Strategies to support the COVID-19 response in LMICs

A virtual seminar series
An Update on COVID-19 Therapeutics and Prophylaxis

Christopher Hoffmann MD, MPH
Lead Author, Johns Hopkins Health System COVID-19 Treatment Guidance Writing Group
Associate Professor
Division of Infectious Diseases
Johns Hopkins University School of Medicine
Outline

• Therapeutics and timing of use
• Supportive and adjunctive care
• Antiviral therapies
• Immune-based therapies
• Prophylaxis
• Summary
Therapeutics and timing of use

Figure: Clinical course and potential therapeutic timing
Supportive & Adjunctive Care
Supportive care in hospital

- Nursing care
- Monitoring of oxygen saturation
- Supplemental oxygen
- Mechanical ventilation
Anticoagulation

• COVID-19 disease is associated with a hypercoagulable state.
  • Endothelial injury – direct viral action and cytokine mediated
  • Stasis
  • Hypercoagulability – increase vWF, d-dimer, fibrinogen

• VTE is common among hospitalized patient with COVID-19
  • Ward patients on VTE prophylaxis: 13% VTE
  • ICU patients on VTE prophylaxis: 30% VTE

• Management
  • Unclear which is appropriate:
    • Standard VTE prophylaxis
    • High dose VTE prophylaxis
    • Therapeutic anticoagulation

Antiviral Therapies
Antivirals and timing of use

Figure: Clinical course and potential therapeutic timing
Selected antiviral therapies

- Remdesivir
- Hydroxychloroquine
- Lopinavir/ritonavir
- Convalescent Plasma
Remdesivir

- Nucleoside RdRp inhibitor
- Dose: 200mg IV load, then 100mg IV qd x 5-10 days
- FDA EUA
  - Eligibility
    - Adults & children
    - SpO2 ≤94% on RA or mechanical ventilation or ECMO
  - Contraindications
    - ALT≥5x ULN
- Pregnancy safety: lack of human data
Remdesivir: Wang et al.

- Double-blind RCT: **237** participants 2:1 RDV & PCB
- Arms:
  - RDV: 200mg IV day 1, then 100mg IV days 2-10
  - PCB
- Time from symptom onset to treatment, median: 10 days (IQR 9-12)
- Primary outcome: clinical improvement (5-point scale)

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<thead>
<tr>
<th></th>
<th>RDV</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Time to improvement, days</td>
<td>21</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Deaths</td>
<td>14%</td>
<td>13%</td>
<td>NS</td>
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<tr>
<td>Time to negative viral RNA, days</td>
<td>21</td>
<td>21</td>
<td>NS</td>
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- Subgroup analysis among patients with ≤10 days symptoms, faster clinical improvement on RDV

Remdesivir: ACTT-1

- Double-blind RCT: 1063 participants 1:1 RDV & PCB
- Arms:
  - RDV 200mg IV day 1, then 100mg IV days 2-10
  - PCB
- Timing of treatment initiation from symptom onset: 9 days (IQR 6-12)
- Primary outcome: time to recovery

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<th>RDV</th>
<th>Placebo</th>
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<tr>
<td>Time to recovery on 8 category scale, median days</td>
<td>11</td>
<td>15</td>
<td>&lt;0.001</td>
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<tr>
<td>Deaths</td>
<td>8%</td>
<td>11.6%</td>
<td>0.06</td>
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- Subgroup analysis: improvement among supplemental O2, no difference with noninvasive or invasive mechanical ventilation.

[Beigel et al NEJM 2020]
Remdesivir: GS-US-540-5773

• Open-label RCT: 397 participants 1:1 10 d & 5d RDV
• Enrollment criteria: SARS-CoV-2; pneumonia; SaO2≤94%
• Arms:
  • 200mg IV day 1, then 100mg IV days 2-10
  • 200mg IV day 1, then 100mg IV days 2-5

• Median duration of symptoms (9 & 8 days; 10 and 5d arm)

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<tr>
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<th>10d RDV</th>
<th>5d RDV</th>
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<tr>
<td>Clinical improvement, 2 point</td>
<td>54%</td>
<td>65%</td>
<td>0.14</td>
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<tr>
<td>Death at 28 days</td>
<td>11%</td>
<td>8%</td>
<td>NS</td>
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<tr>
<td>Serious AEs</td>
<td>35%</td>
<td>21%</td>
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[Goldman et al. NEJM 2020]
JHHS remdesivir use

• 5 day course
• SARS-CoV-2 positive.
• ALT <5 times ULN to initiate and continue RDV. Remdesivir should be stopped if there are signs or symptoms indicating hepatotoxicity.
• Prioritize
  • patients receiving supplemental O2 via nasal cannula over those without supplemental O2 or receiving ventilation.
  • Hospitalized for less than 10 days.
Hydroxychloroquine

• Hypothesized to inhibit viral fusion through changing pH in endosome
• Used widely in China, Europe, & United States
• Studies
  • Retrospective – mostly reporting no benefit; some improvement; some harm
  • Prospective RCTs (open-label and placebo controlled)
Hydroxychloroquine - Tang

• Open-label RCT: 150 participants 1:1 HCQ & standard care

• Arms:
  • HCQ
  • SOC

• Time from symptom onset to treatment: 16 days

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<tr>
<td>Clinical improvement in 28 days</td>
<td>59.9%</td>
<td>66.6%</td>
<td>NS</td>
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<tr>
<td>Negative viral RNA on day 28</td>
<td>85.4%</td>
<td>81.3%</td>
<td>NS</td>
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[Tang et al. BMJ 2020]
HCQ – Recovery Trial

- Multi-arm open-label RCT: 1,561 patients randomized to HCQ; 3,155 SOC
- Arms:
  - HCQ
  - SOC
- Time from symptom onset to treatment: 9 (IQR 5, 14)
- Primary outcome: discharged alive at 28 days

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<tr>
<td>Discharged alive at 28 days</td>
<td>60.3%</td>
<td>62.8%</td>
<td>NS</td>
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<tr>
<td>Composite mechanical ventilation or death</td>
<td>29.8%</td>
<td>26.5%</td>
<td>NS</td>
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- No difference in outcomes with ≤7 vs >7 days of symptoms

LPV/r: Recovery Trial

- Multi-arm open-label trial in the UK
- 1,596 patients in LPV/r arm
- 3,376 patients in usual care alone
- No difference in 28-day mortality, mechanical ventilation, or length of stay

[https://www.clinicaltrialsarena.com/news/recovery-trial-lopinavir-ritonavir/]
LPV/r: Cao B et al.

• Open-label RCT: 199 participants 1:1 LPV/r & SOC
• Arms:
  • LPV/r 400/100mg bid x 14 days
  • Standard of Care (SOC); no PLB
• Time from symptom onset to tx: 13 days (IQR 11-16)
• Outcome: clinical improvement (7 category scale)

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<th>LPV/r</th>
<th>SOC</th>
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<tr>
<td>Time to clinical improvement, days</td>
<td>15</td>
<td>16</td>
<td>NS</td>
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<tr>
<td>Mortality at 28 days</td>
<td>19.2%</td>
<td>25%</td>
<td>NS</td>
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<tr>
<td>Negative viral RNA on d28</td>
<td>60.3%</td>
<td>58.6%</td>
<td>NS</td>
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[Cao B et al. NEJM 2020 DOI: 10.1056/NEJMoa2001282]
IFN β-1b: Hung et al.

- Data source: peer reviewed publication
- Open-label RCT: 127 participants 2:1

Arms:
- If <7 days of sx at randomization
  - LPV/r x14d + ribavirin 400mg q12 x14d + IFNβ 1b 8 mil IU SQ qod (n=52)
  - LPV/r 400/100mg bid x 14d (SOC)
- If 7-14 days of sx at randomization
  - LPV/r x14d + ribavirin 400mg q12 x14d (n=34)
  - LPV/r 400/100mg bid x 14d (SOC)

- Timing of treatment initiation: 5 days for combination, 4 for SOC
- Primary outcome: negative viral PCR; NEWS2=0

<table>
<thead>
<tr>
<th>Time to negative viral PCR, d</th>
<th>Combo</th>
<th>LPV/r</th>
<th>P</th>
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<tbody>
<tr>
<td>Time to negative viral PCR, d</td>
<td>7 (5-11)</td>
<td>12 (8-15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to NEWS2 of 0</td>
<td>4 (3-8)</td>
<td>8 (7-9)</td>
<td>&lt;0.001</td>
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Convalescent Plasma

• Principle
  • Convalescent plasma provides passive antibody therapy
  • May prevent infection or change disease course prior to patient developing neutralizing antibodies
  • There is a long history of successful use in other infectious diseases
  • The neutralizing antibody titer of the unit is critical to its success (units need to be tittered prior to use to assure appropriate use)
  • If effective, it is most likely effective prior to the development of endogenous neutralizing antibodies (in first week of infection)

• Safety: Analysis of 21,987 patients who received convalescent plasma reported <1% of participants with transfusion related events

Convalescent Plasma

• Li et al. open-label RCT;
  • 103 participants; stopped early due to no additional patients in study area
  • Time from symptoms to treatment, median: 30 days
  • Clinical improvement on 6 point scale similar by arm

• Gharbharan et al, open-label RCT
  • 86 participants, stopped early due to futility
  • Time from symptoms to treatment, median: 9 days (IQR: 7-13)
  • The majority of participants had neutralizing antibodies at the time of treatment
  • No difference in mortality, hospital stay, or day-15 disease severity

• Retrospective data are supportive (meta-analysis of studies also supportive)

Immune-Based Therapy
SARS-CoV-2 / COVID-19 therapeutics and timing of use

Figure: Clinical course and potential therapeutic timing

- Fevers
- Cough
- Myalgia
- Dyspnea
- etc.

Days since symptom onset

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

ARDS

Hypoxic respiratory failure, fever, hypotension

Convalescent plasma

Vaccines

Immunoglobulins

Convalescent plasma

Antivirals

Immunomodulators

Adjuvants
Immune-based Therapy

- Corticosteroids (dexamethasone)
- Targeted immune therapies (IL-6 receptor inhibitors)
Corticosteroids – Recovery

• Dexamethasone
  • Less fluid retention than other steroids due to less mineralocorticoid activity

• Multi-arm open label RCT: 2104 participants randomized to dexamethasone; 4,321 standard of care

• Time from symptom onset to treatment: 8 days (IQR: 5-13)

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<tr>
<td>28 day mortality, overall</td>
<td>21.6%</td>
<td>24.6%</td>
<td>&lt;0.001</td>
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<tr>
<td>28 day mortality, invasive ventilation</td>
<td>29.0%</td>
<td>40.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>28 day mortality, supplemental O2</td>
<td>21.5%</td>
<td>25.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>28 day mortality, no supplemental O2</td>
<td>17.0%</td>
<td>13.2%</td>
<td>0.14</td>
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[Horby et al. MedRxiv 2020]
IL-6 receptor inhibitors

- Possible benefit during a cytokine storm phenotype
- RCT enrollment criteria: SaO2<94% & pneumonia; no inflammation criteria.
  - Tocilizumab (monoclonal antibody)
    - Placebo-controlled RCT; 450 participants
    - No significant difference in clinical status by arm
  - Sarilumab (monoclonal antibody)
    - Placebo-controlled RCT; 174+ participants
    - No significant difference in clinical status by arm; halted for futility

Prophylaxis
Prophylactic approaches

- Vaccines
- Convalescent plasma
- Hydroxychloroquine (and antivirals)
HCQ for prevention: Mitja

- Open-label RCT: 2,314 healthy contacts of 672 COVID-19 cases 1:1 HCQ vs standard care
- Arms:
  - HCQ
  - SOC
- Primary outcome: PCR confirmed SARS-CoV-2

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<tr>
<td>PCR confirmed SARS-CoV-2</td>
<td>5.7%</td>
<td>6.2%</td>
<td>NS</td>
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[Mitja et al. MedRxiv 2020]
HCQ for prevention: Boulware

- Double-blind placebo-controlled RCT: 821 healthy contacts of 672 COVID-19 cases 1:1 HCQ vs standard care
- Arms:
  - HCQ
  - Placebo
- Primary outcome: COVID-19 illness

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<tr>
<td>COVID-19 illness</td>
<td>11.8%</td>
<td>14.3%</td>
<td>NS</td>
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[Boulware et al. NEJM 2020]
A treatment approach

- Supportive care and oxygen supplementation
- Anticoagulation (prophylactic/high dose prophylactic/therapeutic)
- Remdesivir (early use)
- Convalescent plasma (may have role for early use)
- Dexamethasone (supplemental oxygen or mechanical ventilation)
- IL-6 receptor antagonists (may have role if elevated inflammatory markers)