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COVID-19: IDSA Treatment Guidelines, Remdesivir, and a Look Back
(Recording Date: May 6, 2020)

Summary: In this Hippo Education update, Primary Care RAP host Dr. Neda Frayha interviews regular guest and Infectious Diseases expert Dr. Devang Patel for a discussion of where the IDSA stands on all the potential treatments for COVID-19, a review of the remdesivir paper that is all the rage lately, and a look back on whether or not their very first conversations on the novel coronavirus have stood the test of time.

Tags: Infectious Diseases (ID)

Sample Tweet: Regular guest & ID expert @pateldevangm & @nedafrayha review the latest @IDSAInfo treatment guidelines for #COVID19, the #remdesivir buzz, & whether their earlier pandemic predictions stood the test of time

Summary of IDSA Guidelines for the Treatment of COVID-19, published April 11, 2020 and updated April 21, 2020.

Recommendation 1	Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap)
Recommendation 2	Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)
Recommendation 3	Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ ritonavir only in the context of a clinical trial. (Knowledge gap)
Recommendation 4	Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)
Recommendation 5	Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)

Recommendation 6	Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)
Recommendation 7	Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap)

References:

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ONLY ABOVE THIS LINE SHOULD BE USED FOR THE SHOW NOTES. BELOW THIS LINE IS FOR THE PURPOSE OF INTERVIEW PREP ONLY.

Intro:

Hi everyone, and welcome to the latest addition to the free open access educational series on covid-19 created by Hippo Education! I'm Dr. Neda Frayha, an internist and host of the Primary Care Reviews and Perspectives podcast, and today I am back with our friend and frequent guest expert in Infectious Diseases, Dr. Devang Patel. Dr. Patel shared his wisdom and expertise in two of our very first podcast episodes on covid-19, back in late January and early March 2020. Now, it's early May, and in this conversation we're going to cover the Infectious Diseases Society of America guidelines on how to treat covid-19; all the latest buzz on remdesivir after data from the big NIH study were released at the end of April; and a look back on our early conversations to reflect on how much has changed since we first began covering this disease. Devang, welcome back!

Part I: IDSA Guidelines, dated April 11 and last updated April 21 (goal: 15 minutes)

What is the goal of these guidelines?

- PLEASE SHARE YOUR SMART ID PERSPECTIVE HERE, WHAT ID PEOPLE ARE SAYING
- So much information coming out every day
- Goal is to sort through & appraise all the new data and provide evidence-based guidelines for the management and treatment of covid-19 patients - so not diagnosis or testing
- Everybody was really for guidance on how to manage a novel infection. We all knew there was limited data and what was out there was very mixed. This is always the concern with anecdotal medicine. The guidelines were meant to provide evidence-based guidance on treatment. Unfortunately, the evidence was still limited at the time of publication.

How were they developed?

- PLEASE SHARE YOUR SMART ID PERSPECTIVE HERE, WHAT ID PEOPLE ARE SAYING
- Multidisciplinary panel of ID clinicians, pharmacists, methodologists *(what a funny word)*
- Did a systematic study of both peer-reviewed and "grey" literature
- Came up with 7 recommendations that all panelists agreed on
- They say their goal is to update these all the time, that it's a "living" document
- Also really push for recruiting as many patients as possible into ongoing clinical trials

Let's get into the 7 recommendations. First there are a few important caveats that apply to all 7 of these!

- These are all for hospitalized patients. So we're not talking about people who are healthy enough to be managed as outpatients. (I am fielding dozens of calls from healthy outpatients asking for hydroxychloroquine, or remdesivir...)

- The IDSA acknowledges that there is a “knowledge gap” behind all 7 of these, so they’re kind of covering themselves, saying they don’t want to be too premature in recommending something

Recommendations 1 and 2 have to do with HCQ +/- azithromycin for hospitalized patients.

- *“Recommendation 1. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine in the context of a clinical trial. (Knowledge gap)*
- *Recommendation 2. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine/chloroquine plus azithromycin only in the context of a clinical trial. (Knowledge gap)”*

(Discuss)

The French study that started all of this was retracted because it really wasn’t very good science. Limited number of patients who were obviously not randomized. Lots of cardiac toxicity! Maybe more than expected with our long history of using plaquenil for other purposes.

(Neda’s notes: some flaws in the studies they looked at include selection bias, use of intermediary outcomes like viral clearance, lack of appropriate comparisons (e.g., mortality rate calculated in treatment arm but not control arm); in the end, there’s lots of uncertainty surrounding risks and benefits of HCQ alone, and then there’s also concern for toxicity in combination with azithromycin, most notably QTc prolongation).

Recommendation 3 looks at lopinavir/ritonavir.

- *“Recommendation 3. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)”*

(Discuss)

Many of the PIs might show some inhibition of viral replication in vitro but none of this is exciting for use as a therapeutic.

(Neda’s notes: lopinavir and ritonavir = protease inhibitors, marketed together as Kaletra, used as ART for HIV; the one trial that looked at this was by Cao et al and published in NEJM in March 2020, randomized 199 patients; found no benefit as measured by detectable RNA, time to recovery (less than one day), mortality; main side effects are GI).

Recommendations 4 and 5 have to do with steroids for patients with covid-19 pneumonia vs ARDS due to covid-19.

- *“Recommendation 4. Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids. (Conditional recommendation, very low certainty of evidence)*

- *Recommendation 5. Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial. (Knowledge gap)"*

(Discuss)
Again, not enough known here. You would think that corticosteroids would be helpful if the thought is that this is an inflammatory process that is driving the disease but that has not been shown.

(Neda's notes: Home steroids - inhaled or systemic, e.g. for asthma - should be continued - that's not the kind of steroid we're talking about. "A systematic review reported on 15 studies, 13 of which were inconclusive to any benefits of corticosteroids. One RCT reported that SARS-CoV-1 viral loads showed delayed viral clearance associated with corticosteroid use." Re: ARDS - "One small RCT in 24 patients using a lower dose methylprednisolone for two days showed possible improvement of ARDS; however, two larger trials showed little or no effect in critically ill patients with pulmonary failure.")

Recommendation 6 gets into IL-6 inhibitors.

- *"Recommendation 6. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial. (Knowledge gap)"*

(Discuss, let's get into some cytokine storm buzz)
A lot of excitement on this topic, a therapy not targeting the virus directly. Again, very little data and anecdotally have seen an increased risk of infections such as fungemia.

(Neda's notes: one study, 21 critically ill patients who got tocilizumab, no control group; based on estimates of baseline mortality in control groups from other studies, estimate that there *could* be a mortality benefit in the patients who got tocilizumab; no documented SEs from this study but can increase risk of serious infections and reactivation of Hep B, some cases of anaphylaxis and liver failure in non-covid patients).

And finally, recommendation 7 gets into convalescent plasma. NOTE: WE'RE GOING TO HAVE A WHOLE EPISODE ON THIS TOPIC COMING UP, SO WE WON'T GET INTO DETAIL

- *"Recommendation 7. Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial. (Knowledge gap)"*

(Discuss)
(Neda's notes: two case series of 15 patients; seemed to do better and no adverse outcomes, stay tuned for more info)

So how would you put this all together for us? What can clinicians take away from these guidelines?
(Discuss)
(Great points in the Discussion section of the guidelines on the tendency to rely on in vitro data, observational studies, fast-tracked publications without peer review, etc. in the midst of a pandemic, but how it's still really important to carry out high quality RCTs so we can be guided by good science). Yes to all of this including the NEJM article on remdesvir.

Interesting that remdesivir doesn't even make its way into the IDSA guidelines, other than a brief mention in "treatments undergoing evaluation"! Speaking of which...

Part II: What's the deal with remdesivir? (goal: 5 minutes)
What IS remdesivir?
Antiviral nucleotide
Shown to have in vitro activity against Ebola, SARS, MERS, RSV
Mechanism of action = premature termination of viral RNA transcription

There has been a lot of buzz about remdesivir recently, after preliminary data from an NIH study was released on April 29. Let's talk about that.
- NIH-sponsored Adaptive Covid-19 Treatment trial (ACTT trial) enrolled 1,063 hospitalized patients with COVID-19
- Prelim analysis from an independent review board found that remdesivir reduced median time to recovery to 11 days from 15 days with placebo ($p < 0.001$)
- Mortality trended towards a benefit (8% with remdesivir vs. 12% with placebo) but results were not statistically significant (p 0.059)
- Clinical benefit similar to oseltamivir in the flu

Should we get excited? Is this the long-awaited panacea? The FDA issued emergency use authorization for it a few days ago (which is not the same thing as FDA approval).
(Discuss, what are ID people saying, lots of EBM purists are very skeptical b/c they changed the goals of the study before releasing data)
(Neda's notes: Too soon to get too excited; smaller studies - including a Chinese one published in The Lancet on the same day as the NIH study data were released - show limited to no benefit - but this study was terminated early because there weren't any more cases - the pandemic was waning!)

- several things to consider here
    - study endpoints changed in the middle. Suggests they knew they wouldn't reach their pre-determined endpoints.
    - Lancet study shows no change in viral load. So then how does remdesivir improve outcomes? This is a drug that specifically targets the virus.
    - does using this as "standard of care" impede our ability to evaluate other treatments effectively?

- Despite all this, could argue that shortening duration of hospitalization would have a huge public health impact.

Part III: A look back (goal: 5 minutes)

When we first recorded about this novel coronavirus, it was late January, and we were still trying to get our patients vaccinated against influenza. The next time we recorded together on covid-19, it was early March, and as a society we hadn't begun to physically distance from each other yet. When we think back to those days, how do you feel now about our early discussions? Did our predictions stand the test of time? Or were we totally off?

(Thoughts)

(I relistened to both pieces and think you did an incredibly good job of respecting what this virus might turn out to be. Things that stand out to me:

- When we first recorded, it was still flu season and we were more worried about flu… here we are, a whole season later, and covid has proven to be more deadly after all
- We still don't know the true mortality due to a dearth of testing. NY state random antibody testing - approx 15% tested positive.
- We talked a lot about early testing, and how everything needed to be run through the CDC… in hindsight it's even clearer what a missed opportunity this has been for the US.
    - Big miss! Would have changed how we approached social distancing, etc sooner.
- The second time we recorded, North America hadn't yet started physically distancing. It's almost sad to look back and realize how different life was, <2 months ago)

Closing:

Thanks so much for listening to this podcast…don't forget to check out other material we have on our site including a WATCH section, full of videos we've found helpful, a READ section full of quick reference infographics, links and resources, and a LISTEN section, where you can find more audio podcasts related to the covid-19 pandemic. It's all publicly available open access medical education, so please share with your colleagues and friends if you think they will find it useful. You can find all of this and much more at COVID.HIPPOED.COM. Tweet us @hippoeducation if you have any questions or would like us to cover other topics. Thanks for listening!