COVID-19 and Pregnancy: What We Know

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Perelman School of Medicine
Director, UPENN MFM Network
DISCLOSURES

NONE
Objectives

- Describe clinical manifestations of COVID-19
  - Symptoms
  - Spectrum of disease
- Review how COVID-19 affects pregnancy
- Recognize severe and critical COVID-19 disease.
- Outline management for pregnant women with COVID-19
- Review Vaccine development and Safety information
References

• World Health Organization
• Centers for Disease Control
• The Society for Maternal-Fetal Medicine
• ACOG
• The American Academy of Pediatrics
• My personal experience caring for pregnant women during the pandemic
• Johns Hopkins Surveillance system
• NIH Surveillance system
• 144 Peer reviewed publications
Background

• Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  • Coronaviruses are a large family of viruses which can cause the common cold, or more serious and life-threatening infections.
• COVID-19 is the name for the disease caused by the novel coronavirus discovered at the end of 2019 in Wuhan, China.
• WHO Global Statistics:
  • https://covid19.who.int/
Global COVID-19 Dashboard

Confirmed Cases
Global: 121,549,152
- US: 29,643,005
- Brazil: 11,693,838
- India: 11,474,605
- Russia: 4,378,656
- UK: 4,294,299

Deaths
Global: 2,685,314
- US: 538,588
- Brazil: 284,775
- Mexico: 195,908
- India: 159,216
- UK: 126,163

Recovered*
Global: 68,846,784
- India: 11,063,025
- Brazil: 10,327,440
- Russia: 3,991,385
- Turkey: 2,752,023
- Italy: 2,655,346

*US country-wide statistic not available.

Last updated: March 18, 2021, 2:26 PM US ET

Modes of Transmission

- Viral shedding from coughing/sneezing
- Settling for person/object contamination
- Dispersion in air
- Deep and continuous respiratory deposition by nasal breathing

Renyi Zhang et al. PNAS 2020;117:26:14857-14863
Symptom Spectrum

- Asymptomatic (~15%)
  - Children more likely to be asymptomatic
- Fever or chills
- Cough
- Dyspnea/Tachypnea
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea, vomiting, diarrhea
COVID-19 Incubation: Infection to Illness Onset

- Median incubation: 5.1 days (95% CI: 4.5-5.8)
- Symptom onset by Day 11.5 of infection in 97.5% of persons

Risk with Pregnancy

Pregnant women may be at increased risk for severe illness from COVID-19 compared with non-pregnant women.

Pregnant women and their families should take steps to stay healthy and reduce their risk for getting COVID-19.

CDC.GOV

bit.ly/MMWR62520
**Maternal Outcomes by Disease Severity**

- NICHD MFMU (Metz et al. Jan. 2021)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Severe</th>
<th>Moderate</th>
<th>Asymptomatic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4.3%</td>
<td>0%</td>
<td>0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>VTE</td>
<td>5.7%</td>
<td>0.2%</td>
<td>0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>ICU</td>
<td>35%</td>
<td>1.2%</td>
<td>0.5%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Cesarean</td>
<td>59.6%</td>
<td>33%</td>
<td>34%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PPH</td>
<td>15%</td>
<td>9%</td>
<td>7.3%</td>
<td>p&lt;0.008</td>
</tr>
<tr>
<td>HTN dis.</td>
<td>40%</td>
<td>24%</td>
<td>18.8%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>NND/IUFD</td>
<td>4%</td>
<td>2.2%</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>PTD</td>
<td>42%</td>
<td>15%</td>
<td>11%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>IUGR</td>
<td>8%</td>
<td>12%</td>
<td>10%</td>
<td>NS</td>
</tr>
<tr>
<td>NICU</td>
<td>50%</td>
<td>19%</td>
<td>16%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
Vertical Transmission

- Probably occurs but very infrequently

- Receptors for SARS-CoV-2 cell entry are only minimally expressed within the human placenta

- Placenta, amniotic fluid, and cord blood PCR are rarely positive, and many positive cases due to contamination

- Clear evidence of vertical transmission in Few published cases
  - The placenta, amniotic fluid, and neonatal blood, rectal, and nasopharyngeal samples all tested positive

Early Pregnancy Infection

**limited data**

- Mixed data regarding the risk of congenital malformations and maternal fever in general
- Inadequate data about risk of miscarriage or congenital anomalies
- NO convincing evidence teratogenic
Pregnant compared to Non pregnant women
Counseling in maternal-fetal medicine: SARS-CoV-2 infection in pregnancy
March 2021
Ultrasound in Obstetrics and Gynecology

• Co-morbidity
  • Death
  • ICU admission
  • Pneumonia
  • PTD
  • VTE
  • IUGR

• No Co-morbidity
  • Death
  • ICU admission
  • Pneumonia
  • PTD
  • IUGR
COVID-19 and Pregnancy: Management
“Should I come to the hospital?”

• Telemedicine for most
• In person care
  • ultrasounds
  • Initial OB labs
  • Vaccinations
  • GBS screening
• Concerning symptoms or vital signs merit in person evaluation
# Disease Severity Index-NIH Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or presymptomatic infection</td>
<td>Positive virologic test for SARS-CoV-2 (ie, NAAT or antigen test) but no symptoms consistent with COVID-19</td>
</tr>
<tr>
<td>Mild illness</td>
<td>Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste or smell) but no shortness of breath, dyspnea, or abnormal chest imaging</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>SpO₂ ≥ 94% and lower respiratory disease evidenced by clinical assessment or imaging</td>
</tr>
<tr>
<td>Severe illness</td>
<td>SpO₂ &lt; 94%, PaO₂/FiO₂ &lt; 300 mm Hg, respiratory rate &gt; 30 breaths/min, or lung infiltrates &gt; 50%</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Respiratory failure, septic shock, and/or multiorgan dysfunction</td>
</tr>
</tbody>
</table>
Arterial blood gas parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-pregnant adult</th>
<th>Pregnant (2nd-3rd trimester)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>7.40-7.49</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>80-100</td>
<td>90-110</td>
</tr>
<tr>
<td>PCO2 (mm Hg)</td>
<td>35-45</td>
<td>25-33</td>
</tr>
<tr>
<td>HCO3⁻ (mEq/L)</td>
<td>21-30</td>
<td>16-22</td>
</tr>
</tbody>
</table>
# Sequential Organ Failure Assessment- qSOFA score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criterion</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>≤ 100 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>≥ 22 per min.</td>
<td>1</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>GCS &lt;15</td>
<td>1</td>
</tr>
</tbody>
</table>

- 1 point = ~3% adverse outcome
- 2 points = ~6-10% adverse outcome
- 3 points = ~>20% adverse outcome

GCS denotes Glasgow Coma Scale (range 3-15)
### Disease Severity

#### Severe

Presence of symptoms WITH any of:

- Respiratory rate >30 per minute
- Hypoxia of ≤ 93% (with supplemental oxygen)
- PaO2/FiO2 ratio <300 (“PF ratio”) (ie PaO2 80/.21 =380)
- > 50% lung involvement on imaging
Imaging in severe disease
Imaging in severe disease
Acute Respiratory Distress Syndrome

• Berlin Criteria

<table>
<thead>
<tr>
<th>ARDS Severity</th>
<th>PaO2/FiO2</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>200 – 300</td>
<td>27%</td>
</tr>
<tr>
<td>Moderate</td>
<td>100 – 200</td>
<td>32%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 100</td>
<td>45%</td>
</tr>
</tbody>
</table>
### Burden of Thrombosis in Patients With COVID-19

<table>
<thead>
<tr>
<th>Study Country</th>
<th>Design</th>
<th>Population</th>
<th>N</th>
<th>Thromboprophylaxis</th>
<th>Screening</th>
<th>VTE Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>China[1]</td>
<td>Retrospective</td>
<td>ICU</td>
<td>81</td>
<td>No</td>
<td>No</td>
<td>25.0</td>
</tr>
<tr>
<td>France[2]</td>
<td>Prospective</td>
<td>ICU</td>
<td>150</td>
<td>Yes</td>
<td>No</td>
<td>11.7*</td>
</tr>
<tr>
<td>France[3]</td>
<td>Retrospective</td>
<td>ICU</td>
<td>26</td>
<td>Yes</td>
<td>Yes</td>
<td>69.0</td>
</tr>
<tr>
<td>France[4]</td>
<td>Retrospective</td>
<td>ICU</td>
<td>107</td>
<td>Yes</td>
<td>No</td>
<td>20.6</td>
</tr>
<tr>
<td>The Netherlands[5]</td>
<td>Retrospective</td>
<td>ICU</td>
<td>184</td>
<td>Yes</td>
<td>No</td>
<td>27.0</td>
</tr>
<tr>
<td>Italy[6]</td>
<td>Retrospective</td>
<td>Inpatient</td>
<td>388</td>
<td>Yes</td>
<td>No</td>
<td>21.0</td>
</tr>
<tr>
<td>United Kingdom[7]</td>
<td>Retrospective</td>
<td>ICU</td>
<td>63</td>
<td>Yes</td>
<td>No</td>
<td>27.0</td>
</tr>
</tbody>
</table>

*Pulmonary embolisms in COVID-19 ARDS vs 2.1% in matched non-COVID-19 ARDS. †Pulmonary embolism vs 6.1% in non–COVID-19 ICU patients.

COVID-19 Coagulopathy: Thromboinflammation

This research was originally published in Blood. Jackson. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019;133:906. © the American Society of Hematology.
Endotheliitis

- Postulated to be a central feature of pathophysiology\textsuperscript{[1]}
- SARS-CoV-2 binds to host cells via the ACE2 receptor\textsuperscript{[1,2]}
- High density of ACE2 receptors on endothelial cells\textsuperscript{[1,2]}
- Endotheliitis and viral inclusions in endothelial cells have been reported in COVID-19 autopsy series\textsuperscript{[2]}

Virchow’s Triad in COVID-19

- Platelet activation
  - Viral RNA
  - DNA-NETs
  - VWF
  - Factor Xla
  - Thrombin-fibrin

- Vascular endotheliitis

- Endothelial dysfunction
  - Altered blood flow
## Guidance on Thromboprophylaxis

<table>
<thead>
<tr>
<th><strong>NIH</strong>[^1]</th>
<th><strong>ASH</strong>[^2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>§ Hospitalized adults with COVID-19 should receive prophylactic dose anticoagulation</td>
<td>§ All hospitalized adults with COVID-19 should receive thromboprophylaxis with low-molecular-weight heparin over unfractionated heparin, unless bleeding risk outweighs thrombosis risk</td>
</tr>
<tr>
<td>§ Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual SoC for patients without COVID-19</td>
<td>§ Fondaparinux is recommended in the setting of heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td>§ Currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside of clinical trial</td>
<td>§ In patients in whom anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (eg, pneumatic compression devices)</td>
</tr>
<tr>
<td>§ Hospitalized patients should not be routinely discharged on VTE prophylaxis (extended VTE prophylaxis can be considered in patients with low bleeding risk and high VTE risk) i.e PREGNANCY</td>
<td>§ Outside of clinical trials, discourage empiric use of full-dose heparin or low-molecular-weight heparin in COVID-19 patients with no other indication for therapeutic anticoagulation</td>
</tr>
</tbody>
</table>

[^1]: NIH

[^2]: ASH
Therapies for mild to moderate COVID-19

Antibodies- MONOCLONAL

- Bamlanivimab, Etesevimab
  - Monoclonal antibodies for the treatment of mild to moderate COVID-19 in adult and pediatric (>12 year of age) patients.

- Casirivimab and Imdevima
  - Polyclonal cocktails of antibodies and are FDA authorized for emergency use in mild to moderate COVID-19
  - Exclusion criteria for use include: supplemental oxygen requirement, hospitalization, or severe disease.
  - Risks and benefits to the mother and fetus should be assessed by providers. However, there is no absolute contraindication to use in the appropriate pregnant patient.
Therapy for Severe Disease


- Supplemental oxygen to keep O2 sat > 95%
  - Consider ambulatory pulse ox to evaluate before discharging patient
- Dexamethasone- RECOVERY TRIAL
  - Blunts overactive immune response which is thought to cause most severe manifestations of COVID
  - Evidence: decreased mortality among ventilated patients and those requiring oxygen- 36% reduction in Mortality
    - No benefit in mild disease
- Hydrocortisone and methylprednisone
  - Similar, though non-fluorinated corticosteroids.
  - Considered as alternatives
  - A survival benefit has yet to be demonstrated with these specific medications.
## Steroids-Meta-analysis

<table>
<thead>
<tr>
<th>Drug and trial</th>
<th>ClinicalTrials.gov identifier</th>
<th>Initial dose and administration</th>
<th>No. of deaths/total No. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
<th>Favors no steroids</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>DEXA-COVID NCT04325061</td>
<td>High: 20 mg/d intravenously</td>
<td>2/7 2/12</td>
<td>2.00 (0.21-18.69)</td>
<td>0.92</td>
<td>0.87</td>
<td>0.87</td>
</tr>
<tr>
<td>CoDEX</td>
<td>NCT04327401</td>
<td>High: 20 mg/d intravenously</td>
<td>69/128 76/128</td>
<td>0.80 (0.49-1.31)</td>
<td>18.69</td>
<td>1.39</td>
<td>1.39</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>NCT04381936</td>
<td>Low: 6 mg/d orally or intravenously</td>
<td>95/324 283/683</td>
<td>0.59 (0.44-0.78)</td>
<td>57.00</td>
<td>6.80</td>
<td>6.80</td>
</tr>
<tr>
<td>Subgroup fixed effect</td>
<td></td>
<td></td>
<td>166/459 361/823</td>
<td>0.64 (0.50-0.82)</td>
<td>76.60</td>
<td>1.39</td>
<td>1.39</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>CAPE COVID NCT02517489</td>
<td>Low: 200 mg/d intravenously</td>
<td>11/75 20/73</td>
<td>0.46 (0.20-1.04)</td>
<td>6.80</td>
<td>1.94</td>
<td>1.94</td>
</tr>
<tr>
<td>COVID STEROID</td>
<td>NCT04348305</td>
<td>Low: 200 mg/d intravenously</td>
<td>6/15 2/14</td>
<td>4.00 (0.65-24.66)</td>
<td>1.39</td>
<td>11.75</td>
<td>11.75</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>NCT02735707</td>
<td>Low: 50 mg every 6 h intravenously</td>
<td>26/105 29/92</td>
<td>0.71 (0.38-1.33)</td>
<td>19.94</td>
<td>6.80</td>
<td>6.80</td>
</tr>
<tr>
<td>Subgroup fixed effect</td>
<td></td>
<td></td>
<td>43/195 51/179</td>
<td>0.69 (0.43-1.12)</td>
<td></td>
<td>3.46</td>
<td>3.46</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Steroids-SARI NCT04244591</td>
<td>High: 40 mg every 12 h intravenously</td>
<td>13/24 13/23</td>
<td>0.91 (0.29-2.87)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (fixed effect)</td>
<td></td>
<td></td>
<td>222/678 425/1025</td>
<td>0.66 (0.53-0.82)</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
</tbody>
</table>

*P = .31 for heterogeneity; $I^2 = 15.6\%$
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of deaths/total No. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
<th>Favors no steroids</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive mechanical ventilation (IMV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ($I^2 = 0%$)</td>
<td>14/70</td>
<td>0.41 (0.19-0.88)</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Yes ($I^2 = 44.1%$)</td>
<td>208/608</td>
<td>0.69 (0.55-0.86)</td>
<td></td>
<td></td>
<td>31.7</td>
</tr>
<tr>
<td><strong>Oxygen treatment without IMV (RECOVERY)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>298/1279</td>
<td>682/2604</td>
<td>0.86 (0.73-1.00)</td>
<td></td>
<td></td>
<td>65.6</td>
</tr>
<tr>
<td><strong>Taking vasoactive medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ($I^2 = 0%$)</td>
<td>51/184</td>
<td>0.55 (0.34-0.88)</td>
<td></td>
<td></td>
<td>50.2</td>
</tr>
<tr>
<td>Yes ($I^2 = 0%$)</td>
<td>76/169</td>
<td>1.05 (0.65-1.69)</td>
<td></td>
<td></td>
<td>49.8</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 ($I^2 = 0%$)</td>
<td>72/338</td>
<td>0.67 (0.48-0.94)</td>
<td></td>
<td></td>
<td>42.7</td>
</tr>
<tr>
<td>&gt;60 ($I^2 = 49.7%$)</td>
<td>150/339</td>
<td>0.69 (0.51-0.93)</td>
<td></td>
<td></td>
<td>57.3</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female ($I^2 = 0%$)</td>
<td>60/202</td>
<td>0.66 (0.43-0.99)</td>
<td></td>
<td></td>
<td>27.4</td>
</tr>
<tr>
<td>Male ($I^2 = 14.7%$)</td>
<td>162/476</td>
<td>0.66 (0.51-0.84)</td>
<td></td>
<td></td>
<td>72.6</td>
</tr>
<tr>
<td><strong>Symptomatic, d</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 ($I^2 = 69.1%$)</td>
<td>51/130</td>
<td>0.63 (0.39-1.04)</td>
<td></td>
<td></td>
<td>22.4</td>
</tr>
<tr>
<td>&gt;7 ($I^2 = 0%$)</td>
<td>139/418</td>
<td>0.64 (0.49-0.83)</td>
<td></td>
<td></td>
<td>77.6</td>
</tr>
</tbody>
</table>
Therapies for severe COVID-19

- Medications
  - Remdesivir, Lopinavir-ritonavir
  - Hydroxychloroquine
  - Azithromycin
  - Interferon-beta
- Significant benefits to these interventions have not been shown in meta-analyses.

Siemieniuk Reed AC et al. Drug treatments for covid-19: living systematic review and network meta-
Analysis BMJ 2020; 370 :m2980
Therapies for severe COVID-19

Antibodies (tocilizumab), convalescent plasma
- Significant benefits have yet to be demonstrated for severe disease.
- Safety data, low quality at present
- Use in pregnancy reported without adverse events

Therapies for severe COVID-19
Therapies for severe COVID-19

Supplemental oxygen strategies

- Common nasal cannula (maximum of 15 L per minute deliverable).

- Face mask: “Non-rebreather” type; maximum dependent on source, typically up to 15 L per minute (LPM) from wall supply; may be increased to ~50 LPM with an additional source (uncommon).

- Venturi face mask: Supplies support via fraction of inspired oxygen (FiO2); maximum of 60% oxygen delivery.

- Non-invasive positive-pressure ventilation, e.g. high flow nasal cannula, bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP).
Therapies for severe COVID-19

- Adjuncts
  - Prone positioning
    - Non-intubated patients.
    - Positions themselves in either the lateral decubitus/recumbent or fully prone position (typically for ~2 hours in each position).
      - Emerging evidence that it may help prevent intubation in some patients.
  - Intubated patients
    - Typically in prone position on stomach for up to 18 hours daily.
Therapies for severe COVID-19

Therapies for severe COVID-19
Therapies for severe COVID-19

• Antibodies (tocilizumab), convalescent plasma
  - Significant benefits have yet to be demonstrated with these modalities for severe disease.
  - Safety data is also of low quality at present, though use in pregnancy has been reported without adverse events believed to be related to its use.

Critical disease

• Presence of symptoms WITH any of:
  • Respiratory failure requiring mechanical ventilation
  • Multi-organ dysfunction or failure
  • Shock
    • MAP <65 mm Hg (SBP <90), refractory hypotension, evidence of end-organ hypoperfusion, etc.)
Severity of Disease

Figure 1. Algorithm for Intensive Care Unit Admission

Hospitalized obstetric patient with COVID-19

Presence of any of the following:
- Inability to maintain oxygen saturation ≥95% (pulse oximetry) with supplemental oxygen/rapidly escalating supplemental oxygen need.
- Hypotension (mean arterial pressure MAP <65) despite appropriate fluid resuscitation (~500-1000 mL bolus of crystalloid fluids, eg, lactated Ringer’s solution).
  - For patients with COVID-19 in acute resuscitation, a conservative fluid strategy should be considered to avoid concomitant fluid overload and worsening pulmonary edema.
  - Further, we recommend judicious fluid administration and starting maintenance intravenous fluids in the setting of clear hypovolemia and NPO status.
- Evidence of new end-organ dysfunction (eg, altered mental status, renal insufficiency, hepatic insufficiency, cardiac dysfunction, etc.).
Triage for severity

**No**
- Continue current inpatient management with frequent reassessment.

**Yes**
- Consult Intensivist/Critical Care
  - Presence of any of the following:
    - Persistence of the above symptoms despite interventions
    - Inability to increase frequency of assessments, eg, a need to transfer to a higher level of care.
    - Intubation/mechanical ventilation.
    - Need for other end-organ support, eg, dialysis, hepatic function replacement.

**No**
- Continue advanced management in intermediate acuity setting with low threshold for further escalation as indicated.

**Yes**
- Admit to intensive care unit.
- Manage collaboratively with Intensivist/Critical Care team.
Management of critical disease

Treatment options

• Largely supportive, including strategies to optimize mechanical ventilation.
  
• Survival benefit shown with dexamethasone
  • 6mg Q12 x 4 doses then (6 mg daily for 10 days).

• No therapies are contraindicated by pregnancy itself.

• Obstetric providers should inquire about compassionate use protocols

• SMFM Advocates for inclusion of pregnant women in these trials
Pregnant and Refractory to therapy

- Persistence of inadequate oxygenation and/or ventilation despite substantial and appropriate measures to optimize it.
- Inability to maintain a partial pressure of oxygen in arterial blood (PaO2) >60-70 mmHg with a fraction of inspired oxygen (FiO2) of 1.0 (100%).
- Despite efforts to optimize ventilation
  - Positive end-expiratory pressure (PEEP)
  - Prone positioning
  - Neuromuscular blockade
  - Inhaled therapies (i.e., inhaled nitric oxide).
Neuromuscular Blockade

• Neuromuscular blockade (paralytics)
  
  • Have shown a benefit in the management of moderate to severe ARDS, especially if used early (within first 12 hours).
  
  • Continuous or intermittent paralysis may be utilized.
  
  • Cisatricurium, rocuronium, vecuronium.
  
  • Ensure adequate blockade with a peripheral nerve stimulator ("twitch monitor").
Pulmonary Vasodilators

• Inhaled nitric oxide

  • Often considered salvage therapy in refractory hypoxemia.

  • Dilate well perfused ventilated lungs, thus allowing for decreased V/Q mismatch and pulmonary shunting in ARDS. They also can decrease pulmonary vasodilation, while avoiding systemic hypotension.

  • Effects are transient with decrease waning effects after 48-96 hours.

  • Because of its instant metabolism, thought not to engage in placental metabolism and is thus not contraindicated in pregnancy.
Pulmonary Vasodilators

- Inhaled prostacyclins (epoprostenol)
  - Prostacyclins do not require special equipment for use; however, this can be offset by systemic hypotension which can be seen in 20% of patients.
  - However, other adverse effects are infrequent, and it has a similar safety profile in pregnancy.
  - Thought not to engage in placental metabolism and is thus not contraindicated in pregnancy.
Extacorporeal membranous oxygenation (ECMO)

- Artificially perform the function of the lungs (venovenous; VV ECMO) or the heart as well as the lungs (venoarterious; VA ECMO) in patients with severe ARDS that is refractory to other measures.

- ECMO cannulation requires placement of large central venous, or venous and arterial vascular access, and multi-site cannulation techniques and devices are available as indicated, such as VAVV ECMO, etc.
ECHMO
Ultrasound Evaluation

• Detailed survey if infection in 1\textsuperscript{st} or 2\textsuperscript{nd} trimester

• Growth US in 3\textsuperscript{rd} trimester
  • 3-4 weeks after infection if 3\textsuperscript{rd} trimester exposure
  • Around 32 weeks if earlier infection

• Surveillance if IUGR
Timing of Delivery

• COVID-19 infection itself is not an indication for delivery.
• In women with COVID-19 early in pregnancy who recover, no alteration to the timing of delivery is indicated.
• For women with suspected or confirmed COVID-19 in the third trimester who recover, postpone until at least 10 days have passed since positive test or symptoms.
• Medical indication for an induction or early cesarean delivery (like preeclampsia) should generally not be delayed.
Delivery timing

• Mild to moderate disease
  • COVID-19 positive at 39 weeks of gestation or later, delivery can be considered to decrease the risk of worsening maternal status.

• Mode of delivery should remain per routine indications.

• During delivery, COVID-19 patients should be instructed to wear a mask throughout labor, delivery, and postpartum, and appropriate PPE should be utilized by all caring for such patients.
Delivery timing

• **Severe and critical disease**
  • Timing of delivery in critically ill pregnant women should be individualized.
  
  • Decisions should be based on maternal status, concurrent pulmonary disease, critical illness, ability to wean from a ventilator and ventilator mechanics, gestational age at time of delivery, and shared decision-making with the patient or healthcare proxy.
  
  • Mechanical Ventilation alone not an indication for delivery
  
  • If worsening status on max vent, or after 32 weeks, delivery is reasonable
  
  • Exhaust other methods to improve oxygen delivery if <30-32 weeks
Breastfeeding

Women with COVID-19 can breastfeed if they wish to do so. They should:
- Practice respiratory hygiene and wear a mask
- Wash hands before and after touching the baby
- Routinely clean and disinfect surfaces

• COVID-19 is unlikely to pass through the breast milk.
• Particles of the virus have been found in breast milk samples
• not expected to cause infection in babies. breast milk provides protection
• Women encouraged to continue breastfeeding or providing breast milk when sick with a virus, such as flu.
Breast feeding

• Remdesivir
  • No studies,
  • Poorly absorbed by GI tract
  • Monitor Renal and hepatic function
Thromboprophylaxis

- Pregnancy is a hypercoagulable state
- Women who are pregnant or in the postpartum period have a fourfold to fivefold increased risk of thromboembolism compared with nonpregnant women
- Data indicate that COVID-19 infection may lead to increased coagulopathy.
- Pregnancy and COVID-19 infection may be additive for risk of thrombosis.
- Evidence is lacking for or against thromboprophylaxis for pregnant and postpartum patients with suspected or confirmed COVID-19.
- Reasonable to consider anticoagulation treatment for these patients, particularly if they have severe or critical disease.
  - During hospitalization for moderate to severe disease
  - Post discharge for 10-30 days depending on composite risks
  - Low dose ASA for remainder of pregnancy

• Postpartum depression and anxiety are increased compared to pre-pandemic data

• There are many mental health resources available. These may include:
  • Social work consultation
  • Local therapy referrals. Many therapists and psychologists are now offering telemedicine consultation.
  • Disaster Distress Helpline run by the Substance Abuse and Mental Health Services Administration (SAMHSA) at 1-800-985-5990 (TTY 1-800-846-8517).

• Some women will may also need medical therapy.
Long-term Sequelae of COVID-19

• Limited peer-reviewed data focused on the occurrence or prevalence of COVID-19–related long-term sequelae

• Reasonable to anticipate manifestations based on established knowledge of SARS-CoV-2 pathophysiology, other coronavirus infection outcomes
  • Pulmonary, cardiovascular, and neurologic perturbations proposed
  • SARS-CoV-2 entry receptor ACE2 expressed across extrapulmonary tissues\textsuperscript{[1-3]}
  • Among patients recovering from severe SARS-CoV or MERS-CoV infection, impaired diffusing capacity for carbon monoxide and exercise capacity common during first 6 mos following discharge; after 6 mos, posttraumatic stress disorder (39%), depression (33%), and anxiety (30%) still considerable\textsuperscript{[4]}
Pulmonary Sequelae

• Diffuse alveolar damage noted in multiple, small postmortem studies of COVID-19

• Platelet–fibrin thrombi indicative of coagulopathy observed in small arterial vessels of some patients[1]

Macroscopic and Histologic Lung Findings[2]
Extrapulmonary Manifestations of COVID-19: Which of These Return or Last?

Dermatologic
- Petechiae
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Renal
- Acute kidney injury
- Proteinuria
- Hematuria
COVID-19 Symptom Persistence

• Post acute outpatient service for patients who recovered from COVID-19
  • Mean hospital stay: 13.5 days

• Assessed by standardized questionnaire at mean of 60.3 days after onset of first COVID-19–related symptom
  • 32% had 1-2 persistent symptoms
  • 55% had ≥ 3 persistent symptoms
  • None with fever, signs of acute illness

• 44% of patients reported lower QoL

Cardiovascular Sequelae

• Prospective, observational cohort study sourcing recovered patients from the University Hospital Frankfurt COVID-19 Registry (N = 100)[1]
  • CV magnetic resonance performed at median 71 days from diagnosis
  • Abnormal findings in 78% of patients, myocardial inflammation in 60%; independent of preexisting comorbidities, severity of acute SARS-CoV-2 infection, and time from diagnosis
  • Reduced left ventricular ejection fraction, increased left ventricle volumes and native T1/T2 vs risk-matched controls

“There are no data on how acute treatment of COVID-19 may affect . . . long-term cardiac recovery and function. Patients with ostensibly recovered cardiac function may still be at risk of cardiomyopathy and cardiac arrhythmias.”[2]
Sensory Deficits: Olfactory and Gustatory Dysfunction

- Systematic review and meta-analysis including 24 studies of confirmed COVID-19 (N = 8438)[1]
  - Pooled prevalence
    - Anosmia: 41.0%, ageusia: 38.2%
    - Decreased among older patients
  - “Not yet clear whether COVID-19–related OGDs are transient or permanent”[1]
    - In one prospective cohort (N = 3191), resolution typical within 3 wks[2]

“Respiratory virus infections are associated with neurological and psychiatric sequelae, including Parkinsonism, dementia, depression, posttraumatic stress disorder, and anxiety . . . Significant long-term neurological and psychiatric sequelae have to be anticipated in COVID-19, especially in survivors of severe disease.”[3]

- Cognitive monitoring of recovered patients may be necessary

POST-COVID Assessment and Recovery Clinic

- Autonomic Function
- Pain
- Hypercoagulability
- Weakness and Poor Endurance
- Impaired Renal Function
- Critical Illness Myopathy/
- Polyneuropathy

- Residual Pulmonary Manifestations
- Psychological Issues: PTSD, Insomnia, Anxiety and Depression
- Cognitive Impairment
- Myocardial Injury
- Progression of Chronic Issues
- Impaired Daily Function and Mobility
• Medication Reconciliation
• Rehabilitation Needs Screen  *Bowel, bladder, pain, ADL/iADL performance, cognition, equipment needs, mobility, sleep, skin*
• Pulmonary Functioning Screen  *Criteria established to automatically refer to Pulmonology*
• Montreal Cognitive Assessment  (MoCA)
• Hospital Anxiety and Depression  Scale (HADS)
• Impact of Event Scale-6 (IES-6)
• General Health Slider
• Will be logged in a database to allow for future research efforts
SARS-CoV-2 Mutations and Variants
Genomic Epidemiology of SARS-CoV-2: Geography

Depicting 3853 Genomes Sampled Between Dec 2019 and Mar 2021

Genomic Epidemiology of SARS-CoV-2: Mutation Rate

rate estimate: 21.842 subs per year
Evidence for increased risk of hospitalization within 14 days of sampling for B.1.1.7. Registered in 83 countries with n ≈ 57,400 cases reported globally vs nonvariant cases (N = 63,609 sequences).

- **Case fatality rate** for confirmed/probable B.1.1.7: 2.6%
  - 2858 deaths (within 28 days) among 109,093 cases as of March 10, 2021
  - Based on preliminary UK data, **RR of death is 1.65** (95% CI: 1.21 2.25) for B.1.1.7 vs matched cohort of nonvariant cases

- No evidence for higher rate of B.1.1.7 reinfection or substantially reduced vaccine efficacy based on data from multiple vaccine manufacturers

- US reported cases: n = 7501 across 51 jurisdictions
South Africa Variant 501Y.V2 (B.1.351)

• Circulating in South Africa since August 2020; preliminary analyses suggest that it is **50% more transmissible** vs previously circulating variants
  • Identified in 40 countries with approximately 1400 cases as of February 11, 2021

• Characterized by 8 defining mutations in the spike protein
  • 3 residues in RBD including N501Y

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Brazil Variant P.1

• Initially reported among Brazilian travelers in Japan, then in Brazil
  • Approximately 200 cases in 17 countries as of February 11, 2021
  • US reported cases: n = 61 across 18 jurisdictions
  • 17 unique mutations (11 spike mutations vs ancestral lineage, 3 in the RBD)

• High frequency in COVID-19 samples from December 2020 coincided with surge in Manaus, Brazil

• No microbiologic/epidemiologic evidence of increased transmissibility
  • However, P.1 contains N501Y—also present in B.1.1.7 and B.1.351—which suggests potential for increased transmissibility

Summary of Potential Implications for mRNA Vaccine Efficacy

• **B.1.1.7 variant (UK):** no significant impact on neutralization activity of sera from either mRNA vaccine

• **mRNA-1273 (Moderna) vaccine against B.1.351 variant (South Africa):** 6.4-fold reduction in neutralization activity
  - Plans to test an additional booster dose with mRNA-1273 to boost neutralizing titers and is advancing an emerging variant booster candidate against B.1.351

• **BNT162b2 (Pfizer-BioNTech) vaccine against B.1.351-like mutant virus (South Africa):** 0.81-fold reduction in neutralization activity

• **Impact on mRNA vaccine efficacy in real-world setting remains unknown**

Vaccine Development Pathway and Remaining Questions

- **COVID-19 vaccine development milestones have been compressed** from a time frame of 10-15 yrs to 1-2 yrs; enabled by:
  - Overlapping preclinical and clinical trials
  - Scale-up manufacturing processes occurring in parallel

- As most individuals infected with SARS-CoV-2 **are asymptomatic** or develop only mild symptoms, **vaccine safety is critically important**
  - Theoretical risk/concern for vaccine-associated disease enhancement not supported by currently available data; ultimately, phase III trials and post licensure surveillance will reveal true risk

- Immune function declines with age, and this decline is likely partially responsible for greater risk of severe COVID-19 in older adults → **vaccine responses may be diminished and may require higher doses in older adults**

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**SARS-CoV-2 Vaccine Candidates in Development**

- Phase I: 44
- Phase II: 32
- Phase III: 22
- Limited/Early Use: 6
- Approved: 7

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Intramuscular administration

> 1 complete COVID-19 vaccination series not recommended

Need/timing for booster doses not established; no additional doses currently recommended

“The second dose of Pfizer-BioNTech and Moderna vaccines should be administered as close to the recommended interval as possible, but not earlier than recommended.”

Second dose grace period, if unavoidable:
4 days earlier than scheduled to 42 days after the first dose
Advantages of mRNA vaccine

• 1. Non-infectious
• 2. No need to enter nucleus
• 3. Rapid production
• 4. Problem- Every cell and tissue can degrade RNA. mRNA is negatively charged as are membranes
  • Solution- Lipid Nanoparticle (LNP)
    • Ionizable lipid
    • Stabilizing agent (cholesterol)
    • Phospholipid – stability to bilayered capsule
    • Polyethylene glycol (PEG) promotes stability
US COVID-19 Vaccine Safety Monitoring: Methods and Implications

• Descriptive safety analyses covering initial month of COVID-19 vaccinations in the US; inclusive of first and second Pfizer-BioNTech doses, first Moderna dose
  • N = 13,794,904 doses administered from December 14, 2020, to January 13, 2021; 61.2% in women, n = 62 confirmed reports of anaphylaxis (ie, 4.5 cases/million doses) - 40K pregnant women. 17K delivered,
  • VAERS: spontaneous reporting system accepting data from healthcare professionals, vaccine manufacturers, and the public
  • V-safe: active surveillance system established by the CDC for COVID-19 vaccinations; data self-reported by vaccine recipients via web surveys

“Monitoring, conducted as part of the US vaccination program, indicates reassuring safety profiles for COVID-19 vaccines. Local and systemic reactions were common; rare reports of anaphylaxis were received. No unusual or unexpected reporting patterns were detected.”

# US COVID-19 Vaccine Safety Monitoring: Local and Systemic Reactions by V-Safe

<table>
<thead>
<tr>
<th>Local or Systemic Reaction, * %</th>
<th>Both Vaccines Days 0-7</th>
<th>Pfizer-BioNTech Vaccine Dose 1, Day 1</th>
<th>Dose 2, Day 1</th>
<th>Moderna Vaccine Dose 1, Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site pain</td>
<td>70.9</td>
<td>72.9</td>
<td>79.3</td>
<td>78.1</td>
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<tr>
<td>Fatigue</td>
<td>33.5</td>
<td>21.9</td>
<td>53.5</td>
<td>25.1</td>
</tr>
<tr>
<td>Headache</td>
<td>29.5</td>
<td>17.5</td>
<td>43.4</td>
<td>19.9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>22.9</td>
<td>14.7</td>
<td>47.2</td>
<td>18.3</td>
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<tr>
<td>Chills</td>
<td>11.6</td>
<td>5.5</td>
<td>30.6</td>
<td>8.4</td>
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<tr>
<td>Fever</td>
<td>11.4</td>
<td>5.8</td>
<td>29.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Injection-site swelling</td>
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<td>6.2</td>
<td>8.6</td>
<td>12.6</td>
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<tr>
<td>Joint pain</td>
<td>10.4</td>
<td>5.3</td>
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<td>7.3</td>
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<td>Nausea</td>
<td>8.9</td>
<td>4.2</td>
<td>14.0</td>
<td>5.5</td>
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</table>
Global Data: Vaccine Intent, February 2021

Query: “If a vaccine for COVID-19 were available, I would get it”

<table>
<thead>
<tr>
<th>Country</th>
<th>Agree</th>
<th>Strongly Agree</th>
<th>Somewhat Agree</th>
<th>Somewhat Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>78%</td>
<td>+8</td>
<td>-13</td>
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<tr>
<td>Brazil</td>
<td>89%</td>
<td>+24</td>
<td>+12</td>
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<tr>
<td>Canada</td>
<td>79%</td>
<td>+21</td>
<td>+12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China*</td>
<td>82%</td>
<td>+21</td>
<td>+12</td>
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<tr>
<td>France</td>
<td>59%</td>
<td>+23</td>
<td>+13</td>
<td></td>
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</tr>
<tr>
<td>Germany</td>
<td>74%</td>
<td>+21</td>
<td>+15</td>
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<tr>
<td>Italy</td>
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<td>+25</td>
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<td>Japan</td>
<td>74%</td>
<td>+16</td>
<td>+3</td>
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<td>Mexico*</td>
<td>80%</td>
<td>+22</td>
<td>+26</td>
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<td>South Africa*</td>
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<td>+9</td>
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<tr>
<td>South Korea</td>
<td>80%</td>
<td>+14</td>
<td>+7</td>
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<tr>
<td>Spain</td>
<td>82%</td>
<td>+31</td>
<td>+19</td>
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<tr>
<td>UK</td>
<td>87%</td>
<td>+24</td>
<td>+18</td>
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<tr>
<td>US</td>
<td>65%</td>
<td>+3</td>
<td>+6</td>
<td></td>
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</tr>
</tbody>
</table>

*Sample more urban, educated, and/or affluent vs general population.

ANF Data: Concerns of US Nurses

• “Please list your concerns about the vaccine development process for COVID-19”

- COVID-19 vaccine development is occurring too quickly: 84%
- Healthcare workers have not received enough information about COVID-19 vaccine safety, side effects, and administration: 79%
- I am skeptical/unclear about the COVID-19 clinical trials process: 75%
- I am skeptical/unclear about the COVID-19 vaccine approval process: 70%
- I mistrust information about the COVID-19 vaccine development: 50%
- I have personal and/or religious reservations about vaccinations: 13%
- COVID-19 vaccine development is occurring too slowly: 1%
- Other: 9%

COVID-19 Vaccines: Unanswered Questions

- Primary endpoint in mRNA vaccine trials was *symptomatic* illness, therefore not yet known if these effectively prevent transmission
- Duration of vaccine immunity still unknown
- Long-term safety data will require years of vaccination follow-up
- No data yet on efficacy or safety in children and pregnant women
- < 200 participants/trial developed symptomatic COVID-19, ie, too few to draw conclusions about efficacy in subpopulations
- SARS-CoV-2 genome appears relatively stable, but not known how virus will respond to selection pressure of mass vaccination
Vaccine Uptake: Recommendations

• **Build trust** with transparent and informative communication about vaccine safety and efficacy
  • To achieve herd immunity, the public needs vaccine literacy and confidence

• **Provide culturally relevant vaccine education**
  • Public health officials and healthcare providers are more trusted than politicians

• Until the clinical trials have published, data can be found on the FDA website
Summary

• To date, reported safety and efficacy of COVID-19 vaccines in development have exceeded expectations
• Open questions include vaccine efficacy in special populations and durability of the vaccine immune response
• An ongoing challenge is fair and efficient vaccine distribution to all persons
• Vaccine hesitancy is a threat to adequate vaccine uptake, which is necessary to control the COVID-19 pandemic
• SARS-CoV-2 variants may affect disease severity and vaccine efficacy
General Prevention Measures

The most important things you can do are:

- Avoid
- Keep clean
- Disinfectant
- Symptoms aware

https://www.tinkerfcu.org/covid-19/
Masks Make a Difference

Your mask may protect them. Their mask may protect you.
