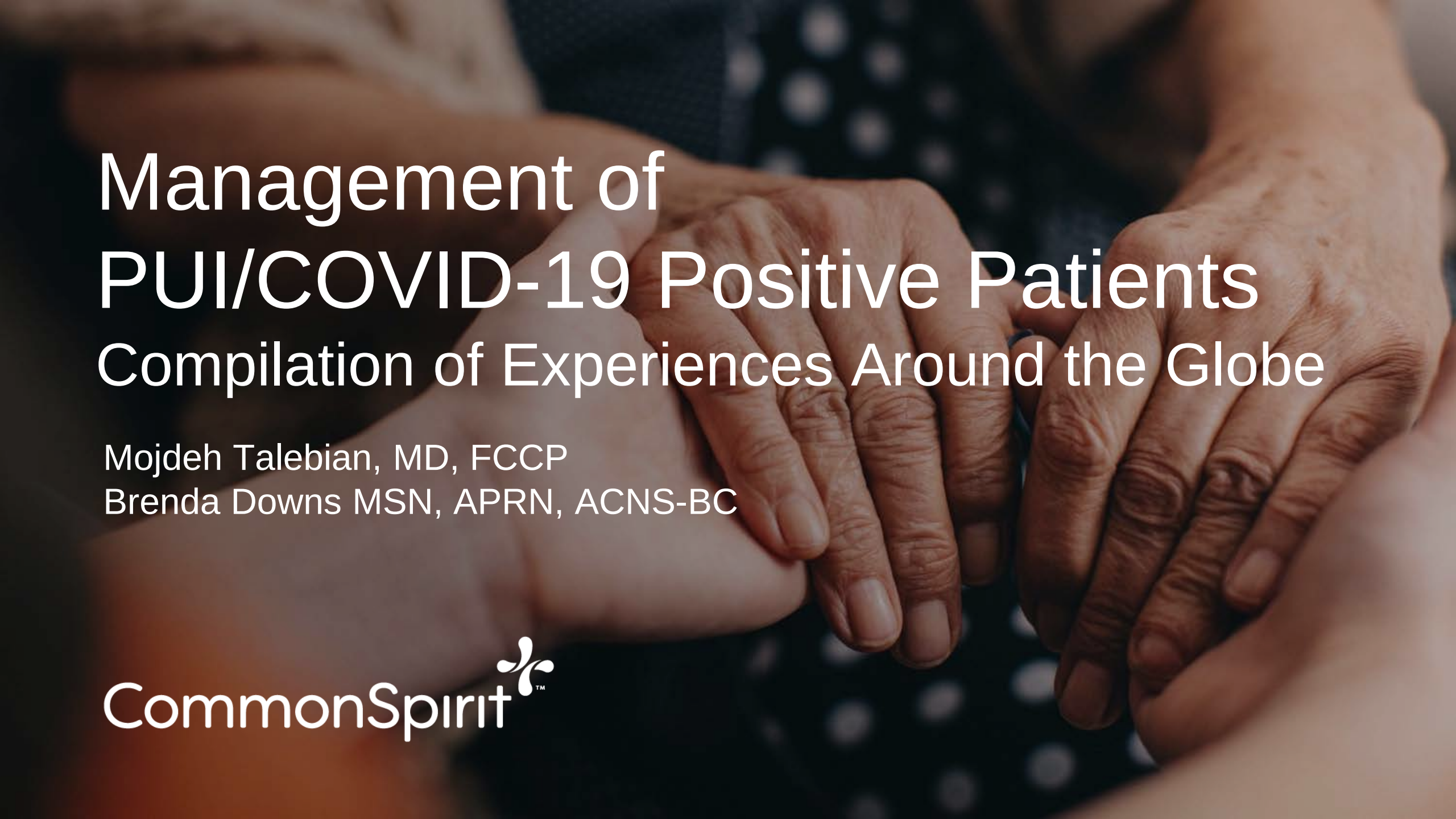

# Management of PUI/COVID-19 Positive Patients

## Compilation of Experiences Around the Globe

Mojdeh Talebian, MD, FCCP
Brenda Downs MSN, APRN, ACNS-BC

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# Many Thanks…

We would like to extend our appreciation to our colleagues from Seattle Washington hospitals including University of Washington, University of California, San Francisco, Stanford University for sharing their data, recommendations,  and experiences which we have incorporated in our presentation.

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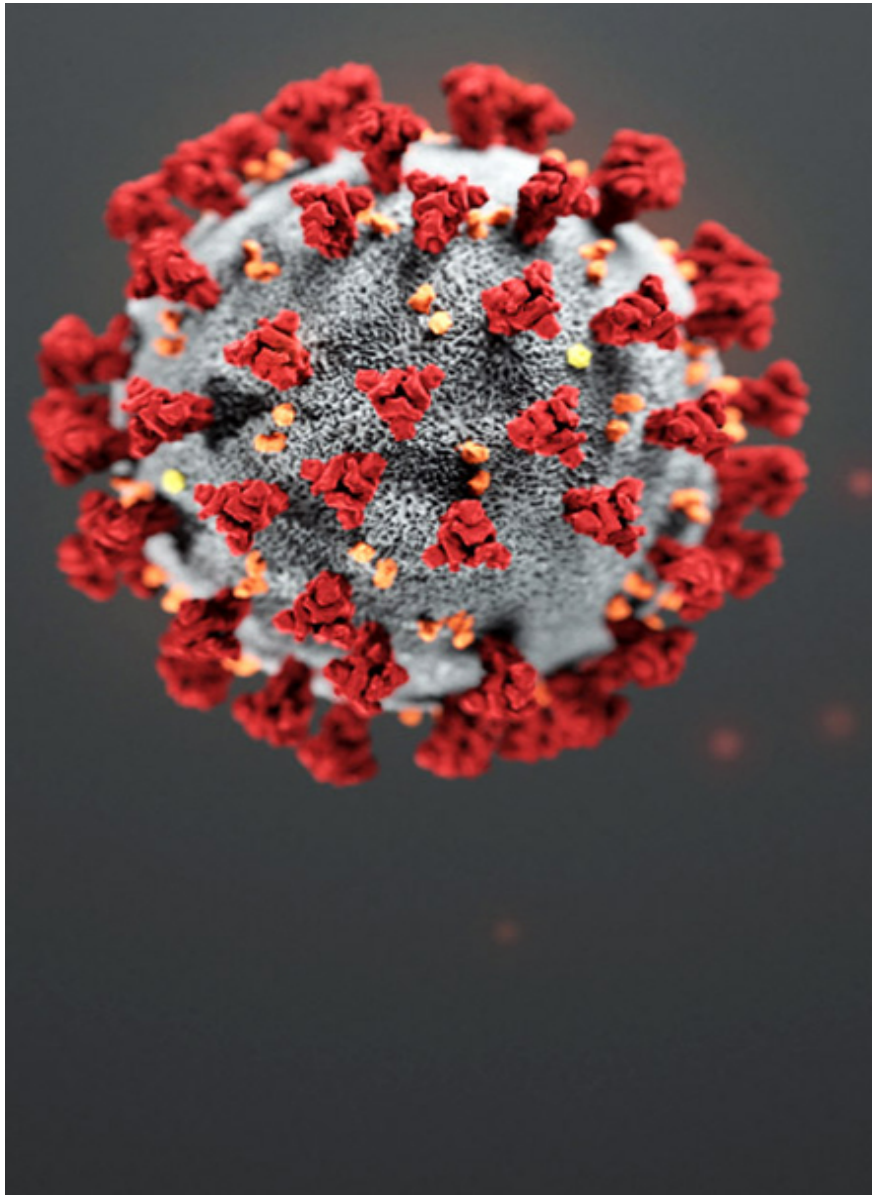
# Coronavirus

- Coronavirus cause 5-10% of community acquired upper respiratory infections
- Can cause severe lower respiratory tract infection in elderly
- ssRNA enveloped virus
- S spike binds to ACE 2 on type 2 pneumocyte
- Name: “Crown” seen in electron micrograph
- Recent outbreaks of coronavirus:
    - SARS-CoV; 1st reported in China 2002
        - 8100 cases, 774 death (10%)
    - MERS; 1st reported in Saudi Arabia 2012
        - 2500 cases, 858 death (30%)
    - SARS-CoV2 is the virus responsible for COVID-19; 1st reported in China 2019



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# Mode of Transmission

- **Contact** with infected surfaces
  - Surfaces that are covered with virus then touching face, mouth
- Person to person
  - **Droplet** & contact; inhalation of droplet or contact with droplets and then touching face, mouth, eyes
- Person to person
  - **Airborne** ; respiratory droplets that are ***aerosolized*** with breathing

# Infection Control

**WHO:**

- Contact & Droplet
  - Simple mask
  - Eye / face protection
  - Distance of 3-6 feet

**CDC:**

- Contact & droplet & eye protection
  - N95 mask
  - Airborne isolation room

# Clinical Features of COVID-19

- China experience (*NEJM March 12, 2020)*
  - 1099 confirmed cases, 552 hospitals
    - Fever (43.8%) cough (67.8%)
    - Diarrhea uncommon (3.8%)
    - Median age 47, 41.7% female
    - Median incubation 4 days
    - 60% abnormal  CXR, 86% abnormal CT
    - Median WBC 4700
    - 61% elevated CRP, 5% elevated Procalcitonin
    - 1.1% septic shock, 3.4% ARDS

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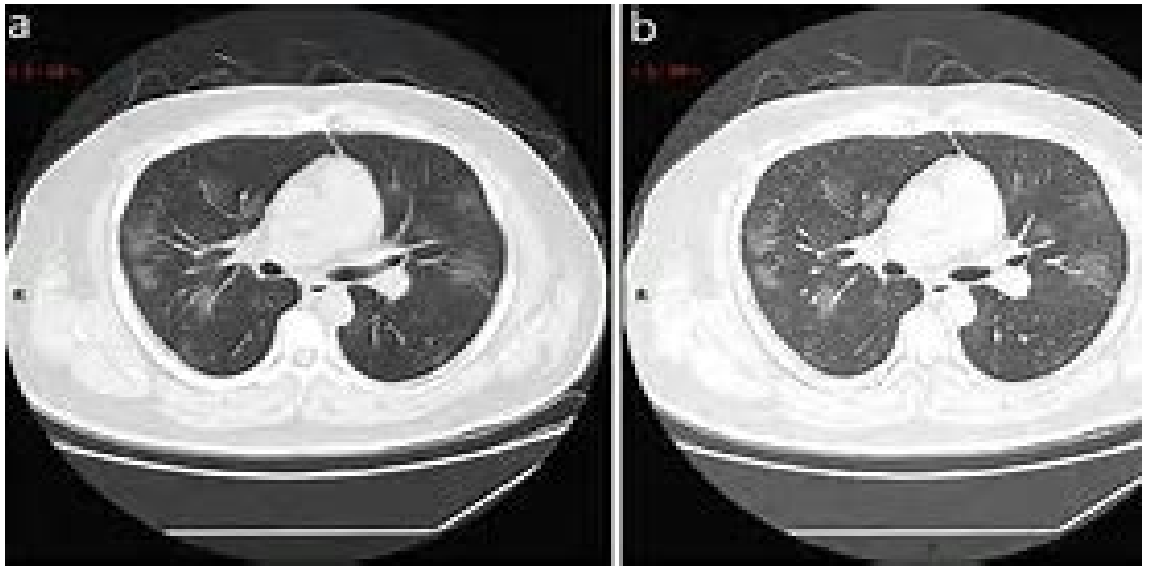
# Radiographic Findings

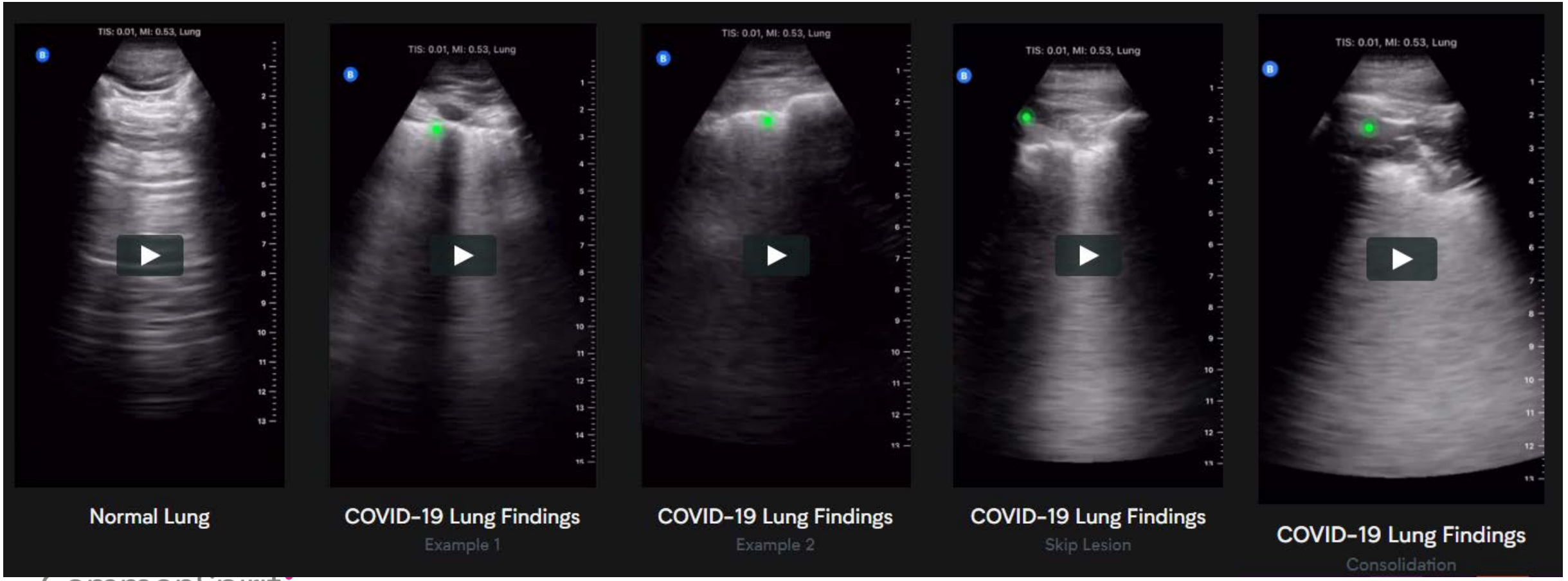
- Bilateral (79%)
- Peripheral (54%)
- Ill defined ( 81%)
- Ground glass opacity (65%) [Crazy paving]
- Unilateral (early disease) → bilateral (late disease)
- GGO → consolidation




# Use of Handheld/Bedside Ultrasound of Lungs

Bedside lung ultrasound could be used to effectively identify patients with COVID-19 pneumonia where radiology is not available.

https://emcrit.org/ibcc/covid19/#lung_ultrasonography




Photos courtesy of: https://www.butterflynetwork.com/covid-19#lungfindings

# Prognosis

- Predictors of poor outcome:
  - Age
  - Comorbidities (DM, COPD, CVD)
  - Admission high SOFA scores
  - Labs associated with higher mortality:
    - Elevated D-Dimer, Ferritin, troponin, cardiac myoglobin
- Complications to watch for:
  - Secondary infection (VAP)
  - Cardiomyopathy
    - Despite viral binding to ACE2, not recommended to stop ACEI/ ARBs (AHI, 2020)

# Recovery from COVID-19

- World Health Organization
    - mild illness recover in about two weeks
    - severe illness may take three to six weeks
        - Mainland China, > 80,000 diagnosed, >70,000 recovered
        - Italy > 53,000 diagnosed, > 6,000 recovered
        - Iran > 20,000, > 7,000 recovered

- John Hopkins dashboard for live global tracking

https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

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# General Concerns for PUI/ COVID-19 Patients

- COVID-19 patients are at risk of rapid deterioration
- Early intubation may reduce morbidity/ mortality
- Early recognition of PUI/COVID-19 patients with respiratory failure is crucial
- High risk procedures (i.e. intubation) require the personal protective equipment, PPE
- Early intubation allows team time for proper PPE and avoids exposing team to more risk
- **Aerosolized inhalers** to any PUI/ COVID-19 patients **should be avoided** –
    - Nebulizer orders to be automatically converted to MDI for patients needing bronchodilators
- Limited resources
    - Running out of ICU Beds – use of alternative areas (PACU, OR space, etc.)
- **Recommend Early Code Status discussion**

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# Limitation of Participation in Care of PUI/COVID-19 Patients

- Avoid Direct care by:
  - Pregnant women
  - Persons currently taking immunosuppressive agents
  - Immunocompromised persons by illness
  - Medical, nursing, respiratory therapy student
- Minimize ancillary service exposure

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# Airway Management and Intubation

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# Oxygen/ NIV for PUI/COVID-19 Patients

- Surgical mask for PUI or COVID-19 patients on oxygen via nasal prongs
- Switch to a non-rebreather (NRB) mask if > 6 LPM of oxygen is required
- A **non-rebreather mask** is the **preferred** option for escalation prior to intubation and consider transfer to ICU
- AVOID BIPAP/CPAP, bag-mask ventilation
- HFO2 is ***discouraged***, but If no other option, HFO2 patient **must be in a negative pressure** room – N95 and protective gear or PAPR are recommended
- PUI/COVID-19 infection and pre-existing sleep apnea deemed at risk for respiratory failure without therapy may receive non invasive ventilator support
    - Provide such treatment using a V30 of V60 ventilator without use of humidification
    - This is considered aerosol generating and requires airborne isolation

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# Airway Concerns in PUI/ COVID-19 Patients

- Avoid crash intubations
    - Increases risk of exposure
    - Reduces time for proper preparation/ appropriate PPE
- Consider creation an institution task team
    - COVID/PUI airway team
        - Notify the team of any new PUI or COVID-positive patient
        - Create COVID surveillance list
    - Notify ICU & COVID airway team early
    - Early discussions with the patient/family about patient's wishes regarding intubation

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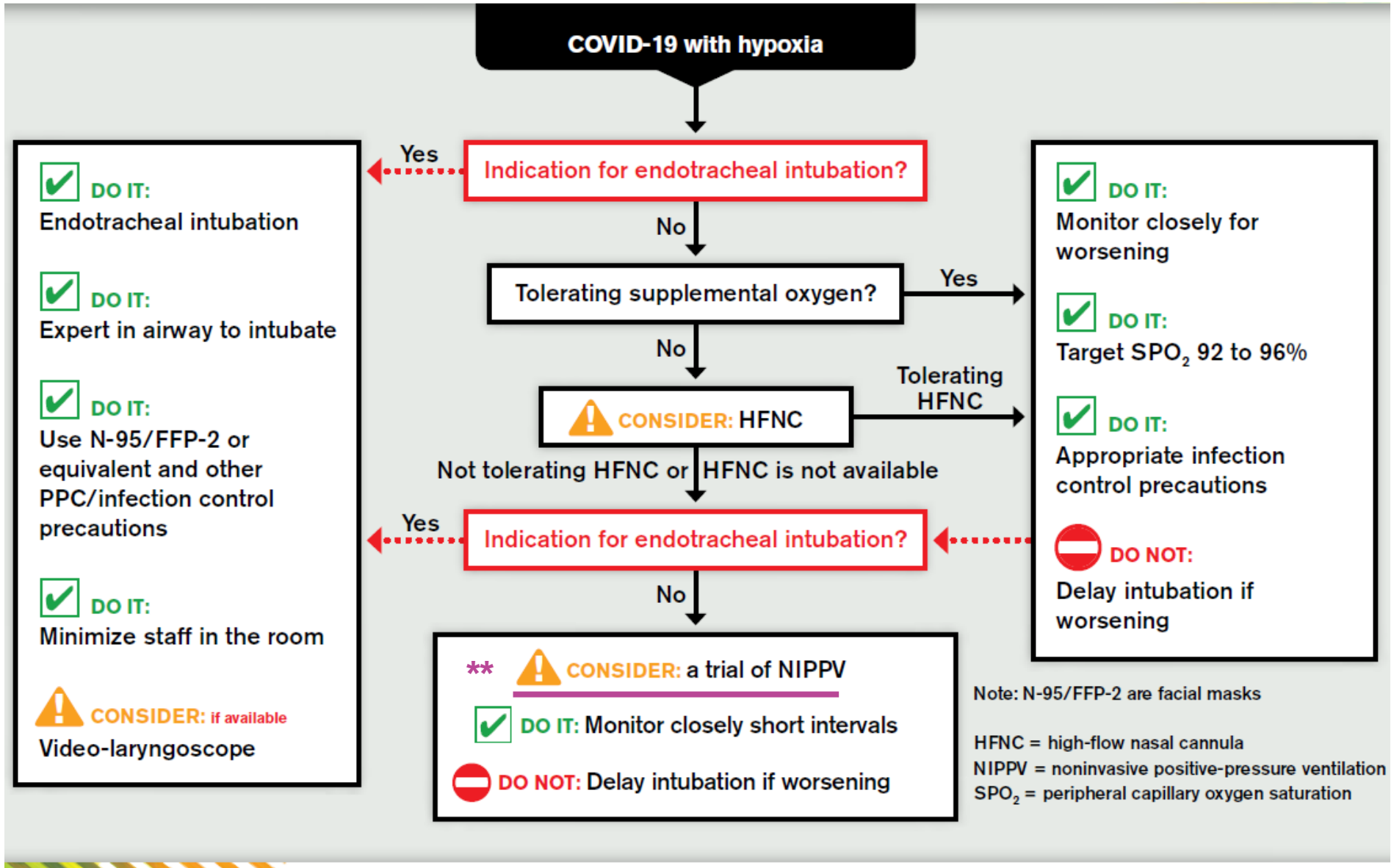
**Data for use of NIPPV suggests lack of efficacy in this population





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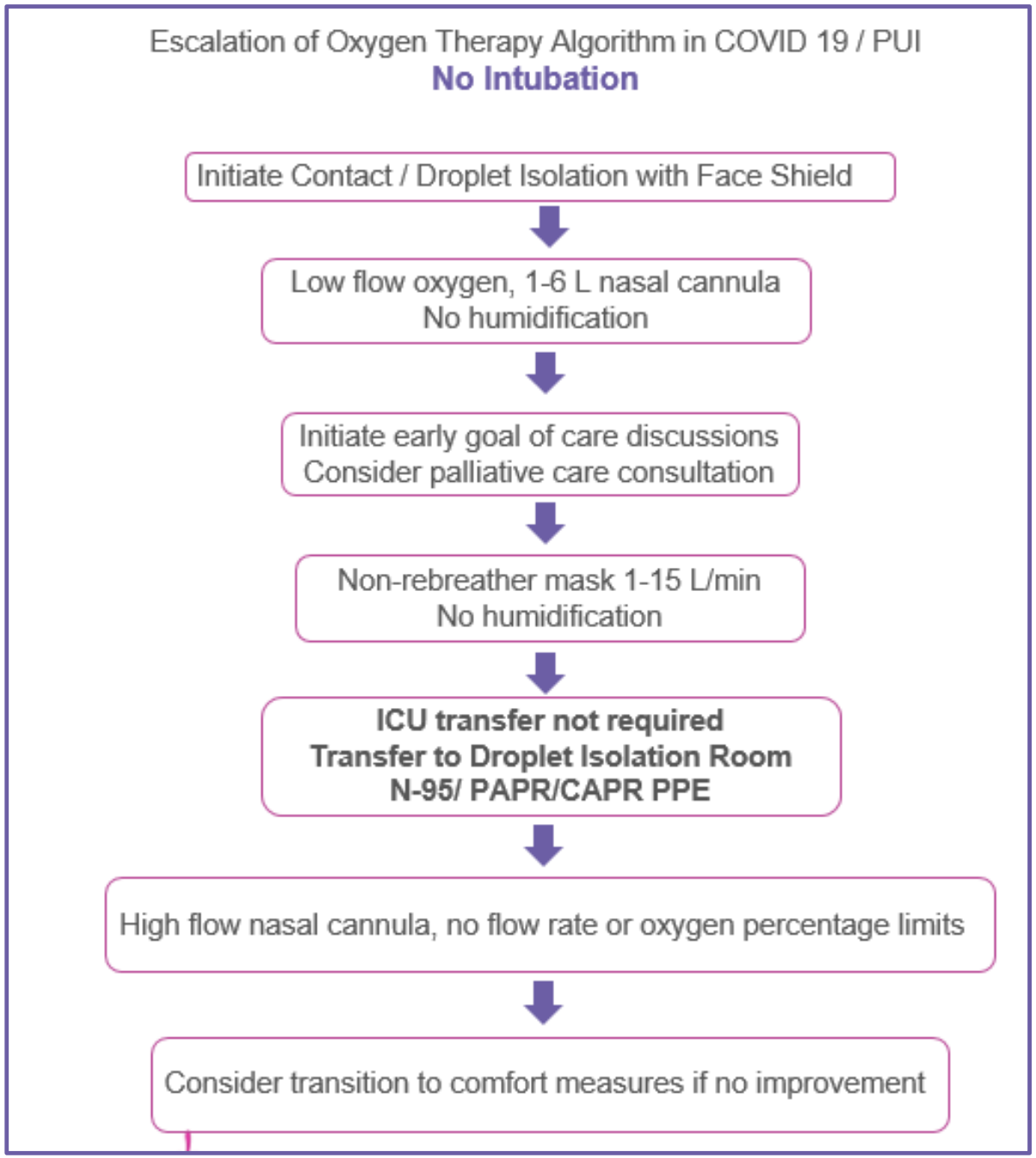
Alhazzaani, W.,., et al. (2020). Surviving sepsis campaign: Guidelines on the management of the critically ill adults with coronavirus disease 2019 (COVID-19).

# NO INTUBATION




*Courtesy of University of Washington

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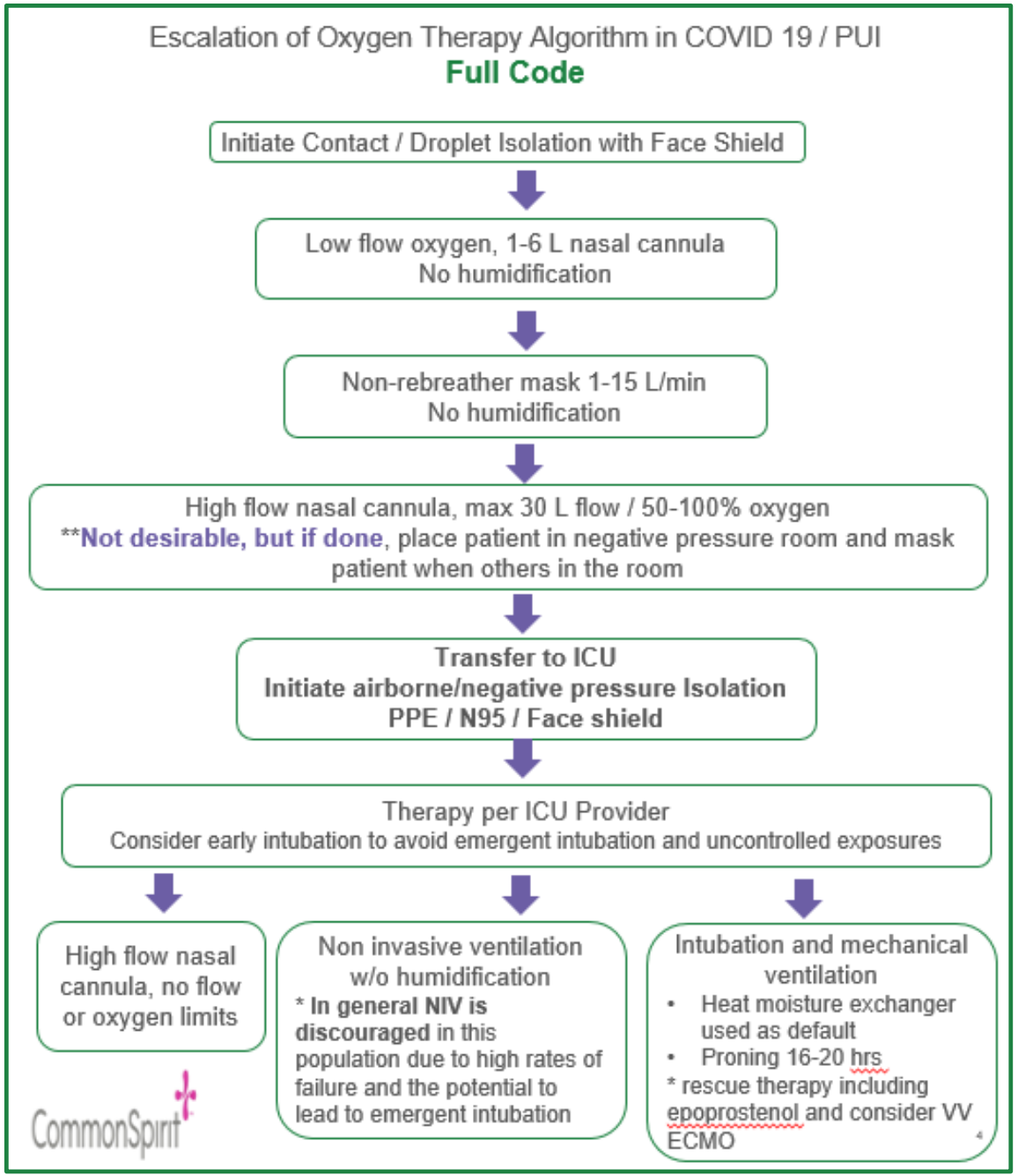
# FULL CODE




*Courtesy of University of Washington

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# Intubation Criteria Guidelines

- $PO_2$ < 65 or $SaO_2$ < 92% on NRB mask
- Labored breathing with RR > 35-40, or $PCO_2$ > 50 (in patient w/o hx of chronic $CO_2$ retention) with pH < 7.30
- **Do not wait** for these criteria to be present before notifying the ICU
- **DO NOT INTUBATE without proper PPE**
- Intubation with Rapid Sequence Intubation (RSI)
- Minimize bagging once patient has been pre-oxygenated.
- Glidescope or C-MAC preferred to minimize operator exposure to droplets

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# Intubation of PUI and COVID-19 Patients

- Intubation should be conducted by the ***most experienced practitioner***
  - to decrease the attempts at intubation
  - to handle a difficult airway if presented
- Consider COVID/PUI airway team
- **Avoid awake fiberoptic intubation** unless specifically indicated
- Avoid using inhaled Gas for intubation induction, or sedation in patients with PUI/confirmed COVID-19, Intravenous sedation is preferred.
- highly qualified CAPR/ PAPR gear are strongly recommended for all intubations
- Intubate in negative pressure rooms if available
- If surgery needed, patients should be intubated in negative pressure rooms PRIOR to transfer to OR

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# Intubation of PUI and COVID-19 Patients

- Avoid atomized/nebulized local anesthetics
- Pre-oxygenate for 5 minutes with 100% oxygen and perform rapid sequence induction
- **Avoid manual ventilation: potential aerosolization** of virus from the airways
  - If manual ventilation is needed, apply small tidal volumes
- Resuscitation bags and ventilators should have **HEPA filters**
- Run ventilator on “dry circuits” using heat-moisture exchangers
- **Video laryngoscopy is recommended** to prevent the face of the person intubating coming in close contact with the patient.
- NO Positive Pressure Ventilation until ETT cuff is INFLATED.

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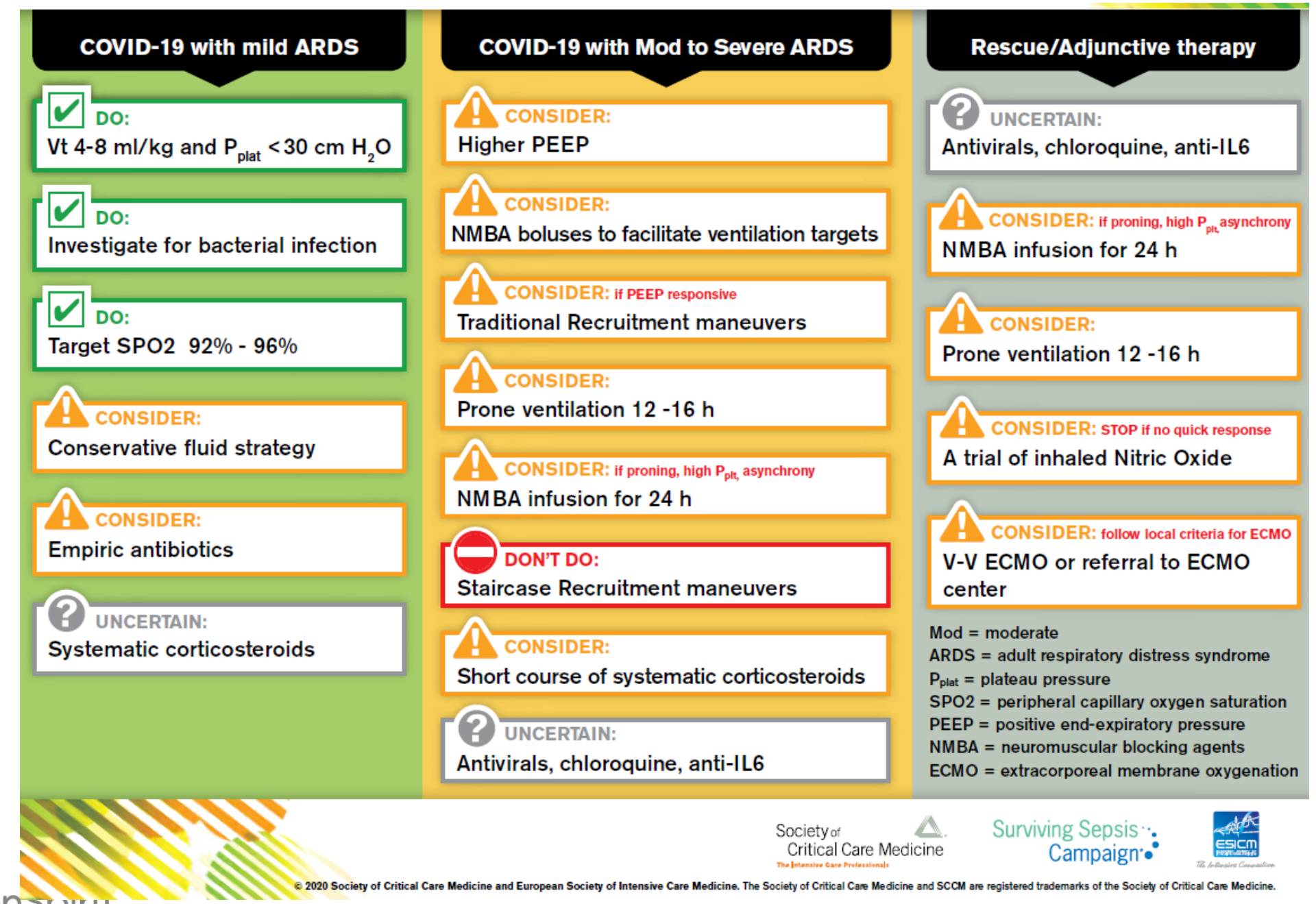
# Ventilator Management

- Heat Moisture Exchangers (HME) rather than humidification of ventilator circuits
- **Droplet isolation** for use of mechanical ventilation
- ARDSnet protective lung ventilation (SCCM 2020) ** **ARDSnet PEEP table or other evidence based practice PEEP tools**
  - Recommend using low tidal volume (Vt 4-8 mL/kg predicted body wt) ventilation (Vt – over higher tidal volumes (Vt > 8 mL/kg) (Strong)
  - Target plateau pressures of <30 cmH2) (strong)
  - Moderate to severe ARDS - higher PEEP (weak)
- May Consider APRV or inhaled epoprostenol
- **No corticosteroids**
  - Potential harm with COVID-19
- Prone Position Ventilation – 12 – 16 hours (SCCM, 2020)
- Neuro-muscular blockers – intermittent boluses over continuous infusion – **exception** is in persistent ventilator dyssynchrony
- May **consider** ECMO in very select patients – (weak- outcome data is not clear)
  - Decision to use ECMO should be determined by a team of experts using the standardized predictive scoring tools.
- Recommend against use of routine inhaled nitric oxide (strong)

# Ventilator Management

- Pre-prepare Ventilator with appropriate settings, shut Vent off before removing mask.
- Have clamp at bed side in case we need to use Ambu bag - filter in place
- Shut vent off first prior to any intended disconnection from vent - clamp - disconnect - ambu or transport vent if needed – unclamp
- Only Use for Bipap is after extubation ( Bipap on vent ) with mask (as the vent has exhalation viral filter valve with low threshold for early reintubation only in a negative pressure room.
- Do not use suction catheter with open ETT
- Minimize travel out of ICU
- No need for daily CXR
- Fiberoptic Bronchcoscopy is discouraged, therefore use catheter directed Broncho Alveolar Levage (BAL) if needed
- Avoid BMV but if clinically needed.
  - # HEPA viral filter must be used with BMV.
  - # LOW VOLUMES and HIGH RATE if bagging is required.
  - # Avoid Laying Patient Flat prior to Meds, Assure no agitation.






Alhazzaani, W.,., et al. (2020). Surviving sepsis campaign: Guidelines on the management of the critically ill adults with coronavirus disease 2019 (COVID-19).

# Bronchoscopy

Bronchoscopy should be discouraged in high risk patients

- Procedure is an aerosol generating procedure and carries risk of transmission
- If required, it should be performed in airborne isolation
- **Appropriate personal protective equipment** should also be used
  - A fit tested N 95 respirator or powered air purifying respirator (PAPR)
  - Goggles, gowns, double gloves and protective footwear
  - A disposable bronchoscope should be used on high risk patients

Bronchoscopy should be performed **only after intubation** and appropriate sedation to minimize risk of aerosolization and transmission

## Avoid

- Deep naso-tracheal suctioning
- Tracheostomy tube changes
- Intrapulmonary percussive ventilator therapy (IPV)
- Metaneb therapy

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# Aerosol Generating Procedures and Current Isolation Recommendations

| Aerosol Generating Procedures | Contact + Droplet Isolation | Airborne Isolation with PPE including face shield/goggles, N-95 or PAPR/CAPR |
|---|---|---|
| Intubation/extubation | Not Recommended | Accepted |
| Mechanical ventilation | Not Recommended | Accepted |
| Bronchoscopy | Not Recommended | Discouraged. Use disposable bronchoscope |
| Open suction catheter use (trach, ETT, or NTS) | Not Recommended | Accepted |
| Placing or exchanging tracheostomy tubes | Not Recommended | Accepted |
| Nebulizer treatments – encourage MDI use | Not Recommended: -use MDI's | Not Recommended : use MDIs except if Aerogen on vent |
| High flow nasal cannula | Not Recommended | Allowed<br>Full code In IMC: Max 30L/50%, then transfer to ICU<br>"No intubation" on floor or IMC: Allowed without restrictions<br>ICU: Accepted without restrictions. |
| OSA CPAP for chronic severe sleep apnea | Not Recommended | Accepted- Do not use humidification; dry circuit only. |
| Non invasive ventilation for respiratory failure (includes CPAP and BiPAP) | Not Recommended | Full Code: allowed only in ICU. No humidification; dry circuit only<br>No Intubation:<br>Accepted in IMC and ICU. Do not use humidification; dry circuit only |
| Aerobika | Allowed, encourage self use by patient | Accepted: encourage self use by patient |
| Chest PT | Not Recommended | Not Recommended |
| IPV/Metaneb | Not Recommended | Accepted |
| Percussion Vest | Accepted | Accepted |
| Active Humidification of Ventilator Circuit | Not Recommended | Requires ventilator circuit modification, discuss with RT prior to initiation |
| Continuous aerosol therapy (eg epoprostenol) | Not Recommended | Requires ventilator circuit modification, discuss with RT prior to initiation |
| Heliox-spontaneously breathing | Accepted | Accepted |
| Heliox-ventilated | Not Recommended | Accepted |

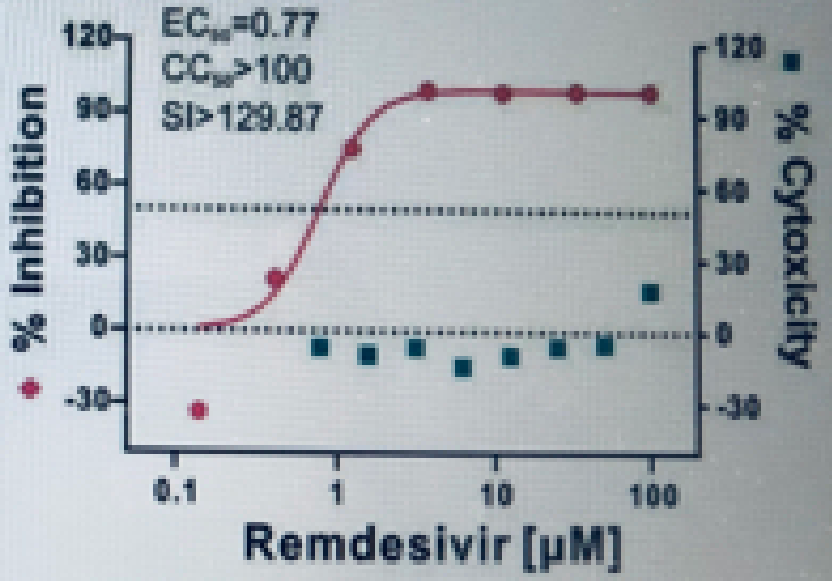
# Medication Treatment

# Treatment

- All treatments are ***investigational***
- No specific treatment seems to be effective
  - **Remdisivir:** blocks RNA dependent polymerase
  - **Tocilizumab:** blocks IL-6R (reduces inflammation)
  - **Chloroquine**: blocks Viral entry in endosome
  - **Hydroxychloroquine**
  - **Lopinavir/ritonavir (Kaletra):** Protease inhibitor
  - **IV Vitamin C**
  - **Chloroquine plus Azithromycin**
- Steroids: to be avoided

# Remdesivir

- Nucleotide analogue that inhibits RNA dependent RNA polymerase
- Broad antiviral activity in vitro: SARS, MERS, hemorrhagic viruses, including Ebola
- RCT ongoing at UCSF & ZSFG campuses
  - 10 days IV remdesivir for hospitalized COVID-19 patients, moderate-severe disease
  - Contact COVID ID service to discuss enrollment




*In vitro, SARS-CoV-2*

Brown *Antiviral Res* 2019, Sheahan *Nature Comm* 2019 , NIH ACTT study NCT04280705

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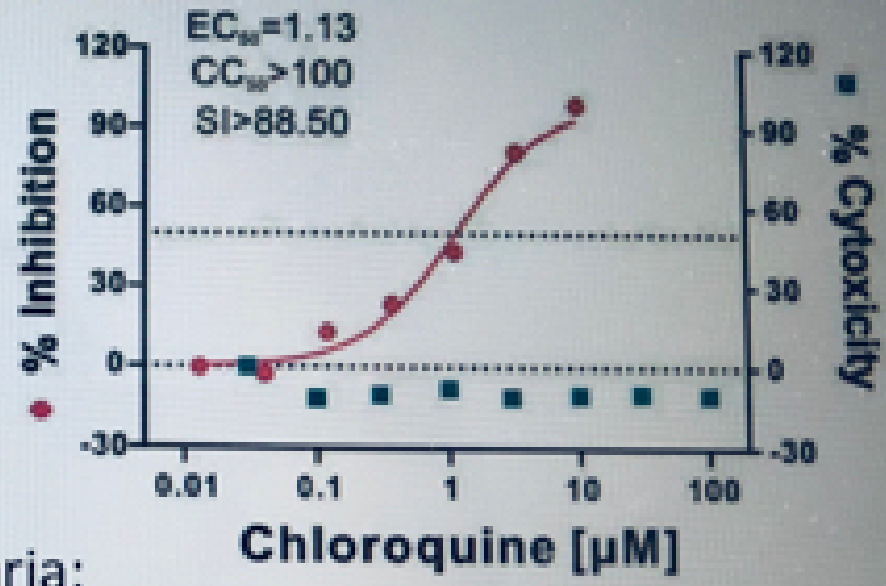
# Chloroquine

Antimalarial with antiviral activity
- Interferes with viral entry
- Inhibits SARS-CoV-2 co-receptor
- Immune modulating activity
  (*good or bad?*)

- Inexpensive, long track record
- Reported to improve pneumonia, viral clearance and disease course in China
- May require higher dose than for malaria: 500 mg BID
- Limited US supply

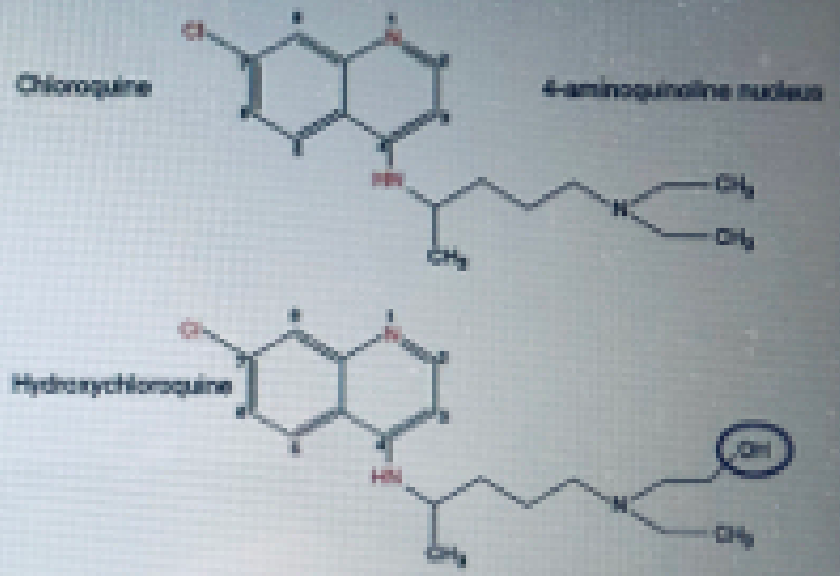


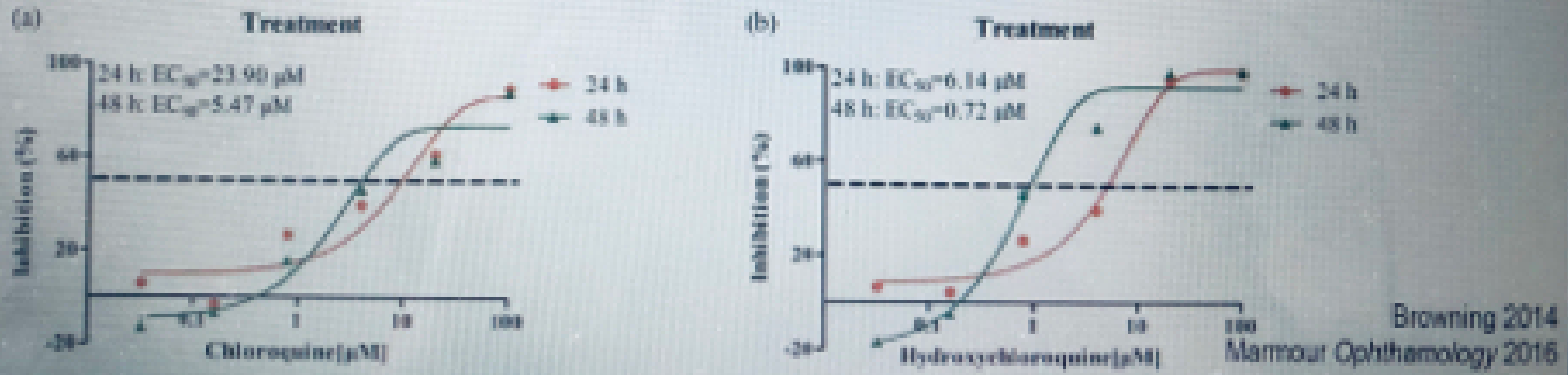

*In vitro, SARS-CoV-2*

Wang et al., *Cell Research*, 2020, Gao BioScience*Trends* 2020

# Hydroxychloroquine

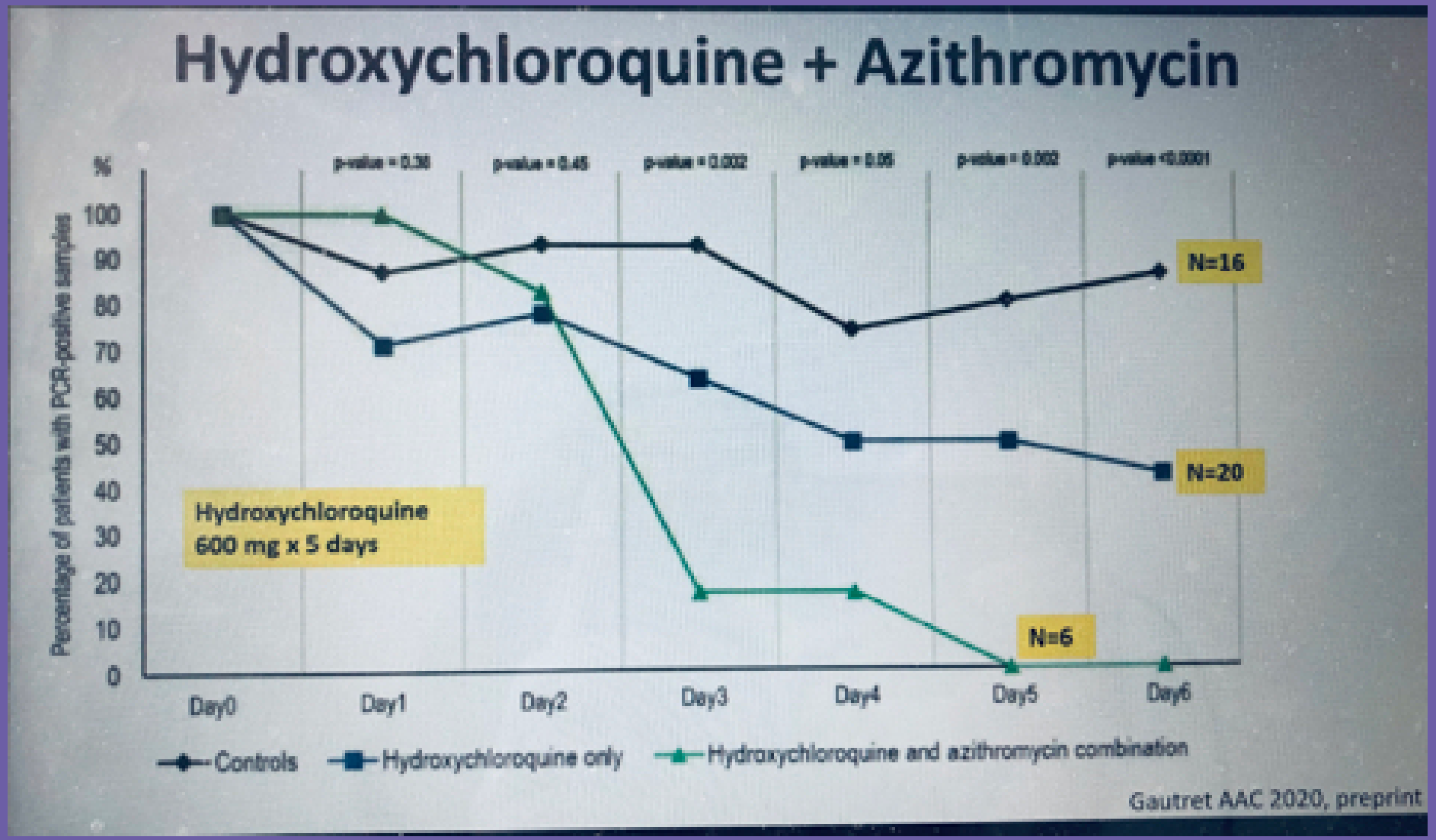
- Closely related to chloroquine
- Preferred due to ability to ↑dose, ↓ drug interactions, ↑tolerability
- More potent against COVID than chloroquine *in vitro*




Browning 2014
Marmour Ophthamology 2016
Yao CID 2020

# Hydroxychloroquine + Azithromycin

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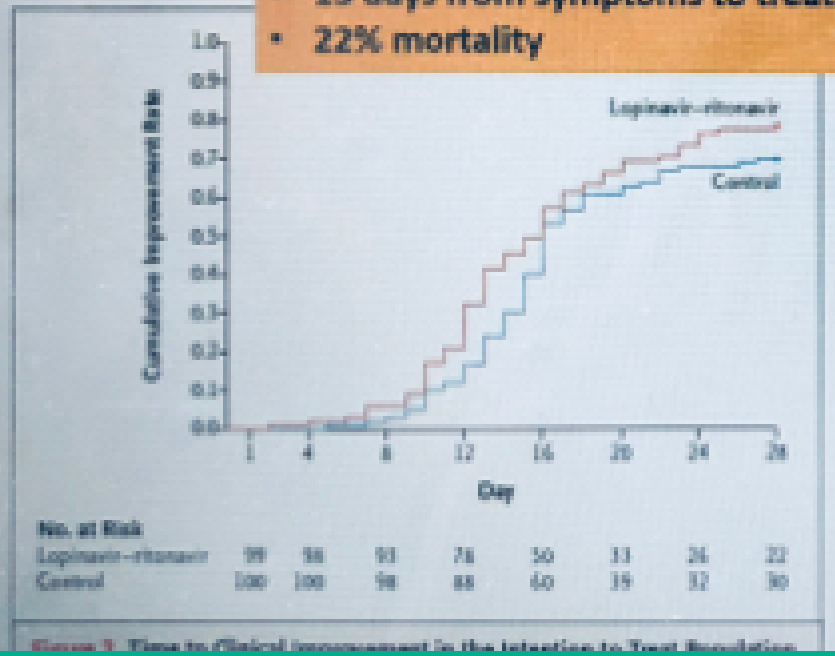
# No effect of Lopinavir/ritonavir in RCT

- HIV protease inhibitor, *in vitro* activity vs. MERS, SARS

**Open-label RCT of Kaletra in hospitalized COVID patients (n=199)**

- **33% on steroids**
- **13 days from symptoms to treatment start**
- **22% mortality**



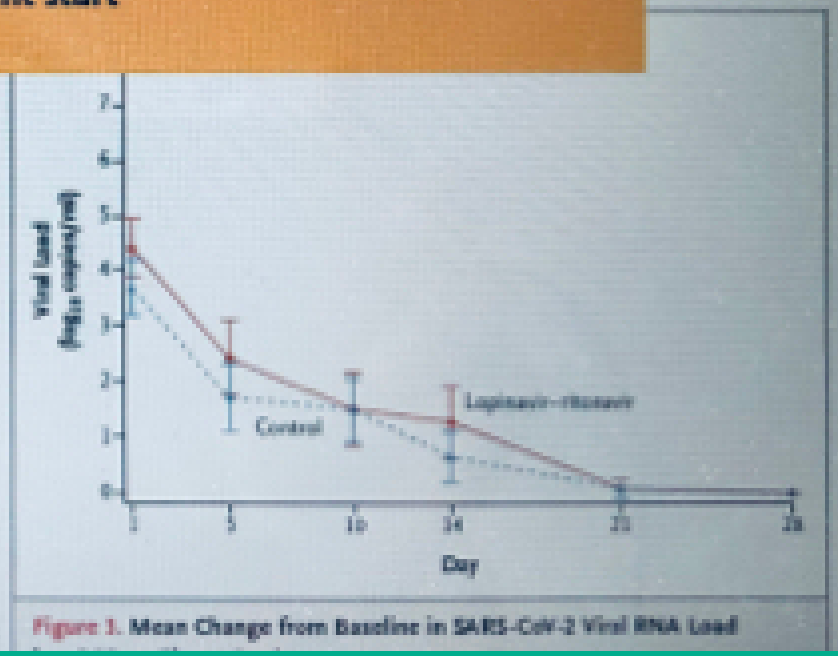




Figure 1. Mean Change from Baseline in SARS-CoV-2 Viral RNA Load

# The Italian Experience

## What the Italians Have Tried…

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| COVID-19 SEVERITY SCORING SCALE | |
|---|---|
| 0 | Room air |
| 1 | Requiers supplemental Oxygen via NC (MAX 6L NC) |
| 2 | Requires supplemental Oxygen in addition to one of the following<br>A. dyspnea or staccato speech (inability to count rapidly to 20 after deep breath) at rest or after minimal activity (sit, getting up, cough, swallowing)<br>B. RR> 22 on 6L<br>C. PaO2 <65mmHg with 6L<br>D. Worsening infiltrates on CT |
| 3 | Requires of HFNC, CPAP or NIV |
| 4 | Intubated with minimal support PaO2/FiO2> 300, or using PS |
| 5 | Intubated PaO2/FiO2>150 |
| 6 | Intubated with PaO2/FiO2< 150 mmHg |
| 7 | Intubated with PaO2/FiO2< 150 AND requiring vasopressors |
| 8 | Intubated in prone position or ECMO |

# COVID-19 Therapy

## STEROIDS

- No benefit in COVID-19
- If ARDS (but NOT concomitant COVID-19) there is some benefit (i.e. low dose dexamethasone)
- Decision of steroids must be reviewed on a case by case basis
- May consider steroids in cases with fit all the criteria listed below:
    - a. Completed acute phase of illness (i.e. low viral load, afebrile for > 72hrs or more than 7 days from beginning of symptoms)
    - b. Bacterial infections have been excluded
    - c. CT Chest shows evidence of worsening infiltrates

# COVID-19 Antiviral Therapy

- Favor early use of Lopinavir/ritonavir (Kaletra, LPV/r) or Remdesivir
    - If clinical suspicion is high start therapy before results
- Lopinavir/ritonavir:
    - Has been beneficial in SARS COV
    - MIRACLE trial is ongoing on patients with MERS-CoV
    - only sporadic case reports available for COVID-19
- Remdesivir: there are ongoing studies in China, promising

# COVID-19 Other Pharmocological Therapy

- **Chloroquine**
  - has antiviral and immunomodulatory activity
  - Chinese studies showed improved outcomes and used as prophylaxis
  - Italian group supports use but NOT prophylaxis use
- **Tocilizumab**
  - Blocks IL6 (elevated in this infection)
  - Utilized in Chinese Study
  - 400mg IV for a maximum of 2 doses
  - Ongoing trial in China studying usage on patients with high levels of IL6

# Tocilizumab Dosing Strategy

- 1st infusion dosed at 8mg/kg max 800mg IV x1
- 2nd infusion dosed similarly can be considered 8-12hrs after 1st
- Recheck IL-6 levels at 24hr
- Can consider 3rd infusion 16-24 hrs after 2nd if response was inadequate
- Max Dosing 3 infusions
- Use with caution in pregnancy: it is not teratogenic but fetal concentration> maternal

| Inclusion criteria | Exclusion criteria |
|---|---|
| • > 18 yo<br>• Interstitial pneumonia with severity score >2<br>• Worsening respiratory status and no access to immediate ventilation<br>• (invasive or non-invasive), severity score 3<br>• Severity score> 3<br>• High IL6 levels (> 40 pg/ml)<br>• D dimer > 1500 | • AST/ALT > 5 times of normal<br>• Neutrophils <500<br>• Platelets <50,000<br>• Sepsis due to another pathogen<br>• Diverticulitis<br>• Skin infection not responding to antibiotics<br>• Transplant patient on immune suppressive therapy<br>• Presence of contraindication |

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# COVID-19 Therapeutic Protocol

Case Scenario 1 – **Severity Score 0**

- a. Asymptomatic or mild symptoms (fever, cough, congestion)
- b. Age<70
- c. No comorbidities
- d. CT chest negative

Monitor and support if meet all of the following criteria

# COVID-19 Therapeutic Protocol

Case Scenario 2

**Severity Score 0-2**

- a. Mild symptoms (fever, cough, congestion)
- b. Age>70
- c. Has comorbidities

***Do not add Antibiotics unless high suspicion for bacterial infection***

**1ST Line:**

- Lopinavir/Ritonavir (LPV/r, Kaletra) 200/50mg q12 or
- Darunavir 800mg qd + Ritonavir 100mg qd or
- Darunavir/Cobicistat 800/150mg qd + Chloroquine 500mg q12 x5-7days

- In the Event of clinical deterioration: Initiate Remdesivir (Compassionate Use)
- If Severity Scale >2: Consider Dexamethasone 20mg qd x5-10days and/or Tocilizumab

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# COVID-19 Therapeutic Protocol

## Case Scenario 3
**Severity Score >2**

a. Severe PNA with increase O2 requirement
b. Respiratory failure requiring NIV or Mechanical Ventilation
c. ARDS
d. Hemodynamic instability

*Do not add Antibiotics unless high suspicion for bacterial infection*

- Remdesivir 200 mg on day 1 followed by 100 mg qd + Chloroquine 500 mg q12hr (or hydroxychloroquine via NG).
- If Remdesivir NOT available, start the following until becomes available:
- Lopinavir/Ritonavir (LPV/r, Kaletra) 200/50mg q12 or
- Darunavir 800mg qd + Ritonavir 100mg qd or
- Darunavir/Cobicistat 800/150mg qd + Chloroquine 500mg q12 x5-7days
- **IF ARDS >24hrs (Severity Score>4):** Consider Dexamethasone 20mg qd x5 days followed by
- 10mg qd x5days and/or Tocilizumab
- Monitor for Durg interactions between lopinavir/ritonavir with other classes of drugs.
- If cannot be used due to side effects, then use only Chloroquine.
- If Lopinavir/Ritonavir is not available, then consider Darunavir 800 mg qd + Ritonavir 100 mg qd or Darunavir/Cobicistat