Ongoing Resources List

Resources from today’s session and past sessions can be found in our ongoing resources list:

https://iecho.unm.edu/sites/uidaho/download.hns?i=440
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Moving Forward, Moving Targets: Recovery and Rebound

May 5, 2020

Carolyn Buxton Bridges, MD FACP
Megan Dunay, MD MPH
Maria Gulan, RN BSN MBA CMPE
Cathy Oliphant, PharmD
Gail Vasquez, LCSW
Idaho Epidemiology Curves and Public Health Updates

Carolyn Buxton Bridges, MD, FACP
Governor’s Coronavirus Working Group, Former CDC Public Health Physician and Researcher
Case Counts and SARS-CoV-2 PCR Testing in Idaho

Lab-confirmed and probable cases: 2,106
Deaths: 64 (3%)
At least 201 (9.5%) hospitalized
At least 83 (3.8%) ICU, ~41% of hospitalized in ICU
At least 266 (12.6%) HCP
Number of people tested: 30,146

https://coronavirus.idaho.gov
Rebound Idaho Criteria

• Epi/capacity criteria required to move to next stage – Epidemiology data examples
  • Downward trend or <20/day on average over 14 days lab confirmed COVID-19 cases
  • Downward trend or <20/day on average over 14 days ED visits for suspected COVID-19 cases

• New guidance for each stage and setting, e.g.
  • Daycare, youth activities, businesses, places of worship

• Next phase – May 16 *if criteria met*
  • Restaurants, indoor gyms, hair salons
Updated Idaho Guidance

Components on employee training, social distancing, sanitation, hygiene, sick leave policy review, screening for illness, etc.

• State Board of Education Criteria released May 4 at https://boardofed.idaho.gov/resources/board-approves-revised-re-entry-criteria-for-public-schools/.
Aligned with Rebound Idaho criteria
Requires collaboration with local public health/school district, assurance of plans for social distancing and hygiene, and closure plans if any cases in a school

Updated Guidance from CDC – Decision Memo on Discontinuation of Isolation


• Recommendation: For persons recovered from COVID-19 illness,
  • Maintain isolation for at least 10 days after illness onset and at least 3 days (72 hours) after recovery = no fever and progressive improvement or resolution of other symptoms.

• While this strategy can apply to most recovered persons, either a test-based strategy (if feasible) or a symptom-based strategy with more stringent requirements may be used for recovered persons for whom there is low tolerance for post-recovery SARS-CoV-2 shedding and infectious risk because they are:
  • Persons who could pose a risk of transmitting infection to
  • Vulnerable individuals at high risk for morbidity or mortality from SARS-CoV-2 infection, or
  • Persons who support critical infrastructure
  • Persons residing in congregate living facilities (e.g., correctional/detention facilities, retirement communities, ships) where there might be increased risk of rapid spread and morbidity or mortality if spread were to occur.
  • Persons who because they are immunocompromised may have prolonged viral shedding.
CDC’s Ten Clinical Tips on COVID-19 for Healthcare Providers Involved in Patient Care
(May 3, 2020)

Treatment Updates

Cathy Oliphant, PharmD
Infectious Disease, Professor and Interim Chair, ISU College of Pharmacy
Investigational Therapies for COVID-19

- Hydroxychloroquine (or chloroquine) +/- azithromycin
- Remdesivir
- Lopinavir/ritonavir +/- interferon-beta +/- ribavirin
- Favipiravir
- Ivermectin
- Famotidine

- Convalescent plasma
  - Collected from COVID-19 survivors
- Interleukin-6 Inhibitors
  - Tocilizumab (Actemra)
  - Sarilumab (Kevzara)
  - Cytokine release (IL, TNFα and other inflammatory mediators) causes severe lung damage in serious COVID-19 infections
*Hydroxychloroquine (Plaquenil)/Chloroquine*

**Use/Rationale**
- Inhibits pH-dependent steps of viral replication – may block virus entry into cells
- Immune modification – decreases production of cytokines – anti-inflammatory

**Dosage - Treatment**
- Hydroxychloroquine (+/- azithromycin)
  - Better tolerated than chloroquine
  - 400 mg BID day 1 then 200 mg BID days 2-5
  - When to initiate therapy
- Chloroquine
  - 500 mg BID x 10 days

**Drug Interactions**

**Adverse Effects**
- Cardiac toxicity
  - QT prolongation (AE of azithromycin too)
  - Use with caution if baseline QTc > 500
- Use with caution if hypokalemia, uncontrolled diabetes, known G6PD deficiency, renal impairment, myasthenia gravis
- GI – N/V/D
- CNS – headache, dizziness, irritability, nightmares, seizures

Clinical Experience: Hydroxychloroquine/Chloroquine

- Limited evidence from small, non-randomized studies in China and France
  - China
    - Mixed results in various studies demonstrated reduced duration of symptoms
    - Other studies did not demonstrate a difference in recovery rates
  - France – hydroxychloroquine +/- azithromycin
    - Several studies have demonstrated reductions in nasopharyngeal viral load
    - Weak evidence:
      - Small sample sizes
      - Low disease acuity/asymptomatic pts
      - Lack of control group
      - Late drug administration
      - Non-homogeneous groups
      - Other methodological flaw
- VA Study
- Brazil Study
  - Chloroquine 450 mg vs 600 mg
  - Increased QTc prolongation with high dose
  - 16/41 patients in high dose group died as compared to 6/40 patients in the low dose group
Clinical Experience: Hydroxychloroquine (HCQ)/Chloroquine

**China Study**
- Randomized controlled trial
  - HCQ 1200 mg daily x 3 days then 800 mg daily for 2-3 weeks
- No difference in resolution of s/s
  - 28 day negative conversion rate
    - HCQ 85.4% vs 81.3% in Std of care
- Groups not equivalent
- Adverse effects more common in HCQ vs std of care group

**France Study**
- 181 patients (84 received HCQ)
- No difference in outcomes
  - Transfer to ICU or death w/in 7d
    - HCQ 20.2% vs 22.1% no-HCQ
  - ARDS w/in 7 days
    - HCQ 27.4% vs 24.1% no=HCQ
- Increased adverse events in HCQ group
Hydroxychloroquine (HCQ)/Chloroquine (CQ): IDSA Guidelines on Treatment Recommendations

• For inpatients, the panel recommends HCQ/CQ use in the context of a clinical trial

• For inpatients, they recommended HCQ/CQ plus azithro only through a clinical trial

• Avoid HCQ/CQ + azithro in the outpatient setting due to lack of adequate monitoring for QT prolongation

• All therapies are recommended in the context of a clinical trial

• Recommend that patients be enrolled into ongoing trials, which will provide much needed evidence on safety and efficacy

• Current data has failed to demonstrate or to exclude a beneficial effect of HCQ/CQ on clinical progression or on viral clearance by PCR

• Harms: QT prolongation, GI
Ongoing Clinical Trials – Hydroxychloroquine/Chloroquine

- Websites
  - NIH
  - Clinicaltrials.gov
- COVID patients
  - Mild
  - Moderate
  - Severe
  - Hospitalized
- Pre-exposure prophylaxis
- Post-exposure prophylaxis or preemptive treatment

- Current clinical trials
  - ORCHID Study (NIH)
  - Post-exposure/Pre-emptive treatment study
    - NCT 04308668
    - https://clinicaltrials.gov/ct2/show/NCT04308668
  - Pre-exposure study
    - Covidpep.umn.edu
Remdesivir – Emergency Use Authorization

• **FDA issued emergency use authorization (EUA) on May 1, 2020**
  “It is reasonable to believe that remdesivir may be effective in treating COVID-19, and that, given there are no adequate, approved, or available alternative treatments, the known and potential benefits to treat this virus currently outweigh the known and potential risks of the drug’s use”

• Emergency use authorization is for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and children with severe disease

• Based on a clinical trial where it was shown to reduce the time to recovery in some patients

• This allows for distribution and emergency use of remdesivir only for the treatment of COVID-19; it remains an investigational drug and is not FDA approved
Gilead’s Investigational Antiviral Remdesivir Receives U.S. Food and Drug Administration Emergency Use Authorization for the Treatment of COVID-19
-- Authorization Enables Broader Use of Remdesivir to Treat Hospitalized Patients with Severe COVID-19 Disease in the United States --
-- Based on Patients’ Severity of Disease, Authorization Allows 5-day and 10-day Treatment Durations --

The U.S. government will coordinate the donation and distribution of remdesivir to hospitals in cities most heavily impacted by COVID-19. Given the severity of illness of patients appropriate for remdesivir treatment and the limited availability of drug supply, hospitals with intensive care units and other hospitals that the government deems most in need will receive priority in the distribution of remdesivir.

Fact Sheet for Patients And Parent/Caregivers
Emergency Use Authorization (EUA) Of Remdesivir For Coronavirus Disease 2019 (COVID-19)

You are being given a medicine called remdesivir for the treatment of coronavirus disease 2019 (COVID-19). This fact sheet contains information to help you understand the risks and benefits of taking remdesivir, which you have received or may receive.

There is no U.S. Food and Drug Administration (FDA) approved product available to treat COVID-19. Receiving remdesivir may benefit certain people in the hospital with COVID-19. Read this Fact Sheet for information about remdesivir. Talk to your healthcare provider if you have questions. It is your choice to receive remdesivir or stop it at any time.
Remdesivir

Mechanism of Action
• Prodrug
• Broad-spectrum antiviral
• Inhibits coronaviruses
• Inhibits SARS-CoV-2 replication in nasal and bronchial cells
• Prematurely terminates viral RNA transcription

Dosage
* Emergency Use Authorization dosing for adults and children > 40 kg
• 200 mg IV day 1 followed by 100 mg IV daily on days 2-5 (for patients not requiring mechanical ventilation) – with option to extend to 10 days of treatment
• 200 mg IV day 1 followed by 100 mg IV daily on days 2-10 (for patients requiring mechanical ventilation)

Clinical Experience: Non-Randomized

Compassionate Use of Remdesivir for Patients with Severe Covid-19 in NEJM 4/10/2020

- 53 patients
  - 57% mechanical ventilation + 18% on ECMO
- Clinical improvement in 36/53 patients after median of 18 days post 1st dose of remdesivir
- 7 deaths (6 on mechanical vent)
- Not randomized, lack of a control group

Phase 3 Study to Evaluate the Safety and Antiviral Activity of Remdesivir

- 397 patients
  - Not on mechanical vent at entry
  - 200 received 5 day regimen
  - 197 received 10 day regimen
- Clinical improvement occurred in 50% of patients in the 5 day group at 10 days vs 11 days in the 10 day group
- Those who received treatment w/in 10 days of s/s had improved outcomes

Remdesivir in adults with severe COVID-19: a randomized double-blind, placebo controlled, multicenter trial (Lancet 4/29/20)

• Hubei, China 2/6-3/12/2020
• Study terminated before target number of patients enrolled
• 237 patients
  • 158 remdesivir
  • 79 placebo
  • > 18 years old
• In-patient w/lab diagnosis
• Interval of s/s onset to enrollment of < 12 days
• O2 sat < 94% on room air
  • Only 0.4% mechanical ventilation
• Concomitant meds
  • Lopinavir-ritonavir, interferons, corticosteroids
• Remdesivir was not associated with statistically significant clinical benefits
• Remdesivir-treated patients, with symptom duration of < 10 days experienced a faster time to clinical improvement than those receiving placebo
  • Not statistically significant
  • Median 5 day reduction in time to clinical improvement (18 days vs 23 days)
• AEs
  • Remdesivir 66% vs placebo 64%
  • Remdesivir was stopped early in 18 patients vs 4 placebo treated
Remdesivir: Adaptive COVID-19 Treatment Trial (ACTT) - NIH randomized, controlled clinical trial

• Randomized, controlled trial sponsored by the NIAID
• Enrollment 2/21-4/19/20
• 68 sites in the US, 21 countries in Europe and Asia
• 1063 patients

• Remdesivir treated patients had a recovery time of 11 days as compared with 15 days in the control group
  • 31% faster recovery time (p<.001)
• Results also suggest a survival benefit
  • Remdesivir treated patients had a mortality rate of 8% vs 11.6% for the control group (p=.059)
Remdesivir Adverse Effects

- Data demonstrates adverse effect incidence of 50-70% (grade 1 -2) in patients receiving 5 – 14 days of therapy
- GI
  - Nausea
  - Dyspepsia
  - Constipation
- Infusion-related reactions (low BP, nausea, vomiting, sweating, shivering)
- Headache
- Extremity pain
- ALT/AST increase
  - Onset 5 – 25 days; resolution 3 – 47 days
- Phlebitis

https://www.sidp.org/COVID19
Ongoing Remdesivir Studies

• Gilead study in patients with moderate disease: NCT04292730
• Gilead study in patients with severe disease: NCT04292899
• NIAID study: NCT04280705
• INSERM study: 2020-000936-23
• China study in patient with mild/moderate disease: NCT04252664
• China study in patients with severe disease: NCT04257656

https://www.gilead.com/purpose/advancing-global-health/covid-19/remdesivir-clinical-trials#
Interleukin-6 Receptor Antagonists: Tocilizumab & Sarilumab

• Monoclonal antibody specific for the interleukin-6 receptor
• IL-6 is an inflammatory cytokine and mediator for fever and inflammation
• Studies have identified elevated IL-6 as a predictor of mortality in COVID
  • Elevated IL-6 associated with hyperinflammation in the lungs of severe COVID patients
• IL-6 receptor antagonists prevent IL-6 binding to soluble and cell associated IL-6 receptors, inhibiting cascade signaling
• Used for reversal of cytokine release syndrome
  • Cytokine release syndrome is thought to be associated with severe COVID disease and pulmonary symptoms
IL-6 Inhibitors

**Tocilizumab (Actemra)**
- Non-randomized trials/case reports have demonstrated rapid reduction in fever and a reduction in the need for supplemental O2 w/in days after infusion
- Single dose with an additional dose if s/s worsen or fail to show improvement
- Randomized, double-blind, placebo-controlled trials in progress or planned
- Randomized, placebo controlled trial (COVACTA) in US – currently enrolling

**Sarilumab (Kefzara)**
- Compassionate use and investigator-sponsored clinical trials
- Randomized, double-blind, placebo-controlled trials assessing the safety and efficacy
  - https://clinicaltrials.gov
- Single dose
COVID-19 Convalescent Plasma

• Plasma obtained from those who have recovered from COVID-19
  • Antibodies may bind to virus, neutralizing its infectivity
• May confer immediate immunity short-term
• May provide benefit
  • May prevent clinical infection
  • May reduce disease severity in those already exhibiting symptoms
COVID-19 Convalescent Plasma

• Who should receive?
  • Timing of treatment unknown
  • Dose unknown
    • Amount
    • # doses
  • Safety unknown
    • Exacerbation of disease severity
    • Allergic reaction
    • Infectious complications
    • Transfusion related complications

• When to collect?
  • Optimal collection time unknown
  • Titers associated with efficacy unknown
  • FDA suggests titer minimum of 1:160
  • FDA suggests donor plasma collection at least 28 days after complete resolution of symptoms or at least 14 days after resolution of symptoms and negative test
Clinical Trials/Websites

• Remdesivir
  • https://rdvcu.gilead.com/

• ClinicalTrials.gov

• Famotidine
  • https://clinicaltrials.gov/ct2/show/NCT04370262?term=famotidine&cond=COVID&draw=2&rank=1
Treatment of Outpatient COVID

- No COVID investigational treatment is currently recommended unless participating in a clinical trial
- Supportive therapy
- Patient education on follow-up/disease progression
- Isolation/quarantine
CDC Recommendations: Duration of Isolation

• “CDC recommends that isolation be maintained for at least 10 days after illness onset and at least 3 days (72 hours) after recovery. Illness onset is defined as the date symptoms begin. Recovery is defined as resolution of fever without the use of fever-reducing medications with progressive improvement or resolution of other symptoms. Ideally, isolation should be maintained for this full period to the extent that it is practicable under rapidly changing circumstances.”

Patient Case Presentation

Megan Dunay, MD MPH
Geriatrician, Boise VA and Medical Director for Geriatrics and Extended Care for VA Pacific Northwest Region
Patient History:
88yo F with a hx of moderate vascular dementia, CVA (stroke) with mild right upper extremity weakness and mild dysphagia, HTN, and urinary incontinence resides at a locked Memory Care unit in an Assisted Living Facility in Canyon County. She has had a progressive functional status decline over the past two weeks and has had a worsening of her cognition over this same time period. Perhaps more frequent urination, but very difficult to say given baseline incontinence.

Meds:
- Amlodipine 10mg daily
- Lisinopril 10mg daily
- Donepezil 10mg daily
- Atorvastatin 40mg daily
- Cholecalciferol 2000 IU daily
- Calcium carbonate 500mg daily
No known drug allergies

Physical exam: was non-focal (normal vital signs – no fever, normal oxygen saturation on room air), no HEENT findings, CV regular, lungs clear, abdomen benign.

Labs:
- CBC shows WBC 3.4 (down from baseline WBC 7.0, PLT 100K, down from baseline 200K).
- Chem notable for BUN 40, Cr 1.6 (up from baseline 1.3).
- Urinalysis shows no nitrites or leukocyte esterase... not sent for culture (given hx of polymicrobial cultures in the past).
- COVID swab obtained and POSITIVE!
Assessment and Plan:
- Keep patient in her facility
- Keep her in her room; restrict movement out of room. Have patient wear mask or gloves if she does leave the room – this is somewhat effective
- Daily vital signs, including oxygen saturation and temperature
- Supportive care

Questions:
1. Should I complete POST form with patient’s family, review advanced directives?
2. Should the patient be transferred out of her facility?
   - Visitors are restricted at this time
   - Would home with home health be an option?
3. Are there any drug trials she should be considered for?
   Are there any medications I should stop?
4. When should she be re-tested? Using an RNA or PCR test?
Closing Pearls

ECHO Panelists
Lachelle Smith, Director, ECHO Idaho
Ongoing Resources List

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https://iecho.unm.edu/sites/uidaho/download.hns?i=440
COVID-19 ECHO More to come...

**Wednesday, May 6:** Noon to 1 p.m. MST


**(ECHO Idaho: Behavioral Health in Primary Care Series)**

**Tuesday, May 12:** Noon to 1 p.m. MST

- COVID-19 Session