COVID-19: Challenges in Advanced Heart and Lung Disease and Cardiothoracic Transplantation

April 29, 2020
Welcome Address

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Relevant Financial Relationship Disclosure Statement

Welcome Address
Stephan Ensminger, MD, DPhil

No relevant financial relationships to disclose related to this presentation.
ISHLT appreciates the support provided by the following companies:

**Premier level**
- Abbott
- CareDx
- Medtronic
- Paragonix

**Supporter Level**
- Liquidia
President’s Message

Stuart Sweet, MD, PhD

W. McKim Marriott Professor of Pediatrics, Division of Allergy and Pulmonary Medicine
Medical Director, St. Louis Children’s Hospital Pediatric Lung Transplant Program
Washington University School of Medicine in St. Louis
St. Louis, MO, USA
Relevant Financial Relationship Disclosure Statement

*President’s Message*
*Stuart Sweet, MD, PhD*

No relevant financial relationships to disclose related to this presentation.
Thanks

• Stephan Ensminger and the 2020 Program Committee
• Peter Hopkins and the 2021 Program Committee
Transition

- Amanda Rowe
- Greg Schultz
Transformation

- Purposes:
  - Emphasize Interdisciplinarity
  - Optimize Infrastructure
  - Enhance Member Engagement with ISHLT Digital Platform

- Benefits:
  - Expand the Voice of the Members
  - Increase Value for ISHLT Members
Translation

- International
- Interdisciplinary
- Innovation

- ISHLT COVID-19 Response
Moderators

Saima Aslam, MD, MS
University of California, San Diego
San Diego, CA, USA

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Cincinnati Children’s Hospital Medical Center
Cincinnati, OH, USA
No relevant financial relationships to disclose related to this presentation.

The following relevant financial relationships exist related to this presentation:
Roche: Research Grant Site Principal Investigator
Ansun BioPharma: Research Grant Site Principal Investigator
Chimerix: Research Grant Site Principal Investigator
Merck: Research Grant Site Principal Investigator; Consultant
Astellas: Research Grant Site Principal Investigator
Shire: Research Grant Site Principal Investigator
Pathogenesis, Clinical Presentation, Epidemiology in Transplantation

Erika D. Lease, MD, FCCP
Associate Professor, Division of Pulmonary, Critical Care, and Sleep Medicine
Medical Director, Lung Transplant Program
Attending, Solid Organ Transplant Infectious Diseases Program
University of Washington
Seattle, WA, USA
I will **not** discuss off label use and/or investigational use of drugs/devices.

The following **relevant financial relationships** exist related to this presentation:

- No relationships to disclose
Background

- Initially described as a cluster of pneumonia cases in Wuhan, China in early 12/2019
  - Initially identified and termed “novel Coronavirus” (2019-nCoV)
  - Presumed zoonotic origin
- Novel enveloped RNA betacoronavirus phylogenetically similar to SARS-CoV thus renamed SARS-CoV-2
- COVID-19 is the disease due to SARS-CoV-2
- March 11, 2020 – WHO designated as a pandemic

https://www.who.int/emergencies/diseases/novel-coronavirus-2019
https://covid19.who.int/
Worldwide Epidemiology
Pathogenesis

• Lung epithelial cells are primary target of the virus\textsuperscript{1}
  • Spike protein binds to host receptor allowing viral entry into host cells
  • Based on early data and similarity to SARS-CoV, SARS-CoV-2 appears to also use the host receptor angiotensin-converting enzyme 2 (ACE2) for cell fusion
• Small number of autopsy cases show pulmonary pathology consistent with diffuse alveolar damage
• Disease appears to promoted by a cytokine storm and complex immune dysregulation

\textsuperscript{1} Wan et al. \textit{J Virol}. 2020 Mar 17;94(7).
Pathogenesis

- Virus has been detected in other clinical samples\(^1\)
- Unclear clinical significance
- Multiple non-pulmonary complications:
  - Cardiac complications – myocarditis, microvascular injury, systemic cytokine-mediated injury\(^2\)
  - Coagulation abnormalities – stroke, thromboembolic events\(^3\)

### Table: Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase-Polymerase Chain Reaction

<table>
<thead>
<tr>
<th>Specimens and values</th>
<th>Bronchoalveolar lavage fluid (n = 15)</th>
<th>Fibrobronchoscope brush biopsy (n = 13)</th>
<th>Sputum (n = 104)</th>
<th>Nasal swabs (n = 8)</th>
<th>Pharyngeal swabs (n = 398)</th>
<th>Feces (n = 153)</th>
<th>Blood (n = 307)</th>
<th>Urine (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test result, No. (%)</td>
<td>14 (93)</td>
<td>6 (46)</td>
<td>75 (72)</td>
<td>5 (63)</td>
<td>126 (32)</td>
<td>44 (29)</td>
<td>3 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Cycle threshold, mean (SD)</td>
<td>31.1 (3.0)</td>
<td>33.8 (3.9)</td>
<td>31.1 (5.2)</td>
<td>24.3 (8.6)</td>
<td>32.1 (4.2)</td>
<td>31.4 (5.1)</td>
<td>34.6 (0.7)</td>
<td>ND</td>
</tr>
<tr>
<td>Range</td>
<td>26.4-36.2</td>
<td>26.9-36.8</td>
<td>18.4-38.8</td>
<td>16.9-38.4</td>
<td>20.8-38.6</td>
<td>22.3-38.4</td>
<td>34.1-35.4</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>28.9-33.2</td>
<td>29.8-37.9</td>
<td>29.3-33.0</td>
<td>13.7-35.0</td>
<td>31.2-33.1</td>
<td>29.4-33.5</td>
<td>0.0-36.4</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ND, no data.

---

Clinical Presentation

- Initial report out of Wuhan, China, most common symptoms in hospitalized patients were fever (~99%), fatigue (~70%), and dry cough (~59%) – dyspnea in ~1/3\(^1\)
- In a larger report from China, fever was seen in ~44% at presentation, but ~89% during hospitalization\(^2\)
  - Cough ~68% (1/3 with productive cough), fatigue ~38%, dyspnea ~19%
- Comorbidities in 23-46%\(^1,2\)
- Incubation 4-5 days (up to 14 days)\(^2,3\)

\(^1\)Wang et al. JAMA 2020;323(11):1061-1069.
Clinical Presentation

• Solid organ transplant recipients – New York
  • 90 patients – 46 kidney, 17 lung, 13 liver, 9 heart, 5 MOT
  • Fever (70%), cough (59%), and dyspnea (43%) were the most common presenting symptoms
  • Myalgias (24%) and diarrhea (31%)
  • 68 patients hospitalized (75%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptom — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>21/36 (58)</td>
</tr>
<tr>
<td>Cough</td>
<td>19/36 (53)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16/36 (44)</td>
</tr>
<tr>
<td>Myalgias</td>
<td>13/36 (36)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8/36 (22)</td>
</tr>
<tr>
<td>Hospitalization — no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>Chest radiographic findings consistent with viral pneumonia — no./total no. (%)</td>
<td>27/28 (96)</td>
</tr>
</tbody>
</table>


Early Outcomes

• Solid organ transplant recipients – New York
  • 90 patients – 46 kidney, 17 lung, 13 liver, 9 heart, 5 MOT
  • 68 patients hospitalized (75%)
    • 35% required intubation
  • 16 patients died (18% overall, 25% hospitalized patients, 52% of ICU patients)

<table>
<thead>
<tr>
<th>Outcomes at a median of 21 days (range, 14–28) — no./total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Intubation</td>
</tr>
<tr>
<td>Death after intubation</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
</tr>
<tr>
<td>Remained hospitalized</td>
</tr>
<tr>
<td>Discharged from hospital</td>
</tr>
</tbody>
</table>

UW SOT COVID-19 Registry: Clinical Presentation

• Thus far, 319 cases – predominantly US cases
  • 33 heart or heart/kidney
  • 22 lung – 16 bilateral, 6 single
• Overall median age 57 years
• Rates of comorbidities appear similar across all groups
• No reported donor-derived cases
• Presenting symptoms (all cases):
  • Cough (74%)
  • Dyspnea (60%)
  • Fever (53%)
  • Diarrhea (35%)

• Presenting symptoms – heart, heart/kidney (33)
  • Median age 55 years
  • Cough (79%)
  • Dyspnea (52%)
  • Fever (48%)
  • Diarrhea (30%)

• Presenting symptoms – lung (22)
  • Median age 63.5 years
  • Dyspnea (73%)
  • Cough (50%)
  • Fever (45%)
  • Diarrhea (27%)
UW SOT COVID-19 Registry: Early Outcomes

• Thus far, 319 cases – predominantly US cases
  • 33 heart or heart/kidney
  • 22 lung – 16 bilateral, 6 single
  • 2 heart/lung
• Early outcomes (all cases):
  • 74% hospitalized
  • 29% required ICU care
    • 22% intubated
  • 8% required new RRT
  • Preliminary mortality is 14% (non-standardized length of follow-up)

• Early outcomes – heart, heart/kidney (33)
  • 85% hospitalized
  • 30% required ICU care
    • 15% intubated
  • 6% required new RRT
  • Preliminary mortality is 9% (non-standardized length of follow-up)

• Early outcomes – lung (22)
  • 82% hospitalized
  • 36% required ICU care
    • 27% intubated
  • 5% require new RRT
  • Preliminary mortality is 32% (non-standardized length of follow-up)
Conclusions

• COVID-19 is a significant concern for our heart and lung transplant recipients

• Perhaps SOT recipients have different clinical presentations – perhaps less fever, more GI symptoms

• High rates of hospitalization (74-85%) with 15-39% requiring intubation, mortality ranging from 9-32%

• Important caveats
  • Data is likely somewhat biased by availability of testing – perhaps less testing of patients with mild symptoms if testing not readily available
  • Unclear if outcomes are associated with organ transplant status vs. comorbidities that are common after transplantation (DM, HTN, CKD, etc.)
Therapeutic Options

Michael Shullo, PharmD
Associate Vice President-Transplant
WVU Medicine
Professor, WVU School of Pharmacy
Morgantown, WV, USA
Relevant Financial Relationship Disclosure Statement

COVID-19 Therapeutic Options
Michael Shullo

I will discuss off label use and/or investigational use of the following drugs/devices:
All drug therapy mentioned

The following relevant financial relationships exist related to this presentation:
No relationships to disclose
Treatment Strategy

Supportive Therapies
- Renal failure
- Clotting anomalies
- Respiratory dysfunction
- Cardiomyopathy

Antiviral and Immunomodulation
- Direct antiviral effects
  - Viral replication
- Viral binding/cell penetration
- Excessive immune response
  - “Cytokine storm”
  - Increased in systemic inflammation
# Proposed Antiviral and Immunomodulatory Therapies

**Antiviral Therapies**
- Baloxavir
- Chloroquine phosphate
- Favipiravir
- Protease inhibitors-Multiple
- Hydroxychloroquine
- Oseltamivir
- Remdesivir
- Unifenovir
- Convalescent plasma

**Immunomodulatory Therapies**
- Anakinra
- Baricitinib
- Corticosteroids
- Ruxolitinib
- Sarilumab
- Sirolimus
- Tocilizumab
## Proposed Antiviral and Immunomodulatory Therapies

**Antiviral Therapies**
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**Immunomodulatory Therapies**
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- Baricitinib
- Corticosteroids
- Ruxolitinib
- Sarilumab
- Sirolimus
- Tocilizumab
Antiviral Therapy

- **Protease inhibitors**
  - Combination antivirals with activity against human immunodeficiency virus (HIV)
  - Lopinavir/ritonavir and darunavir/ritonavir most common

- **Proposed rationale for use in COVID-19**
  - Several ongoing trials
  - In vitro activity against SARS-CoV-2

- **Data**
  - Limited data available
  - Evidence of efficacy lacking

- **Drug interactions**
  - Profound interactions with medications commonly used in advanced heart and lung disease. Including but not limited to:
    - Immunosuppression
    - Pulmonary hypertension therapies
    - Various anticoagulants
    - Antiarrhythmics
    - Multiple statin therapies

- **We DO NOT recommend lopinavir/ritonavir, darunavir/ritonavir** - due to lack of evidence of efficacy and risk of significant drug interactions

Annals of Pharm 2003; 37(12):1793-1796
Antiviral Therapy

• **Hydroxychloroquine**
  - Antimalarial
    - Malaria and autoimmune disorders
  - Proposed rationale for use in COVID-19
    - In vitro activity against SARS-CoV-2
      - Inhibition of fusion/binding to host cell membrane
      - Inhibit nucleic acid replication
    - Systemic immunomodulatory effects
      - Inhibition of cellular functions and molecular pathways involved in immune activation
        - Decreased MHC Class II expression
        - Decreased CD154 expression
        - Decreased Pro-inflammatory cytokines such as IL-1, IFNα and TNF
        - Interference with Toll-like receptor 7 (TLR7) and TLR9 signaling pathways
  - Data
    - Limited efficacy data
    - Several studies show no benefit and may cause harm in severely ill patients
    - Evidence of significant side effects especially in high doses
  - Drug interactions and Adverse effects
    - Elevated risk of arrhythmia
    - Risk of interactions with immunosuppression, PH therapies and anticoagulation is low however there are case reposts of increases in CSA levels

Antiviral Therapy

• **Remdesivir**
  - Broad-spectrum antiviral
    - In-vitro activity against various RNA viruses
    - Nucleotide analog which inserts into viral RNA chains
  - Proposed rationale for use in COVID-19
    - In-vitro activity against SARS-CoV-2, SARS, MERS, and Ebola
    - Ebola treatment in humans demonstrated increased mortality compared to alternate investigational treatment but with a decrease in viral load
  - Data
    - Multiple ongoing clinical trials
    - Trial dosing is variable
    - Currently, little published data showing a benefit outside of a case report
  - Drug interactions
    - The risk of significant drug interactions with immunosuppressive, PH therapies, and anticoagulation is low, however, there is a potential risk of a decreased tacrolimus, sirolimus and cyclosporine levels

Nat Commun. 2020; 11:222
Direct Antiviral Therapy

• **Convalescent plasma**
  - Human derived biologic
    - Plasma obtained from recovered SARS CoV-2 patients which contains antibodies against the virus
  - Proposed rationale for use in COVID-19
    - Demonstrated benefit in SARS patients
    - Contains neutralizing antibodies (IgG and IgM) that may provide short term passive immunity
    - Direct binding
    - May decrease viral load
  - Data
    - Limited data available
    - Two small case series/studies demonstrate feasibility of convalescent serum for treatment of severe COVID-19 with some benefit
    - Multiple ongoing clinical trials
    - Safety of use of convalescent serum in the patients with end-stage heart and lung disease, organ transplantation, and VADs has not been demonstrated

• Drug interactions
  - Risk of interactions with immunosuppression, PH therapies and anticoagulation is low
Immunomodulatory Therapies

• **Anakinra**
  • Rheumatoid arthritis and neonatal-onset multisystem inflammatory disease therapy
    • Recombinant human interleukin-1 (IL-1) receptor antagonist
  • Proposed rationale for use in COVID-19
    • Blocks the effects is of interleukin-1 (IL-1) and may have a benefit reducing cytokine release syndrome (CRS)

• **Data**
  • Currently there is no published data on its use in COVID-19
  • Clinical trials focusing on hyperinflammation induced respiratory distress starting

• **Drug interactions**
  • The risk of significant drug interactions with immunosuppressives, PH therapies, and anticoagulation is low

Immunomodulatory Therapies

- **Sarilumab and Tocilizumab**
  - Rheumatoid arthritis therapies
    - Interleukin-6 (IL-6) receptor antagonist
  - Proposed rationale for use in COVID-19
    - IL-6, secreted by monocytes and macrophages, is considered to be a driver of the immunologic response to SARS-COV-2 in patients with severe disease and CRS
  - Data
    - Currently no published data in sarilumab however, results of a phase 2 trial are due soon
    - One study using non-comparative tocilizumab data suggest some efficacy in severe cases of COVID-19
    - Several clinical trials underway for tocilizumab
  - Drug interactions
    - Limited data exists however, the risk of significant drug interactions with immunosuppressives, PH therapies, and anticoagulation is low. There is a potential risk of a decreased Tacrolimus, Sirolimus and Cyclosporine levels.
      - The manufacturer suggests that these agents may “restore” the activity of several CYP enzymes the impact of this on medication clearance is not known

Actiemera prescribing information April 2020
Immunomodulatory Therapies

• **Methylprednisolone**
  - Corticosteroid
    - Anti-inflammatory properties
    - Decrease cytokine release
  - Proposed rationale for use in COVID-19
    - Due to their systemic anti-inflammatory properties may inhibit CRS or “cytokine storm”
    - Corticosteroid benefits in ARDS
    - No benefit in SARS or MERS
  - Data
    - Limited to observational data but may provide some benefit in COVID-19 patients with ARDS
  - Drug interactions
    - The risk of significant drug interactions with immunosuppressives, PH therapies, and anticoagulation is low/moderate.

Wang Y, et al. medRxiv.2020.03.06.20032342
Additional References

- [https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx?la=en&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C](https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx?la=en&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C)

- [https://www.covid19-druginteractions.org/](https://www.covid19-druginteractions.org/)
Critical Care in COVID-19

Marta Farrero Torres, MD, PhD
Clinical Professor, University of Barcelona
Senior Specialist, Heart Failure and Heart Transplant Unit
Hospital Clinic de Barcelona
Barcelona, Spain
Most of the discussion will not be evidence-based (unavailability of data)

The following relevant financial relationships exist related to this presentation:
No relationships to disclose
Clinical presentation and severity

Table 3. Complications, Treatments, and Clinical Outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N=1099)</th>
<th>Disease Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsevere (N=926)</td>
<td>Severe (N=173)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock — no. (%)</td>
<td>12 (1.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome — no. (%)</td>
<td>37 (3.4)</td>
<td>10 (1.1)</td>
</tr>
<tr>
<td>Physician-diagnosed pneumonia — no./total no. (%)</td>
<td>972/1067 (91.1)</td>
<td>800/894 (89.3)</td>
</tr>
<tr>
<td>Median time until development of pneumonia (IQR) — days*</td>
<td>0.0 (0.0–1.0)</td>
<td>0.0 (0.0–1.0)</td>
</tr>
<tr>
<td>After initial Covid-19 diagnosis</td>
<td>3.0 (1.0–6.0)</td>
<td>3.0 (1.0–6.0)</td>
</tr>
<tr>
<td>After onset of Covid-19 symptoms</td>
<td>3.0 (1.0–6.0)</td>
<td>3.0 (2.0–7.0)</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen therapy — no. (%)</td>
<td>454 (41.3)</td>
<td>331 (35.7)</td>
</tr>
<tr>
<td>Mechanical ventilation — no. (%)</td>
<td>67 (6.1)</td>
<td>67 (38.7)</td>
</tr>
<tr>
<td>Invasive</td>
<td>25 (2.3)</td>
<td>25 (14.5)</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>56 (5.1)</td>
<td>56 (32.4)</td>
</tr>
<tr>
<td>Use of extracorporeal membrane oxygenation — no. (%)</td>
<td>5 (0.5)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Admission to intensive care unit — no. (%)</td>
<td>55 (5.0)</td>
<td>22 (2.4)</td>
</tr>
<tr>
<td>Median length of hospital stay (IQR) — days†</td>
<td>12.0 (10.0–14.0)</td>
<td>11.0 (10.0–13.0)</td>
</tr>
<tr>
<td>Clinical outcomes at data cutoff — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from hospital</td>
<td>55 (5.0)</td>
<td>50 (5.4)</td>
</tr>
<tr>
<td>Death</td>
<td>15 (1.4)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

1. WHO/2019-nCoV/SARI_treatment_center/2020.1
### Clinical presentation and severity

<table>
<thead>
<tr>
<th>VIREMIA</th>
<th>INFLAMMATION</th>
<th>IMCU - ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home-Hospital</td>
<td></td>
<td></td>
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</table>

#### Early Warning Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Age, y</th>
<th>RF, rpm</th>
<th>O2 Sat, %</th>
<th>O2 supply</th>
<th>sBP, mmHg</th>
<th>Pulse, bpm</th>
<th>NRL</th>
<th>T, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;65</td>
<td>&lt;9</td>
<td>&lt;92</td>
<td>Y</td>
<td>&lt;90</td>
<td>&lt;41</td>
<td>N</td>
<td>&lt;35</td>
</tr>
<tr>
<td>1</td>
<td>&gt;65</td>
<td>&gt;25</td>
<td>&gt;95</td>
<td>No</td>
<td>110-219</td>
<td>51-90</td>
<td>AbN</td>
<td>36-38</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;220</td>
<td>&gt;132</td>
<td></td>
<td>&gt;39</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Adapted from:

COVID-19 is not only a viral pneumonia...

VIREMIA

INFLAMMATION

-4 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

Symptom onset

Hospital admission

ARDS

Dyspnea

Death
# Ventilatory options

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxigen</td>
<td>If SatO2&lt;90% in room air</td>
<td>Maintain SpO2 &gt;91%</td>
</tr>
</tbody>
</table>
| Respiratory support | Dispnea, accessory musels, tachipnea (>30bpm)  
PaO2/FiO2 < 200 or need to use FiO2>0.4 to achieve SpO2 >92%  
Respiratory failure: pH < 7,35 with PaCO2 > 45 mm Hg  
Neurological impairment |  
- Oxigenation: SpO2 88-92% PaO2 55 - 85 mmHg  
- Ventilation: PaCO2 < 60 mmHg y pH > 7,20 |
| Non invasive (BiPAP or LAF) |  
Invasive mechanical ventilation:  
- Protective: Plateau P <28  
  Driving P <15 |

- Prone position  
- Recruitment  
- Thracheostomy  
- V-V ECMO
COVID-19 is not only a viral pneumonia...

**INFECTION**
- *Acinetobacter baumannii*
- *Aspergillus fumigatus*

**MECHANICAL VENTILATION COMPLICATIONS**
COVID-19 is not only a viral pneumonia...

NEUROLOGICAL IMPAIRMENT
45% in severe COVID
Central, peripheral nervous system and skeletal muscular injury

KIDNEY FAILURE
20-40% ICU patients
5% RRT

MIOCARDIAL DAMAGE
HEMODYNAMIC SUPPORT
VOLUME MANAGEMENT

COVID-19 is not only a viral pneumonia...

THOMBOSIS
30-50% in ICU patients
Antiphospholipid antibodies?

BLEEDING

Anticoagulation protocols with heparin:
- Prophylaxis (enoxaparin 40mg/kg/d or mg/kg/d if >80Kg): all
- Expanded prophylaxis enoxaparine (mg/kg/d) if: D-dimer >3.000 (X6), ferritine >1000
- Treatment dose: if clinical suspicion. Low threshold for CT scan to direct full anticoagulation

In summary

- 15% severe, 5% critical → high mortality
- Respiratory failure: 10-15 days after symptom onset (inflammation)
- Well tolerated hypoxia
- Early invasive vs. Non invasive ventilation
- Attention to ICU complications
  - Thrombosis
  - Other infections
  - Neurological
- Future evolution: progression to organizing pneumonia and fibrosis ...?
MCS/ECMO in COVID-19

Daniel J. Goldstein, MD

Professor and Vice Chair, Department of Cardiovascular & Thoracic Surgery
Surgical Director, Department of Cardiovascular & Thoracic Surgery, Cardiac Transplantation & Mechanical Assistance Programs
Albert Einstein College of Medicine / Montefiore Medical Center
Bronx, NY, USA
Relevant Financial Relationship Disclosure Statement

*ECMO Utilization During Covid19 Pandemic*

*Daniel J Goldstein MD*

**I will/will not** discuss off label use and/or investigational use of any drugs/devices:

**I have no relevant financial relationships related to this presentation:**
Covid19 is often characterized by the development of respiratory failure associated with ground glass opacities, hypoxemia, pulmonary microvascular thrombosis and ARDS

Conventional management: suppl O2, proning, mechanical ventilation - ARDSnet protocols

Rarely, severe hypoxemia +/- hypercarbia ensue despite above and ECMO support can be considered.
Criteria for Venovenous ECMO

- Generally follow EOLIA Trial criteria
  - < 7 days on vent and:
    - PaO2/FiO2 < 50 for 3 hrs, or
    - PaO2/FiO2 < 80 for 6 hrs, or
    - Arterial pH < 7.25 with pCO2 > 60 mmHg for > 6 hrs despite optimization
Venovenous ECMO Modalities - Dual Cannulae

- Bifemoral
- Femoral - Int. Jugular
Venovenous ECMO Modalities - Single Cannula

Int. Jugular

Protek Duo RVAD Oxy
ECMO Considerations During C19 Pandemic

- Resource-Intensive
- Decision to offer: hospital capacity, personnel, equipment, space - necessary for cannulation, maintenance, weaning and decannulation
- More stringent criteria: age, frailty, more than single organ failure
- Cannulation:
  - At bedside
  - Full PPE
  - Large cannula
- Anticoagulation: high PTT targets with IV heparin, bivalrudin or argatroban - in light of prothrombotic state
- Support times 10-30 days
Additional Considerations

• VA ECMO may be required in patients already on VV who decompensate hemodynamically, often in setting of cytokine storm and/or myocarditis (elevated hsTrop, BNP, TTE systolic dysfxn)

• VA ECMO may be required in patient with cardiogenic shock (acute MI) UNrelated to C19, but test positive

• VV ECMO has been used as a bridge to lung transplant in handful of patients.
Pandemic from the Frontlines

Luciano Potena, MD, PhD
Medical Director Heart Failure and Heart Transplant Program
Bologna Academic Hospital
Bologna, Italy
I will discuss off label use and/or investigational use of the following drugs/devices:

Hydroxychloroquine
Azithromicine

The following relevant financial relationships exist related to this presentation:

No relationships to disclose
Absolute increase in all-cause mortality in Northern Italy

Source: Italian Ministry of Health
Transplant Activity in Italy – 2020*
(source: National Transplant Center)

* Dati preliminari al 22/03/2020
Fonte dati: CNT operativo
ISS COVID-19 Task force collects 52796 cases of Covid-19+ patients
By crossing these data with the Italian Transplant Information System (SIT) we found COVID-19 infection in transplants and waiting list:

• 146 transplanted patients are Covid-19+ - prevalence in transplanted 0.37%

<table>
<thead>
<tr>
<th>HEART</th>
<th>LIVER</th>
<th>PANCREAS</th>
<th>LUNG</th>
<th>KIDNEY</th>
<th>Total transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>21</td>
<td>2</td>
<td>8</td>
<td>103</td>
<td>151</td>
</tr>
</tbody>
</table>

COVID19+ patients
Mean Age 62 year; Range (0-100)
Gender F 42% M 58%

Transplanted COVID19+ patients
Mean Age 61 year; Range (26-81)
Gender F 23% M 77%

• 73 patients waiting for transplant on 22/03/2020 are Covid-19+ - prevalence in waiting patients 0.86%
Issues to face for a HT program during COVID-19 pandemic

• Minimize the risk for patients to get infected in hospital
  • Reduce scheduled in-person visits
  • Develop tele-medicine strategies
  • Identify clean pathways
  • Masks to personnel

• Minimize the risk for personnel to get infected from patients
  • Masks to the patients
  • Appropriate PPI for personnel

• Guarantee necessary care despite pandemic
  • Flexible priorities depending on the stage of the pandemic

• Develop treatment protocols in absence of evidence-based therapies
Objective of remote visits

• Avoid unnecessary travel and hospital exposure for patients at risk
• Triage patients with respiratory/infectious symptoms before they are seen for scheduled appointment
  • Avoid contact with them and try to manage remotely if clinically appropriate
  • Prepare to see them with appropriate DPI if they need to be seen
Remote visits

• Between March 9 and April 27 we performed 218 phone visits
• We identified two patients with suspect COVID-19 and managed them remotely, favoring early treatment and avoiding contact with transplant clinic
Patient -1

- 5 months out of transplant, his daughter had lunch with in-laws family, and her father in law few day later was admitted for COVID-19
- Cough and mild cold. No fever: we arranged for the swab to be performed
- Therapy with MMF TAC and Pred.
- After swab results came in we withdrew MMF, started hidroxyquinidine 400mg b.i.d. first day then 200mg bid for 4 days; azythromicin 500mg/day
- TDM for TAC, which was reduced
- Enoxaparin 4000 UI twice daily (>5000 ng/ml D-dimer)
- Home EKG monitoring every other day
- Negative swab 3 weeks later
Patient - 2

- 63 y old male 9 years after HT
- Complained for diarrhea since two days, no fever
- His wife asymptomatic COVID-19 +, tested after outbreak in the nursing home she works in
- Was sent to local hospital
  - Positive swab
  - Bilateral extensive pneumonia
- Withheld MMF, halved TAC, prednisone at 10mg
- Fever developed, started hydroxychloroquine and withheld TAC (three days later, trough levels were 10 ng/ml)
- Currently admitted in local hospital ICU with O2 nasal cannula - stable
Issues to face for a HT program during COVID-19 pandemic

• Minimize the risk for patients to get infected in hospital
  • Reduce scheduled in-person visits
  • Develop tele-medicine strategies
  • Identify clean pathways
  • Masks to personnel

• Minimize the risk for personnel to get infected from patients
  • Masks to the patients
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• Guarantee necessary care despite pandemic
  • Flexible priorities depending on the stage of the pandemic

• Develop treatment protocols in absence of evidence-based therapies
Protecting personnel: face masks and swabs

Leung NH et al. Nat Med 2020 doi.org/10.1038/s41591-020-0843-2
Protecting personnel: face masks and swabs

Strict Hygiene measures including face masks for all

Need to see a patient with fever during COVID outbreak

• Male, 43 y old, one year after transplant
• Fever-ish for 4 days, associated with malaise and loss of appetite
• No signs of heart failure, normal EKG, SO2 94%, BP 135/90mmHg;
• Labs: Hb 7.2 g/l; Creatinine 6.1 mg/dl; platelets 80,000/mmc; C-RP 13.2 mg/dl
Issues to face for a HT program during COVID-19 pandemic

• Minimize the risk for patients to get infected in hospital
  • Reduce scheduled in-person visits
  • Develop tele-medicine strategies
  • Identify clean pathways
  • Masks to personnel

• Minimize the risk for personnel to get infected from patients
  • Masks to the patients
  • Appropriate PPI for personnel

• Guarantee necessary care despite pandemic
  • Flexible priorities depending on the stage of the pandemic

• Develop treatment protocols in absence of evidence-based therapies
Call a patient from home: check for fever with upper respiratory symptoms within preceding 2 weeks and/or direct contact with COVID positive subjects in the preceding 2 weeks.

Upon arrival:
- Have him/her wear face mask entering the hospital.

Fever or suspected upper trait infection upon admittance:
- Yes: Swab and isolation
- No:
  - CT scan and rapid swab
    - Both negative: Transplant proceeds
    - Anyone positive: No Transplant

No Transplant: re-evaluate the patients and plan appropriate diagnostic procedures.

Recipient already in hospital:
- Monitor with swab and chest CT scan
  - Swab AND CT scan negative:
    - Transplant proceeds
  - Swab negative but CT scan suggestive for interstitial pneumonia:
    - Withhold from listing repeat swab 24hr and 7 days later
  - Swab positive:
    - Withhold from listing and treat as appropriate

Transplant proceeds

No transplant: Swab and isolation
Modulation of activity based upon epidemic phase

Preparing for the post-emergency phase

• Further develop telemedicine
• Maintain face mask policy for all incoming patients and personnel
• Develop patient education
• Develop networking with local hospitals

• How to monitor COVID-19 recovered patients?
• Develop patient screening?
• Don’t forget alternative diagnoses for interstitial pneumonia
It’s not COVID all lungs that glitter

- Everolimus interstitial pneumonia
- Pneumocistis Jirovecii
<table>
<thead>
<tr>
<th>Patients on WL</th>
<th>Patients with HT</th>
<th>Patients with LVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Remote visits for stable patients</td>
<td>• Remote visits for stable/long term patients</td>
<td>• Remote visits for stable/long term patients</td>
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<tr>
<td>• COVID triage for everyone</td>
<td>• COVID triage for everyone</td>
<td>• COVID triage for everyone</td>
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<tr>
<td>• In-person for unstable</td>
<td>• EMB within 3-6 month or if previous rejection</td>
<td>• Improve contact with local centers for</td>
</tr>
<tr>
<td>• Admit if clean wards are available those with urgent pre-HTX evaluation</td>
<td>• In person for clinical problems</td>
<td>• Low threshold for in person visit</td>
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<tr>
<td>• Keep RHC in pts with PH</td>
<td>• Keep labs for patients with unstable through levels or CMV infection</td>
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<td>• Keep planned i.v. therapies</td>
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<td>• Screen for COVID when organ is available</td>
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<td>• Consider LVAD vs. Urgent TX</td>
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</table>
Conclusions

• COVID-19 pandemic is affecting transplant numbers and transplant patients

• Hospital organization should be prepared to increase remote management but also develop safe procedures and pathways to keep seeing patients who need to

• Interstitial pneumonia is challenging and COVID-19 specific diagnosis not necessarily impacts treatment in the context of the current outbreak: admitted transplant patients need to be managed in close collaboration with the transplant team
Relevant Financial Relationship Disclosure Statement

“Donor Evaluation in CT Transplant”
Presenter: Christian Benden

I will **not** discuss off label use and/or investigational use of drugs/devices.

The following relevant financial relationships exist related to this presentation:
**No** relationships to disclose
Principles for allocation of scarce medical interventions

Govind Persad, Alan Wertheimer, Ezekiel J Emmanuel

*Lancet* 2009; 373: 423-431

- In pandemic situations, allocation of scarce interventions to people is absolute instrumental.

- A framework is required expressing widely affirmed values:
  - Priority to the worst-off / Maximizing benefits / Treating people equally

- Dialogue required regarding ongoing transplantation during pandemic between organ procurement networks, procurement hospitals and transplant centers.
## Procurement Center Daily Activity Chart

<table>
<thead>
<tr>
<th>Organ donor detection and procurement</th>
<th>Center 1</th>
<th>Center 2</th>
<th>Center 3</th>
<th>Center 4</th>
<th>Center 5</th>
<th>Center 6</th>
<th>Center 7</th>
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<tr>
<td>Step 1: DCD-programm open (detection and procurement)</td>
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<td>Step 2: DBD-programm open (detection and procurement)</td>
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<td>Step 5: Donor detection and procurement no longer available (no resources)</td>
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<th>Center 10</th>
<th>Center 11</th>
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Donor Screening

- Transmission of SARS-CoV-2 from donor to recipient not yet reported.
- Risk of viral transmission to be balanced against risk not using an organ.
- Donors with history suggestive of SARS-CoV-2 infection to be avoided.
- All donors to be tested for SARS-CoV-2 infection (*where available*; by PCR).
- Potential testing tools:
  - Nasopharyngeal swabs
  - Tracheal aspiration
  - Broncho-alveolar lavage (*protection of health care workers essential!*)
- CT chest recommended to exclude viral pneumonitis (*where available*).
- Regardless of donor screening, a discussion of risk-benefit is needed regarding transplantation during the ongoing pandemic.
During organ donation work-up of a 45-year old potential donor, new scattered, bilateral ground-glass opacities were noted on CT chest imaging that prompted bronchoalveolar lavage and nasal swab specimens for SARS-CoV-2 testing. Tests were positive 24 hours later, and the donation process terminated.
Screening Pathway for **Donor** and Recipient Screening at Time of Organ Offer

**POTENTIAL DONOR/RECIPIENT**
- Screening questionnaire for COVID-19 symptoms negative
- No exposure to confirmed/probable case of COVID-19 within 14 days
- PCR test for SARS-CoV-2 negative*
- Consider thoracic CT to assess for viral pneumonitis

Any positive in donor -> DECLINE donor

Any positive in waitlisted candidate -> DEFER transplant

- Proceed with transplantation
- N-95 masks (or equivalent) plus face shield in operating room for lung transplant
- Current data does not suggest a change in induction or maintenance immunosuppression

* SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Thank you for your attention!
Ethical Considerations for CT Transplant and VAD Programs in COVID-19

Are Martin Holm, MD, PhD
Consultant Pulmonologist and Associate University Professor
Oslo University Hospital
Oslo, Norway
I will not discuss off label use and/or investigational use of the following drugs/devices:

The following relevant financial relationships exist related to this presentation:

No relationships to disclose
The trolley problem
The rationing of a life-saving treatment

- Save lives
  - Urgency

- Maximize number of lives saved
  - (Survival benefit, longevity)

- Efficiency
  - Avoid waste of organs (futility)
  - Maximize use of resources?

- Justice: Favour the worst off
Activity Deceased Donors and Transplants

Spanish National Transplant Organization (ONT) data: [http://www.ont.es/infesp/Paginas/Impacto_tx.aspx](http://www.ont.es/infesp/Paginas/Impacto_tx.aspx).
Thoracic Tx and COVID-19

- Fewer organ donations
  - Stricter allocation
  - Lower tx volume
  - Longer wait time

- Limited resources
  - External competition

- Contagion
  - Patients
    - Survival estimation
  - HCW
    - PPE, attrition
Thoracic Tx and COVID-19

- Fewer organ donations
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  - Lower tx volume
  - Longer wait time

- Limited resources
  - External competition

- Contagion
  - Patients
  - HCW
    - Survival estimation
    - PPE, attrition

Who should be prioritized now?

Redirection of staff?

Good match more important?
Bridging impossible?

ICU for COVID-19 or for transplant/MCS?
Consider resource needs

Who is the most urgent?
Is tx or MCS the best treatment now?

Does the system support the decisionmakers in the field?
The rationing of a life-saving treatment

- Save lives
  - Urgency

- Utility: maximize n. of lives saved
  - (survival benefit, longevity)

- Efficiency
  - avoid waste of organs (futility)
  - maximize use of resources?

- Justice: Favour the worst off

During the COVID-19 pandemic

Life years to lose?

Estimate resource need?
Recommendations

**Anticipation:**
- Do not shut down. Plan. Communicate.

**Active:**
- Do not shut down. Adjust plan. Communicate again.
- Redefine optimal candidates: benefit, justice, efficiency.

**Overwhelmed:**
- Take care of patients and HCW.
- Avoid unproven treatment, contribute to acquiring knowledge.

**Recovery:**
- Adjust, again. Evaluate.

**New Normal:**
- Prepare for relapse.
- Adjust to changed circumstances.
Moderated Q&A
Stuart Sweet, MD, PhD

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Thank you

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