The COVID-19 pandemic: a stress test for clinical epidemiology

La pandemia di COVID-19: uno stress test per l'epidemiologia clinica

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Football might be a good metaphor for clinical research on COVID-19. Usually people gather in a sport arena to attend a single match and then change arena for a new match. We might have a strong interest in one match and be absolutely disinterested in another match played in another arena, depending on which teams are playing. The same approach is applicable to a research hypothesis. Each study is usually planned to evaluate a single main aim using a specific design, that is the most appropriate arena (e.g., cohort, case-control, randomized trial,…). However, a different approach should also be possible for research, especially when time is limited or a head-to-head comparison is not possible, as if we had to plan a single match with more than two opposing teams.

The precision medicine agenda[1] has shown the need of a new point of view in designing medical studies. The discovery of new biomedical technologies, the availability of the entire human genome, and the knowledge of hundreds of thousands possible targets for therapies have made essential to rapidly test several pathways and treatments in the same patients' population.

This new perspective corresponds to settle in a single arena to attend (or participate in) several matches. The so-called 'master protocols',[2] including umbrella, basket, and platform trials, represent this new kind of arena in the context of research medicine. They were originally proposed in oncology in order to efficiently screen the possible genome targets and to speed up the development and the evaluation of treatments. They can be considered as an engine that can be continuously used to facilitate comparisons of therapies interventions, within several subtypes. All of them are a collection of trials or substudies that share design components and operational aspects for coordinating better than in single trials independently conducted.

Also in the field of infectious diseases, platform trials have been used for evaluating antibiotics targeted to resistant pathogens and multiple therapies for Ebola virus disease.[3]

A platform trial has the objective of studying multiple treatments in the context of a single disease (like several matches in the same arena). These therapies can be added or removed from the study based on a predefined decision algorithm. The methods used involve treatment assignment, commonly controlled patients, and sequential analysis with the possibility to early stop the trial for success or failure.

In my opinion, such a study design would have been an appropriate approach to investigate treatments for the Coronavirus disease (COVID-19).

The pandemic has acted as a stress test for healthcare systems of all countries as well as for the World Health Organization (WHO). At the beginning of January 2020, when the first cases were diagnosed outside China, the main problem was the paucity of information about the virus, its contagiousness, and its lethality.

Every clinician who had to evaluate a diseased patient was challenged by a question that is still with no answer: what is the best treatment?

Many treatments have been proposed (and sometimes cheered as a goal in a football match), and then used for a few months, based on existing knowledge on Coronaviruses, similar cross-species infections, severe acute respiratory syndrome Coronavirus and middle east respiratory syndrome, and on the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) genome.

At the beginning, the standard approach was based on the use of any type of supportive care, including oxygen supplementation, thrombosis prevention, nutrition. Then, hydroxychloroquine, an old and cheap antimalarial medication, also used for rheumatoid arthritis and systemic lupus erythematosus, was proposed as the holy grail. Patients were treated with it and the Italian Medicines Agency (AIFA), after a few weeks, allowed its off-label use without the usually needed therapeutic plan.[4] General practitioners (GPs) and patients themselves decided to use it also in non-hospitalised patients and even some influential political leaders suggested its use for both treatment and prevention. For a few weeks, the use of hydroxychloroquine was concomitant with that of azithromycin, entailing increased risk of cardiac side effects (such as the QT interval prolongation and possible ventricular arrhythmia).

Almost at the same time, some anti-HIV drugs were proposed, the association of lopinavir and ritonavir or cobicistat, protease inhibitors, but only for in-hospital use.

The use of these drugs was intense, but shorter than that of hydroxychloroquine and, after some weeks, it was suspended.[5]

After these, a monoclonal antibody (tocilizumab) and another anti-HIV drug (a nucleoside analogue, remdesivir) were introduced, thinking that their mechanism of action against IL-6 and cytokine release syndrome, respectively, could be beneficial also when these pathways are triggered by a viral sepsis.

In the first months, steroids were avoided in the clinical practice except for severe cases as a rescue therapy, but their use increased with time.

The heparins were another medication often used, in March and April, in Italy, for the supposedly increased risk of thrombotic events due to the COVID-19. For this rea-

son, several GPs started prescribing it also before a confirmed infection.
All these treatments were rapidly included in the ongoing therapy of infected patients in order to reduce viral mortality (with an off-label indication to use), but lack of evidence of their clinical efficacy lead to remove them from the therapeutic schemes, except for steroids and remdesivr, in some cases.[6]
In this situation, the question on the best treatment that every clinician is most interested in has not yet found a useful answer. To now, a generally approved treatment for COVID-19 is still under investigation, and no guidelines have been released by WHO[7] or the Centers for Diseases Control and Prevention (CDCs).[8]
Indeed, the SARS-CoV-2 pandemic seems to be paradigmatic for the application of platform trials in evaluating all therapeutic possibilities suggested in the different stages of the pandemic. However, to now, results from similar study designs are not available, and all the on-line registered platform trials are held in countries lately affected by the virus. On the website of United States of America National Library of Medicine clinical trials,[9] by the end of August 2020, only three platform trials were registered and are currently recruiting patients: the multicenter American I-SPY COVID-19 (added at the end of July), REMAP-CAP, held in Australia and New Zealand, and the British TACTIC-R. Two additional registered American platform trials on the use of anti-thrombotic agents, heparins, and direct activated factor X inhibitor are not recruiting yet (last website check on 23 August).
Siemieniuk and colleagues have recently used a different method, a network metanalysis,[6] for investigating treatments for COVID-19 infection.[10]
Network metanalyses are used when head-to-head comparisons of different treatments are not available, like for COVID-19.
They selected twenty-three randomized trials out of a large international literature published on this topic in a few months, designed to evaluate several different outcomes (e.g., mortality, adverse events, hospital and intensive care unit stay, viral clearance, etcetera. See figure 2 in Siemieniuk et al).[6]
Unfortunately, also this study yields only a not completely useful answer. At the beginning of the pandemic, steroids seemed to increase mortality, but now they seem to be helpful in reducing it as well as the need of mechanical ventilation. In addition, remdesivir might be able to reduce hospital length-of-stay.
Although methodologically strong and with ongoing updates planned, these results remain not very useful for bedside management of new cases by leaving unanswered the issue about their treatment and its timing.
As now, a second wave seems to be likely during the Fall, along with the flu session.
The first countries affected by the SARS-CoV-2 pandemic are already involved in a new increase of infected cases and such a scenario seems plausible also for other countries.
In Italy, the first pandemic storm started in February, with the first local cases notified.[11] In a few weeks, the number of cases exponentially increased until the second part of April (about 108,000 currently infected cases) and, at the beginning of March, it forced the government to lockdown the county. Despite this large and early involvement, no definitive answers are available in Italian studies and platform trials are not planned.
The pandemic in Italy has been and is a huge epidemiological and public health stress test. In the worst days, several studies were published, most of which were designed without the possibility of a fruitful connection among different consultants, missing the possibility of a productive collaboration.
It seems evident that there was a lack of preparedness not only from the point of view of clinical care, partially understandable for such a tragic event, but also for research.
For an effective answer, a network of different consultants, with appropriate infrastructures already dedicated and capable of rapid activation would have been necessary. As we now know so well, during the first weeks and, maybe, months of a pandemic, the healthcare system is overwhelmed by urgent measures and it is impossible to plan and conduct appropriate medical research if the system is not prepared.

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