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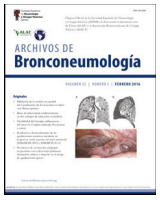

Editorial

Medicine in Dire Straits: Balancing Science and Art

La medicina en situaciones desesperadas: buscando el equilibrio entre ciencia y arte

Bertrand Russell, the great philosopher, has said "science is what we know and philosophy is what we don't know". Science is certainly about facts. On the other hand, philosophy may be about what we don't know but it certainly requires education and formulation of hypotheses, axioms and theories based on reason, intuition and education. Medicine is somewhere between science and philosophy. It certainly requires evidence-based facts and guidelines. But we need to diagnose and treat patients even when we don't have all the facts and even when we don't have all the studies. We also need to diagnose and treat patients with complex or rare diseases and patients with multimorbidities and often, our actions need to be swift. So medicine should be evidence-based but it also requires sound medical thinking, understanding the mechanisms of disease, of physiology and immune responses, understanding the actions, interactions and side effects of medications and importantly, understanding the patient. In the end, medical decisions and actions often require improvising and medical thinking, in the absence of strong or even weak evidence, and this is especially true at times like the present, during this pandemic where we started from no knowledge at all but need for urgent action as we had to deal with a communicable disease that was spreading fast and was lethal.

At first all we could think of doing was (a) prevent the spread by public health measures, personal protective equipment and lockdowns, and (b) provide respiratory support for sick patients. Relatively quickly, the first theories for pharmaceutical treatment started emerging. No studies were available but the need to treat the patients was pressing and unquestionable and researchers and clinicians were in constant discussions and exchange of ideas. In many countries, new protocols for treating COVID-19 patients were instituted across hospitals, information spreading by word of mouth. Soon, journals started getting bombarded by thousands of articles on prognostic markers and on possible therapeutic agents and protocols. There were of course no randomized studies, nor time to design, approve, properly run and analyze them: such studies and results take months or even years and already within the first two months of the pandemic in Europe, thousands of patients were dying daily. And this was soon also true about the USA and across the world.

So, in an era of evidence based-medicine how can we cope with an emergency? How do we treat patients in unchartered territory? What can help us do the best for our patients, prevent deaths and also avoid litigation which seems to be a growing problem worldwide?

In order to produce good quality guidelines,[1] and nowadays this is synonymous to using PICO (patient, intervention, comparison, outcomes) questions and GRADE methodology,[2] a full literature search has to be performed using appropriate key words, all titles and then relevant abstracts are scanned for content and then the irrelevant ones are discarded and the full texts of all relevant ones are appraised. The quality of the evidence is graded and so is the strength of any recommendation. Needless to say that many studies are simply lacking because studies are very expensive, therefore, the majority of the studies are driven by the industry. This is not bad but it is focused on medications that the industry wants to test, usually newer, patented and more expensive ones. And sometimes the information doesn't really provide clinicians with sound clinical advice, either because the evidence is lacking or because differences that may be statistically significant are clinically insignificant. So, even in the normal course of things, guidelines are based on the information of available studies and their appraisal by experts – physicians, researchers and methodologists and nowadays patients too.

Many Societies are trying to improve the clinical relevance of guidelines: the American College of Chest Physicians (CHEST) recognizes that clinicians often seek guidance for important problems for which insufficient research prevents the establishment of fully formalized evidence-based guidelines. In such cases, CHEST has established a hybrid process that includes evidence-based recommendations developed by the GRADE methodology in combination with a Delphi process for consensus achievement resulting in trustworthy consensus statements.[3] In the European Respiratory Society, we discussed the issues of Clinical Practice Guidelines (CGP) and also decided that we would continue to follow the GRADE methodology however, in situations where relevant clinical questions have not been addressed in randomized trials or cannot be formulated as PICO questions, a summary of the best available evidence can well justify a recommendation without a full systematic appraisal of the evidence.[4,5] Such recommendations should also consider factors such as acceptability, availability, feasibility and equity and describe anticipated benefits or harms beyond study results, drug pharmacological properties and intervention characteristics. The aim is to help the clinician make the best decisions quickly and effectively, while keeping the high quality and evidence-based nature of the CPG. In any case,

whether PICO or non-PICO methodology is used, the Evidence to Decision (EtD) framework must be used to clearly and transparently document the kind of information that has been used in order to establish the recommendation.[6] These are lengthy processes.

And we come back to the issues we face during the pandemic. During the first days and months, there can be no robust evidence or randomized studies, let alone guidelines. So how can we help our seriously ill and dying patients? A host of medications have been tested, based on a hypothesis or other, from antibiotics and antivirals to anti-inflammatory medications, anticoagulants and monoclonal antibodies, with an emphasis on immunomodulatory agents.[7] Some have shown benefit, some have not. In Greece, we started admitting COVID patients in late February 2020 and by March, our hospital was a fully COVID hospital. We prescribed chloroquine and azithromycin as it was the only widely used protocol at the time but, some patients could not receive these medications as they had abnormal liver function and G6PD deficiency. Luckily for us, we were not flooded with patients and we did have time to think. We saw the CT scans and X-rays getting worse by the day, we saw inflammatory markers skyrocket and we thought, how can we reverse this course, what have we used in the past to prevent hyperinflammatory responses and pneumonitis-like reactions? Well, we have used steroids. So we tried steroids at a relatively high dose (methylprednisolone 125 mg/day) in six quite ill patients and they all recovered. We thought this was information worth sharing, as patients were dying in thousands. We also thought this was worth testing at a larger scale, the medication is cheap, well known, extensively used and available worldwide. So we wrote a short report and tried to publish it. We got rejected twice, because journals were flooded and ours was a very small study. Fair enough. But among the comments we got back was that we used "such potentially dangerous therapy". We are not advocates of steroids in general but they are used in organizing pneumonia and in many life-threatening immune diseases and exacerbations and they have saved lives. In our short report we said that we did not use them indiscriminately, we had always used them after the first week of symptoms when the viral load seems to have done its course and we did have good results. And we certainly did not advise to use steroids as a guideline. We finally got our report accepted in June[8]. It may not have been proven by large randomized studies. Nevertheless, in unchartered waters, we need to be able to consider solutions, monitoring responses every step of the way. The RECOVERY study has proven that dexamethasone works in a properly conducted study. Perhaps now we need to test other steroid preparations and higher doses too, such as those used in rheumatology, for the severe hyperinflammatory patients. Of course we should try other medications too, provided there is a rational hypothesis, the use is approved by a central or local scientific and ethics committee and, if the medications we try to test are accessible and equitable, even better. Importantly, when designing a study, the exact criteria and timing of the intervention should be clear otherwise it is near impossible to provide safe conclusions, make comparisons or perform metanalyses.

What we should probably not do is do nothing until guidelines become available. What we should probably not do is use medications indiscriminately, without proper reasoning and without close monitoring. Perhaps the best way to act is to use logic and previous knowledge, discuss and establish protocols within hospitals but also in primary care, be meticulous in our follow up and be ready to respond to our patients' needs.

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