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 and β 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
Cases in the U.S.

Last updated on June 17, 2020

TOTAL CASES
2,132,321
27,975 New Cases*

TOTAL DEATHS
116,862
722 New Deaths*

*Compared to yesterday's data

About the Data
**New coronavirus**

Most estimates put the fatality rate below 3%, and the number of transmissions between 1.5 and 3.5.
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).

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.
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

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 result.
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.
| 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\textsuperscript{21}  
• Potent \textit{in vitro} activity demonstrated in SARS-CoV-2-infected Vero E6 cells\textsuperscript{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.\textsuperscript{23} |
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.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA-Approved Indications</th>
<th>Preclinical Data/Mechanism of Action</th>
</tr>
</thead>
</table>
| Azithromycin | • Mycobacterial (non-tuberculosis) 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\(^5\) |
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 of 89,751 patients in five continents. We included patients hospitalised between Dec 20, 2019, and Feb 28, 2020, with a positive laboratory result for COVID-19. 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...

FDA NEWS RELEASE

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

For Immediate Release:  June 15, 2020
ACE inhibitors and angiotensin receptor blockers (ARBs) in COVID-19?

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

Aronson J, Ferner R.

22nd March 2020

#EvidenceCOVID
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.
<table>
<thead>
<tr>
<th><strong>Sarilumab</strong></th>
<th><strong>Siltuximab</strong></th>
<th><strong>Tocilizumab</strong></th>
</tr>
</thead>
</table>
| • Rheumatoid arthritis<sup>20</sup>  
• IL-6 receptor antagonist | • Multicentric Castleman disease  
• Human-mouse chimeric monoclonal antibody  
• IL-6 antagonist<sup>20</sup> | • Cytokine release syndrome (induced by CAR T-cell therapy)  
• Rheumatoid arthritis  
• Giant cell arteritis  
• Polyarticular juvenile idiopathic arthritis  
• Systemic juvenile idiopathic arthritis<sup>31</sup> | • Recombinant humanized monoclonal antibody  
• IL-6 receptor antagonist |
<table>
<thead>
<tr>
<th>COVID-19 Treatment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins</strong></td>
</tr>
<tr>
<td>• Not approved by the FDA</td>
</tr>
<tr>
<td>• Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2. 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.</td>
</tr>
<tr>
<td>For COVID-19:</td>
</tr>
<tr>
<td>• Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports.</td>
</tr>
<tr>
<td>• There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in COVID-19.</td>
</tr>
<tr>
<td>For Other Viruses:</td>
</tr>
<tr>
<td>• The use of convalescent plasma has been evaluated in other viral diseases (e.g., SARS), with some suggestion of potential benefit. No convalescent blood products are currently licensed by the FDA.</td>
</tr>
<tr>
<td>• There are no clinical data on the use of specific immune globulin or hyperimmune globulin in patients with SARS or MERS.</td>
</tr>
</tbody>
</table>
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

11 candidate vaccines in clinical evaluation

<table>
<thead>
<tr>
<th>Platform</th>
<th>Type of candidate vaccine</th>
<th>Developer</th>
<th>Coronavirus target</th>
<th>Current stage of clinical evaluation/regulatory status: Coronavirus candidate</th>
<th>Same platform for non-Coronavirus candidates</th>
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</thead>
<tbody>
<tr>
<td>Non-Replicating Viral Vector</td>
<td>ChAdOx1-S</td>
<td>University of Oxford/AstraZeneca</td>
<td>SARS-CoV2</td>
<td>Phase 2b/3&lt;br&gt;2020-001228-32&lt;br&gt;Phase 1/2&lt;br&gt;2020-001072-15</td>
<td>MERS, influenza, TB, Chikungunya, Zika, MenB, plague</td>
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<tr>
<td>Non-Replicating Viral Vector</td>
<td>Adenovirus Type S Vector</td>
<td>CanSino Biological Inc./Beijing Institute of Biotechnology</td>
<td>SARS-CoV2</td>
<td>Phase 2&lt;br&gt;ChiCTR2000031781&lt;br&gt;Phase 1&lt;br&gt;ChiCTR2000030906</td>
<td>Ebola</td>
</tr>
<tr>
<td>RNA</td>
<td>LNP-encapsulated mRNA</td>
<td>Moderna/NIAID</td>
<td>SARS-CoV2</td>
<td>Phase 2&lt;br&gt;NCT04405076&lt;br&gt;Phase 1&lt;br&gt;NCT04283461</td>
<td>multiple candidates</td>
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<td>Wuhan Institute of Biological Products/Sinopharm</td>
<td>SARS-CoV2</td>
<td>Phase 1/2&lt;br&gt;ChiCTR2000031809</td>
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<tr>
<td>Inactivated</td>
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<td>Inactivated</td>
<td>Inactivated + alum</td>
<td>Sinovac</td>
<td>SARS-CoV2</td>
<td>Phase 1/2&lt;br&gt;NCT04383574&lt;br&gt;NCT04352608</td>
<td>SARS</td>
</tr>
</tbody>
</table>
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
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…
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, esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells. These findings indicated that those organs with high ACE2-expressing cells should be considered as potential high risk for 2019-nCoV infection.
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
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).
SARS CoV2

https://www.rndsystems.com/resources/articles/ace-2-sars-receptor-identified
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 Zuo
  A 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, Junzhu Chen, Xingxiang Wang, Furong Zhang, Yanrong Liu
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.
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.
These patients are so sick! Why are they so HYPOXIC – for being so young and no medical problems!!

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<td>ECMO</td>
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There are only 5 reasons for hypoxemia!

1. Anatomic dead space
2. Ventilation-perfusion mismatch
3. Hypoventilation
4. Heart failure
5. Increased alveolar-arterial gradient
How COVID-19 Causes Hypoxemia

1. v/q mismatch via micro and macro thromboses

2. diffusion impairment via thickened alveolar membrane

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

Elevated Arterial CO₂ Observed Only When Alveolar Ventilation is Severely Impaired (Hypoventilation)

No Ventilation

No perfusion

Shunt

Dead Space

\[ \frac{V}{Q} = 0 \]

\[ V < 1 \]

\[ V = \infty \]

\[ P_{aO_2} < 50 \text{ mm Hg} \]

\[ P_{aCO_2} > 40 \text{ mm Hg} \]
5 Reasons for Hypoxia

- 3. Shunt
5 Reasons for Hypoxia

- 4. Diffusion Impairment – or as Europeans would say “transfer”
5 Reasons for Hypoxemia

5a. Oxygen Delivery – In Context

Cardiac Output

1. preload
2. contractility
3. afterload

\[ \Delta P = SVR \times \text{cardiac output (CO)} \]

\[ \text{stroke volume (SV) } \times \text{heart rate (HR)} \]
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 Oxyhemoglobin carries 1.35cc of O2
- Thus, 15 gm of Hgb can transport 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

\[ \text{CaO}_2 = (\text{SaO}_2 \times 1.39 \times \text{Hb}) + (0.0031 \times \text{PaO}_2) \]

Pulmonologists consider this a rounding error, like our govt considers the number trillion
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

\[ \text{CaO}_2 = [(\text{SaO}_2 \times 1.39 \times \text{Hb}) + (0.0031 \times \text{PaO}_2)] \]

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

\[ \text{CaO}_2 = [(85 \times 1.39 \times 13) + (0.0031 \times 58)] \]
\[ = [(1536) + (0.18)] \]
\[ = 1536 \text{ (Pulmonary doc math)} \]

\[ \text{CaO}_2 = [(100 \times 1.39 \times 13) + (0.0031 \times 700)] \]
\[ = [(1807) + (2.17)] \]
\[ = 1809.17 \text{ (HBO doc math)} \]

Is there a role for HBO?
These patients are so sick! Why are they so HYPOXIC – for being so young and no medical problems!!

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</table>

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

FiO2 and PEEP – MOC?
33yM

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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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**Chem**
- Na: 138
- K: 3.7
- Cl: 106
- CO2: 28
- BUN: 13
- CRT: 0.74
- GLU: 164

**CBC**
- WBC: 5.2
- Hgb: 7.8
- Plt: 202
- lymph: 4% (14-43)
- NI range: 14-43%
- LDH: 453 (35-190)
- D-dimer: 0.44
Preload
Afterload
Starling’s curve
PEEP
Driving Pressure
Peak/Plateau
Pressure
West Zones
V/Q mismatch
Oh my!

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
West Zones of the Lung and Why We Prone

This is one of your MOC ?’s
Remember our 43yf? Hospital course

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</tr>
<tr>
<td>K</td>
<td>3.7</td>
</tr>
<tr>
<td>Cl</td>
<td>106</td>
</tr>
<tr>
<td>CO2</td>
<td>28</td>
</tr>
<tr>
<td>BUN</td>
<td>13</td>
</tr>
<tr>
<td>CRT</td>
<td>0.74</td>
</tr>
<tr>
<td>GLU</td>
<td>164</td>
</tr>
<tr>
<td>Abg</td>
<td>pH</td>
</tr>
<tr>
<td>PCO2</td>
<td>PaO2</td>
</tr>
<tr>
<td>O2 Deliv</td>
<td>Bicarb</td>
</tr>
</tbody>
</table>
The proof is in the proning
43Y F Hospital Course

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

What doing w/ this D-dimer trend?
COVID-19 Causes Thromboses??? 57yM

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

New Chest Pain on DVT Prophylaxis 4/3/20
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”
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.
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
We are Seeing Sequelae of Prolonged Mechanical Ventilation
Several countries have turned the corner, with numbers of new cases now in decline

Daily confirmed cases (7-day rolling average), by number of days since 30 daily cases first recorded
Stars represent national lockdowns ★

Source: FT analysis of European Centre for Disease Prevention and Control; FT research. Data updated April 15, 19:00 GMT
© FT
April 16, 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.
April 16, 2020 When will this rollercoaster ride end???
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
"Sandra you’re trying to ventilate concrete"
Almost out of options
- eNO
- CVVH

<table>
<thead>
<tr>
<th>pH</th>
<th>PCO2</th>
<th>PaO2</th>
<th>Vent</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.18</td>
<td>55</td>
<td>47</td>
<td>PC 54/20</td>
</tr>
<tr>
<td>7.40</td>
<td>40</td>
<td>80</td>
<td>Peak&lt;30</td>
</tr>
</tbody>
</table>

“illegal pressures”
April 19, 2020 – Light at the end?
April 20, 2020 – One month later, how long is this going to last?

I love these graphs Jim. They give me hope.

Sent from my iPhone
April 22, 2020 Wait, I thought things were getting better…. 

Uptick???
April 24, 2020

![Graph showing hospitalizations and ICU hospitalizations over time from March 14 to April 23, 2020.](Image)

- **Hospitalizations**
- **ICU Hospitalizations**
- **ICU Hospitalizations total**

Date markers indicate key dates for the data.
Our COVID-19 Graph
Post COVID/ARDS Pulmonary Sequelae
### Evidence Based Practice (EBM)

<table>
<thead>
<tr>
<th>ARDS – (ARDSNET) low Vt high PEEP with “permissive hypoxemia and hypercapnia” to avoid barotrauma in STIFF lungs</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Novel COVID-19 Experience</th>
</tr>
</thead>
</table>

| ARDS (by P/F ratio and CXR criteria) – lungs were less stiff, more compliant, less hypercapnia, less tolerant of hypoxemia than “nl” ARDS. |

<table>
<thead>
<tr>
<th>Proning – PROSEVA trial</th>
</tr>
</thead>
</table>

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.

<table>
<thead>
<tr>
<th>ARDS – steroids</th>
</tr>
</thead>
</table>

(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.

<table>
<thead>
<tr>
<th>Early Intubation – MGH</th>
</tr>
</thead>
</table>

**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).

### Novel COVID-19 Experience

<table>
<thead>
<tr>
<th>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 – Mortality 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%</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pharmacologic therapies</th>
</tr>
</thead>
</table>

Remdesivir
Plaquenil
Zithromax
Tocilizumab
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 |

| Is there a role for HBO? |
Tiny sponges may soak up coronavirus; old steroid dexamethasone saves lives in COVID-19 study
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
Perhaps this is the moment for which you have been created.
Safety Considerations When Using Hyperbaric Oxygen Therapy for COVID-19

SCOTT A. GORENSTEIN, MD
NYU WINTHROP HOSPITAL
I have no relevant financial interest with commercial entities to resolve
March 5 2020
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
- SpO2 < 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

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>Past Medical History</th>
<th>Oxygen Needs Prior to HBO2 Therapy</th>
<th>Hospital Day of First HBO2 Therapy</th>
<th>HBO2 Therapy Sessions Received</th>
<th>Patient Outcome or Current Status (Hospital Day)</th>
<th>Other COVID-19 Therapies Received</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>43 M</td>
<td>None</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Discharged (4)</td>
<td>AZITH, HCQ</td>
<td>Declined additional treatments</td>
</tr>
<tr>
<td>62 M</td>
<td>HTN, HLD, DM, ASTHM</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>Discharged (8)</td>
<td>AZITH, HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>54 M</td>
<td>None</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>Discharged (12)</td>
<td>AZITH, HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>56 F</td>
<td>HTN</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>Discharged (7)</td>
<td>PLASMA</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>79 M</td>
<td>HTN</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>Discharged (10)</td>
<td>HCQ, anti-L6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>54 M</td>
<td>None</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>Discharged (9)</td>
<td>AZITH, HCQ</td>
<td>Limited sessions due to technician availability</td>
</tr>
<tr>
<td>57 M</td>
<td>HTN, HLD, DM</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>Discharged (12)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Discontinued due to ear pressure</td>
</tr>
<tr>
<td>30 M</td>
<td>None</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>Discharged (10)</td>
<td>AZITH, HCQ</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>54 M</td>
<td>None</td>
<td>6</td>
<td>2</td>
<td>5</td>
<td>Discharged (9)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>58 M</td>
<td>None</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>Discharged (4)</td>
<td>HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>55 M</td>
<td>DM</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>Discharged (12)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>67 M</td>
<td>HTN, DM</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>Discharged (12)</td>
<td>anti-L6, PLASMA</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>55 M</td>
<td>None</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>Discharged (7)</td>
<td>AZITH, HCQ</td>
<td>Discharged before five treatments</td>
</tr>
<tr>
<td>75 M</td>
<td>None</td>
<td>12</td>
<td>9</td>
<td>3</td>
<td>Discharged (38)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Discontinued due to study pause and then deemed medically unstable</td>
</tr>
<tr>
<td>32 M</td>
<td>None</td>
<td>15</td>
<td>4</td>
<td>5</td>
<td>Discharged (9)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Completed all five treatments</td>
</tr>
<tr>
<td>58 F</td>
<td>HTN, CAD</td>
<td>15</td>
<td>1</td>
<td>3</td>
<td>Discharged (10)</td>
<td>AZITH, HCQ, anti-L6, PLASMA</td>
<td>Discontinued due to study hold pending safety review for a different patient</td>
</tr>
<tr>
<td>60 M</td>
<td>HTN, HLD, CAD</td>
<td>15</td>
<td>15</td>
<td>4</td>
<td>Discharged (24)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Discontinued due to study hold pending safety review for a different patient</td>
</tr>
<tr>
<td>68 M</td>
<td>HTN, HLD, DM</td>
<td>15</td>
<td>0</td>
<td>5</td>
<td>Intubated (12), Death (35)</td>
<td>AZITH, HCQ, anti-L6, PLASMA</td>
<td>General anesthesia for removal of large thromboembolism</td>
</tr>
<tr>
<td>73 M</td>
<td>HTN, HLD, DM</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>Discharged (14)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Discontinued due to epistaxis</td>
</tr>
<tr>
<td>77 M</td>
<td>HTN, HLD</td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>Intubated (3), Death (25)</td>
<td>AZITH, HCQ, anti-L6</td>
<td>Hypoxic arrest while off oxygen</td>
</tr>
</tbody>
</table>
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
“I have no relevant financial relationships with commercial interests to disclose”
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
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.
• 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

I have no relevant relationships with commercial interests to resolve
What is meant by ‘Translating Research into Practice?’

A term used in two closely related contexts:

• Using the best available evidence to drive clinical practice
• The process by which an experimental health intervention is brought into clinical practice

• Novel agent
• Old agent for a new use
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

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$_2$T 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.

HBO$_2$T 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

**HBO₂T**
- 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 treatment of COVID-19:

- Dexamethasone
- Prone ventilation strategies
- Hydroxychloroquine
- Antibiotics

None of these interventions have been formally 'approved for use'.
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$_2$T and Phase 3 Studies

- Trial design
  - Larger multicentre 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$_2$T?
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
Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries

Kate Whitfield\textsuperscript{1*}, Karl-Heinz Huemer\textsuperscript{2}, Diana Winter\textsuperscript{3}, Steffen Thirstrup\textsuperscript{4}, Christian Libersa\textsuperscript{5}, Béatrice Barraud\textsuperscript{6}, Christine Kubiak\textsuperscript{7}, Lea Stankovski\textsuperscript{7}, Xina Grählert\textsuperscript{8}, Gabriele Dreier\textsuperscript{9}, Sebastian Geismann\textsuperscript{9}, Wolfgang Kuchinke\textsuperscript{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.
# What’s in a name?

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

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

- Compassionate use cannot replace clinical trials
- Does not inform on 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 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: 2,168,000  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 least 2 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

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

<table>
<thead>
<tr>
<th>Severity of ARDS</th>
<th>P/F ratio</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>200-300</td>
<td>27%</td>
</tr>
<tr>
<td>Moderate</td>
<td>100-200</td>
<td>32%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;100</td>
<td>45%</td>
</tr>
</tbody>
</table>

**PaO2 to FiO2 Ration For ARDS Any Cause**

A normal value might be $100/0.19=526$
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
• 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
“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
• 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

INSIDE THE
HYPERBARIC CHAMBER
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-2 VIRUS IN ASYMPTOMATIC AND MILD SYMPTOM POSITIVE PATIENTS
LONGOBARDI CENTRO IPERBARICA RAFFENNA, 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
- HBO2 exposure 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-19 and 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)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Decision</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient has COVID-19 pneumonia or COVID-19 symptoms for ≥7 days</td>
<td>AND</td>
<td></td>
</tr>
<tr>
<td>Patient is PCR+ OR high suspicion for COVID-19/PCR pending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient wheezing OR unable to speak in full sentences while at rest/with minimal effort</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Respiratory rate &gt;22</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>( \text{PaO}_2 &lt; 65 \text{ mmHg} ) or ( \text{SpO}_2 &lt; 90% )</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Repeat <strong>CXR</strong> is significantly worsening</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Chart 1: The NEWS scoring system

<table>
<thead>
<tr>
<th>Physiological parameter</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration rate (per minute)</td>
<td>≤8</td>
<td>9–11</td>
<td>12–20</td>
<td>21–24</td>
<td>≥25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ Scale 1 (%)</td>
<td>≤91</td>
<td>92–93</td>
<td>94–95</td>
<td>≥96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ Scale 2 (%)</td>
<td>≤83</td>
<td>84–85</td>
<td>86–87</td>
<td>88–92</td>
<td>93–94 on oxygen</td>
<td>95–96 on oxygen</td>
<td>≥97 on oxygen</td>
</tr>
<tr>
<td>Air or oxygen?</td>
<td>Oxygen</td>
<td>Air</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>≤90</td>
<td>91–100</td>
<td>101–110</td>
<td>111–219</td>
<td>≥220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse (per minute)</td>
<td>≤40</td>
<td>41–50</td>
<td>51–90</td>
<td>91–110</td>
<td>111–130</td>
<td>≥131</td>
<td></td>
</tr>
<tr>
<td>Consciousness</td>
<td>Alert</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CVPU</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>≤35.0</td>
<td>35.1–36.0</td>
<td>36.1–38.0</td>
<td>38.1–39.0</td>
<td>≥39.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 deterioration 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 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

- **Laboratory data to collect (depending on availability):**
- 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, TNFα
- 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; Deacron 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