MANAGEMENT OF RESPIRATORY FAILURE IN COVID PATIENTS

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LEARNING OBJECTIVES

- Summarize the Etiology and Pathophysiology of Respiratory Failure in Covid Patients
- Review General Clinical Strategies in Treating Covid Patients
- Evaluate Non-invasive Methods for Treating Respiratory Failure in Covid Disease
- Explore Various Invasive Strategies for Oxygenating and Ventilating Covid Patients
- Describe Adjunctive Therapies
- Furnish Selected Related Resources

DISCLAIMER:

This Presentation Represents a Combination of the Research Evidence, Complemented by Anecdotal Observation and Direct Experience. Research is Still Underway and Some of the Practices in Treating Covid Patients and Contents of This Presentation May Change Over Time as a Result.

COVID 19 -- RISK FACTORS

Serious medical conditions that increase the risk of serious illness from COVID-19 include:

- Serious heart diseases, such as heart failure, coronary artery disease or cardiomyopathy
- Cancer
- Chronic obstructive pulmonary disease (COPD)
- Type 2 diabetes
- Severe obesity
- Chronic kidney disease
- Sickle cell disease
- Weakened immune system from solid organ transplants

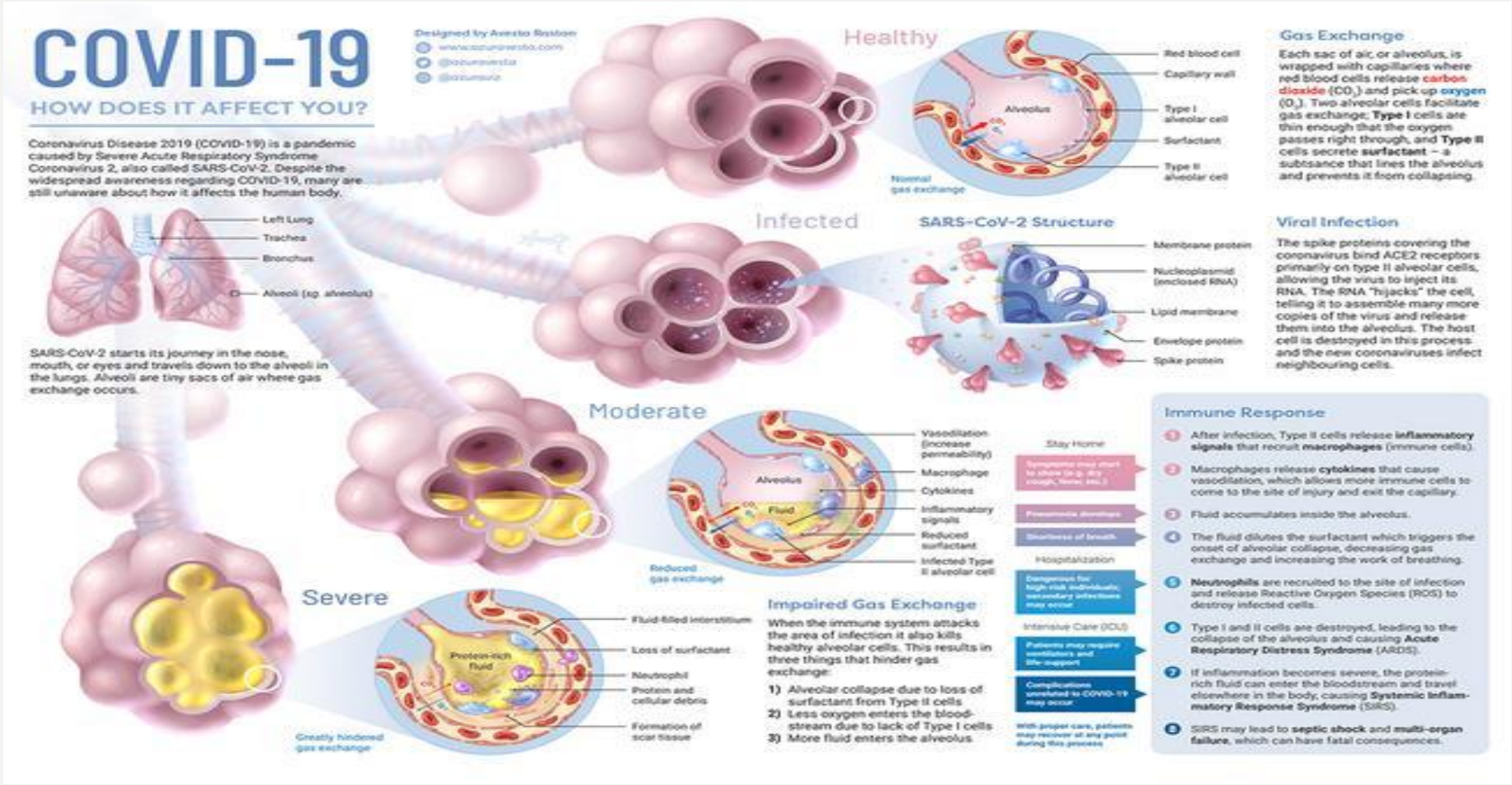
Other conditions may increase the risk of serious illness, such as:

- Asthma
- Liver disease
- Chronic lung diseases such as cystic fibrosis
- Brain and nervous system conditions
- Weakened immune system from bone marrow transplant, HIV or some medications
- Type 1 diabetes
- High blood pressure

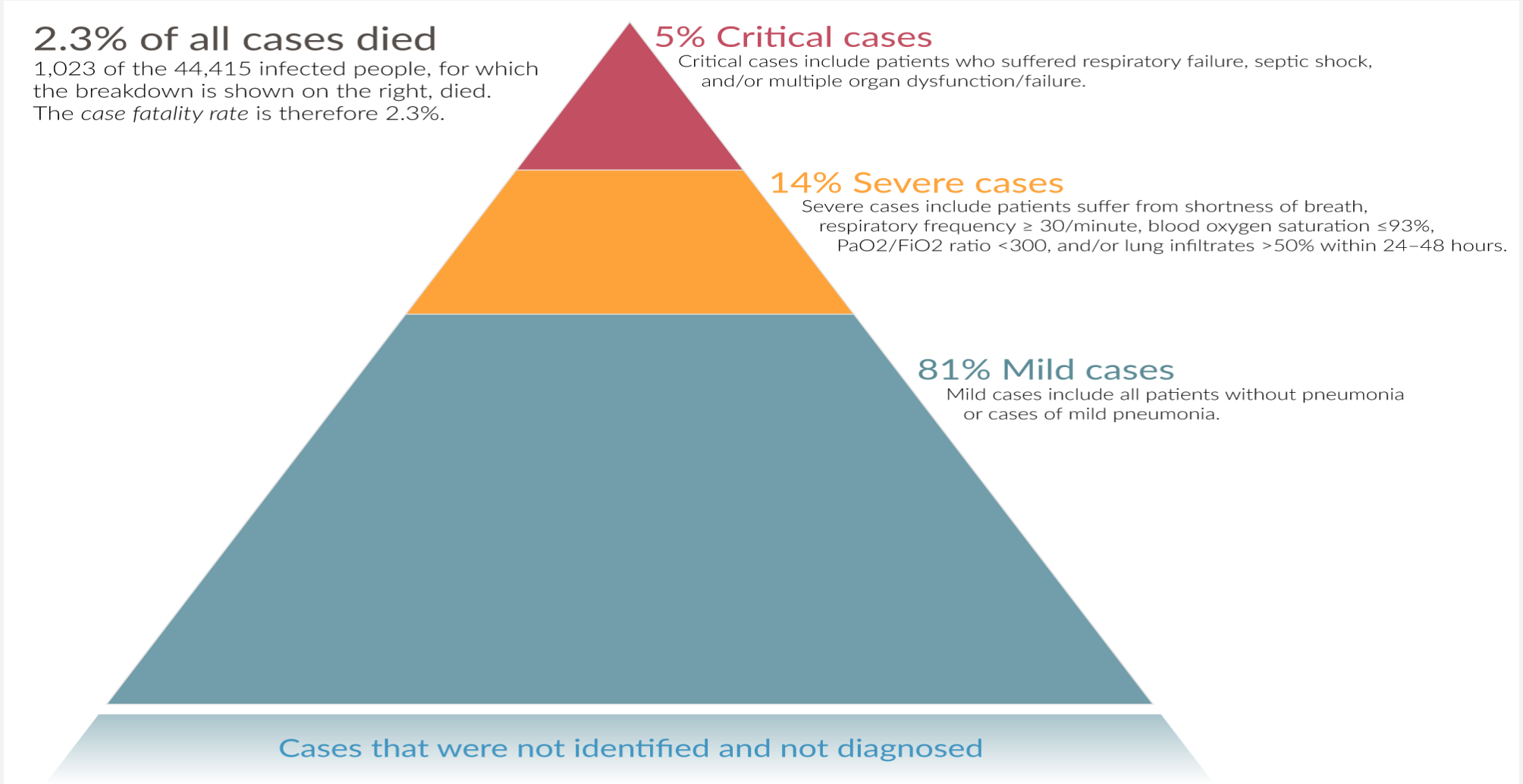
ETIOLOGY OF COVID

- Infection with the new coronavirus (severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2) causes coronavirus disease 2019 (COVID-19).
- The virus appears to spread easily among people, and more continues to be discovered over time about how it spreads.
- Data has shown that it spreads from person to person mainly via respiratory droplets among those in close contact (within about 6 feet, or 2 meters).
- The virus then replicates…
- It can also spread if a person touches a surface with the virus on it and then touches his or her mouth, nose or eyes, although this isn't considered to be a main way it spreads.

PATHOPHYSIOLOGY



VARIABLE SEVERITY OF COVID – STILL SOMEWHAT A MYSTERY

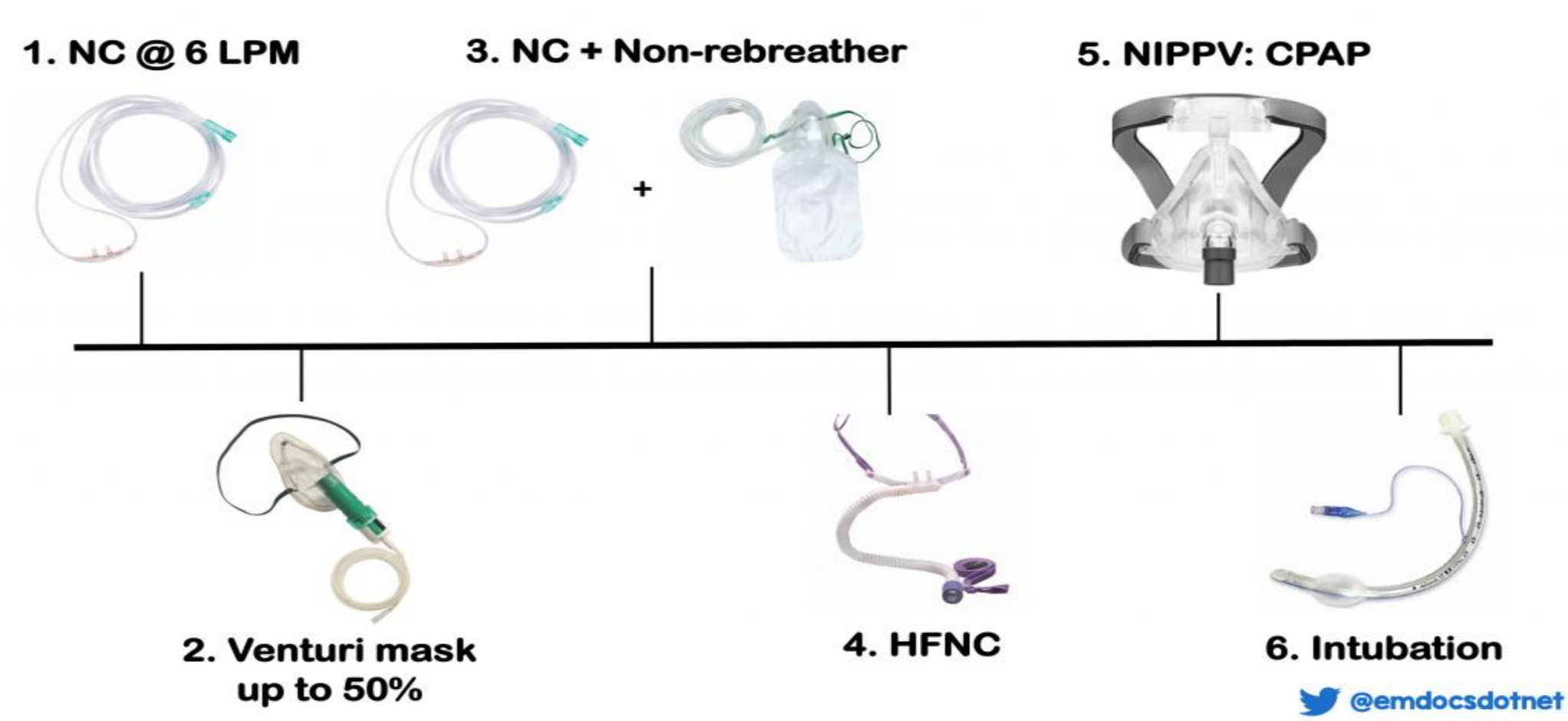


COVID 19 LUNG -- POST-MORTEM

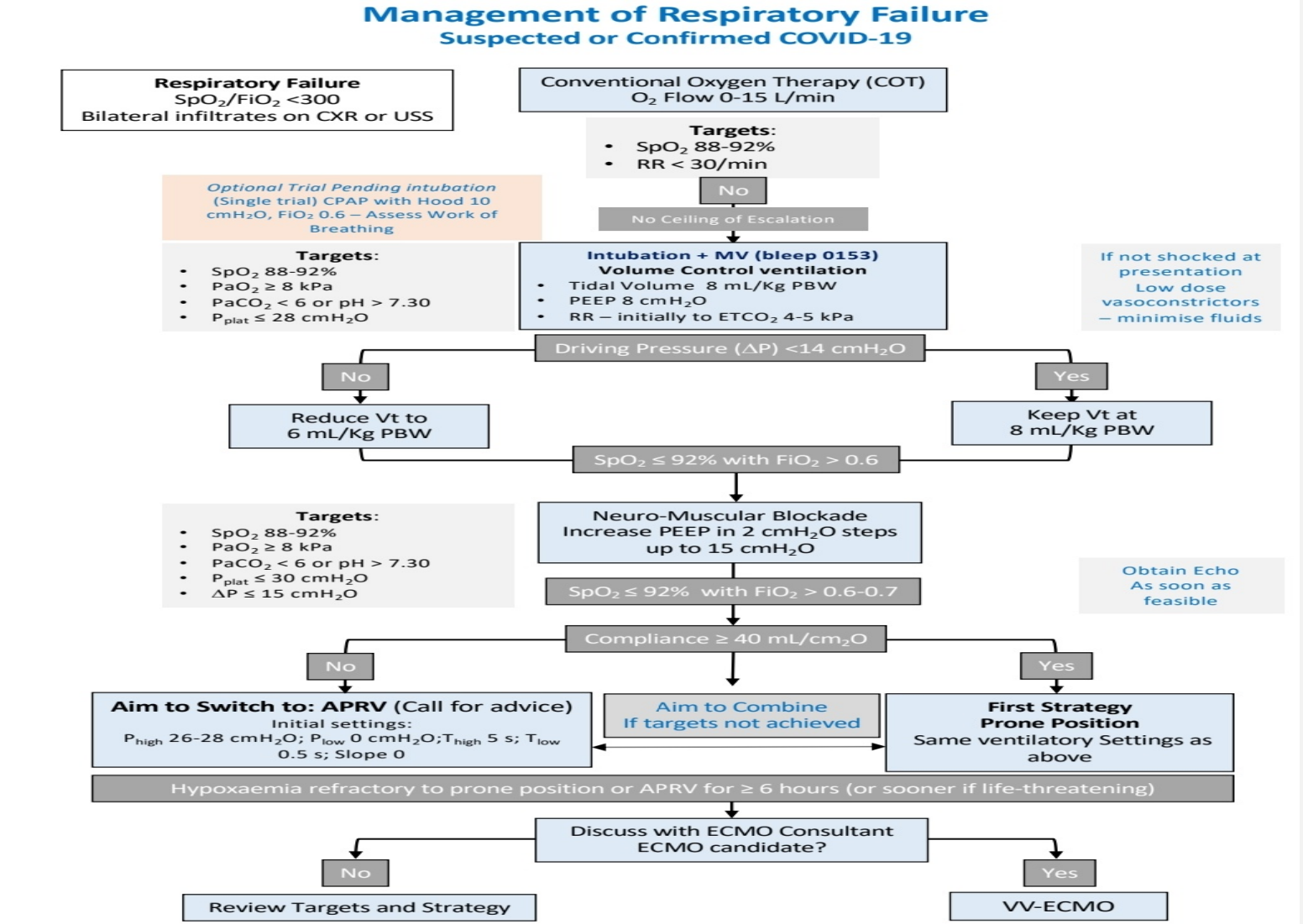
General Clinical Strategies in Treating Covid Patients

- **Prevention:** Social distancing, Isolation & Quarantine
- ***Medications:***
  - ***Remdesirvir*** may offer some clinical advantage in patients with moderate to mild disease, but less so in the especially sick Covid patients.
  - Properly timed ***steroids*** seem to help some patients with the inflammatory phase of the disease called the cytokine storm.
  - ***Convalescent plasma (obtained from recovered Covid 19 patients)*** demonstrates a potential survival benefit and low risk in small studies.
  - Monoclonal Antibody infusion -
    - Indications: treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.
    - Dosage--1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes.
  - ***Anticoagulants*** may aid the approximately 20-30% of those with severe Covid disease who develop concomitant coagulopathies.
  - Though there was early hope for ***hydroxychloroquine***, much of the enthusiasm has faded due to insufficient scientific evidence.
- ***Respiratory Care:***
  - Oxygen Therapy
    - Low-Flow
    - High Flow
  - Non-Invasive Positive Pressure Ventilation (NIPPV)
  - Intubation & Invasive Mechanical Ventilation
  - ECMO
  - Adjunctive Therapies
    - ARDs-NET
    - Prone Positioning
    - Inhaled Pulmonary Vasodilators
    - Other Inhaled Agents
      - Bronchodilators
      - Mucolytics

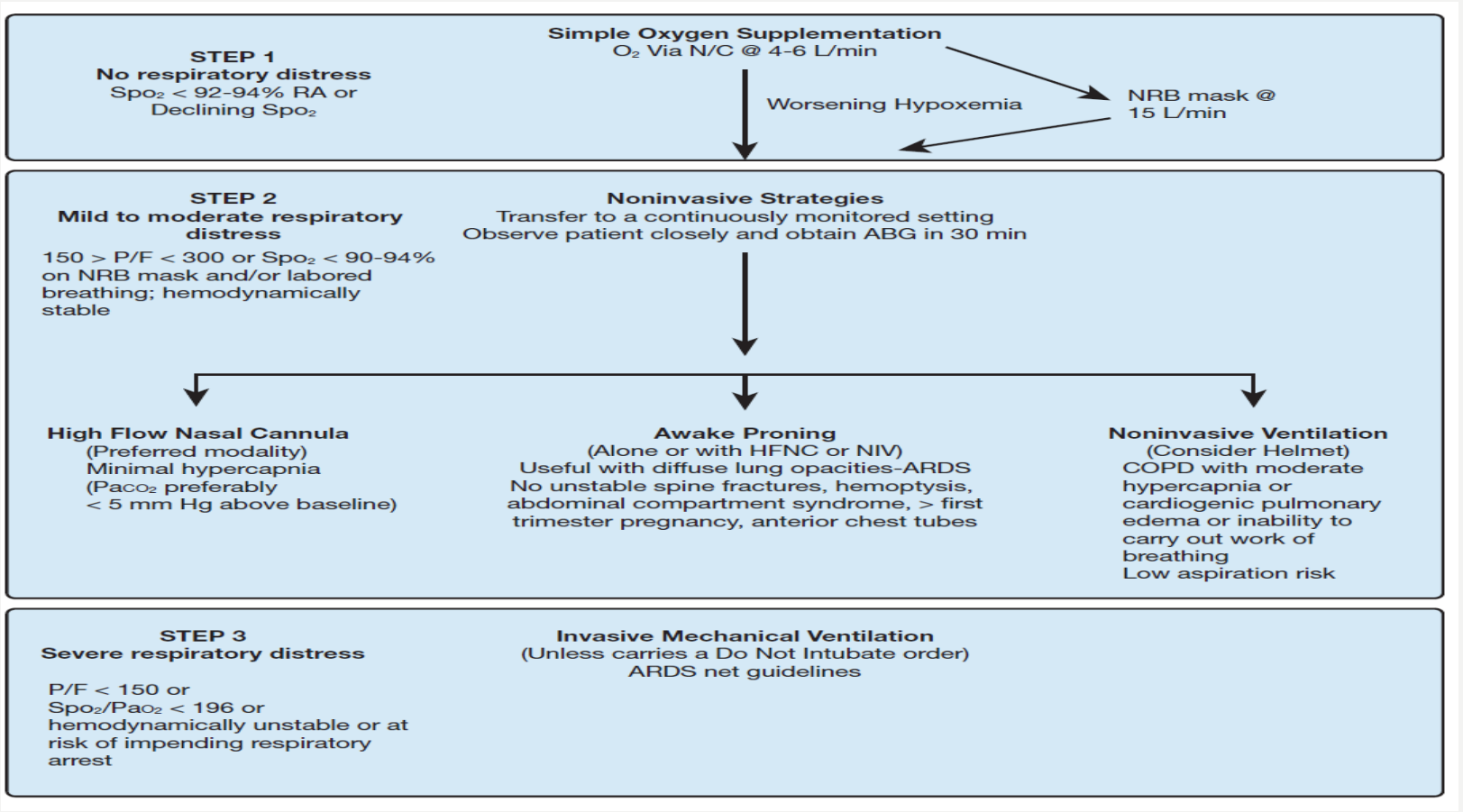
THE OXYGEN THERAPY ARSENAL – COVID 19



Covid 19 – Respiratory Care Algorithm—Earlier Intubation



COVID 19 – RESPIRATORY CARE ALGORITHM – WITH HFNC & NIV—LATER INTUBATION (RAOOF, ET AL, CHEST 2020; 158(5):1992-2002)



Non-invasive Methods for Treating Respiratory Failure in Covid Disease

- Low Flow Oxygen
- High Flow Oxygen
- Non-invasive Ventilation
- Adjunctive Respiratory Therapies
  - Inhaled Vasodilators
    - INO
    - Prostacyclin
  - Prone Positioning
- Combining Strategies

LOW-FLOW OXYGEN

- Device: Nasal cannula 1 – 7 LPM
- Population: Mild to moderate hypoxemia and respiratory distress with Covid 19.
- Advantages:
  - Comfort & Ease of Use
  - Accessibility
  - Can be done in alternate sites including home.
  - Can be combined with other O2 devices (e.g., NRM)
- Limitations: Only Effective in treating mild/moderate disease.

HIGH FLOW OXYGEN THERAPY

- Population: Covid 19-patients with Mild-Moderate hypoxemia.
- Devices:
  - Non-rebreather
  - High-Flow Nasal Cannula
- Advantages:
  - May avert intubation and mechanical ventilation in patients with mild/moderate disease.
  - Easy and relatively simple to set up.
- Disadvantages:
  - May delay but not eliminate intubation and mechanical ventilation, especially in those with moderate to severe disease.
  - Period checks needed risking clinician exposure.
  - Flows should be kept to a maximum of 30-35 LPM to reduce clinician risk due to aerosol.
- Citation: Jingen X, Yi Z, Lan N, et al., High-Flow Nasal Oxygen in Coronavirus Disease 2019 Patients With Acute Hypoxemic Respiratory Failure: A Multicenter, Retrospective Cohort Study, *Crit Care Med*. 2020 Aug 19.
  - Findings/Conclusion: **HFNO may be effective for Covid-2019 patients with mild to moderate acute hypoxemic respiratory failure**.
  - However, high-flow nasal oxygen failure was associated with a poor prognosis.
  - Male and lower oxygenation at admission were the two strong predictors of high-flow nasal oxygen failure.

NON-INVASIVE VENTILATION

- Population: Covid 19 patients with moderate hypoxemic and hypercapneic respiratory failure, and prohibitive breathing pattern/rate.
- Advantages:
  - May avert intubation and mechanical ventilation in patients with mild/moderate disease.
- Disadvantages:
  - May delay but not eliminate intubation and mechanical ventilation, especially in those with moderate to severe disease.
  - Not well tolerated by some patients.
  - Interference with adjunctive therapy such as proning, oral medication admin, nutrition.
  - Period checks needed risking clinician exposure.
  - Clinician risk due to aerosol.
- Citation: Honore P, Gutierrez L, Kugener L, et al., Compared to NIPPV, HFNC is more dangerous regarding aerosol dispersion and contamination of healthcare personnel: we are not sure. *Crit Care.* 2020 Aug 4;24(1):482.

HELMET NIPPV/CPAP

- Not (yet) approved for use in the US. But widely used elsewhere!
- Design: Case Series in a Canadian Hospital
- Findings:
  - For patients unable to tolerate facemask, ***NIPPV helmet provides an alternate interface***.
  - In COVID-19 patients, the ***helmet interface may reduce the risk of virus exposure to health care workers*** from aerosolization.
  - Based on this experience, we recommend that helmet NIPPV be considered for the management of patients with COVID-19, whether the goal is to prevent immediate intubation or avoid post-extubation respiratory failure.
  - Randomized studies are needed to definitively validate the use of helmet NIPPV in this population.
- Citation: Rali A, Howard C, Miller R, et al., Helmet CPAP revisited in COVID-19 pneumonia: A case series. Can J Respir Ther. 2020 Jul 23;56:32-34.

COVID 19 INTUBATION CHECKLIST

- Purpose: Creation of a checklist for use during high-risk intubations of COVID-19 patients, which serves as a pragmatic bedside tool for clinicians
- Personnel: An intubating physician, respiratory therapist, and 2 nurses (ie, a code nurse at bedside and a Virtual Critical Care nurse working remotely).
- Medications:
  - Availability of additional neuromuscular blocking agents were added to the RSI kit.
  - The correct doses of all medications in the RSI kit were not known to everyone involved. An ICU pharmacist created simple weight-based dosing charts for all RSI medications
- Equipment: ICU respiratory therapists were trained on:
  - Intubation assisting, including the ***avoidance of manual ventilation, especially without a filter in place***.
  - Appropriate assembly of the ventilator circuit, using high-efficiency particulate air filters attached to the airway and the ***importance of having all necessary equipment in the patient's room at the outset***!
- After intubation was completed, an immediate debrief should be conducted where possible. Intermittent debriefing should be done as an alternative or adjunctive.
- Citation: Papali A, Ingram A, Rosenberger A, et al. Intubation Checklist for COVID-19 Patients: A Practical Tool for Bedside Practitioners, *Resp Care*, August 2020.

TIMING OF INTUBATION IN COVID PATIENTS

- Some Covid patients were remarkably tolerant of moderate hypoxemia.
- Some patients who were tolerant of hypoxemia quickly decompensated and required emergent intubation.
- This caused the timing of intubation for Covid patients to be questioned.

- Hernadnez-Romieu, et al, (2020)
  - Retrospective Cohort Study of 231 patients admitted to ICU with Covid-19
  - Mortality did not difer by time of intubation (< 8 hrs, 8-24 Hrs> 24 hrs)
- Lee Y, Choi K, Sun C, et al., (2020)
  - Design: Retrospective, Multicenter trial of 39 Covid-19 Patients
  - Findings: ***Early intubation was <u>not</u> associated with improved survival***. This result may help in the efficient allocation of limited medical resources, such as ventilators.

HFNC, NIV & PRONING: RAOOF, S; ET AL, *CHEST,* 2020; 158(5):1992-2002

Mortality of invasively ventilated Covid-19 patients was high and it was not easy to extubate. This raised concerns that HFNC & NIV were underutilized. This article takes a practical approach in describing how to use these techniques.

TABLE 1] Recommendations of International Societies Regarding Use of High-Flow Nasal Cannula and Noninvasive Ventilation in COVID-19 Pandemic

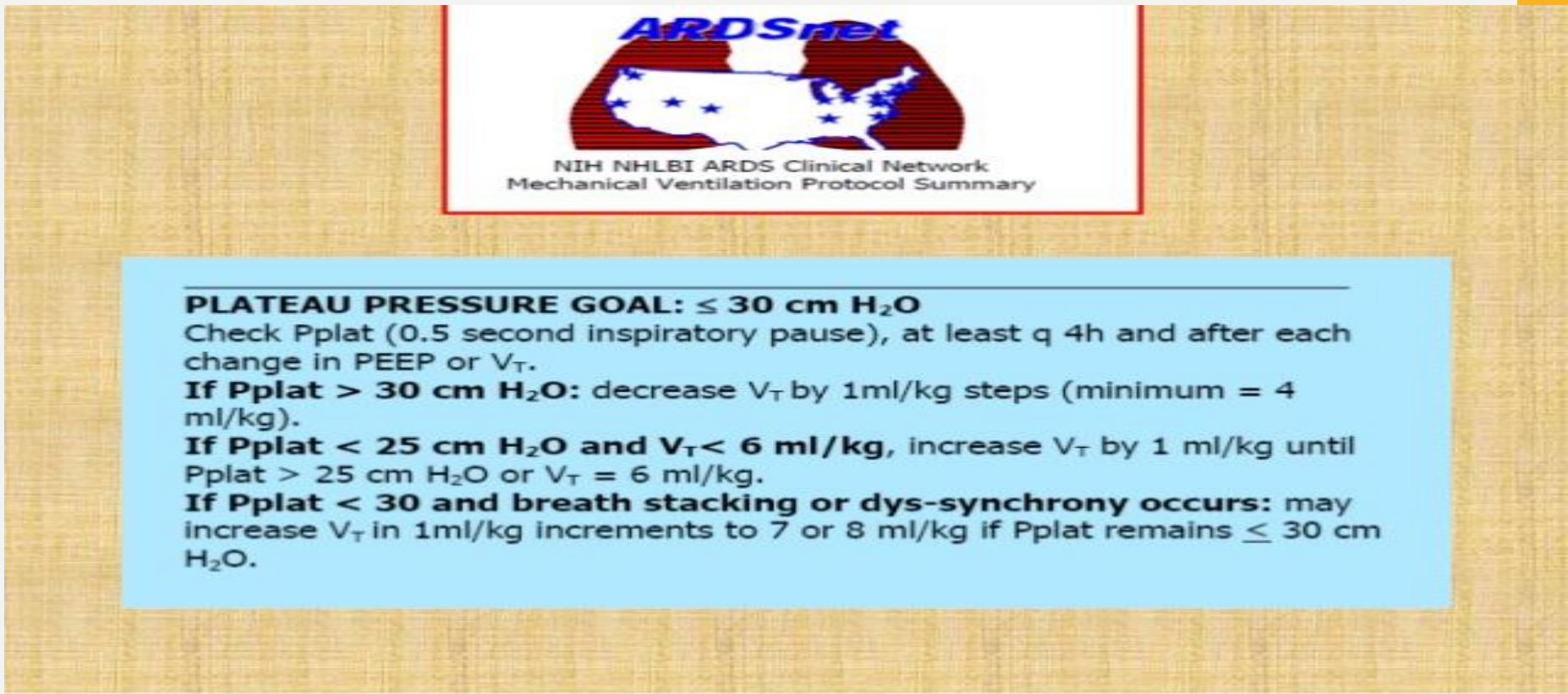
	HFNC		NIV	
Organization/Country	Recommendation	Comment	Recommendation	Comment
Asociación Argentina de Medicina Respiratoria, Argentina	PRO	Nasal prongs tight to minimize aerosol	PRO	Short trial (1 h)
Australian National COVID-19 Clinical Evidence Taskforce, Australia	None	None	CONTRA	Consider only with concomitant COPD with type 2 respiratory failure or CPE
Australian and New Zealand Intensive Care Society (ANZICS), Australia and New Zealand	Suggest	None	Not routine	None
Austrian ICU therapy guideline for the treatment of patients with SARS-CoV-2 infection, Austria	No mention	None	CONTRA	Consider short trial *only* if HFNC is not feasible
Associação Brasileira de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva, Brazil	No mention	None	PRO (conditional)	In certain situations a short trial (30 min)
Canadian Critical Care Society, Canada	None	None	PRO (conditional)	In certain situations a short trial (30 min)
Sociedad Chilena de Kinesiología Respiratoria, Chile	None	None	PRO (conditional)	Short trial *only* if HFNC is not feasible. Helmet suggested
Chinese National Health Commission, China	None	None	PRO	Short trial (1 h)
German recommendations for critically ill patients with COVID-19, Germany	Restrictive	None	Restrictive	Only in patients with P/F > 200; helmet suggested
Irish Thoracic Society, Ireland	PRO	HFNC 30 L/min in negative-pressure room	PRO	Helmet suggested
Italian Thoracic Society and Italian Respiratory Society, Italy	None	None	PRO	None
Société Libanaise de Pneumologie, Lebanese; Society of Critical Care Medicine, Lebanese; Society of Anesthesiologists, Lebanon	CONTRA	Favor early intubation	CONTRA	None
Pakistan Chest Society, Pakistan	Conditional	If in negative-pressure room	CONTRA	None
Sociedade Portuguesa de Pneumologia, Portugal	No mention	None	Conditional	Short trial (1 h) Facial mask suggested
Sociedad Española de Neumología y Cirugía Torácica, Spain	PRO	Maintain > 2-m distance	PRO	None
Swiss Academy of Medical Sciences, Switzerland	None	None	CONTRA	Eventually only in the ICU
National Health Care System guidelines, UK	CONTRA	No benefit but some risk	PRO	CPAP for mild hypoxia and NIV for acute or chronic respiratory failure
American College of Chest Physicians, USA	None	None	Careful use	The recommendations are only for home-based ventilated patients
World Health Organization interim guidance, January 2020	Selected	Not for COPD, CPE, hemodynamic instability	Selected use	None
US Department of Defense COVID management guidelines	PRO	None	CONTRA	Early intubation over NIV if HFNC fails
US Surviving Sepsis Campaign/SCCM guidelines	Suggest[a]	HFNC next modality in those not tolerating supplemental O_2	None	Suggest if HFNC unavailable or patient is not tolerating it

INVASIVE VENTILATORY STRATEGIES

- Modes
- Ventilation
  - VT
  - RR
  - Permissive Hypercapnea
- Oxygenation
  - FIO2
  - PEEP
- Adjunctive Maneuvers
  - Recruitment Maneuvers

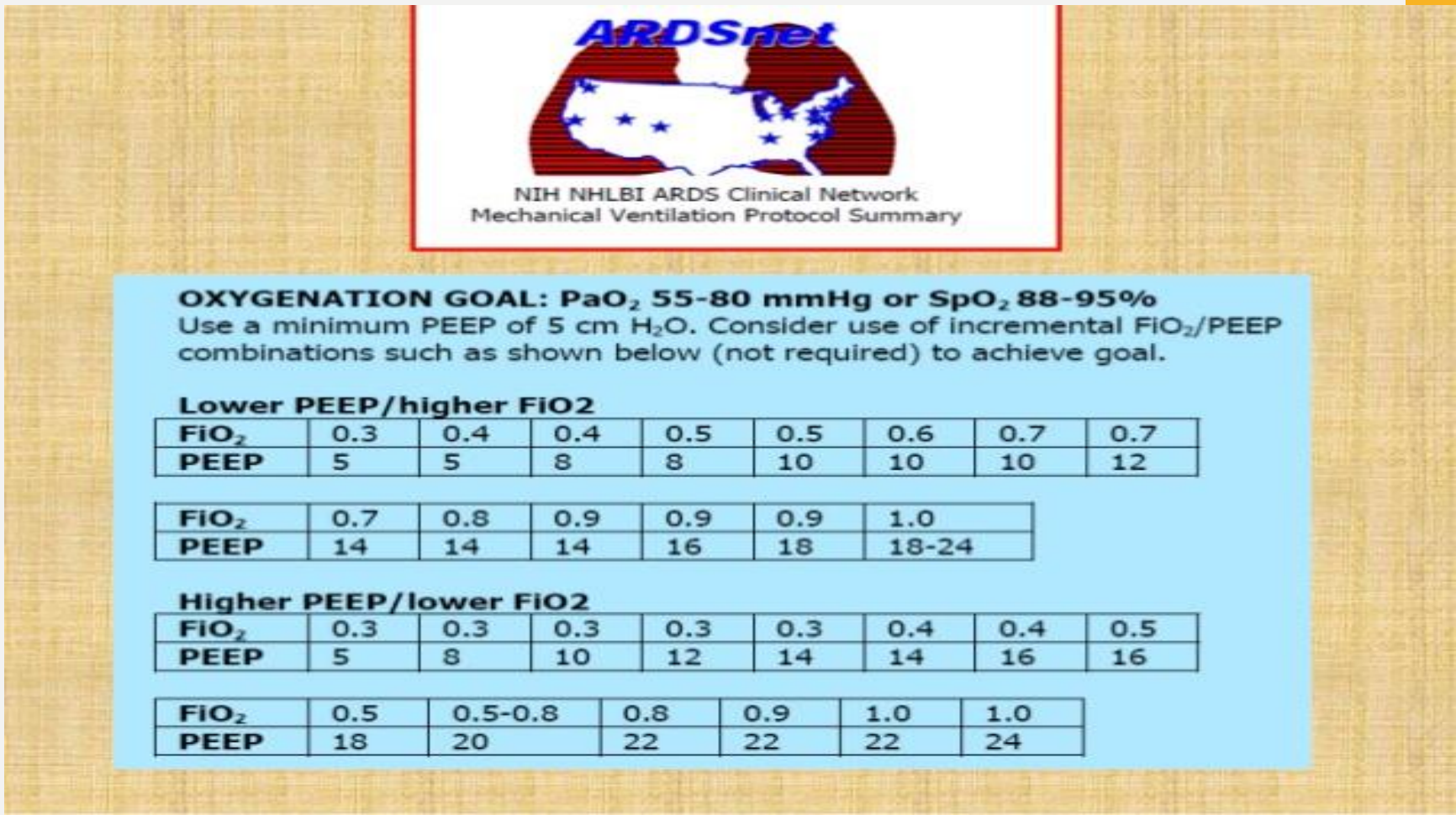
ARDSNET: TIDAL VOLUMES AND PLATEAU PRESSURES

- Previously supported for use of ARDs ***in non-Covid patients***.
- Therefore, is/was commonly used in Covid-19 Patients with ARDs.
- Start with a VT of 6-8 mls / Kg, and titrate as low as 4 mls / Kg to keep Plateau's $\leq$ 30.



ARDSNET: FIO2 AND PEEP

- Again, Previously supported for use of ARDs ***in non-Covid patients***.



OXYGENATION GOAL: PaO_2 55-80 mmHg or SpO_2 88-95%
Use a minimum PEEP of 5 cm H_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/higher FiO2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

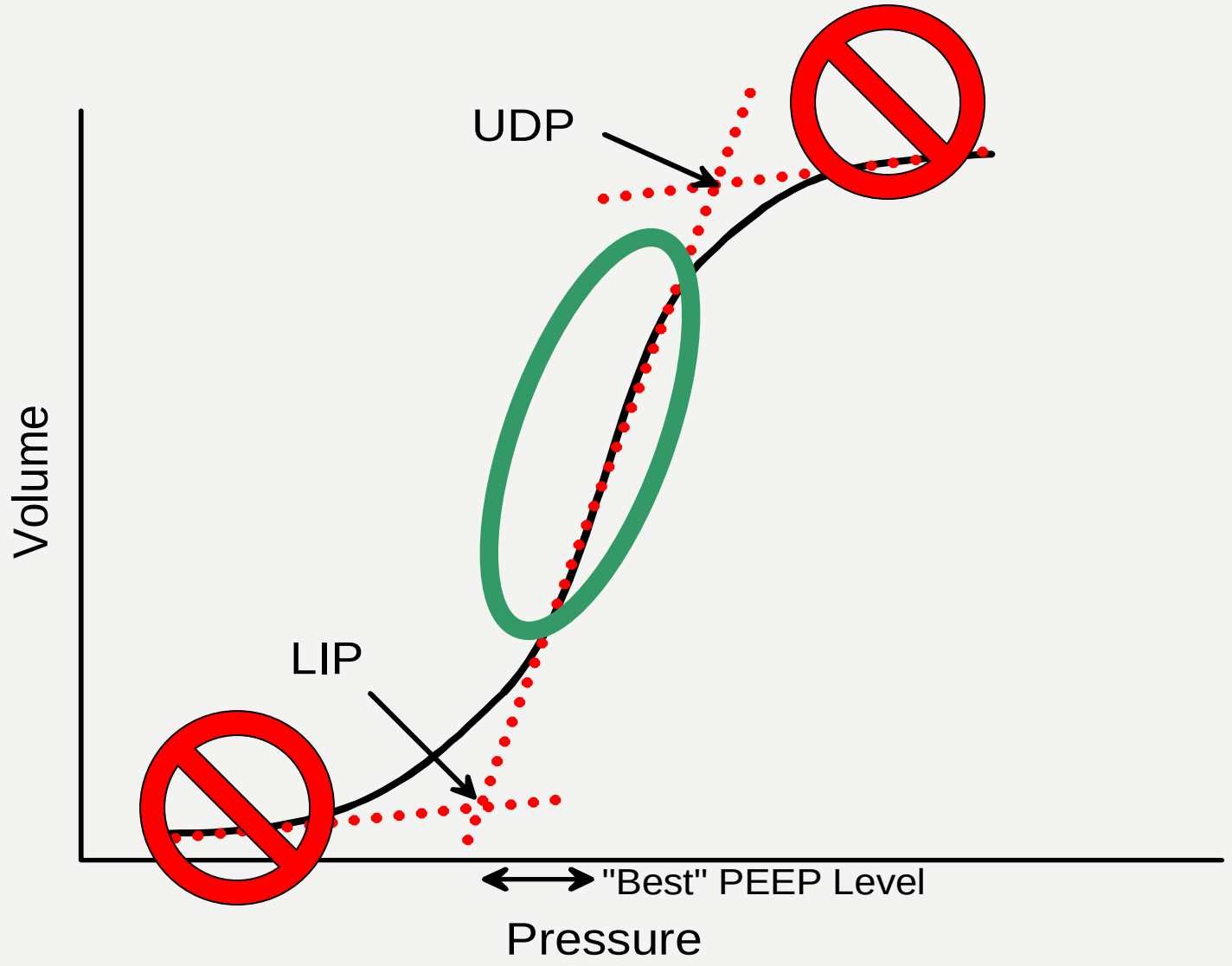
FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18-24

Higher PEEP/lower FiO2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

ADJUSTING PEEP LEVELS



VENTILATOR SHARING FOR COVID 19

- ***Definition:*** Using one mechanical ventilator to ventilator more then one patient at a time.
- Theoretically possible; but at a minimum, ***impractical and possibly outright unsafe***.
- Inadequate ability to individualize volumes, pressures, ventilation and oxygenation.
- ***Citation:*** Hermann J, Da Cruz, Hawley M, et al., Shared Ventilation in the Era of COVID-19: A Theoretical Consideration of the Dangers and Potential Solutions. *Respir Care*. 2020 Jul;65(7):932-945.
  - ***Design:*** Laboratory "Bench" research using specialized valves and circuits.
  - ***Finding:*** Of the strategies considered, shared PCV, with the inclusion of in-line pressure-relief valves in the individual inspiratory and expiratory limbs, offers the greatest degree of safety and lowest risk of catastrophic mechanical interactions.

Adjunctive Respiratory Strategies – ***PRONE POSITIONING*** IN MECHANICAL VENTILATION

- Much Recent Research in proning Covid patients!
- Citation: Munshi, Del Sorbo, Adhikari, et al, *Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis*, Ann Am Thorac Soc. 2017.
  - ***Findings: Prone positioning is likely to reduce mortality*** among patients with ***severe ARDS*** when applied for at least 12 hours daily.
  - Qualifications:
    - Do it early: within 48 hours on ARDS onset
    - Devise a protocol in advance. ETT dislodgment is a risk!

PRONE POSITIONING – SPONTANEOUS BREATHING PATIENTS

- Citation: Damarla M, Zaeh S, Niedermeyer S, et al, Prone Positioning of Nonintubated Patients with COVID-19 Am J Respir Crit Care Med. 2020 Aug 15;202(4):604-606.
  - Study Design: Case Series of 10 Covid-19 patients in respiratory failure
  - Outcomes:
    - ***Oxygenation rapidly improved after prone positioning***, and at 1 hour after assuming a prone position, median oxygen saturations had increased from 94% (IQR, 91–95%) to 98% (IQR, 97–99%)
    - ***Patients reported improved dyspnea*** with prone positioning.
    - Seven of the 10 patients did not require escalation of respiratory care.
    - Eight of the 10 patients did not require intubation.

PRONE POSITIONING – MECHANCIALLY VENTILATED PATIENTS

- Citation: Sherlhamer M, Wesson P, Solari I, et al, Prone Positioning in Moderate to Severe Acute Respiratory Distress Syndrome due to COVID-19: A Cohort Study and Analysis of Physiology, *Res Sq.* 2020 Aug 17;rs.3.rs-56281.

  - Study Design: A cohort study at a New York City hospital of 335 Covid 19 patients who were intubated and mechanically ventilated with moderate to severe ARDS due to COVID-19.
  - Findings:
    - Prone positioning in patients with moderate to severe ARDS due to COVID-19 is ***associated with reduced mortality*** and improved physiologic parameters.
    - One in-hospital death could be averted for every eight patients treated

RECRUITMENT MANEUVERS

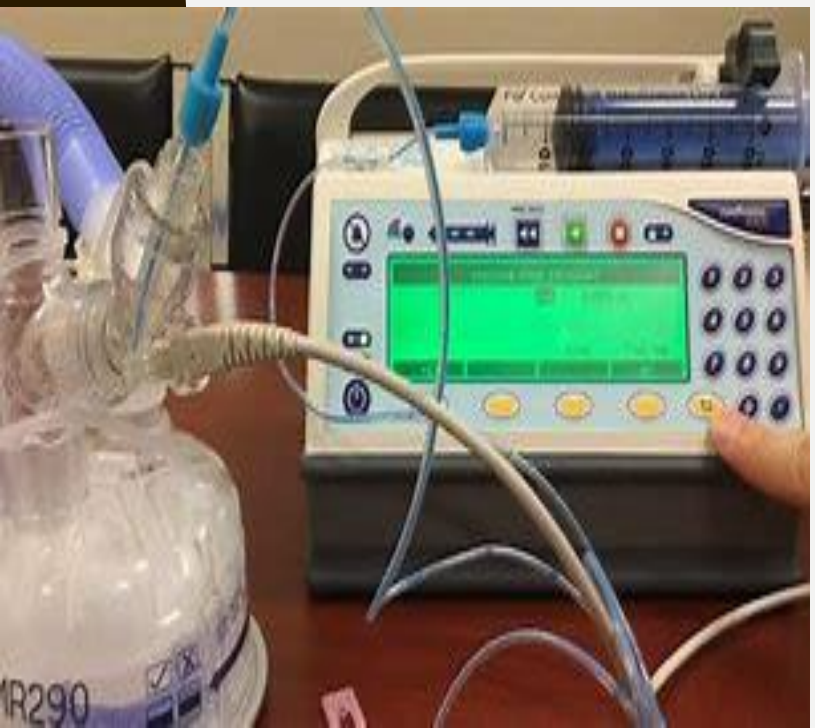
- No studies which specially examine Lung Recruitment Maneuvers (LRM) in mechanically ventilated Covid patients.
- However, there is some evidence on their effectives in ARDS.

- LRM=
  - 30/30 or 40/40 – 30 cm H2O of PEEP for 30 seconds
  - ***APRV: Alternate 7.5 seconds at 40 cms followed by 7.5 seconds at 30 cm H2O for up to five minutes.***
- Citation: Cui Y, Cao Y, Wang Y, Li G. Lung Recruitment Maneuvers for ARDS Patients: A Systematic Review and Meta-Analysis. *Respiration.* 2020;99(3):264-276.

  - Design: Meta analysis of ten trials including 3,025 patients were analyzed.
  - Results:
    - LRMs ***do not*** produce significant reduction of mortality in patients with ARDS.
    - However, they may shorten the length of hospital stay and improve oxygenation on the third day.

ADJUNCTIVE THERAPY – INHALED VASODILATORS

- Inhaled Nitric Oxide (INO)
- Prostacyclin



INO AND COVID

- Spontaneous Breathing Patients:
  - ***Design:*** Case series of 39 spontaneously breathing patients with moderate hypoxemia and Covid 19.
  - ***Findings:*** A total of 21 patients (53.9%) did not require invasive mechanical ventilation after treatment with iNO. Of the 21 patients, 20 were successfully discharged and there was 1 death.
  - ***Discussion:***
    - These findings suggest **that iNO therapy may have a role in preventing progression of hypoxic respiratory failure in Covid-19 patients**.
    - Some researchers hypothesized that iNO may not simply improve oxygenation, but also potentially have an antiviral mechanism of action
  - ***Citation:*** Parikh R, Wilson , Weinberg J, et cal., Inhaled nitric oxide treatment in spontaneously breathing COVID-19 patients, *Ther Adv Respir Dis*, Jan-Dec 2020;14:1753466620933510.

- Mechanically Ventilated Patients:
  - ***Design:*** Case Series of 10 patients with severe hypoxemia due to Covid
  - ***Background:***
    - International guidelines, and experts in the field, all suggest considering iNO even for refractory hypoxemia due to COVID-19.
    - However, there are no strong clinical data to support this indication.
  - ***Findings/Conclusion:*** In this small series of 10 patients with severe hypoxemia due to COVID-19, ***it did not significantly improve arterial oxygenation.***
  - ***Citation:*** Ferrari M, Santini A, Protti A, J Crit Care: Inhaled nitric oxide in mechanically ventilated patients with COVID-19. 2020 Aug 11;60:159-160

INO IN PREGNANT COVID PATIENTS

- ***Design:*** Case Series of six pregnant women with Covid treated at Mass. General
- ***Method***: To treat pregnant patients meeting criteria for severe or critical COVID-19 with high-dose (160–200 ppm) nitric oxide by mask twice daily and report on their clinical response.
- ***Findings***:
  - An increase in systemic oxygenation in each administration session and reduction of tachypnea in all patients in each session.
  - Three patients delivered a total of four neonates during hospitalization. At 28-day follow-up, all three patients were home and their newborns were in good condition. Three of the six patients remain pregnant after hospital discharge.

- ***Conclusion***: Nitric oxide at 160–200 ppm is easy to use, appears to be well tolerated, and might be of benefit in pregnant patients with COVID-19 with hypoxic respiratory failure.
- ***Citation***: Safaee Fakhr B; Wiegand S; Pinciroli R. et al, High Concentrations of Nitric Oxide Inhalation Therapy in Pregnant Patients With Severe Coronavirus Disease 2019 (COVID-19), Obstetrics & Gynecology: August 26, 2020

COVID 19 & INHALED EPOPROSTENOL (FLOLAN)

- Review of pharmacological therapeutics in treating mechanically ventilated Covid 19 patients suggests that ***Flolan should be considered in cases with refractory oxygenation***.
- Should be administered with a vibrating mesh system in the ventilator circuit to minimize contaminating particles.
- Citation: Renyi W, Lujing W, Hsiao-Chen D, et al., An Update on Current Therapeutic Drugs Treating COVID-19. *Curr Pharmacol Rep.* 2020 May 11;1-15.
- ***Caution:*** Replacing expiratory filters in the ventilator circuit (breaking the circuit) to protect the ventilator from sticky glycine buffer may cause risks which outweigh benefits.

EXTRA CORPOREAL MEMBRANE OXYGENATION (ECMO)

- ***Definition/Description:*** ECMO involves bypassing the heart and lungs and having Oxygen added and CO2 extracted by a perfusion machine.
- In many states, though not NJ, Respiratory Therapists can perform ECMO and operate associated equipment.
- Currently, there is ***insufficient evidence to show that ECMO offers a clinical advantage*** in treating respiratory failure in Covid patients.
- ***Citation:*** Cho H, Heinsar S, In Seok J, et al., ECMO use in COVID-19: lessons from past respiratory virus outbreaks-a narrative review. Crit Care, 2020 Jun 6;24(1):301.
- ***Findings:*** Many patients have already been supported with ECMO during the current COVID-19 pandemic, and it is likely that many more may receive ECMO support, although, at this point, the role of ***ECMO in COVID-19-related cardiopulmonary failure is unclear.***

OTHER MEDICATIONS

- Inhaled Medications:
  - Bronchdilators
    - SABA's such as Albuterol
    - Atrovent
  - Mucolytics
    - 10% or 20% Mucomyst
    - 3% or 7% Saline to liquify secretions
- Sedation with Mechanical Ventilation: Versed, Propofol, Precedex.
  - Target a RASS -3 to -4 initially.
  - When respiratory failure improves and weaning is possible, lighten sedation for a RASS of -1 to -2. Paralytics
- Paralyzing Agents: To facilitate ventilator synchrony and reduce ventilator pressures.

COMBINING STRATEGIES:

- Systemic Medications:
  - Antivirals, convalescent plasma, steroids, vaccines
- Spontaneously Breathing Patients (in addition to systemic meds) :
  - Oxygen Therapy + Pulmonary Vasodilators
  - Oxygen Therapy + Prone Positioning
- Mechanically Ventilated Patients (in addition to systemic meds)
  - ARDs-Net + Prone positioning + LRMs + Pulmonary Vasodilators + Paralysis + Mucolytics + Systemic treatments (e.g., Anti-virals)

MORE WORK TO BE DONE

- Much Yet to Be Discovered About Covid
  - Etiology - How it is transmitted, especially non-aerosol transmission..
  - Pathophysiology – Why some are Asymptomatic, and Others are so Vulnerable
  - Treatment – Most Therapies are only Marginally Effective.
  - Prevention— Vaccines?
- Many Articles were Submitted and Published Prematurely and had to be Retracted.
- Many Articles are Smaller and Less Scientifically Rigorous than Large, Randomized Control Trials (RCTs).
- Can Clinical Strategies be Combined to Produce a synergistic effect?
- If there is Another Wave, are we Better Prepared?
- What are the Longer-Term Impacts on our Healthcare Workforce and Society?

SELECTED REFERENCES

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