A look at the latest COVID-19 evidence
Objectives

Introduce a new risk stratification tool developed specifically for COVID-1

Review recent evidence for therapeutic trials
  ◦ Hydroxychloroquine
  ◦ Remdesivir
  ◦ Convalescent Plasma

Discuss PCR test performance and Serology timeline

Leave you hungry for more...
Two hospitals in Fuyang and Beijing
Retrospective analysis of 208 inpatients
  • Severe cases excluded
Clinical course categorized as stable or progressive to severe disease
Multivariate Cox regression to identify predictors of illness progression

Severe Disease:
• RR ≥ 30 breaths/min,
• SpO2 ≤ 93%,
• PaO2/FiO2 ≤ 300 mmHg
• Requiring mechanical ventilation

Risk Stratification – CALL Score

Four key variables identified

CALL score ranging from 4-13 points

- Comorbidity: without = 1 point, with = 4 points
- Age: $\leq 60 = 1$ point, $>60 = 3$ points
- Lymphocyte: $>1,000 = 1$ point, $\leq 1,000 = 3$ points
- LDH: $<250 = 1$ point, $250-500 = 2$ points, $>500 = 3$ points

Comorbidity:

- Hypertension
- Diabetes
- Cardiovascular disease
- Liver disease
- Asthma
- Chronic lung disease
- HIV
- Malignancy

Risk Stratification – CALL Score

AUROC was 0.91 (>0.8 considered “excellent”)
- Cut-off of 6 points: +LR 4.31 (3.2-5.8), -LR 0.06 (0.02-0.20)
- Cut-off of 9 points: +LR 15.1 (6.0, 38.3), -LR 0.57 (0.40-0.80)

Three classes
- 4-6 points: <10% progressed
- 7-9 points: 10-40% progressed
- 10-13 points >50% progressed

So what?
- May be useful in disposition decisions for inpatients

Risk Stratification – CURB-65?

In the same study CURB 65 ranged 0-2 for all participants

In another study of 191 inpatients in Wuhan 30% of the patients who died had CURB 65 01 and 43% had a score of 2

Does not consider comorbidity


Therapeutics - Hydroxychloroquine

Antimalarial with invitro activity

Frequently used in management of RA/Lupus

Proposed mechanisms:
- Inhibition of viral entry
- Inhibition of viral release into host cell
- Reduction of viral infectivity
- Immune modulation (Reduced TLR signaling, inflammatory cytokines)
Hydroxychloroquine - French Study

Pre-publication, posted April 14 2020

Multicenter, 181 hospitalized and hypoxic (>2L NC) with confirmed SARS-CoV-2
Inverse probability of treatment weighting (IPTW) to “emulate” randomization

84/181 received HCQ within 48h of admission vs 97/181 who did not
◦ Primary aim: Transfer to ICU within 7 days from inclusion and/or death from any cause.
◦ Secondary aim: Assess effectiveness of HCQ in preventing ARDS.

Primary endpoint (ICU or death):
  ◦ 20.2% patients in HCQ group vs 22.1% in no-HCQ group (RR 0.91, 95% CI 0.47-1.80).

Secondary endpoint (ARDS within 7 days):
  ◦ 27.4% in HCQ group vs 24.1% in the non-HCQ group (RR 1.14, 95% CI 0.65-2.00)

Safety concerns:
  ◦ 8 patients in the HCQ group had ECG changes, resulting in discontinuation of HCQ.

Interpretation: HCQ was not associated with a reduction of ICU transfers, death, or ARDS development.
Hydroxychloroquine - French Study

Limitations: Not randomized, Potential confounding variables (other treatments), HCQ treatment was not balanced per center, no measure of viral shedding.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=181)</th>
<th>HCQ (n=84)</th>
<th>No-HCQ (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and clinical data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>128 (71.1)</td>
<td>65 (78.3)</td>
<td>63 (64.9)</td>
</tr>
<tr>
<td>Comorbidities – no (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory disease (including asthma)</td>
<td>20 (11.0)</td>
<td>5 (6.0)</td>
<td>15 (15.5)</td>
</tr>
<tr>
<td>Chronic heart failure (NYHA III or IV)</td>
<td>6 (3.3)</td>
<td>1 (1.2)</td>
<td>5 (5.2)</td>
</tr>
<tr>
<td>Cardiovascular diseases (incl. hypertension)</td>
<td>94 (51.9)</td>
<td>38 (45.2)</td>
<td>56 (57.7)</td>
</tr>
<tr>
<td>Diabetes requiring insulin</td>
<td>15 (8.3)</td>
<td>4 (4.8)</td>
<td>11 (11.5)</td>
</tr>
<tr>
<td>Chronic kidney failure</td>
<td>9 (5.0)</td>
<td>1 (1.2)</td>
<td>8 (8.2)</td>
</tr>
<tr>
<td>Liver cirrhosis (Child-Pugh B or more)</td>
<td>1 (0.6)</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Immunodepression</td>
<td>21 (11.6)</td>
<td>8 (9.5)</td>
<td>13 (13.4)</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² – no (%)</td>
<td>43 (27.4)</td>
<td>20 (25.3)</td>
<td>23 (29.5)</td>
</tr>
<tr>
<td>Treatment by ACEIs or ARBs – no (%)</td>
<td>54 (30.3)</td>
<td>26 (31.0)</td>
<td>28 (29.8)</td>
</tr>
</tbody>
</table>

Hydroxychloroquine - VA Study

Pre-publication; posted April 21, 2020

Retrospective analysis of all VA admissions for Covid-19 up to April 11, 2020

368 male patients were evaluated, three groups identified

- HCQ n=97
- HCQ + AZ n=113
- No HCQ n=158
Table 3. Outcomes based on treatment exposure.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HC</th>
<th>HC+AZ</th>
<th>No HC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=97</td>
<td>N=113</td>
<td>N=158</td>
<td></td>
</tr>
<tr>
<td>Death – no. (%)</td>
<td>27 (27.8)</td>
<td>25 (22.1)</td>
<td>18 (11.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Discharge – no. (%)</td>
<td>70 (72.2)</td>
<td>88 (77.9)</td>
<td>140 (88.6)</td>
<td></td>
</tr>
</tbody>
</table>
Hydroxychloroquine - VA Study

Interpretation: HCQ use in hospitalized veterans was associated with increased mortality

Limitations:
- HCQ and HCQ + AZ patients possibly sicker
  - significantly lower SpO2
  - some significantly higher labs (AST/ALT, Cr, CRP)
  - some lower as well (Troponin, Bilirubin)
- Women excluded due to small sample

Hydroxychloroquine - Takeaways

Data is mixed, but some signal for potential harm, likely carried by cardiac toxicity.

IDSA and NIH ➔ limit usage to clinical trials

ATS ➔ Case by Case in hospitalized patients

Covidprotocols ➔ Only in severely ill patients who are not candidates for any other investigational therapy after weighing risks

Shared decision making, should not be first line
Remdesivir

Nucleotide prodrug

- Analog of ATP which inhibits viral RNA-dependent RNA polymerase
- Premature termination of RNA transcription.

Animal model efficacy against SARS-CoV-1 and MERS CoV

In vitro efficacy against SARS-CoV-2

Remdesivir case series

Compassionate-use remdesivir was provided to patients hospitalized with Covid-19 for up to 10 days.

53 patients

No specific endpoints, number of patients, number of sites, or duration time points were predetermined.

Follow-up information obtained through day 28.

Remdesivir case series

36/53 (68%) showed improvement of oxygenation
- median 18 days post-first dose

17/30 (57%) intubated patients were extubated

Mortality: 7/53 (13%) died

Safety: 32 patients reported adverse events, including increased hepatic enzymes, diarrhea, renal impairment, rash, hypotension (more common in those receiving mechanical ventilation).

Limitations:
- Not placebo controlled
- No predetermined endpoints.
- Given at a median of 12 days after symptom onset
- Sponsored by Gilead Sciences

Remdesivir case series

April 21 2020 WHO accidentally released new Chinese trial prior to peer review

237 patients hospitalized with “severe COVID-19”
- 158 treatment vs 79 placebo

No difference in
- Mortality at 28 days (13.9% vs 12.8%)
- Time to clinical improvement (HR 1.23, 95%CI 0.87-1.75)
- Time to viral clearance

Adverse Events in 65.2% in treatment vs 64.1% in placebo recipients

"Remdesivir was not associated with clinical or virological benefits"

Remdesivir takeaways

Should only be used in clinical trials at this point

More data is needed
Convalescent Plasma

Plasma from recovered patients containing immunoglobulins which suppress viremia.

Prior experience with Spanish flu 1918, SARS-CoV-1, MERS and H1N1

With SARS-CoV-1, possibly more effective pre/post exposure PPX rather than treatment of established infection*

Convalescent Plasma

Treatment With Convalescent Plasma for Critically Ill Patients With SARS-CoV-2 Infection
Convalescent Plasma Takeaways

Positive outcomes in very limited number of patients

Associated with risk of TRALI, along with other transfusion related reactions

IDSA recommending use limited to clinical trials

SCCM recommends against
Other studies to look out for


Anti-interleukins
  ◦ Anakinra, siltuximab, tocilizumab,

Janus Kinase inhibitors
  ◦ baricitinib, ruxolitinib
Testing – Antibody responses

173 confirmed positive cases in Shenzhen, China

RNA, total anti-SARS-CoV-2 Ab, IgG and IgM titers followed

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<table>
<thead>
<tr>
<th>Days after onset</th>
<th>No. of patients with undetectable RNA*</th>
<th>Detectable antibody in plasma, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>7</td>
<td>2 (28.6)  2 (28.6)  2 (28.6)</td>
</tr>
<tr>
<td>4-7</td>
<td>28</td>
<td>15 (53.6)  12 (42.9)  8 (28.6)</td>
</tr>
<tr>
<td>8-14</td>
<td>57</td>
<td>56 (98.2)  45 (78.9)  40 (70.2)</td>
</tr>
<tr>
<td>15-39</td>
<td>30</td>
<td>30 (100)  28 (93.3)  22 (73.3)</td>
</tr>
</tbody>
</table>

* RNA was tested using throat/nasal swab sample.

Real world test performance?

A lot can go wrong

Early reports from China showing sensitivity of one-time NP swab PCR ranging 51-67%

April 21 2020 - unpublished study from Cleveland Clinic

- Cleveland Clinic tested 239 specimens known to contain the coronavirus using 5 different machines
- Abbott ID Now: 85.2% detection rate (14.8% false negative)
- Viral transport media used*


Summary

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Discuss PCR test performance and Serology timeline

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References


Resources for COVID-19 EBM

- **Frontline COVID-19 guide**
- **COVID-19 clinical guidelines** from Bigham and Women’s
- **The Weekly COVID-19 Literature Roundup** from Emory ID fellows
  - Excellent summaries of the latest high-impact studies
- **NIH treatment guidelines**, section on treatments under investigation
Questions?