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Informing clinical decision making during a pandemic — a call for better preparedness

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The COVID-19 pandemic exposed flaws in the ability of the nephrology community to efficiently inform clinical decision making. To improve preparedness for the next pandemic, the nephrology community must work more closely together to ensure that research efforts are aligned and put in place a strategy for the effective dissemination of high-quality evidence in real-time.

The COVID-19 pandemic has dominated medicine for the past two and a half years. Particularly in the early stages of the pandemic, the virulence of SARS-CoV-2 and fear of severe consequences forced an unprecedented urgency in clinical decision making. Patients with kidney disease — particularly those on dialysis and recipients of kidney transplants — were quickly identified as a vulnerable population, prompting tremendous efforts from the nephrology community to gather data with which to inform clinical practice in record time. Nearly three years on from the emergence of SARS-CoV-2, the prognosis of these individuals has improved. Fewer patients with kidney disease are admitted to hospital following SARS-CoV-2 infection and, when admitted, more of them survive. But the extent to which these improved outcomes can be attributed to natural evolutionary changes — for example, in the virulence and pathogenicity of SARS-CoV-2, and/or by the development of acquired immunity after natural infection — or to effective vaccines and treatments is not clear. Thus, when we question whether the process of obtaining information with which to support clinical decision making for our vulnerable patients with kidney disease has been optimal during the pandemic, the answer is a resounding 'no'. Now that the COVID-19 pandemic is reaching a manageable level, we must reflect on the challenges in generating and disseminating high-quality clinical evidence and find ways to be better prepared for when the next pandemic hits.

The studies that were performed throughout the COVID-19 pandemic have provided some important insights into disease epidemiology and outcomes; however, these insights were often incomplete. Early in the pandemic, we learned from observational data that patients on dialysis and recipients of kidney transplants are at particularly high risk of severe COVID-19 (ref. [1]). Following the emergence of vaccines, we learned that humoral and cellular response to vaccination is markedly reduced in recipients of kidney transplants because of their immunosuppressed status[2]. Of note, most of the initial evidence of reduced vaccination efficacy in these individuals was derived from small-scale, uncontrolled studies that involved indirect comparisons to data obtained from the general population. However, the rather uniform results obtained from subsequent studies suggested these findings to be true.

Despite the importance of vaccination in protection against severe COVID-19, barely any studies have investigated approaches to improve vaccine efficacy in recipients of kidney transplants. Despite some suggestion from uncontrolled and underpowered studies that temporary withdrawal of mycophenolate mofetil may improve antibody production after vaccination, the only controlled study to investigate this approach did not support this temporary withdrawal[3]. Information about the ability of vaccination to prevent SARS-COV-2 infection and protect against severe COVID-19 in patients on dialysis and recipients of kidney transplants is also limited. Randomized controlled trials of vaccine efficacy specifically in these populations are lacking. Information about vaccine efficacy in these specific populations cannot even be obtained from subgroup analyses of large randomized control trials performed in the general population, because most trials excluded these patients from enrolling. Some observational data suggest vaccine efficacy[4], but overall the observational data are conflicting: one large-scale observational study suggested that vaccination was not associated with a reduction in the risk of SARS-CoV-2 infection[5].

Lastly, we also lack understanding of the efficacy of treatments in patients with kidney disease who develop COVID-19 despite vaccination. In the early stage of disease, patients can be treated with monoclonal antibodies and antiviral drugs; however, evidence in favour of these treatments comes mainly from trials performed in the prevaccination era. The efficacy, safety and cost-effectiveness of these interventions after multiple rounds of vaccination and in the context of currently circulating strains are not clear. Again, some encouraging observational data exists[6], but the level of evidence is low. The same holds true for treatment options for later stages of COVID-19, particularly for patients with kidney disease who are hospitalized, for whom the efficacy of corticosteroids, IL-6 antagonists and temporary discontinuation of one or more immunosuppressive agents (for recipients of kidney transplants) is unclear.

Challenges

The initial studies that aimed to understand the epidemiology of COVID-19 and identify prevention and/or treatment strategies were largely uncoordinated, single-centre studies that were characterized by small sample sizes and varying study designs[7,8]. Moreover, these studies differed in several key aspects, including their case definition of COVID-19, the definitions and presence of relevant comorbidities and complications, and data collection period. These differences prohibited comparison between studies and added to confusion in the context of contradictory findings, which unfortunately were not uncommon

given the small sample sizes. These reasons also made it impossible to directly combine these studies in systematic reviews or meta-analyses.

Electronic health records — which were frequently used in COVID-19 studies — did not always offer data of sufficient quality, mainly owing to a lack of well-defined health data architecture or complete information on the demographics and clinical characteristics of individuals. Different data (for example, clinical data and vaccination history) are often stored by different agencies, and linkage of these data is frequently not possible owing to privacy regulations. Moreover, clinical data sources are typically limited to event-based populations (for instance, hospitalized individuals) and are therefore not representative of the entire population of interest.

As described earlier, the representation of patients with kidney disease in clinical trials for vaccines and treatment was limited[9], most probably on the basis of concerns that an impaired immune system and reduced renal drug clearance in these patients might alter the efficacy and safety profile of the vaccine and therapeutic agents under investigation. As a result, evidence of the efficacy of vaccines and treatments in this vulnerable group of patients lags behind that of other populations.

The large volume of information — sometimes from quite poor-quality studies — challenged the traditional publication process and consequently the route of dissemination for high-quality evidence[10]. The time lag between evidence generation and translation into actionable clinical advice left room for social media platforms to transmit information in real-time without informed assessment of the evidence, which risked the spread of misinformation, delayed the adoption of effective treatment measures and, ultimately, may have resulted in harm to patients.

Potential solutions

We believe that four actions are particularly necessary to ensure better preparedness for the next pandemic.

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First, a pandemic of a global scale warrants a response of equal proportions. As such, it is necessary that international nephrology bodies, such as the International Society of Nephrology, the European Renal Association and the American Society of Nephrology, take an active lead in formulating and executing the research agenda. These leading nephrology societies should work together to form independent committees for the synthesis and evaluation of evidence. These committees should install working groups that focus on specific aspects of the clinical management of patients with kidney disease — for example, protocols for infection prevention during dialysis treatment and the effect(s) of immunosuppressive treatment in recipients of kidney transplants. These working groups should involve clinicians as well as methodologists, epidemiologists and patient representatives. Members of the various working groups and of the evidence synthesis committee should help to identify and facilitate use of the best datasets and other resources worldwide to address given clinical questions.

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Second, it is necessary to strengthen existing data sources for accessibility and completeness. To this end, relevant stakeholders — including investigators, data protection officers, legal experts, policy makers and society at large — must discuss issues relating to patient data-privacy requirements and informed consent for the use of anonymized data in special circumstances. Especially during a pandemic, policy makers need to recognize that they not only have the important responsibility to ensure a patient's privacy, but also that they have an equal responsibility to ensure that data can be used for the greater public good. In our opinion, a separate set of patient data-privacy guidelines should be developed for situations of public health emergency, bearing in mind the immense clinical response required in such situations. For uniformity and completeness of data, the nephrology community must support efforts to facilitate the development of a common health data architecture that enables health data from different resources to be merged.

Third, nephrological bodies need to engage with global trial investigators and regulatory authorities and actively promote the inclusion of patients with kidney disease in large-scale clinical trials. At the same time, the evidence synthesis committee needs to harness the potential of global collaboration and initiate their own trials to investigate the efficacy and safety of promising medications in patients with kidney disease.

Finally, a central resource (for example, a single website) containing actionable information for clinicians, patients with kidney disease and interested members of the wider community should be developed. Such a resource should be widely publicized and regularly updated by clinical and methodological experts.

Conclusions

Uncoordinated research efforts, difficulties in the ability to access and use data resources, and lack of an effective evidence dissemination strategy posed challenges in informing clinical decision making during the COVID-19 pandemic. To be better prepared for the next pandemic, the nephrology community must work more closely together to ensure that research efforts are organized and well supported with the best available data and a judicious and real-time strategy for the dissemination of evidence to guide decision making.

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Competing interests

The authors declare no competing interests.