

## Editorial

# Lessons from a pandemic: “Should we move towards a more comprehensive nephrology practice?”<sup>☆</sup>

## Enseñanzas de una pandemia: «¿Debemos avanzar hacia un ejercicio más integral de la nefrología?»

Eduardo Gutiérrez<sup>a,b</sup>, en representación del Servicio de Nefrología del Hospital Universitario 12 de Octubre

<sup>a</sup> Servicio de Nefrología, Hospital Universitario 12 de Octubre, Madrid, Spain

<sup>b</sup> Instituto de Investigación del Hospital Universitario 12 de Octubre (imas12), Madrid, Spain

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“But, as it is often the case, knowing a lot is too little at the bedside of a sick person.”

«The loneliness of those inside and the pain of those outside, it is terrible».<sup>1</sup>

### Justification

This editorial was born from a need, from the need to capture the reflections and experiences that arose during these difficult months. Months of pain and loss but also a time of a unique opportunity to reevaluate and redefine the prevailing health models. This text attempts to make a simple route that ranges from the definition of the infection, its worldwide impact, the important implications in kidney patients, the possibility of incorporating new diagnostic techniques

to our specialty, a deliberation on techniques of respiratory support, a reflective evaluation on the opportunity of our patients to access to clinical trials and finally make inquiries into history searching for answers and reach final reflections.

### Introduction

Vasili Grossman said that “for a chronically ill person the city has only pharmacies and hospitals, outpatient clinics and committees of medical expertise. For a drunkard, the city is made of half a liter of vodka to share between three. And for a lover, the city is made up of the hands of the street clocks that mark the time of the dates, of the banks in the avenues, of the two kopeck coins for the public telephone”.

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E-mail address: [eduardogutmat90@gmail.com](mailto:eduardogutmat90@gmail.com)

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It is true that from the multiple edges of reality, our gaze only focus on a few of them. However, probably for the first time in the history of many of us, since the end of February our gaze is only able to settle on the pandemic that is devastating us. And this narrow vision has been extended to the entire population. As it is already known to all of us, in the last days of December 2019 in the Wuhan region (Hubei province), at the intersection between the Yangtze and Han rivers, the Chinese authorities informed to the World Health Organization (WHO) several cases of pneumonia of unknown etiology. A week later it was confirmed that the causative agent was a new coronavirus called SARS-CoV-2 (*Severe acute respiratory syndrome coronavirus 2*), received and the disease the name of COVID-19 (*Coronavirus disease 2019*). The disease had predominantly pulmonary manifestations, but as has been described afterwards, the mixture of clinical affectations is significant and complex. The lack of knowledge about its pathophysiology and the orphanhood of treatments have made the practice of medicine a real daily challenge. Our work has been transformed and the first weeks were, as defined by Cunningham et al.<sup>2</sup> in his recent publication, “*The worst days of our careers.*”

## Chronic kidney disease and COVID-19

The first studies have shown that age is one of the essential determinants of the mortality by the infection, with a mean age greater than 55 years in all published series.<sup>3,4</sup> The most frequent comorbidities reported have been arterial hypertension (HTN), diabetes mellitus (DM) and obesity. One of the publications with the largest number of patients collected to date, 5700 patients,<sup>5</sup> concerning to the New York City area, shows an incidence of hypertension of 56.6%, 33.8% of DM and 41.7% obesity in its. In this same series, it is described that 5% had chronic kidney disease (CKD) and 3.5% had end-stage CKD.

It is clear that CKD is a health problem worldwide. CKD affects 10% of the world population, being associated with significant morbidity and mortality and a high burden of health and care.<sup>6,7</sup> CKD has a higher prevalence in the elderly population. Worldwide, nearly 500 million adults have CKD. In Spain, several analyzes have been carried out in recent years, estimating a prevalence of CKD of 15.1%, being more frequent in men (23.1% vs 7.3% in women) and increasing in parallel with the aging of the population (4.8% in the group aged 18–44 years, 17.4% in patients between 45–64 years and 37.3% in those over 65 years). According to data from the latest registry of the Spanish Nephrology Society (SEN), the population on hemodialysis (HD) in Spain over 65 years is 72.1% (38.1%: 65–74 years and 34%: ≥75 years).<sup>8,9</sup>

The percentage of patients older than 65 years of age who receive a kidney transplant has increased substantially in correlation with the aging of donors. The latest data reported by the National Transplant Organization (ONT), 56.4% of donors were 60 years or older, and 8.5% were 80 years or older.<sup>10</sup>

The first data from the registry prepared by the SEN on COVID-19—after an initial analysis of 1765 kidney patients as of August 8th—shows that the highest incidence of infections is limited to outpatients from HD centers (64, 5%) versus only 3.2% on peritoneal dialysis (PD) and only 6 isolated cases on home HD.<sup>11</sup> According to the 2018 Kidney Disease Registry

(REER), 2.8% of the population on renal replacement therapy (RRT) has been infected. In relation According to the RRT modality, the contagion rate was as follows: 4.6% of the total population on HD, 1.8% of the total population on PD, and 1.7% of patients with a kidney transplant.<sup>12</sup> The *United Kingdom Renal Registry* recorded a adjusted rate of infection of 9% in the HD population against 2.9% in DP, and the *Canadian registry (Ontario Renal Network)* shows an incidence of infection three times higher in patients on HD in outpatients centers versus those undergoing home HD.<sup>13</sup>

These results strongly suggest the apparent need to promote policies aimed at increasing both home HD and PD, free of so much interpersonal contact. PD is a widespread and consolidated technique, while HD at home still has a wide margin of development and its extension is necessary in the new scenario we are facing. Some dialysis organizations advocate for appropriate preventive strategies to minimize the risk of infection, preferably in outpatient and home settings. Among them, home dialysis is recommended for as many patients as possible, encouraging the placement of peritoneal catheters and performing vascular access urgently as non-elective surgeries.<sup>14</sup> In North America, there are initiatives to promote home HD (*ESKD Prospective Payment System, Executive Order on Advancing American Kidney Health*). However, a critical analysis must be also performed about the resources required to facilitate its rapid development as well as identify the barriers that must be overcome to achieve these objectives. It should be noted the difficulty in the most disadvantaged social groups to access these techniques.<sup>13,15–20</sup>

Regarding the transplanted population, the registry show that 32% of the patients were transplanted. The mortality described so far in solid organ transplantation, and specifically kidney transplantation, is also very high, with cases described in the first month after transplantation.<sup>21,22</sup> These observations force us to adopt serious and strict security policies when it comes to resuming the normal activity of our kidney transplant lists and probably to carry out profound reforms in the isolation and microbiological care of the recipients, as well as in the most meticulous selection even from potential donors.<sup>23</sup>

The mean age of the patients in the registry (HD, PD and kidney transplantation) was 68 ± 15 years, with two thirds of those infected being males, data that have been reproduced in the different publications referring to both kidney patients and the general population.

From this registry it is extracted that 8.7% of affected kidney patients required admission to intensive care units (ICU), requiring mechanical ventilation in 7 out of 10 cases. However, a significant percentage of patients with criteria of ICU admission (15% [265 patients], probably much higher in some centers), were rejected due to the epidemiological context and the principle of futility. In areas where the wave of the pandemic has been overwhelming, the ability of ICUs to admit patients with acute respiratory distress syndrome (ARDS) has been clearly exceeded and many patients have had to receive maximum supportive treatment, including many cases of non-invasive mechanical ventilation (NIMV), in hospitalization areas together with diverse and desperate therapeutic approaches awaiting improvement or a new opportunity for

invasive respiratory support.<sup>24</sup> This situation should guide us to a deep reflection on how to improve the approach to our patients by the ICUs as well as the treatment of our critical patients in acute or intermediate care units. Recently published data on the preliminary experience in kidney transplant patients in the kidney transplant unit of Columbia University, New York, shows that out of 15 patients analyzed, 4 (27%) were admitted to the ICU.<sup>25</sup> A second study with 36 kidney transplant patients, in the neighborhood of Harlem, New York, confirms the high mortality (28%) of these patients and the significant need for invasive mechanical ventilation (IMV) (39%, with a mortality 64%).<sup>26</sup> Recently published data from our hospital establish that mortality is similar to that described in the different series and short communications (26% overall, 28% in dialysis and 23% in transplantation).<sup>27</sup> It would be interesting to analyze in series from Spain how many transplant patients with bilateral pneumonia and ARDS were candidates for IMV.

In short, the first analyzes point to a high mortality of patients with kidney disease admitted for bilateral pneumonia, as reflected in the SEN registry with figures of 26.1%, figures that with small variations have been confirmed in the different countries. In Spain, in addition to the SEN data, other series have reported mortality rates from 16.2% to 37.5%, with also variable incidences of infections.<sup>28,29</sup> Goicoechea et al.<sup>30</sup> collected an interesting and very well described series of 36 HD patients with a mortality of 30.5%, also showing the predominance of the male gender (54%) and advanced age ( $75 \pm 6$  years). In the general population mortality rates are quite variable: about 2.3% in the first descriptions in Chinese population to 21% in one of the American larger series of patients.<sup>3,5</sup> In the Chinese population registries (*Chinese Center*), age-adjusted mortality was as follows<sup>31</sup>: 50–59 years: 1.3%; 60–69 years: 3.6%; 70–79 years: 8%, and  $\geq 80$  years: 14.8%, while in 5700 patients in New York City the mortality was much higher, as follows: 50–59 years: 10.3%; 60–69 years: 15.8%; 70–79 years: 32.2%; 80–89 years: 54.3%, and  $\geq 90$  years: 52.3%. If in this series a cut-off point is established at 60 years of age, mortality in patients above 60 years would be 32.7%, and in those over 70 years of age this percentage would increase to 42.8%.<sup>5</sup> This entire set of data therefore speaks of high mortality both in the general population and in patients with CKD. However, we are still waiting for new results in large renal registries with adjustments according to age groups.

For all this, and pending new additional data, we must make an effort to find alternatives that allow us to reduce these percentages.

## Respiratory support techniques in nephrology

One of the main limitations for the care of patients in our HD units is our lack of knowledge about the modalities and ventilation techniques. Both NIMV and IMV techniques require long training periods, but just as new interventionist techniques have been incorporated in recent years, it may be time to gradually introduce training in these technique. Training in respiratory techniques is probably complex and may be outside our control, but knowledge of these can help us to better collaborate with other specialties, providing us with knowl-

edge applicable on a day-to-day basis outside the pandemic, especially in services that have units for the care of acute and multi-pathological patients.

In other epidemics due to other coronaviruses, such as MERS-CoV (*Middle East Respiratory Syndrome coronavirus*), the use of NIMV was not associated with a better outcome and 92% of the patients required mechanical ventilation, and for all this it was considered a treatment sterile.<sup>32</sup> In ARDS, early intubation has been associated with a survival benefit over NIMV (especially if  $\text{PaO}_2/\text{FiO}_2 < 150$ ).<sup>33</sup> However, in the SARS epidemic of 2003, in many cases, non-invasive ventilation prevented orotracheal intubation.<sup>34</sup> The FLORANI study also demonstrated that the administration of high flow rates of oxygen with a nasal cannula had a beneficial effect on hypoxemic acute respiratory failure.<sup>35</sup> In SARS-CoV-2 infection no solid information is yet available, but initial data confer a possible benefit to the administration of positive expiratory pressure on the recruitment of atelectasis and the reduction of respiratory effort. In this way, NIMV could have a beneficial effect in a selected group of patients.<sup>36</sup> However, a recent comprehensive study on ICU hospitalized patients concludes that NIMV or high-flow nasal cannula should be reserved only for patients with mild ARDS, since delayed intubation may be associated with higher mortality.<sup>37</sup>

In summary, we consider that the current situation has highlighted the need to assess the incorporation of training in respiratory procedures in our specialty.

While waiting for future epidemics or health crises, and in parallel with the aging of dialysis patients and kidney transplant recipients, we believe that progress should be made towards an even more comprehensive and *invasive approach* to our patients that in circumstances such as those experienced, they are clearly penalized. It is very likely that all nephrologists who have cared for patients affected by this relentless infection have been frustrated for not being able to provide them with techniques that so far are beyond our competence.

## New techniques in the practice of nephrology

Taking advantage of the exposed premise about progress towards a nephrology practice with greater autonomy and interventionism, without ever renouncing what defines or specialty, gradually we should also advance in new exploratory exams, such as basic echocardiography and pulmonary ultrasound. Pulmonary ultrasound, as is already known, has shown a potential benefit in different studies for the adequate adjustment of dry weight and the treatment of HTN in dialysis patients.<sup>38</sup> In turn, the incorporation of telemetry in some of the hospitalized patients in our services would also provide us with a safer *management* of some of our patients, as has been demonstrated in this pandemic through its establishment in some of the main services involved such as the case of pulmonology. Finally, the gradual recovery of continuous extrarenal clearance techniques should be another priority to consider for a more complete and enriching exercise of nephrology.

## Clinical trials and kidney patients

Clinical trials with new antiviral drugs (RNA-dependent viral inhibitors)—probably the only effective treatments to have an impact in the disease—, such as remdesivir have, as one of the fundamental inclusion criteria a glomerular filtration rate greater than 50 ml/min/1,73 m<sup>2</sup>, so many of our patients are once again excluded from this opportunity. Again, there are no consistent studies to establish this cut-off point as an exclusion criterion. As published by Adamsick et al.,<sup>39</sup> the pharmacokinetics of Remdesivir have not been evaluated in patients with impaired renal function. The remdesivir may cause mitochondrial damage in cells of the renal tubular epithelium, but this requires long exposure and generally high doses.

The 10 ongoing trials with faripiravir exclude patients on renal replacement therapy or those with a glomerular filtration rate of less than 20–30 ml/min/1.73 m<sup>2</sup>, depending on the study.<sup>40,41</sup>

All of the above leads us to think that our patients are often deprived of opportunities due to the fact of having kidney failure, being immunosuppressed as they are carriers of a normal functioning kidney transplant. . . which although it is not something new, is more evident in this context and translates into a significant decrease in years of life robbing them of the right to age.

Robust randomized prospective studies are needed. Once the initial anxiety is over, and recognizing the often moving effort to find an effective treatment, we must return to the rigor for which everyday medicine has been distinguished to avoid sterile and erroneous attempts. Doctors must manage uncertainty from the scientific method, from the evidence in search of a principle of clinical equilibrium that prevents conclusions attributable to chance from being considered conceptually valid.<sup>42</sup> Act quickly but without losing your mind.

## What can we learn from history?

History should always serve as a learning point. The XIX century has two important figures such as French Louis Pasteur (1822–1895) and the German Robert Koch (1843–1910), who created laboratory medicine generating the hypothesis that epidemics were due to the action of microorganisms and confirming that each disease is due to a specific pathogen.<sup>43</sup> In a time when it was easier to believe in conspiracies and blame doctors for pandemics, they were able to impose the basic principles of the scientific method. In this sense, it is also fair to highlight the figure of the French-Swiss doctor and bacteriologist Alexandre Yersin, who, after many ventures and efforts, was able to identify the plague bacillus, as it is masterfully recounted in the Patrick Deville novel entitled *Plague & Cholera* and which is introduced with the phrase by Jules Laforgue: «Ah, yes! – to pass into legend On the threshold of the chattering centuries!».

Elisabeth Noelle-Neumann, a German philosopher and political scientist, asserted that “what comes from simplified images of reality is reality as people actually experience it.” Echoing this statement, we consider that the popula-

tion's view of medicine has changed, and it is a good time to demand changes, improvements and reforms for an even more comprehensive practice of nephrology. Epidemics reveal weaknesses in systems and structures. If our medicine has distinguished itself for something, it is for its efficiency (accomplishments according to resources), but this crisis has shown that the seams of the system are cracking because they were already at the limit. Therefore, it is time to claim these changes, as we are in the right scenario with the *wind in our favor*; that is, with the recognition of the population, which has been able to highlight what is really important and value the “men of bronze.”

Being better prepared for the next wave or a future pandemic seems like an inescapable act of responsibility. It is known that it is always easier to see misfortune than injustice in the afflictions of others, since resignation is always more comfortable than responsibility and the search for individual and social guilt. We must fight and reveal ourselves against that accommodating resignation of “things are as they are.” The capacity for moral resistance includes protest and rebellion against the real, as Jean Améry outlined at the end of World War II. We face a world that demands leadership figures of greatness who flee from lukewarmness.

The history of Humanity is largely the history of its epidemics, a history that offers solid teachings that test the historical knowledge of its inhabitants and evaluate whether they are capable of responding wisely.<sup>44</sup>

## Final thoughts

We begin and complete stages like children's notebooks. In order to live, we are always starting over. All in all, there is a difference. In living, everything written conditions what is to be written. In addition, there are sheets that we cannot tear off and notebooks that we cannot close. Hopefully we do not turn the page over without having taken note.

The disease modifies our reality. This has been demonstrated to us by this pandemic. There are many families who have not been able to overcome the pain caused by the loss of their loved ones, they have endured it with even greater stoicism than the setbacks of history, with a strength worth emulating. The hope of being able to change the course of history has always been a burning desire; let us hope that the early and successful discovery of a vaccine marks a milestone in the history of medicine. To all those battered families we dedicate, as a tribute, these words destined to enrich our professional practice.

Grossman's Ivan Grigorievich, after what he had lived through, “saw in that city what he had not seen before, as if his life had moved from one apartment to another. His eyes discovered street markets, police stations, taverns. . . And the world he had known had disappeared into the fourth dimension”.

It is very likely that our world has changed, and therefore the way of doing medicine, and specifically nephrology. However, as long as we do not move our gaze from one floor to another, nothing will have changed.

## Thanks

“But I knew that, nevertheless, this chronicle cannot be the story of the ultimate victory. It cannot be more than the testimony of what it was necessary to do and that without a doubt they should continue to do against terror and its indefatigable weapon, despite their personal tears, all the men who, unable to be saints, refuse to admit the plagues and they strive, nevertheless, to be doctors” [Albert Camus, *The plague*].

There are countless people to whom we must express our gratitude; that of the family is given, but that of the patients is probably the only one that currently forces us to continue in the stormy world of medicine. To the books that aroused our interest in the history of medicine and infectious diseases.

Thanks to my colleagues who allowed us, encouraged and helped us write this editorial. And very special thanks to our colleague and friend Enrique Morales Ruiz, the driving force and continuous encouragement to write these modest words in a time of so much pain for him. Thank you for that generosity that was expressed in generosity.

We hope to continue honoring what we have learned during these two months in our day-to-day professional work, in our performance with patients whom we largely consider our only judges, and to continue waiting for better times to be able to contradict Fernando Savater in his recent words: «Above all I have an unforgettable affection for what is missing, for what has not arrived yet or no longer returns».

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