Welcome to those who are currently logging in to the live Zoom Conference, as well as to those watching the live stream on our Facebook and YouTube channels. We are glad to have each and every one of you with us today. We will begin the presentation in just a few moments.
James F. Holmes, Jr., MD, MPH
University of California
Davis Health System
SAEM President

Moderator
Richard Eric Rothman, MD, PhD
Johns Hopkins University
School of Medicine

SAEM COVID-19 Planning Chair
Efficiencies in Education: How to Hack Educational Training to Get From 10,000 to 100 Hours
Learning science as a potential new source of understanding and improvement for continuing education and continuing professional development

Thomas J. Van Hoof & Terrence J. Doyle

@sherbino
Fig. 2. Histograms showing accumulated hours of deliberate practice for “master” (n = 16), “expert” (n = 31), and “intermediate” (n = 43) chess players (Gobet & Campitelli, 2007). Deliberate practice refers to study above.
5 Key Ideas

1. Teachers can’t ‘drag & drop’ information
2. Wicked learning environments require feedback
3. The ‘one-timer’ is low reward
4. Throw out your highlighters
5. Learning 2.0 = Groups
1: Knowledge is constructed, not transferred

(COGNITIVIST) MODAL MODEL OF MEMORY

CONSTRUCTIVISM

@sherbino
2: Complex learning requires specific, immediate feedback

Kolb’s Learning Cycle  Deliberate Practice  Mastery Learning

@sherbino
Curve of Forgetting
For newly learned information

% Memory Retention

Weeks

4th repetition
3rd repetition
2nd repetition
1st repetition
Forgetting curve

0
1
2
3
4
50
100

McMaster University
Health Sciences
MERIT
MCMaster Education Research, Innovation & Theory

@sherbino
3: To sustain learning, you need re-inoculation

Spaced repetition

Spiral curriculum

@sherbino
Learn more, faster.

Anki App is a cross-platform mobile and desktop flashcard app.

Study flashcards in your downtime. Make flashcards with text, sound, and images, or download pre-made ones. Studying is extra-efficient, thanks to our unique algorithm. Automatically does backups and sync to all your devices, via the cloud.

Download on the Mac App Store
Download on the App Store
Download from Windows Store
Android App on Google Play
Available on Kindle Fire
Download from Windows Phone Store
4: Effortful, mixed recall is best

INTERLEAVING (NOT BLOCKED PRACTICE)

ELABORATION

DESIRABLE DIFFICULTY

VYGOTSKY’S ZONE OF PROXIMAL DEVELOPMENT

@sherbino
5: We learn by observation, modelling, imitation, and shared values.

Bandura’s Social Learning Theory
Myths

☑️ FALSE

☑️ TRUE
1. Learning Styles
2. Multi-tasking
3. Self-assessment
Q & Eh

I need to:
• research...
• talk to...
• start...

@sherbino
5 Key Ideas

1. Teachers can’t ‘drag & drop’ information
   Knowledge is constructed, not transferred

2. Wicked learning environments require feedback
   Complex learning requires specific, immediate, progressive feedback

3. The ‘one-timer’ is low reward
   To sustain learning, you need re-inoculation

4. Throw out your highlighters
   Effortful, mixed recall of knowledge is best

5. Learning 2.0 = Groups
   We learn by observation, modelling, imitation and shared values.
Special Session on COVID-19 Therapeutics will begin at
1 pm ET/12 pm CT/11 pm MT/10 am PT
Special Session on COVID-19 Therapeutics
James F. Holmes, Jr., MD, MPH
University of California
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SAEM COVID-19 Planning Chair
Paul G. Auwaerter, MD, MBA
Sherrilyn and Ken Fisher Professor of Medicine
Clinical Director of the Division of Infectious Diseases
Johns Hopkins School of Medicine

COVID-19 Therapeutics
Disclosures

• Johnson and Johnson (equity holder)
Treatment v. Trials

Ethics

Values

Clinical Equipoise

Which treatment works better?

Treatment A

Which treatment has the least side effects?

Treatment B
Illness Phases/Approaches

Figure: Schematic of clinical course of severe COVID-19 with representation of SARS-CoV-2 RNA levels, common symptoms, and possible timing of therapeutic use of greatest benefit.
How many drug intervention trials for COVID-19?

Clinicaltrials.gov (5/11/2020)
Many approaches/SARS-CoV-2

So much “promise,”
...so little to show

SAR-CoV-2

Hydroxychloroquine
Chloroquine
Ivermectin
Lopinavir/ritonavir

Favipiravir
Baloxivir
Indomethacin
Zinc
Vitamin C
Famotidine

Viral Tissue Culture studies, *in vitro*

Human studies, *in vivo*
Early opinions shaped by Chinese COVID-19 Guidelines

- Hydroxychloroquine or chloroquine
- Lopinavir/ritonavir
- Oseltamivir, favipiravir or umifenovir
- Tocilizumab
- Traditional Chinese medicine

- Many used in combination based on limited data (in vitro), expert opinion, case series
Remdesivir: Antiviral

Remdesivir
Potential repurposed drug for COVID-19

SARS-CoV-2
ACE2 receptor

Ribosome

Translation of viral polymerase protein (RdRp)

RdRp

Inhibition of RNA replication

Cytoplasm

Remdesivir (Prodrug)

GS-441524 (Active molecule)

Genomic replication

Subgenomic (nested) transcription

Nucleocapsid (N)

Spike (S)

Membrane (M)

Envelope (E)

RdRp SARS-CoV-2
PDB ID: 6M71

GS-441524 binding pocket
RDV: why is this trial in NEJM?

- 61 pts, open label, no comparator
- 40 (75%) had 10d course
- 34 (69%) mechanical ventilation
- Majority had co-morbidities

- At d18, 68% had improved oxygenation
- At time of writing
  - 47% discharged
  - 13% died
  - Usual range if in ICU, ventilated 20-40%?

- No conclusions possible from this case series
- 23% had severe side effects
Remdesivir in Adults with Severe COVID-19: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

- N = 237 patients, halted
- Confirmed infection, 12 days or fewer of symptoms, lung involvement
- Remdesivir 200 mg day 1, then 100 mg IV daily vs placebo

Findings:

- No clinical improvement (subgroup <10 days with trend)
- No difference in mortality (subgroup <10 days with trend)
- No effect on viral load in upper or lower respiratory tracts

Sponsor: NIAID/NIH
RCT: Remdesivir vs placebo (began 2/21/20)
N = 1063 patients, 68 sites (47 in US; 21 from Europe and Asia)

Preliminary results
• Remdesivir pts 31% faster time to recovery than those who received placebo (P <0.001)
• Median time to recovery: 11 days remdesivir vs 15 days placebo
• Survival benefit? trend
  – Mortality rate 8.0% remdesivir vs 11.6% placebo group (P = 0.059)
• Awaiting more analysis
• Trial is adapting—starting mid May
  – RDV v. RDV plus baricitinib
    • JAK1/JAK2 subtype inhibitor, interferes w/ signal transduction STAT proteins, stopping gene expression in immunomodulatory cells
Haphazard Rollout of Coronavirus Drug Frustrates Doctors

Remdesivir was shipped to small hospitals even as besieged medical centers were denied access.

By Gina Kolata

May 8, 2020
Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial

Prof Ivan Fan-Ngai Hung, MD  Kwok-Cheung Lung, FRCP  Eugene Yuk-Keung Tso, FRCP  Raymond Liu, FRCP  Tom Wai-Hin Chung, MRCP  Man-Yee Chu, MRCP  et al.  Show all authors

Published: May 08, 2020  DOI: https://doi.org/10.1016/S0140-6736(20)31042-4  Check for updates

• Open-label, randomized, phase 2 trial
• Hong Kong, (2:1) 14-day
  – Combination: lopinavir 400 mg/ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million international units of interferon beta-1b on alternate day
  – lopinavir 400 mg and ritonavir 100 mg every 12 h (control group)
  – primary endpoint was the time to providing a nasopharyngeal swab negative
Findings

- 127 patients, 86 combination/41 control
- Median days symptom onset 5 days (IQR 3–7)
- Combination group
  - Reduced viral carriage x 5 days
    - Negative nasopharyngeal swab (7 days [IQR 5–11]) v. control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], p=0.0010)
  - Faster alleviation of symptoms x 4 days
    - NEWS2 of 0 (4 days [IQR 3–8] in the combination group vs 8 days [7–9] in the control group; HR 3.92 [95% CI 1.66–9.23], p<0.0001)
    - Adverse events included self-limited nausea and diarrhea with no difference between the two groups.
- Need for larger study, true placebo arm
# Hydroxychloroquine (HCQ) and Chloroquine (CQ)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type (n)</th>
<th>Drug(s)</th>
<th>Viral carriage reduction</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao</td>
<td>Series (100)</td>
<td>CQ, CQ</td>
<td>“superior”</td>
<td>Inhibits pneumonia, ↓ duration</td>
</tr>
<tr>
<td>Chen J</td>
<td>RCT (30)</td>
<td>HCC</td>
<td>86% (HCC), 93% (control)</td>
<td>None</td>
</tr>
<tr>
<td>Chen Z</td>
<td>RCT (62)</td>
<td>HCC</td>
<td>n/a</td>
<td>↓ fever x 1d, improved imaging</td>
</tr>
<tr>
<td>Gautret P</td>
<td>Non-RCT (36)</td>
<td>HCQ, HCQ+ AZ</td>
<td>Combination = ↓ shedding (6 pts)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gautret P</td>
<td>Non-RCT (90) mild dz</td>
<td>HCQ+ AZ</td>
<td>80% with negative PCR d8 (no comparator arm)</td>
<td>N/A</td>
</tr>
<tr>
<td>Molina J</td>
<td>Non-RCT (11)</td>
<td>HCQ + AZ</td>
<td>80% positive d5-6</td>
<td>1 death 1 QT prolonged</td>
</tr>
<tr>
<td>Borba M</td>
<td>RCT IIb (81)</td>
<td>CQ (high dose)</td>
<td>1/14 negative PCR (d4)</td>
<td>High dose = lethality trend (17%), low dose (13%)</td>
</tr>
</tbody>
</table>
Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Eli S. Rosenberg, PhD; Elizabeth M. Dufort, MD; Tomoko Udo, PhD; et al

Original Investigation
May 11, 2020

25 hospitals, retrospective
N = 1438 patients
adjusted HR in-hospital mortality
HCQ 1.08
Azithromycin 0.56
HCQ + AZ 1.35
None were statistically significant
Growing Safety Concerns Regarding HCQ & CQ

- **French National Agency for the Safety of Medicine and Health Products (ANSM, from 3/27/20 forward)**
  - Pharmacovigilance surveys re: COVID-19
  - Sub-analysis, 43 of 53 cardiac adverse events occurred
    - Receiving HCQ or HCQ plus azithromycin
    - 7 cases cardiac death
    - 12 rhythm disorders → syncope
    - All others, prolonged QT
- **VA retrospective series (Magagnoli et al, 2020 pre-print)**

<table>
<thead>
<tr>
<th>Table 5. Subdistribution hazard of ventilation, death and death after ventilation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted Hazard Ratio (95% Confidence Interval)</strong></td>
</tr>
<tr>
<td>Ventilation</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>HC</td>
</tr>
<tr>
<td>HC+AZ vs. No HC</td>
</tr>
</tbody>
</table>
HCQ or CG meta-analysis

• 155 “studies” evaluated (preprint or published)
• No double blind, placebo-controlled RCT of high quality
• Data neither to endorse or to refute use of HCQ or CQ

Fajgenbaum et al

https://www.medrxiv.org/content/10.1101/2020.05.07.20073981v1.full.pdf (pre-print, release 5/11/20)
COVID-19 Cytokine Storm

Multiple organs affected
Lungs
Kidneys
Brain
GI
Cardiac
Vasculature
CNS
Liver
Acute Respiratory Distress Syndrome (ARDS, bacterial sepsis or pneumonia)

Alveolar Changes

Typical Acute Respiratory Distress Syndrome

Healthy alveolus

Injured alveolus

- Sloughing of damaged bronchial epithelium
- Widening of alveolar septae
- Migrating neutrophils
- Inflamed endothelial cells
- Gap formation
- Neutrophils
- Fibrin
- Cellular debris
- Activated neutrophils
- Alveolar macrophages
- Type II pneumocyte
- Type I pneumocyte
- Surfactant layer
- RBC
- Endothelial cell
- Fibroblast

SAEM20
SARS-CoV-2 lung injury

Likely similar to Influenza-related ARDS

COVID-19: Effects on Vasculature

ACE2 receptors & virus --> clots, MIs

Thrombotic vasculopathy postulates:
- Elevated D-Dimers & vWF antigen/activity
- Weibel-Palade bodies from endothelial cells
  -> ultralarge vWF multimers bind platelets, deposit in vessel walls and yield acquired ADAMTS13 deficiency, a TTP-like state
- Elevated levels of lupus anticoagulant --> change aPTT values
Clots, clots and more clots (selected papers)

- **Italy, 388 pts, 68% men, 16% ICU**
  - Prophylaxis 100% ICU, 75% on ward.
  - Thrombosis 21% (27.6% ICU, 6.6% ward).
  - 50% diagnosed in first 24h
  - Overt DIC in 8 (2.2%) [Lodigiani, Thromb Res 2020; 191:9-14]

- **France, High incidence in fully anticoagulated patients**
  - ICU (n=26) 100% vs. 56% p=0.03 [Litjens JF J Thromb Haemost 2020]

- **Netherlands, high incidence thrombosis in ICU**
  - N = 184, 31% incidence thrombotic complications [Klok, Thromb Res 2020, Apr 10]

- **China, hospitalized patients**
  - 19.7% of 416 pts, cardiac injury [Shi, JAMA Cardiology, 2020]

- **Debate: who to anticoagulated, prophylactically? High – intensity? Multiple guidelines.**
COVID-19

Plasma & Immunotherapies
History of convalescent serum/plasma use

Post-exposure prophylaxis & treatment

- Hepatitis A
- Hepatitis E
- Polio
- Mumps
- Measles
- Rabies
- Ebola
- MERS-CoV
### Convalescent plasma SARS-CoV-1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Good outcome</th>
<th>Poor outcome</th>
<th>P value</th>
<th>Logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>33</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>37.9±12.5</td>
<td>50.2±15.1</td>
<td>&lt;0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>Admission LDH (IU/l)</td>
<td>268.6±117.6</td>
<td>334±183.7</td>
<td>0.08</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean day of plasma infusion</td>
<td>11.7±2.3</td>
<td>16.0±6.0</td>
<td>&lt;0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean plasma volume</td>
<td>253.6±99.9</td>
<td>297.23±141.4</td>
<td>0.11</td>
<td>0.174</td>
</tr>
<tr>
<td>PCR positive and seronegative for SARS</td>
<td>20</td>
<td>10</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Convalescent Plasma

- Convalescent plasma for Severe COVID-19
  - eIND from FDA (3/26/20)
  - Multiple trials: Treatment (early & late), prevention

Serum from recovered COVID-19 patients containing virus neutralizing antibodies can be infused into sick patients with the goal of reducing symptoms. (J Clin Invest. 2020. https://doi.org/10.1172/JCI138003)
Convalescent Plasma & COVID-19

- Possible mechanisms of action
  - Direct neutralization of the virus
  - Control of hyperinflammation
    - Impact similar to IVIG
    - Impact Th1/Th17 ratio, complement activation
  - Immunomodulation of a hypercoagulable state

Rodriquez, Autoimm Rev 2020
• 5 critically ill/ARDS, also steroids/antivirals—all had improvement [Shen, JAMA 2020]

• 10 severe patients, all improved, 7/10 with (+) viral loads → negative [Duan, PNAS 2020]

• 4 severe/critical (mech vent/ ECMO/ pregnancy), all recovered [Zhang, Chest 2020]
Convalescent Plasma Risks—all rare

- Pathogen transmission
- Antibody-dependent enhancement of infection
- Allergic transfusion reactions
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
Sarilumab study

Regeneron, Sanofi shut down part of arthritis drug study after trial shows benefit for only sickest coronavirus patients

- Phase 2/3 of Kevzara (sarilumab) IL-6 receptor blocker
- Study compared low and high dose in those with “severe” or “critical” illness
- Preliminary phase 2 analysis
  - Negative trends for most outcomes in the severe group
  - Positive trends for all outcomes in critical group
- The phase 3 results in those patients with severe illness showed the drug appeared to have no effect.
- Ongoing portion of trial will enroll 600 patients with critical illness
Immunomodulators—reversing the Cytokine Storm? Tocilizumab
Tocilizumab (anti-IL6R mab)

Slides from E Tso MD (Hong Kong)

1 day post Tocilizumab
Tocilizumab

No published data

According to French press, Entire DSMB resigned
COVID-19 Therapeutics

- In very early phases of understanding
- Numerous trials
- Remdesivir, some promise
  - Antivirals need early treatment
- Immunomodulatory therapies
  - Earlier better than later?
Questions