• 44th in a series of weekly calls, initiated in January by CDC as a forum for information sharing among frontline clinicians caring for patients with COVID-19

• The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.

• This webinar is being recorded and can be found online at www.idsociety.org/podcasts.
Ask the Experts: Q&A with IDSA’s Treatment & Management Guideline Panel

Adarsh Bhimraj, M.D., FIDSA
Head, Section of Neurologic Infections
Cleveland Clinic Foundation

Jason C. Gallagher, Pharm.D., FCCP, FIDP, FIDSA, BCPS
Clinical Professor and Clinical Specialist, Infectious Diseases
Director, Post Graduate Year Two Residency in Infectious Diseases Pharmacy
Temple University School of Pharmacy

Rajesh Gandhi, M.D., FIDSA
Director, HIV Clinical Services and Education Massachusetts General Hospital
Professor of Medicine, Harvard Medical School

John C. O’Horo, M.D., MPH, FACP
Consultant, Division of Infectious Diseases, Joint Appt. Division of Pulmonary & Critical Care Medicine
Associate Professor of Medicine, Mayo Clinic College of Medicine

Amy Hirsch Shumaker, PharmD, BCPS
Clinical Specialist, Infectious Disease
VA Northeast Ohio Healthcare System
Senior Clinical Instructor
Case Western Reserve University, School of Medicine
Disclosures

• Adarsh Bhimraj- nothing to disclose

• Jason Gallagher- advisory role for Astellas, Shionogi, Spero and Qpex; receives research funding from Merk

• Rajesh Gandhi- nothing to disclose

• John O’Horo- nothing to disclose

• Amy Hirsch Shumaker- nothing to disclose
To Ask a Question:
Use the “Q&A” Button

Like a Question?
Upvote in the Q&A box

Phone Participants:
Text Your Question to
415-559-1736

Comment?
Use the “Chat” Button
What should I do?...
Should I use Rx “X” for my COVID-19 patient?

The **what** and the **how** matter not if the **WHY** is not right …

- **WHY?**: Evidence for the choice
- “Trustworthy” guidelines should
  - Appraise and synthesize evidence (**why**)
  - Recommend actions based on evidence (**What** & **How**)
GRADE RECOMMENDATION “language”

“Recommend” FOR (STRONG)
Guideline panel is confident...
- Desirable effects of an intervention outweigh undesirable effects
- Most or all individuals will be best served by the recommended course of action

“Suggest” FOR (weak or conditional or qualified)
Guideline panel after discussion concludes...
Desirable effects probably outweigh undesirable effects, but appreciable uncertainty exists
Not all individuals will be best served by the recommended course of action
Need to consider more carefully than usual the individual patient’s circumstances, preferences, and values
Caregivers need to allocate more time to shared decision making, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.

Balance scales to depict strong vs. weak recommendations.
Outcomes: Patient important outcomes
“What ultimately matters to patients”

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Least importance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Limited importance</strong> (not included in evidence profile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Important, but not critical</strong> (included in evidence profile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Critical</strong> (for making a decision) (included in evidence profile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patient important outcomes ("CRITICAL")**
- Death (mortality)
- Disability
- Discomfort (clinical symptom improvement)

**Disease/dysfunction-oriented outcomes (IMPORTANT)**
- Viral clearance
- CRP or IL 6 levels
- O2 sats

Minimize use of surrogate end points/disease-oriented outcomes like viral clearance or lab data as they are causally INDIRECT.
How to read an Evidence Profile: e.g. Corticosteroids in critically ill patients

### Clinical outcomes

#### Mortality (follow up: 28 days)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Directness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (^1) randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td></td>
<td>280/749 (37.4%)</td>
<td>OR 0.66 (0.54 to 0.82)</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

#### Hospital discharge (follow up: 28 days)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Directness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (^2) randomized trials</td>
<td>serious (^a)</td>
<td>not serious</td>
<td>serious</td>
<td>not serious</td>
<td>none</td>
<td>1360/2104 (64.8%)</td>
<td>RR 1.11 (1.04 to 1.19)</td>
<td>IMPORTANT</td>
</tr>
</tbody>
</table>

#### Serious adverse events

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Directness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (^1) randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious (^b)</td>
<td>none</td>
<td>8 trials reported 64 events among 364 patients randomized to corticosteroids and 80 events among 342 patients randomized to standard care (Stern 2020).</td>
<td>MODERATE</td>
<td>CRITICAL</td>
</tr>
</tbody>
</table>

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio

**Explanations**

a. Analysis adjusted for baseline age.
b. Indirectness due to different health care system (allocation of intensive care resources in an unblinded study). Indirectness to other corticosteroids.
c. The 95\% CI includes the potential for both harm as well as benefit. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

**References**

Quality of evidence/ Confidence in evidence

Criteria to evaluate clinical studies in COVID 19

Methodological/study limitations

Inconsistency of results

Indirectness of evidence

Imprecision of results

Publication bias

Risk of bias: (systematic error)
- Allocation concealment
- Blinding
- Intention-to-treat
- Follow-up
- Stopped early

Sources of indirectness:
Indirect comparisons-
- Patients
- Interventions
- Comparators
- Outcomes

Modified slides from Dr. Yngve Falck-Ytter
What after apprising the evidence?  
...From evidence to recommendations

1. Quality of evidence (systematic error and random error)
2. Balance between Benefits, harms & cost
3. Variability & uncertainties in patient values and preferences
4. Resource considerations
Recommendation 4: Among hospitalized critically ill patients with COVID-19, the IDSA guideline panel RECOMMENDS dexamethasone rather than no dexamethasone. (Strong recommendation, Moderate certainty of evidence)

Remark: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used. Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 5: Among hospitalized patients with severe, but non-critical, COVID-19 the IDSA guideline panel SUGGESTS dexamethasone rather than no dexamethasone. (Conditional recommendation, Moderate certainty of evidence)

Remark: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 6: Among hospitalized patients with non-severe COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel SUGGESTS AGAINST the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)
Treatment Across the COVID-19 Spectrum

<table>
<thead>
<tr>
<th>Stage/Severity:</th>
<th>Asymptomatic/Presymptomatic</th>
<th>Mild Illness</th>
<th>Moderate Illness</th>
<th>Severe Illness</th>
<th>Critical Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ SARS-CoV-2 test but no symptoms</td>
<td>Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea</td>
<td>$O_2$ saturation $\geq 94%$, lower respiratory tract disease</td>
<td></td>
<td>$O_2$ saturation $&lt; 94%$, respiratory rate $&gt; 30$/min; lung infiltrates $&gt; 50%$</td>
<td>Respiratory failure, shock, multi-organ dysfunction/failure</td>
</tr>
</tbody>
</table>

Frequency:  
- ?  
- 80%  
- 15%  
- 5%

Disease Pathogenesis:  
- Viral replication  
- Inflammation

Potential treatment:  
- Antivirals  
- Antibody therapy  
- Decrease inflammation

Host Severity Interventions

Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020
Monoclonal antibodies against SARS-CoV-2 being studied for treatment and prevention

In outpatients with mild to moderate disease (n=452), participants randomized to received iv infusion of placebo or one of three doses of a neutralizing antibody directed against SARS-CoV-2 spike protein (LY-CoV555)
• At day 11, 2800 mg dose of antibody appeared to accelerate decline in viral load as compared to placebo
  3.4-fold lower in 2800 mg group than in the placebo group
  Viral load decline did not differ significantly between other antibody doses and placebo
• In all 3 dose groups, there appeared to be a separation in virus level decay as compared to placebo

Chen P et al, NEJM, 2020; https://www.fda.gov/media/143602/download
LY-CoV555 (Bamlanivimab)

- ED visit or hospitalization:
  1.6% in antibody group, 6.3% in placebo group
  >65 year old, BMI >35: 4% in antibody group, 15% in placebo group

Median time to symptom improvement:
  6 days for participants who received bamlanivimab and 8 days for those who received placebo.

Safety profile of bamlanivimab and placebo similar

---

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>156</td>
<td>9</td>
<td>6%</td>
</tr>
<tr>
<td>700 mg</td>
<td>101</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>2800 mg</td>
<td>107</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>7000 mg</td>
<td>101</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Pooled antibody</td>
<td>309</td>
<td>5</td>
<td>2%</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>69</td>
<td>7</td>
<td>10%</td>
</tr>
<tr>
<td>700 mg</td>
<td>46</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>2800 mg</td>
<td>46</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>7000 mg</td>
<td>44</td>
<td>2</td>
<td>5%</td>
</tr>
<tr>
<td>Pooled antibody</td>
<td>136</td>
<td>4</td>
<td>3%</td>
</tr>
</tbody>
</table>

Chen P et al, NEJM, 2020; https://www.fda.gov/media/143602/download
Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression

Body mass index (BMI) ≥35
Chronic kidney disease
Diabetes
Immunosuppressive disease or receiving immunosuppressive treatment
≥65 years of age
≥55 years of age AND have cardiovascular disease, OR hypertension, OR chronic obstructive pulmonary disease/other chronic respiratory disease
Criteria also listed for those who are 12 – 17 years of age

https://www.fda.gov/media/143602/download
Expanded Use Authorization Criteria: Ambulatory Patients with Mild to Moderate COVID-19 at High Risk for Progression - 2

12 – 17 years of age

BMI 85th percentile for their age and gender

Sickle cell disease

Congenital or acquired heart disease

Neurodevelopmental disorders, eg cerebral palsy

Medical related technological dependence, for example tracheostomy, gastrostomy or positive pressure ventilation

Asthma, reactive airway or other chronic respiratory disease that requires daily medicine

https://www.fda.gov/media/143602/download
LY-CoV555 in Hospitalized Patients

• LY-CoV555 sub-study of ACTIV-3 trial closed after data suggested a lack of clinical benefit for LY-CoV555 in a hospitalized population
Remdesivir and SOLIDARITY

(a) Remdesivir vs its control

Mortality (%)

Rate ratio, 0.95 (95% CI, 0.81-1.11)
P=0.50 by log-rank test

Days since Randomization

Numbers at risk at the start of each week, and numbers dying

<table>
<thead>
<tr>
<th></th>
<th>Remdesivir</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers at risk at the start of each week</td>
<td>2743, 2708</td>
<td>129, 126</td>
</tr>
</tbody>
</table>

https://doi.org/10.1101/2020.10.15.20209817.
## Remdesivir and SOLIDARITY

<table>
<thead>
<tr>
<th>Trial name, and initial respiratory support</th>
<th>Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%)</th>
<th>Remdesivir deaths: Observed-Expected (O-E)* Var (O-E)</th>
<th>Ratio of death rates (RR) &amp; 95% CI (or 95% CI, for total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solidarity: no O₂</td>
<td>11/661 (2.0)</td>
<td>-0.6</td>
<td>0.90 [0.31-2.58]</td>
</tr>
<tr>
<td>Solidarity: low/hi-flow O₂</td>
<td>192/1828 (12.2)</td>
<td>-16.9</td>
<td>0.85 [0.66-1.09]</td>
</tr>
<tr>
<td>Solidarity ventilation</td>
<td>98/254 (43.0)</td>
<td>7.6</td>
<td>1.20 [0.80-1.80]</td>
</tr>
<tr>
<td>ACTT: no O₂</td>
<td>3/75 (4.1)</td>
<td>-0.3</td>
<td>0.82 [0.10-6.61]</td>
</tr>
<tr>
<td>ACTT: low-flow O₂</td>
<td>9/232 (4.0)</td>
<td>-8.0</td>
<td>0.30 [0.11-0.81]</td>
</tr>
<tr>
<td>ACTT: hi-flow O₂ or non-invasive ventilation</td>
<td>19/95 (21.2)</td>
<td>0.2</td>
<td>1.02 [0.44-2.34]</td>
</tr>
<tr>
<td>ACTT: invasive ventilation</td>
<td>28/131 (21.9)</td>
<td>1.7</td>
<td>1.13 [0.57-2.23]</td>
</tr>
<tr>
<td>Wuhan: low-flow O₂</td>
<td>11/129 (8.5)</td>
<td>-0.8</td>
<td>0.81 [0.21-3.07]</td>
</tr>
<tr>
<td>Wuhan: hi-flow O₂ or ventilation</td>
<td>11/29 (37.9)</td>
<td>0.6</td>
<td>1.40 [0.20-9.52]</td>
</tr>
<tr>
<td>SIMPLE: no O₂</td>
<td>5/384 (1.3)</td>
<td>-0.9</td>
<td>0.64 [0.10-3.94]</td>
</tr>
<tr>
<td><strong>Subtotals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower risk groups (with no ventilation)</td>
<td>231/3309 (7.0)</td>
<td>-27.6</td>
<td>0.80 [0.63-1.01]</td>
</tr>
<tr>
<td>Higher risk groups</td>
<td>156/509 (30.6)</td>
<td>10.1</td>
<td>1.16 [0.85-1.60]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>387/3818 (10.1)</td>
<td><strong>-17.5</strong></td>
<td><strong>188.2</strong></td>
</tr>
</tbody>
</table>

For balance, controls in the 2:1 studies count twice in the control totals and subtotals.

* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.log₁₀HR for ACTT strata (with the weight w being the inverse of the variance of log₁₀HR, which is got from the HR’s CI). RR is got by taking log₁₀RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the log₁₀RR values.

**2p = 0.20**
Recommendation 8: Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap)

<table>
<thead>
<tr>
<th>Table 8. GRADE evidence profile, Recommendation 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question:</strong> Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>convalescent plasma</td>
<td>no convalescent plasma</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td>Mortality (RCT) (follow up: range 15 days to 60 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 \textsuperscript{,2} randomized trials</td>
<td>serious \textsuperscript{a,b} not serious</td>
<td>not serious very serious \textsuperscript{c} none</td>
<td>14/95 ( (14.7%) )</td>
<td>23/94 ( (24.5%) )</td>
</tr>
<tr>
<td>Mortality at 30 days (NRS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 \textsuperscript{,3} observational studies</td>
<td>serious \textsuperscript{d,e} not serious</td>
<td>not serious not serious not serious none \textsuperscript{f}</td>
<td>115/515 ( (22.3%) ) \textsuperscript{g}</td>
<td>166/561 ( (29.6%) ) \textsuperscript{h}</td>
</tr>
<tr>
<td>Mortality at 7 days (NRS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 \textsuperscript{,3} observational studies</td>
<td>serious \textsuperscript{d,e} not serious</td>
<td>not serious not serious not serious none \textsuperscript{f}</td>
<td>46/515 ( (8.9%) ) \textsuperscript{g}</td>
<td>77/561 ( (13.7%) ) \textsuperscript{h}</td>
</tr>
</tbody>
</table>
Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID

We want to hear from you! Please complete the post-call survey.

Next Call: Saturday, November 21st on Monoclonal Antibodies

A recording of this call will be posted on Monday at www.idsociety.org/cliniciancalls

-- library of all past calls now available --

Contact Us:
Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)
COVID-19 Real-Time Learning Network

With funding from the Centers for Disease Control and Prevention, IDSA has launched the COVID-19 Real Time Learning Network, an online community that brings together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.

Specialty Society Collaborators:

- American Academy of Family Physicians
- American Academy of Pediatrics
- American College of Emergency Physicians
- American College of Physicians
- American Geriatrics Society
- American Thoracic Society
- Pediatric Infectious Diseases Society
- Society for Critical Care Medicine
- Society for Healthcare Epidemiology of America
- Society of Hospital Medicine
- Society of Infectious Diseases Pharmacists

www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID
CDC-IDSA Partnership: Clinical Management Call Support

Announcing a new service for clinicians:

FOR WHOM?
- Clinicians who have questions about the clinical management of COVID-19

WHAT?
- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

HOW?
- Clinicians may call the main CDC information line at 800-CDC-INFO (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form