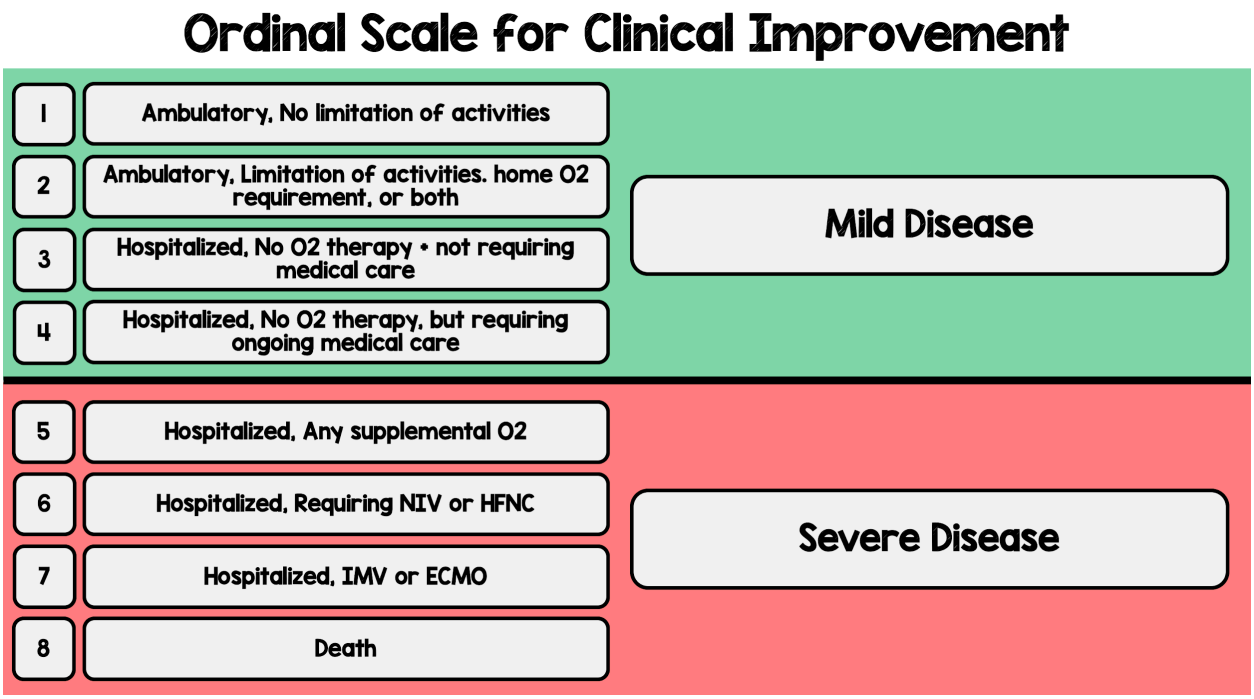
The Saga Continues with Remdesivir and Hydroxychloroquine/Chloroquine

Marketing Assets

- Salim Rezaie @srrezaie

- Tweet copy: Hot off the press!! 2 important studies just published on Remdesivir and Hydroxychloroquine... @srrezaie brings us his breakdown of the science & these Rxs efficacy @hippoeducation #ercast #covid19 #covidFOAM

Use this graphic in tweet [tag rob orman, delaney, miz, paul]



Site Assets

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Written Assets Template

Title: <**The Saga Continues with Remdesivir and Hydroxychloroquine**>

Summary:

In this Hippo Education short, Dr.Salim Rezaie from REBEL EM and Lit Matters critically appraises two papers published on Friday May 22nd, 2020. He discusses what the evidence shows for both remdesivir & hydroxychloroquine/chloroquine as effective treatment or prophylaxis for COVID-19.

References:

1. Mehra MR et al. **Hydroxychloroquine or Chloroquine With or Without a Macrolide for Treatment of COVID-19: A Multinational Registry Analysis.** Lancet 2020.

2. Beigel JH et al. **Remdesivir for the Treatment of COVID-19 – Preliminary Report.** NEJM 2020.

SHOW NOTES

Two important studies just got published on the efficacy of remdesivir and hydroxychloroquine for covid19...we asked our ER cast lit matters team to do a critical appraisal of these two papers and how they change our practice...take a listen.

Outro: Thanks for listening to this podcast...don't forget to check out other material we have on our site at COVID.HIPPOED.COM. Feel free to reach out to us on twitter with comments and questions. Thanks for listening!

Salim Rezaie here from REBEL EM and Lit Matters. I wanted to put out an audio update on two papers that were just published on Friday May 22nd, 2020. There currently is no conclusive evidence that remdesivir or hydroxychloroquine/chloroquine is effective the treatment or prophylaxis of COVID-19. What you are about hear is my review, critical appraisal, and thoughts on both of these papers.

Paper: Mehra MR et al. **Hydroxychloroquine or Chloroquine With or Without a Macrolide for Treatment of COVID-19: A Multinational Registry Analysis.** Lancet 2020. [Epub Ahead of Print]

This was a multinational registry analysis of 96,000 patients from 671 hospitals across 6 continents. Patients who received one of the treatments of interest ≤48hrs of diagnosis were included in one of 4 treatment groups:

- Chloroquine Alone (CQ)
- Chloroquine + Macrolide (CQM)

- Hydroxychloroquine Alone (HCQ)
- Hydroxychloroquine + Macrolide (HCQM)
- Patients who received none of these treatments formed the control group (Control)

The primary outcome was in-hospital mortality and the important secondary outcome was occurrence of de-novo ventricular arrhythmias defined as non-sustained or sustained VT/VF.

Critical Results:

- **In-Hospital Mortality:**
  - CQ: 16.4%
  - CQM: 22.2%
  - HCQ: 18.0%
  - HCQM: 23.8%
  - Control: 9.3%
  - All independently associated with increased risk of in-hospital mortality compared to control
- **De-Novo Ventricular Arrhythmia During Hospitalization:**
  - CQ: 4.3%
  - CQM: 6.5%
  - HCQ: 6.1%
  - HCQM: 8.1%
  - Control: 0.3%
  - Also, all independently associated with increased risk of de-novo ventricular arrhythmia during hospitalization compared to control

As best I can tell this is the largest, most comprehensive data set to date evaluating the use of hydroxychloroquine and chloroquine (with or without a macrolides). The authors evaluated patients from across multiple geographic regions which increases generalizability and is one of the most robust real-world pieces of evidence to date on these medications. One thing I have found frustrating in previous trials is they publish, before everyone in their cohorts have met an endpoint. In this study all included patients completed their hospital course (discharged or died).

This is an observational data set, which cannot account for unmeasured confounding factors. Due to lack of randomization, unable to control for other parts of management, minimal discussion of what was standard care. Additionally, as this is an observational trial a causal relationship between drug therapy and survival cannot be inferred (i.e.

association but not causation). Finally, overall these patients weren't that sick (>80% had a SOFA score of 1 and only 10% had an O2 saturation of <94%)

Clinical Take Home Point: This study not only suggests an absence of efficacy for hospitalized patients with COVID-19, but a real signal of harm with increased ventricular arrhythmias with Hydroxychloroquine/Chloroquine (with or without macrolides) compared to a control population. These medications should simply not be used outside of a randomized clinical trial.

Paper: Beigel JH et al. **Remdesivir for the Treatment of COVID-19 – Preliminary Report.** NEJM 2020. [Epub Ahead of Print]

The National Institute of Allergy and Infectious Diseases (NIAID) put out a little teaser a few weeks ago but didn't release the actual results. Despite this the FDA approved remdesivir for use despite having no robust data supporting its use except for the tease of the NIAID study. We finally have a preliminary report published in the NEJM. This is the 1st part of a series of multicenter, phase 3, double-blind, placebo-controlled trials of IV remdesivir vs placebo in adults hospitalized with COVID-19. The trial was called Adaptive COVID-19 Treatment Trial Part 1 (ACTT-1). This was also a rather large trial with just over 1000 patients from 60 trial sites globally.

The primary outcome was time to recovery, which was defined as the 1st day during the 28 days after enrollment in which the patient was category 1, 2, or 3 based on the ordinal scale below. Important secondary outcomes were 14d mortality, grade 3 and 4 adverse events, and serious adverse events.

- 1059 are included in the analysis
  - Remdesivir: 538pts
  - Placebo: 521pts
- Median number of days between symptom onset and randomization was 9d (Range 6 to 12d)
- 943 patients (88.7% had severe disease at enrollment (Mild/moderate disease was defined by a SpO2>94% and respiratory rate <24BPM without supplemental oxygen)
  - Would argue that category 5 (hospitalized is moderate disease and not severe disease. Therefore, looking at Category 6 and 7 as severe disease, this number should be more like 44.1%)
- Median Recovery Time:
  - Remdesivir: 11d (95% CI 9 to 12)

- Placebo: 15d (95% CI 13 to 19)
- Rate Ratio for recovery: 1.32; 95% CI 1.12 to 1.55; p<0.001

· 14d Mortality:
- Remdesivir: 32/538 (5.9%)
- Placebo: 54/521 (10.4%)
- HR 0.70; 95% CI 0.47 to 1.04 (Not statistically significant)

The good news is this was a multicenter, international, double-blind, placebo-controlled trial. All the words we like to read when reviewing a study. Now for the bad news…The trial was stopped early due to an interim analysis that showed a shortened time to recovery and therefore unblinding of the arms occurred. My head actually hurt trying to parse all this out, so hopefully I can do that for you, and spare you the same pain:

· The primary outcome of the study was changed, however the authors state that investigators and statisticians remained blinded (only 72 patients had been enrolled at the time of change)

· At stoppage, the enrollment of patients was already completed, but only 482 recoveries and 81 deaths had been entered into the database (50% of the total enrolled patients)

· At stoppage, physicians could request to be made aware of the treatment assignment of patients who had not completed their medications if clinically indicated (i.e. worsening clinical status), so that patients in the placebo group could be given remdesivir. Unfortunately, we don't have any information on how frequently this occurred

· 65 to 70% of patients in both arms had completed the study (i.e. 29d) at the time of the publication. Since not everyone in the study had completed the full course, we don't have outcomes for almost 1/3rd of patients. This could change the overall results

· All these factors can cause an overestimation and unfortunately overexaggerate the effect size seen

· At the end of the discussion, the authors state, **"However, given the high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should evaluate antiviral agents in combination with other therapeutic approaches or combinations of antiviral agents to continue to improve patient outcomes in COVID-19."**

· In the supplement figure S1, is a 15-day outcome by baseline ordinal scale in the intention to treat population. This figure shows that there is a more impressive decrease in progression of disease in patients with lesser severity of illness, but no real improvements in patients who are mechanically ventilated or on ECMO (Ordinal score of 7).

Clinical Take Home Points:

- Part 1 of the ACTT trial is far from perfect
- Although there was significant unblinding and a change in the primary outcome, the upside of this trial is we see a 4 day decrease in hospital length of stay (11d vs 15d) favoring remdesivir.
- The drug did not significantly decrease mortality, but again in the middle of a pandemic in hospitals getting a surge of patients, a 4 day decrease in recovery time can have significant ramifications on a health system.