COVID 19 & Rxs

Mizuho sits down with emergency medicine pharmacist/toxicologist Bryan Hayes, PhD to answer some pertinent questions and myth-bust clarifications about pharmaceutical options in covid-19 treatment.

As front line providers, trying to keep up with anything COVID has become much like drinking out of a firehose...and when it comes to potential treatments...the various opinions and lack of evidence makes our anxiety rise even higher…

We know that this is a moving target...but many of you have sent in great questions that we wanted to address...so here joining me today is

Bryan Hayes + miz
Bryan D. Hayes, PharmD, DABAT, FAACT, FASHP

@PharmERToxGuy

emergency medicine pharmacist and board certified toxicologist at Massachusetts General Hospital and Assistant Professor of EM at Harvard Medical School in Boston

You can follow his blog at https://pharmertoxguy.com

Controversy:
NSAIDS...background...how did they come to this suggestion? based on one french study...is there any basis behind this that we know at this point? YAY/Nay?

https://pharmertoxguy.com/2020/03/19/nsaids-in-covid-19/

(Peds): should we be holding off on ibuprofen for febrile kids with URI's if no testing is available?

For patients being managed at home, ibuprofen should be ok. Acetaminophen is ok too. Because they work through different mechanisms, they can be taken together at the same time or in an alternating fashion.

ARB/ACEi: same question what was the background to this concern, and is there validity to it? (current AHA states NOT to remove pts off of these drugs).

https://pharmertoxguy.com/2020/03/26/ace-inhibitors-and-arbs-during-covid-19/#more-2577

https://www.nejm.org/doi/full/10.1056/NEJMsr2005760?query=RP

Let's talk about **Hydroxychloroquine/chloroquine** and the fact that there is increasing evidence that this may be helpful with COVID. Regardless of the fact that Its hard to find it now in pharmacies, b/c ppl are hoarding it, let's talk about the RISKS and BENEFITS of this RX!

- not completely benign: SE profile; blood dyscrasias, SJS, TEN, retinal damage, cardiomyopathy (some concern namely that this might be sending ppl into heart failure later), QT prolongation and the list goes on!
- What is your stance? Despite this list of side effects, it is an overall well tolerated drug. Lots of patients take it for immune-related conditions such as SLE and RA
- What do you tell patients? The FDA issued an emergency use authorization on March 28 for treatment (https://www.fda.gov/media/136534/download)
- In my shop currently reserved for inpatient use. We also reserve it for inpatient use.

French study https://www.sciencedirect.com/science/article/pii/S0924857920300996

China study http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03#1

New China study: https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1

Most derived from in vitro studies inhibiting growth of coronaviruses like SARS. French study, very small, open label, really a case series. Figures look good at viral eradication at day 6. But, lots of limitations.

Safety concerns:

1) QT prolongation - both can do this, but it is rare (same as azithromycin) - is there synergistic effect when combining them? Get an ECG first and minimize exposure to other QT prolonging meds.
2) Hypoglycemia (both) - rare; enhanced insulin release and sensitivity; maybe more likely in diabetic patients
3) CNS effects (both) - disorientation all the way to psychosis - be on the lookout early in therapy
4) Drug interactions: additive QT effects; both inhibit 2D6 which can affect metabolism of other medications (metoprolol, carvedilol, codeine)
5) Theoretical hemolysis concern (primaquine, dapsone) - maybe with severe G6PD variant
6) Pregnancy - no major concerns
7) Retinopathy - concern if using prophylaxis for extended periods

Robbie O:Brian had a really strong tweet stream about not using chloroquine and I agree with what he said with it not being studied, we should wait for peer review but I think that that is also a little bit inconsistent with what's happening in real life because everyone I've talked to is using it for inpatients Is there something about inpatients where we think it's a more valid treatment versus someone who is not in the hospital?

if the answer is that the inpatients are sicker and may benefit more or at least have less to lose, how do you reconcile that with the limited data on efficacy and safety?

My tweet was specifically directed at the toxicology perspective of using an unproven drug in mass populations. Chloroquine is one of the more feared poisons. It can kill in as little as 3 hours and pediatric patients are particularly vulnerable (https://www.ncbi.nlm.nih.gov/pubmed/15837026). More availability means more overdoses, especially in a time when depression and suicide risk is likely increased. We already had a case with presenting with CNS depression, hypotension, potassium 2.0, QRS > 130, QTc > 700. These cases are difficult to treat.

I am ok with expanding access for COVID (+) patients who might benefit (data very iffy), but am wholly against the hoarding of this drug and prescribing for friends/family for prevention.

Azithromycin: Why does this help? Prevent 2ndary PNA?
Why do recommendations state either standard Zpack (500 then 250 x 5 days) or 500mg daily x 7 days.

Azithromycin has been shown to be active *in vitro* against Zika and Ebola viruses and to prevent severe respiratory tract infections when administered to patients suffering viral infection

Also for secondary PNA

Other study drugs:
Remdesivir: is an investigational intravenous drug with broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related betacoronaviruses." Currently, 3 clinical trials are examining the drug's effect on patients with COVID-19. Further, the drug has been used in the US and other countries on an uncontrolled compassionate use basis.

negative study on **l*opinavir/ritonavir***- CDC also note that lopinavir-ritonavir was also tested in a clinical trial in China, but "did not show promise for treatment of hospitalized COVID-19 patients with pneumonia." It is currently involved in a World Health Organization (WHO) study.

https://www.consultant360.com/exclusive/consultant360/primary-care/covid-19-roundup-new-cdc-guidance-idsa-testing-prioritization

The Centers for Disease Control and Prevention (CDC) have created a document detailing the current research into two previously approved drugs (chloroquine and

hydroxychloroquine) and one investigational drug (remdesivir) for us in patients with COVID-19 in the US.[1]

Remdesivir, they wrote, “is an investigational intravenous drug with broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related betacoronaviruses.”

Currently, 3 clinical trials are examining the drug’s effect on patients with COVID-19. Further, the drug has been used in the US and other countries on an uncontrolled compassionate use basis.

Hydroxychloroquine and chloroquine, previously approved treatments that have been used for the treatment of malaria and other inflammatory conditions including rheumatoid arthritis and systemic lupus erythematosus that have been shown to have in-vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses. Hydroxychloroquine has been administered to patients with COVID-19 in the US due to its wide availability.

CDC also note that lopinavir-ritonavir was also tested in a clinical trial in China, but “did not show promise for treatment of hospitalized COVID-19 patients with pneumonia.” It is currently involved in a World Health Organization (WHO) study.

Long-Term Care Guidance

CDC has updated its guidance for preparing long-term care facilities and nursing homes for COVID-19.[2]

Among the recommendations:

- Restrict visitation except for certain compassionate care situations.
- Restrict volunteer and non-essential healthcare personnel.
- Cancel group activities and communal dining.
- Implement screening for fever and respiratory symptoms.

They also offer additional guidance on the evaluation and management of healthcare providers and residents with symptoms of respiratory illness and procedures to follow if COVID-19 is suspected.

FDA Emergency Use Authorization

The US Food and Drug Administration (FDA) issued the first emergency use authorization for a point-of-care COVID-19 diagnostic for the Cepheid Xpert Xpress SARS-CoV-2 test, which provides results “within hours, rather than days like the existing tests,” they wrote.[3]

FDA on NSAIDs

In response to recent reporting that treatment with non-steroidal anti-inflammatory drugs (NSAIDs) could worsen COVID-19, the FDA wrote:

“At this time, FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms. The agency is investigating this issue further and will communicate publicly when more information is available. However, all prescription NSAID labels warn that “the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.”[4]

IDSA: Prioritization of Diagnostic Testing

The Infectious Diseases Society of America has released recommendations on the prioritization of diagnostic testing for COVID-19. The recommendations offer detailed descriptions of potential cases ranked by tier of necessity for testing.[5]

Tier 1: Critically ill patients receiving ICU-level care with unexplained viral pneumonia or respiratory failure, regardless of travel history; any patient with fever or signs of lower respiratory tract illness and close contact with confirmed COVID-19 patients within 14 days or history of travel to regions with sustained community transmission; immunocompromised patients, elderly patients, and those with underlying chronic conditions with fever or signs of lower respiratory tract illness; and those with fever or signs of lower respiratory tract illness who are critical to pandemic response.

Tier 2: Hospitalized patients and long-term care residents with unexplained fever and signs of lower respiratory tract illness.

Tier 3: Outpatient-setting patients meeting CDC’s criteria for influenza testing, including those with diabetes, COPD, congestive heart failure, over the age of 50 years, and immunocompromised patients.

Tier 4: Community surveillance as directed by public health and authorities.

References:

1. https://pharmertoxguy.com/2020/03/19/nsaids-in-covid-19/
2. https://pharmertoxguy.com/2020/03/26/ace-inhibitors-and-arbs-during-covid-19/#more-2577
3. https://www.nejm.org/doi/full/10.1056/NEJMsr2005760?query=RP
4. French study https://www.sciencedirect.com/science/article/pii/S0924857920300996
5. China study http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03#1
6. New China study: https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1
7. https://www.ncbi.nlm.nih.gov/pubmed/15837026

8. Information for Clinicians on Therapeutic Options for COVID-19 Patients. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Updated March 21, 2020. Accessed March 23, 2020.
9. Preparing for COVID-19: Long-term Care Facilities, Nursing Homes. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/prevent-spread-in-long-term-care-facilities.html. Updated March 21, 2020. Accessed March 23, 2020.
10. Coronavirus (COVID-19) Update: FDA Issues first Emergency Use Authorization for Point of Care Diagnostic. News release. US Food and Drug Administration; March 21, 2020. Accessed March 23, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-first-emergency-use-authorization-point-care-diagnostic.
11. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. News release. US Food and Drug Administration; March 19, 2020. Accessed March 23, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19.
12. COVID-19 Prioritization of Diagnostic Testing. News release. Infectious Diseases Society of America; March 17, 2020. Accessed March 23, 2020. https://www.idsociety.org/globalassets/idsa/public-health/covid-19-prioritization-of-dx-testing.pdf.