Today’s Agenda

<table>
<thead>
<tr>
<th>Time (MT)</th>
<th>Presentation</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noon – 12:05 pm</td>
<td>Welcome, Announcements, Introductions</td>
<td>Lachelle Smith, Director, ECHO Idaho</td>
</tr>
<tr>
<td>12:05 – 12:10 pm</td>
<td>Idaho Epidemiology Curves and Public Health Updates</td>
<td>Carolyn Buxton Bridges, MD, FACP</td>
</tr>
<tr>
<td>12:10 – 12:15 pm</td>
<td>Treatment Updates</td>
<td>Cathy Oliphant, PharmD</td>
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<tr>
<td>12:15 – 12:55 pm</td>
<td>COVID-19 Cases from the Infectious Disease Perspective</td>
<td>Sky Blue, MD</td>
</tr>
<tr>
<td>12:55 – 1 pm</td>
<td>Closing Pearls, Announcements, Call to Action</td>
<td>Lachelle Smith, Director, ECHO Idaho</td>
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The University of Idaho, WWAMI Medical Education Program is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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Idaho Epidemiology Curves and Public Health Updates

Carolyn Buxton Bridges, MD, FACP
Governor’s Coronavirus Working Group, Former CDC Public Health Physician and Researcher

• The information and any errors are mine

• This information was based on published data available as of mid-June 2020. As COVID-19 information is rapidly evolving, providers are reminded to consider additional information that has come to light since this presentation.
<table>
<thead>
<tr>
<th></th>
<th>5/19/2020</th>
<th>6/15/2020</th>
<th>7/13/2020</th>
<th>7/20/2020</th>
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</thead>
<tbody>
<tr>
<td><strong>Total lab-confirmed</strong></td>
<td>2,455</td>
<td>3,462</td>
<td>11,402</td>
<td>15,266</td>
</tr>
<tr>
<td>and probable</td>
<td>(△556)</td>
<td>(△7940)</td>
<td></td>
<td>(△3864)</td>
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<tr>
<td><strong>Deaths</strong></td>
<td>74</td>
<td>88</td>
<td>102</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>CFR =2.5</td>
<td>CFR =0.18</td>
<td>(△14)</td>
<td>(△20)</td>
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<tr>
<td><strong>Hospitalizations</strong></td>
<td>213</td>
<td>270</td>
<td>500</td>
<td>621</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(△230)</td>
<td>(△121)</td>
</tr>
<tr>
<td><strong>ICU admissions</strong></td>
<td>89</td>
<td>100</td>
<td>144</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(△44)</td>
<td>(△42)</td>
</tr>
<tr>
<td><strong>Healthcare</strong></td>
<td>295</td>
<td>366</td>
<td>760</td>
<td>908</td>
</tr>
<tr>
<td>personnel</td>
<td></td>
<td>(△57)</td>
<td>(△394)</td>
<td>(△148)</td>
</tr>
<tr>
<td><strong>Total tests</strong></td>
<td>37,847</td>
<td>65,306</td>
<td>129,540</td>
<td>150,142</td>
</tr>
<tr>
<td></td>
<td>(△17,436)</td>
<td>(△64,234)</td>
<td></td>
<td>(△20,602)</td>
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</table>

[https://coronavirus.idaho.gov](https://coronavirus.idaho.gov)
Patients currently hospitalized in an inpatient bed who have suspected or confirmed COVID-19

Patients currently hospitalized in the Intensive Care Unit (ICU) with confirmed COVID-19
Epidemic Curves for Selected Counties

*Note differences in scales for different counties*
Cotton facial coverings or masks required in Missouri county.

Hair stylist (A) developed COVID-19 and infected coworker (B) with whom she took non-mask wearing breaks with between clients.

A and B stylists wore masks while working with clients, also masked.

Worked combined 13 person-days with 139 clients while infectious
  – Contributor was delay in test results

No clients or other stylists developed COVID-19 or COVID-19 symptoms.

4 of 4 household contacts of stylist A got COVID-19 infection.

Thus, someone very infectious to others without a mask, did not cause illness in contacts where masks were worn.

https://www.cdc.gov/mmwr/volumes/69/wr/mm6928e2.htm?s_cid=mm6928e2_w.
Change in CDC Guidance on Duration of Isolation and Precautions for Adults with COVID-19 – CDC Position Paper

• Increasing evidence that replication-competent virus unlikely isolated after 10 days from illness onset in mild-moderate illness
  – May be longer in immune compromised and severe cases
• Virus titers begin to decline after symptom onset
• Investigation of 285 “persistently positive” persons, including 126 persons who developed recurrent symptoms, found no secondary infections among 790 contacts. Efforts to isolate replication-competent virus from 108 of these case patients were unsuccessful (Korea CDC, 2020).”
• Specimens from patients who recovered from an initial COVID-19 illness and then developed new symptoms and retested positive by RT-PCR did not have replication-competent virus detected (Korea CDC, 2020; Lu et al., 2020).
• Currently, 6 months after the emergence of SARS-CoV-2, there have been no confirmed cases of SARS-CoV-2 reinfection.

CDC Recommendations on Duration of Isolation and Precautions for Adults with COVID-19

• Isolation and precautions can generally be discontinued 10 days after symptom onset¹ and resolution of fever for at least 24 hours, without the use of fever-reducing medications, and with improvement of other symptoms.
  – Persons with severe illness or immune compromised, consider 10-20 days

• If no symptoms, isolation and other precautions can be discontinued 10 days after the date of their first positive RT-PCR test for SARS-CoV-2.

• For severely immunocompromised, a test-based strategy could be considered in consultation with infectious diseases experts.

• For all others, a test-based strategy is no longer recommended except to discontinue isolation or precautions earlier than 10 days.

For persons previously diagnosed with symptomatic COVID-19 who remain asymptomatic after recovery,
  - retesting is not recommended within 3 months after the date of symptom onset
  - quarantine is not recommended in the event of close contact with an infected person.

For persons who develop new COVID-like symptoms <3 months after initial symptom onset, if an alternative etiology cannot be identified by a provider, can consider retesting in consultation with infectious disease experts

For persons who never developed symptoms, the date of first positive RT-PCR test for SARS-CoV-2 RNA should be used in place of symptom onset date

Treatment Updates

• Remdesivir - NIH Update 7/17/20
  – “In situations where supplies are limited, it recommends prioritizing remdesivir for use in hospitalized patients who require supplemental oxygen but not mechanical ventilation”
  – Based on data demonstrating that patients with severe COVID requiring oxygen, but not ventilation, had the most benefit from remdesivir (shorter recovery time)
COVID & Thrombosis

• Severe COVID can result in cytokine storm, systemic inflammatory response and coagulopathy (that is prothrombotic)
• The enhanced prothrombotic state induced by severe COVID is associated with venous and arterial microthrombi
• Data demonstrates incidence of VTE of up to 27% with mortality rates up to 40-60%
  – Rates up to 69% have been observed using routine ultrasound in ICU patients
• CDC estimates that ~90% of hospitalized COVID patients have at least one increased risk of thrombosis
• VTE prophylaxis is essential in these patients

CENTRAL ILLUSTRATION: Postulated Mechanisms of Coagulopathy and Pathogenesis of Thrombosis in COVID-19

A Risk Factors
- Acute illness
- Bedridden, stasis
- Genetics
- Fever
- Diarrhea
- Sepsis
- Liver Injury
- CKD
- COPD
- HF
- Malignancy

B Hemostatic Abnormalities
- Pulmonary microthrombi
- Intravascular coagulopathy
- Myocardial injury
- ↑Cardiac biomarkers

C Clinical Outcomes
Venous Thromboembolism
- Myocardial Infarction
Disseminated Intravascular Coagulation

Inflammatory Response
Endothelial Dysfunction
Superimposed Infection

Lymphopenia
Inflammatory cytokines
↑IL-6, CRP

↑D-Dimer, FDPs, PT
↑↑Platelets

COVID & Risk of Thromboembolism

• Several studies have demonstrated the increased risk of VTE
  – Hubei, China Study
    • Demonstrated that 25% of patients who did not receive VTE prophylaxis developed DVTs
    • VTE prophylaxis decreased VTE incidence by up to 60%
  – Netherlands Study
    • Demonstrated an incidence of pulmonary embolism of 25% in ICU patients
    • 72% of these patients were receiving VTE prophylaxis
  – Italy Study
    • Demonstrated a cumulative VTE rate of 21%
COVID & Anticoagulation: Management

• NIH
  – https://www.covid19treatmentguidelines.nih.gov/

• WHO

• International Society for Thrombosis and Haemostasis
  – https://www.isth.org/page/covid19

• American Society of Hematology

• Anticoagulation Forum
  – https://acforum.org/web/
COVID & Anticoagulation: Recommendations

- Bikdeli et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up. JACC 2020;75(23). DOI: 10.1016/j.jacc.2020.04.031
  - NIH
  - Anticoagulation Forum
  - International Society for Thrombosis and Haemostasis
COVID & Anticoagulation: Efficacy of Prophylaxis

  – 449 COVID patients
    • 99 received heparin (primarily LMWH)
  – DVT prophylaxis reduced 28 day mortality by 20% in patients with an SIC score $\geq 4$ or D-dimer $\geq 3,000$ ng/ml (or 6x ULN)
    • 28-day mortality 40% vs 64.2%, $p=.029$ for SIC Score $\geq 4$
    • 28-day mortality 32.8% vs 52.4%, $p=.017$ for elevated D-dimer
    • No increase in major bleeding
SIC = Sepsis Induced Coagulopathy

<table>
<thead>
<tr>
<th>ISTH SIC score</th>
<th>Score</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (X 10^9/L)</td>
<td>1</td>
<td>100 - 150</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1</td>
<td>1.2 - 1.4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&gt; 1.4</td>
</tr>
<tr>
<td>Total SOFA score*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Total score for SIC</td>
<td></td>
<td>≥ 4</td>
</tr>
</tbody>
</table>

*Total SOFA score is the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA)
COVID & Anticoagulation: VTE Prophylaxis in non-ICU Patients

• All hospitalized patients with COVID should be considered for VTE prophylaxis

• Standard dose VTE prophylaxis
  – Enoxaparin 40 mg daily if BMI < 40
  *Preferred over UFH – due to dosing schedule (once or twice daily)
    • BMI ≥ 40: Enoxaparin 40 mg Q12
    • If CrCl < 30 ml/min, enoxaparin 30 mg daily
  – UFH – standard dose
COVID & Anticoagulation: VTE Prophylaxis in ICU Patients

• All hospitalized patients with COVID should be considered for VTE prophylaxis

• VTE prophylaxis Dosing
  – Enoxaparin 30 mg Q12 if BMI < 40
    *Preferred over UFH – due to dosing schedule
      • BMI > 40: 40 mg Q12
        *Up to 50% increase in obesity
      • If CrCl < 30 ml/min, enoxaparin 30 mg daily
  – UFH – standard dose
  – Data demonstrate that patients with D-dimer > 2,000 or SIC score > 4 benefit from BID dosing of enoxaparin
  – Data do not support treatment doses for prophylaxis
    • Use of higher-intensity anticoagulation regimens should be done in the context of a clinical trial
COVID & Anticoagulation: Duration of VTE Prophylaxis

• Extended post-discharge thromboprophylaxis should be considered for all hospitalized patients with COVID-19 that meet high VTE risk criteria
  – IMPROVE VTE score ≥ 4; IMPROVE VTE Score ≥ 2 plus D-dimer > 2x ULN; advanced age; cancer; severe immobility; ICU admission; h/o VTE

• VTE prophylaxis post-discharge for 2 – 6 weeks
*Non-COVID trials have evaluated VTE prophylaxis (in medically ill) post-discharge using the following durations
  – Enoxaparin 6-14 days
  – Rivaroxaban (Xarelto) 31-39 days
  – Betrixaban (Bevyxxa) 35-42 days
<table>
<thead>
<tr>
<th>VTE Risk Factors</th>
<th>Bleeding Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Previous VTE</td>
<td>□ Gastro-duodenal ulcer</td>
</tr>
<tr>
<td>□ Thrombophilia</td>
<td>□ Bleeding prior 3 months</td>
</tr>
<tr>
<td>□ Lower limb paralysis</td>
<td>□ Admission platelets &lt; 50 x 10⁹</td>
</tr>
<tr>
<td>□ Current cancer</td>
<td>□ Hepatic failure</td>
</tr>
<tr>
<td>□ Immobilization ≥ 7 days</td>
<td>□ ICU/CCU stay</td>
</tr>
<tr>
<td>□ ICU/CCU stay</td>
<td>□ CV catheter</td>
</tr>
<tr>
<td>□ Age &gt; 60 years</td>
<td>□ Rheumatic diseases</td>
</tr>
<tr>
<td></td>
<td>□ Current cancer</td>
</tr>
<tr>
<td>Sex</td>
<td>Sex Female</td>
</tr>
<tr>
<td>Age</td>
<td>Age &lt; 40 years</td>
</tr>
<tr>
<td>GFR</td>
<td>GFR ≥ 60 mL/min/m²</td>
</tr>
</tbody>
</table>

**Probability of Symptomatic VTE**: 0.4%

**Probability of Bleeding**: Major 0.1%

**Clinically Important**: 0.5%
<table>
<thead>
<tr>
<th>Investigational COVID-19 Therapy</th>
<th>Mechanism of Action of COVID-19 Therapy</th>
<th>P2Y&lt;sub&gt;12&lt;/sub&gt; Platelet Receptor Inhibitors</th>
<th>Phosphodiesterase III Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A4 metabolism increasing lopinavir levels.</td>
<td>CYP3A4 Inhibition (minor pathway): Reduction in clopidogrel active metabolite. Do not coadminister or if available utilize P2Y&lt;sub&gt;12&lt;/sub&gt; platelet function assays for monitoring. With limited clinical data, prasugrel may be considered as alternative, if no contraindications.</td>
<td>CYP3A4 Inhibition: Decreased active metabolite but maintained platelet inhibition. Can administer with caution.</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Inhibits IL-6 receptor; may potentially mitigate cytokine release syndrome symptoms in severely ill patients.</td>
<td>Reported increase in expression of 2C19 (major pathway) and 1A2, 2B6, and 2A4 (minor pathways): no dose adjustment recommended.</td>
<td>Reported increase in expression of 3A4 (major pathway): no dose adjustment recommended.</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>Binds specifically to both soluble and membrane-bound IL-6Rα (sIL-6Rα and mIL-6Rα) and has been shown to inhibit IL-6-mediated signaling; may potentially mitigate cytokine release syndrome symptoms in severely ill patients.</td>
<td>Reported increase in expression of 3A4 (minor pathways): no dose adjustment recommended.</td>
<td>Reported increase in expression of CYP3A4 (major pathway): no dose adjustment recommended.</td>
</tr>
</tbody>
</table>

Other drugs being studied to treat COVID-19 include azithromycin, bevacizumab, chloroquine/hydroxychloroquine, aciclovir, fingolimod, interferon, locturan, methylprednisolone, piperidone, and ribavirin. Drug-drug interactions between these medications and antiplatelet agents have yet to be identified. *Gastric, aspirin, dipyridamole, and glycoprotein IIb/IIIa inhibitors (eptifibstat, tirofiban, abciximab) are not known to interact with investigational therapies for COVID-19. Monitoring of P2Y<sub>12</sub> levels can be assessed through the VerifyNow assay, or others. Evaluation of effect of protease inhibitors on P2Y<sub>12</sub> inhibitors has not been extensively studied. Dose reduction recommendations for P2Y<sub>12</sub> inhibitors or P2Y<sub>12</sub> platelet function assay monitoring is not commonly practiced.

IL = Interleukin; other abbreviations as in Table 1.
<table>
<thead>
<tr>
<th>Investigational COVID-19 Therapies</th>
<th>Vitamin K Antagonists</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Betrixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>CYP3A4 induction</td>
<td>P-gp inhibition: May increase plasma concentration. Adjust dose based on INR.</td>
<td>P-gp inhibition: May increase plasma concentration. No dose adjustment recommended.</td>
<td>CYP3A4 and P-gp inhibition: Administer at 50% of dose (do not administer if initial dose is 2.5 mg twice daily).</td>
<td>P-gp and ABCB1 inhibition: Decrease dose to 80 mg once followed by 40 mg once daily.</td>
<td>CYP3A4 and P-gp inhibition: Do not coadminister.</td>
</tr>
<tr>
<td>TollAzumab</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Interferon,</td>
<td></td>
<td></td>
<td>Unknown mechanism: Decreased dose may be needed.</td>
<td></td>
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<tr>
<td>Ribavirin</td>
<td>Mechanism not well known: Possibly decreased absorption of warfarin in the presence of ribavirin (156); increased dose may be needed.</td>
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<tr>
<td>Methylprednisolone</td>
<td>Unknown mechanism: Decreased dose may be needed.</td>
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<tr>
<td>Sarilumab5</td>
<td>Unknown mechanism: Decreased dose may be needed.</td>
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</tr>
<tr>
<td>Azithromycin</td>
<td>Unknown mechanism: Decreased dose may be needed.</td>
<td>P-gp inhibition: May increase plasma concentration. No dose adjustment recommended.</td>
<td>P-gp inhibition: Decrease dose to 80 mg once followed by 40 mg once daily.</td>
<td>P-gp inhibition: VTE: Limit dose to 30 mg daily. Nonvalvular AF: No dose adjustment recommended.</td>
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<tr>
<td>Hydroxychloroquine and chloroquine</td>
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</tbody>
</table>

Other drugs being studied to treat COVID-19 include bezafibrate, chloroquine/hydroxychloroquine, ecublum, feglimid, loxatane, and pirfenidone. Drug-drug interactions between these medications and oral anticoagulants have yet to be identified. Bevacizumab has been reported to cause deep vein thrombosis (9%), arterial thrombosis (5%), and pulmonary embolism (1%). It is also reported to cause thrombocytopenia (58%). *Parenteral anticoagulants (including unfractionated or low-molecular-weight heparins, enoxaparin, argatroban, and fondaparinux) are non-CYP metabolized and do not interact with any of the investigational agents. **These recommendations are based on the US package insert. The Canadian package insert considers the combination of these agents to be contraindicated. Thrombosis has been reported to case pulmonary embolism (<5%), thrombosis (<5%), decreased platelet count (9%–15% with Alfa-2b formulation), and ischemic stroke (<5%). $Sarilumab has been reported to cause decreased platelet count, with decreases to 100,000/mm³ in 1% and 0.7% of patients on 200-mg and 150-mg doses, respectively. †Reported with interferon alfa.

CYP = cytochrome P system, INR = international normalized ratio, P-gp = P-glycoprotein, other abbreviations as in Table 1.
COVID-19 Cases from the Infectious Disease Perspective

Sky Blue, MD
Sawtooth Epidemiology and Infectious Diseases
Case 1

- 32 yo woman
- Seen in ED 7/14/20 for cough
- Sent from outpt clinic for evaluation with SARS-CoV-2 NAAT pending
- Temp 100.4°F, HR 110, RR 20, O₂ sats 93-96% RA
Case 1

• CT scan
Case 1

• Decisions:
  – COVID-19?
  – Hospital admission?
  – Treatment? What options?
  – Anticoagulation?

• What other information do you need?
Case 1

- Sx onset
  - Exposure Sister SARS-CoV-2 + 7/6 through 7/10
  - 7/10/20 Fever, malaise
  - 7/12/20 Cough

- Risk Factors
  - BMI 36

- SARS-CoV-2 NAAT
  - Collected 7/15/20 Abbott ID Now (TMA) Positive 7/15/20
  - Collected 7/14/20 BDmax (RT-PCR) Positive 7/16/20

- Tmax 101.3

- O2 Sats 96%→90% and was admitted

- Next day O2 Sats 94% RA
Case 1

- Labs
  - ANC/ALC 3700/1800=2
  - CRP 46 (nl 0-10)
  - ProCal <0.05
  - LDH 443
  - BNP <50
  - D-Dimer 1000
Case 1

- Labs
  - ANC/ALC 3700/1800=2 → 2100/1800=1.2
  - CRP 46 (nl 0-10)
  - ProCal <0.05 → <0.05
  - LDH 443
  - BNP <50
  - D-Dimer 1000→ 855
Case 2

- 67 yo woman with baseline cognitive disorder.
- Was seen in OR and had been admitted 10 days ago for fever. CXR was abnormal but SAR-CoV-2 was negative twice. She was treated for possible UTI with cephalexin.
- She was admitted for increased SOB and abnormal CT.
- Started on broad spectrum antibiotics.
- On Hospital day 3 she was tested for COVID again and found to be SAR-CoV-2 positive (Abbott IDNow).
Case 2
Case 2

• Hospital course:
  – Intubated
  – Not given Remdesivir
  – Was given steroids per recovery trial
  – Prophylactic anticoagulation was increased to full-dose heparin drip due to suspicion of PE, elevated D-Dimer and inability to get CTPA
  – Had GI bleed and taken off heparin
  – Developed possible line associated candidiasis
  – Family decided on comfort care pathway

| CRP 37.5->37.2->32->30->10->37->234 |
| ProCal 0.14->0.2->0.62->0.14->0.19 |
| BNP 108->176->71->1600->1120->1300 |
| CK 584->461->97->31 |
| LDH 973->619->492 |
| Ferritin 734->477 |
| D-Dimer 1095->1600->1600->35,000!->3931->4584 |
| N/L ratio (on steroids) 8->5.3->32->10->6.9->11.4 |
Case 3

- 69 yo woman
- Seen in ED 7/16/20 SOB
- Tested SARS-CoV-2 positive 6/29/20 after sx started the day prior
- Remained as an outpatient. Fever broke 7/8/20
- Increasing SOB and pulse ox at home registered 87% she called EMS
Case 3

• CT Scan

Small volume bilateral segmental and subsegmental pulmonary emboli.
JOIN US FOR OUR NEXT SESSION!

For information, please visit uidaho.edu/echo

- Tuesday, July 28 at noon MT
RESOURCES FROM TODAY’S SESSION AND PAST SESSIONS CAN BE FOUND IN OUR ONGOING RESOURCE LIST.

https://iecho.unm.edu/sites/uidaho/download.hns?i=440