

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>

Today's Agenda

Time (MT)	Presentation	Presenter(s)
Noon – 12:10 pm	Welcome, Announcements, Introductions	Lachelle Smith, Director, ECHO Idaho
12:10 – 12:15 pm	Idaho Epidemiology Curves and Public Health Updates	Carolyn Buxton Bridges, MD FACP
12:15 – 12:30 pm	Treatment Updates	Cathy Oliphant, PharmD
12:30 – 12:50 pm	Patient Case Presentation	Megan Dunay, MD MPH
12:50 – 1 pm	Closing Pearls, Announcements, Call to Action	ECHO Panelists Lachelle Smith, Director, ECHO Idaho

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

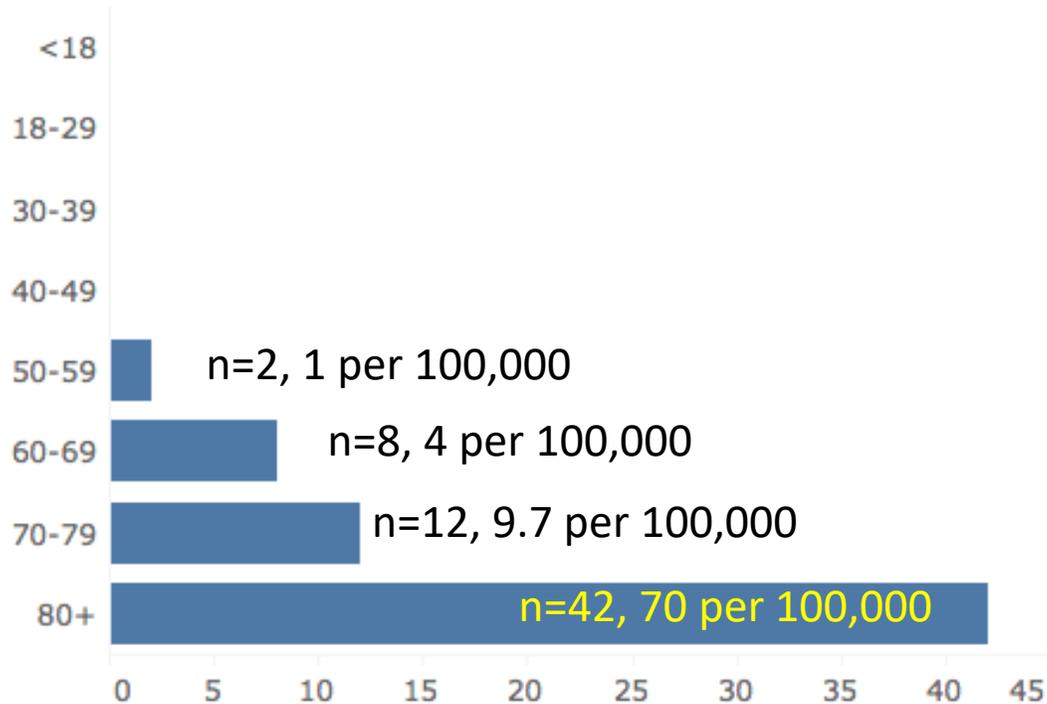
Carolyn Buxton Bridges, MD, FACP

Governor's Coronavirus Working Group, Former CDC Public Health Physician and Researcher

Case Counts and SARS-CoV-2 PCR Testing in Idaho



Lab Confirmed COVID-19-related Deaths in Idaho
by Age-Group



- 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

<https://rebound.idaho.gov/stages-of-reopening/>.

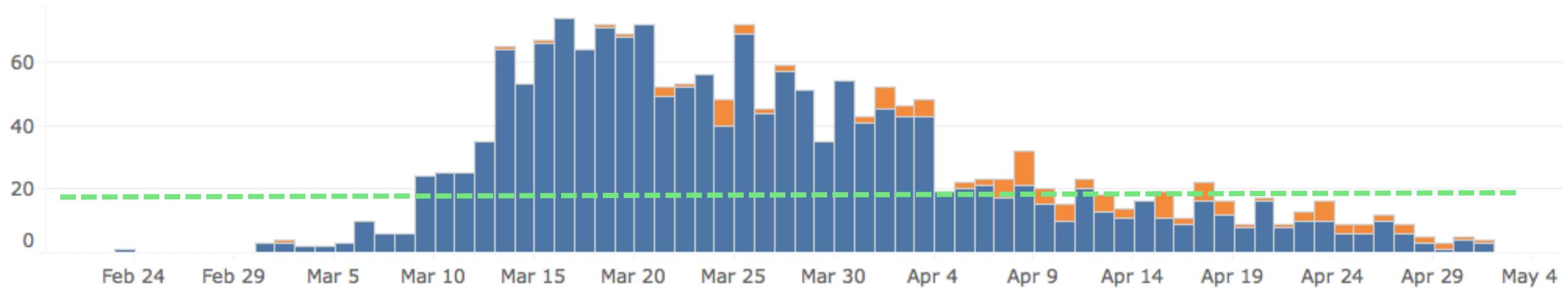
- Epi/capacity criteria required to move to next stage –
Epidemiology data examples
 - Downward trend or <20 /day on average over 14 days lab confirmed COVID-19 cases
 - Downward trend or <20 /day on average over 14 days ED visits for suspected COVID-19 cases
- New guidance for each stage and setting, e.g.
 - Daycare, youth activities, businesses, places of worship
- Next phase – May 16 ***if criteria met***
 - Restaurants, indoor gyms, hair salons



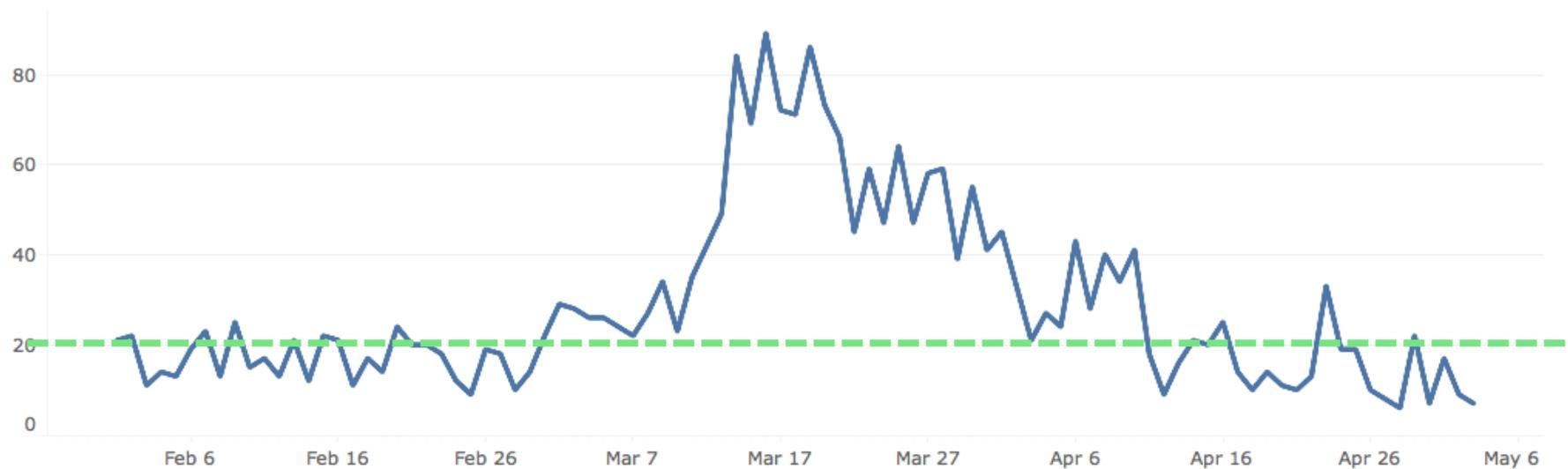
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COVID-19 Cases by Date of Onset and Emergency Department Visits for COVID-like Illness, Idaho

COVID-19 by Date of Onset



Number of Emergency Department Visits for COVID-Like Illness



Updated Idaho Guidance

- Guidance for agricultural workers at:

<https://coronavirus.idaho.gov/wp-content/uploads/2020/04/Guidance-for-Agricultural-Workers.pdf>.

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

https://www.cdc.gov/coronavirus/2019-ncov/community/strategy-discontinue-isolation.html?deliveryName=USCDC_2067-DM27395.

- . 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)

<https://www.cdc.gov/coronavirus/2019-ncov/downloads/hcp/fs-ten-clinical-tips.pdf>



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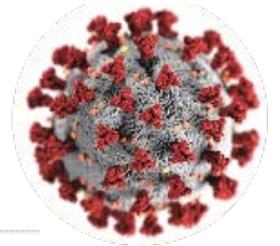
Ten Clinical Tips on COVID-19 for Healthcare Providers Involved in Patient Care

Accessible link: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-tips-for-health-care-providers.html>

Treatment and Prophylaxis



1. The National Institutes of Health has developed **guidance on treatment** (<https://covid19treatmentguidelines.nih.gov/>), which will be regularly updated as new evidence on the safety and efficacy of drugs and therapeutics emerges from clinical trials and research publications.
2. There is currently **no FDA-approved post-exposure prophylaxis** for people who may have been exposed to COVID-19 (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html>).



Symptoms and Diagnosis



3. **Non-respiratory symptoms** (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>) of COVID-19 – such as gastrointestinal (e.g., nausea, diarrhea) or neurologic symptoms (e.g., anosmia, ageusia, headache) – might appear before fever and lower respiratory tract symptoms (e.g., cough and shortness of breath).
4. **Children** (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html>) with COVID-19 may have fever and cough at symptom onset as often as adult patients. Although most children with COVID-19 have not had severe illness, clinicians should maintain a high index of suspicion for SARS-CoV-2 infection in children, particularly infants and children with underlying conditions.
5. **CT scans** (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html>) **should not be used** to screen for COVID-19 or as a first-line test to diagnose COVID-19. CT should be used sparingly, reserved for hospitalized, symptomatic patients with specific clinical indications for CT (<https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection>).

Coinfections



6. Patients can be infected with more than one virus at the same time. **Coinfections with other respiratory viruses** (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html>) in people with COVID-19 have been reported. Therefore, identifying infection with one respiratory virus does not exclude SARS-CoV-2 virus infection.
7. Several patients with COVID-19 have been reported presenting with **concurrent community-acquired bacterial pneumonia** (<https://www.atsjournals.org/doi/pdf/10.1164/rccm.201908-1581ST>). Decisions to administer antibiotics to COVID-19 patients should be based on the likelihood of bacterial infection (community-acquired or hospital-acquired), illness severity, and antimicrobial stewardship issues (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html>).

Severe Illness



8. Clinicians should be aware of the potential for some patients to **rapidly deteriorate** (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>) one week after illness onset.
9. The median **time to acute respiratory distress syndrome (ARDS)** ranges from 8 to 12 days (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>).
10. Lymphopenia, neutrophilia, elevated serum alanine aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenase, high CRP, and high ferritin levels may be associated with **greater illness severity** (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>).

[cdc.gov/coronavirus](https://www.cdc.gov/coronavirus)

CS 110791-4 04/18/2020



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, TNF α 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



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.

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.



Remdesivir



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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 \leq 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 \leq 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

Ongoing Remdesivir Studies

- Gilead study in patients with moderate disease: [NCT04292730](https://clinicaltrials.gov/ct2/show/study/NCT04292730)
- Gilead study in patients with severe disease: [NCT04292899](https://clinicaltrials.gov/ct2/show/study/NCT04292899)
- NIAID study: [NCT04280705](https://clinicaltrials.gov/ct2/show/study/NCT04280705)
- INSERM study: [2020-000936-23](https://clinicaltrials.gov/ct2/show/study/2020-000936-23)
- China study in patient with mild/moderate disease: [NCT04252664](https://clinicaltrials.gov/ct2/show/study/NCT04252664)
- China study in patients with severe disease: [NCT04257656](https://clinicaltrials.gov/ct2/show/study/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
 - <https://clinicaltrials.gov/ct2/results?cond=COVID-19>
- 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.”

https://www.cdc.gov/coronavirus/2019-ncov/community/strategy-discontinue-isolation.html?deliveryName=USCDC_2067-DM27395



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Closing Pearls

ECHO Panelists

Lachelle Smith, Director, ECHO Idaho

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COVID-19 ECHO More to come...

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

- Facing a Pandemic: Practical Steps Using the Principles of Acceptance and Commitment Therapy (ACT) by Jeremy Stockett, LCSW St. Luke's Psych Wellness
(ECHO Idaho: Behavioral Health in Primary Care Series)

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

- COVID-19 Session