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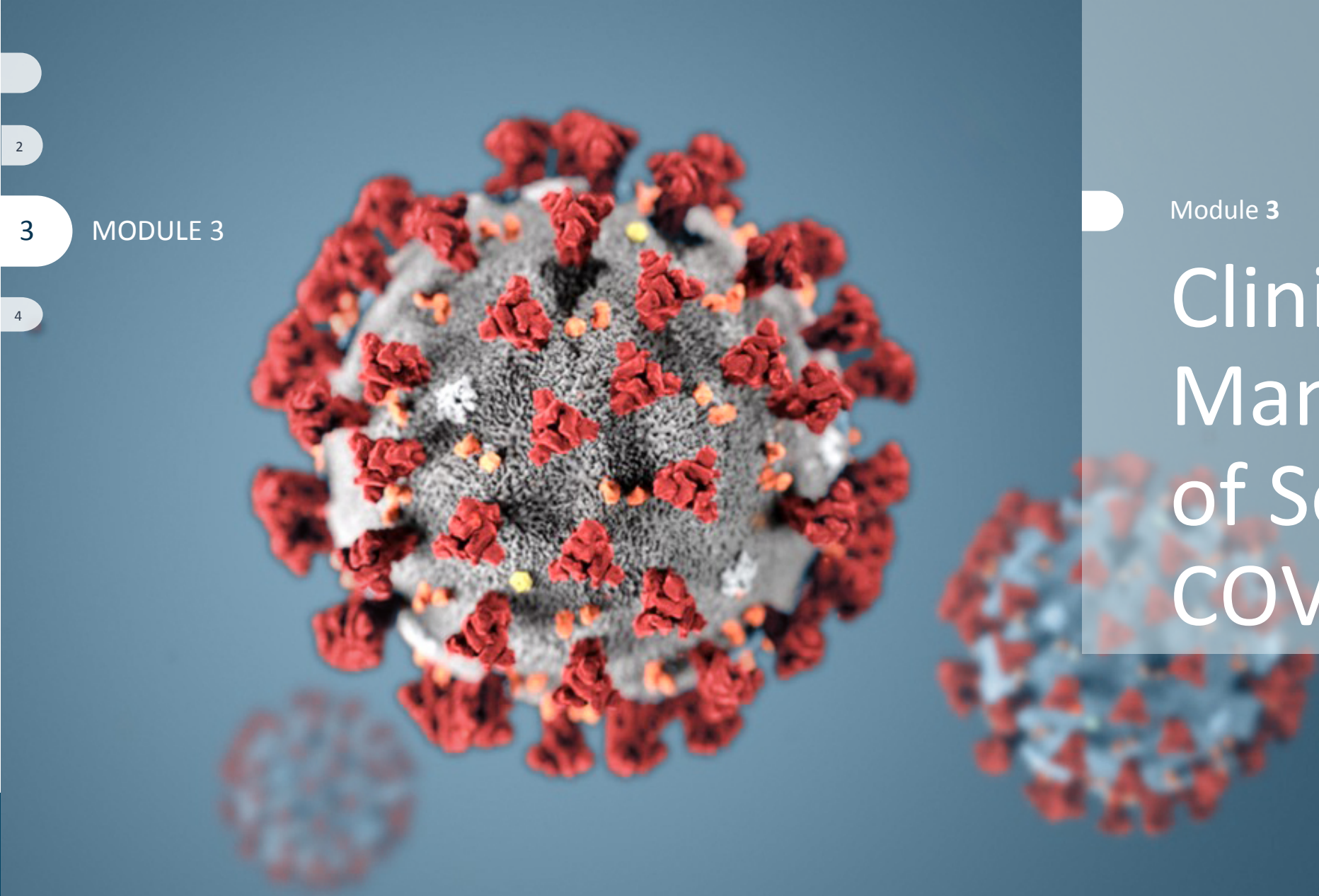

Module **3**

Clinical Management of Severe COVID-19

ICAP
Columbia University
Mailman School
of Public Health

V 1.0 July 2020

Module 3 Outline

1) **Learning Objectives**
2) Classification as Severe COVID-19
3) Risks for Deterioration & Death
4) Testing & Monitoring in Severe COVID-10
5) Treatment of Severe COVID-19

Photo by Tai's Captures on Unsplash

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By the end of this module,
the learner should be able to:

1. Classify a given patient as having severe or critical illness
2. Identify risk factors for progressing to severe COVID-19
3. Describe dimensions of COVID-19 critical Illness
4. Describe the time course to development of severe disease
5. Order and interpret tests appropriately
6. Administer and apply symptom management
7. Understand and demonstrate the use of oxygen therapy

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By the end of this module,
the learner should be able to:

8. Describe and apply the use of anti-inflammatory agents
9. Describe available antiviral agents
10. Describe the rationale for use of convalescent plasma
11. Describe use of antibiotics for community acquired pneumonia or sepsis in patients with COVID-19
12. Describe management of concomitant medications and common comorbidities in patients with COVID-19
13. Describe and apply palliative modalities

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COVID-19 inpatient management: best buys in resource-constrained settings

- PPE for staff
- Staff training
- Oxygen supply
- Pulse oximeters

[Michele Spatari/AFP]

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Patient 1: an elderly male truck driver

- 74-year-old male truck driver presents with fever and cough for 5 days
- He complains of increasing difficulty sleeping and now feels short of breath
- He notes decreased oral intake and dark colored urine
- PMHx- diabetes mellitus poorly controlled on Metformin 500mg BID, hypertension on Enalapril
- Admits because of his work he does not take metformin as prescribed
- Social Hx- lives alone and spends most of his time in his truck driving

What are some of the concerning parts of this history?

What information is needed to classify his disease severity?

COVID-19 WHO Adult Disease Severity Classification: Severe vs Critical

Category	Definition	Management
Severe Illness 	Adult with clinical signs of pneumonia, respiratory frequency >30 breaths per minute, severe respiratory distress, SpO_2 < 90% on room air	• Hospitalize (consider up-referral) • Use PPE (N95 for aerosolizing procedures) • Airborne infection isolation room where available • Oxygen therapy (nasal cannula or high-flow) • Consider antibiotics or steroids
Critical Illness 	Individuals with worsening respiratory failure, septic shock, and/or multiple organ dysfunction not explained by cardiac failure or fluid overload (may include hypotension, decreased urine output, worsening respiratory status, coagulopathy, acidosis, altered mental status, etc.)	Above plus : • ICU to manage co-morbidities • Critical care management

COVID-19 WHO Pediatric Disease Severity Classification: Severe vs Critical

Category	Definition	Management
Severe Illness 	Child with clinical signs of pneumonia, increased respiratory frequency (based on age), central cyanosis or severe respiratory distress (grunting, chest indrawing), SpO_2 < 90% on room air, danger signs (inability to eat or drink), lethargy, unconsciousness or convulsions	• Hospitalize (up-referral if possible) • Use PPE (N95 for aerosolizing procedures) • Airborne infection isolation room if available • Oxygen therapy (nasal cannula or high-flow) • Consider antibiotics for secondary bacterial pneumonia or sepsis
Critical Illness 	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction	Above plus: • ICU to manage co-morbidities • Critical care management

Patient 1: an elderly male truck driver (continued)

Exam:

- Vitals: Temp 39.8^{0}C, RR 35, RR 120, BP 135/90,
- **Oxygen saturation (SpO_2) 89% room air**
- Mucous membranes are dry
- CVS: tachycardia
- Chest: Tachypneic with bilateral decreased breath sounds with bibasilar crackles
- Abdomen: soft, nontender
- CNS: awake, alert, oriented , WNL

Labs:

- WBC 4, [85 % N 15% L; ALC- 600] Plts 137,
- CRP 12 mg/L; D-Dimer > 0.5 mg/L; LDH 980 U/L
- Chemistry normal except for glucose 250 mg/dL
- Urinalysis positive for ketones (1+)
- Rapid COVID-19 test **positive**

Classify this patient in terms of disease severity.

Is he at risk for clinical deterioration or death?

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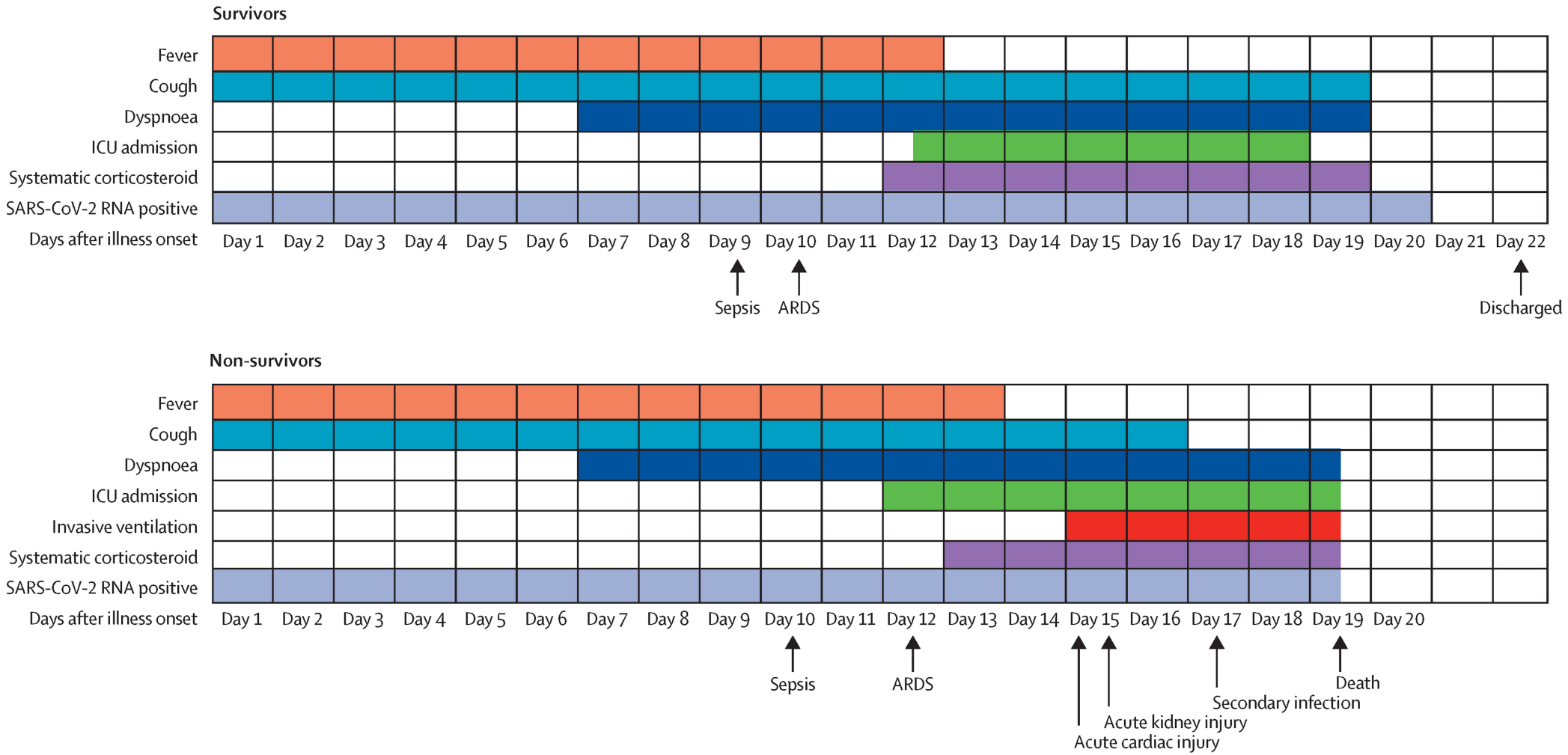
Time course of symptoms and viral shedding in COVID-19 survivors and non-survivors in Wuhan, China



Reference: *Zhou et al, Lancet March 2020*

Who is at Risk for Severe Disease ?

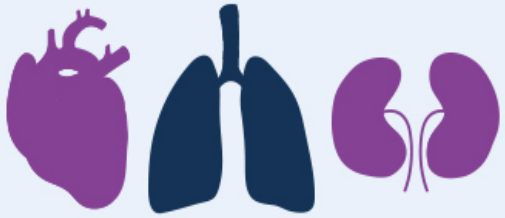
Stop the Spread @NCDHHS • #COVID19NC

Are You High Risk?

These people are at higher risk of getting very sick from COVID-19.
Take actions to reduce your risk of getting sick.

Those in **close household contact** with person diagnosed with COVID-19

People **65+ years old**



People with **underlying health conditions** (ie. heart/lung/ kidney disease, diabetes, weakened immune system, etc.)

Source: https://www.cdc.gov/coronavirus/2019-ncov/downloads/COVID19-What-You-Can-Do-High-Risk.pdf

Image sources: https://www.kdhnc.com/ImageRepository/Document?documentID=12201

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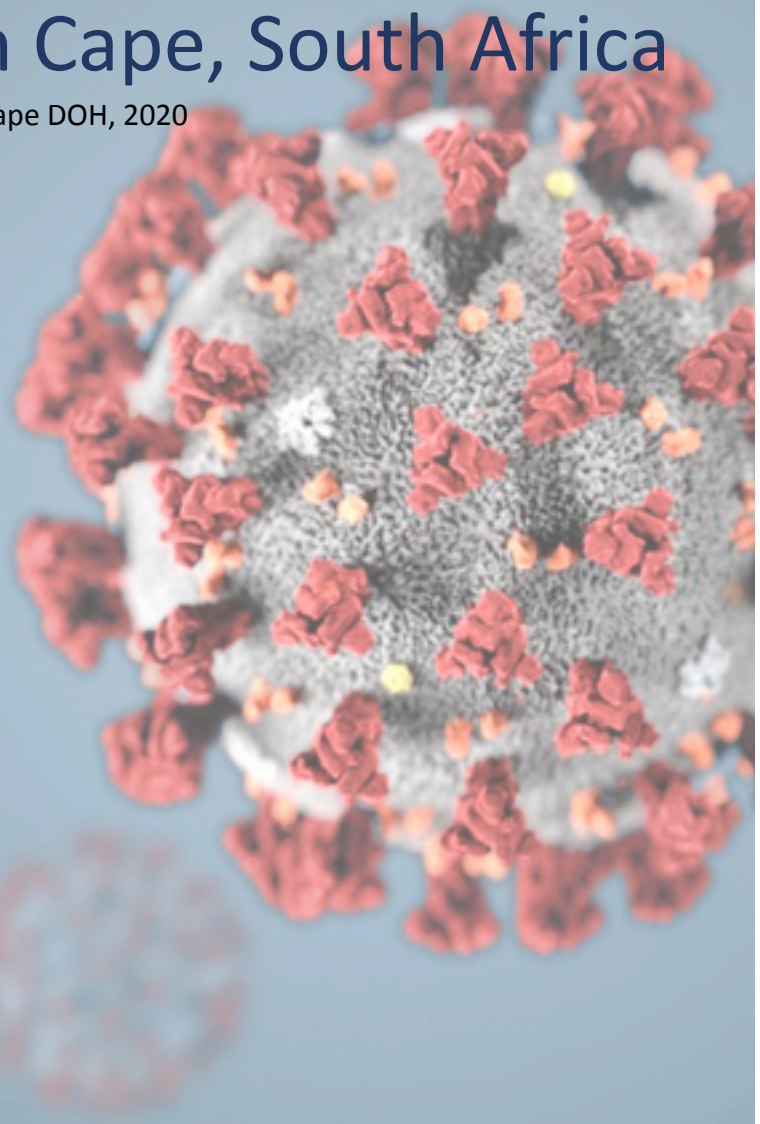
Risks for COVID-19 Mortality Western Cape, South Africa

Davies & Western Cape DOH, 2020



Patient characteristics	Adjusted Hazard ratio	95% Confidence Interval
Sex		
female	1	
male	1,40	1,16; 1,70
Age		
<40 years	1	
40-49 years	3,12	1,88; 5,17
50-59 years	9,92	6,34; 15,54
60-69 years	13,55	8,55; 21,48
≥70 years	19,53	12,20; 31,26
Non-communicable diseases		
none	1	
diabetes well controlled (HbA1c <7%)	4,65	3,19; 6,79
diabetes poorly controlled (HbA1c 7 - 9%)	8,99	6,65; 12,14
diabetes uncontrolled (HbA1c ≥9%)	13,02	10,06; 16,87
diabetes – no measure of control	3,34	2,39; 4,68
hypertension	1,46	1,18; 1,81
chronic kidney disease	2,02	1,55; 2,62
chronic pulmonary disease	0,98	0,75; 1,30
Tuberculosis		
never tuberculosis	1	
previous tuberculosis	1,41	1,05; 1,90
current tuberculosis	2,58	1,53; 4,37
HIV		
negative	1	
positive	2,75	2,09; 3,61

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Risk factors for hospital mortality in study in New York City

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age (per 10-year increase)	1·49 (1·29–1·73)	1·31 (1·09–1·57)
Male sex	0·85 (0·57–1·27)	1·13 (0·71–1·81)
Symptom duration before hospital presentation (per day)	0·98 (0·93–1·02)	1·01 (0·96–1·05)
Hypertension	2·24 (1·40–3·59)	1·58 (0·89–2·81)
Chronic cardiac disease*	2·21 (1·44–3·39)	1·76 (1·08–2·86)
Chronic obstructive pulmonary disease or interstitial lung disease	3·15 (1·84–5·39)	2·94 (1·48–5·84)
Chronic kidney disease	1·50 (0·92–2·45)	..
Diabetes	1·65 (1·11–2·44)	1·31 (0·81–2·10)
Body-mass index ≥40	0·76 (0·40–1·47)	..
Interleukin-6 (per decile increase)	1·12 (1·04–1·21)	1·11 (1·02–1·20)
D-dimer (per decile increase	1·18 (1·10–1·27)	1·10 (1·01–1·19)

HR=hazard ratio. *Coronary artery disease or congestive heart failure.

Reference: Cummings, Lancet 2020

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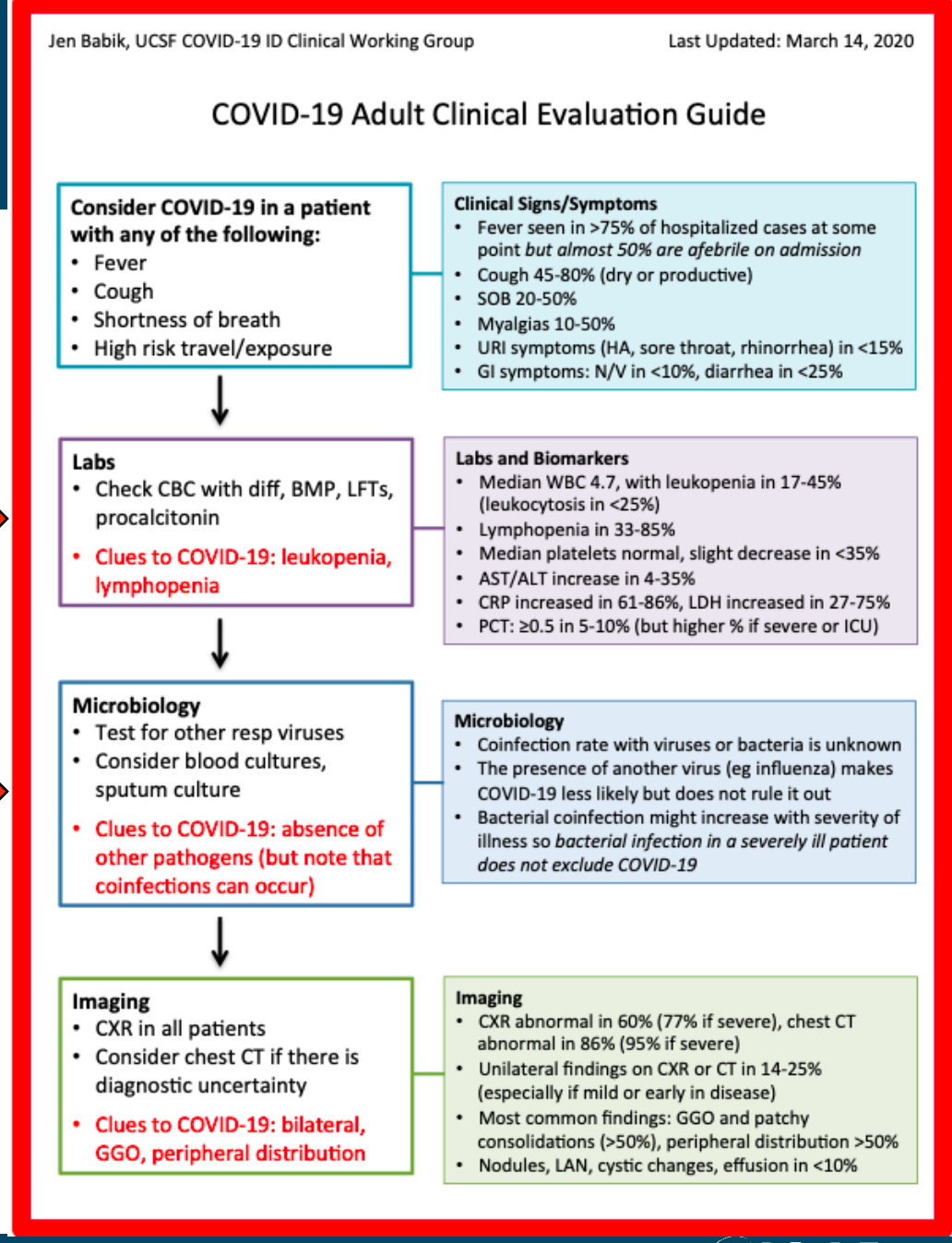
- Rapid COVID-19 test **positive**

74-year-old man: symptoms for 5 days – worsening; hypertension and diabetes
COVID-19 +; lymphopenia, high inflammatory markers and d-dimer

Which of these tests yield significant information regarding his illness? Is additional testing indicated?

Baseline/follow-up laboratory tests

- CBC
- Electrolytes, creatinine
- CRP
- Blood cultures, urinalysis
- Sputum, tracheal aspirate
- Coagulation profile, D-dimer
- *Evaluate for locally endemic infections such as malaria, tuberculosis, dengue, etc.*



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Chest imaging in COVID-19

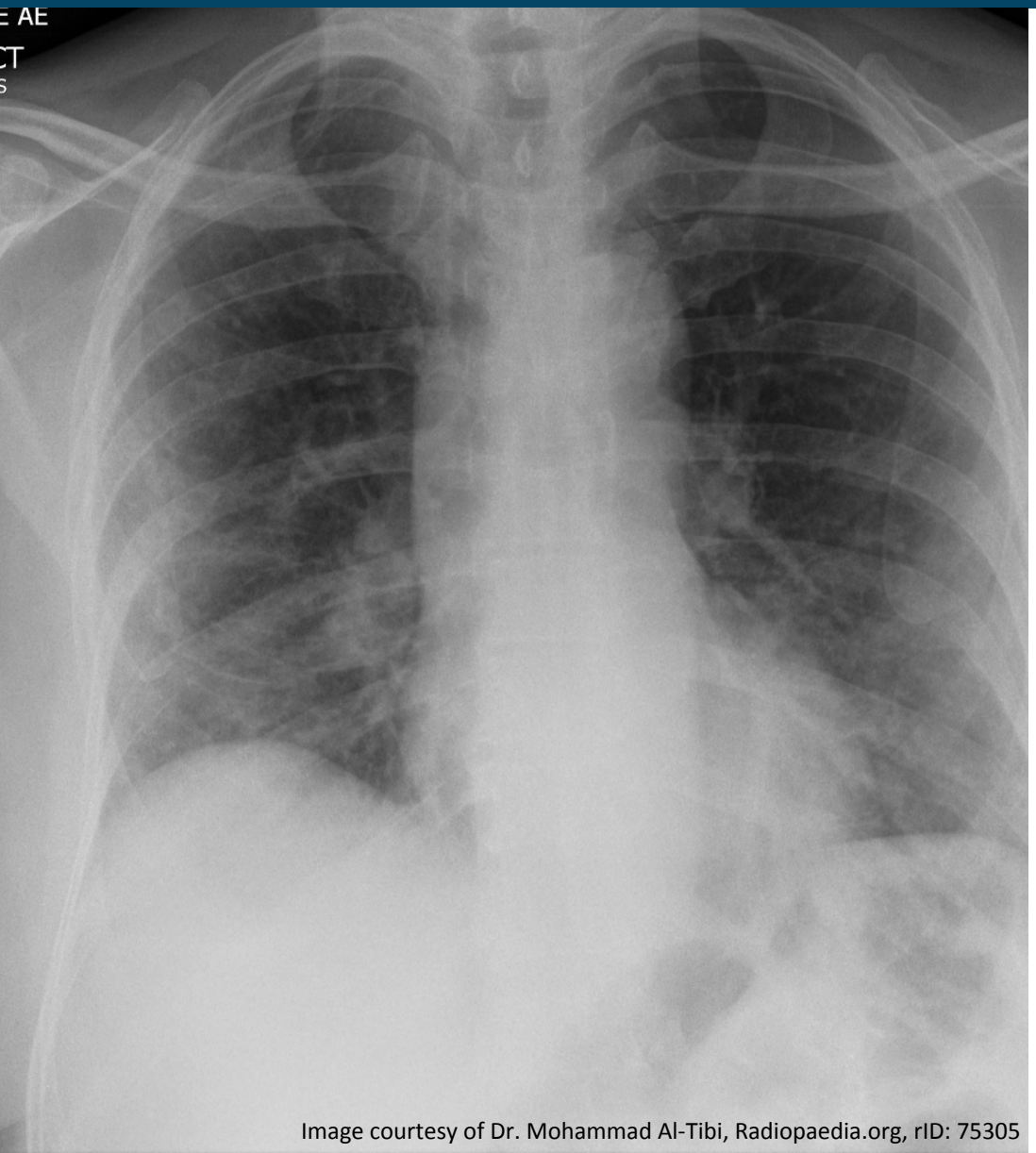
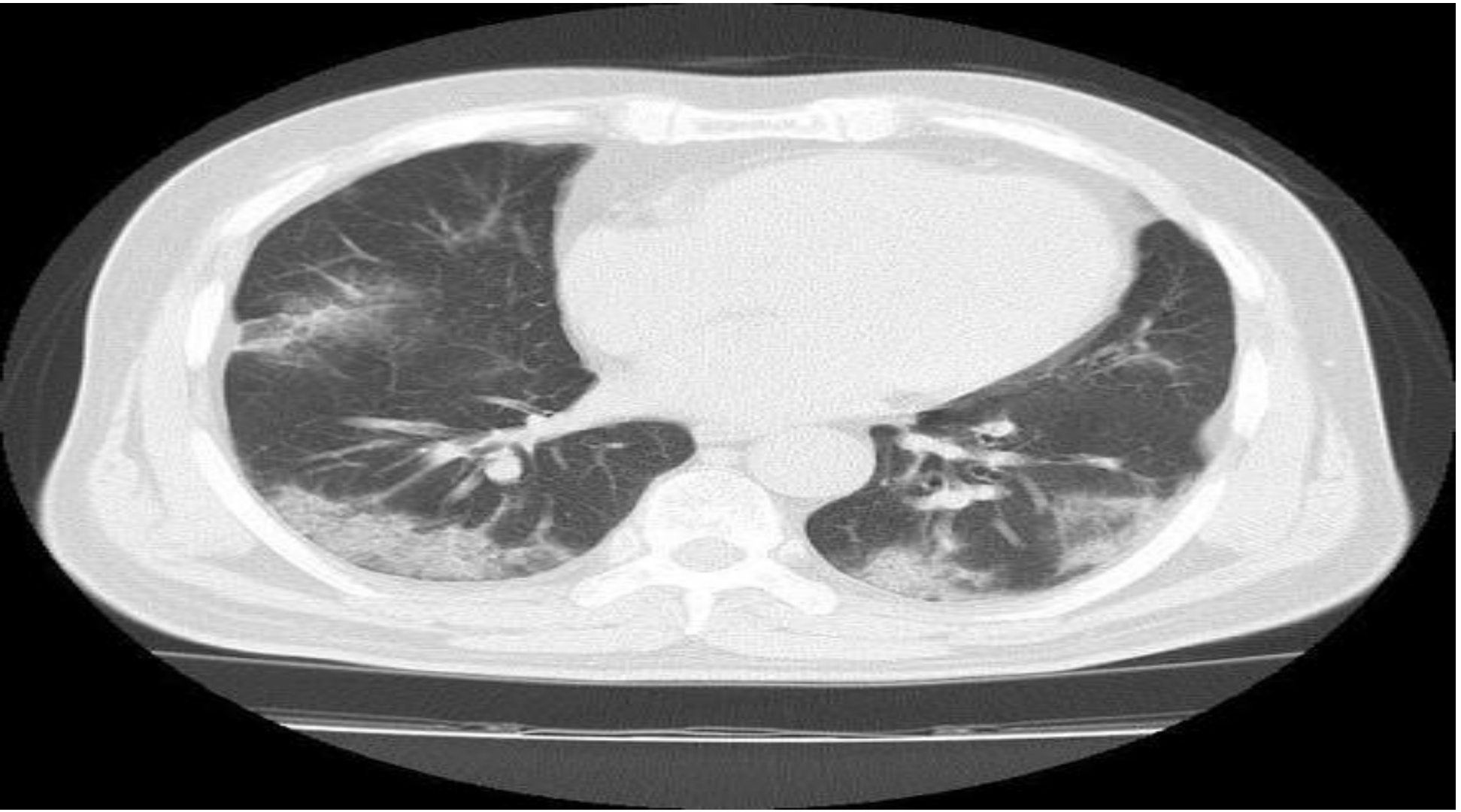


Image courtesy of Dr. Mohammad Al-Tibi, Radiopaedia.org, rID: 75305

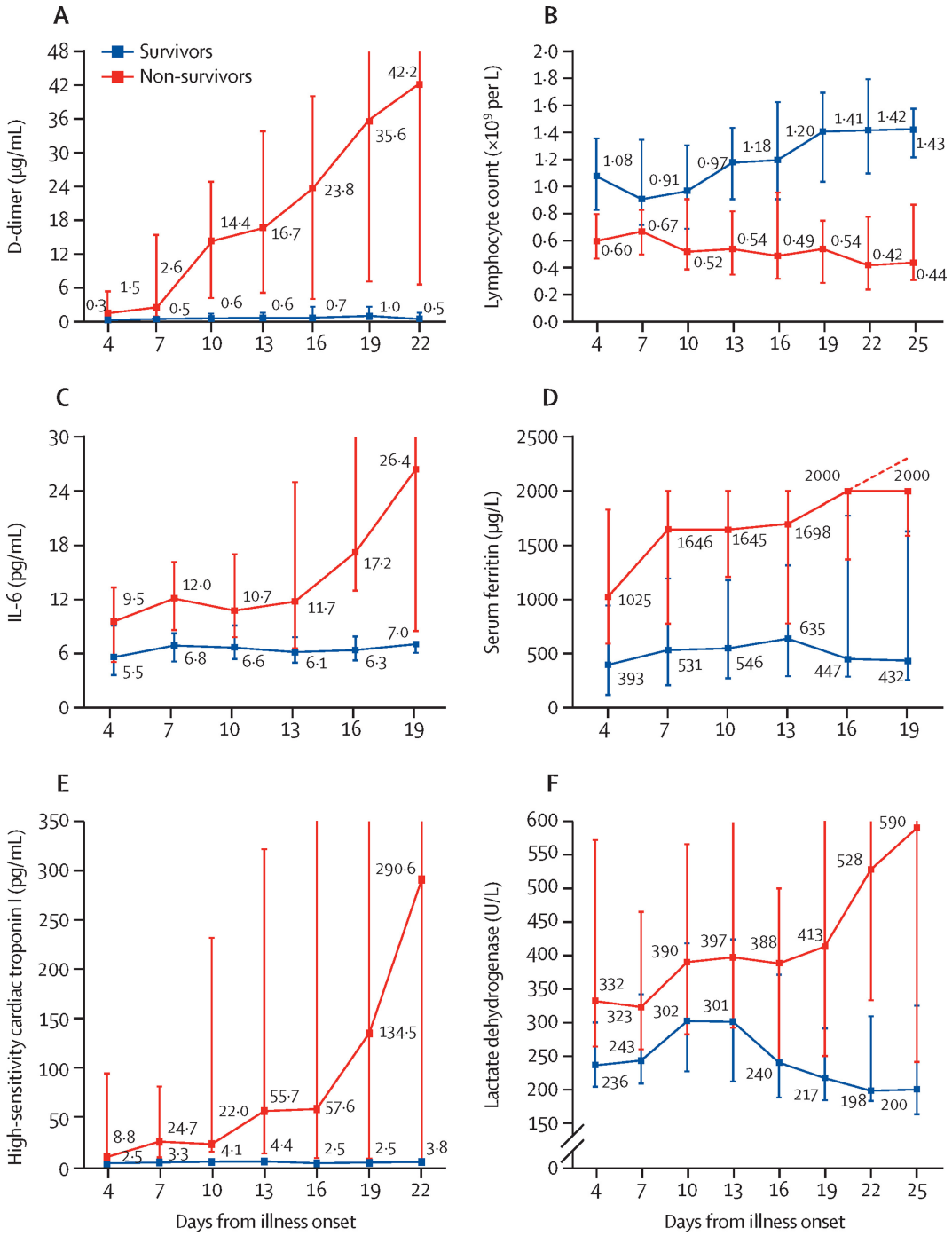
- For patients with suspected or confirmed COVID-19 with moderate to severe symptoms, chest imaging may be helpful in deciding on regular ward admission versus intensive care unit (ICU) admission
  - Imaging is one element of the patient evaluation
  - Patients most likely to benefit are those who are at increased risk of progression or not responding to supportive treatment
- CT is much more sensitive and specific than CXR, but incurs higher costs and exposure to more radiation
- The differential diagnosis and clinical presentation should be considered in decisions about imaging
  - CT angiography for suspect pulmonary embolism (PE)
  - Ultrasound for pleural effusions or assessment of cardiac functioning (not usually helpful in assessing the lungs)

CT scan



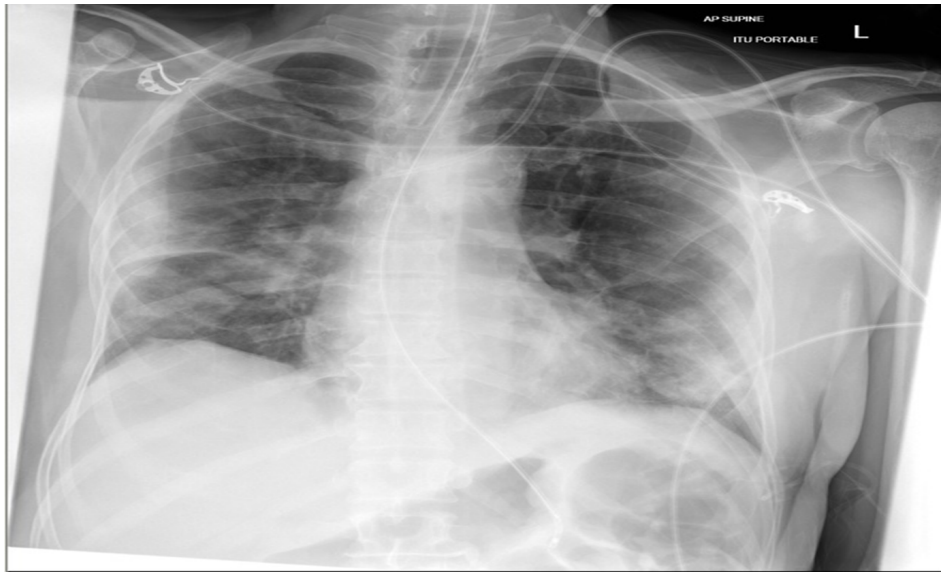
Most common finding: Peripheral ground glass opacities involving multiple lobes and greatest posteriorly

Caruso, 2020; Ai, 2020



Warning signs for severe infection in Patients in China

- Low and declining number of peripheral lymphocytes
- Progressive increase in levels of inflammatory markers (CRP, etc.)
- Progressive increase in lactic acid concentration
- Rapid progression of pulmonary lesions on CXR in short time



Reference: *Zhou et al, Lancet March 2020*

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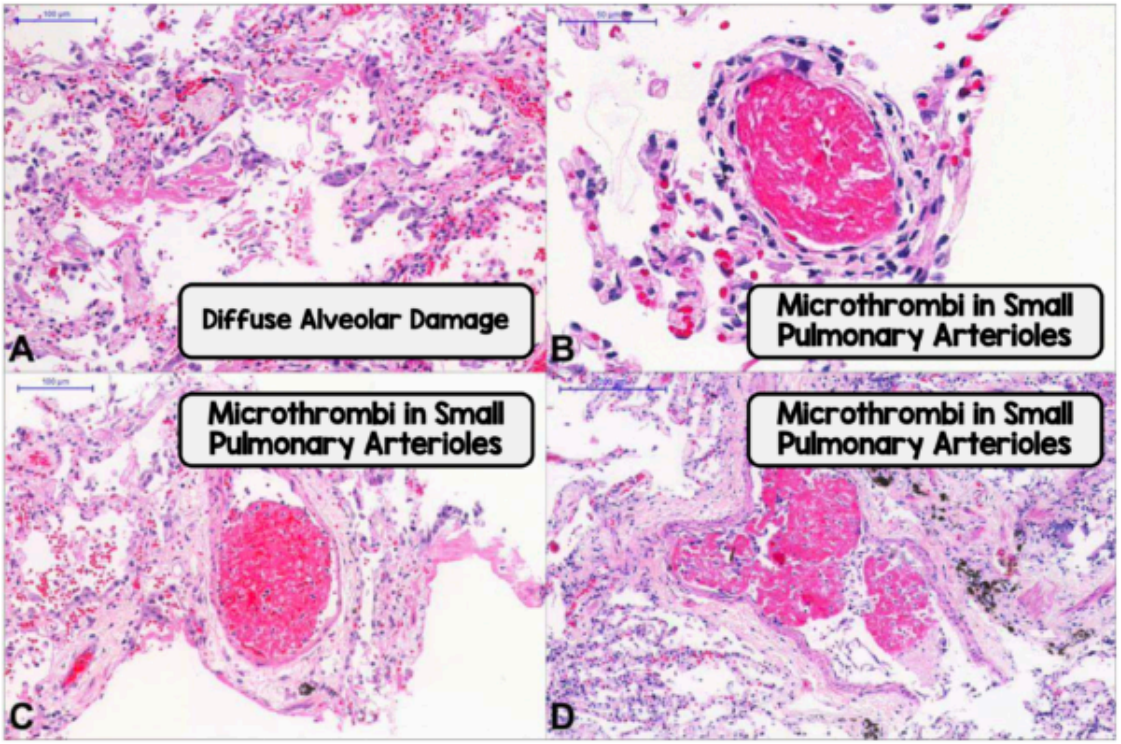
74-year-old man: symptoms for 5 days – worsening; hypertension and diabetes

Consider:

- Why is he hypoxemic?
- How do we treat his hypoxemia?

Pulmonary processes in patients with COVID-19



https://rebelem.com/covid-19-thrombosis-and-hemoglobin/histopathology-of-lungs-in-severe-covid-19/

- Pneumonia
- Thromboembolic disease
- Acute respiratory distress syndrome (ARDS)
- Pulmonary microthrombi/endothelial dysfunction/cytokine storm

*** Autopsy findings among patients who died with severe COVID-19 in Italy revealed diffuse alveolar damage, focal interstitial lymphocytic pneumonia, focal areas of fibrosis, and diffuse thrombotic vascular involvement. Ultrastructural examination revealed particles c/w virions in type 1 and type 2 pneumocytes. The lungs of 4/38 (11%) of patients had bacterial abscesses and one (3%) had a fungal abscess. Carsana, 2020*

Clinical management of severe COVID-19 disease

1. Respiratory management
2. Proning (intubated or non-intubated)
3. Encourage mobility if not intubated
4. General management : antipyretics, conservative fluid management, electrolyte balance and enteral nutrition
5. Venous thromboembolism (VTE) prophylaxis
6. Low dose vasopressor as necessary to support MAP >65 mmHg
7. Avoid benzodiazepines (ICU delirium)
8. Manage acute co-infections
9. Manage concomitant noncommunicable diseases (NCDs)

Respiratory Management: Oxygen Therapy

- All areas where severely or critically ill COVID-19 patients will receive care should be equipped with:
  - Pulse oximeters
  - A functioning oxygen system*
    - Oxygen concentrators are **electrically powered** devices that remove the nitrogen from ambient air, increasing the oxygen concentration (can be done at a large PSA plant or using a portable device at the bedside)
    - Oxygen can also be compressed and stored in cylinders (centrally piped to the patient or from a cylinder at the patient's bedside)
  - Disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask, mask with a reservoir bag)

* WHO: Oxygen sources and distribution for COVID-19 treatment, Interim guidance, April 2020

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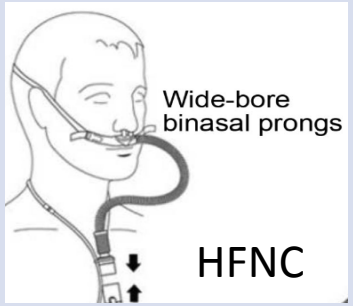
Types of oxygen delivery

Nasal cannula	Simple face mask	Face mask with reservoir bag
FiO_2 estimate 0.25-0.40	FiO_2 estimate 0.60	FiO_2 estimate 0.60-0.95
O_2 dose 1-5 L/min	O_2 dose 6-10 L/min	O_2 dose 10-15 L/min

Image from PIH Guide COVID-19

Supplemental oxygen support

Type	Definition	Action	
Hypoxemia	O_2 saturation < 90% on ambient room air	• Initial oxygen delivery should be humidified nasal cannula (NC) titrated from 1 to 6 L/min to meet goals of therapy	 Nasal cannula/prongs
Refractory hypoxemia	O_2 saturation < 90% on nasal cannula	• Move to a Venturi mask or non-rebreather (NRB) mask • Initiate at 6 L/min and titrate to maximum of 15L/min to meet goals of therapy	 Non-rebreather
Respiratory failure	if O_2 saturation < 90% on NRB mask, significant work of breathing or significant hypercapnia	• Intubation, BiPAP, or high-flow nasal cannula (HFNC) may be warranted	

Oxygen Treatment Goals

- All COVID-19 patients who have emergency signs (respiratory distress, cyanosis, shock, coma, reduced consciousness, convulsions, severe dehydration) and all COVID-19 patients who have SpO_2 < 90% should receive supplemental oxygen
- Initiate oxygen, then check the saturation again by pulse oximeter after just a few minutes
- Titrate the oxygen (increase the flow or change to a mask if still low) to achieve the goal*:
  - SpO_2 > 90% in a stable patient (adult or pediatric)
  - SpO_2 > 94% in an unstable patient (adult or pediatric)
  - SpO_2 92-95% in a pregnant patient
- Monitor oxygen saturation at regular intervals (with the pulse, blood pressure, temperature and respiratory rate).
- Patients who do not meet goals for oxygen saturation or those who continue to show evidence of respiratory distress should be up referred to sites that have capacity to manage critically ill patients

* Oxygen goal may be lower in patients with COPD or other underlying lung disease

* WHO: Oxygen sources and distribution for COVID-19 treatment, Interim guidance, April 2020

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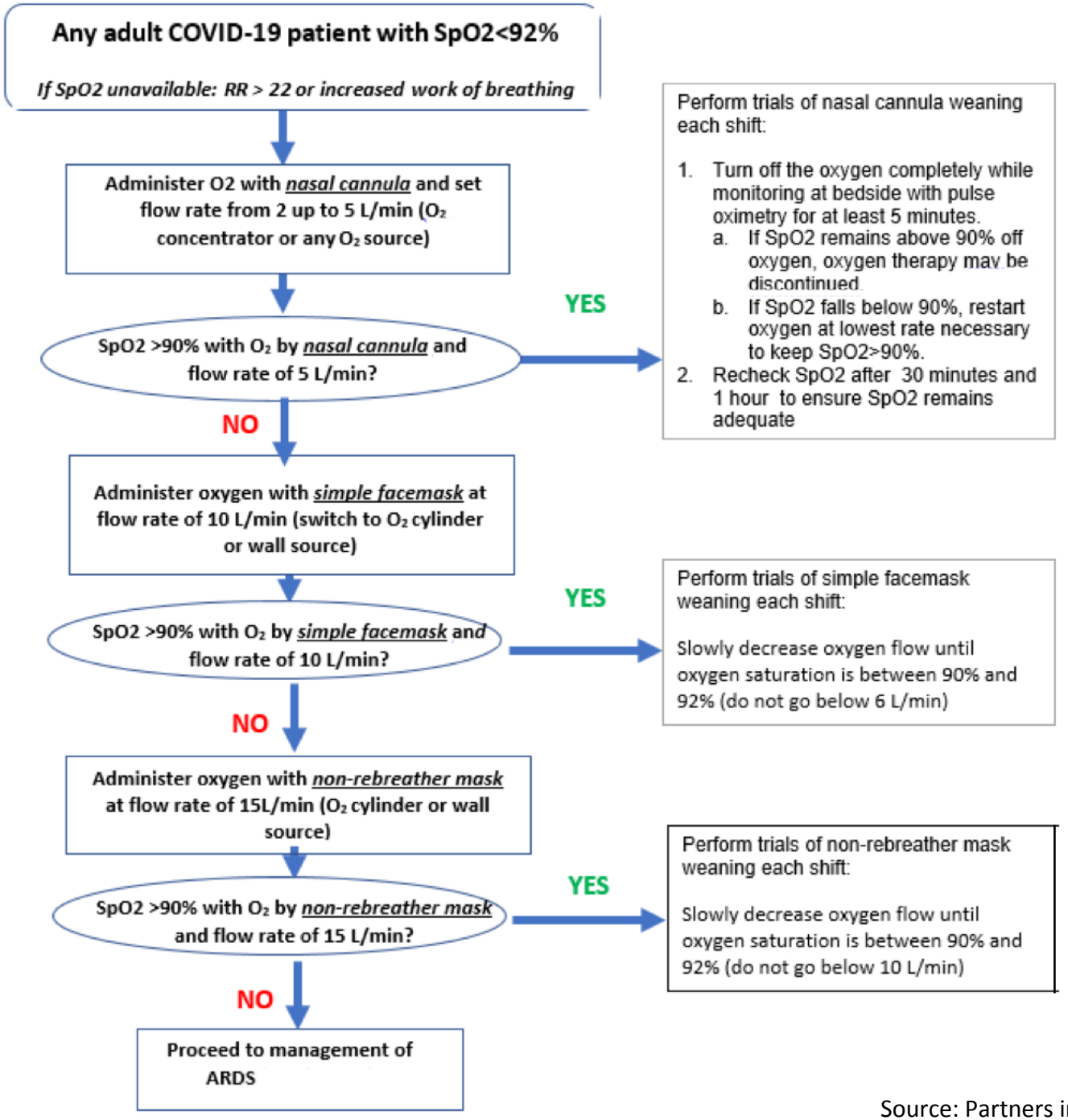
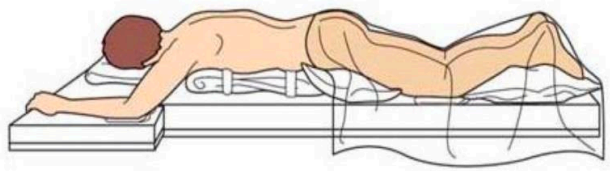
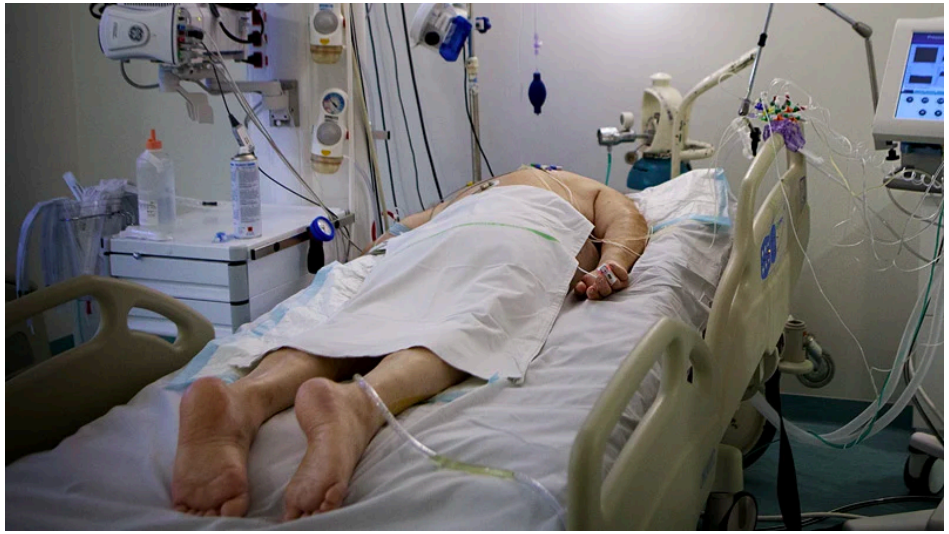


Source: Partners in Health Guide- Clinical Management of COVID

Proning



Prone position



https://www.medscape.com/viewarticle/908549

- Proning refers to the practice of turning a patient into the prone (face down) position
- In ventilated patients in the ICU setting, placement of patient in the prone position [as compared to the supine position] has been demonstrated to improve both oxygenation and survival
- Proning can be used as an addition to a variety of oxygen therapies (NC, face masks, BIPAP, ventilators)

Guérin, et al, 2013; Sun et al, 2020; Caputo et al, 2020

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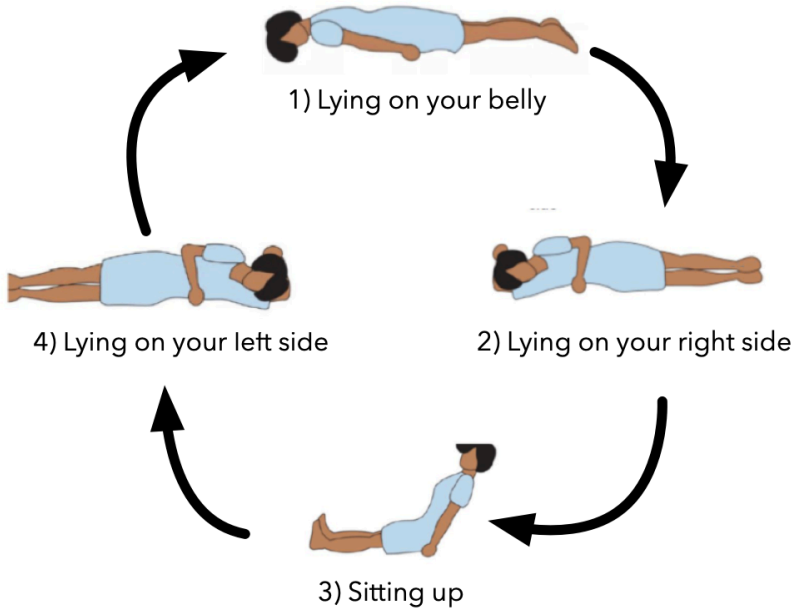
Proning

- Prone positioning of awake COVID-19 patients has now been demonstrated to also improve oxygenation
  - Pronation appears to interrupt basilar atelectasis (allowing collapsed areas of lung to re-expand and contribute to oxygenation)
  - The effect is transient
    - Oxygenation will worsen slowly over several hours if the patient returns to the supine position
    - Cycles of position changes, including sitting upright and proning, should continue
  - Rotating positions also facilitates patient comfort
  - Most awake non-ventilated patients can prone themselves

Patient Instructions: Proning

To improve air entry into the different parts of your lungs,
your healthcare team is recommending you try the following:

Please try each position for 30 minutes to 2hours before moving to the next :



IMPORTANT: If you develop difficulty breathing when you change position - especially when you are on your belly:
1) Roll to your side or back
2) Immediately let your nurse or doctor know so they can assess you.

Source: Columbia University Department of Emergency Medicine, New York Presbyterian & Weill Cornell Medicine, Emergency Medicine

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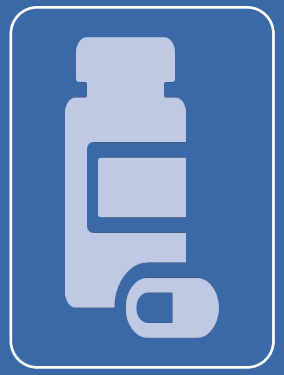
Contraindications for awake proning

- Hemodynamic instability – vasopressors, arrhythmias
- Evidence of acutely/rapidly worsening respiratory distress or fatigue, anticipated need for urgent mechanical ventilation
- SpO_2/FiO_2 <1, RR > 35
- Any mechanical contraindications to prone positioning such as
  - Facial/chest trauma
  - Fractures
- Altered mental status, delirium
- Refusal/inability to comply/collaborate with prone positioning

General Management : antipyretics, fluids, electrolytes and enteral nutrition

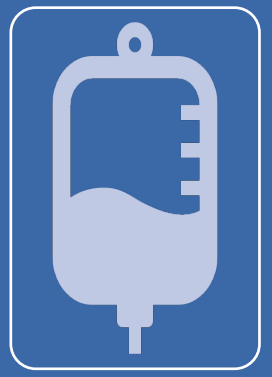


Relieve high fever with acetaminophen

1 Gram Q6H either PO or IV (children 10-15mg/kg/dose Q 6H)

NSAIDS are second line choices due to side their effects

For patients requiring NSAIDs for chronic comorbidities, continue the NSAID



Persons with mild or moderate disease can take oral fluid and food

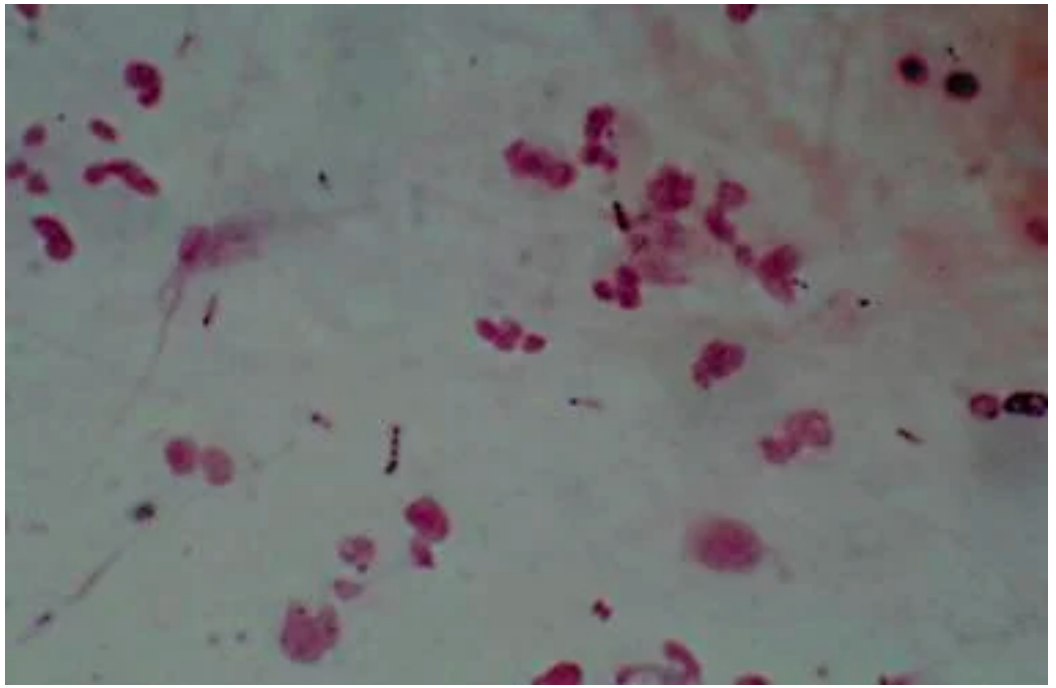
Moderate and severe disease may require IV fluid therapy. Avoid excessive IV fluid as it may worsen pulmonary function.

Pay close attention to electrolytes (K, Mg, Ca) if rehydration is needed

Monitor kidney function [urine output over every eight hours & creatinine daily or as per local guidance] if renal function is abnormal or unstable

Treatment: Acute Co-infections

- Community acquired pneumonia (CAP) is not common in COVID-19 patients
- Antibiotic therapy or prophylaxis is **not** recommended for suspected or confirmed mild/moderate COVID-19

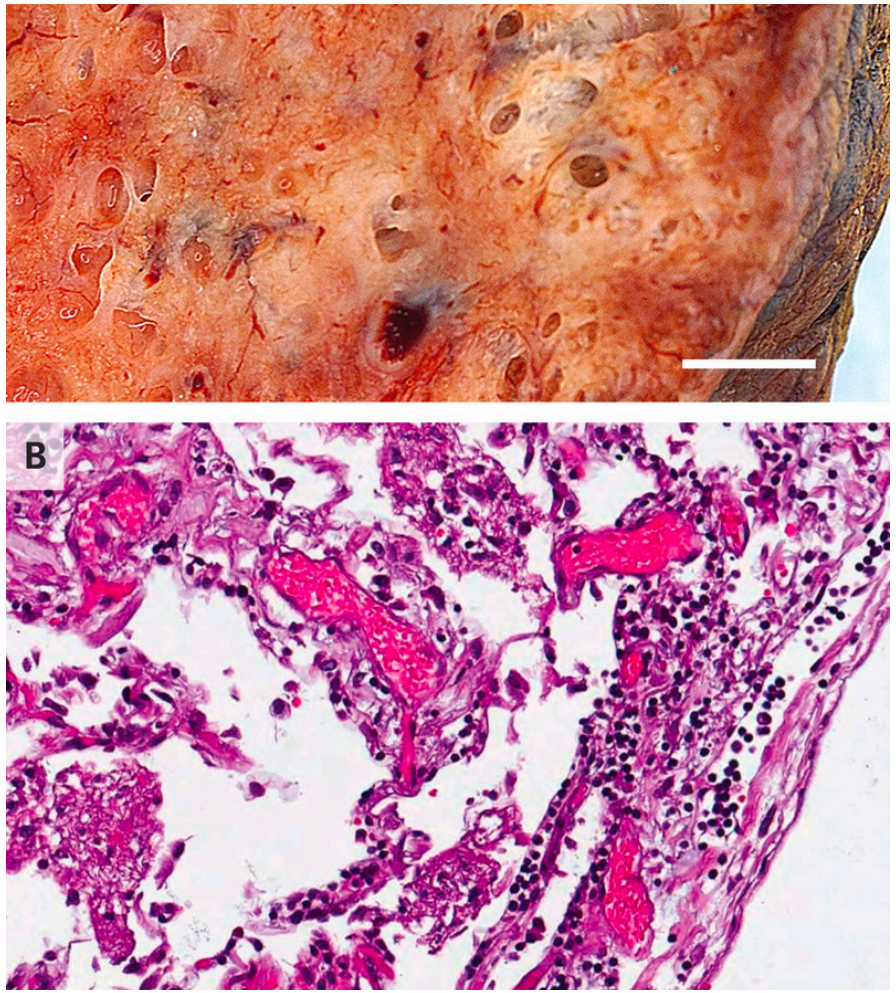


https://emedicine.medscape.com/article/234240-overview

Treatment: Acute Co-infections

- For suspected or confirmed severe COVID-19:
  - Give empiric antimicrobials to treat all likely pathogens, based on clinical judgment, patient host factors, local epidemiology, and national guidelines
  - If there is a suspicion of CAP, follow local guidelines (e.g. augmentin + azithromycin)
  - Administer antibiotics within 1 hour of initial assessment if possible
    - Ideally obtain blood cultures prior to antibiotics
  - Antimicrobial therapy should be assessed daily for de-escalation
  - Duration of empiric antibiotic treatment should be as short as possible
- Treatment of other co-infections is based on a laboratory-confirmed diagnosis, epidemiological criteria, and national guidelines
  - Consider other chest infections (e.g. TB, PCP) and other endemic infections (e.g. malaria, dengue)

Venous thromboembolism (VTE) prophylaxis



Lymphocytic Inflammation in a Lung from a Patient Who Died from Covid-19. Ackerman, NEJM 2020
https://www.nejm.org/doi/full/10.1056/NEJMoa2015432

- COVID-19 patients seem to be at increased risk of deep venous thromboembolism (DVT)
- They are immobile, hypercoagulable, and the SARs-CoV-2 virus appears to cause endothelial damage
- They are at risk of both large clots and disseminated intravascular coagulation (DIC)
- Encourage mobility if not bed-bound
- Follow local guidelines for deep vein thrombosis (DVT) prevention
  - May include low molecular weight heparin or pneumatic compression devices
- Full anticoagulation is often considered in those with D-dimer >3 mcg/ml and platelets >50, Hb>8 g/dL and no evidence of bleeding

NIH COVID-19 Treatment Guidelines Recommendation: Antithrombotic Therapy

- Monitoring
  - Data are insufficient to recommend for or against routine screening for DVT or routine monitoring of coagulation parameters in COVID-19 patients
- Prophylaxis
  - COVID-19 patients who are receiving anticoagulant or antiplatelet therapies for other underlying conditions should continue their prior medications
  - Patients hospitalized with COVID-19 should receive VTE prophylaxis per the standard of care

NIH COVID-19 Treatment Guidelines Recommendation: Antithrombotic Therapy

- Evaluation
  - For hospitalized COVID-19 patients, the possibility of thromboembolic disease should be evaluated in patients who suffer rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion
- Treatment
  - Treat with therapeutic doses of anticoagulant as per local guidelines for patients without COVID-19

Management of severe COVID-19: other considerations

- Use of medical early warning scores that facilitate early recognition and escalation of treatment of the deteriorating patient have been used for other conditions, but not yet validated for COVID-19
    - NEWS2: https://www.mdcalc.com/national-early-warning-score-news-2
    - PEWS: https://www.mdcalc.com/pediatric-early-warning-score-pews
    - SOFA (Sequential Organ Failure Assessment)
- These scoring systems were developed to improve the assessment of acute-illness severity of patients in hospital and pre-hospital settings
- Patients with COVID-19 may deteriorate with unusual rapidity

Back to our patient…..

Interventions

- Patient was moved to the COVID-19 isolation unit
- An IV was placed and the patient received a gentle bolus of fluids (250 mL Ringer's lactate over 30 minutes) followed by maintenance fluid
- Oxygen via nasal cannula was begun at 2 mL/min then rapidly increased to 6 mL/min
- Prone positioning every 4 hours as tolerated
- Acetaminophen every 6 hours for fever
- Amoxicillin/clavulanic acid given for possible community acquired pneumonia
- Tests for HIV, TB, and malaria were negative
- Low molecular weight heparin was begun for DVT prophylaxis
- Metformin and enalapril continued

74-year-old man
Symptoms for 5 days - worsening
Hypertension and diabetes

Are there any more specific treatments for COVID-19?

Medications

Many medications have shown some activity against SAR-COV-2 in the laboratory, but most have been disappointing in clinical studies. This presentation will focus on treatments that have been demonstrated to have some efficacy including:

- Anti-inflammatory agents
  - Steroids
- Antiviral medications:
  - Antivirals (e.g. remdesivir or favipravir)
- Antibodies
  - Convalescent plasma (single donor vs pooled hyperimmune globulin)

Randomized **E**valuation of **C**OVid-19 th**ERapY** (RECOVERY) Trial Among Hospitalized Patients

- Patients randomized to SOC plus: no additional treatment, **lopinavir/ritonavir, dexamethasone, hydroxychloroquine (HCQ), or azithromycin**
  - Factorial design with simultaneous allocation to no additional tx vs **convalescent plasma**
  - If progressive disease (hyper-inflammatory state), subsequent randomization to no additional treatment vs **tocilizumab**
- > 11,500 patients enrolled from > 175 NHS hospitals in UK

- **6/5/2020**: statement on closure of recruitment to HCQ arm for lack of clinical benefit
  - 28-day mortality: 25.7% with HCQ + SOC (n = 1542) vs 23.5% with SOC alone (n = 3132) (RR: 1.11; 95% CI: 0.98-1.26; *P* = .10)
- **6/8/2020:** recruitment to dexamethasone arm halted because sufficient patient numbers enrolled to establish potential benefit

https://www.recoverytrial.net. https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf. https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_final.pdf.

Slide credit: clinicaloptions.com

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RECOVERY Trial: Partial Dexamethasone Results Reported by Press Release

- Data suggest 1 death prevented by treatment of ~ 8 ventilated patients or ~ 25 patients requiring oxygen alone

Outcome, %	Dexamethasone 6 mg QD PO or IV + SOC for 10 D (n = 2104)	SOC Only (n = 4321)	RR for Death With Dex + SOC vs SOC Alone (95% CI)	P Value
28-day mortality				
▪ Patients requiring ventilation	NR	41	0.65 (0.48-0.88)	.0003
▪ Patients requiring oxygen only	NR	25	0.80 (0.67-0.96)	.0021
▪ Patients requiring no respiratory intervention	NR	13	1.22 (0.86-1.75)	.14

https://www.recoverytrial.net. https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_final.pdf.

Slide credit: clinicaloptions.com

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Steroids for COVID-19

- Based on RECOVERY TRIAL preliminary results, the NIH now recommends using dexamethasone (6mg per day for up to 10 days) in patients requiring supplemental oxygen and/or who are mechanically ventilated.
- The NIH recommends against using dexamethasone in patients not requiring supplemental oxygen
  - https://www.covid19treatmentguidelines.nih.gov/dexamethasone/
- Potential harms of steroids
  - Patients receiving a short course of steroids may experience hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of bacterial and fungal infection
  - www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5

The immune pathogenesis of COVID-19: Hamid Bassiri MD PhD 20200423

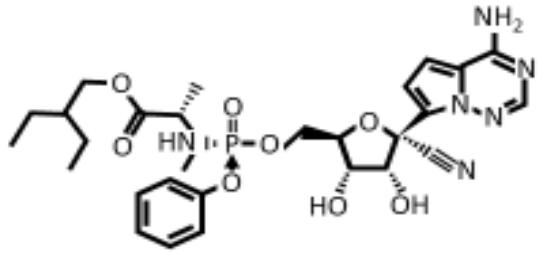
Remdesivir

FDA Emergency Use Authorization of Remdesivir for Severe COVID-19

- Remdesivir is a nucleoside analogue of ATP that inhibits SARS-CoV-2 RNA polymerase by competing with ATP for inclusion into nascent RNA→ delayed chain termination during viral RNA replication

The FDA Emergency Use Authorization (EUA)

"...permits the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO_2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO)"

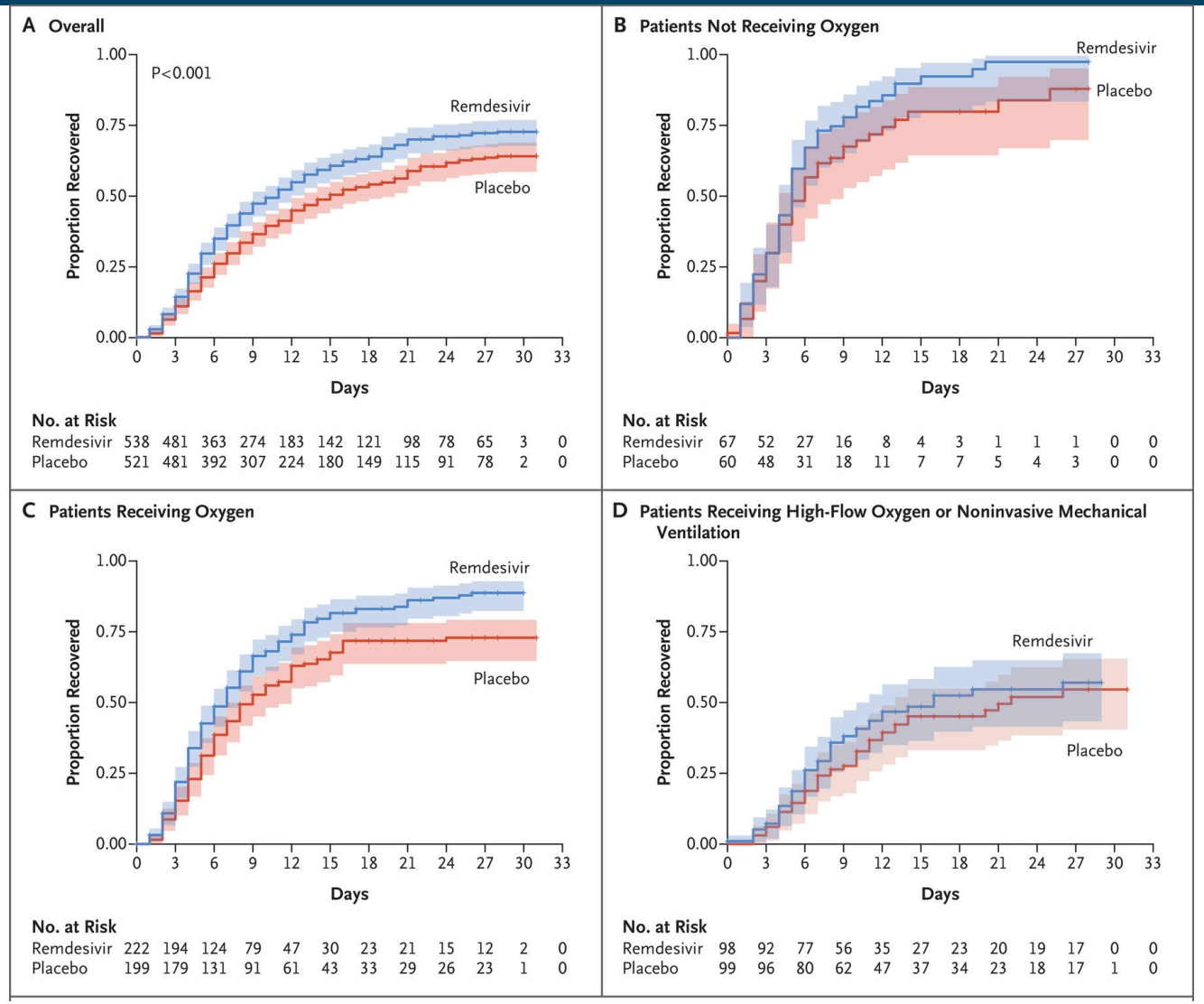


Remdesivir EUA Provider Fact Sheet.

Slide credit: clinicaloptions.com

Adaptive Covid-19 Treatment Trial (ACTT-1)

- Multicenter double-blind, randomized, placebo-controlled trial of IV remdesivir
- Enrolled and randomized 1063 people hospitalized with COVID-19 pneumonia
- Study halted when a preliminary analysis demonstrated a significant reduction in time to recovery (11 days vs. 15 days)
- There was a trend toward better survival (7.1% vs. 11.9% mortality) but the study was stopped prior to reaching statistical significance



Grein, et al 2020; Beigel, et al 2020

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Remdesivir: Global Perspectives

- Japanese Ministry of Health, Labour and Welfare approved remdesivir as a treatment for SARS-CoV-2 infection, referencing the United States' FDA EUA[1,2]
- The EMA human medicines committee has recommended expanding the compassionate use recommendations for remdesivir to treat patients with COVID-19 in Europe[3]
  - In addition to treatment of patients undergoing mechanical ventilation, the recommendation now includes treatment of hospitalized patients requiring supplemental oxygen, noninvasive ventilation, high-flow oxygen devices, or ECMO

in-japan-for-patients-with-severe-covid19. 2. Remdesivir EUA Provider Fact Sheet. 3. EMA Summary of Compassionate Use: Remdesivir.

FDA EUA for Remdesivir: Treatment Initiation and Dosing Regimens

- Treatment of hospitalized patients with suspected COVID-19 can be considered pending laboratory confirmation of SARS-CoV-2
- Treatment can be started any time after symptom onset
- All patients must have eGFR and hepatic laboratory testing prior to start

IV Dosage Over 30-120 Mins	Patients Requiring Invasive Mechanical Ventilation and/or ECMO	Patients Not Requiring Invasive Mechanical Ventilation and/or ECMO
Adults and pediatric patients ≥ 40 kg		
▪ Loading	200 mg on Day 1	200 mg on Day 1
▪ Maintenance	100 mg on Days 2-10	100 mg on Days 2-5*
Pediatric patients between 3.5 kg and 40 kg†		
▪ Loading	5 mg/kg on Day 1	5 mg/kg on Day 1
▪ Maintenance	2.5 mg/kg on Days 2-10	2.5 mg/kg on Days 2-5*

*Treatment maybe increased to 10 days in patients not demonstrating clinical improvement at Day 5 of treatment.
†Use remdesivir for injection, 100 mg, lyophilized powder only.

Remdesivir EUA Provider Fact Sheet.

Slide credit: clinicaloptions.com

FDA EUA for Remdesivir: Safety Information and Warnings

"There are limited clinical data available for remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with remdesivir use."

Adverse Events,* %	Remdesivir 5 Days (n = 200)	Remdesivir 10 Days (n = 197)
Any	71	74
Serious	21	35
Grade ≥ 3	31	43
Discontinued due to AE	5	10
All-cause mortality at Day 28	10	13

*Reported for open-label study GS-US-540-5773.

- Recommended daily monitoring: serum chemistries, hematology, ALT, AST, renal function tests, bilirubin, alkaline phosphatase (ALP)
- Infusion-related reactions have occurred in patients receiving remdesivir; immediately discontinue if signs of clinically significant infusion reaction occur
- Transaminase elevations have occurred in healthy controls and patients with COVID-19 receiving remdesivir
  - Do not administer if ALT ≥ 5 x ULN at baseline
  - Discontinue if ALT ≥ 5 x ULN; resume treatment when ALT elevation resolves

Remdesivir EUA Provider Fact Sheet.

Slide credit: clinicaloptions.com

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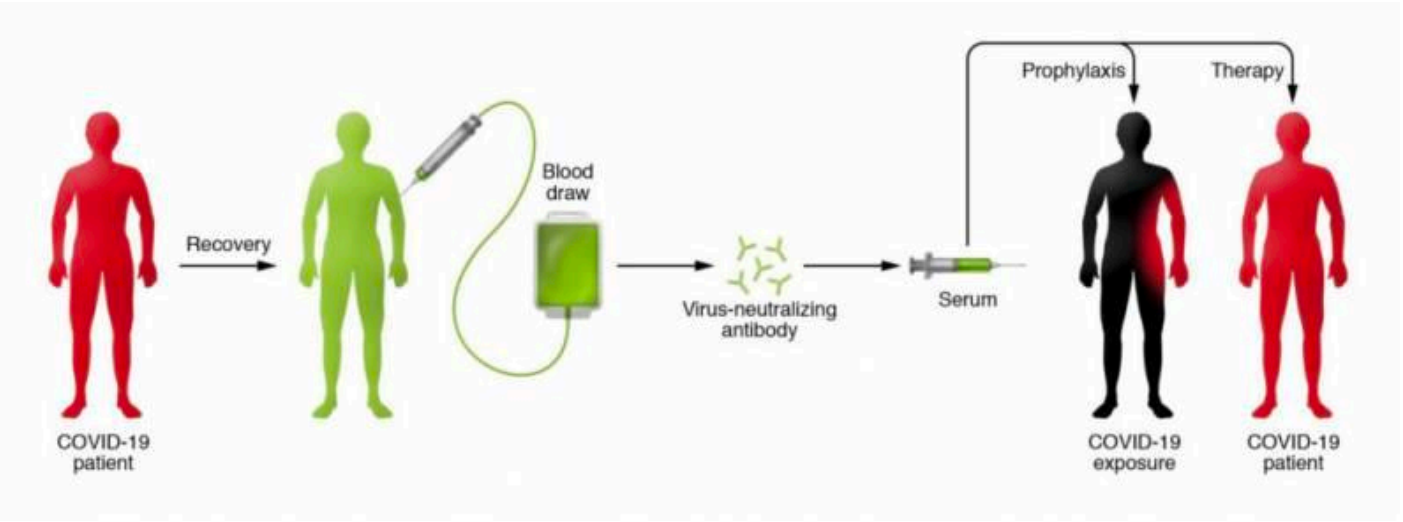
Favipravir

- Approved as a treatment for novel strains (H1N1) of influenza in Japan
- It is an oral medication
- Studies have involved relatively small groups of patients with mild to moderate COVID-19
- Study endpoints: treatment leads to faster resolution of fever, more rapid clearance of virus, and faster improvement in CXRs of patients who have COVID-19 pneumonia
- Approved for mild to moderate COVID-19 in China, India, and received a temporary registration certificate in Russia
- Also has in-vitro activity against many of the hemorrhagic fever viruses, flaviviruses (Yellow Fever and West Nile), RSV, Rabies, Ebola, Noroviruses and others

Use of convalescent plasma (CP)

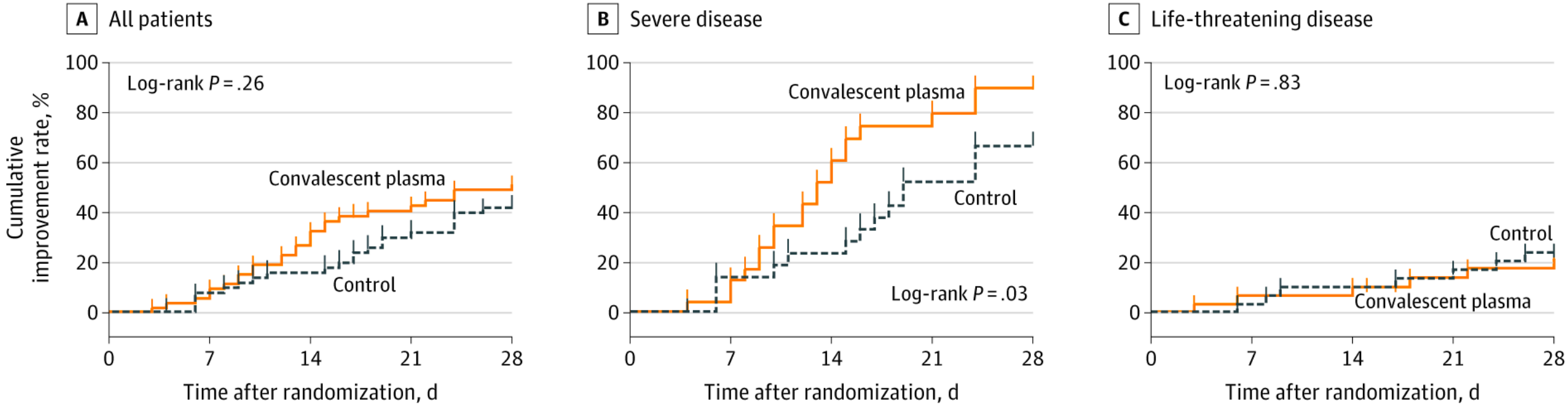


- CP has been used in a number of viral infections (e.g. H1N1, Polio, SARS-CoV-1, MERS, etc.)
- CP is thought to be most effective when used early in infection
- SARS-CoV-1 case series suggested possible benefit for some patients
- CP has been widely used on a compassionate use basis
- a number of small case series have been published

The immune pathogenesis of COVID-19: Hamid Bassiri MD PhD 20200423

Convalescent Plasma in severe and life-threatening COVID-19

- A recent randomized clinical trial of CP performed in 7 medical centers in Wuhan, China was terminated early as the epidemic waned
- Enrolled subjects with severe or critical COVID-19 (52 received CP and 51 were controls)



No. at risk															
Control	51	46	42	35	29	22	18	16	10	7	29	28	26	25	22
Convalescent plasma	52	49	38	28	24	23	22	11	5	2	29	27	27	23	22

*differences not statistically significant

Li L, et al, JAMA, June 2020

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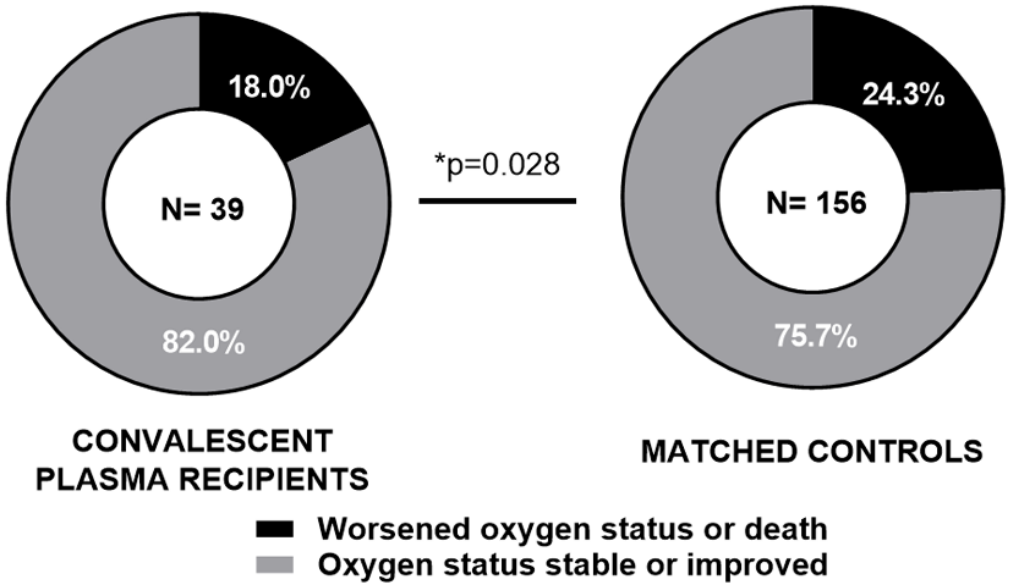
Convalescent Plasma of severe COVID-19: A matched control study

Mt. Sinai Medical Center, New York City

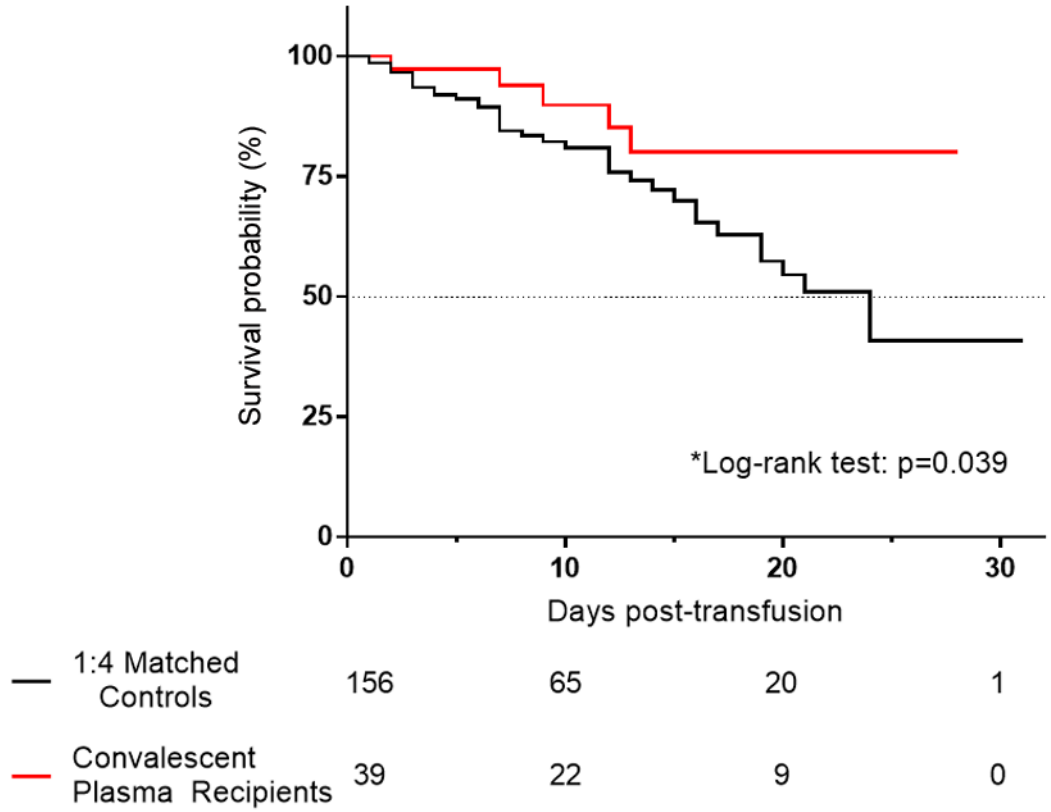
CP treated patients were propensity matched to other patients with COVID-19 in the same centers during the same time

CP was associated with improved survival only among non-intubated patients

Figure 1. Comparison of oxygen requirements between Day 14 versus Day 0.



*** Covariates adjusted. No significant differences were observed at day 1 (p=0.444) or day 7 (p=0.425).**



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Clinical management of severe COVID-19 disease

1. Respiratory management
2. Proning (intubated or non-intubated)
3. Encourage mobility if not intubated
4. General management : antipyretics, conservative fluid management, electrolyte balance and enteral nutrition
5. Venous thromboembolism (VTE) prophylaxis
6. Low dose vasopressor as necessary to support MAP >65 mmHg
7. Avoid benzodiazepines (ICU delirium)
8. Manage acute co-infections
9. **Manage concomitant noncommunicable diseases (NCDs)**

Back to our patient – Day 2 in hospital [Day 7 of illness]

Continuing Care

- Acetaminophen, amoxicillin-clavulanic acid, metformin, enalapril, and low molecular weight heparin were continued
- Received minimal IV fluid, but was able to drink liquids and eat small amounts
- Urine output was adequate, and BP remained around 110/80
- Oxygen therapy was escalated to a face mask at 10 mL/min in order to maintain SpO_2 > 90%
- After some debate, his clinicians gave him a bolus of dexamethasone 6 mg [to be continued daily]

During the evening hours he was reassessed because his oxygen saturation continued to drop. He was changed to a nonbreather mask with oxygen at 15 mL/min. His SpO_2 came up to 90%. He was cooperative and in no distress. His vitals were stable but his fingerstick glucose reached 390 mg/dL.

Recall: 74-year-old man

- Hypertension and diabetes
- Symptoms worsening

What are your next steps?

Management of concomitant NCDs

- Continue or modify previous medical therapy for COVID-19 patients with pre-existing NCDs based on:
  - Cardiovascular disease
  - Diabetes
  - Chronic respiratory disease
  - Hypertension
  - Cancer
- Antihypertensive drugs should not routinely be stopped in patients with COVID-19
- Adjust therapy based on general considerations for patients with acute illness
  - Maintain normal blood pressure and renal function
- For people living with HIV already on treatment, continuity of antiretroviral therapy and prophylaxis for co-infections is essential

Other considerations for our patient….

- This patient presented with severe COVID-19
- He has risk factors for critical illness and mortality
- He is entering the second week of illness, a time when people often worsen rapidly
- Reconsider whether the COVID-19 isolation unit is the best place for his continued care
- This decision must be made in the context of local resources and guidelines
  - Is BiPAP or HFNC (high flow nasal oxygen) available?
  - Can he be intubated and receive ventilatory support here?
- If transfer is planned, it should happen as soon as possible

Advanced Learner Clinical Scenarios

Back to our patient – Day 4 in hospital [Day 9 of illness]

Continuing Care

- Acetaminophen, amoxicillin clavulanic acid, metformin, dexamethasone, and low molecular weight heparin were continued
- Enalapril dose was decreased
- Insulin was given, based on fingerstick glucose values
- Received minimal IV fluid, but was able to drink liquids and eat small amounts
- Urine output was adequate and BP remained around 110/80
- Oxygen therapy on non-rebreather mask at 15 mL/min maintained SpO_2 ~ 90%
- He has been repositioning and proning as instructed

During the evening hours he was reassessed because his oxygen dropped precipitously to 85%. He was irritable and a bit confused. He complained of chest pain, but was also talking about snakes and guns (neither of which were present).

Recall: 74-year-old man

- Symptoms for 5 days – worsening
- Hypertension and diabetes
- On steroids for 2 days

What might be causing his worsened condition?

Thoughts and considerations regarding our patient…..

- Chest pain – might be due to cardiac ischemia, pulmonary embolus, musculoskeletal pain from the work of breathing
- Worsening oxygenation – might be due to progression of COVID-19 (possible development of ARDS), pulmonary embolus, superimposed infection (TB, bacterial infection)
- Confusion – might be due to hypoxemia, “steroid-induced psychosis”, delirium (related to age, hospitalization, sleep deprivation), neurologic manifestations of COVID-19

Management of neurological and mental manifestations associated with COVID-19

- Delirium
  - Common in critically ill COVID-19 patients, especially the elderly but can also be seen in young patients
  - Patients should be evaluated using standardized protocols, aimed at the prevention of and/or early recognition of delirium
  - If detected, immediate evaluation by a clinician is recommended to address any underlying cause of delirium and treat appropriately
  - Avoid benzodiazepines, facilitate normal sleep/wake cycles, reassure and reorient confused patients

Management of mental health manifestations of COVID-19

- Mental health and psychosocial support
  - Provide basic mental health and psychosocial support for all persons with suspected or confirmed COVID-19 by asking them about their needs and concerns, and addressing them
  - Assess for anxiety and depressive symptoms
    - Promptly initiate psychosocial support and first-line intervention if present
  - Psychosocial support strategies should be the first-line intervention for management of sleep problems for acute stress

Cardiovascular complications of COVID-19

Pathophysiology:

i. SARS-CoV-2 invades cardiac myocytes and endothelial cells

ii. Systemic cytokine storm causing a cardiomyopathy

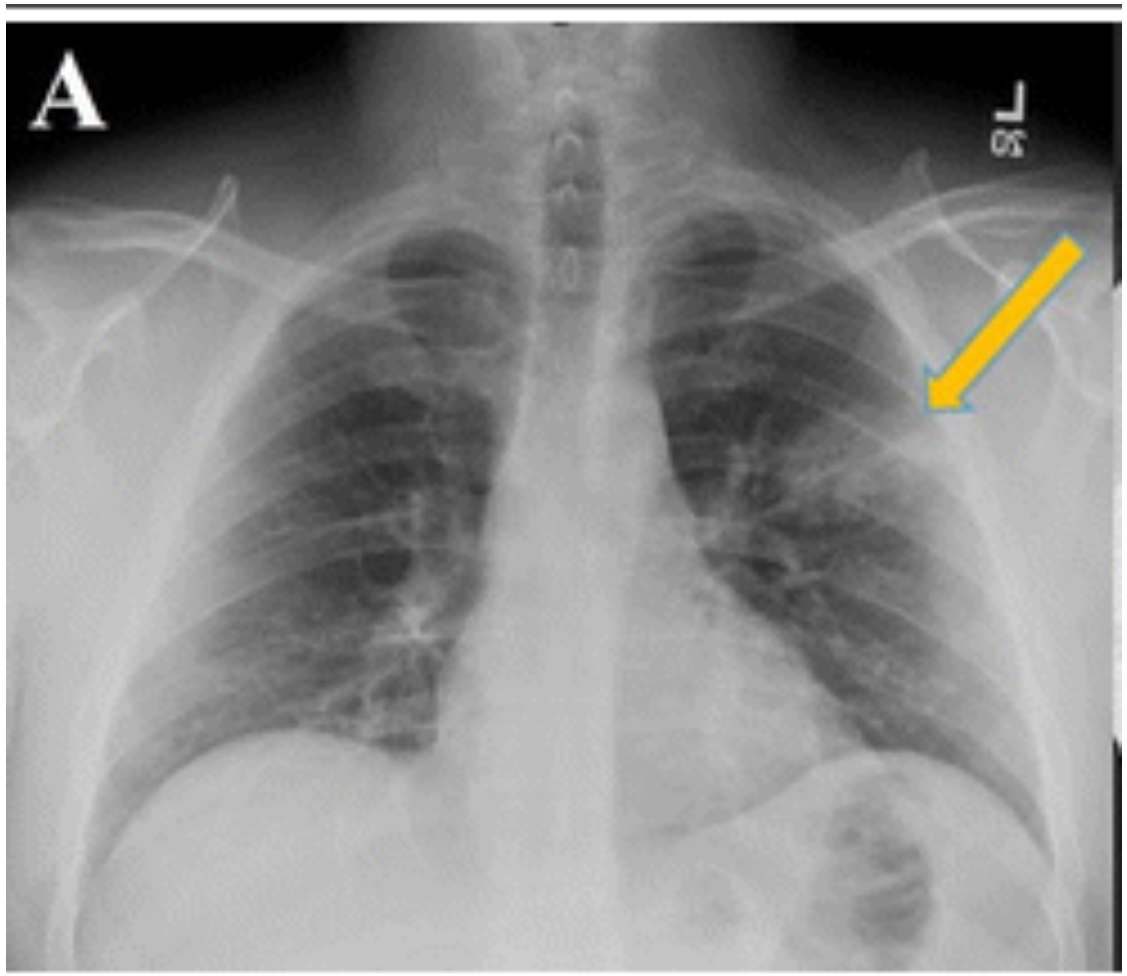
CV complications include:

- cardiomyopathy/cardiogenic shock
- acute myocardial infarction
- myocarditis
- arrhythmias
- thromboembolic disease

Management:

1. Rule out septic shock
2. Correct electrolyte imbalance (K, Mg, Ca)
3. Inotropic support to maintain MAP>65 mm
4. Anticoagulation if D-dimer >3 mcg/ml

Clinical Case Day 5 in hospital [Day 10 of illness]



X-ray courtesy of Whitney J. Palmer

- Exam
  - Vitals: Temp 38^{0}C, RR 35, P 140, BP 90/65, O2 Sat 85% on nonbreather mask at 15 mL/min
  - Mucous membranes dry
  - CVS: tachycardia
  - Chest: coarse crackles in both lung fields
  - Abdomen: soft, nontender
  - CNS: irritable, confused
- Labs
  - WBC 3 [85 % N 15% L], Plts 110,
  - CRP 12mg/L; D-Dimer 3.5 mg/L; LDH 1100 U/L
  - Troponin 50 ng/mL; ferritin 1000 mg/L
  - Chemistry normal except for glucose 250mg/dL

Day 5 in hospital [Day 10 of illness]

Continuing Care

- Acetaminophen, metformin, dexamethasone, and low molecular weight heparin were continued.
- Minimal insulin was needed and enalapril was discontinued
- His antibiotics were escalated to ceftriaxone because of the focal infiltrate and worsening oxygenation
- He received minimal IV fluid, but drank liquids and ate small amounts
- Urine output was adequate, and BP remained around 100/60
- Oxygen was via non-rebreather mask at 15 mL/min with SpO_2 85-88%
- Patient remained confused and complained of chest pain and snakes in his bed
- A venous doppler revealed extensive clot in the right iliac vessels

What is the diagnosis? What symptoms does it explain? How will you manage this?

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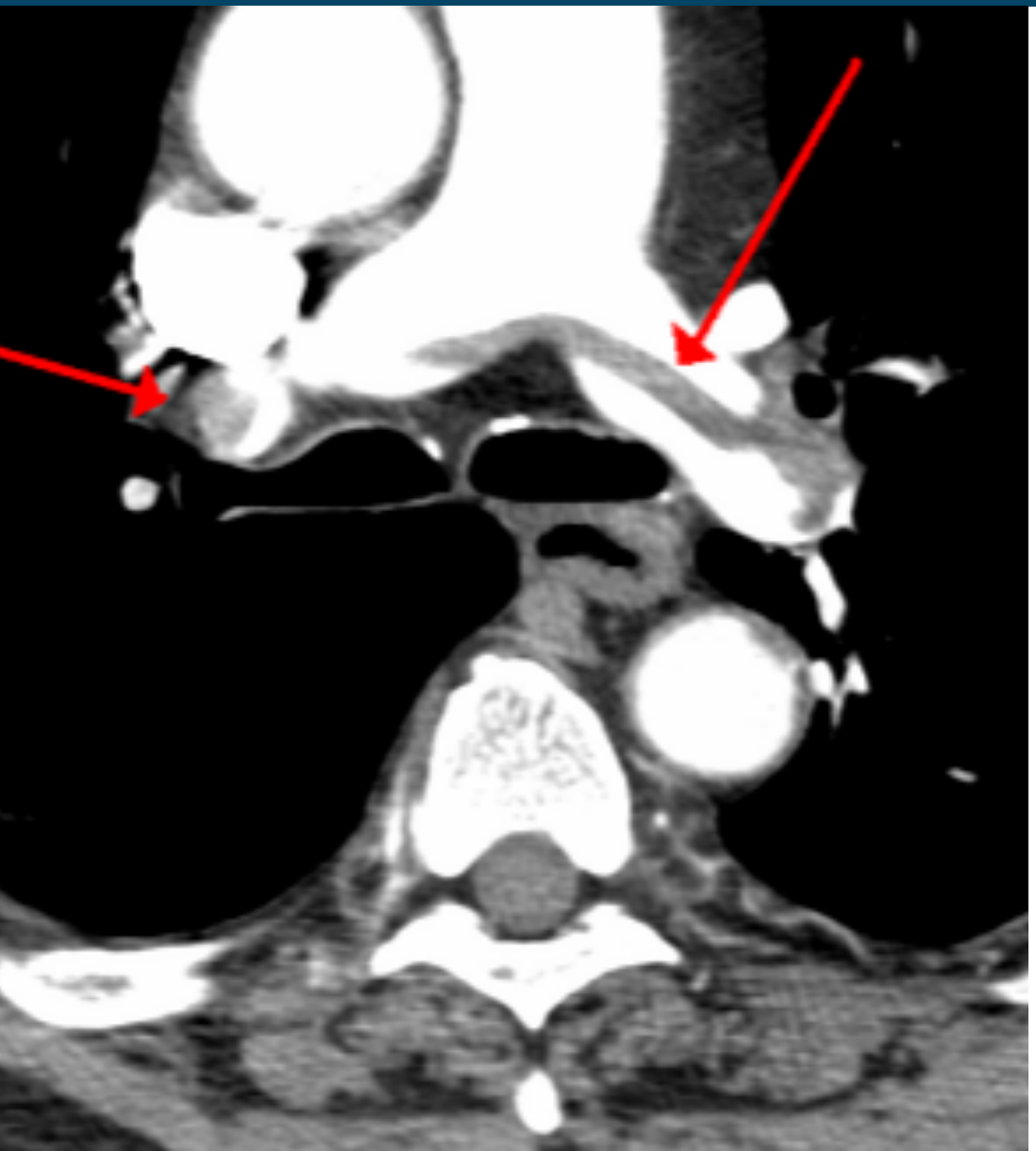
Diagnosing Pulmonary Emboli



- CT angiography
- Elevated d-dimer
- Venous doppler

Photo Credit: James Heilman, MD

Our patient: 74 year-old man with severe COVID-19

Continuing Care

- Acetaminophen, metformin, and dexamethasone were continued
- Therapeutic infusion of heparin was initiated
- Antibiotics were stopped after the diagnosis of pulmonary embolus
- Insulin was given, based on fingerstick glucose values
- IV fluids continued gently
- Urine output was adequate and BP remained at ~ 110/80
- Patient was transferred to the ICU and placed on high flow nasal oxygen SpO_2 ~ 90-92%
- Patient was cooperative with proning and care during the day, but was moderately confused at night

- His respiratory status stabilized and then slowly began to improve. He was ultimately discharge to home after 42 days in the hospital

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Palliative care

- Basic palliative care, including relief of dyspnea or other symptoms should be practiced by all health care providers
- Consider opioids and other pharmacologic and non-pharmacologic interventions for relief of dyspnea that is refractory to treatment of the underlying cause and/or as part of end-of-life care
  - Follow institutional guidelines regarding the potential use of opioids for dyspnea in patients with COVID-19
- Reassurance and pharmacotherapy may be required for patients who experience anxiety and delirium
- Patients often need social support as contact with families may be limited by infection control concerns

Goals of Care

- Intensive care support may not be appropriate if survival is unlikely
- Carefully consider the goals of care, involving patient and family in these discussions
- Assess whether patients have advance directives
- Respect patient priorities and preferences to tailor the care plan
- Provide the best care irrespective of treatment choice

Resources

Type of Resource	Link
Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected.	https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
Coronavirus disease (COVID-19) technical guidance: Patient management	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management
NIH: COVID-19 Treatment Guidelines	https://www.covid19treatmentguidelines.nih.gov/
Operational considerations for case management of COVID-19 in health facility and community	https://www.who.int/publications-detail/operational-considerations-for-case-management-of-covid-19-in-health-facility-and-community
Oxygen sources and distribution for COVID-19 treatment centres	https://www.who.int/publications/i/item/oxygen-sources-and-distribution-for-covid-19-treatment-centres

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Acknowledgements

- Frontline clinical staff caring for COVID-19 patients
- Patients with COVID-19
- [Ministry of Health]
- Resolve to Save Lives, an initiative of Vital Strategies
- Dr. Hamid Bassiri
- Centers for Disease Control and Prevention
- World Health Organization
- National Institutes of Health
- Partners in Health
- Investigators who rapidly moved to COVID-19 research

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