



SPECIAL ARTICLE

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**Hospital pharmacist challenges in evaluation of scientific evidence and its incorporation to pharmacotherapeutic protocols through therapeutic committees in COVID-19 times**

Retos del farmacéutico de hospital en la evaluación de la evidencia científica y su incorporación a los protocolos farmacoterapéuticos a través de las comisiones en tiempos de COVID-19

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**Abstract**

Type 2 coronavirus pandemics that is plaguing almost all the world has caused qualitative and quantitative strains in health systems that have had to be responded to. The lack of known vaccines and effective treatments has generated the need to use drugs with very little evidence for their incorporation into pharmacotherapeutic protocols agreed by the clinical team. The hospital pharmacist, within the multidisciplinary team, has been responsible for critically evaluating the alternatives and positioning them in these protocols.

Finally, some ethical and legal questions that should be considered in this scenario are analyzed in this article.

**Resumen**

La pandemia por coronavirus tipo 2 que está azotando prácticamente todo el mundo ha provocado en los sistemas sanitarios tensiones cualitativas y cuantitativas a las que ha habido que dar respuesta. La inexistencia de vacunas y de tratamientos eficaces conocidos ha generado la necesidad de utilizar fármacos con muy escasa evidencia para su incorporación en protocolos farmacoterapéuticos consensuados por el equipo clínico. El farmacéutico de hospital, dentro del equipo multidisciplinar, ha sido en muchas ocasiones el responsable de evaluar críticamente las alternativas para su posicionamiento en estos protocolos.

Se analizan en el presente artículo algunas cuestiones éticas y legales que deben ser consideradas en este escenario.

**KEYWORDS**

COVID-19; Clinical practice guideline; Evidence based practice; Hospital pharmacist; Multidisciplinary team; Ethical issues.

**PALABRAS CLAVE**

COVID-19; Protocolos clínicos; Práctica basada en la evidencia; Farmacéutico de hospital; Equipo multidisciplinar; Aspectos éticos.



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## Introduction: challenges and objectives

When the first cases of acute respiratory disease secondary to coronavirus infection were reported in December 2019, healthcare professionals discovered that this was a different outbreak from the previous ones of severe acute respiratory syndrome (SARS) and Middle-East respiratory syndrome (MERS).

The syndrome was named SARS after type 2 coronavirus, also referred to as COVID-19 (COroNaVirus Disease of year 2019). As the epidemic rapidly spread, healthcare centers and professionals adapted under great strain to a new disease with completely different epidemiological characteristics that made avian and swine flu look like an anecdote.

Hospital pharmacy also adapted to the new situation and had to reinvent itself in some areas of competence, as described in other articles included in this issue. The evaluation of drugs prior to inclusion to pharmacotherapeutic protocols was our most critical area of responsibility. The aim of this article is to provide an insight into this essential task of hospital pharmacists.

## Developed strategy

### Protocolization: objectives and challenges

The Institute of Medicine (IOM) defines clinical practice guidelines as recommendations aimed at the optimization of patient care after a review of the literature and a risk/benefit analysis of the different therapeutic options have been performed<sup>2</sup>. In relation to therapeutic protocols, clinical guidelines are intended to promote the use of effective drugs and discourage the administration of the least cost-effective drugs to reduce mortality, morbidity, and increase the quality of life of patients<sup>3</sup>.

When a protocol is optimized and implemented in an effective way, it contributes to the optimization of clinical outcomes, thereby reducing inconsistencies in clinical practice.

However, the design and incorporation of therapeutic protocols is beset by many challenges, especially in critical situations where the evidence available is changing and scarce. One of these challenges is that protocols contain excess information based on evidence that has not been subjected to an appropriate, thorough, critical review. In addition, protocols may not be implemented in an effective, homogeneous way, or may not be evaluated and updated with sufficient regularity, or updates may not be communicated effectively.

### Protocolization in the trenches

The lack of an effective vaccine and the scarcity of evidence from randomized clinical trials on the potential benefits of a drug on the clinical outcomes of patients with suspected or confirmed COVID-19 infection<sup>4,5</sup>, along with the need for a treatment, make the critical review of the literature and the application of evidence-based medicine a major challenge, and of protocolization a global need.

From the very first moment, international entities such as the World Health Organization (WHO) or the International Pharmaceutical Federation (FIP) issued therapeutic protocols for the management of the infection<sup>6,7</sup>. These protocols are mainly based on the use of drugs that demonstrated to be effective in the previous outbreaks of SARS-CoV, occurred in China in 2002, and MERS-CoV, occurred in the Middle East in 2012<sup>8,9</sup>.

In Spain, the Spanish Agency of Medicines and Medical Devices (AEMPS) provided updated information on the treatments available<sup>10</sup> on the "Protocol for the management and treatment of patients with SARS-CoV-2 infection" prepared by the Spanish Ministry of Health. Other technical documents intended for professionals<sup>11</sup> have also been issued based on the contributions of the scientific societies related to each of the areas of knowledge affected.

However, as it occurred in health centers in China<sup>1,12</sup>, clinical committees were created for the preparation of therapeutic protocols based on an evaluation of the scientific evidence available, where regional/national recommendations are adapted to their area of competence. In addition, clinical committees must consider the application of protocols according to the availability of the recommended therapies. Additionally, protocols must include recommendations on the dosage, handling and preparation

conditions, adverse effects, and special cautions, drug-interactions, dose adjustments in subpopulations of patients such as pregnant women, children, elderly patients, patients on dialysis or extracorporeal membrane oxygenation (ECMO), to name a few.

In the light of the increase of severe cases of acute respiratory distress, local protocols included recommendations for the use of potentially effective antiviral agents and immunomodulators. As the number of patients with different symptoms (thromboembolic, cardiac, neurologic, skin events...) increased dramatically, new specialists incorporated to COVID-19 clinical committees for the preparation of protocols, which were extremely dynamic.

On the other hand, the procedures for the requisition of therapeutic agents changed constantly according to their availability. However, the international market was pressured by an overwhelming demand for marketed and expanded-access drugs and requests for use in clinical trials.

Another challenge was the huge demand for care caused by a tsunami of extremely complex critical patients, with very high rates of mortality in our country. This setting forced the prioritization of health resources based on survival criteria, which contravened the ethical principles of healthcare.

This situation has resulted in the search for new therapeutic targets and tools, which were prematurely incorporated to protocols for the mere fact of being tested in a clinical trial, although the treatment regime and outcomes were unknown.

### Bad times for evidence

*"Truth is hardest to find when anything could be the truth"* (S. J. Lec).

The emergence of evidence-based medicine (EBM) in the '70s and '80s was a breakthrough in the paradigm of healthcare and a hallmark in the development of clinical practice and applied clinical research. Although it has been ideologized and questioned in the recent times (probably intentionally), the value of evidence-based practice (EBP) as a boost to the development of knowledge and research on biomedical sciences is unquestionable. Thus, EBP plays a major role in the genesis and development of the so-called "right care", "choosing wisely", and "do not do" initiatives, and the appropriate use of healthcare resources.

For these reasons, it is striking that one of the first victims of the pandemic was the so solidly consolidated EBP (at least its theoretical fundamentals). As soon as the first cases of COVID-19 were reported in Europe (mainly in Spain and Italy), a flood of methodologically-flawed clinical trials of low evidentiary weight rapidly became the global reference for the therapeutical approach to the disease.

It is not exaggerated to say that it was a "flood". A search of articles published on PubMed between January 2019 and January 2020 yielded 720 results vs 6,525 between January 2020 and May 2020. As to clinical research, a recent editorial of *Lancet*<sup>13</sup> questioned the usefulness of so many clinical trials and raised the question of whether it was a good use of resources. We are aware that a large portion of studies are unnecessary<sup>14</sup>, but answering this question is not easy. It is true that replicating studies that largely demonstrate the effectiveness of an intervention is a waste of resources and exposes patients to a study that will contribute little data, which has ethical implications.

But it is not less true that a large proportion of publications provide fake results<sup>15</sup> and replication studies generally yield conflicting or less significant results, as compared to the pivotal study<sup>16</sup> that led to the approval of the new molecules by regulatory agencies.

The sudden outbreak of the CoV-2 pandemic unveiled deficiencies in the management of this unusual type of virus. Few certainties, some *in vitro* studies, and no clinical trials composed the body of knowledge on this virus. The only certainty was that decisions were made in a context of absolute uncertainty. A paradigmatic example is hydroxychloroquine.

Prior to the publication of the pioneer study of Gautret *et al.* on the effectiveness of this drug in combination with azithromycin for COVID-19, the only evidence available was provided by *in vitro* studies where risky dosage recommendations were made<sup>18</sup>. Then, a multiplicity of studies of variable methodological quality (generally in proof version and frequently not subjected to peer-review) were published supporting the use of this agent in clinical practice while warnings about its uncertain effectiveness and potential safety problems were ignored<sup>19</sup>.

We should not forget that we are confronting an infectious agent against which there is no known treatment and the few antiviral therapies available are not effective. This has put a great strain on the social and healthcare system. When evidence is not available, decisions are made on the basis of a critical review of the literature, regardless of the quality of the publications<sup>20</sup>. In this scenario, hospital pharmacists have the skills and capacities to lead decision-making in clinical committees.

We can draw lessons from the pandemic. First, the striking phenomenon of the inverted pyramid of evidence<sup>21</sup>, with the top at the base. The lack of quality studies (mainly randomized, controlled trials) has resulted in therapeutic decisions being made only based on the opinions of experts

Second, this crisis has given rise to numerous examples of doubtful, non-evidence-based clinical practice, which should be avoided in the future, such as the oral administration of zinc or vitamin C megadoses as presumed therapies for COV-2 pneumonia.

A major challenge was managing shortages of some of the drugs used for the diseases, which run out of stock early (muscle relaxants, anesthetics, some biological antirheumatic agents, to name a few). Clinical practice based on the best evidence available first turned into practice based on maximum emergency possible, and then into practice based on the largest stock of drugs available.

Bad times for evidence. When we disguise lies and call them post-truth\* and learn that it was declared Word Of The Year by the Oxford Dictionary<sup>22</sup>, we realize that our paradigm is starting to break up. Only the determinate attitude of professionals can brace the building of evidence-based practice, which was raised with so many efforts.

An example is the recent case of the supposed effectiveness of lactoferrin in the management of COVID-19, which was so irresponsibly promoted by the manufacturer<sup>23</sup> and critically reviewed by hospital pharmacy professionals through different channels and ultimately warned by the General Directorate of Pharmacy and Medical Devices of the Autonomous Community of Valencia (<https://www.efe.com/efe/comunitat-valenciana/economia/sanidad-apercibe-a-sesderma-por-publicitar-un-supuesto-producto-anti-covid/50000882-4242871>).

## Ethical and legal aspects

Our robust health system never found itself in the position of deciding the patients who had or had not to be treated. Something changed in our society when the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care recommended to apply restrictions to the provision of intensive care<sup>24</sup>. A week later, similar recommendations were issued by scientific societies<sup>25,28</sup> and the Ministry of Health<sup>29</sup> of Spain, which was hardly hit by the pandemic. All these documents addressed the ethical conflict of

\*According to Oxford Dictionary ([www.rae.es](http://www.rae.es)), "post-truth" is an adjective defined as 'relating to or denoting circumstances in which objective facts are less influential in shaping public opinion than appeals to emotion and personal belief'.

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providing healthcare services using structural (intensive care beds) or inventory (ventilators, ECMO) resources in a context of scarcity of resources. Only a brief reference is made to medicines in the document of the Ministry of Health<sup>29</sup>, thereby ignoring the relevance of some drugs (muscle relaxants, anesthetics) in critical care. In the light of the recent events, it is necessary that a protocol is established to prioritize the use of some medicines in specific patients based on transparency, consistency, responsibility and proportionality criteria<sup>26,30,31</sup>.

As said above, this pandemic has brought about numerous collateral effects. Thus, this crisis has posed ethical questions that would have been unimaginable only three months ago. However, the implementation of the so-called "new normality" (<https://www.fundeu.es/blog/nueva-normalidad/>) will raise other ethical questions, including immunity passports<sup>32,33</sup> or restrictions on freedom based on the status of vaccination, among others.

From the legal point of view, one of the most relevant issues was the continuous off-label use of medicines or the administration of experimental drugs (remdesivir). In any case, these settings are categorized as "special situations" and are regulated by the widely known Royal Decree 1015/2009<sup>34</sup>. The first case, off-label use, required obtaining written informed consent from the patient, which was hindered by the fact that many patients were isolated or sedated in the case of intubated patients. In these circumstances, oral consent recorded in the medical history of the patient in the presence of a witness is legally valid.

## Lessons learned. Future applicability in pharmacy services

In this context, the COVID-19 pandemic has demonstrated the crucial role of hospital pharmacists in clinical committees, as they contribute their expertise on the critical review and evaluation of medicines.

Before regional or national authorities incorporate changes to general protocols based on the data of a study, it is essential to ensure that the study is methodologically robust and adequately designed to identify the data that may impact therapeutic protocols even before the authorities. We cannot allow ourselves to be deceived by siren songs.

The clinical skills of pharmacists allowed them to communicate the findings of quality studies to multidisciplinary teams after having performed a critical review of their methodological quality and clinical applicability.

The pandemic has demonstrated the versatility of hospital pharmacists and their ability to adapt and do their best in a highly stressing and demanding situation. In a highly demanding setting where numerous scientific studies are published and rapidly disseminated through the social media, among other channels, hospital pharmacists must make an effort to extract the best evidence available to ensure it is incorporated and disseminated through local pharmacotherapeutic protocols. This way the hospital pharmacist will be able to contribute their expertise to clinical committees.

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