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Pandemic analysis and bioethical considerations on early treatment

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Abstract

The global crisis caused by the SARS-CoV-2 virus, responsible for COVID-19, can be interpreted in different ways, including epidemic behavior, waves of impact on health systems and consequences of measures directly or indirectly linked to fighting the pandemic. Thus, the responses to these challenges must be comprehensive, covering the different levels of prevention. As a possible answer, early treatment should not be seen in isolation, but in a context of comprehensive care. This article presents ways to analyze the current crisis and the ethical elements relevant to early treatment.

Keywords: Bioethics. COVID-19. SARS-CoV-2.

Resumo

Análise da pandemia e considerações bioéticas sobre o tratamento precoce

A crise global gerada pelo vírus SARS-CoV-2, responsável pela covid-19, pode ser interpretada de diversas formas, incluindo comportamento epidêmico, ondas de impacto sobre os sistemas de saúde e consequências de medidas direta ou indiretamente ligadas ao enfrentamento da pandemia. Assim, as respostas a esses desafios devem ser integrais, contemplando os diversos níveis de prevenção. Como uma possível resposta, o tratamento precoce não deve ser visto isoladamente, mas num contexto de cuidado integral. Este trabalho apresenta formas de analisar a presente crise e os elementos éticos pertinentes ao tratamento precoce.

Palavras-chave: Bioética. Covid-19. SARS-CoV-2.

Resumen

Análisis de la pandemia y consideraciones bioéticas sobre el tratamiento precoz

La crisis mundial generada por el virus del SARS-CoV-2, responsable de la covid-19, se puede interpretar de varias maneras, incluido el comportamiento epidémico, las olas de impacto en los sistemas de salud y las consecuencias de las medidas directas o indirectamente relacionadas con el enfrentamiento de la pandemia. Por lo tanto, las respuestas a estos desafíos deben ser integrales, considerando los diversos niveles de prevención. Como posible respuesta, el tratamiento temprano no debe ser visto aisladamente, sino en un contexto de atención integral. Este trabajo presenta formas de analizar la crisis actual y los elementos éticos pertinentes al tratamiento precoz.

Palavras clave: Bioética. Covid-19. SARS-CoV-2.

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The global crisis caused by the new coronavirus (SARS-CoV-2) and the public health emergency of national importance (ESPIN) [1] made it necessary to reflect on the various ethical, economic, cultural, scientific, and political aspects involved. One of the elements hugely impacted at political level was the treatment during the viral replication phase, or "early treatment," exemplified in the Informative Note 9/2020-SE/GAB/SE/MS [2] by the Ministry of Health (MS), a document on possible therapeutic regimens for early intervention against COVID-19 used at the time in several private and public health services in Brazil and abroad.

Since then, evidence about the management possibilities in the different phases of the disease and stages of the patient's case severity have grown progressively [3-5]. This article aims to present ways to understand the complex scenario that is observed and to deepen the reflection on the ethical elements relevant to the early treatment of COVID-19.

Understanding the crisis

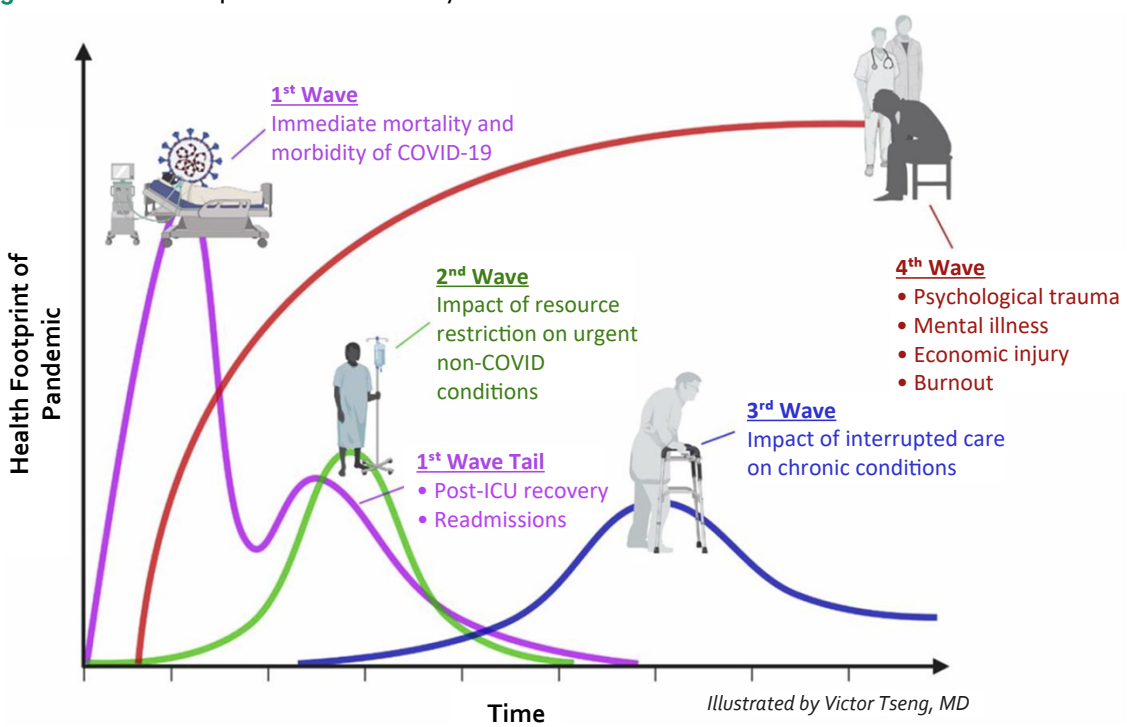
The current scenario can be analyzed by looking into the number of cases or deaths and identifying seasonal patterns reactive to certain behaviors of the population or to prevention measures. Variations in incidence have been called epidemic waves [6,7] and may be linked to several events with more or less strong causal links.

However, additional ways to understand the pandemic exist, based on the natural history of the disease [8], with the objective of not only improving analytical capacity, but also possible responses. These alternative ways range from primary prevention (avoiding illness) to quaternary (avoiding iatrogenic damage) and include comprehensive health care plans.

Waves of impact on the health system

One possibility is to analyze the effects of the pandemic on the health system [9,10], measuring the impact in four large waves (Figure 1).

Figure 1. Waves of impact on the health system



Source: Bourgeault [9].

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The first wave is generated by the impact of the disease itself, which, in its more severe evolution, requires many days of mechanical ventilation, consuming large amounts of oxygen and medication for sedation and muscle relaxation. This creates the constant need to monitor and strengthen the multidisciplinary team in this complex environment.

The second wave is caused by the damming of the normal demand for urgent cases, so that the mobilization of efforts and equipment and the possibility that health professionals get sick and need isolation hinders the care of other patients. Patient themselves, motivated by the fear of falling ill and misguided guidelines, may neglect the treatment of chronic diseases and have acute complications. This wave demands additional human and material resources and can have a huge impact on the already overstretched health care system.

The third wave, caused by chronic complications from COVID-19 itself or from other diseases that have been neglected, can have a long-term economic impact on the health system and families. This is because in many situations, patients demand specialized, multidisciplinary and multiprofessional care that requires high investment. For example, a patient with diabetic retinopathy can progress to blindness if timely care is not provided [11].

Furthermore, chronic diseases and their complications, which are often severe and disabling, can favor the emergence of psychiatric conditions such as anxiety and depression, which characterize the fourth wave, generated by the development of less or more severe psychic alterations.

Neglecting the psychic effect of an epidemic process also causes a great economic impact, increasing absenteeism at work and harming the livelihood of many families. Thus, as waves can occur simultaneously, even if they do not coincide, public health management must respond to the challenge, adapting to the different moments of each wave and its interactions.

Consequentialist interpretation

A third possibility of analysis may derive from the levels of impact of a new technology and the division of power and social facts into three spheres: political, economic, and cultural. It can be called a "consequentialist interpretation of social impact analysis of a pandemic" and has implications for responsible crisis management, by projecting the impact caused by the way society applies technologies and policies in responding to the pandemic.

In this interpretation, the first wave is the direct political impact of a technology, since, to deal with the pandemic, several technologies were researched and norms changed: modification of labor laws to avoid unemployment and bankruptcy; emergency financial aid to families in financial difficulty; changing health care processes; investment in technology transfer and international funds to develop vaccines; increased State interference in citizens' lives to prevent the spread of the disease; and vaccine development through innovative technology platforms. This wave of immediate technological, regulatory, and political impact has an almost instantaneous effect on daily life and State power.

The political sphere of reaction is characterized by a more direct association between cause and effect and, according to Allenby and Sarewitz [12], it can be linked to what has been called level I, which is the direct effect of the intentionality of an act or technology. Many consequences of an administrative act or new technology implemented in society are predictable and can be properly managed. This concern with checking consequences and managing risks is reflected, for example, in policy formulation manuals [13].

This first intervention, however, generates later and less predictable consequences, constrained by the human response and by a constantly changing context. This leads to the second wave of social impact – economic – equivalent to level II or systemic complexity. Thus, the economy suffers the direct effect of the disease itself and the waves on health systems, as well as the expected or unforeseen impact of the actions, technologies and political measures adopted.

The Brazilian industry, for example, had to respond to the need to produce personal protection and hygiene equipment – highly demanded due to new sanitary guidelines and rules for the operation of commercial establishments. As a result, home deliveries intensified and restaurants

reduced their in-person service capacity. If many jobs were lost, others were created in response to new needs.

High consumption rates of certain drugs led to an international increase in the price of pharmaceutical material, hindering purchase processes and impacting regulatory mechanisms for importing in several countries. The purchase of electronic equipment, such as personal computers and laptops, and the development of software for videoconferences greatly escalated because the number of home office workers increased.

Finally, the political and economic components lead to the most unpredictable wave of social impact: the cultural one. Every technological, political, and economic change in society can generate long-term behavioral and even civilizational change. This is level III, the global systemic, which has a diffuse and subtle impact on the perception of the environment and society.

The acceleration in the search for an effective therapeutic solution in this context of political conflict, for example, in the early or late stages of the disease billions can be invested in the search for new solutions or investment in old ones, but also the potential to put in check all the credibility deposited in science. International institutions, such as the World Health Organization (WHO), underwent moments of loss of credibility when they took as reference data of an uncertain nature, which were published and later withdrawn, after extensive technical and scientific questioning [14].

The difficulty in acquiring materials from abroad led countries to review their handling of national strategic issues, such as the capacity to produce active pharmaceutical materials and medical and personal protection equipment. More than an economic change, this can have a profound impact on geopolitics and international relations. Restrictive policies not only devastated countless economic processes, but also altered the perception that many have of the State and its coercive capacity.

The impacts of this third social wave are relatively unpredictable, as the interactions that shape culture are intricate and multifactorial, involving all that can impact society in the long run. This form of analysis gives rise to a reflection on the monitoring of response actions in terms of changes generated in society. It is a call to responsibility.

Sociological and philosophical aspects

The last form of analysis is the approach based on sociological and philosophical aspects [15] and covers three dimensions of the disease. The first is the unidimensional or abstract understanding of the disease, seen as an evolutionary "entity," so that its natural history and interventions at different levels are discussed. The causal agent and its pathological and biochemical processes are studied in depth, so knowledge is accumulated and transformed into an "object of study."

A two-dimensional form of perception would encompass not only the disease, understood as an object of abstract study, but also the human body, the individual. It would, therefore, be the analysis of the interaction between disease and human organism.

A three-dimensional understanding would unite knowledge about the disease and its interaction with the human organism with the fact that it integrates a society with several others and presents a multitude of associations with the environment. There are moral, economic, political, and cultural issues that involve the human organism, healthy or not, and it is in this space that the State specifically intervenes, unlike health professionals.

With tertiary spatialization, disease becomes understood in terms of epidemics. Space and time (...) *come to constitute the conditions for the possibility of the disease to appear. This shift in focus gave rise to a very nascent concept of public health, a health that the state could manage and promote. So, Foucault claims, the most politically important space for the emergence of the clinic shifted from the abstract space of the forms of disease – disease essences – to the political space of society* [16].

Not having addressed other forms of analysis does not mean that they are irrelevant or that only those mentioned are important. Those that offer a set of useful tools for a context assessment were chosen.

Early treatment as a response

Against this challenging backdrop, the efforts of healthcare systems around the world were put to the test. It was necessary to keep the health system functional, so as not to abandon the population, and simultaneously make efforts at all levels of health care and prevention to fight COVID-19. In this context, one of the possible responses is treatment in the viral replication phase of the disease.

Actions must be taken at different levels of prevention for comprehensive patient care. In the case of early treatment or treatment at a later stage of the disease, the role of secondary and tertiary prevention should be noted, which act in the rapid diagnosis and possible treatment of the disease, identifying risks and performing the differential diagnosis to avoid disease worsening, not just from COVID-19 – if possible – but also from other agents. Early treatment, which demonstrates multiple forms and results at different scientific levels of quality, may reduce the risk of progression to severe disease.

The therapy must be adapted if the patient progresses to more severe stages of the disease, including more complex medications and measures to deal with inflammatory and thrombotic elements, which can compromise the prognosis and generate serious sequelae. Appropriate secondary or tertiary prevention enables correct diagnosis and treatment as quickly as possible by several means beyond clinical judgment, such as laboratory and imaging tests.

The therapy, or treatment, which is one of the moments of care, is precisely (...) *the action or set of actions designed to protect, maintain or restore the patient's health. Be it medication, surgery, diet, physiotherapy or of any other nature recommended by health sciences. Two or more of these actions are often combined to achieve better results* [17].

In case of strong suspicion of COVID-19, early treatment can be done immediately through clinical diagnosis, even without laboratory confirmation. The notion of treatment can range from an act contained in the therapeutic relationship between doctor and patient to a more systemic and complex conception, such as that which occurs in the Singular Therapeutic Project, which (...) *is a set of proposals for articulated therapeutic approaches, for an individual or collective subject, result of the collective discussion of an interdisciplinary team, with matrix support if necessary* [18].

The emphasis on early treatment was partly due to the need to review the previous guidance, which led individuals to remain in their homes until the occurrence of dyspnea, a more advanced and potentially lethal condition of COVID-19. Furthermore, the low specificity of the initial symptoms could lead to confusion with other diseases, highlighting the importance of providing care not only for early intervention aimed at COVID-19 and its complications, but also for the possible diagnosis and treatment of other health conditions that, when evolving, could compromise the patient's prognosis. Next, bioethical elements linked to the early treatment of COVID-19 will be discussed.

Information, non-maleficence, and patient safety

Several guidelines were published by private and public entities, such as the Federal Council of Medicine (CFM), which published off-label use of drugs against COVID-19 [19], and the MS, which edited informative notes with relevant data and analysis from the point of view of public administration, providing information capable of qualifying the autonomous exercise of medicine [20]. This should consider the best available evidence, practical professional experience and the values underlying any therapeutic relationship [21].

When dealing with public health elements of enormous impact, an imperative principle is that of non-maleficence, which includes patient safety [22-27]. Thus, the environment of insecurity and conflicting information generated the need to offer minimum safety parameters for therapeutic options that were already in use since the first months of the pandemic.

The safety profile and pharmacokinetic and pharmacodynamic data on widely used drugs such as chloroquine, hydroxychloroquine, dexamethasone, azithromycin, ivermectin and

nitazoxanide have been known for decades. However, side effects and the potential to worsen the condition of an already debilitated patient may occur if misapplied. Thus, the access to information must be ensured so the use of certain drugs is safer, avoiding even greater impacts of the pandemic on the health system.

For decades, certain drugs have been used by thousands of people worldwide, not only for inflammatory conditions, but in some cases also for viral diseases, even if evidence levels were below the maximum – as it also occurs with most of the drug therapies used in medicine [28]. This experience of using medicines aiming at their potential alternative effects reinforces the need and the possibility of disclosing safe doses, as there were similar actions in previous times, such as off-label prescription against the chikungunya virus to reduce the impact of arthritis:

despite the lack of studies comparing the efficacy of methotrexate and hydroxychloroquine in chikungunya, we chose to recommend hydroxychloroquine as the first choice for the treatment of this phase, due to its known anti-inflammatory effects in the control of arthritis and musculoskeletal pain. There is also potential antiviral action, but mainly because it is a safer drug when compared to the use of methotrexate to be prescribed by non-specialists [29].

It is worth emphasizing that the concern with patient safety must always be reinforced by the emphasis on adequate medical care, including anamnesis, physical examination and, according to clinical judgment, complementary exams.

Charity: potential to save lives and reduce impact on the health system

Charity translates into the duty to help others and promote their legitimate interests [26]. Surviving the infection with the least possible impact on physical and mental health and daily activities is what is desired and the sooner and more effective the measure adopted, the better the potential benefit.

Reducing the proportion of infected patients who require hospitalization or, unfortunately, end up dying is an obligation of any therapeutic action to combat COVID-19. Even if primary prevention through immunization (vaccine) or non-drug measures are effective possibilities, the need for rapid diagnosis and treatment remains in patients with the disease, especially if they are on a risk group. Actions at a certain level of prevention do not dispense with or prevent the adoption of different measures at other levels.

Late diagnosis and, consequently, late treatment onset can result in greater systemic involvement by the disease and worse prognosis. Maximizing the individual's chance of survival and promoting their autonomy and quality of life are essential objectives of a therapeutic effort that promotes the patient's good in a systemic way [30-32]. In the current scientific scenario, there is no justification for guiding patients to bear the disease and seeking care only when they present a serious symptom, that is, dyspnea (shortness of breath).

There is no consensus on the treatment, but there are several proposals for drug combinations based on research findings around the world, with different levels of evidence and quality. Therefore, the opportunity for the therapeutic encounter must not be neglected or suppressed.

Thus, in the current context of public health emergency and in view of drug therapies repositioned to COVID-19 and used in safe doses known for decades, there is a technical, ethical, and professional condition to prescribe a therapy in more favorable situations, that is, in the early stages of the disease. This is especially true if this therapeutic option occurs through the manifestation of the patient's autonomy together with the autonomy and clinical judgment of the professional (assisting physician).

In terms of evidence on the benefit of proposed drugs for early treatment, considering the emergency scenario and the risk of death brought to millions of people worldwide, data based on consistent observational studies [33] or clinical trials should not be ignored.

Autonomy: respect for the patient and the health professional

Given the physician's autonomy to practice medicine based on the best available scientific

evidence and ethical precepts focused on the patient's good and professional experience [21], the principle of respect for the patient evokes the possibility of prescribing early treatment, even if a stable protocol is unavailable.

Presenting the possibilities of therapies in use and study is an element of a technically adequate medical consultation. Therefore, given the risk of a patient's death, stating that there is no evidence in favor of early treatment configures an information gap and puts the outcome of medical care at risk, restricting the clarification necessary for a conscious and responsible decision making process by the patient and the physician.

Health care must consider evidence at different levels, valuing the greatest possible benefit to the patient in a context of maximum risk reduction. Thus, being informed about the existing therapeutic possibilities based on the different levels of evidence consists of good medical practice and is an inalienable right of the patient, required for the due respect to human dignity. Neglecting the direct study of scientific literature in the current context may constitute disrespect for the true concept of autonomy and what this implies: the clarification that precedes the therapeutic plan to be adopted and the consent for its application.

The precept of respect for the patient, affirmed in the *Belmont Report* and further formalized by the bioethical principle of autonomy – understood as self-government, free from both controlling interference by others and personal limitations that prevent the expression of choices [26] –, it is an essential element of medical ethics. The physician's freedom to prescribe the therapy they deem appropriate, as long as supported by the patient's acceptance and by the best evidence available at the time of the medical act, is an example of using all possible resources for the patient's good [35].

In fact, the current scenario is extremely complex and problematic in terms of health, science, economics, and politics. However, given the provisional evidence, it is not recommended to arbitrarily prohibit the prescription of drugs in safe doses in the face of a potentially lethal pandemic. On the contrary, respect for one of the most consecrated ethical manifestations of medicine is valued: when proven procedures do not exist or are inefficient, the physician can resort to unproven interventions that, in their judgment, offer the hope of saving life, restoring health or alleviating suffering.

This type of conduct must be followed with expert help and informed consent from the patient or their legal representative. When possible, such interventions should be the subject of research designed to assess safety and efficacy. In all cases, they must be registered and, where appropriate, published [36].

Justice: freedom of conscience and the good of society

Alongside non-maleficence, justice is one of the most prominent principles in the public sphere, oriented towards solving problems with a focus on collective actions [22], which encompass expressions and concepts such as equity, merit, and prerogative. Injustice, on the other hand, is an unfair act or omission that denies people the benefit to which they are entitled or fails to distribute something equitably [26].

Considering the current scenario, early treatment occurs regularly in certain public or private services, but citizens who depend exclusively on the care provided by the Unified Health System (SUS) may be deprived of this possibility by restrictive administrative decisions. Not allowing the prescription and dispensing of such drugs in SUS can violate principles of equity and integrality, resulting in a failure in what is conventionally called distributive justice.

[Which] (...) *refers to a fair, equitable and appropriate distribution within society, determined by justified norms that structure the terms of social cooperation. Its domain includes policies that share various benefits and burdens, such as property, resources, fees, privileges, opportunities, food distribution, legal services, and services as a research subject* [37].

Given the evidence present in an emergency scenario, with a potentially lethal disease and capable of generating a huge impact on the health system [9] and on quality of life, not providing minimally equitable means of assistance, informing, and allowing early treatment for all who wish, can configure injustice.

Responsibility: complex decisions in unprecedented scenarios

Responsibility dictates a need for caution in the face of unprecedented events and potentially irreversible acts. It is a principle that considers the impossibility of fully predicting the results of actions in a context of uncertainty [38,39].

The various forms of early treatment being studied for COVID-19 include drugs that are well known by the therapeutic community, which are not in recent use or are still being studied. In addition, antimalarials and dewormers with potential or effective antiviral action [40] have been used for decades and shown to be safe when administered in adequate doses [41]. Thus, the use of well-known and recommended doses in the early stages of the disease reinforce the responsibility element of early treatment, when the probability of systemic inflammatory damage is still small and the body is more likely to effectively react to the disease effectively.

From the administrative perspective of public health and public health policies, early treatment is not a substantial innovation, as long as it is approached through informative notes, opinions, and manuals. This is one more element that reinforces the principle of responsibility, calling for continuity in terms of administrative action within the scope of the Executive Branch and autarchies, such as the CFM.

Therefore, it is concluded that the risk of consequences is within responsible expectations, considering that: 1) no legal institution has been radically changed; 2) the economy was not significantly impacted by the recommendation – because it is low-cost and off-patent medication –, contrary to what happened with other measures (such as diffuse social isolation or radical restriction to mobility); and 3) there was no impact on the Brazilian administrative publication culture, as similar recommendations were made by the CFM or the MS in similar situations.

Final considerations

Achieving definitive scientific evidence can take time that costs a lot in human lives and cause irreparable damage to society. As a matter of science and humanity, solutions supported by evidence of different levels of trust and quality and that meet the principles listed here may be included in the list of responsible assistance and administrative activities. Therefore, each physician is responsible for justifying the proposed therapy to their patient, according to their professional autonomy, so that suppressing the freedom to seek or provide treatment in the early stages of the disease incurs a strong ethical risk.

The available scientific evidence, even if provisional, is to be noted when considering the potential catastrophic and often fatal clinical evolution of COVID-19. In addition, the uncertainty surrounding the identification of new mutations [42] reinforces the need to safely promote the good of the patient using the available means.

The expectation of patients and professionals to exercise their freedom to rationally receive and prescribe early treatment in no way violates the freedom of others but responds to a potential therapeutic benefit. For this reason, it cannot be supplanted by the distortion of the use of science, used as a pretext for political disputes or purposes adverse to those of medicine. Decontextualized evidence, for example, using high drug dosages applied at late and much more severe moments of the disease [43] are not a parameter to disqualify the responsible and safe therapeutic options applied in the viral replication phase.

With or without maximum proof of the effectiveness of one or more of the various treatment modalities currently in use and research, it should be borne in mind that each situation and phase of the historical evolution of this crisis presents its own context and difficulties. The challenge to the technical, scientific and humanistic capacity of physicians who care for patients with COVID-19 is one of the greatest of our times. Therefore, it is up to each professional, depending on their clinical experience and with respect for their patient, to make the necessary clarifications and to promote the principles, virtues and values that govern medical ethics and favor the patient's good as much as possible.

As new scientific evidence emerges, updated information with ethical and technical-scientific bases should be published by the responsible

bodies, always aiming at the greatest possible good for the population of Brazil. In the greatest health crisis experienced by this generation, the evolution of knowledge and actions must be constant, as well as the respect for the principles that guide good medical practice must be permanent.

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