



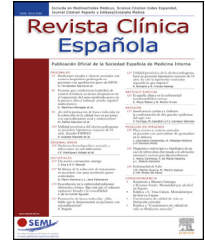
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REVIEW

Beyond acute SARS-CoV-2 infection: A new challenge for Internal Medicine[☆]



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Abstract Infection with the new SARS-CoV-2 coronavirus has reached pandemic proportions, with a very high death toll worldwide. Despite the scientific community's strenuous efforts to address this disease in its acute phase, as well as in prevention through the development of vaccines in record time, there remains another important workhorse: understanding and treating the persistence of symptoms beyond the acute phase, the so-called protracted COVID-19 syndrome or persistent COVID. These persistent manifestations affect several organs and systems and may depend on both the pathogenic mechanisms of the virus and the pathophysiological response of the patient. One year after the onset of this pandemic, there is an urgent need to address this situation from a comprehensive approach.

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PALABRAS CLAVE

COVID persistente;
Síndrome COVID-19
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Síndrome pos-COVID;
Síndrome
pos-COVID-19 agudo

Más allá de la infección aguda por SARS-CoV-2: un nuevo desafío para la Medicina Interna

Resumen La infección por el nuevo coronavirus SARS-CoV-2 ha alcanzado proporciones de pandemia, con un número de muertes muy elevado en todo el mundo. A pesar del esfuerzo ímprobo desarrollado por la comunidad científica para abordar esta enfermedad en su fase aguda, así como en la prevención mediante la creación de vacunas en tiempo récord, aún queda otro caballo de batalla importante: comprender y tratar la persistencia de síntomas más

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allá de la fase aguda, el llamado «síndrome COVID-19 prolongado» o «COVID persistente». Estas manifestaciones persistentes afectan a varios órganos y sistemas y podrían depender tanto de los mecanismos patogénicos del virus como de la respuesta fisiopatológica del paciente. Un año después del inicio de esta pandemia es una necesidad urgente abordar esta situación desde un enfoque integral.

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Infections caused by the new coronavirus SARS-CoV-2 have reached epidemic proportions, with over 155 million confirmed cases and more than 3 million deaths around the world^{1,2}. In response, the scientific community has been working at an unprecedented rate to analyse this new virus, discover its biological characteristics, and diagnose, treat, and prevent COVID-19.

Nevertheless, limited studies have been conducted to date on the follow-up and long-term effects of SARS-CoV-2 infection, though there are ever-increasing data that support the numerous patients infected by SARS-CoV-2, even those with mild symptoms or who are asymptomatic, who develop either long-term symptoms that affect their quality of life, or sequelae that may be incapacitating or decisive in terms of their survival.

To approach this reality in an adequate manner, the first issue we must address is the definition of uniform criteria to describe such a polymorphous and heterogeneous clinical presentation beyond the severe infection phase. In this regard, on 18 December 2020, the National Institute for Health and Care Excellence published a guideline defining the stages of COVID-19 disease³. The guideline defines the acute phase of infection as the start of infection through to 4 weeks of evolution. ‘‘Ongoing symptomatic COVID-19’’ is defined as cases in which signs and symptoms of disease are present from 4 to 12 weeks, and ‘‘post-COVID-19 syndrome’’ as when the signs and symptoms developed during or after an infection compatible with COVID-19 continue for more than 12 weeks and cannot be explained via an alternative diagnosis. The guideline also uses the term ‘‘long COVID’’ to describe signs and symptoms that continue or develop after acute COVID-19, with both post-COVID-19 syndrome and ongoing symptomatic COVID-19 included under this umbrella term.

Along these lines, in Spain, the Spanish Society for General Medicine (SEMG according to the Spanish acronym) published the data from its survey of patients with ‘‘long COVID’’, a term the society uses to refer the set of symptoms affecting multiple organs of patients who have had COVID-19 (without or without a confirmed diagnosis), and who continue to experience symptoms after what is considered to be the acute phase of the disease has ended⁴. A total of 2,120 patients participated in the survey, of which 1,834 presented symptoms compatible with long COVID. All age groups were represented in the survey. A total of 79% of the surveyed individuals were female with a mean age of 43 years. A total of 200 symptoms that fluctuated over time

were gathered with an average of 36 symptoms per person. An interesting datum from this survey was the significant impact on quality of life resulting from these ongoing symptoms, with considerable incapacity in terms of performing activities of daily living: personal hygiene, working outside the home, familial obligations, etc.⁴.

To date, a ‘‘living’’ systematic review has been created (a term alluding to a system that is continuously updated with new data as they are generated) as well as a meta-analysis analysing COVID-19 symptoms following the acute phase of the disease. Both are in the pre-publication phase^{5,6}.

The living systematic review includes studies through September 2020⁵. It analyses 28 studies: 16 cohort studies, 10 cross-sectional studies, and 2 case series. The analysis included 9,442 adults with COVID-19 from 13 different countries. The longest average follow-up time was 111 days after hospital discharge. A wide range of systemic, cardiopulmonary, gastrointestinal, neurological and psychosocial symptoms are listed, of which the most common were dyspnoea, altered sense of smell and taste, the presence of fatigue, and anxiety. Persistent symptoms were described in both admitted patients and those seen in outpatient services. However, the quality of the evidence of the studies included in this review is low, with an elevated risk of bias and extensive heterogeneity in terms of disease prevalence. In addition, its external validity is very limited, with no control groups and limited studies including children. None were performed in developing countries or a primary care setting⁵.

The meta-analysis conducted by Lopez-Leon et al.⁶ includes 15 studies published through 1 January 2021 with a total of 47,910 patients. A total of 55 long-term effects were detected. The follow-up time ranged from 14 to 110 days from disease diagnosis. Age ranged between 17 and 87 years. Some 80% (95% CI: 65-92%) of the patients infected with SARS-CoV-2 developed one or more long-term symptoms. The five most common symptoms were: fatigue (58%), headache (44%), attention impairment (27%), hair loss (25%), and dyspnoea (24%). All the specific meta-analyses showed medium (n=2) to high heterogeneity (n=13)⁶.

Another significant problem we are facing is that we currently do not know why certain individuals experience a full recovery or continue to suffer specific long-term symptoms. The main sequelae observed in other coronaviruses (SARS, MERS) are of a respiratory, musculoskeletal, and neuropsychiatric nature⁷. In patients with COVID-19, admission to ICU due to acute respiratory distress syndrome is associated with

long-term functional disability with both pulmonary and extrapulmonary conditions⁸. The data on disease prevalence varies greatly: some studies estimate that 20% of patients present symptoms at 4 weeks and 10% at 12 weeks⁹, while others detect up to 70% 4 months post-onset of COVID-19¹⁰.

To date, three theories have been suggested in an attempt to explain the pathogenesis of long COVID manifestations: the presence of the virus in immunologically privileged locations such as the central nervous system, an abnormal immune response, and autoimmune phenomena secondary to infection¹¹.

Along these lines, Gaebler et al.¹² studied the evolution of humoral and cell immunity for 6.2 months in a cohort of 87 patients after infection with SARS-CoV-2 and observed that the titres of IgM and IgG antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein decreased significantly over this time period, with IgA being less affected. By contrast, the number of RBD-specific memory B cells remained unchanged following infection. The memory B cells showed clonal turnover after 6.2 months and the antibodies they express had greater somatic hypermutation, resistance to the RBD mutations, and higher potency, which could indicate continuous evolution of the humoral response. On the other hand, immunofluorescence and PCR analyses of intestinal biopsies obtained from asymptomatic individuals at 4 months post-onset of infection revealed the persistence of fragments of nucleic acid from the SARS-CoV-2 virus and the presence of immunoreactivity in the small bowel in 7 out of 14 individuals, which could cause the chronic inflammation that is responsible for long-term symptoms.

A recent study in the pre-publication phase using the high-throughput technique Rapid Extracellular Antigen Profiling to identify autoantibodies against 2,770 extracellular and secreted proteins in a cohort of 194 patients with SARS-CoV-2 infection and a control group of healthy healthcare workers, showed a dramatic increase in autoimmune reactivities in the infected subjects, particularly against immunomodulatory proteins, including cytokines, chemokines, complement components and cell surface proteins¹³.

In a murine model of SARS-CoV-2 infection, it was found that equivalent autoantibodies altered the immune response and impaired virological control by inhibiting immunoreceptor signals and modifying the distribution of peripheral immune cells, thereby exacerbating disease severity. The analysis of autoantibodies targeted against tissue antigens revealed their association with specific clinical characteristics and disease severity¹³. Many of those cell antigens are found in specifically affected tissue and organs in patients with long COVID, though their potential association with this clinical presentation has not yet been studied.

Another challenge we face is how to therapeutically manage patients with persistent symptomatology, which to date has been symptom-based and with few satisfactory results. The National Library of Medicine database has currently recorded 58 clinical trials with different approaches to treating this clinical process. One of them, Esperanza COVID, is conducted in Spain using montelukast; others are aimed at therapies with naltrexone/food supplements with NDA+, or drugs already used in patients with myalgic encephalomyelitis/chronic fatigue syndrome

(ME/CFS); another with deupirfenidone (LYT-100), with leronlimab, monoclonal antibody against the CCR5 cell receptor, with physical exercise-based therapy or psychological therapy, as well as antivirals such as remdesivir or favipiravir.

When determining the healthcare system's response to the COVID-19 pandemic, we must consider the full cost of the chronic consequences of SARS-CoV-2 infection, and we must design strategies to provide comprehensive care to individuals suffering from these sequelae. In this regard, in December 2020, the prestigious journal *Nature Medicine* posed a challenge to the scientific community: to address and produce solutions for long COVID syndrome¹⁴. Caring for patients with long COVID may require the participation of multiple specialists, resulting in a logistical nightmare for patients seeking diagnosis and treatment. As such, a more comprehensive approach is needed to take the weight off of patients and to improve their care. Along this line, multidisciplinary units are being established to care for patients with long COVID such as those implemented at Mount Sinai hospital in New York and Penn-Presbyterian hospital in Pennsylvania, or the clinics established in the United Kingdom.

Specialised units or clinics have also been founded in Spain to care for patients with long COVID. These have drafted various consensus documents and interdisciplinary collaboration agreements, such as the "MARCO-19 project for the care of individuals with long COVID", promoted by the SEMG and with the participation of 27 scientific societies¹⁵⁻¹⁸.

The complex nature of post-COVID-19 sequelae surpasses and exceeds the specific competencies of the different medical specialties. Therefore, according to the various consensus documents, these specialised units should include specialists in internal medicine, neurology, mental health, and rehabilitation, as well as support from nursing staff, particularly that involved in case management, and in close contact with primary care professionals and other specialists. These units should also rely on collaboration from basic researchers in the fields of virology, genetics and immunology.

The fundamental aims of these units will be to: define the clinical spectrum, pathogenesis, pathophysiology, and natural history of the disease, rule out patients with suspected long COVID in the presence of other processes unrelated to the infection, evaluate functional affectation, identify groups of patients with specific needs and characteristics in order to schedule specific interventions, and evaluate the safety and efficacy of specific interventions or treatments in controlled clinical trials.

There is a clear need to conduct controlled, prospective cohort studies that include different at-risk populations and settings. Likewise, there is also a clear need to gather data in a standardised manner through national and international platforms in order to take the utmost advantage of all the scientific work that is being done.

Internal Medicine must not remain indifferent to these initiatives, considering the leading role it has played from the very start of the effort to address the pandemic in Spain. This effort can be seen in the COVID-19 patient registry from the Spanish Society for Internal Medicine, one of the largest in the world, which has already gathered data on more than 18,000 patients¹⁹.

Internal Medicine, with its comprehensive vision and holistic training of its specialists, which has enabled them to adapt and respond to the wide-ranging challenges and crises that have arisen in recent years²⁰, is in a strategic position to take on the challenge of creating and coordinating multidisciplinary units to care for patients with persistent symptoms post-SARS-CoV-2 infection. On the other hand, beyond the symptomatology of long COVID, we cannot forget both the physical as well as psychological or psychiatric sequelae that patients who have overcome severe COVID-19 may present and that are currently still unknown to us. Nor must we forget the repercussions that SARS-CoV-2 infection may have on the evolution of common chronic diseases such as ischaemic heart disease, COPD or diabetes mellitus. In this scenario, the role of Internal Medicine is once again fundamental to the post-COVID-19 era.

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