Update on Treatment of COVID-19

Michael Haden, MD
Assistant Professor of Medicine
Division of Infectious Diseases
The Ohio State University Wexner Medical Center

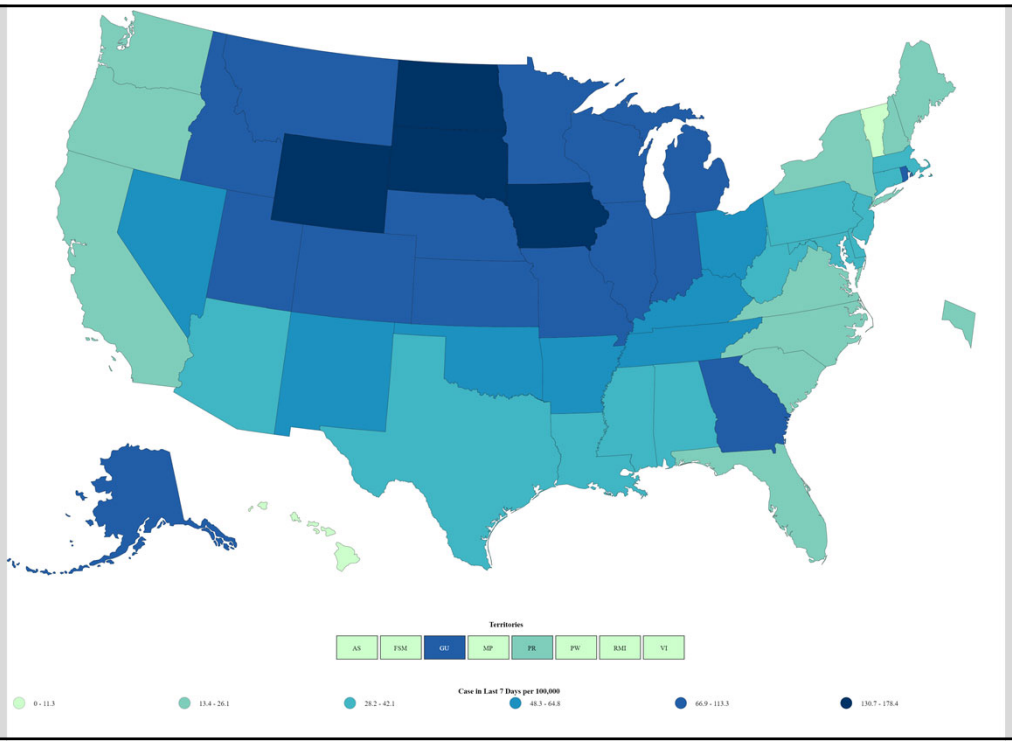
MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

Situation in United States

As of November 2020 in the U.S.

- Over 11 million total cases
- Nearly 250,000 deaths



SARS-CoV-2

Incubation period can be up to 14 days from time of exposure

- Median 4-5 days

Spectrum of illness asymptomatic to severe illness and death

COVID-19

Primarily a pulmonary disease, however emerging data also suggests cardiac, dermatologic, hematological, hepatic, neurological, renal and other complications

Thromboembolic events are common, highest risk in critically ill patients

The long-term sequelae of COVID-19 survivors are currently unknown

COVID-19

80% infected have mild illness

15% severe: SpO2 < 94% on room air

5% critical: mechanical ventilation or ECMO

10% of all infections are hospitalized

- 10% requiring ICU level of care

Infection Prevention and Control

Infection Prevention and Control

Limit potential facility exposure

- Consider postponing elective procedures
- Use telehealth options when possible
- Limit points of entry
- Screen all patients and visitors for signs and symptoms of COVID-19
  - This will miss asymptomatic / pre-symptomatic individuals

Infection Prevention and Control

Patients and visitors should wear a mask upon arrival and throughout their stay

Restrict visitors who have suspected or confirmed SAR-CoV-2 infection, or have had close contact with SARS-CoV-2 person

Infection Prevention and Control

Symptomatic patients should be isolated in an exam room with the door closed

Airborne infection isolation rooms should be reserved for those undergoing aerosolizing procedures

Consider universal pre-admission or pre-procedural testing of patients

Re-evaluate admitted patients for signs and symptoms of COVID-19

Infection Prevention and Control

Healthcare workers (HCWs) should wear a facemask at all times within the facility

- This includes in breakrooms or other common areas

Encourage physical distancing (6 feet) as much as possible

Testing

Viral (nucleic acid or antigen) tests are recommended for diagnosis of acute infection

Antibody testing not approved or recommended as sole basis for diagnosis of acute infection

Nasopharyngeal, mid-turbinate or nasal swabs are preferred to oropharyngeal or saliva alone

Lower respiratory tract specimens can be tested if suspicion remains high

Personal Protective Equipment (PPE)

Facemask and eye protection for all patient encounters

- Glasses are not sufficient

SARS-CoV-2 positive patients require addition of gown and gloves

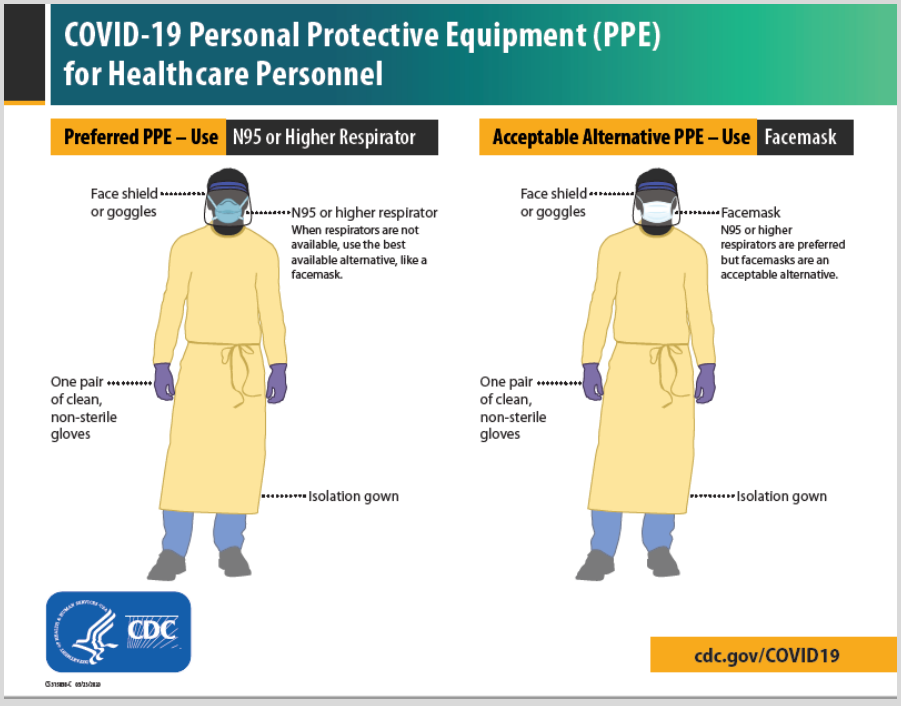
N95 (or equivalent) or higher level respirator for AGP and surgical procedures with high risk of COVID transmission (nose, oropharynx, respiratory tract)

Aerosol generating procedures

- Procedures:
  - Intubation / Extubation
  - Endoscopy (EGD, Bronchoscopy, TEE)
  - CPR
  - Tracheostomy placement
- Bedside Care:
  - Nasopharyngeal swab (testing for COVID)
  - NG / OG tube placement
  - Suctioning, sputum induction or tracheal aspiration

PPE

- Follow the recommended sequence for safely donning and doffing PPE to avoid self contamination
- Hand hygiene should be performed before and after all patient contact, before putting on and after removing PPE
  - Alcohol based hand sanitizer or soap and water



Donning (putting on the gear):

More than one donning method may be acceptable. Training and practice using your healthcare facility's procedure is critical. Below is one example of donning.

1. **Identify and gather the proper PPE to don.** Ensure choice of gown size is correct (based on training).
2. **Perform hand hygiene using hand sanitizer.**
3. **Put on isolation gown.** Tie all of the ties on the gown. Assistance may be needed by another HCP.
4. **Put on NIOSH-approved N95 filtering facepiece respirator or higher (use a facemask if a respirator is not available).** If the respirator has a nosepiece, it should be fitted to the nose with both hands, not bent or tented. Do not pinch the nosepiece with one hand. Respirator/facemask should be extended under chin. Both your mouth and nose should be protected. Do not wear respirator/facemask under your chin or store in scrubs pocket between patients.*
   - » **Respirator:** Respirator straps should be placed on crown of head (top strap) and base of neck (bottom strap). Perform a user seal check each time you put on the respirator.
   - » **Facemask:** Mask ties should be secured on crown of head (top tie) and base of neck (bottom tie). If mask has loops, hook them appropriately around your ears.
5. **Put on face shield or goggles.** Face shields provide full face coverage. Goggles also provide excellent protection for eyes, but fogging is common.
6. **Perform hand hygiene before putting on gloves.** Gloves should cover the cuff (wrist) of gown.
7. **HCP may now enter patient room.**

Doffing (taking off the gear):

More than one doffing method may be acceptable. Training and practice using your healthcare facility's procedure is critical. Below is one example of doffing.

1. **Remove gloves.** Ensure glove removal does not cause additional contamination of hands. Gloves can be removed using more than one technique (e.g., glove-in-glove or bird beak).
2. **Remove gown.** Untie all ties (or unsnap all buttons). Some gown ties can be broken rather than untied. Do so in gentle manner, avoiding a forceful movement. Reach up to the shoulders and carefully pull gown down and away from the body. Rolling the gown down is an acceptable approach. Dispose in trash receptacle.*
3. **HCP may now exit patient room.**
4. **Perform hand hygiene.**
5. **Remove face shield or goggles.** Carefully remove face shield or goggles by grabbing the strap and pulling upwards and away from head. Do not touch the front of face shield or goggles.
6. **Remove and discard respirator (or facemask if used instead of respirator).*** Do not touch the front of the respirator or facemask.
   - » **Respirator:** Remove the bottom strap by touching only the strap and bring it carefully over the head. Grasp the top strap and bring it carefully over the head, and then pull the respirator away from the face without touching the front of the respirator.
   - » **Facemask:** Carefully untie (or unhook from the ears) and pull away from face without touching the front.
7. **Perform hand hygiene after removing the respirator/facemask** and before putting it on again if your workplace is practicing reuse.

Facilities implementing reuse or extended use of PPE will need to adjust their donning and doffing procedures to accommodate those practices.

Optimizing PPE supply

Cancel elective and non-urgent procedures / appointments

Reserve PPE for healthcare workers

Use re-usable PPE that can be reprocessed if able

Consider extending use of respirators, facemasks and eye protection beyond a single patient contact

Occupational Exposure

HCW with prolonged close contact with SARS-CoV2- positive patient, visitor or staff (cumulative period of 15 minutes or longer)

- No facemask or respirator: quarantine for 14 days

- Face mask / respirator: continue to work, monitor symptoms and quarantine if symptoms develop

Community Exposure

HCW with prolonged close contact with SARS-CoV2-positive person in community should quarantine until 14 days from last exposure

Return to work

Confirmed or suspected SARS-CoV-2 infection:

- Mild-moderate: 10 days since symptom onset, 24 hours afebrile, symptoms improved
- Moderate-severe: 10-20 days

Test based strategy no longer recommended

Discontinuation of Isolation

Mild to Moderate:

- 10 days from symptom onset
- 24 hours afebrile
- Symptoms overall improved

Moderate to Severe

- At least 10 days from symptom onset, can extend up to 20
- 24 hours afebrile
- Symptoms overall improved

Treatment

Dexamethasone

RECOVERY trial

- Lower 28 day mortality seen in those on supplemental O2 or mechanical ventilation
- No benefit among those not requiring respiratory support

Dexamethasone 6 mg IV or PO daily for 10 days

- Equivalent glucocorticoid may be used if dexamethasone unavailable

Remdesivir

Inhibitor of the viral RNA-dependent RNA polymerase

FDA approved October 22, 2020

In setting of limited resource, remdesivir is most beneficial in those with severe illness, not critical

Given as 5 day course in severe illness, extended to 10 days in critical illness

Bamlanivimab

Monoclonal antibody against directed against SARS-CoV-2 spike protein

Designed to block virus' attachment and entry into human cells

FDA issued EUA November 9, 2020

Authorized for outpatients with high risk for severe COVID-19

Not authorized for hospitalized patients or those requiring oxygen therapy due to COVID-19

Convalescent Plasma

FDA issued EUA on August 23, 2020

IDSA guidelines recommend convalescent plasma be used in setting of a clinical trial

Casirivimab and Imdevimab (Regeneron)

Recombinant human IgG1 monoclonal antibody that targets receptor binding domain of the spike protein of SARS-CoV-2

FDA issued EUA November 21, 2020

Indicated for mild to moderate COVID-19

NOT indicated for hospitalized patients or those requiring oxygen therapy

Therapies not recommended

Hydroxychloroquine or Chloroquine with or without Azithromycin

Lopinavir / ritonavir, except in setting of a clinical trial

Tocilizumab, except in setting of a clinical trial

Famotidine

Vaccine

Operation Warp Speed

Partnership between multiple federal and private agencies to expedite vaccine development

Goal is to deliver 300 million doses of vaccine, initial doses by January 2021

Three vaccine candidates have been funded for phase 3 trials

Vaccine

Manufacturer	Mechanism	Status
Moderna mRNA-1273	mRNA-based vaccine	Phase 3
Pfizer / BioNTech BNT162	mRNA-based vaccine	Phase 3
University of Oxford / AstraZeneca AZD1222	Replication-deficient viral vector (chimpanzee adenovirus)	Phase 3

Inpatient Management of COVID-19

Rachel Quaney, MD
Clinical Instructor of Internal Medicine
Division of Pulmonary, Critical Care, and Sleep Medicine
The Ohio State University Wexner Medical Center

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Wexner Medical Center

Outline

- Respiratory failure
- ARDS
- Coagulopathy
- Special groups
- Outcomes

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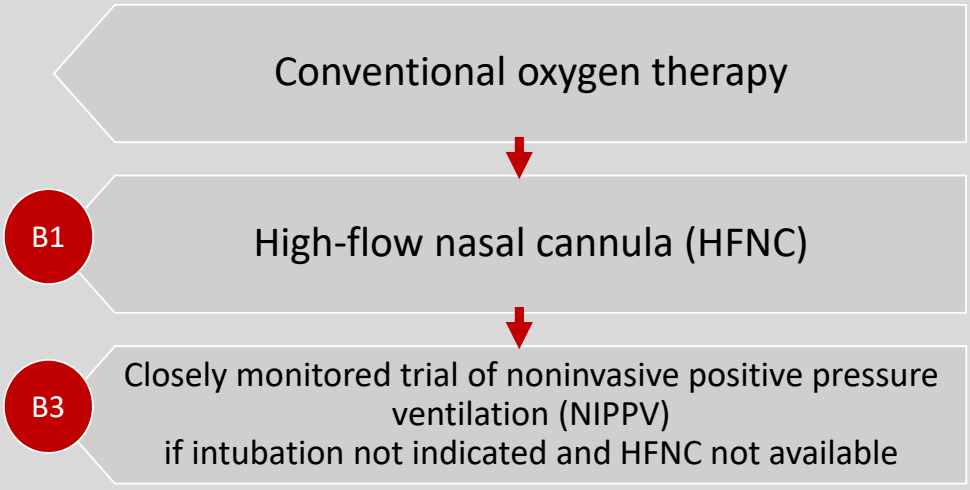
Hospital course

- Median time from illness to dyspnea → 5-8 days
- Median time from illness to ARDS → 8-12 days
- Median time from illness to ICU admission → 9.5-12 days

Respiratory failure



https://www.covid19treatmentguidelines.nih.gov/critical-care/

Respiratory failure

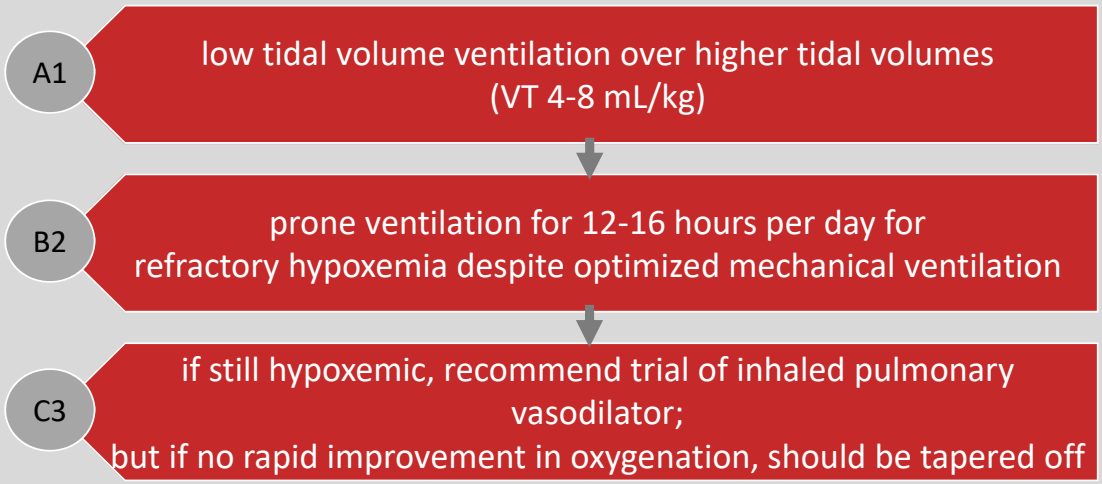
C3	Trial of awake prone positioning with persistent hypoxemia if no indication for intubation
A3	Recommendation against awake proning as rescue therapy to avoid intubation
A2	Close monitoring and intubation, if necessary, is performed by experienced practitioner in controlled setting

https://www.covid19treatmentguidelines.nih.gov/critical-care/

ARDS definition

Imaging	Bilateral opacities
Etiology	Not fully explained by heart failure or volume overload
Timing	≤ 1 week since onset or insult
PaO_2/FiO_2 (P:F) ratio calculated with PaO_2 as whole number (mmHg) & FiO_2 as decimal	< 300 (measured with PEEP ≥ 5 cmH_2O)

ARDS



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Principles of ventilator settings

- We determine → independent variables
  - Ventilator Mode: volume or pressure cycled

- We measure → dependent variables
  - Peak pressure or tidal volume

Principles of ventilator settings

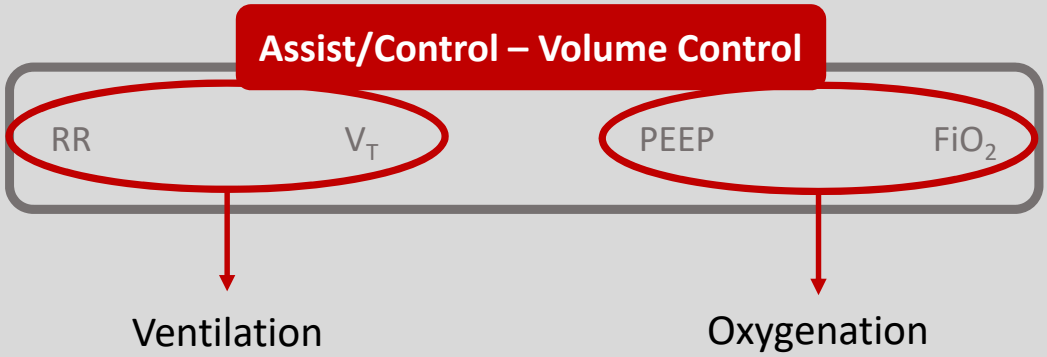
- We determine → independent variables
  - Ventilator Mode: volume ~~or pressure~~ cycled
  - Oxygen Concentration (FiO_2): 0.21 - 1.0
  - Minimum Respiratory Rate: set rate
  - PEEP
- We measure → dependent variables
  - Peak pressure ~~or tidal volume~~
  - Plateau pressure
  - Auto PEEP (sometimes)

Ventilator mode most appropriate for acute hypoxemic respiratory failure

Assist/Control
Volume Control

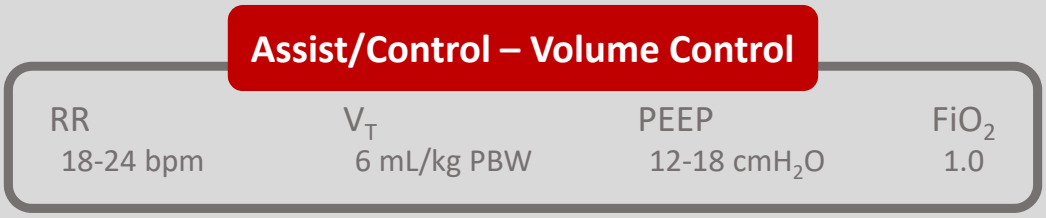
- Vent supports all breaths to a targeted tidal volume
- A minimum rate (RR) is set and delivered to the patient
- All spontaneous breaths will be supported to the same targeted volume

Independent Regulation of Ventilation and Oxygenation



RR x V_T = minute ventilation
= volume of air moved per minute

Initial settings — Hypoxemic respiratory failure with or at risk for ARDS



<u>Key point:</u> The 6 mL/kg tidal volume is based on "predicted body weight"

Males: PBW = 50 kg + 2.3 kg for each inch over 5 feet

Females: PBW = 45.5 kg + 2.3 kg for each inch over 5 feet

<u>Key point:</u> Permissive hypercapnia is okay – low V_T may require pH as low as 7.2

Initial settings— Hypoxemic respiratory failure with or at risk for ARDS

Assist/Control – Volume Control

RR	V_T	PEEP	FiO_2
18-24 bpm	6 mL/kg PBW	12-18 cmH_2O	1.0

Goals for "lung protection"

- Low tidal volume 4-8 mL/kg PBW
- Plateau pressure < 30 cmH_20
- Driving pressure < 15 cmH_20

Data: Lung protective ventilation strategy is the only intervention that has been definitively shown to reduce mortality in patients with ARDS

Principles of ventilator settings

- We determine → independent variables
  - Ventilator Mode: volume ~~or pressure~~ cycled
  - Oxygen Concentration (FiO_2): 0.21 - 1.0
  - Minimum Respiratory Rate: set rate
  - PEEP
- We measure → dependent variables
  - Peak pressure ~~or tidal volume~~
  - Plateau pressure
  - Auto PEEP (sometimes)
- We look for and respond to:
  - Oxygenation (PaO_2 or SpO_2)
  - Ventilation (pCO_2 and pH)
  - The Obvious: ventilator dyssynchrony or "blowouts" like pneumothorax
  - The Occult: auto PEEP

Monitors

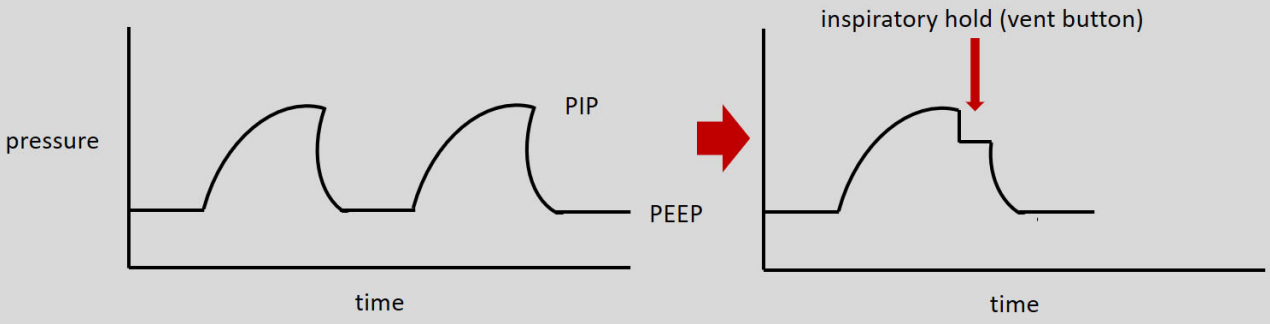
- **Blood gas (arterial)**
  - pH
  - $PaCO_2$
  - PaO_2
- **Pulse oximetry**
  - SpO_2

Goals

- **Oxygenation (FiO_2 and PEEP)**
  - PaO_2 ~65 mmHg
  - SpO_2 ~90%
- **Ventilation (RR and V_T)**
  - pH 7.2-7.45

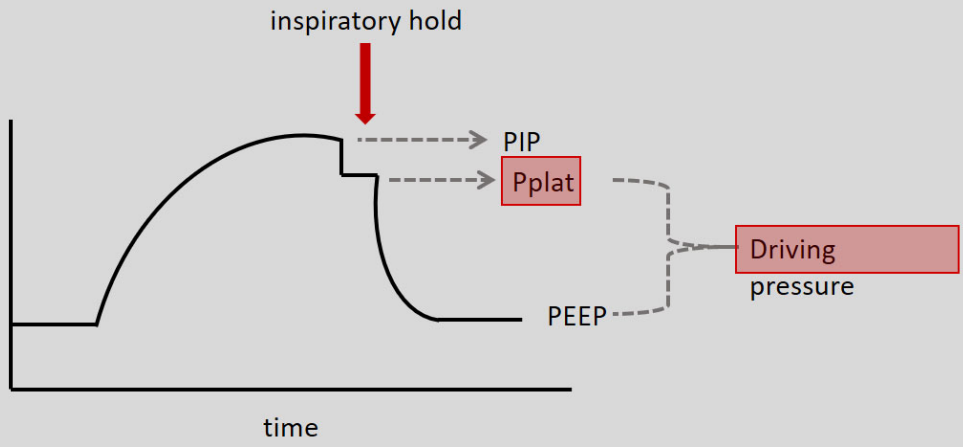
    >>
  - $PaCO_2$
    - permissive hypercapnia except with increased intracranial pressure

Using plateau pressure



Using plateau pressure

- Goal plateau < 30 cmH_2O
- Goal driving < 15 cmH_20



Adjusting PEEP and FiO2

ARDSnet

NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary

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

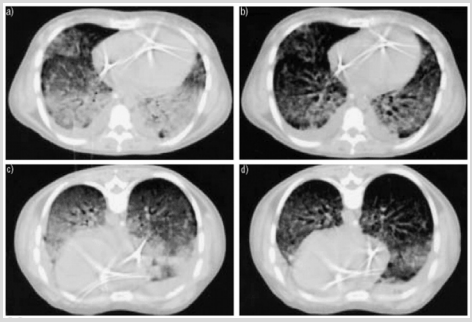
Higher PEEP/lower FiO2

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

Prone positioning

- Early prone positioning in **severe** ARDS improves oxygenation and may have a mortality benefit
  - Consider **early** if P:F < 150 despite low tidal volume ventilation



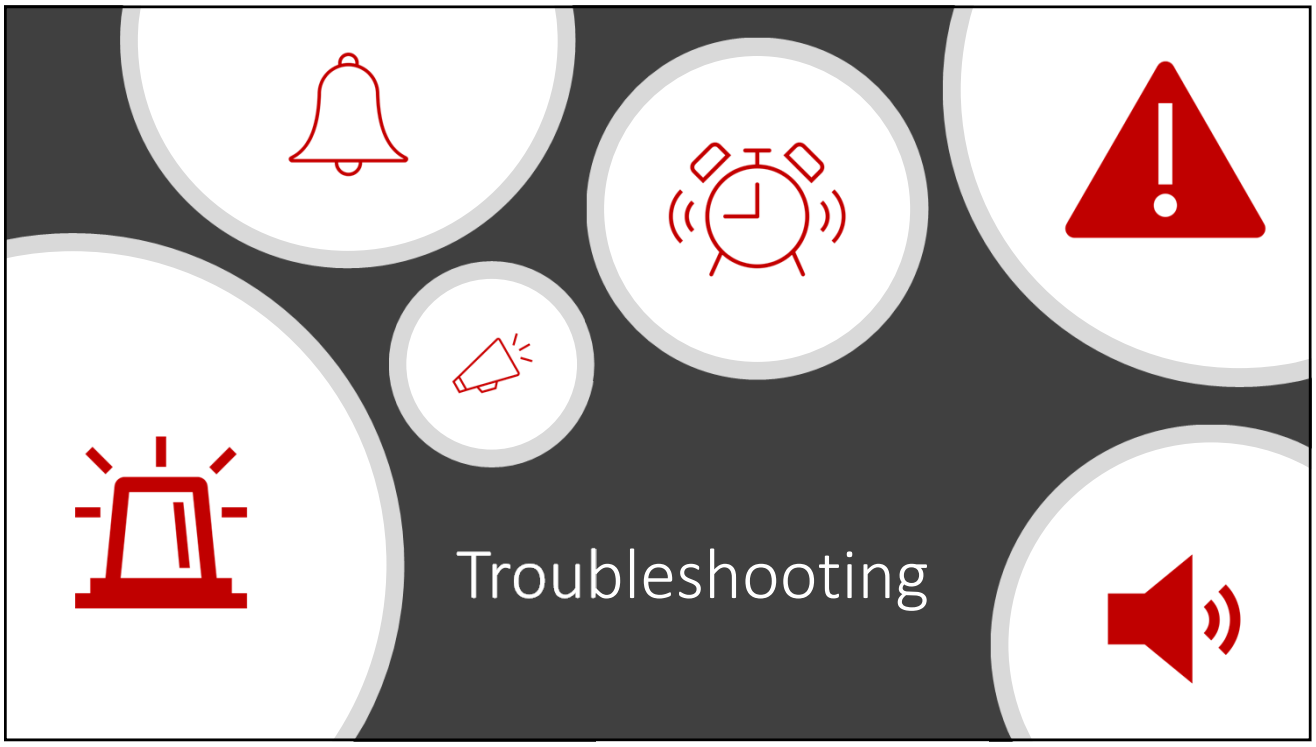
- How it works:
  - ↓ compression of left lung by the heart
  - ↓ dependent atelectasis from interstitial edema
  - Allows more lung regions to be functional
  - Improves V/Q mismatch by impacting both blood flow and ventilation in more alveoli

Neuromuscular blockade

- 2010 ACURASYS trial → mortality benefit
- 2019 ROSE trial → no mortality benefit compared to lighter sedation

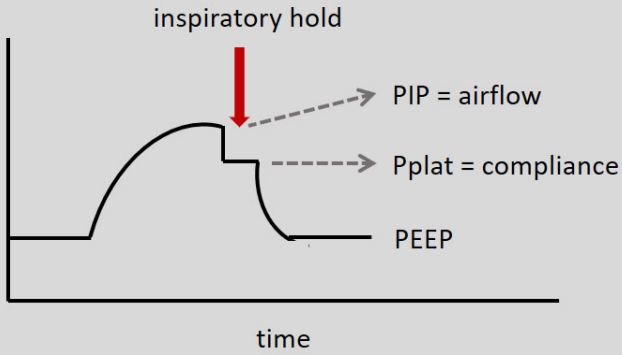
- Bottom line:
  - Not needed for all ARDS patients
  - Still useful for significant vent dyssynchrony OR refractory hypoxemia/hypercapnia

- If used:
  - Ensure adequate continuous sedation and analgesia
  - Ensure VTE prophylaxis

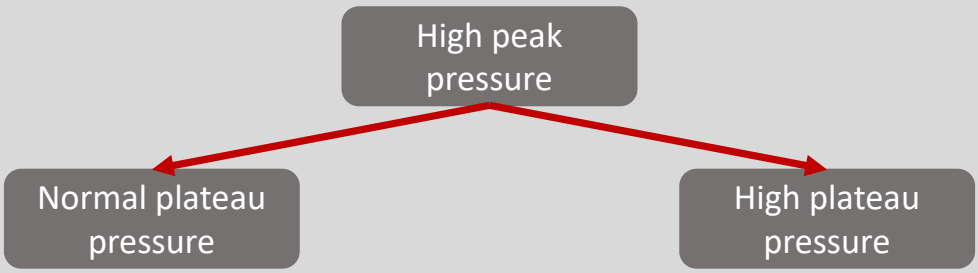


Using plateau pressure

- May be helpful in identifying/differentiating complications
  - Peak pressure (PIP) reflects airway resistance
  - Plateau pressure (Pplat) reflects lung/pleural compliance, elastic recoil
- Peak *minus* plateau is normally < 5 cmH_2O



Causes of high peak pressure



- Mucus plugging
- Bronchospasm
- Biting endotracheal tube

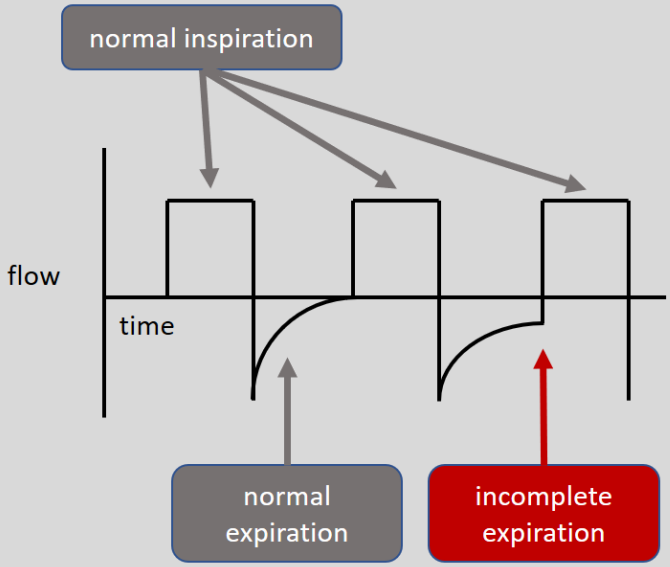
- Pneumothorax
- Right mainstem intubation
- Excessive alveolar distension (auto PEEP)
- Abdominal distension (rigid abdomen, severe obesity)

Auto PEEP

- Also known as “dynamic hyperinflation” or “breath stacking”
- Incomplete exhalation before a new breath is delivered
- Why it is bad:
  - Inadequate ventilation
  - Increased intrathoracic pressure, can lead to cardiovascular compromise

Auto PEEP

- How to tell:
  - Ventilator flow waveform →
  - Increasing peak pressure



- What to do:
  - Increase exhalation time
    - Decrease respiratory rate
    - Decrease I:E ratio
    - Increase inspiratory flow
  - Decrease tidal volume
  - Adjust PEEP to improve airway patency
  - In extreme circumstances, disconnect circuit

Mucus plugging

- Increase in peak pressure, usually WITHOUT plateau pressure
- Decreased breath sounds on affected side, or bilaterally if plug is in ET tube or trachea
- May have asymmetric chest rise
- Should still have lung sliding on ultrasound, though may be lessened
- Confirmation with chest X-ray if not acutely hypoxemic

Pneumothorax

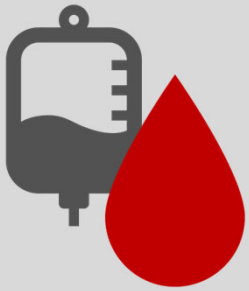
- Increase in peak pressure AND plateau pressure
- Decreased breath sounds, or hyperresonance, on affected side
- May have asymmetric chest rise, subcutaneous emphysema (later)
- Due to closed ventilator circuit, increasing intrathoracic pressure can have hemodynamic consequences = TENSION
- Lack of lung sliding on ultrasound
- Confirmation with chest X-ray if not acutely hypotensive

Outline

- Respiratory failure
- ARDS
- **Coagulopathy**
- Special groups
- Outcomes

Coagulopathy

Incidence of VTE in COVID-19 ranges from 1.1% to 69%



Coagulopathy

	American Society of Hematology	National Institutes of Health
Therapeutic anticoagulation	continue some form	continue some form
Thromboprophylaxis	LMWH > UFH > mechanical	per standard of care
Empiric anticoagulation	clinical trials	clinical trials
Clotting devices	may be reasonable to increase intensity or switch anticoagulant	antithrombotic therapy per standard institutional protocols
Post-discharge thromboprophylaxis	not routinely, but consider VTE risk, bleeding risk, and feasibility	not routinely, but consider only if high VTE risk & low bleeding risk

NIH treatment guidelines found at nih.gov
ASH treatment guidelines found at hematology.org

Outline

- Respiratory failure
- ARDS
- Coagulopathy
- Special groups
- Outcomes

Special groups

increased risk for severe COVID-19

Age

- Cancer
- Chronic kidney disease
- COPD
- Heart conditions
- Solid organ transplant recipient
- Obesity
- Pregnancy
- Sickle cell disease
- Smoking
- Type 2 diabetes mellitus

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Special groups
increased need for precautions

Individual situation

- Racial and ethnic minority groups
- Disabled
- Developmental disorders
- Behavior disorders
- Drug and substance use disorders

Living situation

- Rural communities
- Experiencing homelessness
- Refugee populations
- Nursing homes
- Longer-term care facilities
- Group homes

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

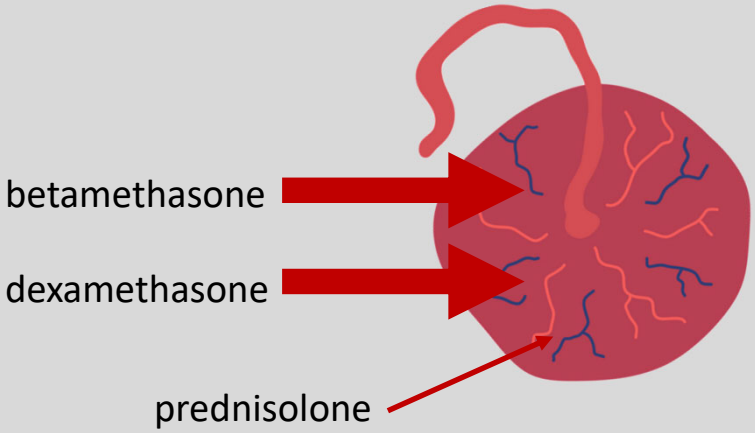
Pregnancy

↑ risk of hospitalization, ICU admission, and mechanical ventilation

- Management nuances:
  - Presume difficult airway
  - Left lateral decubitus position improves pre-load
  - Maintain SpO2 > 95%

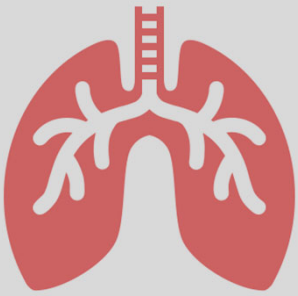
Ellington et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status. MMWR M&M Weekly. 2020;69:769–775.

Pregnancy and steroids

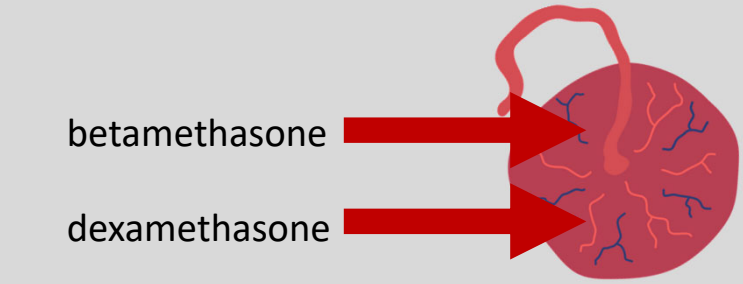


ARDS and steroids

- ☑ methylprednisolone
- ☑ dexamethasone

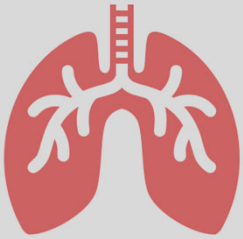


Steroids for pregnancy and COVID-19



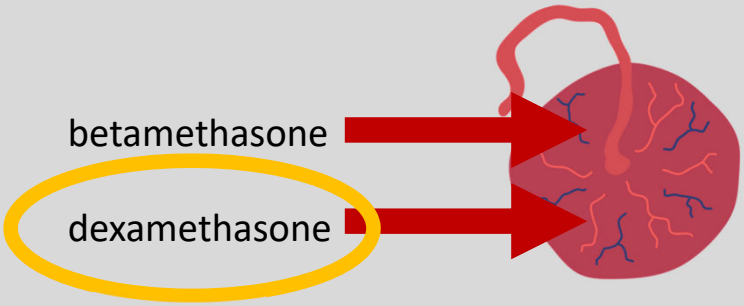
betamethasone

dexamethasone



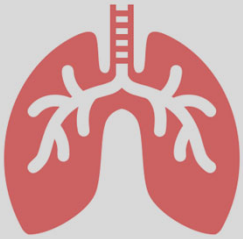
- [x] methylprednisolone
- [x] dexamethasone

Steroids for pregnancy and COVID-19



betamethasone

dexamethasone



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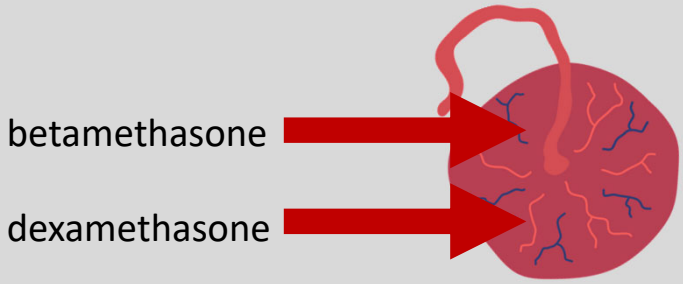
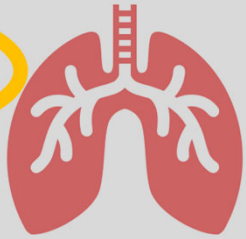
- [x] dexamethasone

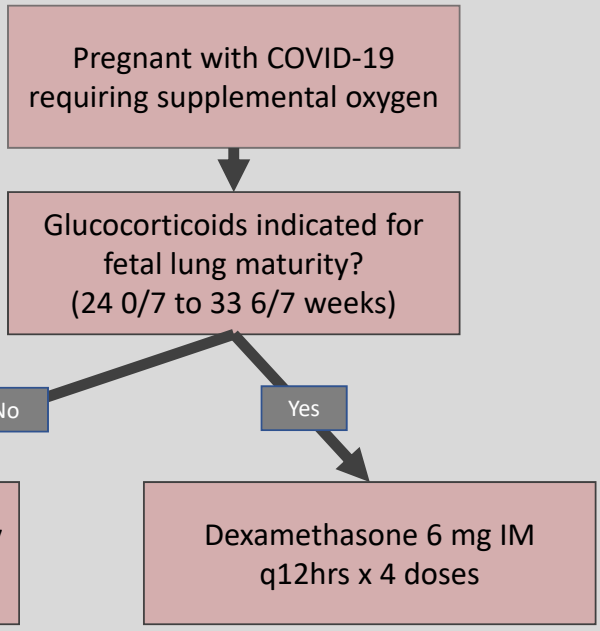
Steroids for pregnancy and COVID-19



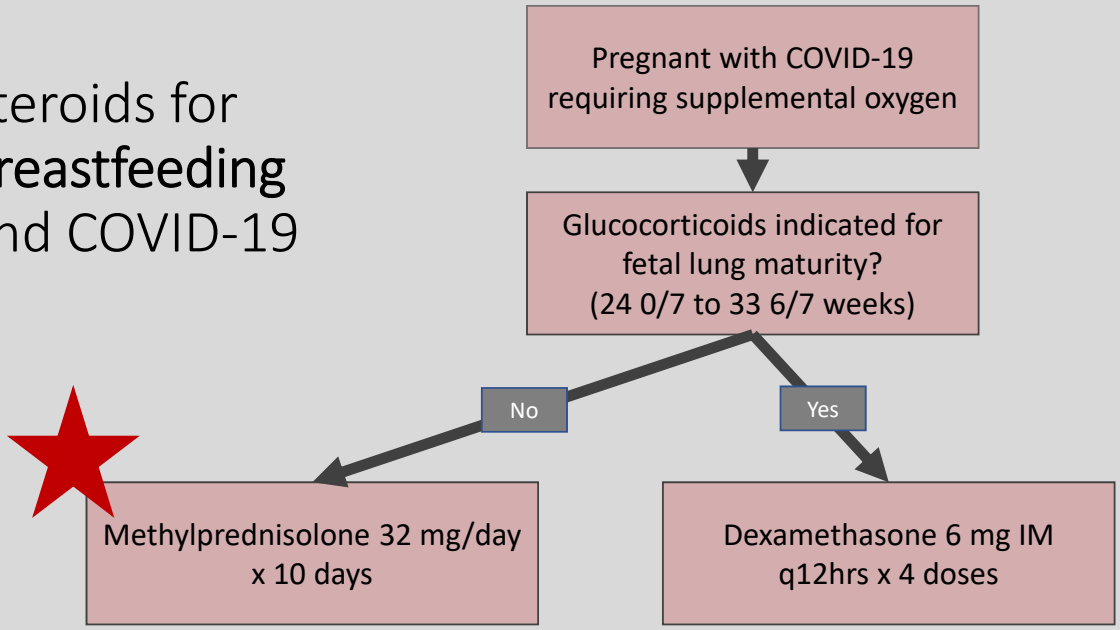
- ☑ methylprednisolone
- ☑ dexamethasone



Steroids for pregnancy and COVID-19



Steroids for **breastfeeding** and COVID-19



Outline

- Respiratory failure
- ARDS
- Coagulopathy
- Special groups
- Outcomes

Outcomes

- 1648 patients hospitalized with COVID-19 in Michigan March - July

- 60 days after discharge

Chopra et al. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Annals of Internal Medicine*. Nov 2020.

Outcomes

- 405 patients receiving ICU treatment

- 15.1% of hospital survivors were rehospitalized within 60 days

Chopra et al. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Annals of Internal Medicine*. Nov 2020.

Issues after discharge

- 488 (41.8%) were able to be contacted 60 days postdischarge
  - 159 with cardiopulmonary symptoms
  - 65 with anosmia or ageusia
  - 58 with ADL difficulties
  - Of 195 employed prior to hospitalization:
    - 117 returned to work but 30 of those with reduced or modified duties
    - 78 could not return to work
  - 238 emotionally affected by their health
  - 179 financially impacted

Chopra et al. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. *Annals of Internal Medicine*. Nov 2020.

Summary

- Respiratory failure
- ARDS
- Coagulopathy
- Special groups
- Outcomes

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