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## COVID-19, colleagues, confusion, and conversations

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## REFLECTION ON CLINICAL DECISION SCIENCE: COVID-19, colleagues, confusion, and conversations

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We were on the inpatient medicine team during the last week of March 2020 when the first COVID-19 patient was admitted to our hospital. We were eyewitnesses and literally the front-line doctors to respond to the crisis and chaos as the healthcare system went through convulsive changes in a matter of days, turning an entire floor of the hospital into a COVID service. We believe Clinical Decision Science is advanced by sharing our thoughts, experiences, and emotions related to meeting that challenge.

The world was watching this deadly virus rip through China, Iran, South Korea, Japan, and Italy. As American physicians, we were taking careful notes about the way the pandemic affected the healthcare system in Italy. They were running out of ventilators, having to make difficult decisions about who received life-saving intervention and who did not.

What was most striking was the exuberant response for doctors to “do something,” a challenge we readily accepted in an effort to replace our feelings of helplessness. One of our first COVID-19 patients was a 60 y/o woman who presented to the ED in respiratory distress; she ended up requiring intubation, developing multi-organ failure, and passing away despite our best efforts. She spent most of her hospitalization without her husband by her side because of the strict visitor restrictions at our hospital. Another was a 54 y/o athletic man who we discharged, only for him to return to the ED with worsening respiratory distress once again. Experiences like these made us desperately desire an answer in order to feel empowered to fight back. Most doctors were prescribing Azithromycin, hydroxychloroquine, and zinc, though the evidence for these medications was limited due to the novelty of this disease. There were no clinical trials in humans, merely speculation and theories from laboratory models.

Our hospital had no access to antiviral drugs; however, we did receive a supply of hydroxychloroquine for use during the pandemic. We debated the use of hydroxychloroquine during that whole week. We have been admonished to consider BOTH the risk of harm and risk of benefit of prescribing, compared to the risk of harm and risk of benefit of not prescribing.

In this scenario, the potential benefit was that hydroxychloroquine might help prevent progression of disease into ARDS requiring intubation and ventilator support. This, in theory, would reduce mortality for the patient treated. The less obvious potential benefit was that reduction in the number of patients on ventilators optimizes our healthcare workforce, inadvertently reducing mortality by decreasing the strain on the system. Unfortunately for us, there was no high-quality evidence to support either of these potential benefits; the benefits remained speculative. We reviewed one non-peer reviewed pre-publication report out of France that showed decreased viral shedding at 6 days after treatment with azithromycin and hydroxychloroquine.<sup>1</sup> However, there were many problems with this study: it was not randomized, not published or peer-reviewed, and the sample size was small, only 36 including both the treatment and control groups. But it did point us toward a treatment option for a disease that previously had none. At that time in history, the only other clinical research we had was another retrospective study from China.<sup>2</sup> This study was the origin of prognostic labs that we routinely ordered to guide our decision making.

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The most obvious potential harm of hydroxychloroquine was cardiac arrhythmia by prolonged QTc. Hydroxychloroquine is not a new drug, so its side effects are well known. The problem with this potential side effect is that we were also using other drugs that could prolong QTc, such as Azithromycin and Ondansetron. Combined, this risk was amplified. To reduce this risk, we obtained a baseline EKG and one 48 hours after starting hydroxychloroquine.

One of the (rarely realized) roles of the physician in the US is the responsibility for allocation of healthcare resources. Many people with diseases like RA and SLE take hydroxychloroquine for control of symptoms, a practice that is evidence-based. Another potential harm of prescribing this hydroxychloroquine to so many people having COVID-19 is that we could potentially clear the market of hydroxychloroquine so that people with RA and SLE could not find their medication at the pharmacy. We heard media reports that this was actually the case.

In our hospital, patients were admitted from the Emergency Department (ED) on Ceftriaxone and Azithromycin for community acquired pneumonia and a pending swab for COVID-19 (which took about 24 hours to result at the time). During this 24-hour period, we assessed in what direction the patient was heading based on oxygen requirement. For patients testing positive for COVID, we would discontinue their Ceftriaxone, and start Zinc. Then we had to decide whether to use hydroxychloroquine. This decision was discussed in depth by the team, along with the pros and cons described above.

One physician said if he was hospitalized with COVID-19 and was declining, he would want this unproven treatment. Another physician said they used it regularly in China and South Korea and it seemed to work. He went on to cite the per capita use of hydroxychloroquine in high mortality countries compared to low mortality countries, specifically South Korea. This argument was met with opposition from another physician who said that doing something just because someone else did it is “what lemmings do.” Using our critical appraisal skills, we realized that attempting to make this comparison was flawed because of confounding. South Korea also used aggressive identification and contact tracing for COVID-19, which undoubtedly had a much greater effect than anything having to do with hydroxychloroquine. Yet another physician on our team began referring to the combination of Azithromycin, Zinc, and Hydroxychloroquine as “all the good stuff,” despite any real evidence for that claim. Referring to this regimen as such further entrenched our team in the belief that what we were doing was helping.

After these discussions, we decided together as a team to assess the patient’s risk of progressing to ARDS. If they were requiring the same amount or more oxygen at 24 hours than at initial presentation, we decided that we would start them on hydroxychloroquine because it was really the only therapeutic option we had. For patients requiring less oxygen at 24 hours than at initial presentation, we decided to not start them on hydroxychloroquine.

As we started using hydroxychloroquine, our health system started requiring an infectious disease consult to make sure this medication was used appropriately (see increased demand above). After discussion with the ID specialist, he had a favorable view of hydroxychloroquine because of the potential benefit supported by the French study and the fact that we were given some hydroxychloroquine to use. He went on to prescribe it on all hospitalized patients that our primary team consulted him on. We began choosing which patients to refer to Infectious Disease.

As the week progressed, another study abstract came out of China.<sup>3</sup> It had the same flaw as the French study in that the number of participants was small – this time only 20 - but it was better in that it was peer-reviewed and published. This study showed no benefit from hydroxychloroquine. This study was discussed by our team, but because of the lack of other therapeutic options and there still being potential benefit, this study did not alter our practice.

Another attending pointed out that many doctors had strong opinions about what to do; the problem was that the opinions contradicted each other. This doctor said that because of the lack of evidence, the overriding value that should drive our behavior is to support the team leader who was bearing the brunt of the logistical, political, and care-giving burden. In fact, acting as a unified team, being willing to discuss a question that had no answer had more value in that moment than being technically correct. This mutual support among physicians allowed us to care for our patients and care for ourselves. Being aware of how we make decisions and behave as doctors is the goal of Clinical Decision Science. This pandemic allowed us a glimpse of how physicians have had to make decisions during the major pandemics of history. As we write this, we are awaiting the first quality clinical trials that will guide us when we are next called upon to provide care for COVID-19 patients.



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