COVID-19 Overview

Kialing Perez, MD

June, 2020

COVID-19 Overview

No disclosures

COVID-19 Overview

About the virus

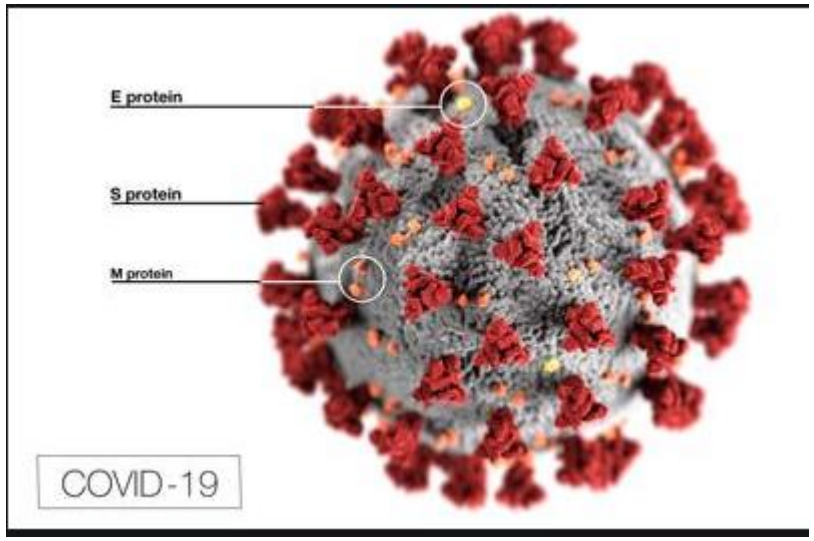
Numbers

Testing

Treatment

Vaccines

Coronaviruses



RNA virus

Four genera: α,β,γ,δ (α andβ infect mammals)

- α corona (cold/croup)
- β corona (SARS-MERS-SARS-CoV2)

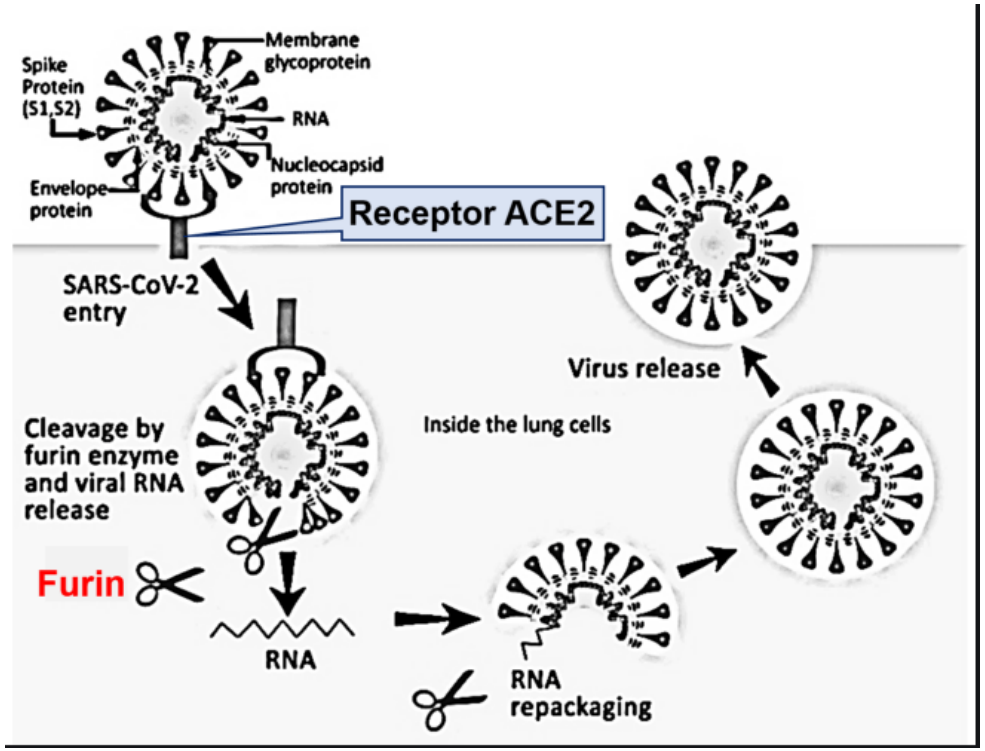
Life cycle: Attachment, penetration, biosynthesis, maturation and release

Structural proteins : S spike, M membrane, E envelop, N nucleocapsid

S1 for binding into host cell receptor (ACE2 for COVID-19)

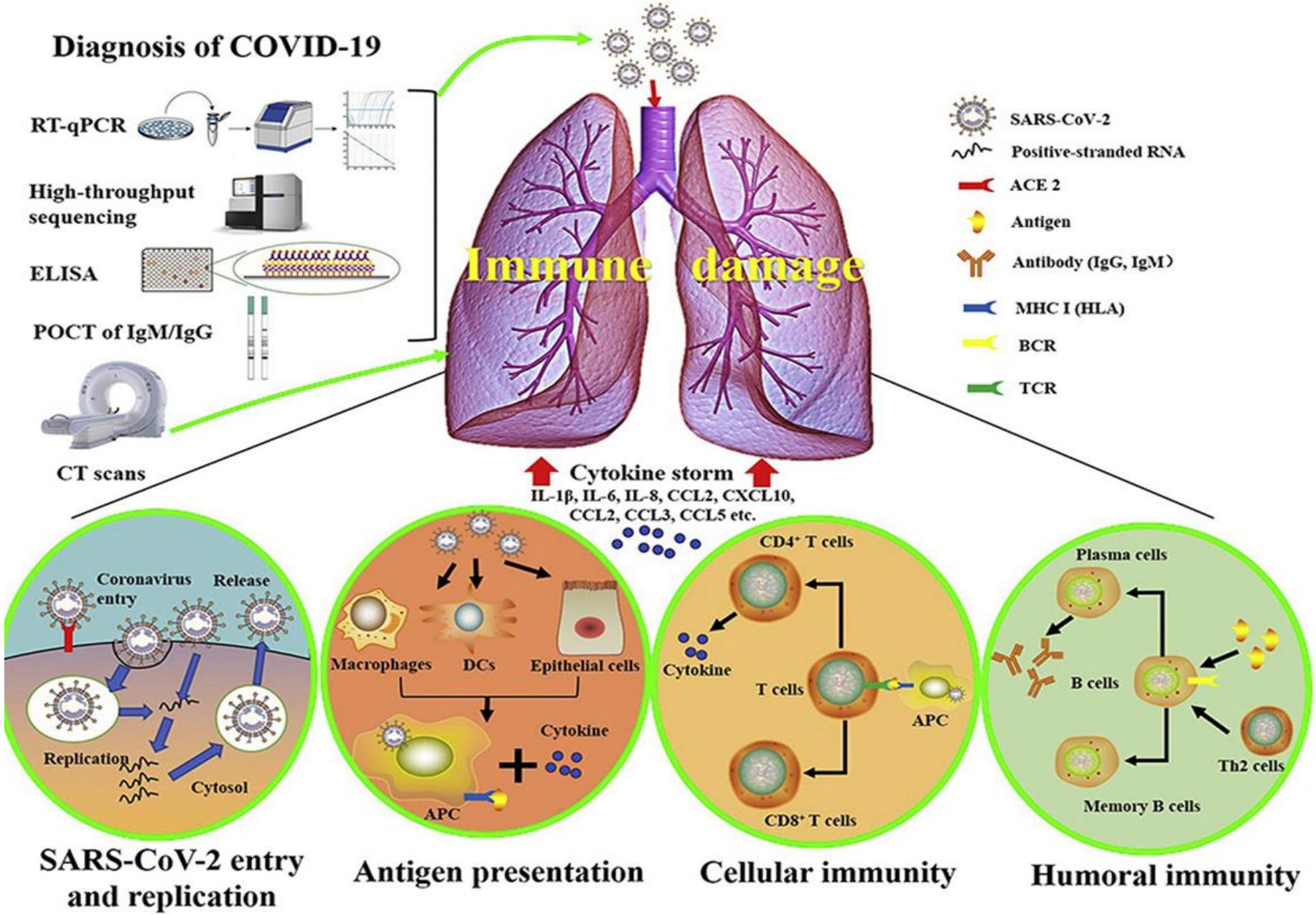
S2 for fusion of viral-cellular membranes

COVID-19 Overview



ACE 2 expression

- Lungs (epithelial cells), high expression
- Heart
- Ileum
- Kidneys
- Bladder


Diagnosis of COVID-19
RT-qPCR
High-throughput sequencing
ELISA
POCT of IgM/IgG
CT scans
Immune damage
Cytokine storm
IL-1β, IL-6, IL-8, CCL2, CXCL10, CCL2, CCL3, CCL5 etc.
SARS-CoV-2
Positive-stranded RNA
ACE 2
Antigen
Antibody (IgG, IgM)
MHC I (HLA)
BCR
TCR
Coronavirus entry
Release
Replication
Cytosol
Macrophages
DCs
Epithelial cells
Cytokine
APC
CD4⁺ T cells
Cytokine
T cells
APC
CD8⁺ T cells
Plasma cells
B cells
Th2 cells
Memory B cells
SARS-CoV-2 entry and replication
Antigen presentation
Cellular immunity
Humoral immunity

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

Total Confirmed
8,075,962

Confirmed Cases by Country/Region/Sovereignty

- 2,118,798 US
- 888,271 Brazil
- 544,725 Russia
- 343,091 India
- 299,594 United Kingdom
- 244,328 Spain
- 237,290 Italy
- 232,992 Peru
- 194,305 France
- 192,439 Iran
- 188,220 Germany
- 184,449 Chile
- 179,831 Turkey
- 150,264 Mexico
- 148,921 Pakistan
- 136,315 Saudi Arabia

Admin0 | Admin1 | Admin2

Last Updated at (M/D/YYYY)
6/16/2020, 8:33:15 AM

Cumulative Confirmed Cases | Active Cases | Incidence Rate | Case-Fatality Ratio | Testing Rate | Hospitalization Rate

188
countries/regions

Lancet Inf Dis Article: Here. Mobile Version: Here.
Lead by JHU CSSE. Technical Support: Esri Living Atlas team and JHU APL. Financial Support: JHU and NSF. Click *here* to **donate** to the CSSE dashboard team, and other JHU COVID-19 Research Efforts. FAQ. Read more in this blog. Contact US.
Data sources: WHO, CDC, ECDC, NHC, DXY, 1point3acres, Worldometers.info, the COVID Tracking Project (testing and hospitalizations), and city, county, state and national public health departments. Full list of sources available *here*.

Global Deaths
437,939

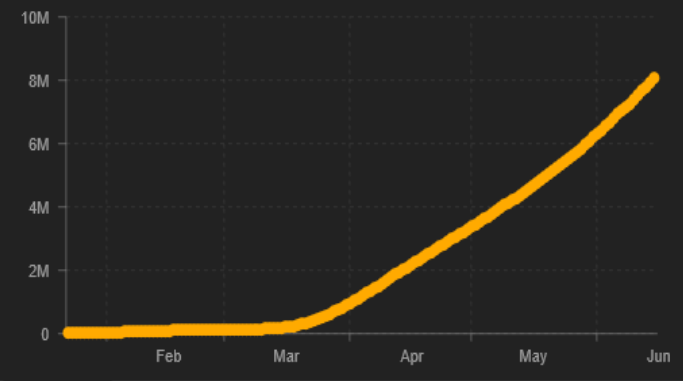
- 116,250 deaths US
- 43,959 deaths Brazil
- 42,054 deaths United Kingdom
- 34,371 deaths Italy
- 29,439 deaths France
- 27,136 deaths Spain
- 17,580 deaths Mexico
- 9,900 deaths

Global Deaths

US State Level
Deaths, Recovered

- 30,856 deaths, 68,851 recovered New York US
- 12,708 deaths, 28,819 recovered New Jersey US
- 7,647 deaths, recovered Massachusetts US
- 6,326 deaths, recovered Illinois US
- 6,243 deaths, 58,549 recovered Pennsylvania US
- 6,018 deaths, 44,964 recovered Michigan US
- 5,116 deaths, recovered California US
- 4,204 deaths, 7,611 recovered

US Deaths, Recovered



Confirmed | Logarithmic | Daily Cases

Cases in the U.S.

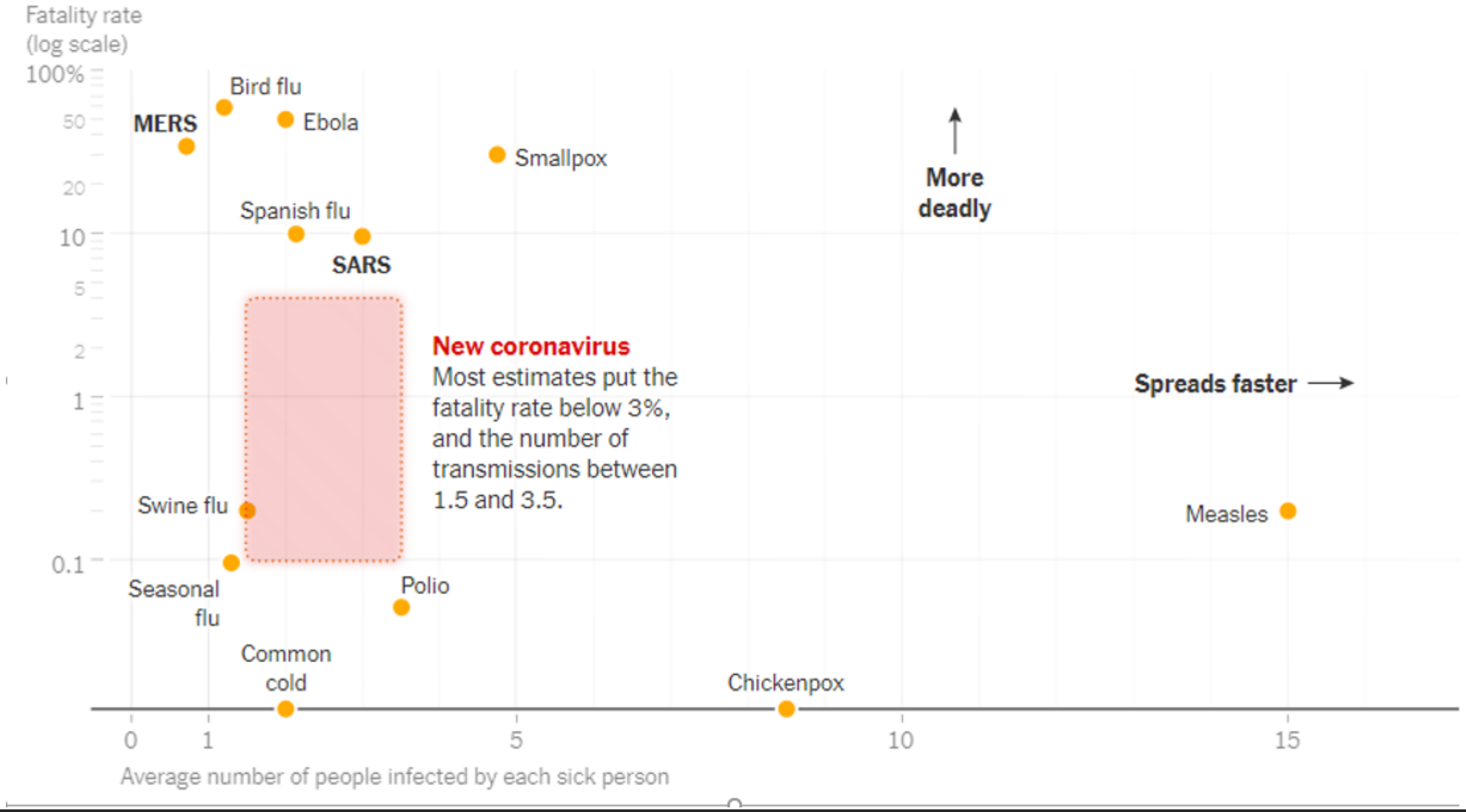
Other Languages ▾ Print Page

Last updated on June 17, 2020

TOTAL CASES	TOTAL DEATHS
2,132,321	116,862
27,975 New Cases*	722 New Deaths*

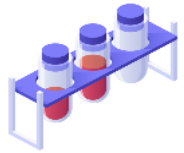
*Compared to yesterday's data

About the Data


Fatality rate
(log scale)
100%
50
20
10
5
2
1
0.1
Bird flu
MERS
Ebola
Smallpox
Spanish flu
SARS
More
deadly
New coronavirus
Most estimates put the
fatality rate below 3%,
and the number of
transmissions between
1.5 and 3.5.
Spreads faster
Swine flu
Measles
Seasonal
flu
Polio
Common
cold
Chickenpox
0
1
5
10
15
Average number of people infected by each sick person

Testing

The Two Test Types



What is the test?	A viral test is an oral or nasal swab or saliva test that looks for **evidence of an active viral infection**. There are two major types: a PCR test and an antigen test.	A serology test is a blood test that looks for **evidence of someone's prior infection** with the virus.
What does the test do?	PCR tests look for the **presence of a virus's genetic material**, while antigen tests look for **specific proteins on a virus's surface**. Antigen tests produce results more quickly, but may be less sensitive.	The test provides evidence that someone may have been exposed to the virus in the past, potentially even if they did not have symptoms, by **detecting antibodies specific to the virus**.
What doesn't the test do?	Viral tests do not indicate **whether someone was infected in the past**.	The test does not **diagnose an active infection or identify who is protected from reinfection** (antibodies have not been proven to guarantee immunity).
FDA How does the FDA handle the test?	The FDA formally **evaluates these tests prior to use**.	The FDA **does not formally evaluate these tests prior to use**, though a few have Emergency Use Authorization.

FDA STATEMENT

Coronavirus (COVID-19) Update: FDA Authorizes First Antigen Test to Help in the Rapid Detection of the Virus that Causes COVID-19 in Patients

For Immediate Release: May 09, 2020

Statement From: Commissioner of Food and Drugs - Food and Drug Administration
Stephen M. Hahn M.D.
Director - CDRH Offices: Office of the Center Director
Dr. Jeffrey E. Shuren MD, JD

RT-PCR : TEST FOR GENETIC MATERIAL OF THE VIRUS, HIGHLY ACCURATE, EXPENSIVE TO PERFORM, TAKES HOURS TO RESULT

ANTIBODY TESTING: CHECKS THE BLOOD FOR ANTIBODIES, NOT USEFUL FOR DIAGNOSIS OF ACTIVE INFECTION

ANTIGEN TESTING: NOT YET AVAILABLE, DETECTS VIRAL PARTICLES AS OPPOSED TO THE GENETIC CODE (PCR), TAKES MINUTES TO RESUL

NIH COVID-19 Treatment Guidelines

Testing for SARS-CoV-2 Infection

Last Updated: June 11, 2020

Summary Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that a molecular or antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be used to diagnose acute SARS-CoV-2 infection **(AIII)**.
- The Panel **recommends against** the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**.
- The Panel **recommends against** the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion


NIH
COVID-19 Treatment Guidelines

Remdesivir (GS-5734)	• Not approved by FDA • Investigational antiviral agent	• Adenosine nucleotide analog prodrug that undergoes hydrolysis to its active form, which inhibits viral RNA-dependent RNA polymerase[21] • Potent *in vitro* activity demonstrated in SARS-CoV-2-infected Vero E6 cells[22] • In a rhesus macaque model of SARS-CoV-2 infection, animals who were started on RDV soon after inoculation had lower lung virus levels and less lung damage than control animals.[23]

NIH | COVID-19 Treatment Guidelines

Multinational Randomized Controlled Trial of RDV Versus Placebo in Hospitalized Patients:[24]

ACTT is an NIH-sponsored, multinational, randomized, double-blind placebo-controlled trial in hospitalized adults with COVID-19. Participants were randomized 1:1 to receive IV RDV or placebo for 10 days

Of 1,063 enrolled participants, 1,059 had preliminary results available for analysis (n = 538 for the RDV group; n = 521 for the placebo group)

Interpretation: In patients with severe COVID-19, RDV reduced the time to clinical recovery

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action
Azithromycin **Note:** Studies on COVID-19 use AZM with HCQ.	• Mycobacterial (nontuberculous) infection • STIs and various bacterial infections[1]	**Proposed Antiviral Effects:** • Induction of IFN-stimulated genes, attenuating viral replication[2] **Immunomodulatory Effect:** • Enhanced neutrophil activation[3] **Anti-Inflammatory Effects:** • Attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells[2]
Chloroquine	• Malaria • Extra-intestinal amebiasis	**Proposed Antiviral Effects:** • *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5] • Inhibits glycosylation of the cellular ACE2 receptor, which may interfere with the binding of the virus to the cell receptor[6] **Immunomodulatory Effect:** • CQ may lead to a reduction in pro-inflammatory cytokines.[5]

THE LANCET

ARTICLES | ONLINE FIRST

RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Prof Mandeep R Mehra, MD • Sapan S Desai, MD • Prof Frank Ruschitzka, MD • Amit N Patel, MD

Published: May 22, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31180-6 • Check for updates

Summary

Background

Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

Methods

We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received

RETRACTED

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine

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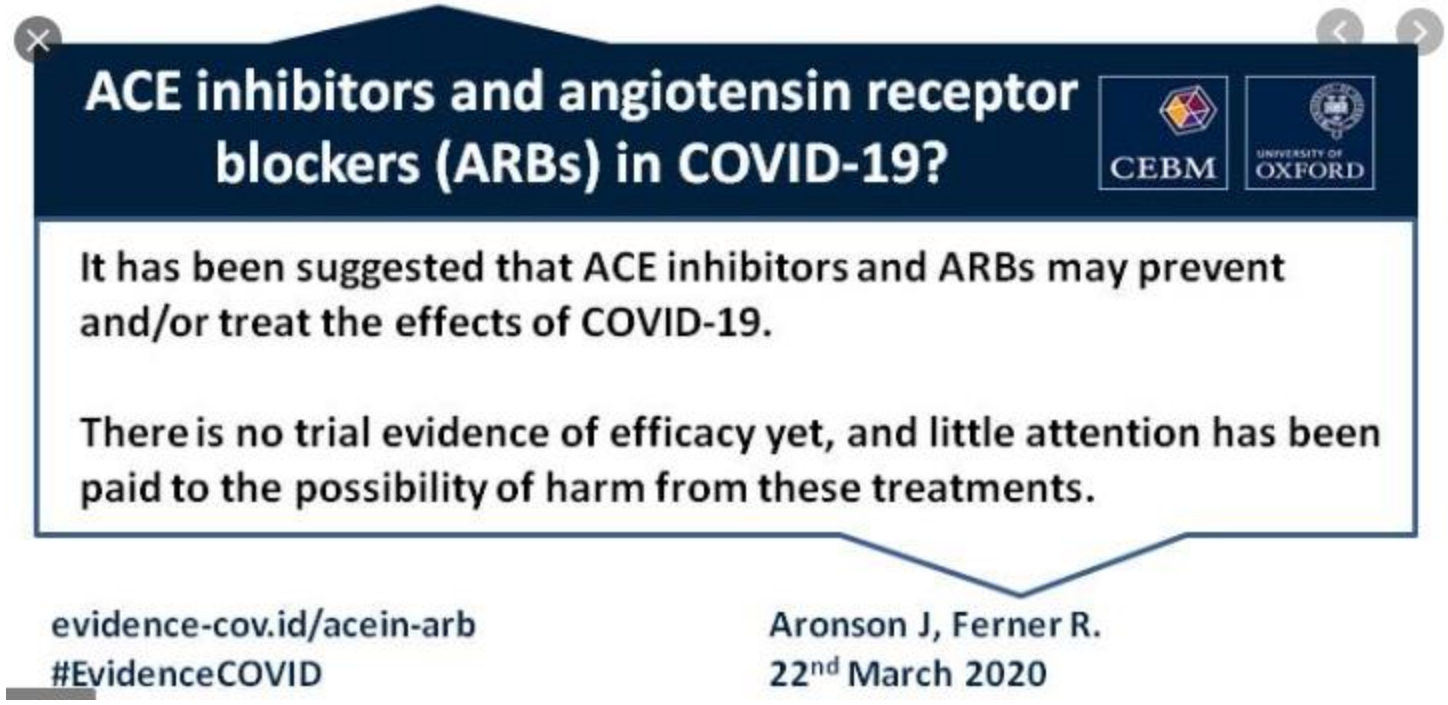
For Immediate Release: June 15, 2020


ACE inhibitors and angiotensin receptor blockers (ARBs) in COVID-19?
CEBM
UNIVERSITY OF OXFORD
It has been suggested that ACE inhibitors and ARBs may prevent and/or treat the effects of COVID-19.
There is no trial evidence of efficacy yet, and little attention has been paid to the possibility of harm from these treatments.
evidence-cov.id/acein-arb
#EvidenceCOVID
Aronson J, Ferner R.
22nd March 2020

PUBLISHED
16 JUN 2020

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Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

RESEARCH SCIENCE HEALTH CORONAVIRUS

16 June 2020

Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75; p=0.14).

Based on these results, 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone.

Sarilumab	• Rheumatoid arthritis[26]	• Human recombinant monoclonal antibody • IL-6 receptor antagonist
Siltuximab	• Multicentric Castleman disease	• Human-mouse chimeric monoclonal antibody • IL-6 antagonist[29]
Tocilizumab	• Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis[31]	• Recombinant humanized monoclonal antibody • IL-6 receptor antagonist

NIH COVID-19 Treatment Guidelines

COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	• Not approved by the FDA	• Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[1] Similarly, SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19. Both products may help suppress the virus and modify the inflammatory response.	**For COVID-19:** • Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports. • There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in COVID-19. **For Other Viruses:** • The use of convalescent plasma has been evaluated in other viral diseases (e.g., SARS), with some suggestion of potential benefit.[2-9] No convalescent blood products are currently licensed by the FDA. • There are no clinical data on the use of specific immune globulin or hyperimmune globulin in patients with SARS or MERS.

Persons at Risk for Infection with SARS-CoV-2

Last Updated: April 21, 2020

Pre-Exposure Prophylaxis

The COVID-19 Treatment Guidelines Panel (the Panel) **does not recommend** the use of any agents for SARS-CoV-2 pre-exposure prophylaxis (PrEP) outside the setting of a clinical trial **(AIII)**.

At present, no agent given before an exposure (i.e., as PrEP) is known to be effective in preventing SARS-CoV-2 infection. Clinical trials using hydroxychloroquine, chloroquine, or HIV protease inhibitors as PrEP are in development or underway.

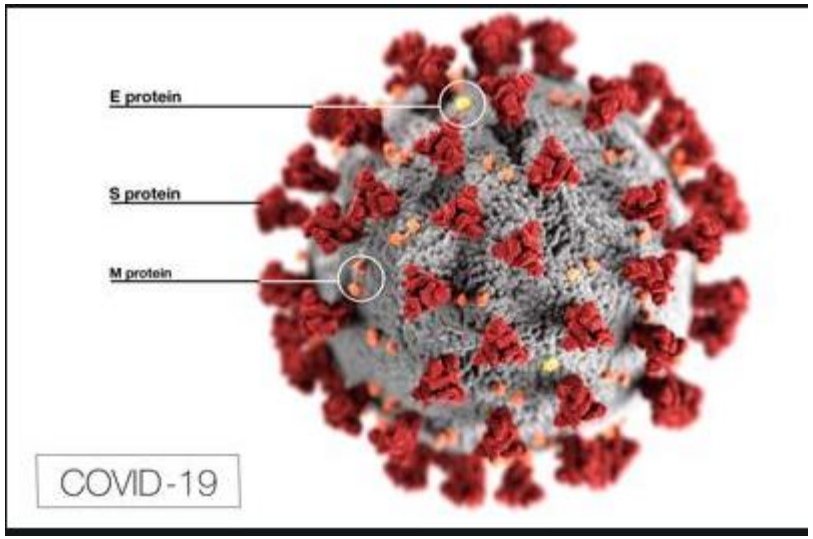
Post-Exposure Prophylaxis

The Panel **does not recommend** the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP) outside the setting of a clinical trial **(AIII)**.

At present, no agent is known to be effective for preventing SARS-CoV-2 infection after an exposure (i.e., as PEP). Potential options for PEP currently under investigation in clinical trials include hydroxychloroquine, chloroquine, or lopinavir/ritonavir.

COVID-19 VACCINE

- Coronavirus (RNA virus)
  - Common cold (15% of colds)
  - Severe acute respiratory distress syndrome (SARS)
  - Middle East respiratory syndrome (MERS)
  - Infects animals: pigs, chickens, mice, cats, dogs, turkeys, calves, rabbits, bats



COVID-19 is very similar to SARS virus (SARS CoV-2)

Types of vaccines: Live, attenuated, genetically engineered

Good news: Not starting from scratch (SARS-MERS vaccines)

Bad news: Safety, long term protection, older patients don't respond as well as young ones

Draft landscape of COVID-19 candidate vaccines

16 June 2020 | Publication

11 candidate vaccines in clinical evaluation

Platform	Type of candidate vaccine	Developer	Coronavirus target	Current stage of clinical evaluation/regulatory status-Coronavirus candidate	Same platform for non-Coronavirus candidates
Non-Replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca	SARS-CoV2	Phase2b/3 2020-001228-32 Phase 1/2 2020-001072-15	MERS, influenza, TB, Chikungunya, Zika, MenB, plague
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	SARS-CoV2	Phase 2 ChiCTR2000031781 Phase 1 ChiCTR2000030906	Ebola
RNA	LNP-encapsulated mRNA	Moderna/NIAID	SARS-CoV2	Phase 2 NCT04405076 Phase 1 NCT04283461	multiple candidates
Inactivated	Inactivated	Wuhan Institute of Biological Products/Sinopharm	SARS-CoV2	Phase 1/2 ChiCTR2000031809	
Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm	SARS-CoV2	Phase 1/2 ChiCTR2000032459	
Inactivated	Inactivated + alum	Sinovac	SARS-CoV2	Phase 1/2 NCT04383574 NCT04352608	SARS

Resources

National Institute of Health

World Health Organization

CDC

Infectious Diseases Society of America

John Hopkins and Mayo Clinic COVID-19 Resource Center

FDA

Thank you

Yale NewHaven Health

Pulmonary Pathophysiology of COVID-19 and the Possible Role of Hyperbaric Oxygen Therapy

Sandra Wainwright, MD

June 20,2020

I was supposed to be on vacation…

Article | Open Access | Published: 24 February 2020

High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa

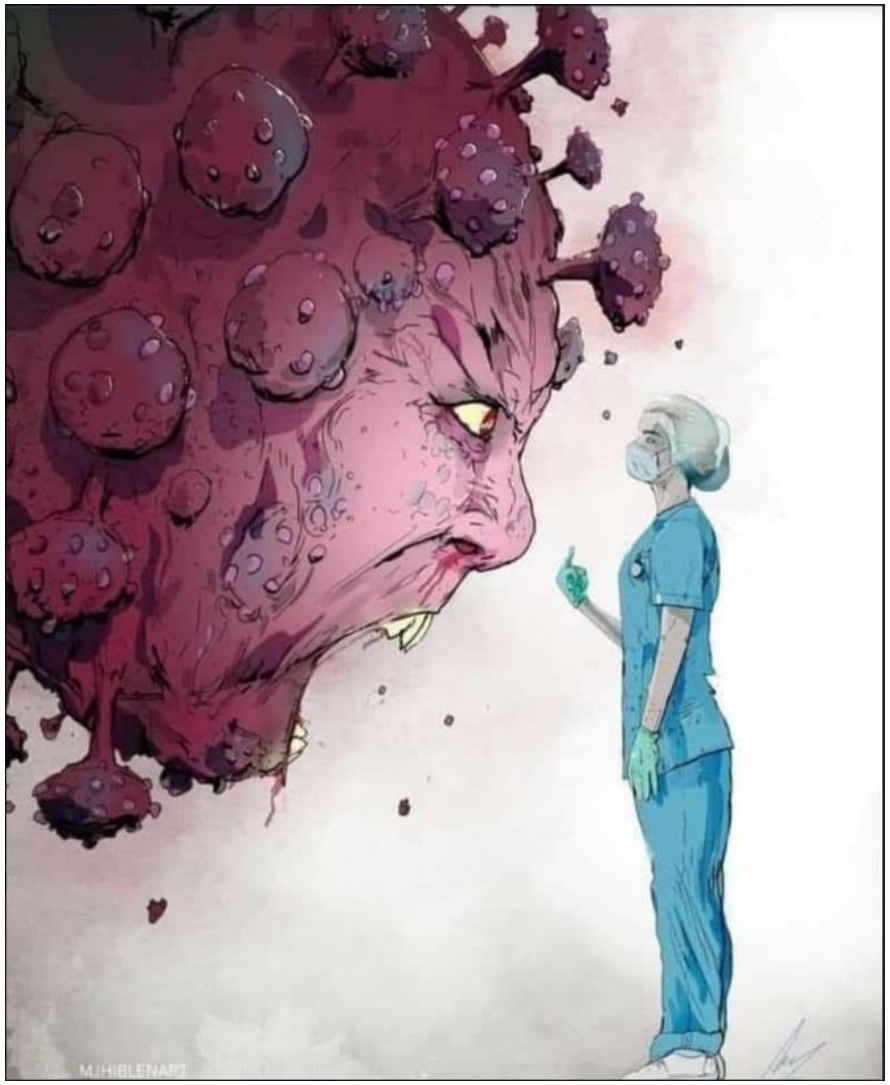
Hao Xu, Liang Zhong, Jiaxin Deng, Jiakuan Peng, Hongxia Dan, Xin Zeng, Taiwen Li & Qianming Chen

- The expression and distribution of the ACE2 in human body may indicate the potential infection routes of 2019-nCoV. Through the developed single-cell RNA sequencing (scRNA-Seq) technique and single-cell transcriptomes based on the public database, researchers analyzed the ACE2 RNA expression profile at single-cell resolution. High ACE2 expression was identified in type II alveolar cells (AT2) of lung[10,11,12], esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon[12], cholangiocytes[13], myocardial cells, kidney proximal tubule cells, and bladder urothelial cells[10]. These findings indicated that those organs with high ACE2-expressing cells should be considered as potential high risk for 2019-nCoV infection[10].

Yale NewHaven Health

Typical COVID-19 presentation

- Fever, dry cough, chest pain, myalgias, joint pain, dyspnea
- Headache, anosmia (40%), dysgeusia, nausea, vomiting, diarrhea
- VS – hypoxic to 60-80% room air, normotensive, inappropriately normal heart rate
- Labs – Lymphopenia common, in general - sodium on lower side, LFT's elevated
- Nocturnal symptoms were severe for home bound and hospitalized patients. Hosp'd pts were afraid they would stop breathing and die
  - Exacerbation of osa? Or chronobiology of the virus?
- Tylenol inexplicably helped the coughing at night
- Day 7 parenthetical (6-9) sx peaked
- Usually resolved by day 14



Our ‘Typical’ COVID-19 patient

- Male 30’s-50’s
- Latino
- Mildly overweight to obese
- Rarely other comorbidities, like DM2, renal failure, immunosuppression

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Why Obese Patients?

INAUGURAL ARTICLE

Regulation of adipose tissue inflammation by interleukin 6

Myoung Sook Han, Alexis White, Rachel J. Perry, Joao-Paulo Camporez, Juan Hidalgo, Gerald I. Shulman, and Roger J. Davis

PNAS February 11, 2020 117 (6) 2751-2760; first published January 24, 2020 https://doi.org/10.1073/pnas.1920004117

Contributed by Roger J. Davis, December 19, 2019 (sent for review November 15, 2019; reviewed by Robert E. Lewis and Evan D. Rosen)

Interleukin 6 (IL6) is a cytokine with many physiological actions that regulate metabolism (1). Indeed, studies using IL6 infusion in healthy humans demonstrate increased insulin-stimulated glucose disposal, increased lipolysis, increased glucose and fatty acid oxidation, and increased energy expenditure (2, 3). IL6 therefore targets multiple physiological processes that impact whole-body metabolism. The physiology of IL6 signaling is complex because the effects **of IL6 on metabolism requires signal integration between cell types (4) that involve proinflammatory, anti-inflammatory, and noninflammatory mechanisms (5).**

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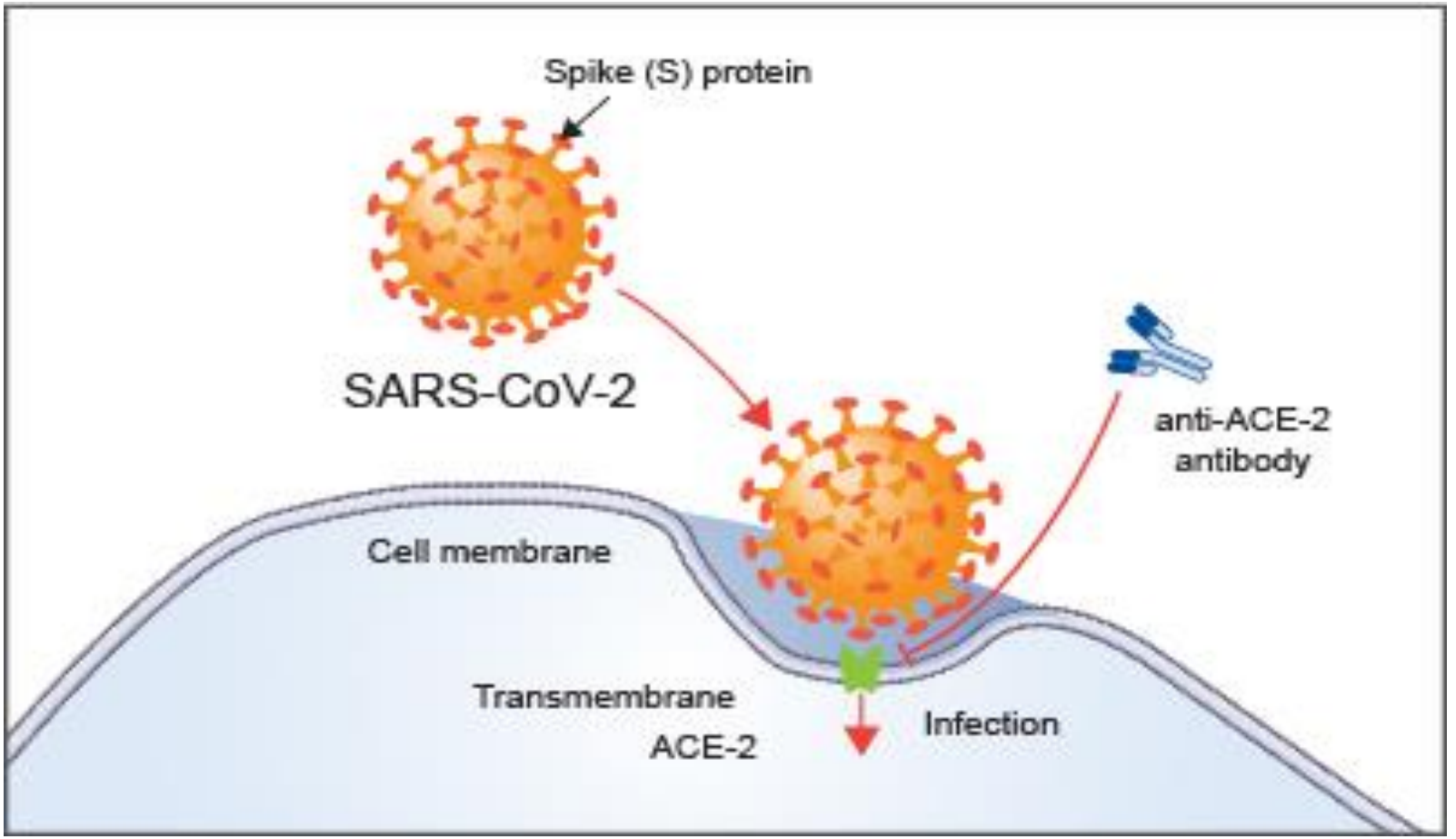
SARS CoV2



https://www.rndsystems.com/resources/articles/ace-2-sars-receptor-identified

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Health

Why young patients and male patients?

- **RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov**
- Yu Zhao, Zixian Zhao, Yujia Wang, Yueqing Zhou, Yu Ma, Wei ZuoA comparison between eight individual samples demonstrated that the Asian male one has an extremely large number of ACE2-expressing cells in the lung.

- **Age- And Gender-Related Difference of ACE2 Expression in Rat Lung**
- Xudong Xie [1], Junzhu Chen, Xingxiang Wang, Furong Zhang, Yanrong Liu

Yale NewHaven Health

Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors FREE

Iziah E Sama, Alice Ravera, Bernadet T Santema, Harry van Goor, Jozine M ter Maaten, John G F Cleland, Michiel Rienstra, Alex W Friedrich, Nilesh J Samani, Leong L Ng ... Show more

European Heart Journal, Volume 41, Issue 19, 14 May 2020, Pages 1810–1817,

- We measured ACE2 concentrations in 1485 men and 537 women with heart failure (index cohort). Results were validated in 1123 men and 575 women (validation cohort).
- The median age was 69 years for men and 75 years for women. The strongest predictor of elevated concentrations of ACE2 in both cohorts was male sex (estimate = 0.26, $P < 0.001$; and 0.19, $P < 0.001$, respectively). In the index cohort, use of ACE inhibitors, angiotensin receptor blockers (ARBs), or mineralocorticoid receptor antagonists (MRAs) was not an independent predictor of plasma ACE2. In the validation cohort, ACE inhibitor (estimate = –0.17, $P = 0.002$) and ARB use (estimate = –0.15, $P = 0.03$) were independent predictors of lower plasma ACE2, while use of an MRA (estimate = 0.11, $P = 0.04$) was an independent predictor of higher plasma ACE2 concentrations.

Yale NewHaven Health

Dr. S Wainwright Day#1 COVID

March 20th 2020 –The Pandemic finally hit our hospital, we'd been "preparing" for weeks-but you're never really prepared. I was the MICU attending on call. I looked into the house-staffs' and nurses' eyes and saw fear and uncertainty. I was afraid too, but leaders can't show fear. Walking into an ICU whose COVID volume had doubled overnight, I realized we needed a General Patton moment.

I told my "troops" that the reason why then went into medicine was because they wanted to save lives. I told them that they were ***created*** for this very moment in time, to make a difference, to participate in a moment in history that would define who they are and what they're made of. I told them we would no longer practice sub-par critical care medicine, that they would be practicing evidence based good medicine going forward. A tube in every orifice and a couple more became our mantra – ETT, OGT, foley, rectal, central line, arterial line. I told them that the ICU is the safest place in the hospital and that I'd rather be in the ICU than any other location in the hospital because intubated patients' exhaled air is double filtered by the vent so our viral exposure would be lower.

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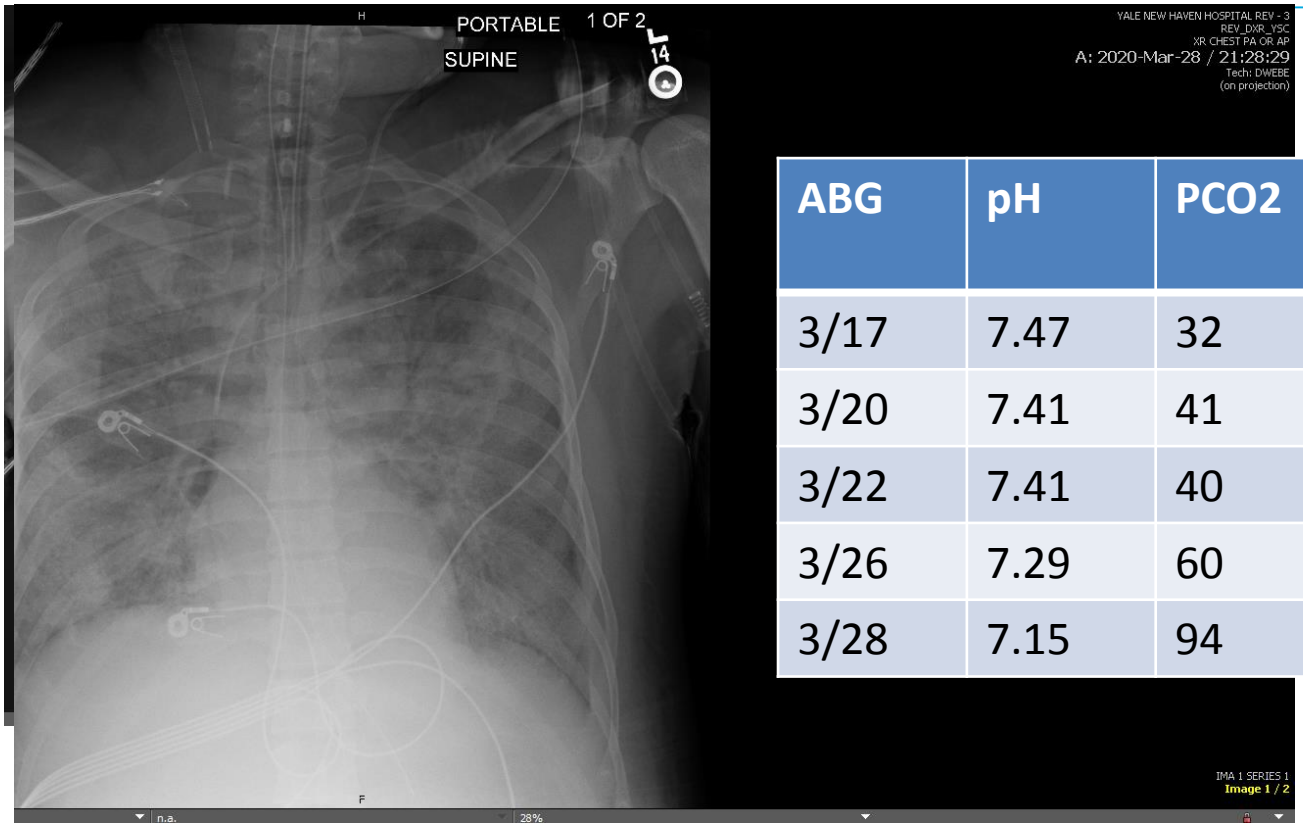
33y March 17, 2020

These patients are so sick! Why are they so HYPOXIC – for being so young and no medical problems!!



ABG	pH	PCO2	PaO2	O2 device	HCO3
3/17	7.47	32	109	100%nrb	23
3/20	7.41	41	191	100%nrb	25
3/22	7.41	40	355	350/15	25
3/26	7.29	60	68	260/30	24
3/28	7.15	94	96	ECMO	31

There are only 5 reasons for hypoxemia!

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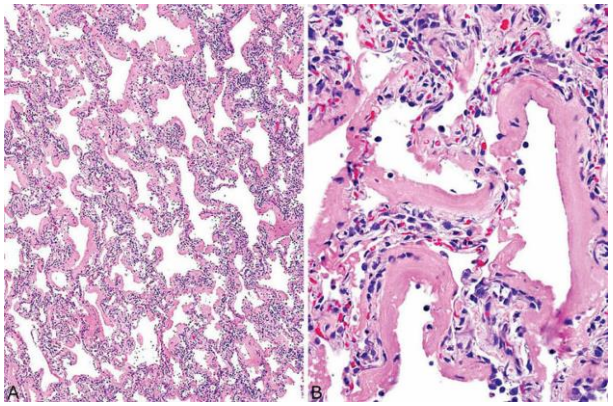
How COVID-19 Causes Hypoxemia

1. v/q mismatch via micro and macro thromboses

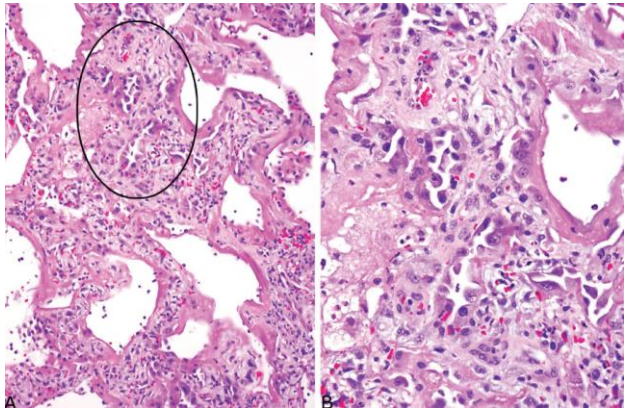
Volume 26, Number 8—August 2020 *Research Letter :*Pulmonary Embolism and Increased Levels of d-Dimer in Patients with Coronavirus Disease

2. diffusion impairment via thickened alveolar membrane

3. shunt via high peep, alveolar filling and mucus plugging



Thickened Alveolar Membrane



Diffuse Alveolar Damage

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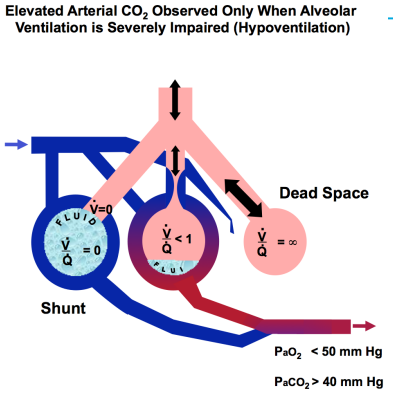
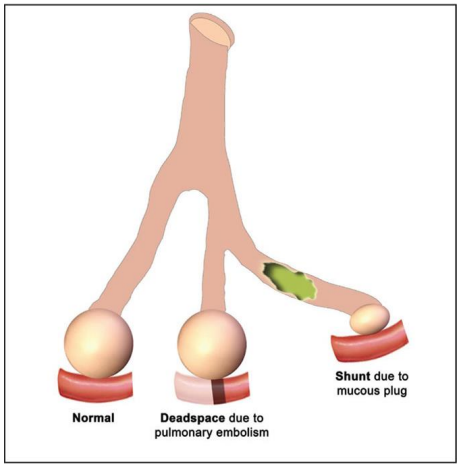
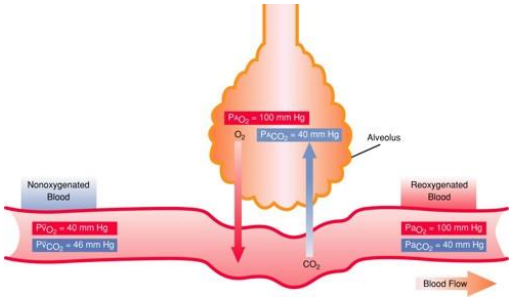
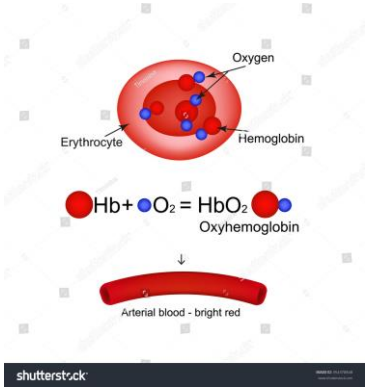
5 Reasons for Hypoxia

1. FiO2
2. V/Q mismatch
3. Shunt
4. Diffusion impairment
5. Oxygen delivery (hemoglobin, cardiac output, toxins)



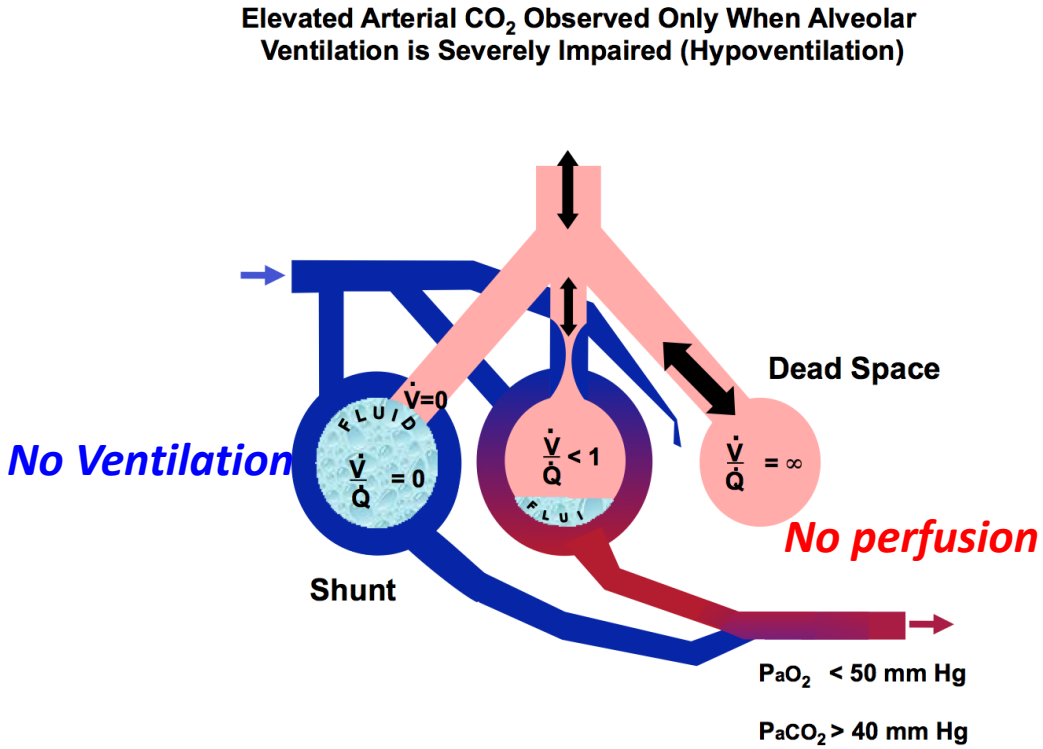






5 Reasons for Hypoxia

- 2. V/Q Mismatch



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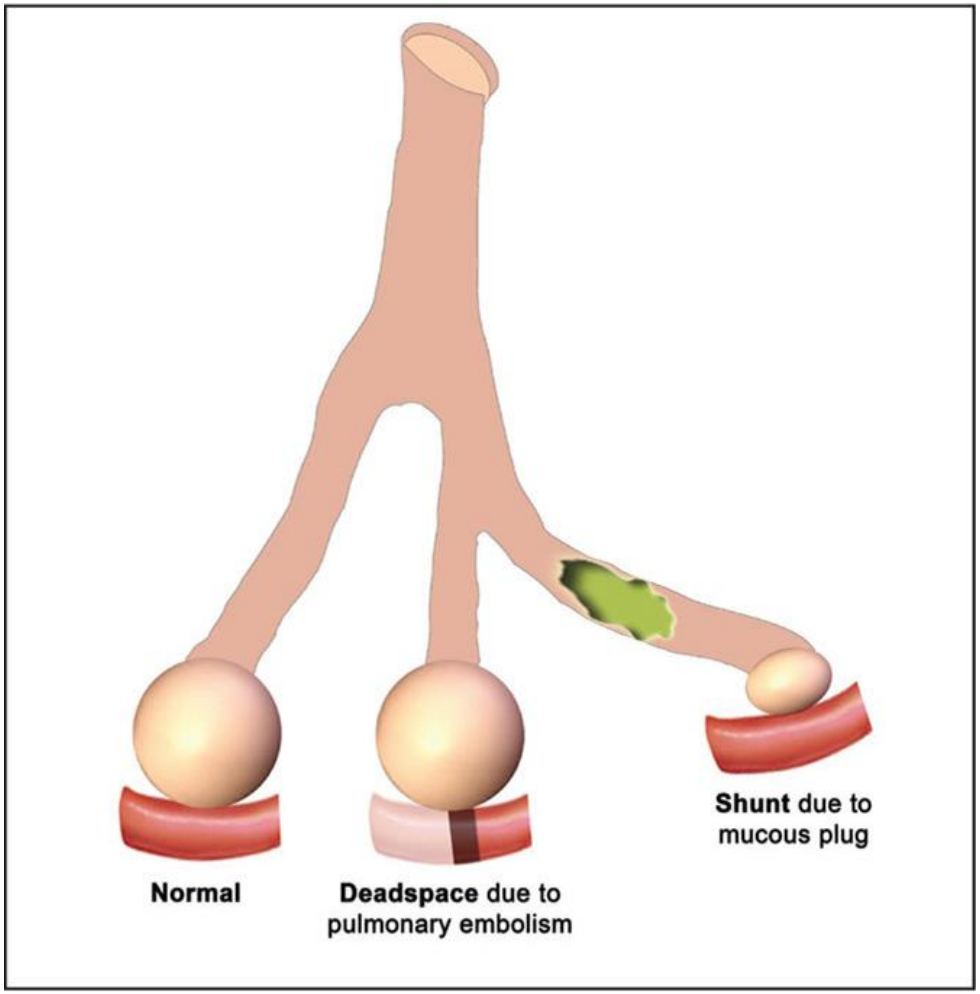
5 Reasons for Hypoxia

- 3. Shunt



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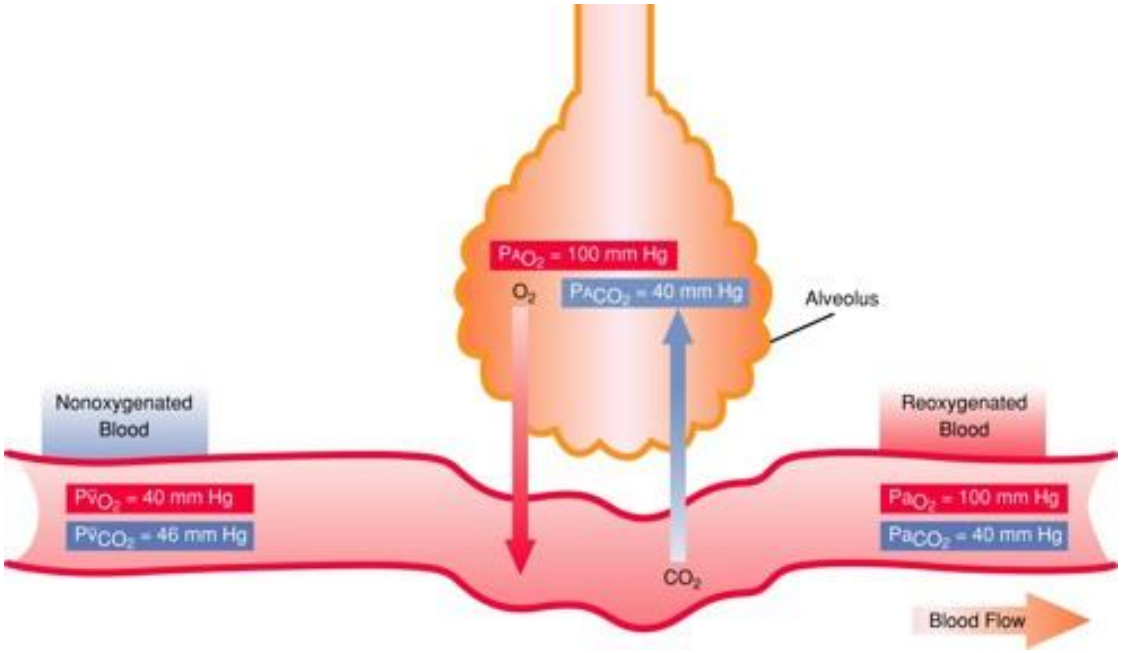
5 Reasons for Hypoxia

- 4. Diffusion Impairment – or as Europeans would say “transfer”



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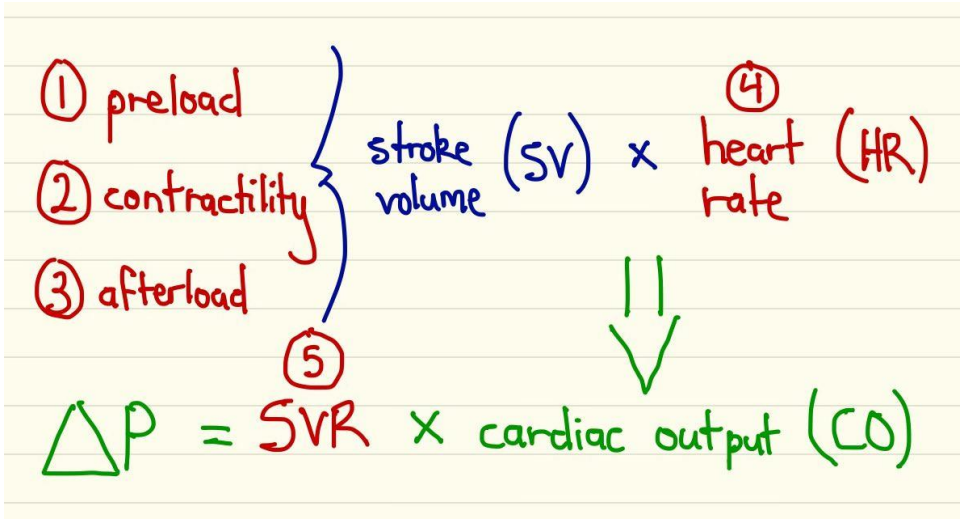
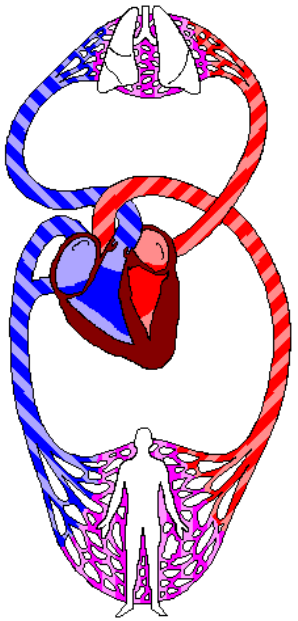
5 Reasons for Hypoxemia

5a. Oxygen Delivery – *In Context*

Cardiac Output





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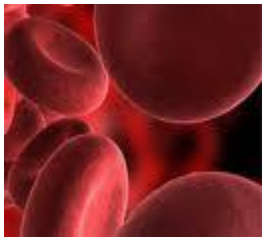
5 Reasons for Hypoxemia

5b.

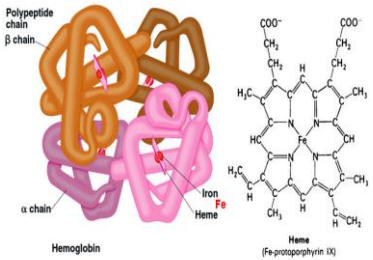
Oxygen is transported by 2 mechanisms

Reversible binding to hemoglobin subunits

Physical dissolution in plasma



- Each Hgb combines with 4 O2 molecules
- Each gm of Oxyhemoglbin carries 1.35cc of O2
- Thus, 15 gm of Hgb can trans port 20cc of O2 per 100cc of blood
- i.e. 20 vol %



At a PaO2 of 100mmHg only 0.031 ml of O2 are dissolved per 100cc of blood, 0.031 vol % is carried by plasma

$CaO_2=[(SaO_2 * 1.39x\ Hb) + (\underline{0.0031} * \underline{PaO_2})$

Pulmonologists consider this a rounding error, like our gov't considers the number trillion

Yale NewHaven Health

A Pulmonologist's Trash is a Hyperbaricist's Treasure?

At a PaO2 of 100mmHg only 0.031 ml of O2 are dissolved per 100cc of blood, 0.031 vol % is carried by plasma

$CaO_2 = [(SaO_2 * 1.39x\ Hb) + (\underline{0.0031} * \underline{PaO_2})]$

Pulmonologists consider this a rounding error, like our gov't considers the number trillion

Many COVID-19 patients' best O2 sat and PaO2 on high peep and 100% FiO2 were 60

CaO2 = [(85x1.39 x 13) + (0.0031 x 58)
= [(1536) + (0.18)]
= **1536** (Pulmonary doc math)

CaO2 = [(100x1.39 x 13) + (0.0031 x 700)
= [(1807) + (2.17)]
= **1809.17** (HBO doc math)

Is there a role for HBO?

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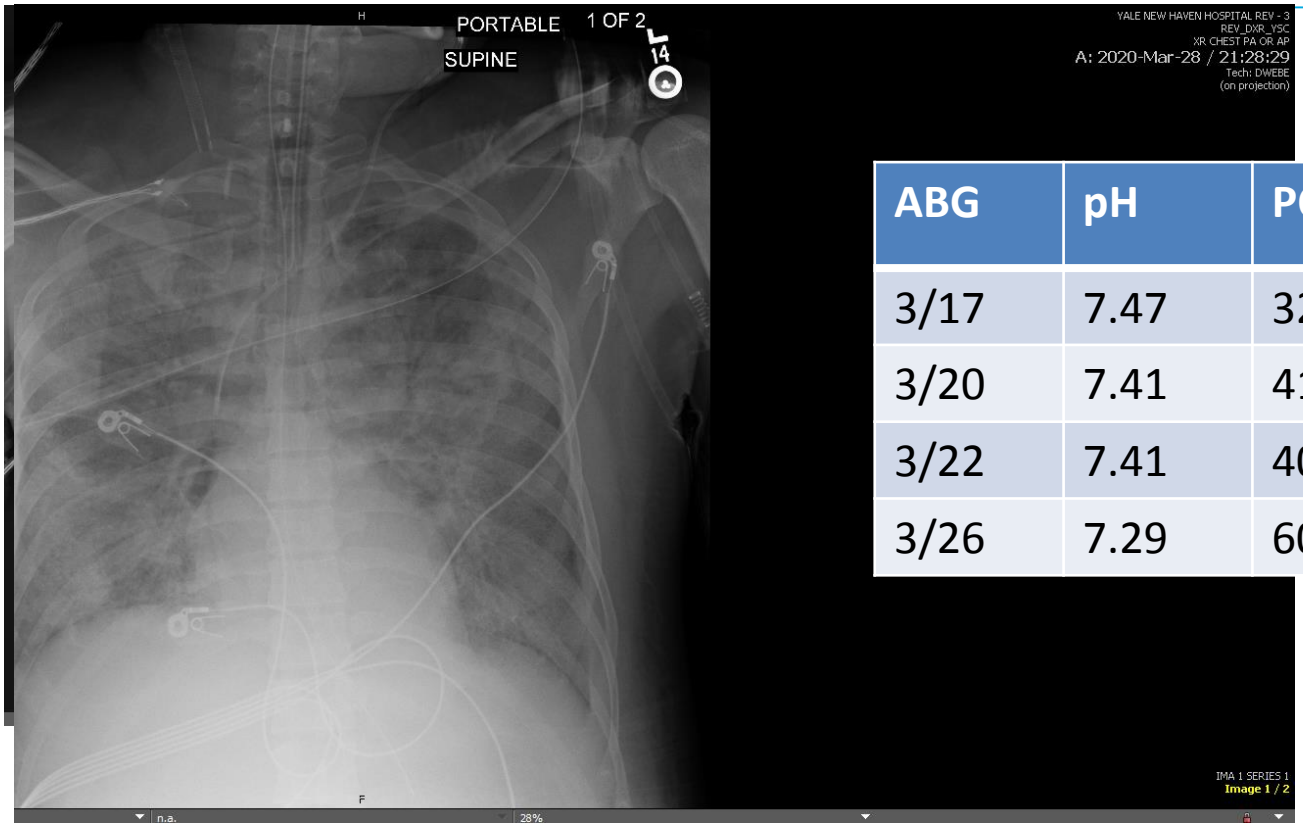
33y March 17, 2020

These patients are so sick! Why are they so HYPOXIC – for being so young and no medical problems!!



ABG	pH	PCO2	PaO2	O2 device
3/17	7.47	32	109	100%nrb
3/20	7.41	41	191	100%nrb
3/22	7.41	40	355	350/15
3/26	7.29	60	68	260/30

There are only 5 reasons for hypoxemia!
AND only 2 (normobaric) things you can do about it!!

Is there a role for HBO?

FiO2 and PEEP – MOC ?

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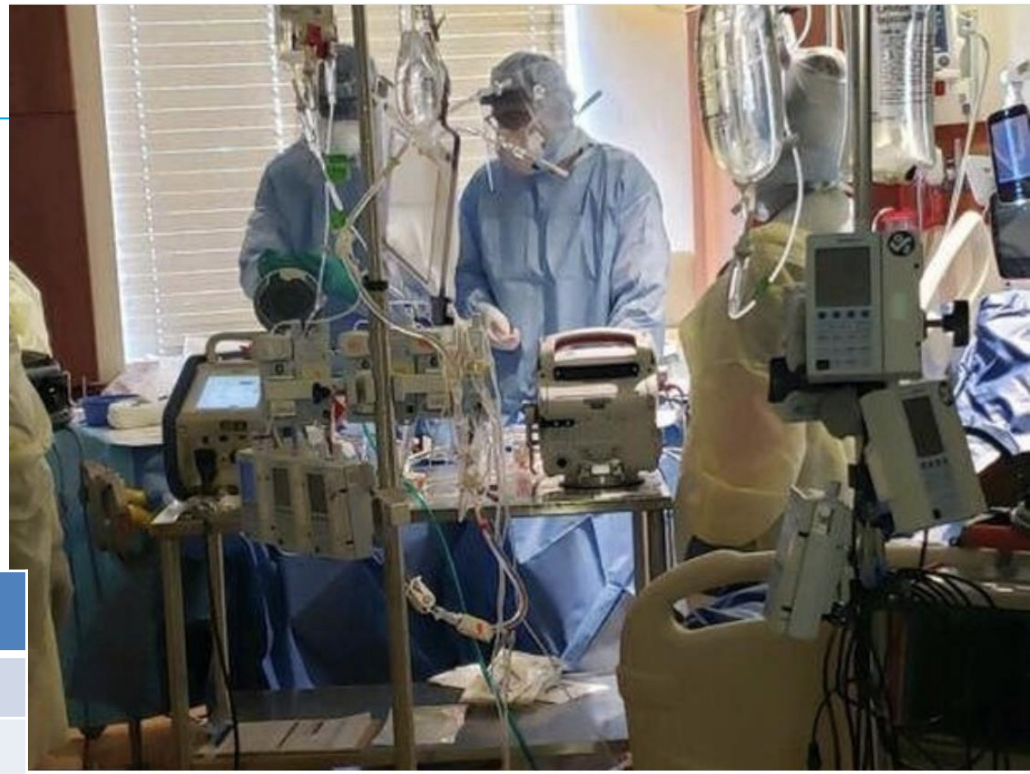
33yM

ABG	pH	PCO2	PaO2	O2 device
3/17	7.47	32	109	100%nrb
3/20	7.41	41	191	100%nrb
3/22	7.41	40	355	350/15
3/26	7.29	60	68	260/30
3/28	7.15	94	96	ECMO



unitednations

28,561 likes

unitednations "I'm profoundly grateful for the heroic efforts of all health workers on the front lines of the global fight against the... more

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4 days ago

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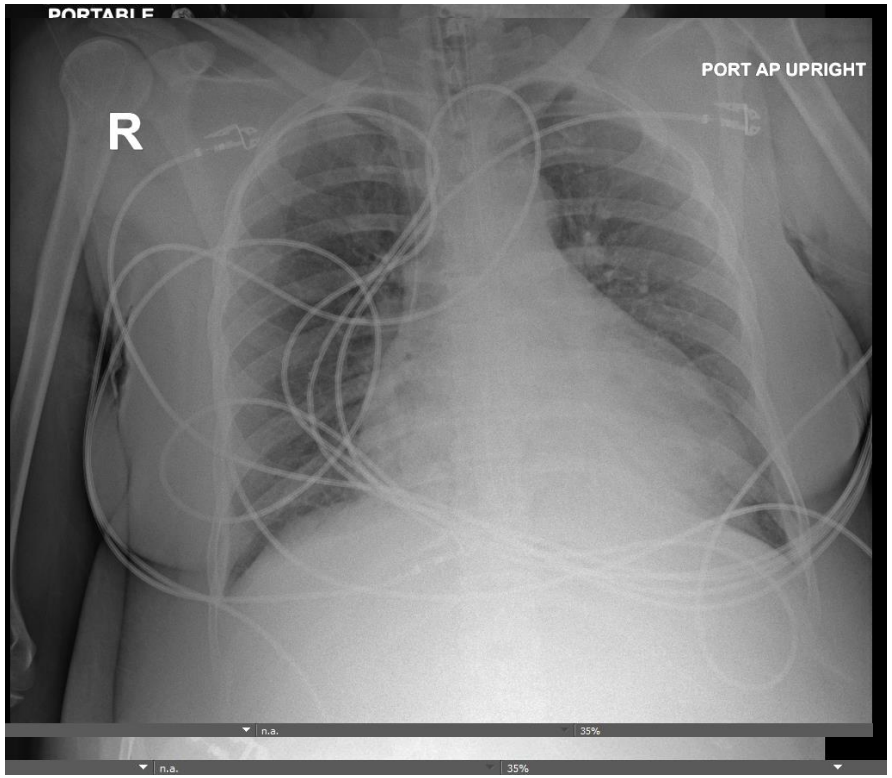
Health

March 21 2020 (43yf)



Chem			CBC	
Na	138		WBC	5.2
K	3.7		Hgb	7.8
Cl	106		Plt	202
CO2	28		lymph	4% (14-43)
BUN	13		Nl range	14-43%
CRT	0.74		LDH	453 (35-190)
GLU	164		D-dimer	0.44

Abg	pH	PCO2	PaO2	O2 Deliv	Bicarb
3/21	7.21	62	72	450/18	23
3/24	7.28	54	64	340/24	24
4/11	7.40	47	52	6Lnc	28

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Profile Chest
Why we Prone
A
P
heart
Upside down triangle
ARDS = "baby lung" ventilation
Together.
Unstoppable.
Recruit
trauma

unitednations

28,561 likes

unitednations "I'm profoundly grateful for the heroic efforts of all health workers on the front lines of the global fight against the... more

View all 224 comments

Preload
Afterload
Starling's curve
PEEP
Driving Pressure
Peak/Plateau Pressure
West Zones
V/Q mismatch
Oh my!

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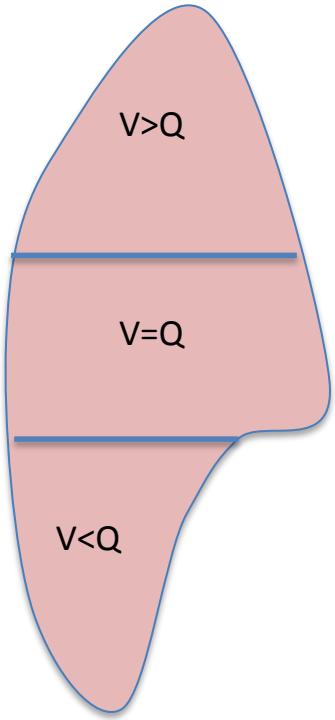
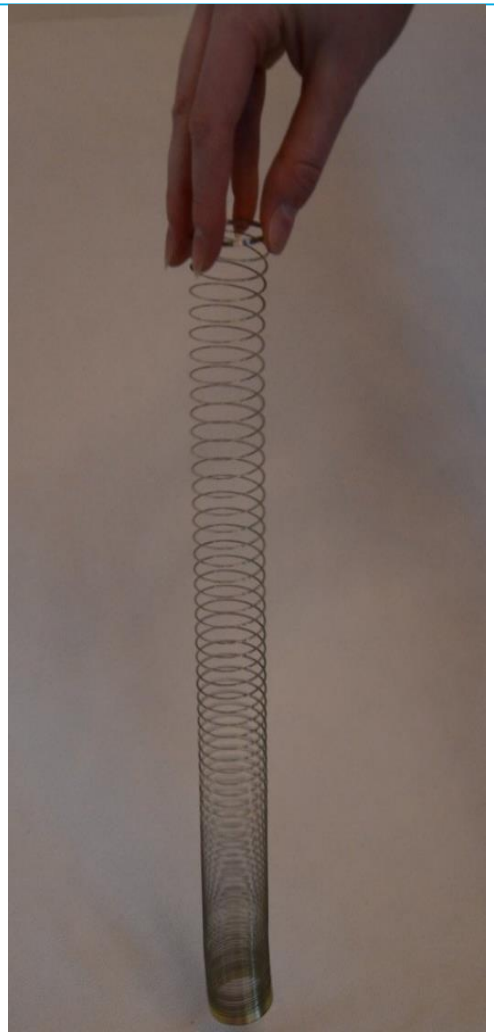
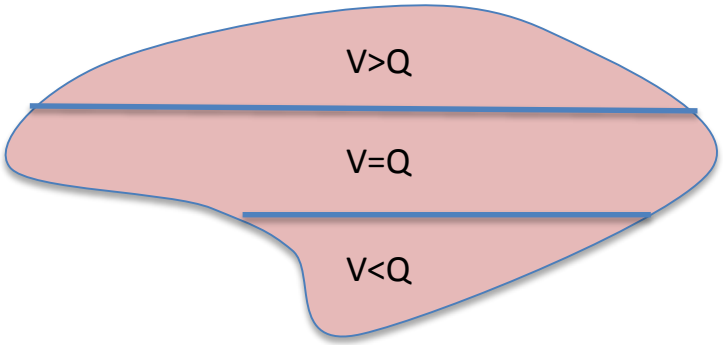
West Zones of the Lung and Why We Prone







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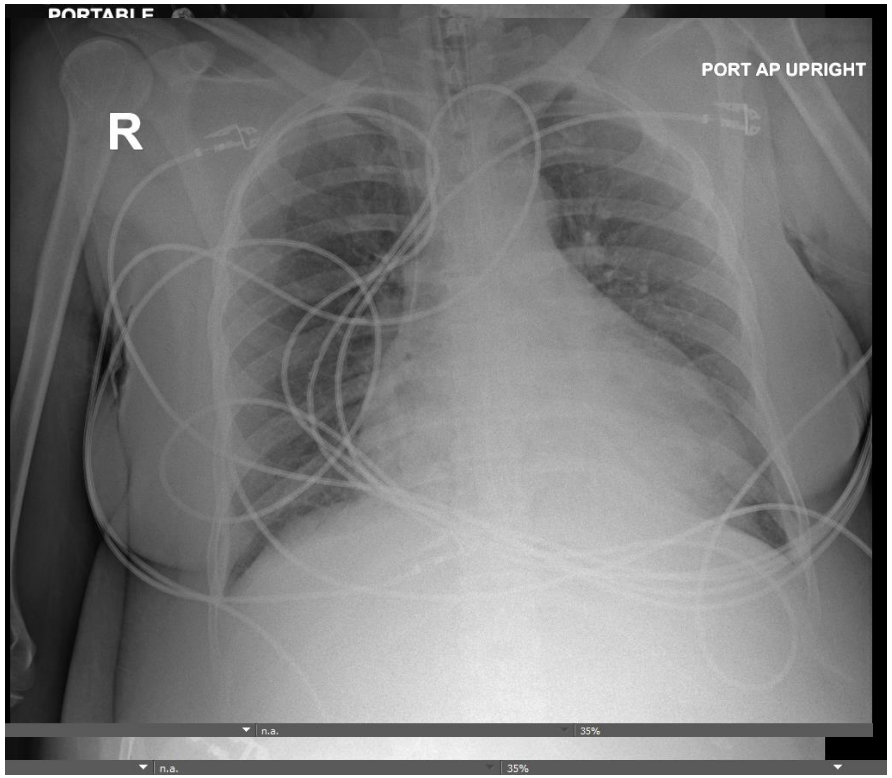
This is one of your MOC ?'s

Remember our 43yf? Hospital course



Chem			CBC	
Na	138		WBC	5.2
K	3.7		Hgb	7.8
Cl	106		Plt	202
CO2	28		lymph	4% (14-43)
BUN	13		Nl range	14-43%
CRT	0.74		LDH	453 (35-190)
GLU	164		D-dimer	0.44

Abg	pH	PCO2	PaO2	O2 Deliv	Bicarb
3/21	7.21	62	72	450/18	23
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4/11	7.40	47	52	6Lnc	28

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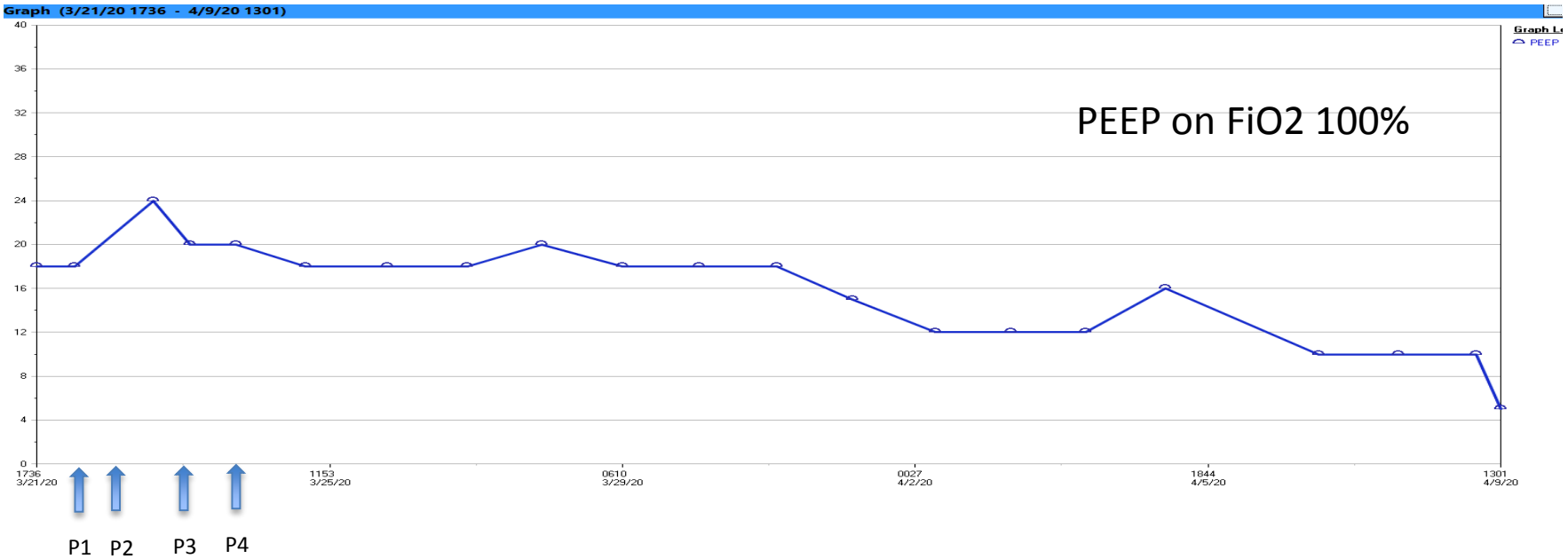

The proof is in the proning

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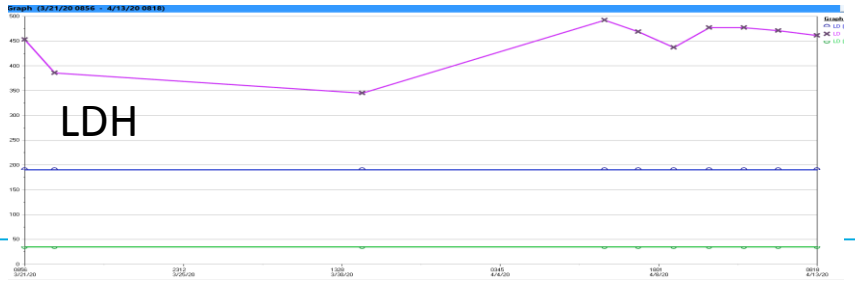
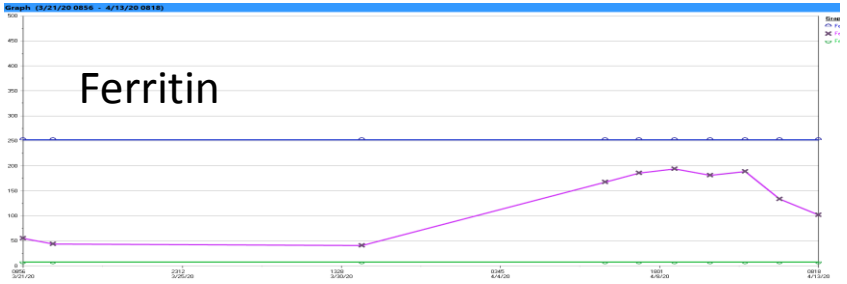
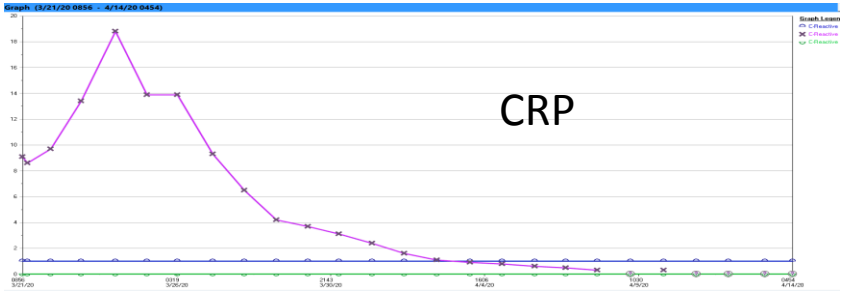
43Y F Hospital Course

- She completed 5 days of azithromycin on March 25th.
- She completed 10 days of Hydroxycholoroquine on March 30th
- She completed 10 days of atazanavir on April 1st.
- She received 1 dose of tocilizumab on April 5th.







D1
(d#6 covid)

D18

D35

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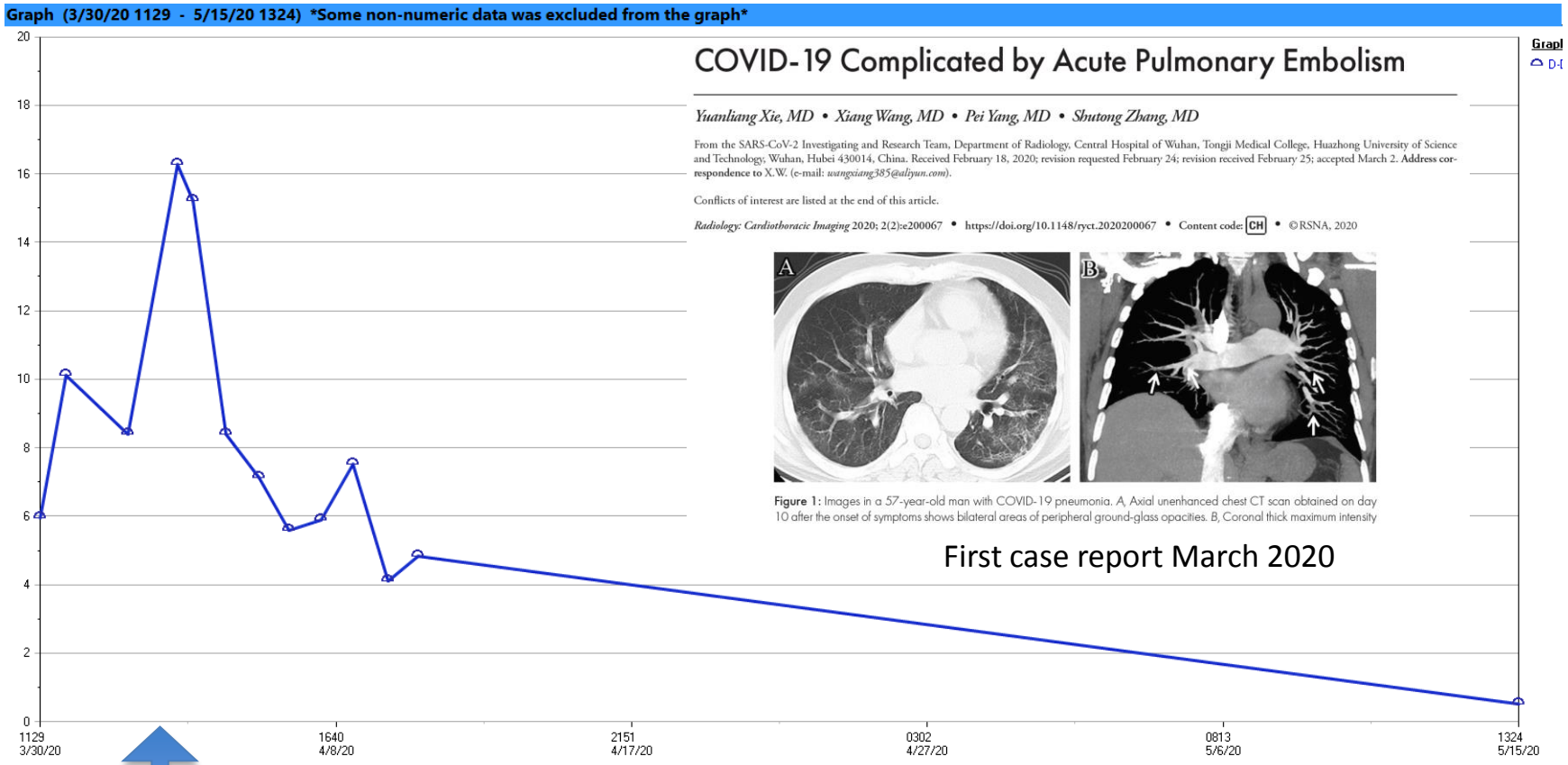
COVID-19 Causes Thromboses??? 57yM



First case report March 2020

New Chest Pain on DVT Prophylaxis 4/3/20

2 days later Hospitalists and Intensivists decided full dose a/c was the right thing to do despite no evidence yet…

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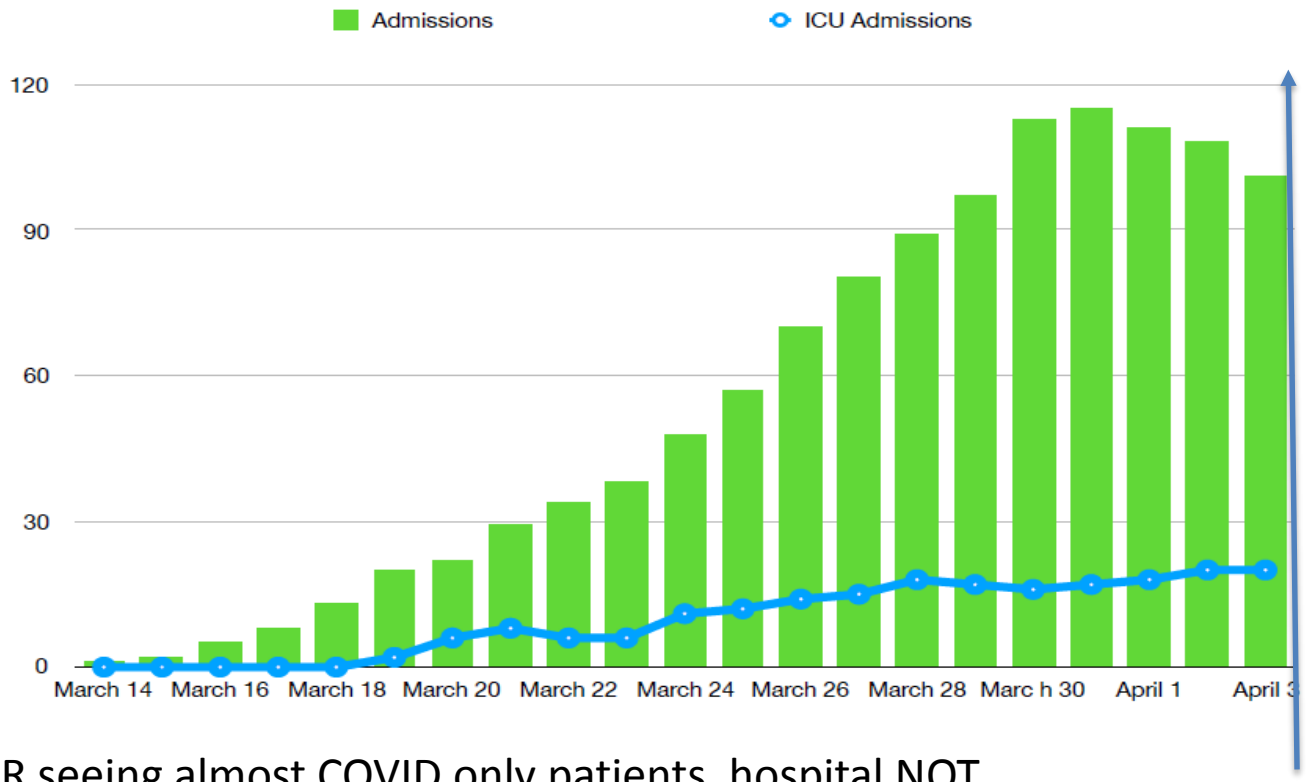
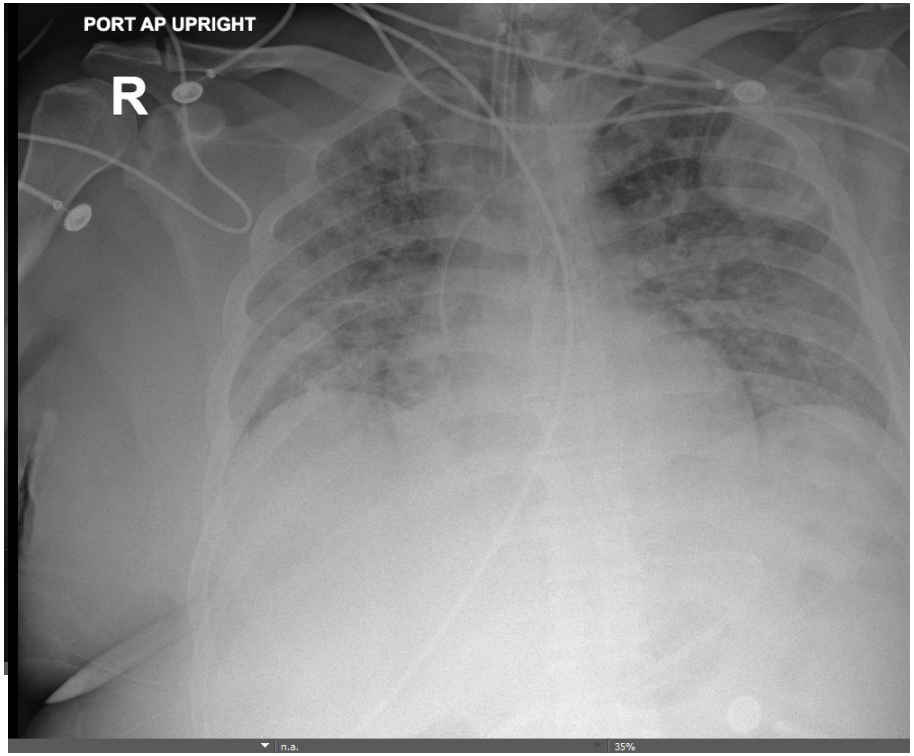
Oh MY, this is getting REAL!
April 3, 2020



ER seeing almost COVID only patients, hospital NOT seeing usual flu, COPD exacerbation, MI's, Cholecysititis, appendicitis, CVA's etc.

“We’re gonna need a bigger boat”

April 12, 2020 (44ym)



Chem			CBC	
Na	143		WBC	5.1
K	4.3		Hgb	15.3
Cl	107		Plt	178
CO2	26		Lymph	13
BUN	0.19		LDH	605
CRT	0.8		Ferritin	2523
Gluc	82		D-dimer	

Pt got tocilizumab on April 12th
on Zithromax prior to presenting and then received an additional dose on the 12th
He was on hydroxychloroquine for 7 days from April 12 to April 18th.
He entered the Remdesivir expanded access program on April 18th. He completed the 10 days of the remdesivir on April 27th.

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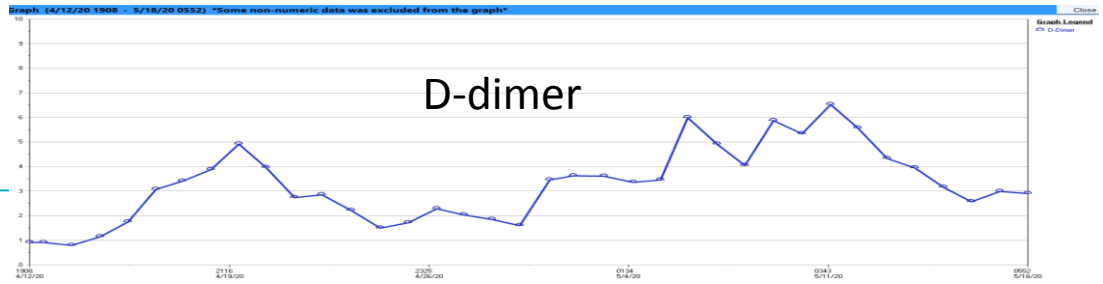
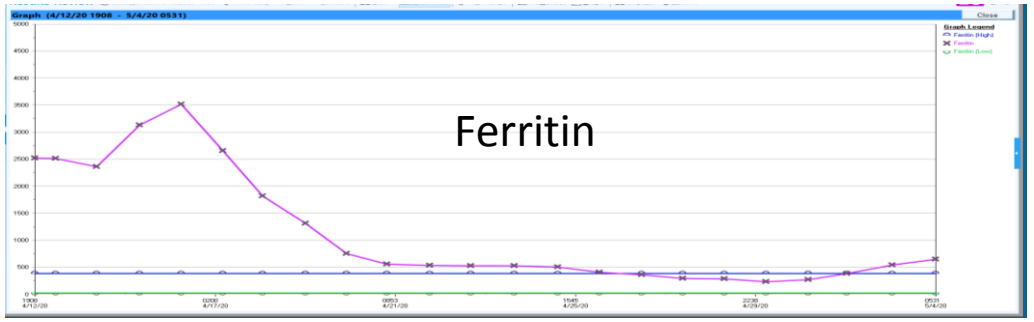
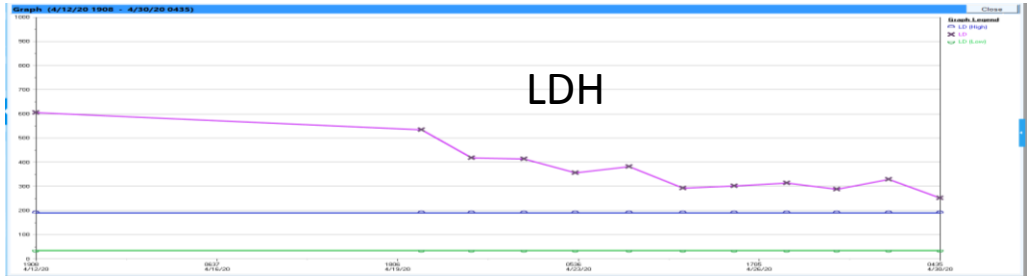
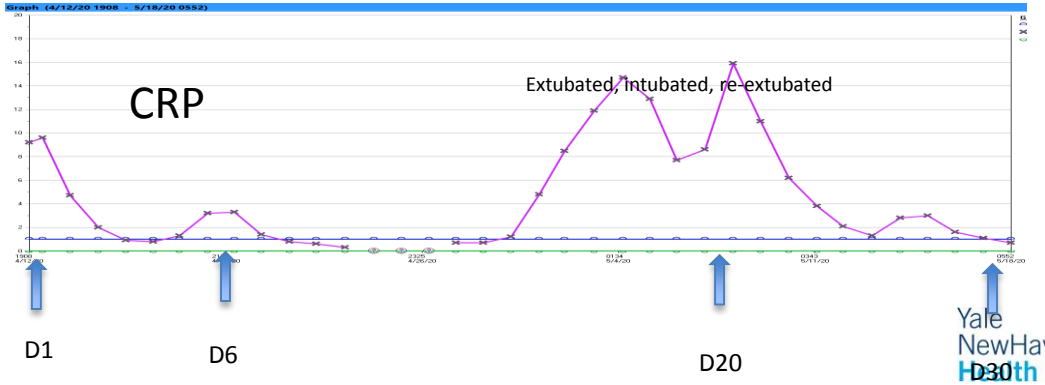
4/12/2020 (44ym)

Day 1 Admission
Day 6 intubation
Day 18 extubated
Day 20 reintubated
Day 22 extubated again
Day 30 d/c home on O2









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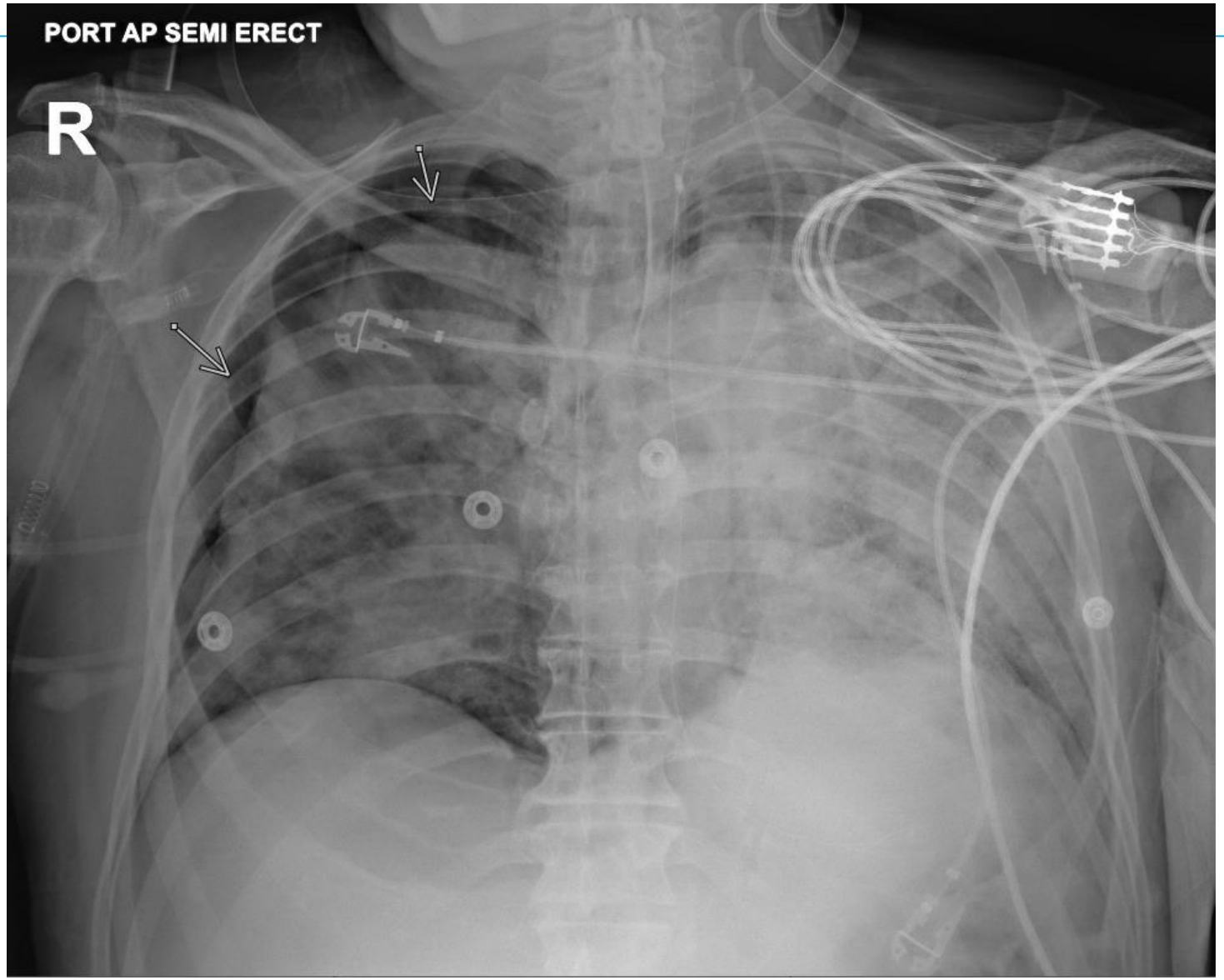
We are Seeing Sequelae of Prolonged Mechanical Ventilation



4/6/20

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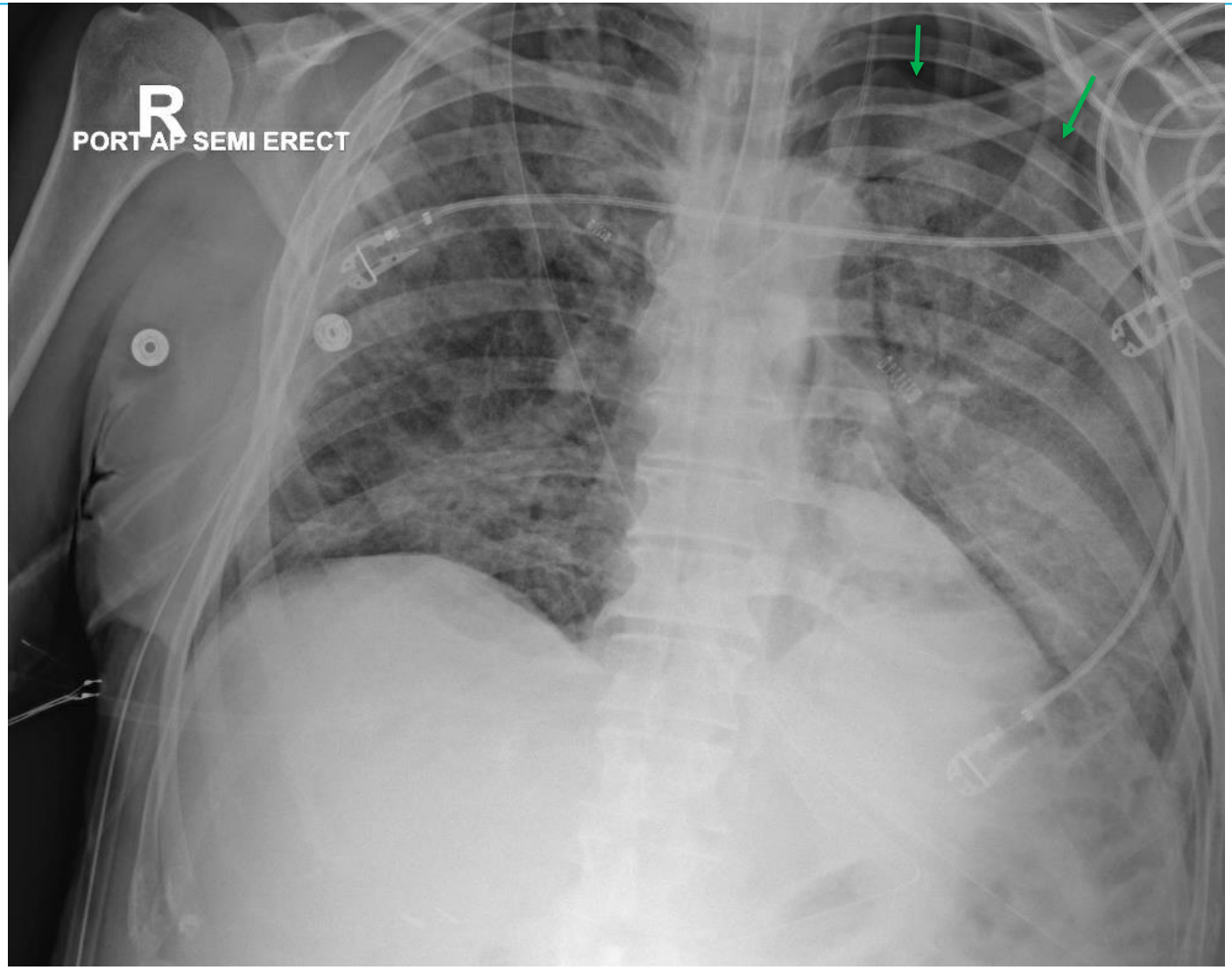

4/9/20

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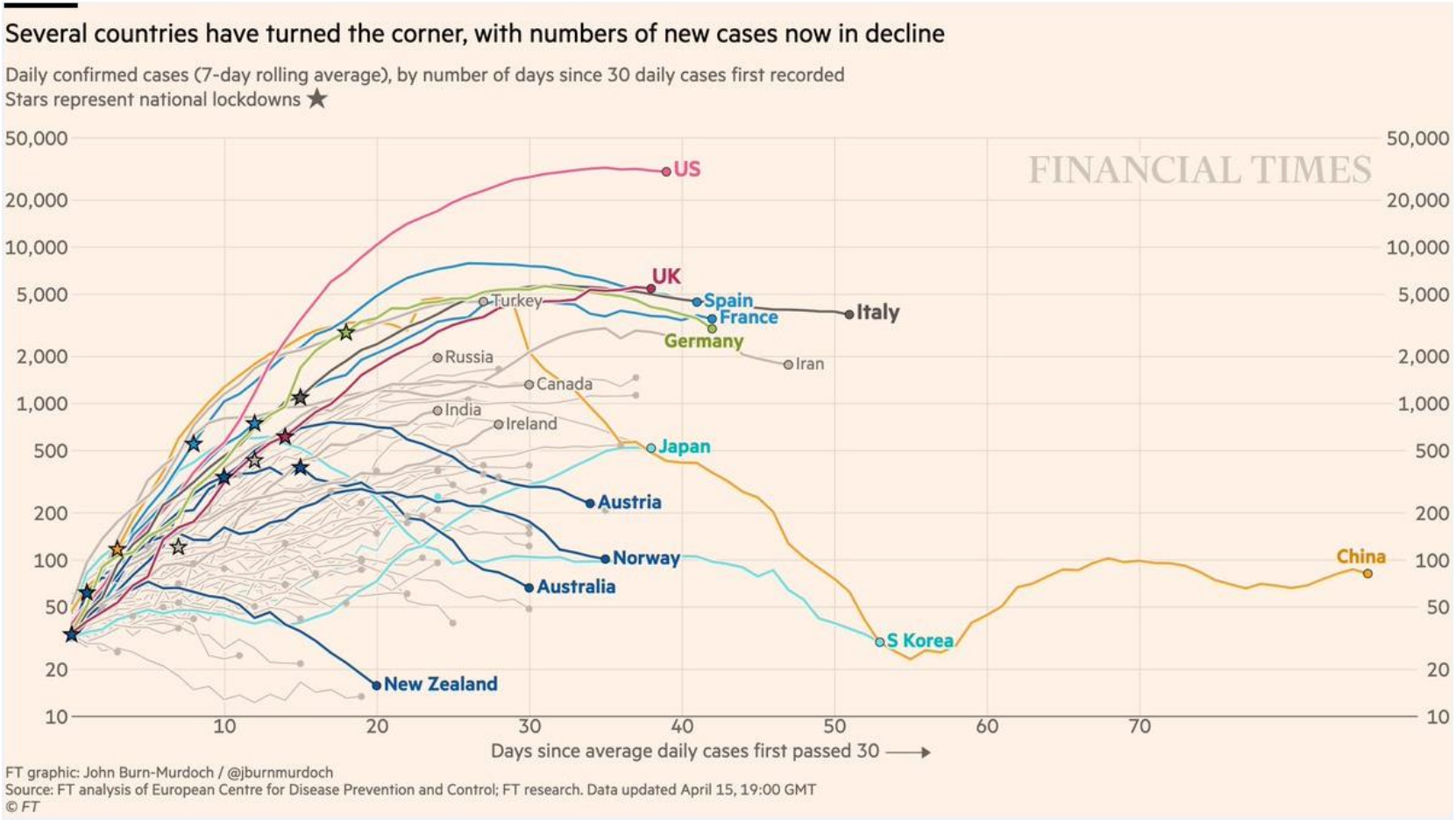
April 15, 2020



NewHaven Health

April16, 2020

Dear Medical Staff and House Staff,

I just wanted to bring you up to date on the situation at Greenwich Hospital regarding COVID-19.

We have had **366 admissions** to the hospital, with the **daily census about 120,** with a **daily ICU census of 24**, most all on ventilators.

We have had a stable ICU census, as each day 1-2 cases are transferred to Yale to keep the census near 20 for staffing purposes.

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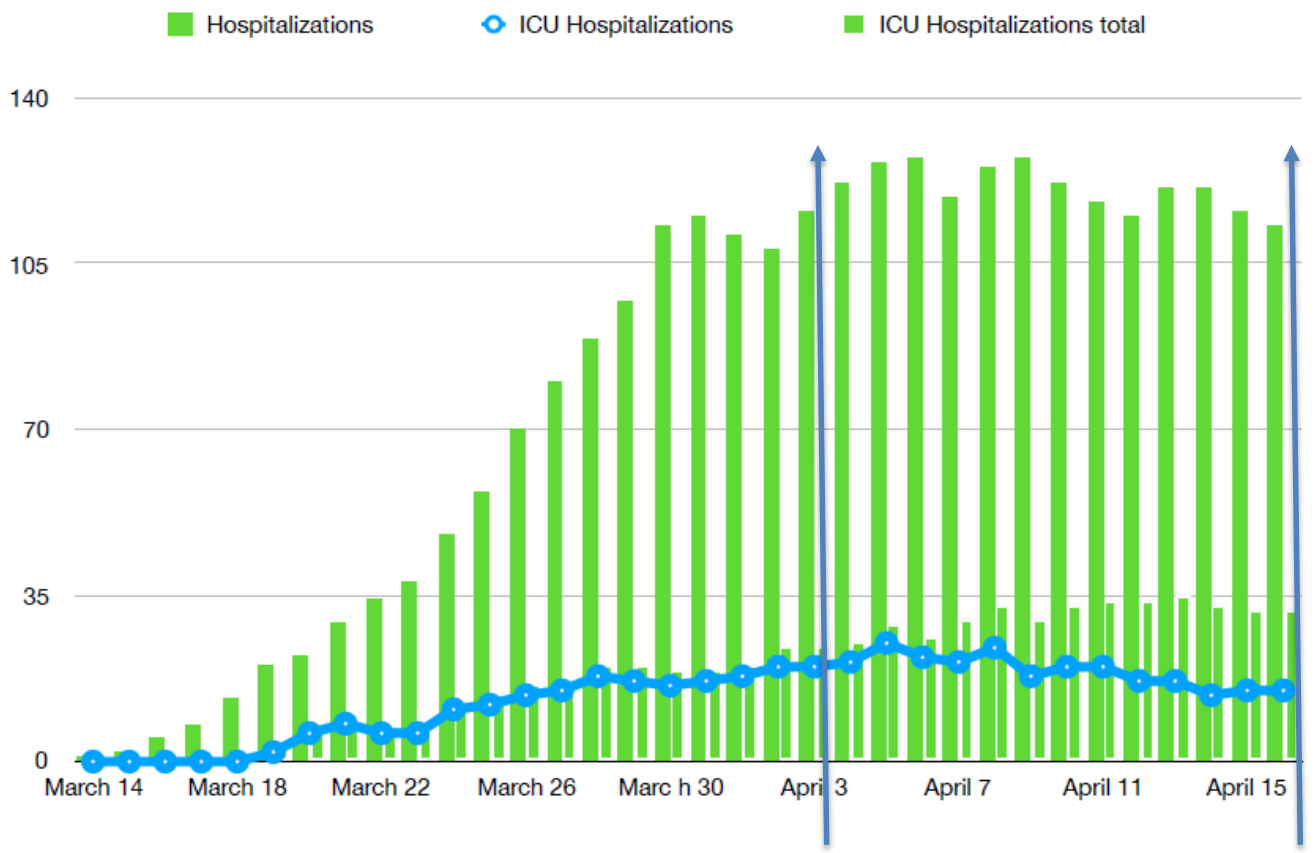
April 16, 2020 When will this rollercoaster ride end???



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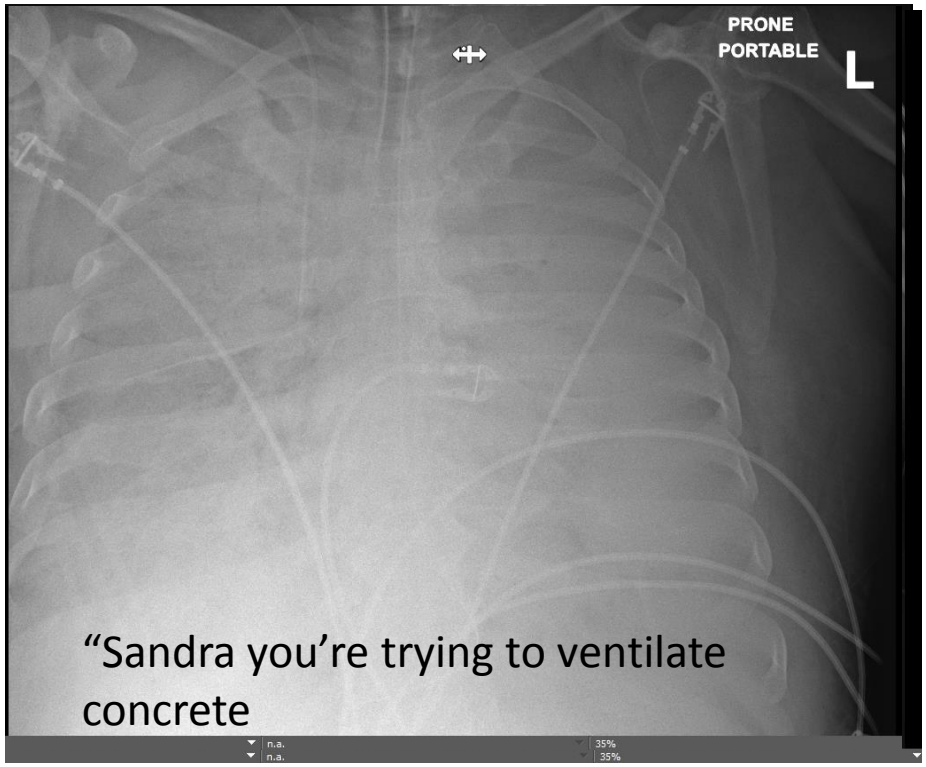
April 16, 2020 - Passover

- COVID-19 does things in clusters: severe respiratory failure, increasing inflammatory markers, thrombosis, renal failure, pulmonary barotrauma, sudden cardiac arrest. The plagues of COVID-19
- The angel of Death passed over our little hospital and took three of our patients in a matter of 30 minutes – the staff were devastated
- We had decided that CPR wasn't an indication because death occurs from non-cardiac reasons
- Most patients by this time were already getting full ACLS support with 4 pressors, bicarb, antibiotics, steroids, dialysis, heparin, famotidine
- No convalescent plasma yet

4/30/2020 53ym no medical problems - obesity



Chem			CBC	
Na	139		WBC	8.1
K	3.6		Hgb	14.4
Cl	105		Plt	228
CO2	24		Lymph	12.6
BUN	17		LDH	803
CRT	1.19		Ferritin	1196
Gluc	112		D-dimer	0.5

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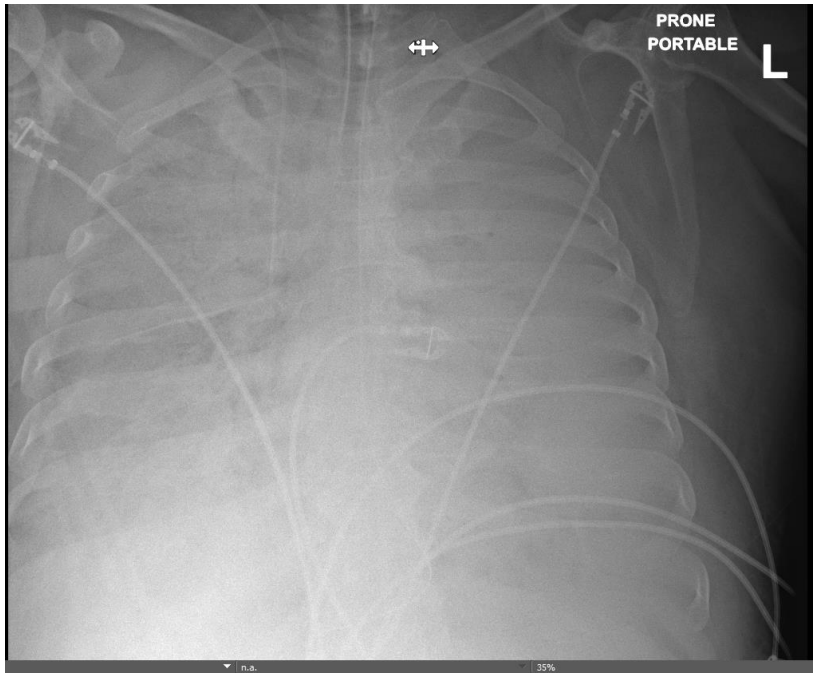
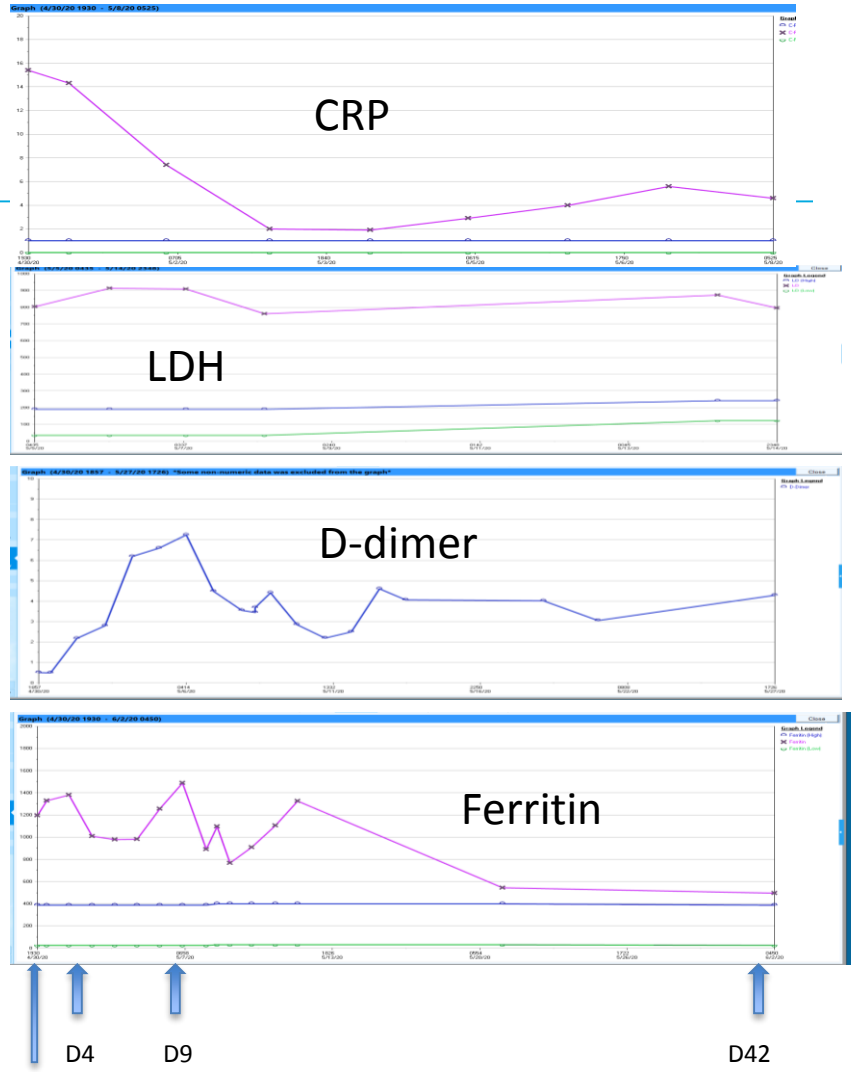
4/30/2020 53ym





Almost out of options
-eNO
-CVVH

pH	PCO2	PaO2	Vent
7.18	**55**	**47**	**PC 54/20**
7.40	*40*	*80*	*Peak<30*

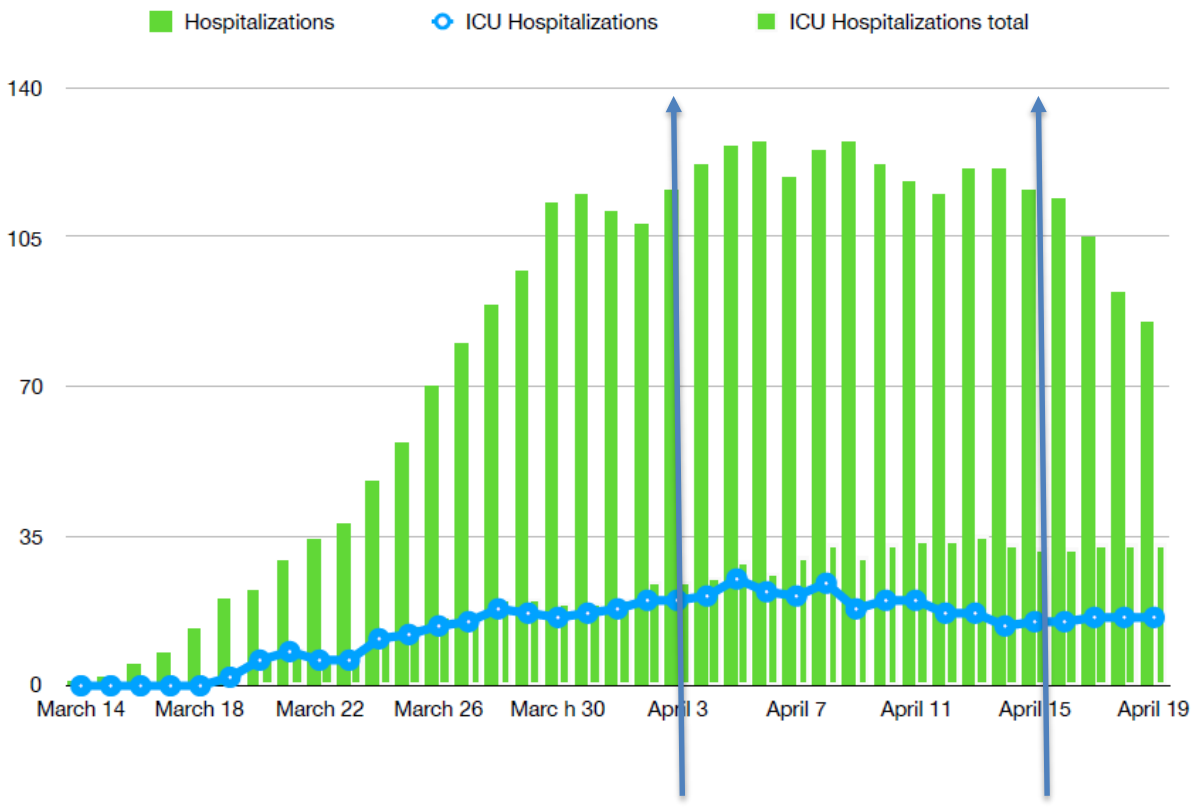
"illegal pressures"

Yale NewHaven Health


RN
Yale
NewHaven
Health
Greenwich
Hospital

Yale
NewHaven
Health

April 19, 2020 – Light at the end?



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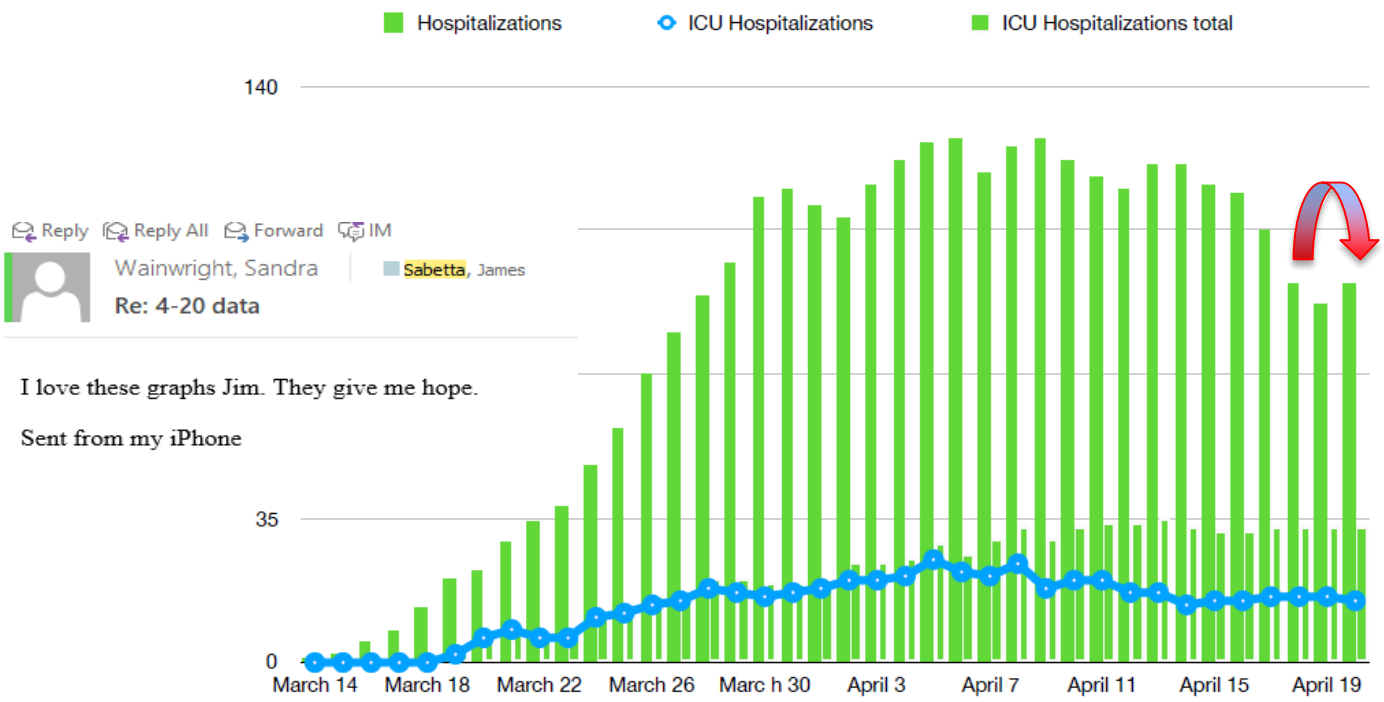
Health

April 20, 2020 – One month later, how long is this going to last?



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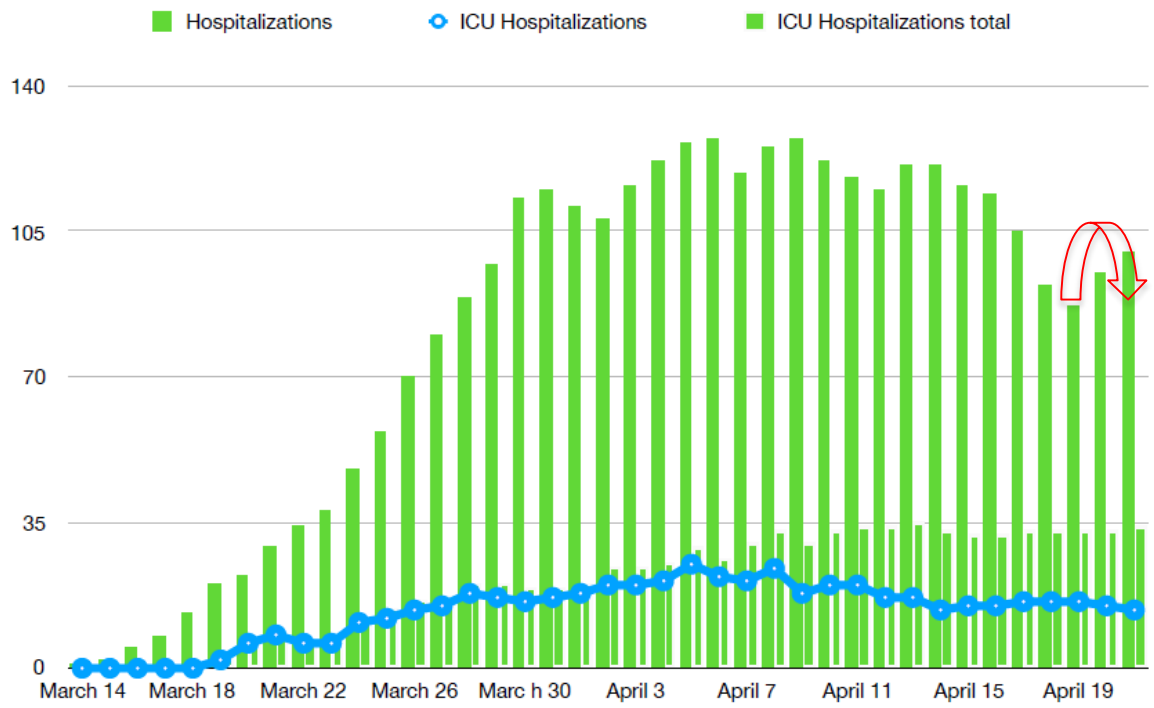
April 22, 2020 Wait, I thought things were getting better….

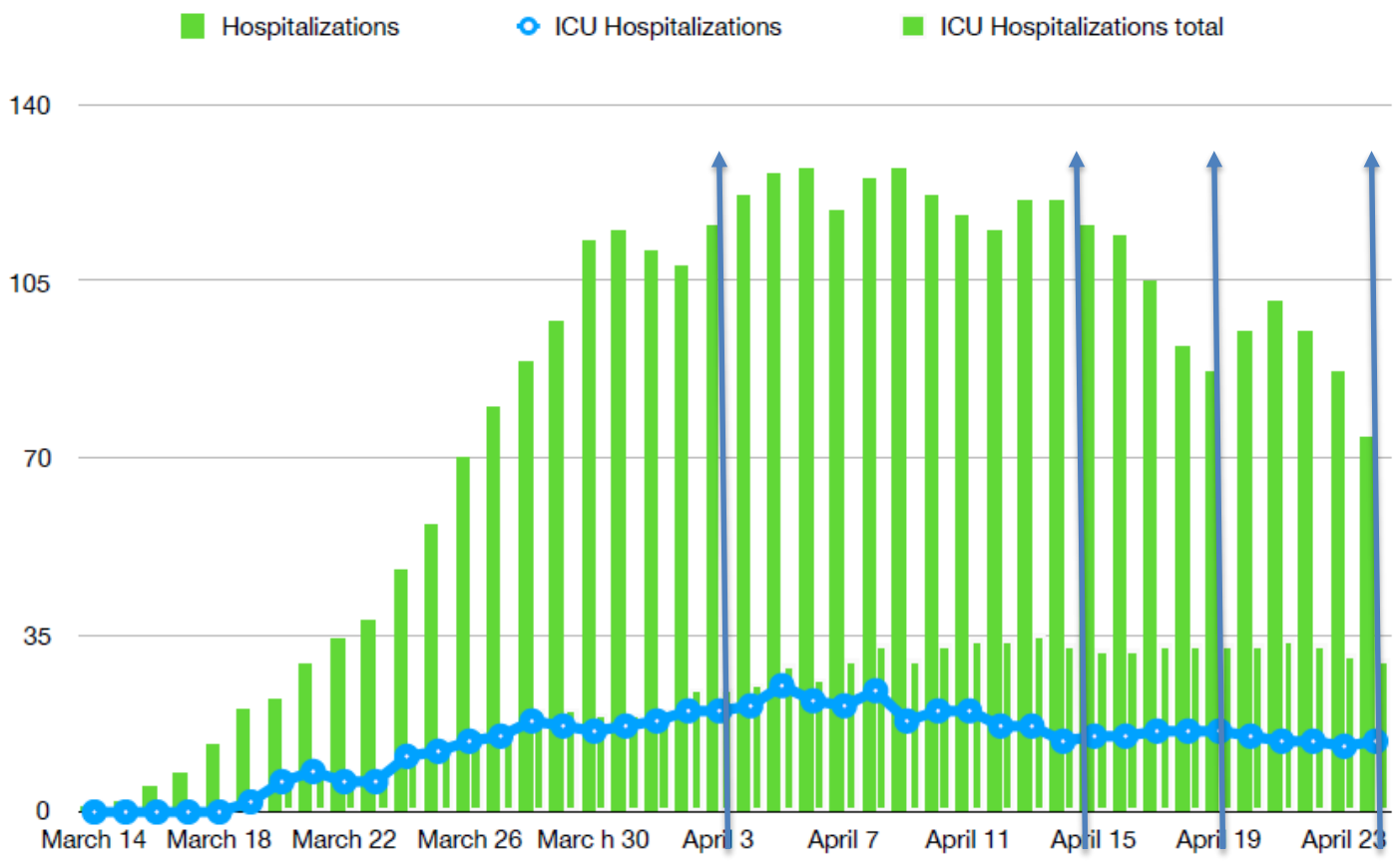


Uptick???

After a review of GH COVID-19 vents dating back to 3/20/20 (our first COVID-19 intubation).
As of 4/21.

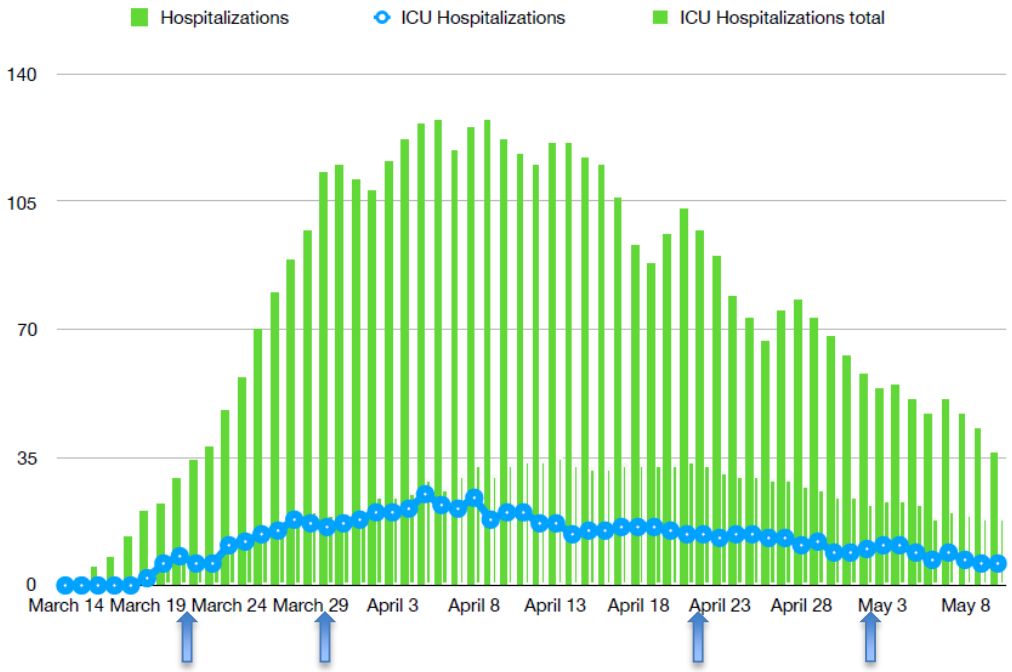
Total intubations (vents)	68		
Extubations	17	(25%)	of these 8 discharges (12%)
Deceased	18	(26%)	
Still on vent GH	16		
Still on vent YNHH	17		

April 24, 2020



NewHaven Health

Our COVID-19 Graph



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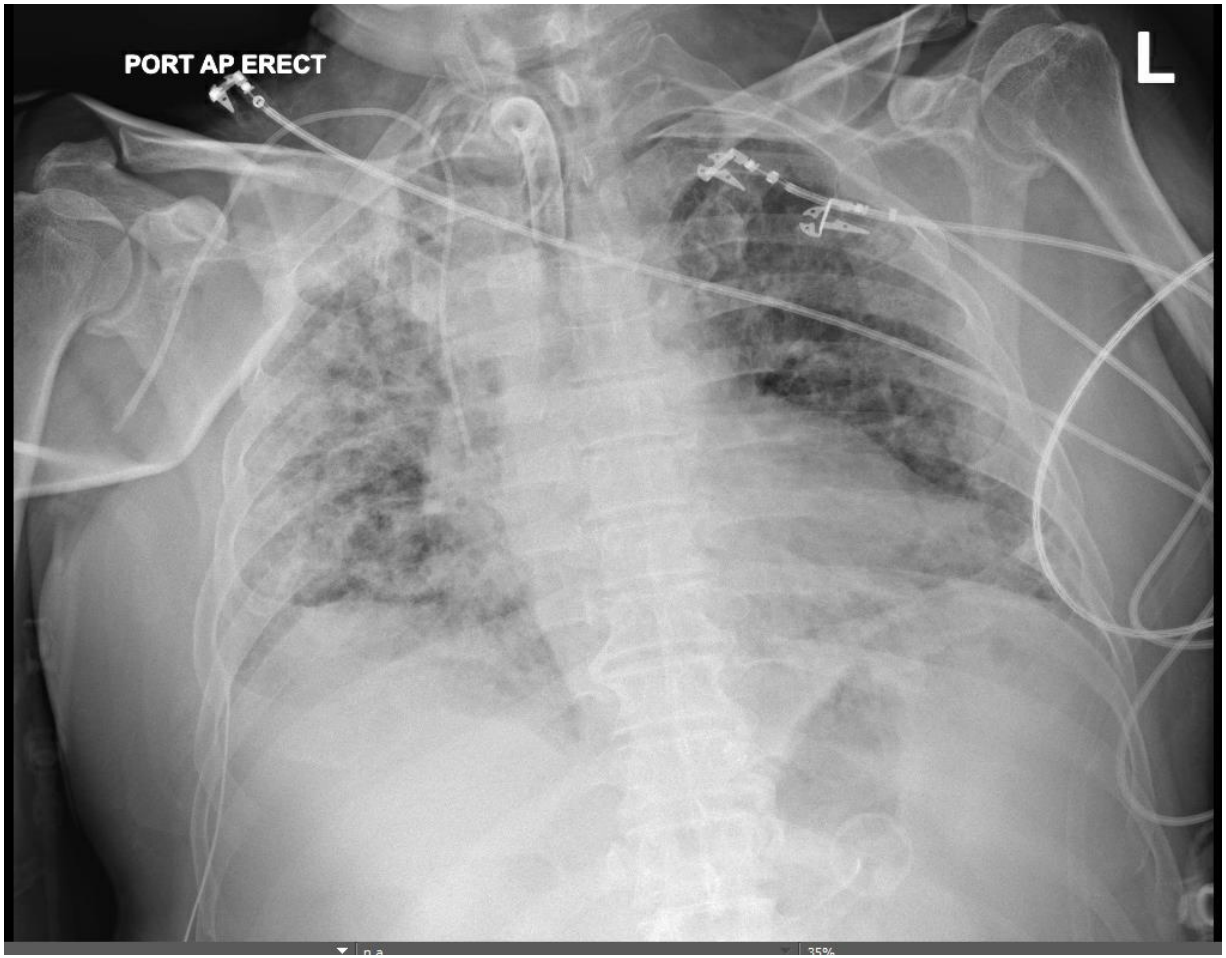
Post COVID/ARDS Pulmonary Sequelae



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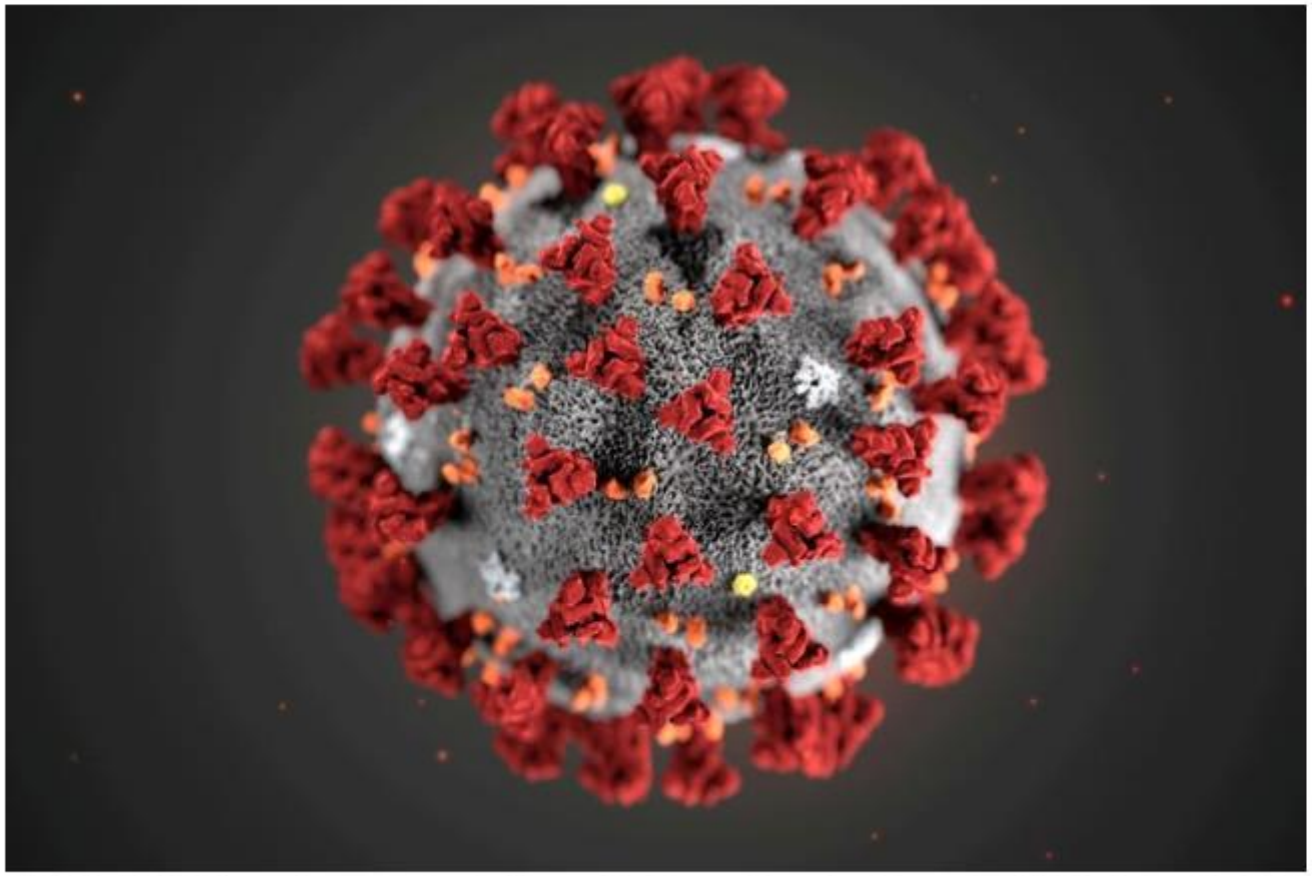
EBM		Novel COVID-19 Experience
ARDS – (ARDSNET) low Vt high PEEP with "permissive hypoxemia and hypercapnia" to avoid barotrauma in STIFF lungs		ARDS (by P/F ratio and CXR criteria) – lungs were less stiff, more compliant, less hypercapnia, less tolerant of hypoxemia than "nl" ARDS.
Proning – PROSEVA trial In the Proning Severe ARDS Patients (PROSEVA) trial, patients with severe ARDS were randomized to either prone-positioning for 16 hours or left in supine position. In summary, proning significantly reduced 28- and 90-day mortality compared to leaving patients in the supine position. Proned patients also experienced significantly higher rates of successful extubation and fewer days requiring ventilation compared to those in the supine group.		Proning – made a big difference! We began proning non-intubated patients on the floors, then the ER
ARDS – steroids (Gattinoni)-combined trials showed statistically important improvements in some clinically relevant endpoints, including oxygenation, ventilator-free days, and, for those randomized within 14 days of the onset of illness, survival. However, it has been more difficult to show a consistent mortality benefit overall		Steroids – anecdotally pt's on chronic steroids didn't get as sick, tried to time steroids with "cytokine storm" n=too small to know
Early Intubation – MGH **The Case Against Conventional Management of Hypoxia** Hypoxemia is often a presenting sign of COVID-19 and can progress rapidly. Noninvasive positive-pressure ventilation aerosolizes respiratory droplets and increases the risk of transmitting SARS-CoV-2. In a case series from China, it had a very high failure rate, so it exposed health care workers without much benefit in preventing intubation. In addition, a patient on noninvasive ventilation has a very high respiratory drive, taking large breaths at a rapid rate with large pleural pressure swings. This can actually worsen lung injury and propagate acute respiratory distress syndrome (ARDS).		Early Intubation – GH filled ICU in 3days and 2 weeks later pts still on vents – with no hope of impending extubation. Pt's looked "ok" on max O2, some survived to not be intubated. JAMA 4/22/20 – Safiya et al – Motality for 18-65y who rec'd mech vent were 76.4-97.2% As of the writing of this presentation our ICU mortality was 45%
Pharmacologic therapies Remdesivir Plaquenil Zithromax Tocalizumab Lopinavir/ritonavir **Dexamethasone** Convalescent plasma		Meh?? Timing the doses was always the question and none of these therapies seemed to be the 'magic bullet' we were hoping for 

Tiny sponges may soak up coronavirus; old steroi dexamethasone saves lives in COVID-19 study

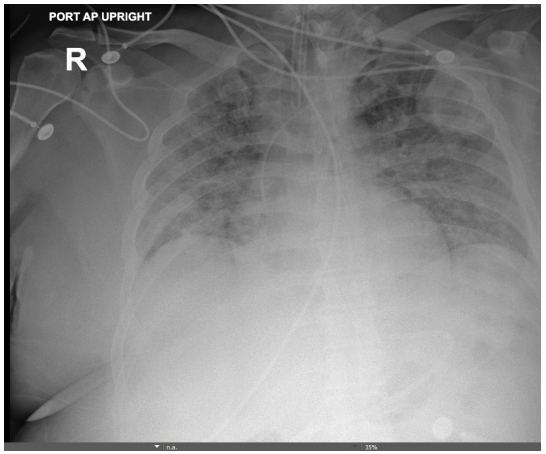
REUTERS **Nancy Lapid**, Reuters • June 17, 2020

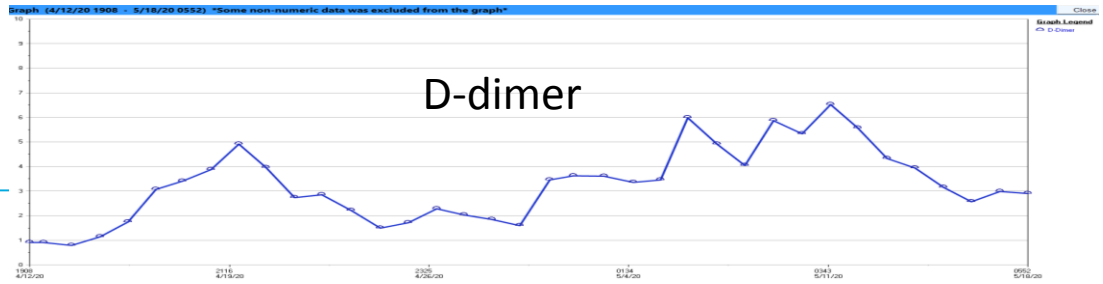


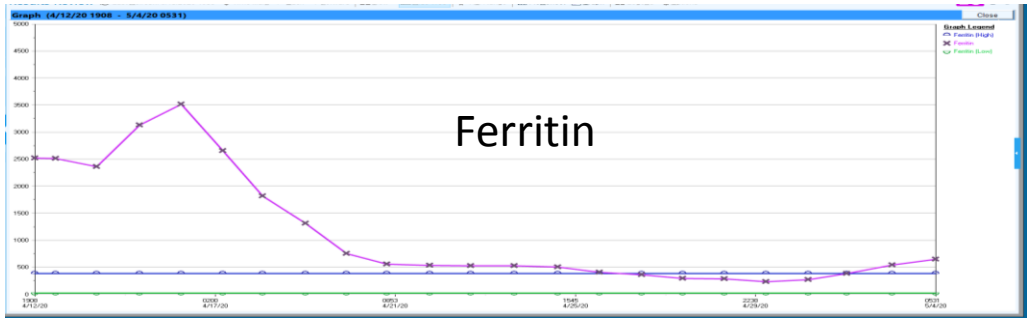
FILE PHOTO: An illustration, created at the Centers for Disease Control and Prevention (CDC), depicts the 2019 Novel Coronavirus

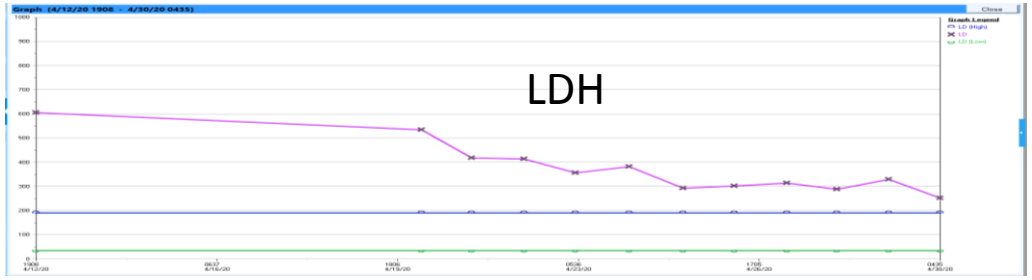
4/12/2020 (44ym)

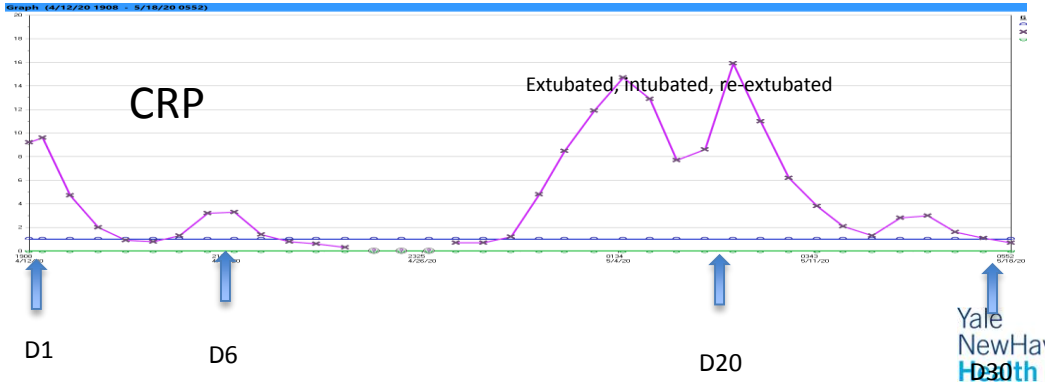
Day 1 Admission
Day 6 intubation
Day 18 extubated
Day 20 reintubated
Day 22 extubated again
Day 30 d/c home on O2











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Discharge #
2,500
#inthistogether
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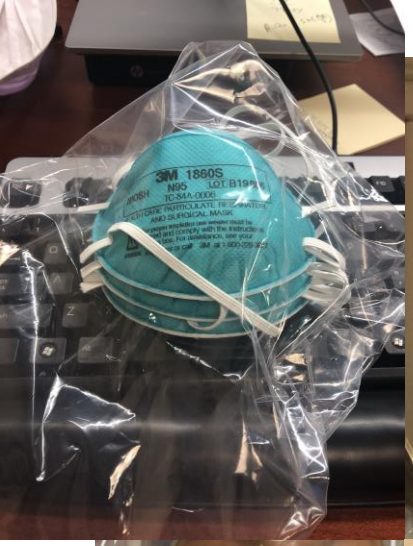
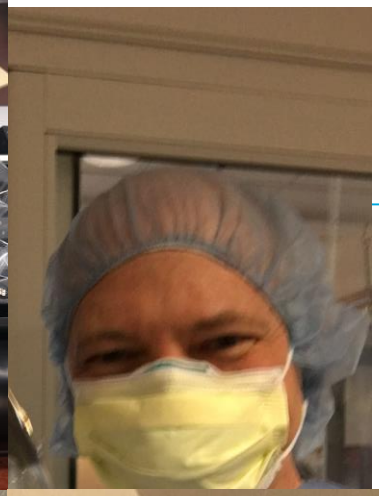
Discharge #
2,500


3M 1860S
N95




Face Shie
Protective Isolation

SW Day #67 and Counting

Yale NewHaven Health

Perhaps this is the moment for which you have been created.

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

NYU Langone Health

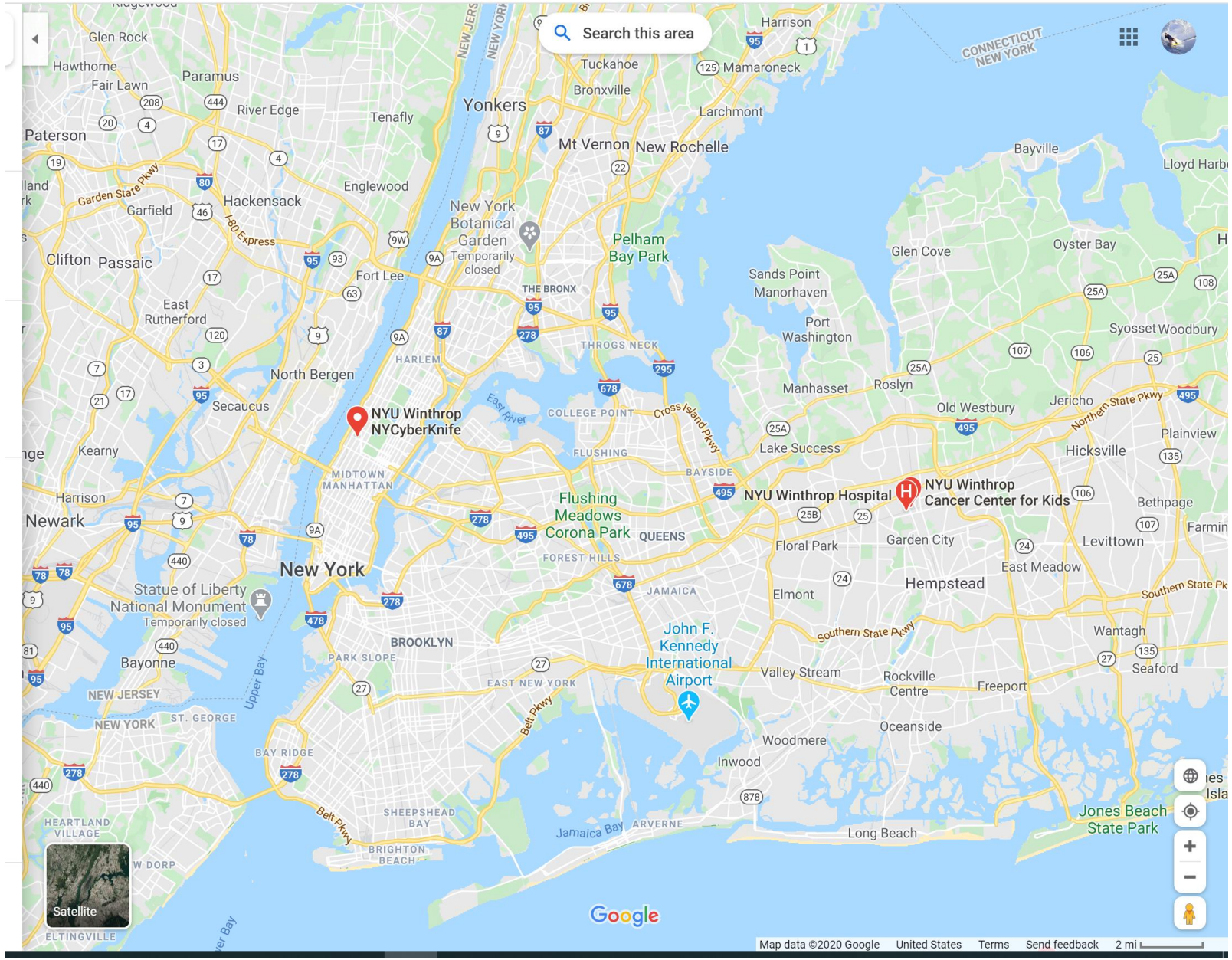
Safety Considerations When Using Hyperbaric Oxygen Therapy for COVID-19

SCOTT A. GORENSTEIN, MD
NYU WINTHROP HOSPITAL

NYU Langone Health

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

I have no relevant financial interest with commercial entities to resolve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March 5 2020


WINTHROP
University Hospital
CORONAVIRUS OUTBREAK
news 12
42-YEAR-OLD UNIONDALE MAN HOSPITALIZED WITH CORONAVIRUS

CASE-CONTROL STUDY DESIGN

- IRB approved case control series
- 40 patients with interim analysis at 20 patients
- Primary endpoint: Mortality / Secondary: Intubation
- Monoplace chambers that were not being utilized to treat any other patients
- Only treating patients admitted to hospital
- All personnel with full PPE
- Physician with advanced airway skills in attendance of entire treatment

CASE-CONTROL STUDY DESIGN

- COVID-19 positive test required
- Sp02 < 93% on RA and responds to supplemental oxygen
- Age > 18
- Negative pregnancy test
- No pneumothorax
- Patients were referred by managing team and then a chart evaluation was done and if eligible the patient was evaluated by the hyperbaric physician to perform risk benefit analysis and obtain informed consent

TREATMENT PROTOCOL

- 2.0 ATA for 90 minutes. Air breaks were an option per treating MD; however, no patient was given air breaks
- Patient was called for and transported to unit with oxygen and surgical mask by hospital transport
- Full assessment with Sp02 was done prior to treatment and supplemental oxygen via mask or NC was continued until treatment initiated
- Patients with diabetes had POCT glucose testing prior to treatment with reading >120 required to begin therapy

TREATMENT PROTOCOL

- During treatment CHT in constant visual attendance with frequent communication
- Upon completion of treatment supplemental oxygen via device resumed and patient removed from chamber. Full assessment performed and transport notified by MD when patient stable to return to floor
- Infection control measures were maintained with full PPE, chamber cleaned with standard solution between patients and at EOD a terminal clean with dilute bleach (1:10) with 5 minute wet time performed

CASES TREATED WITH HYPERBARIC OXYGEN

Age and Sex	Past Medical History	Oxygen Needs Prior to HBO2 Therapy	Hospital Day of First HBO2 Therapy	HBO2 therapy Sessions Received	Patient Outcome or Current Status (Hospital Day)	Other COVID-19 Therapies Received	Comments
43 M	None	2	0	2	Discharged (4)	AZITH, HCQ	Declined additional treatments
62 M	HTN, HLD, DM, ASTHM	3	2	4	Discharged (8)	AZITH, HCQ	Discharged before five treatments
54 M	None	4	7	4	Discharged (12)	AZITH, HCQ	Discharged before five treatments
56 F	HTN	4	2	5	Discharged (7)	PLASMA	Completed all five treatments
79 M	HTN	4	1	5	Discharged (10)	HCQ, anti-IL6	Completed all five treatments
54 M	None	5	4	2	Discharged (9)	AZITH, HCQ	Limited sessions due to technician availability
57 M	HTN, HLD, DM	5	4	2	Discharged (12)	AZITH, HCQ, anti-IL6	Discontinued due to ear pressure
30 M	None	6	1	5	Discharged (10)	AZITH, HCQ	Completed all five treatments
54 M	None	6	2	5	Discharged (9)	AZITH, HCQ, anti-IL6	Completed all five treatments
58 M	None	6	2	2	Discharged (4)	HCQ	Discharged before five treatments
55 M	DM	7	7	5	Discharged (12)	AZITH, HCQ, anti-IL6	Completed all five treatments
67 M	HTN, DM	8	5	5	Discharged (12)	anti-IL6, PLASMA	Completed all five treatments
55 M	None	9	4	3	Discharged (7)	AZITH, HCQ	Discharged before five treatments
75 M	None	12	9	3	Discharged (38)	AZITH, HCQ anti-IL6	Discontinued due to study pause and then deemed medically unstable
32 M	None	15	4	5	Discharged (9)	AZITH, HCQ, anti-IL6	Completed all five treatments
58 F	HTN, CAD	15	1	3	Discharged (10)	AZITH, HCQ, anti-IL6, PLASMA	Discontinued due to study hold pending safety review for a different patient
60 M	HTN, HLD, CAD	15	15	4	Discharged (24)	AZITH, HCQ, anti-IL6	Discontinued due to study hold pending safety review for a different patient
68 M	HTN, HLD, DM	15	0	5	Intubated (12), Death (35)	AZITH, HCQ, anti-IL6, PLASMA	General anesthesia for removal of large thromboembolism
73 M	HTN, HLD, DM	15	6	4	Discharged (14)	AZITH, HCQ, anti-IL6	Discontinued due to epistaxis
77 M	HTN, HLD	15	1	2	Intubated (3), Death (25)	AZITH, HCQ, anti-IL6	Hypoxic arrest while off oxygen

Patient Safety Issues

Patients with COVID 19 are very unstable and decompensate quickly

During transport to and from the hyperbaric unit patient must be monitored and maintained on supplemental oxygen at all times

Patients should be informed that during the transport they may become more hypoxic

Pulse oximetry must be maintained at all times during the transport

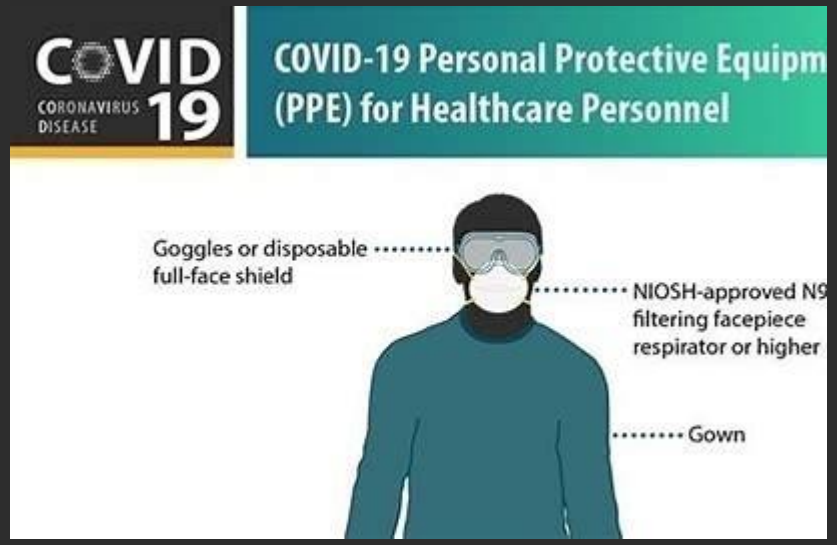
During the treatment patients must be observed by CHT with frequent communication, ideally should have cardiac monitoring

After the treatment patients become hypoxic when exiting chamber, must maintain oxygen via chamber supply and rapidly change to tanks to prepare for transport

Communication with the receiving team is vital to ensure patients are not returned to the floor unexpected

During transport patient required to have mask on at all times

Transport staff in full PPE with N95, face shield , gown and gloves



STAFF and FACILITY Safety Considerations

All staff must be wearing full PPE at all times

Ideally Chambers should be located in Negative Pressure Room

If treating routine non-COVID patients chamber area needs terminal clean

Advanced area equipment with glide scope or fiber optics suggested,

Viral filters must be used if intubating or BVM

Patients should have the appropriate HBO approved garments prior to arrival in unit

Due to Severity of illness a 1:1 provider to CHT ratio with direct and constant physician attendance

Oxygen consumption likely to be much higher than normal, facility may need back up liquid oxygen supply

HBOT & COVID-19

Marcus S. Speyrer, RN, CWS, DAPWCA

Opelousas
GENERAL HEALTH SYSTEM

“I have no relevant financial relationships with commercial interests to disclose”


Opelousas
GENERAL HEALTH SYSTEM
The WOUND TREATMENT CENTER
"Entrust Steps Here"
NEW HYPERBARIC
TREATMENT AVAILABLE
FOR COVID PATIENTS

Objectives

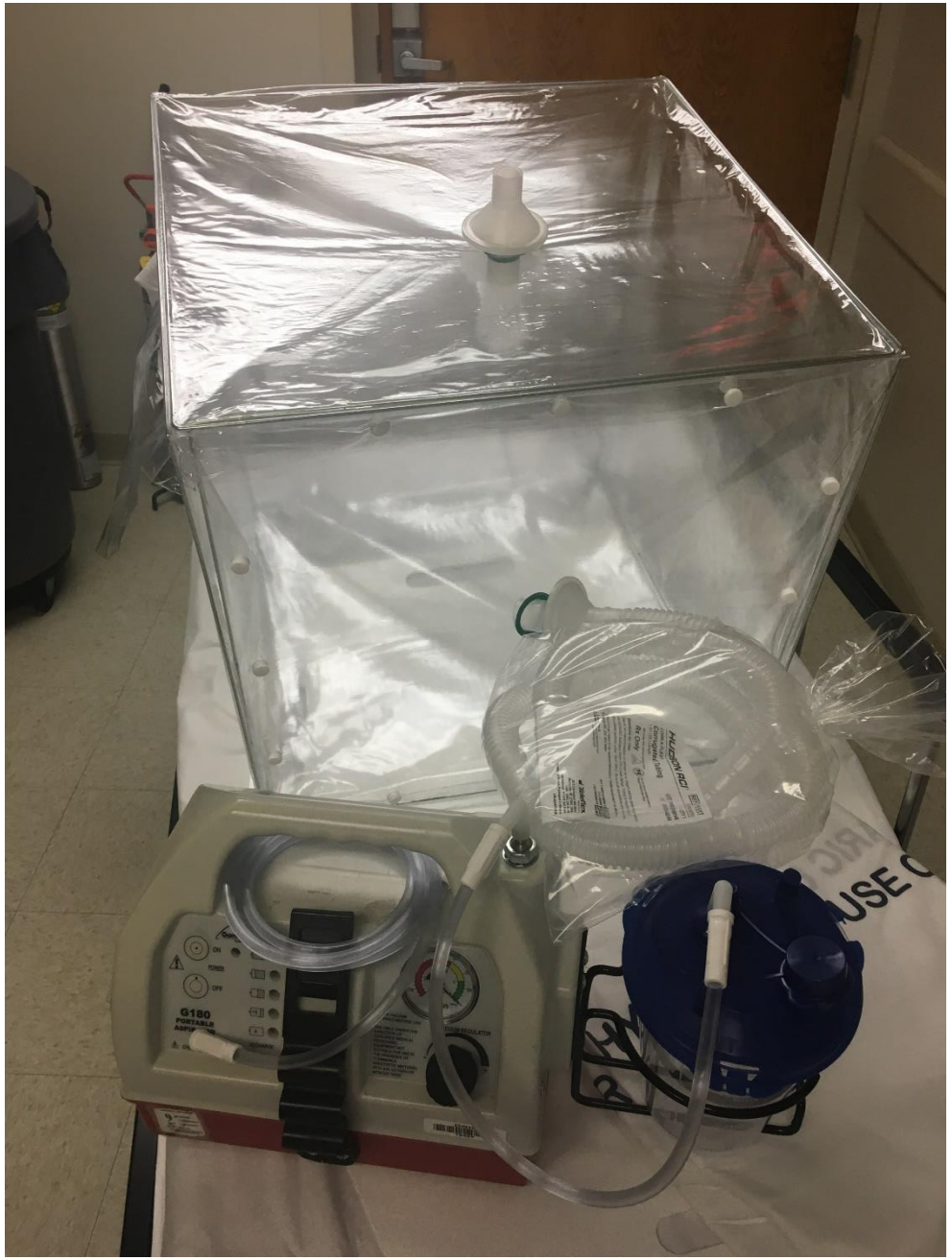
- Review process & protocol for HBOT & Covid-19 patients
- Review transporting Covid-19 patients
- Review disinfecting process

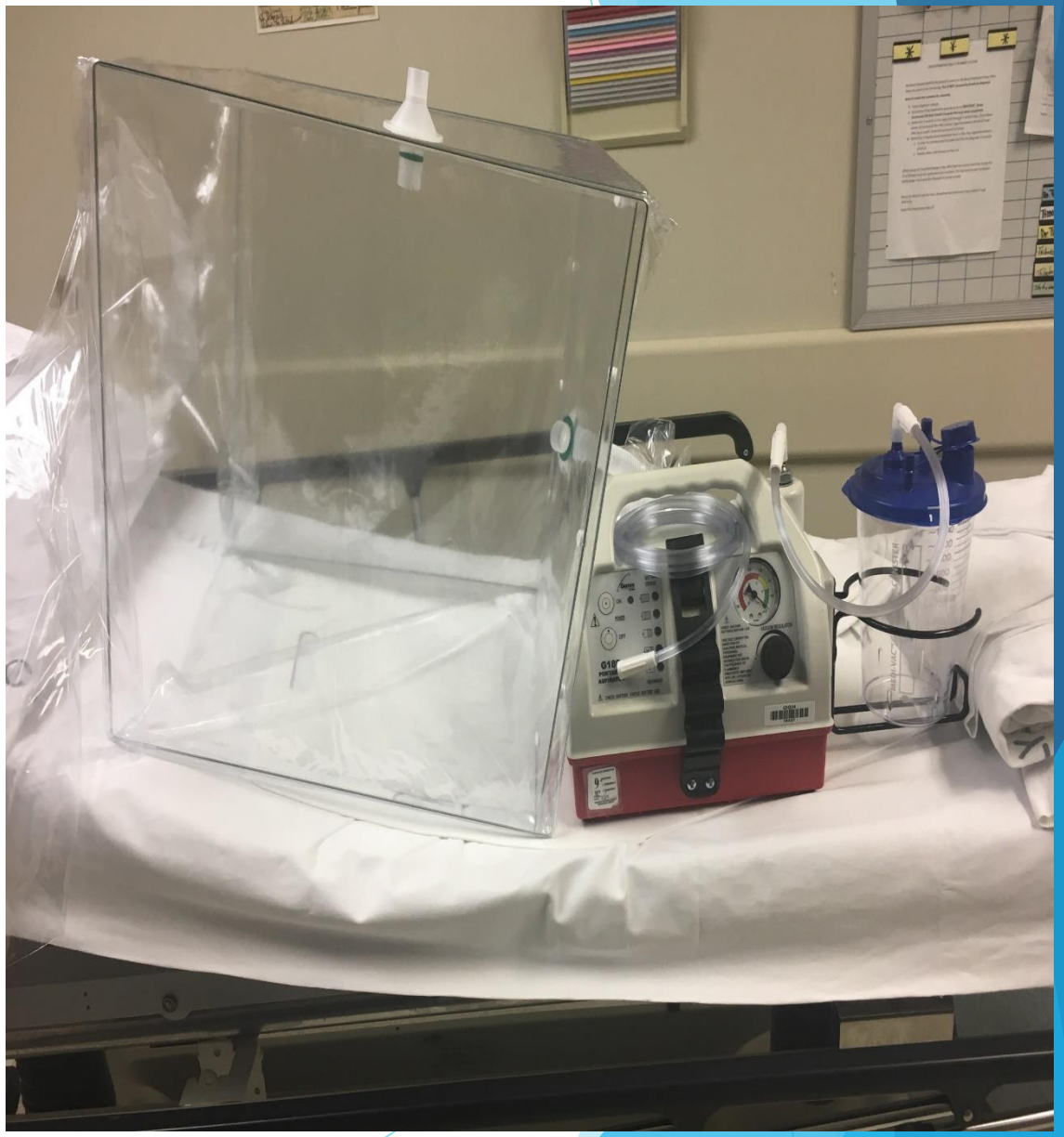
Processes & Protocol

- 13 Covid-19 patients treated with HBOT
- Initiated HBOT on April 13, 2020 – May 14, 2020 (12 patients)
- Patient 13 began June 13, 2020
- 64 HBO Treatments
- 9 fully recovered and discharged from hospital
- 3 deaths
- Age Range: 39-80
- 9 Females: 6 African American, 3 Caucasian
- 4 Males: 1 African American, 3 Caucasian
- Protocol: HBO consult sent from Hospitalist and Critical Care Pulmonologist—FI O2 >50 and tachypnea.
- HBOT: 2.0 ATA X 90 minutes daily

Transport of Patients

- Develop plan to transport patient, protect staff and environment
- Covid-19 patients transported on HBO gurneys
- Staff full PPE & Social Distancing
- Security on site to secure corridor
- Environmental Services for terminal clean of corridor post transport
- Pre HBO screenings obtained from ICU
- Patients transported will supplemental O2, surgical mask and negative pressure hood.
- Monitored with ECG & BP. Continue vital IV drips
- Post HBOT patients transported back to ICU using same protocol


G180
PORTABLE




PHOENIX


PHOENIX

Cleansing Guidelines

- Chamber cleansed with approved disinfectant.
- Disinfectant applied to inside of chamber. PPE for staff
- Chamber pressurized to 3 ATA for 20 minutes. Emergency vent after 20 minutes and completely wiped down inside of chamber.
- Outside of chamber disinfected while chamber pressurized
- HBO stretcher, mattress and pillows disinfected with approved cleanser
- Environmental Services does terminal clean of hyperbaric facility daily

Approved Chamber Cleaners

LpH®-se—Steris Corporation

Asepti-HB—Ecolab

Virasept—Ecolab

Oxycidie—Ecolab

Stat III TB--Ecolab

Quaternary Disinfectant--Ecolab

Coverage®Spray--Steris

Sani-Cloth Bleach Wipe--PDI

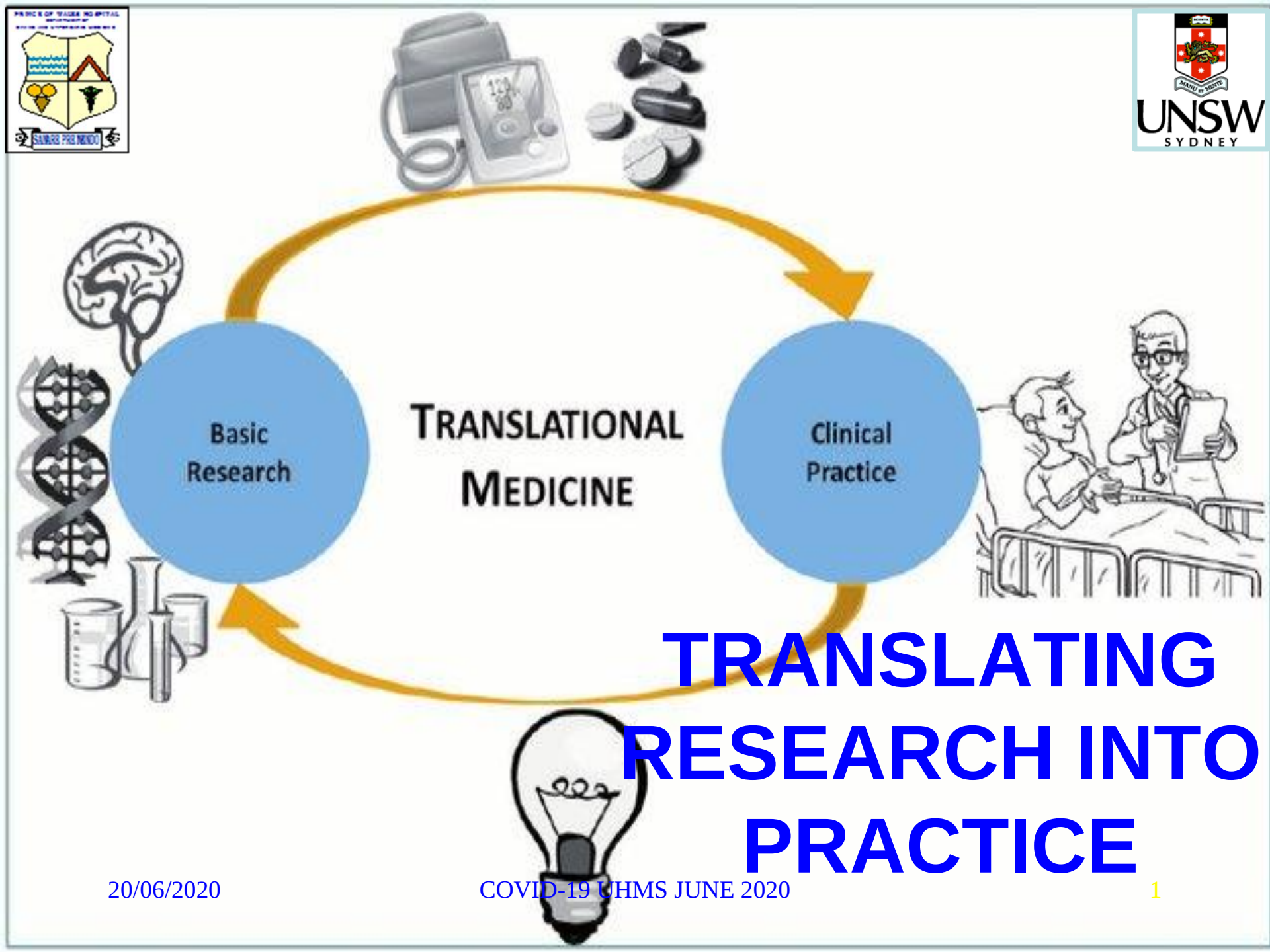
Sani-Cloth HB--PDI

- Chamber manufacturers will have approved list of disinfectants
- Follow guidance of CDC, chamber manufacturers, and your hospital infection prevention group.
- UHMS Safety Committee can provide guidance based on literature available but Safety Committee does not endorse a particular product or procedure.

TISSUEANALYTICS

- Developed an app to collect HBOT_COVID data into the Tissue Analytics data base.

- Contact by email:
- Thomas Serena, MD FACS
  serena@serenagroups.com



TRANSLATING RESEARCH INTO PRACTICE

Conflicts of Interest

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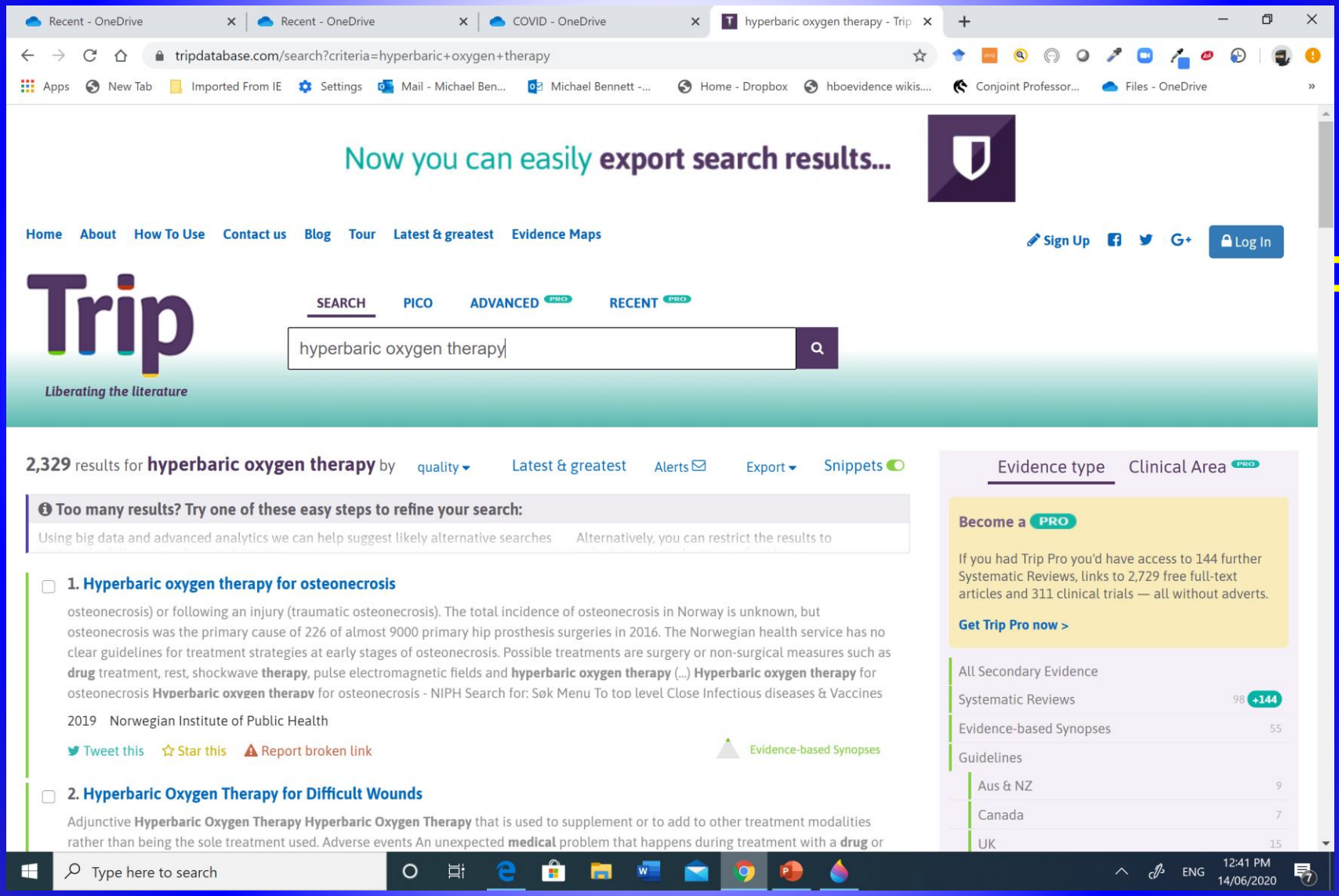
What is meant by ‘Translating



The Phases of Clinical Research

- Clinical trials involving new drugs are commonly classified into four phases.
- Primarily designed for the introduction of novel drugs
- Not all needed for a novel indication for an established intervention

DeMets, D., Friedman, L., and Furberg, C. (2010). *Fundamentals of Clinical Trials* (4th ed.). Springer.

Built on a lot of preclinical work

Preclinical Studies

- In vitro and animal experiments using wide-ranging doses. Toxicity and kinetic studies

- Phase 0 studies
- Optional microdosing exploratory trials conducted in accordance with the FDA.
- Confirm pharmacokinetics in humans

Sarapa N. Exploratory IND: a new regulatory strategy for early clinical drug development in the United States. 2007

PHASE I STUDIES

- First stage of testing in humans.
- Safety, side effects, best dose, and formulation method for the drug.
- Typically 20-100 in a specialized trial unit

HBO_2T and Phase 1 Studies

- Largely irrelevant?
  - Toxicity and pharmacology is well-established
- We are proposing a new use for an old drug
- No compelling need for Phase 1 studies of HBO_2 for COVID-19?

PHASE II STUDIES

- Assess efficacy and side effects.
- “Proof of concept.”
- Also covers ‘optimum dose’ work.

Yuan et al. Seamless Phase Iia/Iib and enhanced dose-finding adaptive design. *Journal of Biopharmaceutical Statistics*. **26** (5): 912–923, 2016.

HBO_2T and Phase II Studies

- Trial design
  - Case series.
  - Small to modest sized RCTs
  - Typically 50 to 300 cases
- Efficacy rather than effectiveness
  - Does the drug work for suitable patients?
  - May be part of the decision process in identifying the most appropriate patients.

Two potentially useful agents to improve outcomes in COVID-19

Hydroxychloroquine

- Existing agent with proven effectiveness for specific uses
  - RA/SLE et
  - Immune modulation
- Complex adverse effect profile
  - QT interval, N+V, hypoglycaemia, cardiomyopathy
- Highly available
- Cheap
- Enthusiastically endorsed by POTUS

HBO_2T

- Existing agent with proven effectiveness for specific uses
  - DCI/DFU etc
  - Immune modulation and oxygenation
- Generally benign (BUT)
  - Pulmonary toxicity, barotrauma, CNS toxicity
- Limited availability
- More expensive
- Enthusiastically endorsed by (well, not POTUS)

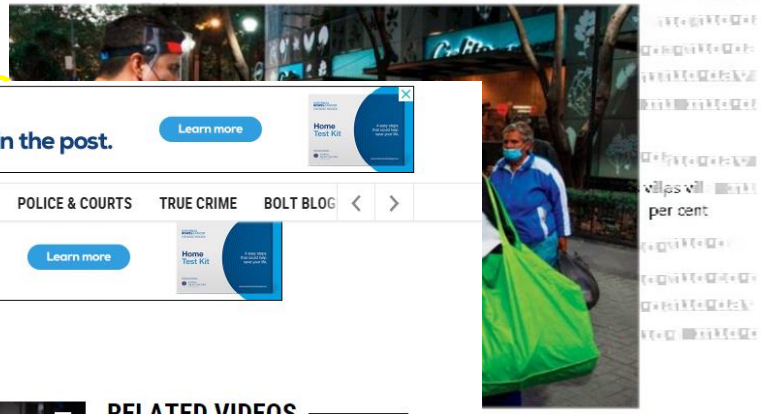
Some interventions adopted for the tre

Home / News / International News

United Kingdom OKs Dexamethasone Use To Treat COVID

Updated: Jun 18, 2020, 08:03 IST | Agencies | London

According to scientists, the drug has been proven to reduce the risk of death significantly in COVID-19 patients on ventilation by as much as 35 per cent and patients on oxygen by 20 per cent



...he state-funded National Health ...e "world's first" novel Coronavirus ...ong severely ill patients. The ...available anti-inflammatory

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NSW GOVERNMENT
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Health Minister Greg Hunt has revealed the medical expert panel approved the use of dexamethasone in Australia as a COVID-19 treatment. In clinical trials, the widely availa...

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Nats applaud the free trade deal with the UK
10m ago 02:25

Unemployment rate soars to 7.1 per cent: 'These are our dark times'
22m ago 01:15

PHASE III STUDIES

Phase 3 studies

- Designed to assess effectiveness.
  - How well does the agent work in practice?
  - Efficacy, effectiveness and safety
- Allow ‘compassionate use’ simultaneously
- Often used for ‘label expansion’.

HBO_2T and Phase 3 Studies

- Trial design
  - Larger mulitcentre RCTs. Typically 300 to 3000.
- Expensive, time-consuming and difficult
  - Does the drug work when successfully delivered to suitable patients?
  - Identify the most appropriate patients.
- The ‘ideal’ pathway for HBO_2T?

Compassionate use

- Allow the use of an unlicensed intervention to be made available to patients
  - severe disease
  - no other satisfactory treatment available

The goal is to serve the interests of the patient

n Union: Regulation 726/2004/EC of the European Parliament and of the Council of 31 March 2004. Official Journal of the European Union 2004

Whitfield *et al. Trials* 2010, **11**:104
http://www.trialsjournal.com/content/11/1/104

TRIALS

RESEARCH Open Access

Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries

Kate Whitfield[1*], Karl-Heinz Huemer[2], Diana Winter[3], Steffen Thirstrup[4], Christian Libersa[5], Béatrice Barraud[6], Christine Kubiak[7], Lea Stankovski[7], Xina Grählert[8], Gabriele Dreier[9], Sebastian Geismann[9], Wolfgang Kuchinke[10],

Accessing medicinal products with little knowledge of their benefit or harm should not be labelled as the most compassionate strategy.

Relief of suffering is not always achieved through intervening and certainly does not come through causing more harm than good.

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://www.coronavirus.gov.
Get the latest research information from NIH: https://www.nih.gov/coronavirus.

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Save this study

Compassionate Use of Hyperbaric Oxygen Therapy

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04386265

Recruitment Status : Enrolling by invitation
First Posted : May 13, 2020
Last Update Posted : May 19, 2020

Spc

Col

Info

US Food and Drug Administration - Final Rules for Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs. [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm172492.htm].

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

What's in a name?

Table 1 Access to medicinal products, through 'compassionate use', 'off-label' use and randomised clinical trials

	'Compassionate use' European regulation	Off-label use	Randomised clinical trial
Purpose	Serves the needs of patients where no alternative treatment exists	Serves the needs of patients with an indication other than that the product is marketed for	Serves the needs of society and future patients and may benefit some of the included participants
Party involved	Patients	Patients	Participants
Disease	A life-threatening or chronically or seriously debilitating disease	Any indication for which the product is not authorised	Any
Informed consent	Required in some member states	Not required	Required
License	Medicinal product is not yet licensed	Medicinal product is licensed for other indication(s)	Medicinal product can be licensed and not licensed
Responsible party	Prescribing physician with approval from the regulatory authorities	Prescribing physician	Sponsor with approval from the regulatory authorities
Control group	Without control group	Without control group	With control group
Data	In some member states, some data are reported to the regulatory authorities	Spontaneous adverse events may be reported	Outcome measure and adverse event data are reported to the regulatory authorities
Access to the intervention	Medicinal product accessed through the programme, afterwards those patients can have access before the product is licensed	Medicinal product available on prescription	Declaration of Helsinki stipulates that participants "are entitled to...share any benefits that result from the trial, for example, access to interventions..."

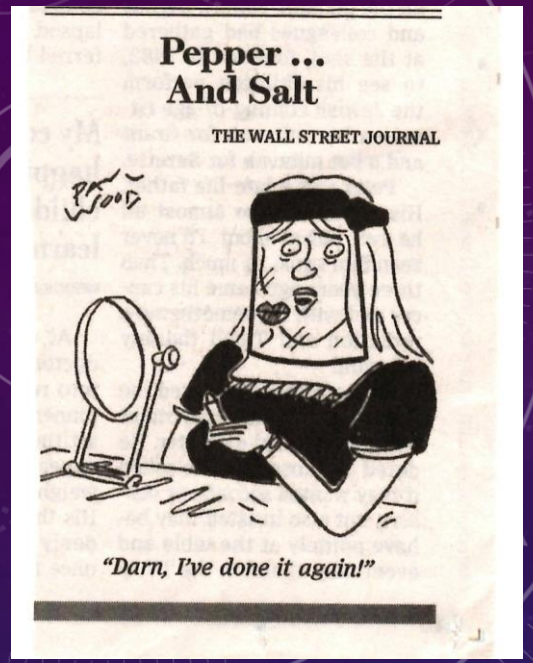
Slippery slope

- Compassionate use cannot replace clinical trials
- Does not inform on the the benefits and harms of an intervention (as do RCTs)
- Blurring the lines is an easy way to collect information instead of RCTs.
- When this happens, the safeguards inherent to clinical trials are all circumvented.

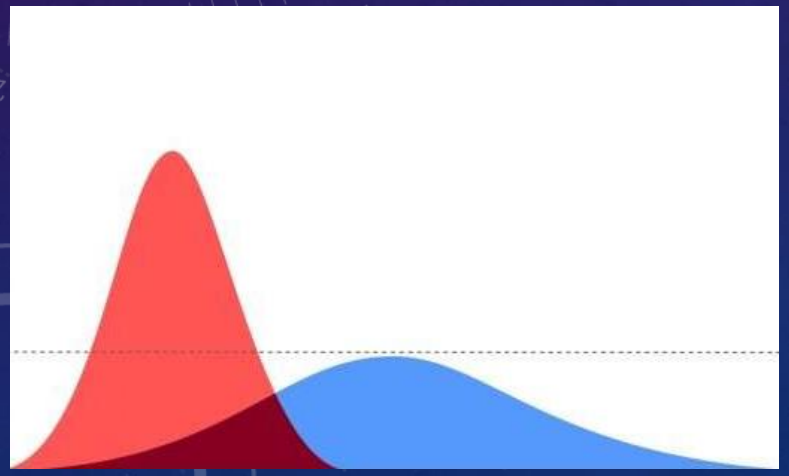
PHASE IV STUDIES

Phase 4 studies

- Post-acceptance surveillance
  - Safety – rare and long-term adverse effects
- HBO2T
  - Role for registries
  - Outside the scope of this talk
- Total cost typically $1bn – but a lot of the work already done



COVID-19 SUMMING IT UP
-WHAT WE KNOW
-WHAT WE NEED TO LEARN
-STUDY DESIGN
RECOMMENDATIONS



JOHN J. FELDMEIER D.O., FACRO, FUHM

PAST PRESIDENT OF UHMS

PRESENT CO-CHAIR

RESEARCH COMMITTEE

- No conflicts of interest to report

AT THIS TIME-STILL A MAJOR PUBLIC HEALTH ISSUE

- U.S. Cases: 2,168,00 Worldwide Cases: 8,392,000
- U.S. Deaths: 118,000 Worldwide Deaths: 449,000
- Recent Spikes due to relaxation of “social distancing” measures
- Compared to the Bubonic Plague which caused an estimated 75-200million deaths (30 to 60% of population of Europe)
- Compared to the Spanish Flu where U.S. deaths were estimated at 675,000

RECENT DEVELOPMENTS

- Hydroxychloroquine-at least2 negative trials; both FDA and WHO approval for trial entry or compassionate care removed
- Remdesivir-one study shows a shortened hospital stay
- Decadron-just released information indicates that it can reduce mortality
- Jury is still out on convalescent plasma though some impressive anecdotal results
- Hyperbaric experience to date presented here
- Mechanisms, anecdotal results and a few case series suggest promise

HYPERBARIC OXYGEN IN PRINT

- Original Chinese Study of 5 patients form Wuhan
- Study by Thibodeaux et al updated here now with 12 patients
- Several anecdotal reports (Dr, Daphne Denham has treated about 20 patients
- More from results today

STUDIES POSTED ON CLINICAL TRIALS.GOV

Site	Status	Design	Primary Outcome
1. Ochner Clinic	Not recruiting yet	Randomized Biostat and rad blinded	Decreased intubatons
2. NYU	Terminated	Single arm	Mortality
3. France de Sante des Armes	Recruiting	Randomized Blinding not clear	Normalization of O2 status
4. Karolinska	Recruiting	Randomized No blind	PaO2/FiO2
5. Maimonides Med Ctr	Not yet recruiting	RCT single blind	PaO2/FiO2
6.Serena Group multi-ctr	Initial reports	Compassionate use	reduction of ventilator need
7. Assaf-Harofeh Medical Center	Recruiting	Randomized double blind	PaO2/FiO2

PaO2 to FiO2 Ration For ARDS Any Cause

Severity of ARDS	P/F ratio	Mortality
Mild	200-300	27%
Moderate	100-200	32%
Severe	<100	45%

A normal value might be 100/.19=526

DISEASE TRANSMISSION

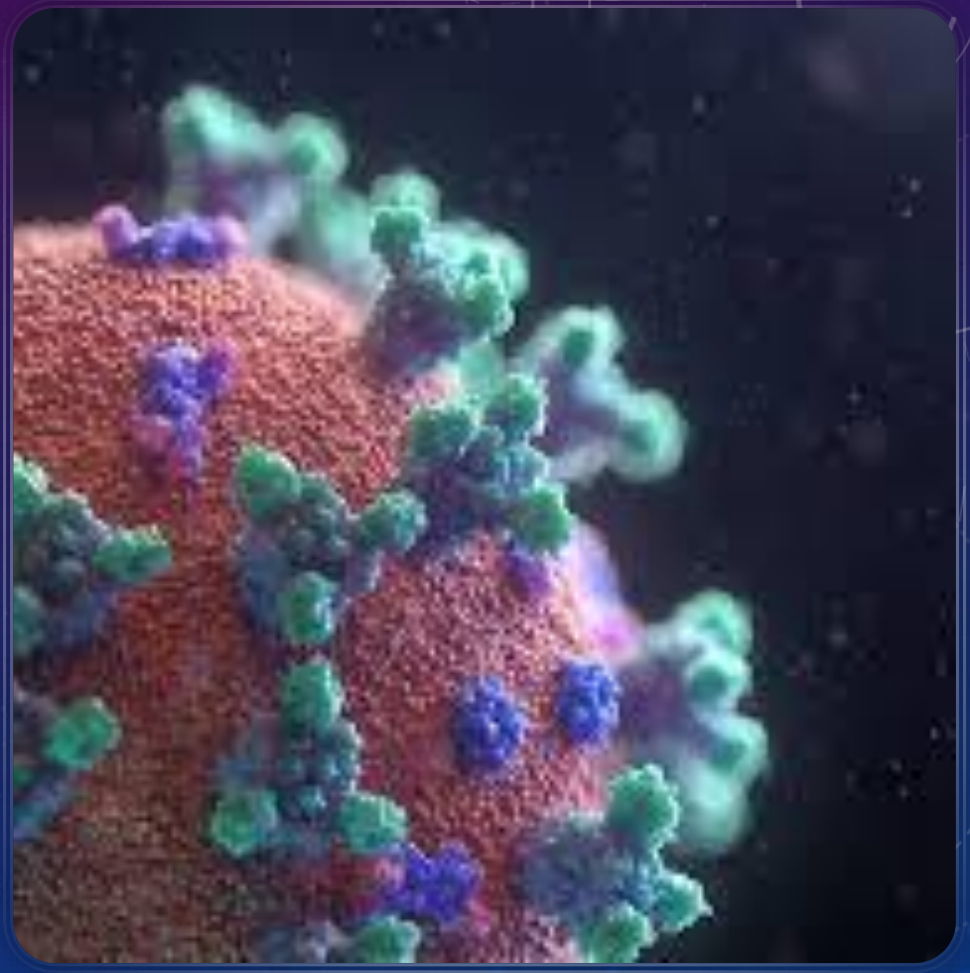
- Primarily air borne droplets
- Questionable surface contact
- Incubation period typically 2 to 14 days
- R0 value 5.7, i.e. typically an infected patient infects 5.7 others
- Makes it about three times as contagious a seasonal flu but about one half as contagious as measles

EFFORTS TO FLATTEN THE CURVE

- Cessation of commerce and manufacturing for 2 + months except for essential activities
- Self-quarantine for anyone in contact and others traveling from high risk area
- Social distancing-maintaining 6 ft distance
- Late adoption of masks to protect those around mask wearer
- Curve flattened (see NY State stats)
- Spikes on going in U.S. in multi-focal fashion (consider Florida)
- No Plans to again close down business
- Concern that arrival of fall will lead to second flareup of pandemic

PATHOPHYSIOLOGY AND HBO MECHANISMS

- Realization that the over-exuberant response of the immune system and not direct effect of virus is the key
- This response is mediated by release of several cytokines (IL-6, IL-1beta, TNF-alpha)
- A characteristic cytokine storm occurs typically about a week after admission with massive release of offending cytokines often leading to rapid deterioration, ventilator dependence and death
- Hypercoagulation leading to possible stroke, MI, PE also Contributing to lung toxicity



PUTATIVE MECHANISMS FOR HBO2

- Much more efficient of transporting Oxygen across the pulmonary membrane
- “pays” the oxygen debt
- Reduces pro-inflammatory and inflammatory reactions
- Hyperbaric oxygen has shown anti-inflammatory results
- New data (See Thibodeaux’s presentation) of reduction of D-dimers
- In disease processes of inflammation in avascular hip necrosis (Bosco) (TNFalpha and IL-6) and TBI (Qian)(IL-1) HBO has been shown to reduce these inflammatory inducing cytokines

KIALING PEREZ, MD, PEACH HEALTH RIVERBEND OREGON
PATHOPHYSIOLOGY OF COVID-19

- Structure and Infectivity
- Predominance of the Inflammatory Patient Response
- Cytokine Storm
- Testing
- Treatment Guidelines from NIH
- Dexamethasone 6mg survival advantage-full paper pending
- Vaccines-leg up with similarity to prior viruses
- No discussion of O2 toxicity

DR. SANDRA WAINWRIGHT NORWALK HOSPITAL (YALE)

- “Physiology saves patients”
- Normal vitals
- NSR in spite of profound hypoxia
- Lymphopenia
- Bilateral pulmonary infiltrates
- Chemistries normal except Na
- Tylenol helped cough
- Afraid to sleep
- Not all patients had co-morbidities
- Helped by steroids
- Preponderance of middle aged Hispanic men
- Tubes everywhere
- Proning, PEEP, Dangers of pneumo
- ECMO
- V/Q mismatch in part due to coagulopathy
- Sequelae

SCOTT GORENSTEIN, MD
NYU WINTHROP

- Transport of patients to HBO
- Able to get approved IRB in 2 weeks-case control study
- 2.0 ATA-90 mins. Air breaks not typically given
- Transport biggest risk-desaturation-monitored and on O2
- Pts immediately better resp status- more alert
- Cardiac monitoring
- Air on ascent to prevent crash
- Terminal cleaning chlorine bleach
- 20 pts treated
- O2 consumption higher than normal

MARCUS SPEYRER, RN
OPELOUSAS GENERAL HEALTH SYSTEM

- Infection Control
- Emergency Procedures
- Staff Education
- Protocol 90 minutes at 2.0ATA daily
- Communication
- Disinfectants from chamber manufacturers
- Suggestion of UV light-likely to damage acrylic

MICHAEL BENNETT, MBBS
PRINCE OF WALES MED CTR

- Balancing compassionate use with evidence-based research
- How to translate limited evidence into clinical practice
- Only 20 cases in NSW
- Novel agent or old agent in new use
- 4 phases of study progression
- Compassionate Use likely justifiable
- Formal trials must be done
- RCT’s preferred

EFFECTS OF VOLATILE GASEOUS COMPOUNDS INDUCED BY HYPERBARIC OXYGEN IN COUNTERACTING THE SAR-COV-2VIRUS IN ASYMPTOMATIC AND MILD SYMPTOM POSITIVE PATIENTS

LONGOBARDI CENTRO IPERBARICA RAVENNA, ITALY (6A)

- A single arm study of asymptomatic or minimally symptomatic but + test individuals who will receive HBO2
- Will specifically study individuals with NOS polymorphism who have reduced levels of NO
- HBO will consist of 5 exposures each of 76 minutes once daily for 20 participants at 2.0 ATA
- Primary outcome conversion of nasal swabs to negative as well as need for hospitalization and for ICU admission
- Premise is that HBO2 will increase NO and thereby have a favorable effect on progression of disease
- Induction of anti-viral effects

EFFICACY AND SAFETY OF HYPERBARIC OXYGEN FOR ARDS IN PATIENTS WITH COVID-19; RATIONALE AND PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL. KJELLBERG ET AL, KAROLINSKA INSTITUTE, STOCKHOLM (6B)

- Prospective Randomized Trial enrolling 200 with moderately severe patients who require O2 on admission and have a least 2 high risk factors
- HBO2 30-60 minutes at pressures from 1.6 to 2.4 ATA for a maximum of 5 treatments over 7 days
- Control Group will receive best practice treatment for COVID-19 pneumonitis
- Primary Endpoint how many require ICU admission; secondary 30-day mortality, time to intubation, change in inflammatory response
- Secondary does HBO reduce inflammation and reduce demands made on ICU staff
- Importance of adhering to trial design

HYPERBARIC OXYGEN IN PREVENTING MECHANICAL VENTILATION IN COVID-19 PATIENTS; A MULTI-CENTER CASE SERIES
THIBODEAUX K OF THE SERENA GROUP (6C)

- 12 patients from 3 sites of which 11 (91%) have avoided mechanical ventilation
- Total of 10 sites are enrolling
- In initial patient group majority of patients have seen oxygen saturation improve, tachypnea resolve and D-dimer and inflammatory markers decrease
- NO ADVERSE EVENTS!
- Patient enrollment continues
- At least one patient had convalescent plasma mixing therapies
- All patients on heparin drips
- Perhaps special impact on AA patients
- One treatment per day
- TCPO2 to monitor

HYPERBARIC OXYGEN FOR COVID-19 PATIENTS WITH RESPIRATORY DISTRESS: A CASE CONTROLLED STUDY GORENSTEIN SA ET AL, WINTHROP HOSPITAL, NYU DR. LEE PRESENTING (6D)

- Single center case-controlled study of pts requiring O2 of 2-15 liters per minute
- HBO2exposure was 2.0 ATA for 90 minutes daily for a maximum of 5 treatments
- Controls matched by propensity scoring and 60 matches made
- 20 patients aged 30 to 79; 10% were intubated and died and none still in hospital
- In matched non-HBO group 30% required intubation; 22% died 8 % still in hospital and 8% of these still on ventilator
- Hazard ratio for in-patient mortality was 0.37 and for mechanical ventilation was 0.26
- Conclusion: study demonstrated safety and possible efficacy of HBO2
- Well matched groups
- Stave off intubation at all costs
- Some patients do die in spite of HBO2

STUDY DESIGN RECOMMENDATIONS WORKING GROUP

- **Study Group**
- **Co-Chairs of Research Committee:**
- John J. Feldmeier, D.O. John Kirby, M.D. Jay Buckey, M.D

- **Other Committee Members (alphabetically):**
- Daphne Denham, M.D. Jose Evangelista, M.D. Helen Gelly, M.D.
- Nicole Harlan, M.D. Ziad Mirza, M.D. Kristi Ray, D.O.
- Marc Robins, D.O. Davut Savaser, M.D. Sandra Wainwright, M.D.

WORKING GROUP BEGAN ABOUT 6 WEEKS AGO

- Challenges
- 1. Design a relatively simple design that could be followed by almost any HBO2 Center
- 2. Discuss the Pathophysiology of COVID-19and Define a Reasonable and Comprehensive Mechanism of Action for HBO2 related to treatment schema
- 3. Suggest outcome parameters
- 4. Outline a treatment profile
- 5. Generate a model consent
- 6. Consider toxicities

STUDY DESIGN CONSIDERATIONS

- 1. We agreed early on that the Study Design should be simple enough that even community centers could enroll patients.
- 2. We felt that the group of patients in whom intervention was likely to achieve the most significant advantage were those who had respiratory issues, seemed to be progressing toward the need for ventilatory support, but that this risk was not yet imminent
- 3. From the beginning we indicated that RCT design was preferable but thought that for the short-term Phase I/II Studies were more likely and that well designed single arm studies could justify grant sponsorship of subsequent RCT's.
- 5. Felt that when RCT's were initiated our design for our single arm study could serve as research arm in the RCT.
- 6. We considered blinding and felt that since there were ethical issues in transporting subjects who are unstable from an ICU bed and that because major outcome parameters are so objective (death) and not likely to be impacted by placebo blinding was not essential . We also anticipated difficulties in obtaining IRB approval.
- 7. We recommended core laboratory and imaging outcome determinants that were recommended for all studies but also identified additional studies that were recommended if human and financial resources were available to support them
- 8. Timing of tests and intervals between testing were also addressed. As a minimum testing should be compared before during and after HBO treatments.
- 9. Some testing (again if resources were available to support) would be useful to have just before an HBO2 exposure, shortly after and even just before subsequent hyperbaric exposures.
- 10. In regard to dangers of HBO2 exposures in this severely ill group of patients we felt that providing oxygen was a much greater consideration than O2 Toxicity

Brescia-COVID Respiratory Severity Scale (BCRSS)/Algorithm (Italian)

[Patient has COVID-19 pneumonia or COVID-19 symptoms for ≥7 days]
AND
[Patient is PCR+ OR high suspicion for COVID-19/PCR pending]

Patient wheezing OR unable to speak in full sentences while at rest/with minimal effort	**No**	Yes
Respiratory rate >22	**No**	Yes
PaO_2 <65 mmHg or SpO_2 <90%	**No**	Yes
Repeat CXR is significantly worsening	**No**	Yes

NEWS IS NATIONAL EARLY WARNING SYSTEM (ENGLISH)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

RECOMMENDED TREATMENT SCHEMA

- Target protocol of 2.0 ATA for 90 minutes no planned air breaks once a day (with the local flexibility of up to 2 – 3 treatments in the first 24 – 72 hours or at other times with patient deteroration akin to other urgent HBO indications) and a Utilization Review mechanism locally in place to be used as patients approach study totals of 10 treatments in any 2 – 10 day period
- Study sites may elect to study lower pressures (<2.0 ATA) or higher pressures (>2.0 ATA) or longer or shorter treatment times with or without Air Breaks, although some preliminary experiences have demonstrated patient instability with air breaks, such that although the committee is recommending the above initial study recommendations to derive maximal clinical conclusions and statistical validity

PRIMARY OUTCOME PARAMETERS

- **Primary Outcome Measures** (This data should be collected on all patients in any trial):
- Mortality rate per numbers treated, within 30 days post treatment
- Incidence of intubation (within 24 hours of HBO2 initiation and duration of hospitalization)
- Incidence rate for days on nasal cannula, high flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV – includes BiPAP, CPAP), and invasive mechanical ventilation (intubation))
- Clinical Response Criteria: respiratory rate, vitals, pulse oximetry, O2 requirements and delivery route (including CPAP/BiPAP/etc), serial blood gases—per local protocol
- Duration of intubation or NIPPV
- Length of Hospital Stay (LOS)
- Use of ECMO
-

SECONDARY OUTCOME PARAMETERS

- Decrease in renal injury
- Decrease in LFT's, D-dimer, fibrinogen
- Time to defervescence
- Decrease in inflammatory markers, specifically IL-1-a/b, IL-6, TNFa
- CT/CXR evidence of interstitial opacity (severity/ evidence of consolidation)
- Additional association with co-morbidities
- Consider collecting plasma for later use or analysis

LABS/IMAGING: *INDICATES TO BE OBTAINED BY ALL

- **<u>Laboratory data to collect (depending on availability):</u>**
- D-dimer* The reference concentration of D-dimer is < 250 ng/mL, or < 0.4 mcg/mL. [1]
- Fibrinogen*
- CRP/ESR* and or any other inflammatory markers – specific or non-specific
- Lactic acid
- Blood gases* (Venous or Arterial)
- Ferritin
- Procalcitonin
- CBC-with differential*
- CMP (LFT's)*
- Additional inflammatory markers including IL-1, IL-6, IL-10, TNFa
- CXR/ CT*
- Frozen sera for repository use

FREQUENCY OF TESTING

- Before, During and After HBO2
- Useful intervals of some tests would be immediately before, just after and several hours after a single HBO2 treatment

SUMMARY OF THE SUMMARY

- 1. Learning curve has been steep
- 2. Over exuberant Immune Response is the major contributor to morbidity
- 3. Effective treatment still sadly lacking; Deacdron promise in severe cases
- 4. Social distancing, quarantine etc have “flattened the curve.”
- 4. HBO2 does reduce inflammation by impacting cytokine production and action
- 5. Concur with Dr. Moon that results cannot be temporary improvement in oxygenation
- 6. Basic science support and Thibodeaux results suggest it reduces D-dimers
- 7. Consistent reports of improvement and feeling of well being
- 8. Well-designed trials are needed and study design should be consistent to do multi-center analysis
- 9. Randomized controlled trials are necessary to have level1 evidence supporting HBO application
- 10. We must have a vaccine