PHARMACY TO DOSE
THE CRITICAL CARE PODCAST

Research Principles for COVID-19

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When you read a new research article how do you interpret and analyze the publication?

- What is the question being addressed?
  - This is the key aspect of study design
  - "The question is: 'What is the question?'"
    - If you have a clear question, finding the right answer for a study design becomes much easier
  - For questions trying to determine the effectiveness of a treatment, it is essential to have a control group
    - It is generally impossible to create conclusions (effectiveness or lack thereof) from a study without a control group
      - The only time this might be okay would be if the mortality is near 100% (parachute use when jumping out of an airplane)
        - Most treatments we use don't have large effects

- What is the sample size?

- How well were the methods described?
  - Do you have a good idea of what they did?
  - Can you replicate what they did?
  - If they didn't describe it in their methods, assume they didn't do it
    - If they put a lot of thought into their study design, that will likely be reflected in the Methods section

- General issues with study result analysis
  - Need pre-specified data analysis
    - Look for evidence from this
    - More common for studies to be pre-registered (all types of studies) for pre-specified data analysis
      - Reduces the potential for "cherry picking" data
    - Post-hoc analysis has the potential to report a random finding

- Deciding in advance what is the primary outcome
- What time point will we measure and make a comparison?
- How will we analyze it? What statistical test will be used?

Why do you think we are seeing and reading more single-center, single-arm research without concurrent control groups right now rather than our gold standard multicenter double-blind randomized controlled trial?

- Everyone is motivated to find answers
- The deluge of data may be poor, but everyone has a sense of urgency
- Many journals have gotten caught up in the urgency as well
  - Low quality research being published in high impact journals
- Some believe that some data is better than no data
  - This may not be the case
  - Bad data may be worse than no data
- Science is hard and it certainly doesn't care about our urgency
- We don't know the full implications of this early research yet
  - But there will likely be long-term effects both positive and negative

Why doesn't in vitro efficacy always translate to in vivo efficacy/safety?

- In vitro – in the test tube
  - Data that came from an artificial environment, outside of the organism
- In vivo – in the organism
  - Includes both animal and human studies
- Once you establish in vitro efficacy the question is whether that will translate to in vivo efficacy
- The factors that determine this question are related to PK/PD principles
  - How is the drug delivered?
    - What dose? What duration? To whom?
    - Will this dosing regimen achieve an effective concentration at the site of action?
- In vitro data gives no information on if it will actually get to the site of action and if it's safe
  - Example: Ivermectin for COVID-19
- Unfortunately, in vitro data does not always translate to in vivo efficacy

Using the HCQ+AZ for COVID-19 article as an example, what are the risks of applying information from a non-blinded, non-randomized study?

- 42 patients non-randomized patients
- 26 patients treated with Hydroxychloroquine (HCQ) compared to 16 patients not treated with HCQ
    - 6 patients in the HCQ group also received Azithromycin (AZ)
    - This group had the pronounced treatment effect

- Random Component of Error in a Study
- Small studies tend to be underpowered, more likely to miss an effect
    - Only powered to find large effect sizes (most are small to moderate)
- Small studies also have more random error (both false positive & false negative)
    - Observed effect = (sum of true effect) + (random error)
- A smaller study is more likely to underestimate the true effect and more likely to overestimate the true magnitude of benefit
- Even if the results reflect the true effect, the magnitude of benefit is likely an overestimation
    - Assuming everything else with the study was done perfectly

- Systematic Sources of Error
- Confounders
    - Differences in the risk for the study outcome at baseline
    - Compare baseline characteristics
        - Are the groups similar?
    - This is the only benefit that randomization provides, reduces confounding
    - Observational studies have no randomization, so assume there is likely confounding present
        - We don't give treatments at random
    - The HCQ+AZ article doesn't describe baseline characteristics of the 2 groups

- Selection bias
    - How were patients included in the analysis population?
    - Likelihood of being included in the study is related to both treatment and outcome

        - Treated patients were systematically more or less likely to be included in the study based on their outcome risk
    - This can distort the treatment effect estimates
        - A red flag is when inclusion criteria applied after study time 0
        - "For patients to be included in the study, need a minimum of 5 days follow-up"
            - This exclusion criteria is a set-up for selection bias
    - This study included treated patients with 6 days of follow-up with no discussion as to why
        - Out of 26 patients, 6 HCQ patients were dropped out because they didn't have 6 days of follow-up
            - 5 patients dropped out because their disease worsened
            - 1 patient dropped out because of side effects
    - Systematic exclusion of patients in the treatment arm, based on their outcome.
        - We don't know if this invalidates the findings, but it does make these results uninterpretable
            - The study doesn't add useful information.

- Information bias/Measurement error
    - How accurately/clearly the exposure of interest and the study outcome is defined
        - Did they define exposure? Define the doses used? Duration? Frequency?
        - Need good thorough outcome definitions

How much should we be concerned about publication bias during this deluge of COVID-19 research that we are experiencing?

- Studies that have positive results tend to be published more often than studies with negative results
- Is this risk different now than what it has been historically?
- We use p-values and statistical tests to test hypotheses
    - Threshold used is 0.05 – willing to accept a 5% rate of false positive
        - These false positives are more likely to be published
- How can we deal with publication bias? Not a simple answer
    - Solution would be to publish every single research study ever

- For now, have a higher level of suspicion when reading results that may seem too good to be true

Can we take anything away from patient outcome-focused studies that have a percent of included patients still hospitalized in the ICU?

- Classic example of: "The question is: 'What is the question?'"
- If the question is the effect of a treatment on 28-d mortality and only 10% of patients have 28-d follow-up. Your study does not address the question of interest.
    - If you don't clearly specify that question in your mind, you have a study with indeterminate results
        - Ask yourself: What is a relevant outcome? Does the study have adequate information to address this outcome?

What should be the primary outcome for COVID-19 trials in an ideal world?

- Patient-oriented clinical outcomes that we care about
    - Depends on the patient population as well
        - Ambulatory care patients will differ from critically ill patients
- The most meaningful outcomes are typically the most difficult to study
    - This leads us to try to use surrogate outcomes
    - Only put value in surrogate outcomes if it reliably predicts the ultimate outcome we care about
- We put a premium on fast and first rather than being right and that is unfortunate

Are we able to apply evidence from research studies with international patients to patients here in the US?

- In general, the answer is likely yes but there are things to consider and assuming those don't create major issues
    - Are there plausible reasons why the effect observed in international populations might not be observed in US patients?
        - Genetic variations in metabolism that affects the dose response?
        - Differences in the natural history of the disease that may vary across the populations
        - Differences in the way the therapy is implemented
            - Doses, timing, frequency

Is there any risk of using experimental drug therapy?

- Weigh risk v. benefit
- This is where clinicians are well equipped to think and analyze this
    - The benefit should plausibly outweigh the risk to justify using this experimental drug treatment

- HCQ and AZ can cause life-threatening arrhythmias
    - What is the risk of this occurring with HCQ+AZ?
        - Combination risk may be higher than either drug alone
    - Incidence is likely fairly low, but still a major risk
- Should we use this combination at all?
    - We don't even know if it works and it has a rare but major ADE
- Depends ultimately on the risk v. benefit
    - Benefit may outweigh the risk in the ICU, but risks may outweigh the potential benefits in an outpatient setting

Do you think the COVID-19 coronavirus will affect research that is enrolling concurrently or planning on doing that in the near future?

- It is having a large effect
- Many centers have halted research that requires anything but an electronic data set due to COVID-19
    - Many researchers have taken a pause from the issue/question they've devoted years of their life to and shifted gears
- Progress in other disease states may be slowed down for awhile

What advice would you give to practitioners looking to create their own COVID-19 research protocol at their institution?

- If you're starting to design COVID-19 research, don't worry about being first because there are many other trials that have started enrolling patients
- Now is the time to focus on creating high-quality research rather than being fast
- Come up with a clear research question
- Single-center v. Multi-center depends on the outcome of interest

What terms should be red flags when reading research, especially as it relates to COVID-19?

- Small studies tend to both underestimate and overestimate the effect in even the most perfectly designed small study
- Lack of control groups
- How were patients selected for study inclusion?
    - To be included: patients needed a minimum amount of follow-up