COVID-19 Conversations

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#COVID19Conversations
Multidimensional Challenge of Treating COVID-19

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Disclosure: Dr Gandhi has served on scientific advisory board for Merck & Co, Inc. (Updated 6/1/20)
# Multidimensional Challenge of Treating COVID-19

## Host
- Adults
- Children
- Risk factors for severe disease

## Stage and Severity
- Early vs. late infection
- Mild, moderate, severe, critical disease

## Intervention
- Antivirals
- Immunomodulators
- Combination therapy
- Rx complications: anticoagulation, ventilation
Host: Clinical Presentation of SARS-CoV-2 Infection in Adults

Respiratory
- Dyspnea
- Cough
- Hypoxemia
- Pulmonary infiltrates
- Pneumonia
  - Ventilator
  - Community
  - Superinfection
- ARDS
- Pulmonary Embolus

CNS/Neurological
- Stroke
- Syncope
- Anosmia
- Dysgeusia

Cardiovascular
- Elevated CK, troponin
- Myocarditis, pericarditis
- MI
- Arrhythmia
- Cardiomyopathy
- Shock

Renal
- Elevated Creatinine

Skin
- “COVID toes”
  - pseudo-chilblains
- Vesicles, pustules
- Maculopapular rash
- Urticaria
- Livedo
- Emboli
- Kawasaki
  - Conjunctivitis
  - rash

Systemic
- Neutrophilia
- Lymphopenia
- Thrombocytopenia
- Inflammation
- Viremia
- Coagulopathy
- Multisystem Inflammatory Syndrome

Gastrointestinal
- Nausea
- Diarrhea
- Loss of appetite
- Elevated liver function tests

Slide courtesy of Dr. Jay Fishman
Immunosuppression, including advanced HIV (CD4 cell count <200), is risk factor for complications of other respiratory viruses. Not known if people with HIV are at increased risk for severe COVID-19.

Disproportionate burden of COVID-19 among racial and ethnic minorities, Native Americans.
Host: Multisystem Inflammatory Syndrome in Children

- Acute vasculitis with some similarities to Kawasaki disease
- Fever, rash, conjunctivitis, abdominal pain, shock and cardiac dysfunction
- Children may have had recent SARS CoV-2 infection – MIS-C may represent a post-infectious hyper-inflammatory syndrome
## COVID-19 Spectrum

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic/presymptomatic infection</td>
<td>▪ Positive test for SARS-CoV-2 but no symptoms</td>
</tr>
<tr>
<td>Mild illness</td>
<td>▪ Varied symptoms (eg, fever, cough, sore throat, taste/smell disturbance) but no shortness of breath or abnormal imaging</td>
</tr>
<tr>
<td>Moderate illness</td>
<td>▪ SpO₂ &gt;94% &amp; lower respiratory disease (clinical or imaging findings)</td>
</tr>
<tr>
<td>Severe illness</td>
<td>▪ SpO₂ &lt; 94%, PaO₂/FiO₂ &lt; 300, respiratory rate &gt;30/min, or lung infiltrates &gt; 50%</td>
</tr>
<tr>
<td>Critical illness</td>
<td>▪ Respiratory failure, shock, and/or multiorgan dysfunction</td>
</tr>
</tbody>
</table>

Wu Z et al, JAMA 2020

Goals of Treatment Across the COVID-19 Spectrum

**Phase:**
- **Before exposure**
- **After exposure**
- **During illness**
- **After illness**

**Goal:**
- **Prevent infection:** Pre-exposure prophylaxis
- **Prevent acquisition/disease:** Post-exposure prophylaxis
- **Treat disease to prevent progression/complications/death:** Early treatment may prevent transmission
- **Hasten recovery/clearance of infection**

**Disease Pathogenesis:**
- **Viral replication**
- **Inflammation**

**Potential intervention:**
- **Antivirals**
  - Boost immune responses
  - Decrease inflammation

Adapted from slide by Dr. Arthur Kim, MGH
Antiviral targets

- Viral entry: ACE2 and TMPRSS2: camostat
- Membrane fusion and endocytosis: hydroxychloroquine (HCQ)
- Viral protease: lopinavir/ritonavir
- RNA-dependent RNA polymerase: remdesivir, favipiravir
Case of HCQ: From single arm studies and observational cohorts ...
HCQ: To randomized controlled trials...

Post-exposure prophylaxis

Hospitalized patients

Limitations: most participants enrolled 3-4 days after exposure; only 2-3% had confirmed dx
The Case of Remdesivir (RDV)

- Nucleotide prodrug: inhibits viral RNA polymerase: chain terminator
- Macaques: reduced SARS CoV-2 levels in lung (not upper respiratory tract), ameliorated disease
- Preliminary analysis of randomized ACTT-1: recovery more rapid with RDV than placebo (11 vs 15 d)
  - Mortality at 14 days: 7.1% RDV, 11.9% placebo (hazard ratio 0.7, 95% CI, 0.47 to 1.04).
  - Benefit of RDV clearest in those on oxygen supplementation but not yet intubated
- SIMPLE trial: in people with severe COVID-19 but not yet intubated, 5 days of RDV as good as 10 days
Passive Antibody Therapy

- Passive transfer of neutralizing Ab: eg convalescent plasma (CP), monoclonal antibodies (mAb)
- CP used to treat other viral infections, eg Argentine hemorrhagic fever
- Case series of CP in people with COVID-19 showed radiographic improvement, reduction of viral shedding
- Open label randomized trial suggested benefit of CP in severe COVID-19 (treatment given late in disease course)
- Risks: transfusion reactions (rare), antibody dependent enhancement (theoretic)
- Ongoing prophylactic and therapeutic trials of CP, mAb
Controversy regarding use of steroids in viral pneumonia, acute respiratory distress syndrome.

Given hyperinflammatory state in COVID-19, steroids evaluated as potential intervention.

Open label, randomized trial among hospitalized patients in the UK: 2104 received dex, 4321 usual care.

**Steroids: Case of Dexamethasone**

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Usual Care</th>
<th>RR mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No oxygen required</td>
<td>85/501 (17%)</td>
<td>137/1034 (13%)</td>
<td>1.22 (0.86 – 1.75)</td>
</tr>
<tr>
<td>Oxygen only</td>
<td>275/1279 (21.5%)</td>
<td>650/2604 (25%)</td>
<td>0.8 (0.67 – 0.96)</td>
</tr>
<tr>
<td>Ventilation/ECMO</td>
<td>94/324 (29%)</td>
<td>278/683 (40.7%)</td>
<td>0.65 (0.45 – 0.88)</td>
</tr>
<tr>
<td>All participants</td>
<td>454/2104 (21.6%)</td>
<td>1065/4321 (24.6%)</td>
<td>0.83 (0.74-0.92) p=0.0007</td>
</tr>
</tbody>
</table>

Conclusion: Dexamethasone associated with decreased mortality among those on supplemental oxygen or on mechanical ventilation/ECMO. No benefit in those not requiring oxygen.
Treating Complications: Role of Anticoagulation

- Infection with SARS-CoV-2 associated with an inflammatory and pro-thrombotic state
- Thromboembolic disease reported in people with COVID-19, particularly in those with critical illness
- Hospitalized patients should receive venous thromboembolism prophylaxis
- Ongoing and upcoming trials of anticoagulation in COVID-19
Goals of Treatment Across the COVID-19 Infection Spectrum

**Phase:**
- Before exposure
- After exposure
- During illness
- After illness

**Goal:**
- Prevent infection: Pre-exposure prophylaxis
- Prevent acquisition/disease: Post-exposure prophylaxis
- Treat disease to prevent transmission/progression/complications/death
- Hasten recovery/clearance of infection

**Disease Pathogenesis:**
- Viral replication
- Inflammation
- Remdesivir
- Dexamethasone

**Potential intervention:**
- Antivirals
- Boost immune responses
- Decrease inflammation

**NB:** most COVID-19 is mild whereas most trials have focused on moderate, severe or critical disease

Adapted from slide by Dr. Arthur Kim, MGH
Treatment Across the COVID-19 Infection Spectrum

- At Risk
- Exposed
- Infected
- Symptomatic
- Hospitalized
- Resp Failure
- Death

**Bang for the Buck?**

- HCQ Minnesota PEP Study

**Interventions**

- HCQ: RECOVERY, Hubei, NYP Study, UM ACTT1/2, Remdesivir Trials
- Favipiravir Trials
- IL-6 Inhibitors, Plasma, NO, Anticoagulation, Stem Cells, ACEI/ARBs, IFN, sirolimus, steroids, prazosin, ivermectin, Vit C, etc, etc
Final Thoughts

• COVID-19 treatment requires multidimensional approach, with an understanding of the host, the stage/severity of disease, and intervention
• Depending on host, stage and severity of disease, optimal intervention may differ: antiviral therapy, immunomodulator, combinations (antiviral + immunomodulator)
• Lessons from HIV
  • Pressure to deploy interventions must be tempered by importance of finding out if a treatment works: our guide must be the science
  • Iterative process, building on advances until tipping point is achieved
  • Critical to address disparities & inequities revealed by these “twin” pandemics