PSW COVID-19 Clinical Webinar – Part Deux

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Objectives

• Review current and future state of the COVID-19 pandemic

• Discuss considerations, limitations and updates related to COVID-19 testing and treatment

• Recognize lessons learned and future challenges for the pharmacy profession

• Answer audience questions
Coronavirus Has Now Killed More Americans Than Vietnam War

April 28, 2020 · 5:55 PM ET

DAVID WELNA

•> 60,000 deaths in the U.S. and counting...
COVID in the U.S.


CRUDE MORTALITY 5.8%
COVID Amplifies Health Disparities

<table>
<thead>
<tr>
<th>City or State</th>
<th>% Population that is African American</th>
<th>% COVID Deaths that were African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicago</td>
<td>32%</td>
<td>70%</td>
</tr>
<tr>
<td>Michigan</td>
<td>14%</td>
<td>41%</td>
</tr>
<tr>
<td>Louisiana</td>
<td>32%</td>
<td>70%</td>
</tr>
<tr>
<td>Milwaukee</td>
<td>26%</td>
<td>81%</td>
</tr>
</tbody>
</table>

• Opportunity for our health care system to address fundamental disparities – will we?

The U.S. is the Epicenter of COVID Worldwide

COVID in WI: The “Curve”

State may have seen COVID-19 peak without big surge, but officials say risk remains
GATING CRITERIA

- **SYMPTOMS**: Downward trajectory of influenza-like illnesses (ILI) reported within a 14-day period AND downward trajectory of COVID-19-like syndromic cases reported within a 14-day period.

- **CASES**: Downward trajectory of positive tests as a percent of total tests within a 14-day period.

- **HOSPITALS**: Treat all patients without crisis care AND Robust testing programs in place for at-risk healthcare workers, with decreasing numbers of infected healthcare workers.

CORE RESPONSIBILITIES

- **TESTING**: Every Wisconsin resident who has symptoms of COVID-19 can get a lab test.

- **TRACING AND TRACKING**: Greatly increase capacity.

Estimated ~300 lives saved.

Social Distancing

An evidence-based, deliberate public health strategy to spread out the volume and pace of viral spread.

- Will allow the healthcare system to manage treating patients over a longer period of time

As a pharmacist you must relay the importance of social distancing to all family, friends, etc. in your orbit

Until we have:

- Increased testing capacity (including serology);
- Treatment; and
- A vaccine(s)

we must continue social distancing.

*Treatment = prevention


Temporal Association between Social Distancing and COVID-19: Wuhan, China

Temporal Association between Social Distancing and COVID-19: Wuhan, China

Figure 4. The Effective Reproduction Number ($R_e$) Estimates Based on Laboratory-Confirmed Coronavirus Disease 2019 (COVID-19) Cases in Wuhan, China

The Basic Reproduction Number: R naught (R₀)

- R₀ indicates how contagious an infectious agent is – how well it can be transmitted to new hosts.

- R₀ < 1 = disease dies out
- R₀ = disease stays present, no pandemic
- R₀ > 1 = disease transmission increases, possible pandemic

**The average number of people that one person with a virus infects, based on the R₀ scale**

- COVID-19: 2–2.5*
  - Infected person → Average people infected
- H1N1: 1.2–1.6
  - Infected person → Average people infected
- Ebola: 1.6–2
  - Infected person → Average people infected
- SARS: 2–4
  - Infected person → Average people infected
- MERS: 2.5–7.2**
  - Infected person → Average people infected

*As of February 28, 2020  **R₀ calculated solely during the 2015 outbreak in South Korea

Sources: ScienceMag; WHO; Journal of the ISIRV

2.2 NEJM 2020
COVID Testing

• Nasopharyngeal swab – PPE!
• Testing Capacity & **Priority patients**
• Reverse transcriptase polymerase chain reaction (RT-PCR)
• **False negatives possible** – early/asymptomatic infection, specimen collection, specimen shipping/handling
• If high clinical suspicion for COVID re-test multiple respiratory sites
• **NO VIRAL CULTURE // SAFETY**

‘It’s Just Everywhere Already’: How Delays in Testing Set Back the U.S. Coronavirus Response

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COVID Testing Options

- CDC
- Local/State Lab
- Site Lab
- Commercial Lab

**NO home testing - Beware of scams!**

Emergency Use Authorization
Pharmacists & Testing

• Allowed per DHHS (4/8/20)
• Logistics remain –
  • PPE
  • Test ordering and limitations
  • Reporting results
• Potential to assess community spread

PSW Statement on Pharmacists Roles in COVID-19 Testing

• System changes are needed to address pharmacist and pharmacy technician access to appropriate personal protective equipment (PPE) and testing supplies, pharmacy reimbursement, and integration of reporting.
• Addressing these important factors will support pharmacists moving into this expanded point of care testing role.
• Our profession stands ready to support the Wisconsin Department of Health Services’ efforts and local public health departments in the fight against COVID-19.

Provided that the necessary resources can be made available to support and maintain COVID-19 testing by pharmacies, we strongly recommend that HHS pursue the recommendations outlined above.
COVID Serology

- Studies have found high rates of SARS-CoV-2 antibodies in various U.S. populations
- Used as fodder to argue against a need for social distancing
- Heavily criticized
  - Non-random samples (generalizability)
  - Different tests, test accuracy
- Many more studies coming

Antibody tests support what’s been obvious: Covid-19 is much more lethal than the flu

Antibody testing has garnered the attention of many researchers and government officials in the fight against the coronavirus outbreak. (John Farrell, Jonathan Baran/The Washington Post)

By Joel Achenbach
April 28, 2020 at 2:06 p.m. CDT

<table>
<thead>
<tr>
<th>Seasonal Influenza</th>
<th>COVID-19</th>
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<tbody>
<tr>
<td>R₀</td>
<td>~1.3</td>
</tr>
<tr>
<td>Mortality</td>
<td>24-62,000 from 10/19 – 4/20</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment</td>
<td>Yes</td>
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COVID Serology: NOT Ready for Prime Time

- Immunological correlates for SARS-CoV-2 protection and the proportion of a population who must achieve them are unknown\(^1\)
  - Do Abs to SARS-CoV-2 spike protein lead to functional/durable protection?
- 10-20% of symptomatic SARS-CoV-2 patients have little or no detectable antibody.\(^2\)
- SARS survivors have Ab but ?non-hospitalized SARS patients
- With \(R_0\) of \(~2.2\), we need \(~60\%\) protective immunity\(^3\)

Did we over-react?

“If it looks like you’re over-reacting then you’re probably doing the right thing.”
– Anthony Fauci, MD

Germany: $R_0$

<table>
<thead>
<tr>
<th>$R_0$</th>
<th>Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>reach the limits of what our health system and intensive care beds can manage in October</td>
</tr>
<tr>
<td>1.2</td>
<td>reach the health system's limit in July</td>
</tr>
<tr>
<td>1.3</td>
<td>reach the health system's limit in June</td>
</tr>
</tbody>
</table>
Masks in Public?

• CDC recommends wearing cloth face coverings in public settings where other social distancing measures are difficult to maintain (e.g. pharmacies)
• Masks may remind people to continue practicing physical distancing

The Time for Universal Masking of the Public for COVID-19 is Now

Monica Gandhi MD, MPH, Diane Havlir MD

THREE REASONS:
1. SARS-CoV-2 is HIGHLY contagious
2. Asymptomatic persons can shed viable SARS-CoV-2
3. Contributes to core distancing public health strategies for curbing transmission

COVID Vaccine

- Global R&D effort is remarkable
- SCOPE: > 100 candidates
- SPEED: vaccines could be available under emergency use by early 2021 (DHHS).
  - Historical vaccine timeline ~10 years
    - Ebola 5 years

- Vaccine(s) will be CRUCIAL to our COVID public health armamentarium going forward
- Given rapid R&D MUST focus on vaccine safety
Current Count of Treatments and Vaccines

197 treatments in consideration

111 vaccines in development

COVID-19 Treatments and Vaccines (combined)

Source: Milken Institute

- Antibodies
- Antivirals
- Cell-Based Therapies
- RNA Based Treatments
- Dormant/Discontinued
- Scanning Compounds to Repurpose
- Devices
- Others
- Vaccines

• ACE/ARBS are not harmful in hospitalized COVID+ adults with hypertension (China, UK, Italy and US)
  • N= 5 observational studies (one pre-print)
  • May have benefit...
• Ongoing RCTs to study the impact of ACE/ARB as COVID “therapy”
The "Infodemic" (as coined by WHO)

- An over-abundance of information – some accurate and some not – that makes it hard for people to find trustworthy sources and reliable guidance when they need it.

- Unprecedented rate of scientific discovery and literature publication

- Much literature not yet peer reviewed ("pre-print")

- BE SKEPTICAL
- APPRAISE DATA CRITICALLY
- DON'T LOST SIGHT OF HISTORICAL PRECEDENT!

- Journalistic response to pre-print data can be problematic

- "A lie gets halfway around the world before truth puts on its boots." – Winston Churchill


“We need to retain a healthy skepticism and remember the principle of clinical equipoise, particularly when considering interventions that could cause harm.”

“...we have an increased tendency to inappropriately favor recently acquired information because of its ease of recall...”

“In a time when the rational–emotional scale is tipping to the emotional side, we begin relying more heavily on anecdotes, particularly personal experiences that may carry inordinate weight in our minds.”

“...prescribing medications on the basis of case reports does little to help advance science or our ability to combat future recurrences of coronavirus.”

“Throughout the world, therapeutic management for SARS-CoV-2 has largely been supportive, and to date, no specific therapy has been scientifically proven to reduce mortality.”

“...the intense desire to try new, unproven remedies may distract health care providers from offering patients the best-quality supportive care possible.”
COVID19 Therapeutics - Focus on providing excellent care

• Supportive care is only recommended practice

• Can you provide excellent supportive care?
  • Pain, agitation, delirium practices regarding sedation
  • Pharmacokinetic/pharmacodynamics dose optimization
  • Conservative fluid management strategies
  • Low tidal volume ventilator management strategies
  • Appropriate BP/MAP goals

• Is your hospital ready to provide care to critically ill patients?
  • [www.uwhealth.org/cckm](http://www.uwhealth.org/cckm) - search for vasoactive agents, Pain/agitation and delirium, COVID guidance documents
  • SCCM – Surviving Sepsis Guidelines for COVID19
April 10, 2020

- **61 patients** received remdesivir
- Age 64 years (IQR 48-71)
- Critically ill patients (57% mech vent, 8% ECMO)
- 36 (68%) patients improved oxygen support class
- 7 (13%) patients died
- 32 (60%) patients reported adverse events by day 28
  - LFT increase, Diarrhea, Rash, AKI, hypotension AFIB
- 12 (23%) had serious adverse events
  - MSOF, septic Shock, AKI, hypotension
Placebo-controlled, RCT funded by Chinese Academy of Medical Sciences

2:1 randomization of 453 planned
- 236 actual – stopped early due to control of COVID19

Primary endpoint: time to clinical improvement

Overall less sick population

Confounders: allowed use of interferon (18%), lopinavir/ritonavir (18%), corticosteroids (39%)

Highlighted subanalysis: If you started remdesivir within 10 days of symptoms (ITT group analysis), numerically faster time to clinical improvement [median 18.0 days (IQR 12-28 days) vs 23.0 days (15-28 days); HR 1.52 (0.95-2.43)]

Adverse events were reported in 102 (66%) of 155 patients in the remdesivir group and 50 (64%) of 78 in the control group
- 28 (18%) serious adverse events were reported in the remdesivir group and 20 (26%) were reported in the control group.
Remdesivir Confusion

Published online ~10am April 29th

Published about 2 hours later

About 30 minutes later
NIH – Adaptive COVID19 Treatment Trial
NCT04280705

- Adaptive, randomized, double-blind, placebo-controlled trial
  - If one arm demonstrates efficacy, it becomes the control arm
  - If safety signal reached, that arm is stopped

- Goal enrollment of 800 patients

- Includes moderate, severe, and critically ill patients

Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (p<0.001). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (p=0.059).
Current State of Remdesivir

• Approved for Emergency Use Authorization (EUA) on Friday May 1
  • Last drug for EUA status = peramivir

• CEO of Gilead says 150,000-200,000 vials available
  • Distribution through US Government
  • 3-5 days of new cases

• Cautiously optimistic
Hydroxychloroquine/Chloroquine Status

- Hydroxychloroquine > chloroquine
  - Supply chain improved

- Preferred in clinical trial setting only

- Absolutely should have cardiac monitoring
  - Not for outpatient use
  - QTc increases of 25ms (equal to FQ and voriconazole)
  - Especially if giving with azithromycin
Convalescent Plasma – AN AVAILABLE OPTION!

- Available through Expanded Access Program (Clinical Trial)
- Inclusion criteria: adults with severe or critical illness from COVID19
- Dose: ~200-250ml blood
- Monitoring: TRALI

Severe COVID-19 is defined by one or more of the following:
- dyspnea
- respiratory frequency ≥30/min
- blood oxygen saturation ≤93%
- PaO2/FiO2 ratio <300
- lung infiltrates >50% within 24 to 48 hours

Life-threatening COVID-19 is defined as one or more of the following:
- respiratory failure
- septic shock
- multiple system organ dysfunction or failure
Stage I (Early Infection)
- Viral response phase
  - Clinical Symptoms
    - Mild constitutional symptoms
      - Fever >99.6°F
      - Dry Cough, diarrhea, headache
  - Clinical Signs
    - Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)

Stage II (Pulmonary Phase)
- IIA
- IIB
- Host inflammatory response phase
  - Clinical Symptoms
    - Shortness of Breath
    - Hypoxia (PaO2/FiO2 ≤ 300 mmHg)
  - Clinical Signs
    - Abnormal chest imaging
    - Transaminitis
    - Low-normal procalcitonin

Stage III (Hyperinflammation Phase)
- ARDS
- SIRS/Shock
- Cardiac Failure
  - Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
  - Troponin, NT-proBNP elevation

Potential Therapies
- Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
- Reduce immunosuppression
- Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors
## Anti-cytokine Therapy – Cautious Optimism

### Patients to consider for anti-cytokine therapy

Consider enrollment in UW clinical trial before proceeding with off-label use of tocilizumab or other anti-cytokine agents

**Note:** anti-cytokine therapy requires approval from Critical Care and Special Pathogens faculty or clinical trial enrollment

### Respiratory status

- Patients needing HFNC/non-invasive/invasive mechanical ventilation

**OR**

- Need for supplemental O\(_2\) via nasal cannula with evidence of worsening respiratory status, where worsening respiratory status defined as:
  - Tachypnea (>30 breaths/min)
  - Requiring O\(_2\) >2 L/min to maintain sat >92% or those on home O\(_2\) needing >2 L/min over their usual home O\(_2\) requirement
  - Progressive respiratory failure and/or progressive O\(_2\) requirement

### Laboratory evidence of hyperinflammation

One or both of the following:

- CRP level >70 mg/L (7 mg/dL)
- Serum Ferritin >2000 ng/mL or Serum Ferritin >1000 ng/mL and rising over serial assessment

**PLUS** one of the following:

- Lymphopenia defined as <800 lymphocytes/mL
- D-dimer >1 mcg/mL
- Lactate dehydrogenase >400 Units/L
# Anti-cytokine Therapy – Cautious Optimism

## Anti-cytokine therapy dosing, contraindications, and warnings

### Tocilizumab (IL-6 inhibitor) Dosing:
- 8 mg/kg actual body weight (max 800 mg) IV once; may repeat once at least 12 hours later

### Siltuximab (IL-6 binding antibody) Dosing:
- 11 mg/kg actual body weight IV once

### Contraindications

- Systemic bacterial
- Invasive fungal infection
- Active tuberculosis
- Receipt of TNF blocker within 5 half-lives of the agent
- Known hypersensitivity or allergic reaction to tocilizumab or siltuximab

### Warnings/Precautions

- Treatment with another anti-cytokine within preceding 4 weeks.
- On immunosuppression, including prednisone 15 mg equivalent per day.
- Severe intercurrent medical condition such as active solid or hematological malignancy; history of primary immunodeficiency (e.g. CVID); decompensated liver disease; ongoing IV drug use; pulmonary disease requiring $O_2 > 3$ L/min at rest; severe heart failure NYHA Class III/IV; inadequately treated HIV (viremia not controlled, CD4 <300 cell/mL); other conditions with similar prognosis per treating physician’s judgement.
- (Tocilizumab only) History of demyelinating illness, demyelinating illness on treatment - discuss with Neurology.
- (All anti-IL6 agents) History of perforation or active inflammatory bowel disease or bout of diverticulitis within the last 6 months - discuss with Gastroenterology.
- Alanine transaminase/aspartate transaminase (ALT/AST) >5 times of the upper limit of normal if due to alternate etiology or >10 times upper limit of normal if due to SARS-CoV2.
- Absolute neutrophil count <1000 cells/mL due to an etiology other than SARS-COV2 infection.
- Platelets <50,000/mL due to an etiology other than SARS-COV2 infection.
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Reason for Not Recommended</th>
<th>NOT Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient data to NOT recommend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Not available in US</td>
<td>Ivermectin</td>
</tr>
<tr>
<td>Umifenovir</td>
<td>Not available in the US</td>
<td>Nitazoxanide</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Theoretical decrease in IL6 pathway</td>
<td>Interferon</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>Most data not supportive of use, lots of drug interactions, a few pending studies</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Anti-IL1 agent</td>
<td>Niclosamide</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>Anti-oxidant and may protect lung epithelium</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Lung protective anti-inflammatory</td>
<td>Sarilumab</td>
</tr>
<tr>
<td>JAK-inhibitors</td>
<td>Broad immunosuppressive effect</td>
<td>ACE/ARB</td>
</tr>
<tr>
<td>Tocilizumab/Siltuximab</td>
<td>Anti-IL6 activity</td>
<td>Statin Therapy</td>
</tr>
</tbody>
</table>

**NOT Recommended**

- Ivermectin: Cannot dose high enough w/o toxicity
- Nitazoxanide: Cannot dose high enough w/o toxicity
- Interferon: No benefit in COVID trials, high toxicity
- Ribavirin: No benefit in COVID trials, high toxicity
- Baloxavir: No drug target on SARS-CoV
- Oseltamivir: No drug target on SARS-CoV
- Niclosamide: Not commercially available in US
- Sarilumab: No benefit in COVID trial
- ACE/ARB: FDA statement to continue therapy
- Statin Therapy: NIH treatment recommendations continue therapy (do not discontinue)
# Anticoagulation Recommendations

**VTE prophylaxis**
- Initiate pharmacologic prophylaxis unless contraindicated (i.e. active bleeding, platelet count fewer than 25,000 or fibrinogen below 0.5 g/mL with routine prophylactic dosing).
- Initiate mechanical prophylaxis if chemoprophylaxis is contraindicated.

**DVT/PE treatment**
- Initiate full-dose anticoagulation when DVT/PE is confirmed OR if clinical suspicion for DVT/PE is high but confirmatory testing cannot be obtained.
- If therapeutic anticoagulation is contraindicated, management should be determined on a case-by-case basis.

**Alteplase**
- Use of alteplase is *not* recommended for COVID-19-associated coagulopathy outside of a clinical trial. Thrombolysis may be considered for patients with confirmed or high suspicion for specific indications for thrombolytic therapy (e.g. acute ischemic stroke, PE, acute myocardial infarction).
Lessons Learned from History

Three Factors Standing in the Way of Prevention
1. People do not appreciate the risks they run
2. Personal character required to implement containment measures
3. Highly infectious nature of the respiratory infection
Summary

1. We are at the peak. It may not be a steep downhill. There may be another peak.
2. Social distancing and PPE use most important to bend curve
3. Testing recommendations change rapidly, including serology
4. A vaccine is still a ways off
5. Supportive care is the only recommended treatment – are you prepared?
6. Cautious optimism about remdesivir and emerging clinical trials
7. Be ready to talk to your patients about pros and cons of HCQ and azithromycin
8. Clinical trials are starting rapidly
9. Continue to be great pharmacists - what will your patients/hospital/clinic need from you?
QUESTIONS?

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Appendix Slides
Renin-Angiotensin System (RAS)

• ACE converts Angiotensin (Ang) I to Ang II
• Ang II is a vasoactive peptide → systemic vasoconstriction and aldosterone release
  • Aldosterone = Na+ and water retention, ↑ BP
• Downstream Ang II effects blocked by ACEIs and ARBs
  • Also increase ACE2 expression
• ACE2 provides check against RAS
  • Catalyzes Ang I and Ang II
  • Ang I and Ang II degradation products promote vasodilation