Pursuing Evidence Ethically for COVID-19

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Outline

The need for research
Beyond “research ethics” to ethical research
Communication ethics
Case 1: Ivermectin
Case 2: Hydroxychloroquine
Case 3: Remdesivir
Seeking wisdom in the weeds
Uncertainty Abounds

“There are currently no antiviral drugs with proven clinical efficacy, nor are there vaccines for its prevention, and these efforts are hampered by limited knowledge of the molecular details of SARS-CoV-2 infection.”


What should policy-makers do?
What should clinicians recommend?
What should we all do?

Ethical Imperative for Research

“Conducting research is linked to ‘a moral obligation to learn as much as possible, as quickly as possible’. … research – implemented as policy and practice – can save lives.”

Pursing Evidence involves
Conducting Research and
Communicating Results and
Critically appraising Reports

Research Ethics or Ethical Research?

O'Mathúna DP. The dual imperative in disaster research ethics. In: *SAGE Handbook of Qualitative Research Ethics*, eds. Iphofen R, Tolich M. 2018; 441-454. fuld.nursing.osu.edu
What Sort of Research … in a Crisis?

“In critical situations, large randomized controlled trials are not always feasible or ethical, and critically ill patients may need to be treated empirically during times of uncertainty. Hence, small sample sizes, unvalidated end points, non-random allocation, and blinding “may be acceptable.”

“But with speed borne of desperation comes risk and confusion—of trials too small to yield answers, of treatments overhyped, and of uncertainty about how to design the best studies possible.”


Couzin-Frankel J. *Science* 16 June 2020 doi:10.1126/science.abd3588

“Qualitative and quantitative evidence may both contribute to understanding an intervention or practice and ultimately what works” (3-5).

“We have to do our best science to make sure that we answer the questions as definitively as possible.”

Different questions require different methods.

Flexibility where appropriate.

Couzin-Frankel J. *Science* 16 June 2020 doi:10.1126/science.abd3588
Balancing Ethical Priorities

If overly cautious: clinical development will be impeded or delayed, and leave more patients without treatments for longer.

If insufficiently cautious: patients will be exposed to unknown risks and resources will be diverted to ineffective treatments or more reasonable options.

“In both cases, misestimation threatens the integrity of the scientific enterprise, because it frustrates prudent allocation of research resources.”


Racing for Results

“There are no winners in these races if harm—even though unintentional—is wrought by the dissemination of hurried, incomplete, biased misinformation.”


Good communication “has intrinsic value” as transparency promotes “respect for persons and communities” (6-13).

http://nap.edu/25650
Case 1: Ivermectin

Antiparasitic; FDA-approved orally for parasitic worms; topically for headlice and rosacea; animal use; 2.5 billion doses – excellent safety record
Caly L, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research 2020;178:104787. But… at 10x the FDA-approved dose, it was not effective in vitro. Effective at 50-100x peak plasma conc after usual human dose. Inhibits in lab single-stranded RNA viruses, e.g. dengue, Zika, yellow fever.

In vitro study triggers widespread use in Latin America → shortages
10 April: FDA warns about using veterinary products
6 April: SSRN preprint based on Surgisphere database: ivermectin strongly associated with improved survival of COVID-19 patients on ventilators: 7.7% death rate (n=52) v. 18.6% not receiving ivermectin (n=1,900)
20 April, version 2: 704 case-control analysis: 1.4% v. 8.5%

Ethical Dilemmas

Peru’s Health Minister didn’t have time “to wait for scientific evidence.”
South American tropical medicine expert: “what do you do? … Give them water?”

May 8: Ivermectin added to COVID-19 clinical guidelines in Peru
May 12: in Bolivia; later Brazil, Chile

Consequences

Veterinary formulations led to adverse effects, e.g.:
Doctors pressured by patients to give them ivermectin.
RCTs more challenging, especially with placebos.
Eventually:
“I think people have lost faith in science… and it has been very, very bad for us in Latin America” (Patricia Garcia, Peruvian global health researcher).

A Deeper Dive

Carlos Chaccour: Venezuelan physician and researcher; worked in the Amazon and with Ivermectin for 12 years: “It was so weird.”

<table>
<thead>
<tr>
<th>Surgisphere paper</th>
<th>Reality</th>
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<tbody>
<tr>
<td>52 patients on ivermectin</td>
<td>Ivermectin not widely known</td>
</tr>
<tr>
<td>3 patients on ventilators in Africa</td>
<td>Only 2 COVID-19 cases known in African (3rd identified later) – none serious</td>
</tr>
<tr>
<td>Death rate among US ventilator patients: 2%</td>
<td>Most African hospitals didn’t have the electronic systems Surgisphere used</td>
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</tbody>
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Systematic Review

Antimicrobial, antiviral, anti-cancer “wonder drug.”

50 years of widespread *in vitro* activity against many viruses “has not been reproduced in mouse infection models … and has not been clinically proven either.”

- pharmacokinetics and safety

Heidary F, Gharebaghi R. *Journal of Antibiotics* 12 June 2020 10.1038/s41429-020-0336-z

[fuld.nursing.osu.edu](http://fuld.nursing.osu.edu)
Case 2: Hydroxychloroquine and Chloroquine

FDA-approved to treat or prevent malaria. HCQ approved for autoimmune conditions like lupus, rheumatoid arthritis. Emergency use authorization for hospitalized COVID-19 patients.

The French Connection

20 March: 42 patients, open-label, non-randomized study
PI Didier Raoult: “dictatorship of the methodologists”
Presidential involvement and public support
460,000 sign French petition for access: former Minister for Health; infectious disease expert, Prof Christian Perronne: refused to do RCTs because a placebo was “unethical” for a fatal disease. Uses HCQ widely.
Convoluted Controversy

1 May: *NEJM* study: Surgisphere database: 8910 patients in 169 hospitals in 11 countries; heart patients have higher risk of death


22 May: *Lancet* hydroxychloroquine study: 96,000 Surgisphere pts in 1200 hospitals; HCQ increased risk of heart problems and deaths


23 May: WHO halted hydroxychloroquine arm of Solidarity trial; 131 other trials registered, and many halted.

“Its findings, to many, seemed definitive.”


However...

More Australia data than there were patients – correction in *Lancet*.
Desai: “The real question here is, with data like this, do we even need a randomised control trial?” Bigger questions
2019: from medical textbook publisher to data analytics and AI.
Media investigation: no Australian hospital knew Surgisphere.
   - How did the hospitals have time to de-identify patient data?
   - How was the data being uploaded and synced?
   - Data on race reported for countries where not collected
June 4: *NEJM* and *Lancet* articles retracted.
Ongoing questions about Desai’s career

Communication Ethics

“It is incumbent upon the publisher, editors, authors, and readers to ensure that the highest standards of scientific scholarship are upheld.”


“Rushing publication, if there are mistakes, will ultimately undermine public trust in science.”

Bauchner et al. *JAMA* 26 June 2020;

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Back on the Roller Coaster

The New York Times

Malaria Drug Helps Virus Patients Improve, in Small Study


A group of moderately ill people were given hydroxychloroquine, which appeared to ease their symptoms quickly, but more research is needed.

By Denise Grady April 1, 2020

“It’s going to send a ripple of excitement out through the treating community,” said Dr. William Schaffner, an infectious disease expert at Vanderbilt University.

Trial Registration and Protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Pre-print Report</th>
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<tbody>
<tr>
<td>Patients</td>
<td>Over 18 years</td>
</tr>
<tr>
<td>Groups</td>
<td>2 groups of 31 (200 mg bid; standard care). No power analysis</td>
</tr>
<tr>
<td>Blinding</td>
<td>No placebo mentioned</td>
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<tr>
<td>Randomization</td>
<td>“a computer-generated list stratified by site”</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Time to recovery of body temp or cough, or to severe illness; chest CT comparisons</td>
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Single Trials vs. Accumulating Evidence

27 May: Meta-analysis of 24 small studies: very weak & conflicting evidence

5 June: RECOVERY trial: 11,000 patients, 175 UK hospitals, RCT with 6 drug arms + placebo: Based on 4674 in HCQ or placebo:
“These data convincingly rule out any meaningful mortality benefit.”

8 June: Postexposure prophylaxis (PEP) studies in Minnesota and Barcelona: no benefit

17 June: WHO stops hydroxychloroquine arm of Solidarity trial

17 June: FDA revokes emergency use authorization

18 June: observational study, 1446 NY patients

20 June: NIH stops large ORCID RCT: no benefit, no harm

Clinical Ethics and Evidence

“Given the toll of COVID-19, the pressure to do something is enormous and understandable… As health care providers, we should inform patients about the evidence behind experimental therapies, work to enrol patients in randomized clinical trials, and consider the needs of patients without COVID-19 who may be effected by drug shortages… Although we may be tempted to bypass enduring principles in this time of uncertainty and fear, the best way to protect patients is to stay grounded in evidence and to fight misinformation.”

These drugs have already been used by “hundreds of thousands of patients, but with scant evidence about the risks and benefits.”
Isn’t something better than nothing?

Chloroquine recommendation: 600 mg twice daily x 10 days = high-dose arm (13 g total)
Compared with 450 mg twice on Day 1, then once daily x 4 days = low-dose arm (2.7 g total)
Placebo viewed as unethical: compassionate use and media pressure
Planned sample size: 440; after 81 patients, study stopped:
  High-dose: lethality, 39.0%; QTc adverse effect, 18.9%
  Low-dose: lethality, 15.0%; QTc adverse effect, 11.1%
Mortality rate: not lower compared to historical cases


Case 3:
Remdesivir

In vitro and animal studies showed potential.

ACTT-1: randomized, double-blind, placebo trial of IV remdesivir in adults hospitalized with COVID-19 with respiratory problems

60 trial sites in 10 countries

After 1063 participants, data & safety monitoring board stopped trial

Changed primary outcome: recovery: 15 days, placebo; 11, remdesivir

Trend to lower mortality: 11.9% placebo; 7.1% remdesivir

Those on ventilators: no benefit.

"Conducting such a clinical trial only a few months after SARS-CoV-2 was discovered is an extraordinary achievement."


Ethical Issues

Usual RCT ethical issues with severely ill patients.
Also, resource allocation issues when little drug was available.
Tiered access based on symptoms and drug availability.
Criteria changed with changing evidence (e.g. 5 versus 10 day treatment)

“Solidarity” clinical trial for COVID-19 treatments

Coordinated by the World Health Organization (WHO)
Adaptive trial design: random allocation to 1 of 5 groups; patients and clinicians blinded; doses, drugs, groups, etc. can be adapted based on accumulating evidence reviewed by independent DSMB.
4 treatment arms: Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir, Lopinavir/Ritonavir + Interferon beta-1a
3 June: >3,500 patients at 400 hospitals in 35 countries with over 100 countries interested in becoming involved.
In 60 countries, WHO assists with IRB, training, ship drugs
17 June: Hydroxychloroquine arm ended


Ethics Conclusions

Transparency: patients should be informed if interventions are unapproved, uncertain, experimental, etc.
Rigor: controlled studies are needed to answer effectiveness questions.
Flexibility: what can be changed?
Honesty: data should be collected and disseminated accurately.
Diligence: all reports must be appraised carefully, including peer-reviewed ones, but especially pre-prints, press releases, and other media.
Assess harm broadly: from hoarding & diverting drugs to issues of trust.
Justice and fairness: disparities, allocation decisions, global implications.
Humility: keep to the facts, acknowledging limitations, and admitting that if we don’t know, we don’t know.
Thank you

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