Prospective Systematic Data Collection in Early COVID-19 Patients: A Protocol for Individualized Treatment and Outcomes Research

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ABSTRACT

Human infection caused by the SARS-CoV-2 virus (COVID-19) is a new pandemic disease with devastating effects worldwide. There is no scientifically proved effective prophylaxis or treatment in the early phase of the disease. To prevent harm, In parallel with the running of randomized controlled trials, there is room for developing prospective systematic data collection studies correlating therapeutic measures with safety and effectiveness outcomes, on the assumption that a medical practice is effective if it produces more good than harm. The protocol aims to provide doctors with information on reduction of harm in early COVID-19 patients by different and individualized strategies for treating them, including comparison with no treatment strategies. Besides laboratory confirmation of COVID-19, the evaluation of the clinical status is done with an individualized symptom score for each patient, self-perception of overall severity of disease, clinical improvement ordinal scale developed for WHO clinical studies on COVID-19 and doctors´ global impression on clinical prognosis at the first consultation and evolution at the closing. It respects the autonomy and preferences of doctors and patients to decide the best options for treatment in uncertain situations and allows the gathering of useful information for future more rigorous clinical trials, trying to link science, ethics, and personal clinical experience. A case report form was developed that could easily be built in free software platforms as well as dedicated platforms. All data are anonymized and could be analyzed by descriptive and inferential statistics.

Keywords: COVID-19; Treatment outcome; Data Collection; Pharmaceutical Preparations; Outcome Assessment, Health Care

INTRODUCTION

"Medicine is a *science* of uncertainty **and** an *art* of probability" according to a famous quote by William Osler, considered for many the father of modern medicine and of bedside teaching. Medicine as a *science* tries to discover useful generalizations in order to apply its product for other similar people while as and *art* is guided by personalized care and human needs consideration.

The implications of this dissonance can be seen in the evaluation of pharmacological treatments for humans. It has been characterized by a *tension* between the implementation of strategies based on *biomedical* models - emphasizing efficacy, statistical significance, internal validity and group analysis - and the use of strategies based on *biopsychosocial* (or humanistic) models that favor effectiveness, clinical relevance, external validity and the analysis of individual results[1],[2] In one hand, medical researchers want to know the e*fficacy* of the drug, which refers to the extent in which a specific intervention, procedure, regime or service produces a benefit under *ideal conditions*. On the other hand, *effectiveness* indicates the point in which they produce what is expected for a certain population when used under *routine circumstances*[3]. It is usually accepted that efficacy is determined through randomized clinical trials, while effectiveness

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requires a larger variety of strategies, including observational studies (cohorts, case-controls), and even randomized studies comparing different treatments in real operational settings where consultation is provided[4].

Medicine and physicians face daily decisions that require maximum certainty in settings with permanent uncertainties. This uncertainty has immutable roots, the most important being the nature of Human Beings: **at the same time** every person is *equal* by law, *similar* to each other in various aspects although completely *unique* and different from all other people. Besides this, doctors as professionals have diverse background, values and experiences that could lead to different decisions for the same situation, given the rapid changes in knowledge and technology environment surrounding their practice. COVID-19 constitutes a good example of this changing patterns as new information is being incorporated over time in an ambience of growing politicization of technical decisions on health, to be guided by unbiased science and ethical standards.

Evidence-Based Medicine (EBM) considers study design a decisive factor for judging the scientific validity of conclusions. In therapeutics, randomized clinical trials (RCT) or systematic reviews of RCT were top choice until September 2000, when individualized randomized studies (n-of-1) were also included as top of the rank, in terms of validity[5]. This was decided by the leaders of the EBM after a clear awareness that RCT, despite their strong internal validity, presents insufficient external validity or low generalization capacity for other patients that doesn´t meet the stringent and highly selective inclusion and exclusion criteria in RCT, thus lacking applicability in many cases. Clinical applicability is an attribute considered more important by those who practice medicine and need to apply the knowledge to each particular patient. A year before, concerned about clinical outcomes that could modify the practice in primary care, and after analyzing 8,085 research papers in primary care published by 85 medical journals in 6 months, a group of MBE enthusiasts came to the conclusion that only 2.6% of the papers addressed *Patient Oriented Evidence that Matters* (POEMs), 50% of these being published by 10 medical journals[6].

RCT are sometimes unnecessary, inappropriate, impossible or inadequate. For COVID-19 it would not be reasonable and proportionate to require RCT to substantiate treatment decisions soon after its onset. The indiscriminate acceptance of RCT as a guideline for minimally acceptable conclusions in therapeutic efficacy has led institutions that are responsible for boosting medical research and medical journal editors to consider only this study category, denying the potential scientific value of rigorously conducted observational studies[7]. In pandemics such as COVID-19, prospective systematic documentation of a cohort of patients and correlation of relevant clinical outcomes, obtained after the use (or not) of concurrent therapeutic procedures, could be a cheap and easier opportunity to get reliable data in order to decide which are the best candidates to RCT, in case they are still needed.

THE PROPOSAL

The prospective data collection and evaluation of significant clinical outcomes, after interventions prescribed by large number of doctors under normal circumstances, is a viable strategy to get good quality and large amount of information on the effects of different pharmacologic and non-pharmacologic interventions in suspected or confirmed patients of COVID-19. The proposal must be oriented towards the benefit of patients and the improvement of health care in a collective perspective, open to different and concurrent medically driven interventions and be assessed by rigorous and simple scales and clinimetric tools for measuring clinical outcomes[8].

The main assumptions of the proposal are:
i.   Human Beings are at the same time similar to other and different from all other people
ii. A medical practice is effective if it produces more good than harm
iii. Physicians have the right to decide on the best treatment to patients under their responsibility and, in situations of high uncertainty, shouldn´t abdicate of their legitimate and legal right to take this decision. They should take decisions, after informed consent of their patients, according to their own values, knowledge and experience
iv. First try simple things to do less (or no) harm later
v.   For patients, doing something under medical supervision is better than nothing, notably if what is being done is safe, simple, cheap and has clinical plausibility
vi. For some physicians it is better something doubtful than nothing (skeptical empiricism) and for others it is better nothing than something doubtful (therapeutic nihilism): in both cases the accountability remains the same and the patient deserves a careful follow-up and documentation of the case

vii.   There is no better and exclusive study design to be accepted as evidence in highly uncertain and urgent situations such as COVID-19: observational and experimental studies could contribute, at their own pace and time, to better explain and take adequate clinical decisions exclusively in the best interests of patients.

Ethics

The protocol was designed to comply with ethical requirements needed for research in pandemics, as recommended by WHO and World Medical Association. An informed consent and authorization term for use of drugs not approved for COVID-19, as well as for the use of symptomatic medications or no-medicine at all according to individualized physician´s decision, with a clause on the anonymized use of clinical information gathered from the personal care, should be obtained by physicians for collection of data. It obeys WHO orientations for *off-label* drug prescription in patients with COVID-19 outside clinical trials, since there is no proven effective treatment and it will be well documented[9]. It is also aligned with the paragraph 37 of the Declaration of Helsinki which recommends that "the physician may use an unproven intervention if in his judgment it offers hope of saving life, restoring health or relieving suffering", adding that this new information "must be recorded and, where appropriate, made publicly available"[10]. It is focused on the respect for the autonomy of doctors and patients, taking advantage of all potentially useful and available therapeutic procedures that could be effective for suspected or confirmed patients with early COVID-19 diagnosis.

Outcomes

The main outcomes will include: (1) change in total score of individualized COVID-19 symptoms; (2): Clinical improvement assessed by WHO clinical progression scale for COVID-19[11] and patient´s self-perception overall severity of disease; (3) Number and seriousness of adverse effects; (4) Proportion of hospitalized patients, particularly for those considered to be at high risk in the first consultation; (5) time to symptoms resolution and return to regular activities after adoption (or not) of medical interventions and (6) Initial favorable response time of the organism after starting the treatment.

Clinical protocol elements

Each clinical protocol shall be structured taking into account the following criteria: simplicity, feasibility and methodological quality. It may contain a minimum number of mandatory elements, and others could be added according to local conditions and viability. It shall be built with the purpose of improving the clinical art, aligned with the conceptual framework of *Clinimetrics* as proposed by Feinstein[12]. The following chart summarizes the foregoing elements as well as an example of the suggested scales for COVID-19 assessment:

Area	Mandatory items	Example of assessment scales
Admission of patients	- Clinical and epidemiological information with laboratory confirmed COVID-19 (RT-PCR) - Onset of symptoms	
Recording of clinical information	-Comorbidities -Degree of severity for each symptom - Use of other medicines for treating previous health problems	
Treatment	-Description of all medicines in use as well as non-pharmacological interventions -Dosage regimen -Minimum period of time for patient follow-up	
Evaluation of therapeutic outcomes	-Measurement of clinical progression -Changes in Individualized symptom score -Description of adverse effects and complications	

INDIVIDUALIZED SYMPTOM SCORE FOR EARLY COVID-19 PATIENTS

Current signs and symptoms : Identify, in the box next to each symptom, its intensity in the patient using **0** if it is absent, **1** if it is mild, **2** if it is moderate and **3** if it is severe, calculating the score at the end.

A (general)	Grade	**B** (local)	Grade	**C** (local and other)	Grade
☐ Fatigue		☐ Headache		☐ Nausea or Vomiting	
☐ Fever		☐Conjunctivitis		☐ Abdominal pain	
☐ Myalgia		☐ Rhynorrhoea		☐ Diarrhoea	
☐ Chill		☐ Sore throat		☐ Other (specify)	
☐ Ageusia		☐ Cough			
☐ Anosmia		☐ Dyspnoea			
TOTAL SCORE (A+B+C) =					

WHO CLINICAL PROGRESSION SCALE FOR COVID-19

Patient state	Descriptor
Uninfected	No viral RNA detected
Ambulatory mild disease	Asymptomatic, viral RNA detected
Ambulatory mild disease	Symptomatic, independent
Ambulatory mild disease	Symptomatic, needs assistance
Hospitalized moderate disease	No oxygen therapy
Hospitalized moderate disease	Oxygen by mask or nasal prongs
Hospitalized severe disease	Non-invasive ventilation or high-flow oxygen
Hospitalized severe disease	Intubation and mechanical ventilation, pO2/FiO2 _150 or SpO2/FiO2 _200
Hospitalized severe disease	Mechanical ventilation pO2/FIO2 <150 (SpO2/FiO2 <200) or vasopressors
Hospitalized severe disease	Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO
Dead	Dead

ECMO=extracorporeal membrane oxygenation. FiO2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO2=partial pressure of oxygen. SpO2=oxygen saturation. **If hospitalised for isolation only, record status as for ambulatory patient.

GLOBAL SELF-PERCEPTION SCALE ON SEVERITY FOR COVID-19

Globally, how ill does THE PATIENT feel (s)he is NOW?

Extremely ill		A little ill
Seriously ill		A little bit ill, almost cured
Very ill		Disease-free, cured, back to normal
Moderately ill		

Analysis of data

Observational studies may be approached from an exploratory data analysis perspective[13]. Data description strategies should be performed comprehensively, through graphs and charts, or applying influence analysis or sensitivity analysis[14,15]. Data gathering will inform most used pharmacological or non-pharmacological interventions, their associated (or not) use, dosage regimen, adverse effects and clinical complications. From an exploratory perspective (hypotheses generation), preliminary associations between main outcomes for each package of medical interventions would be useful to search for most effective treatment strategies as well as to identifying possible adverse effects related to it. Other information such as presence of specific comorbidities, age or sex could be correlated with outcomes to propose clinical prognostic scales, as well as the occurrence of eventual side effects derived from the interaction of concomitant use of other medicines with COVID-19 interventions.

DISCUSSION

Science is a social, cumulative, and complex activity, to be done with maximal transparency and strict honesty. Respect for Human Beings is the only absolute principle of moral life, to be daily exercised by physicians in clinical practice and research. Good and useful medical science begins with careful observation of facts by physicians and continues with rigorous documentation, unprejudiced interpretation of data and honest conclusions, for better clinical decisions. In a JAMA editorial commenting a publication of a halted clinical trial done in Brazil in which a group of critically ill COVID-19 patients used an extravagant 20g of chloroquine diphosphate for 10 consecutive days, it was stated that "science poorly conducted or poorly reported is counter to the public interest"[16]. No one would disagree with this, although a nuclear and common attribute to both medical science and medical art is **ethics**, and in particular the virtue of *prudence*. *Ars Medica* (AM) can be expressed in the equation $\mathbf{AM = E\ [EBM+ (E_x\ BM)^2]}$ where E is Ethics and E_x BM is Experience Based Medicine[17]. Without Ethics there is no good medicine or even medicine at all.

COVID-19 is a disease with wide clinical presentation and uncertain prognosis where there is no efficacious treatment or preventive measures. To treat any viral disease, physicians should consider two general strategies: to increase the defense power of the organism and to inhibit the aggression power of the virus, mainly by stopping or reducing its replication. It appears that only the last is being object of focus in COVID-19 pandemics with a search for effective pharmacological interventions. With the same intention of doing not more harm than good, some doctors and health authorities advocate that, in the early stage, no treatment is often the best treatment and patients should stay quiet at home until the development of more severe symptoms, albeit others argue on the importance of empirical treatment and close observation of its outcomes in order to prevent later 'cytokine storm' and the need of hospitalization and admission to intensive care units. Given the short time since the pandemics started, both sides don´t have sufficient and robust empirical or experimental findings to support their beliefs or opinions.

However, even if the drugs prescribed as *off label* in the early phase of COVID-19 are later proved in RCT to have no specific effects against SARS-CoV-2 virus, the prescriber could argue that it was used after informed consent of patients and documentation of its outcomes, incorporating the contribution of context effects from the doctor-patient relationship which could be linked to better therapeutic effects. In fact, when explaining the reasons for prescribing the medicine and getting the consent of patients for use of the medicine (and of his data for documentation), physicians could also explore preferences of patients and discuss non-pharmacologic treatments[18]. A recent systematic review concluded that there are convincing effects on objective and subjective health outcomes from doctor-patient communication in clinical practice[19]. On the other side, if these drugs show later to be effective in rigorous studies, it could be argued in judicial courts, against health authorities or physicians that prohibited or didn´t made available the drugs, the right to obtain damages for a heightened risk of death or injury. Medicine is not Mathematics, patients are not numbers and emotions must count in order to restoring health to patients or alleviating their suffering.

According to the founders of EBM, the two other tenets of EBM that must be integrated to best research evidence are physician´s clinical expertise and patient values and preferences[20]. By stimulating the use of all procedures that could help patients and respect their preferences in observational studies, such as doctors´ communication and use of empathy with patients for deciding on the best intervention as well as specific educational recommendations (e.g. smoking cessation) and non-pharmacological procedures (such as regular gargling and nasal irrigation to prevent more harm), there is an addition of non-specific placebo effects which could lead to better therapeutic results. This kind of medical

attitude is not usually adopted in RCT for drugs since the main objective is to observe if the drug alone could explain for the results and to reduce as much as possible all possible factors that could affect the outcomes. Only 5 papers in PubMed addressed the role of gargling and nasal irrigation in helping to combat coronavirus invasion in the early phase of COVID-19. It could be an important procedure since nasopharynx or oropharynx are the locus of installation and replication of the virus, and a recent study showed that gargling/nasal irrigation with a hypertonic saline solution made at home reduced in 2 ½ days the duration of coronavirus common cold[21,22]. This simple and cheap procedure, done early, could possibly help to reduce the viral load in patients, thus reducing the burden of disease and possibly its transmissibility rate.

The proposed protocol has several utilities and can be easily modified or adapted by any doctor or health manager interested in using it, being especially suitable for publicly funded healthcare systems such as the Brazilian SUS or the UK NHS. As a data collection of a prospective observational cohort, it could be useful to the early assessment of COVID-19 severity by correlating age of the patient, vital signs (e.g. fever), symptoms, comorbidities and other health indicators with later outcomes, including hospitalization and death. It could also be useful to compare patients who don´t want to use antiviral drugs but only gargling and nasal irrigation while others could use pharmacological interventions (e.g. chloroquine phosphate/hydroxychloroquine, azithromycin, zinc sulphate, ivermectin, nitazoxanide, homeopathic medicines, herbal medicines, Traditional Chinese Medicine) associated or not to non-pharmacological interventions. A more sophisticated prognostic scale using weighed criteria could be developed along the follow-up, helping to more accurately predict the risk of severe COVID-19 from the early phase[23]. A full version of the proposal, with the case report form and informed consent declaration, is available at https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1102394. The electronic google form in English could be accessed at https://forms.gle/B7CFd3Nm4oywk9T49 and in Portuguese it is available at https://forms.gle/Wu9rRJBoh9ZZ22iQA .

It has also some drawbacks related to the compliance of doctors to fulfil the CRF or the electronic form, and in the admission and follow up of all sequentially included patients to reduce bias. It is time consuming, particularly in a pandemic where time is a critical resource for doctors and health professionals. It cannot lead to the conclusion of efficacy for a given procedure, only to the effectiveness of the whole set of adopted procedures. It could be that despite the global effectiveness of the package, a particular drug on it could be a mere placebo. According to Shapiro, "the history of medical treatments is characterized by the introduction of new placebos by successive generations of physicians, often accompanied by vehement and vituperative denunciation of opposing physicians who prefer other placebos". And conclude that "the strong beliefs of physicians, objectively unjustified, suggest that they have been as defensive about their treatments throughout medical history as they are today", mentioning in the sequence some studies that "demonstrate that physicians attribute the use of placebos to other physicians three times as often as they attribute it to themselves"[24]. Patients would be pleased if they are assisted by good doctors in which they trust, and doctors are responsible for the prescription (or not) of a safe and possibly effective medicine to help patients. The prescription (or not) of medicines in early COVID-19 is a medical decision and must be done, given the uncertainty and the need to do more good than harm, without any kind of discrimination.

There is a political and unhealthy debate in Brazil and in other countries on the early use of repurposed drugs in COVID-19 among doctors and health scientists. There is no strong evidence to support the early use of drugs or only staying at home in the initial phase of viral replication. Patients are educated by medical industry and doctors to take some drug when they feel sick, and there is some pressure on this. When taking medical decisions, autonomy and preferences of both patients and physicians must be respected. There is a growing need to individually empower physicians making them again the protagonists in independently building medical science, based in careful and honest experiential learning and rigorous trials. Osler, in his 1905 farewell address to American doctors, preached union between homoeopaths and allopaths by saying "long past the time when a difference of belief in the action of drugs—the most uncertain element in our art!— should be allowed to separate men with the same noble traditions, the same hopes, the same aims and ambitions"[25]. Perhaps this is the right time to practice tolerance, honesty, equanimity and prudence in conducting observational studies and gathering useful data, guided by doctors and public health authorities, to take better informed and less harmful clinical decisions to benefit COVID-19 patients and society as a whole in the early stage of the disease, helping them to quickly restore or protect their health.

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