

# Post COVID syndrome: a new challenge for medicine

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**Abstract.** – The huge concern raised by SARS-CoV2 pandemic about public health management and social impact is still under debate, particularly because COVID-19 may affect infected people much longer than expected from a typical air-borne viral disease. The scientific community is actually wondering about the etiopathogenesis and clinical development of this “post-COVID” complex symptomatology, very close to symptoms typically observed in chronic fatigue syndrome, so recently named as “post-acute sequelae of COVID-19 (PASC)”. This commentary tries to focus on the most recent news about this issue.

*Key Words:*

COVID-19, PASC, Post-COVID syndrome, Chronic fatigue syndrome, Diagnosis and therapy, Long COVID.

## Introduction

The coronavirus 2019 disease (COVID-19) still represents a fundamental concern for medicine. This is not solely for the huge spreading of pandemic worldwide but for the complex pathogenesis, yet not fully elucidated, which thoroughly engaged medical science in retrieving sound responses towards this challenge. A recent contribution from Carli et al<sup>1</sup>, reported that in Italy at least 55% patients in the following 60 days after early COVID-19 onset, showed 3 or more post-COVID symptoms. Scientific research<sup>2,3</sup> about the long-lasting consequences of COVID-19 is becoming a straightforward topic of interest. Noticeably, Amy Watson’s case, the woman who suffered 344 days of fever because of COVID-19, is one of the most renowned examples of long-haulers still experiencing physical pain and debilitating symptoms after COVID-19. This did not find a sound pathogenetic explanation to date. A “post-COVID

syndrome” seems to characterize these apparently anecdotal, though rapidly increasing, new sickness cases, which are rapidly enhancing in their number. The term “post-COVID”, to indicate symptoms-sequelae subsequent to COVID-19, is currently replaced with “post-acute sequelae of COVID-19” (PASC), the most complete terminology of post-acute COVID-19 syndrome<sup>4</sup>. Amy Watson<sup>5</sup> herself in Oregon (USA) led a huge crowd of patients who, being discharged from COVID-19 and testing negative to molecular swabs yet continued to show symptoms. Actually, she gathered tens of thousands of post-COVID syndrome patients globally known as “long-haul COVID fighters”. The majority of these individuals were fairly young women, 40-45 years aged, therefore quite different from the typical elderly patients with pre-existing health problems upon a developing COVID-19<sup>5</sup>. Post-COVID syndrome has started its existence in the widest way.

## ***Post-COVID Syndrome: A Concern of the Utmost Importance for Healthcare and Caregivers***

Post-COVID syndrome shows symptoms, such as severe body aches, gastro-intestinal issues, chronic fatigue, intense migraine and “brain fog”, quite perfectly recalling the ones lamented by patients suffering from chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). For this reason, CFS patients started support and alliances with PASC ones. Furthermore, in the UK, a British “long-COVID aid group” started a solidarity campaign for recognition, research and support of PASC in the country, whereas in Italy a group called “post-COVID syndrome patients”, was recently set. The idea to join post-COVID syndrome patients altogether, creating a crowded group of people sharing the same puzzling symptomatology

gy, is fundamental for physicians and research experts<sup>6</sup>. Actually, numerous attorneys, lawyers for civil rights, scientists, disease experts and therapy drug developers have also joined together creating a network called “The Long COVID Alliance” (despite the term “long COVID” is currently dis-used) to leverage their collective knowledge and resources and educate policy makers. Therefore, our understanding of how to diagnose patients and manage them is still evolving.

What is certain is that patients’ condition can be very debilitating, having a serious impact on people’s ability to support their job life and have a normal social habit<sup>7</sup>. In this perspective, the WHO has now introduced post-COVID emergency using ICDs to support the implementation of a surveillance system in order to define and describe post-COVID events.

***PASC (Post-COVID Syndrome)  
Symptomatology: Two Classifications  
May Be Described***

A significant number of patients following their health recovery, keeps in having highly troublesome symptoms, at least three months later the onset of COVID-19, even if repeated molecular tests no longer showing SARS-CoV2 in the swabs<sup>5</sup>. The most common symptoms are exhaustion, generalized pain, shortness of breath, cognitive impairment, inability to exercise, headaches, and sleep disruption<sup>8,9</sup>. As COVID-19 is a novel, puzzling disease, burst in China at the end of 2019, we are not endowed with any sound and efficacious information about how to manage post-COVID syndrome. Moreover, we are unable to forecast who will develop a post-COVID syndrome. What we are becoming aware of, to date, is that both development and severity do not appear to correlate with the nature and extent of symptoms during the acute phase of the SARS-CoV2 infection. Therefore, even subjects who have only been affected by mild or moderate forms of COVID-19, can exhibit a post-COVID syndrome, whereas patients who were instead affected by the disease in a severe form can return to normality about two months later. Actually, post-COVID syndrome, with the aforementioned symptoms, is yet more likely to occur in people aged over 50, i.e., individuals with co-morbidity (two or three chronic diseases) and people who had experienced severe forms of COVID-19. So, there is no orthodox definition of what is known as post-COVID syndrome or PASC, yet. A reasonable definition would come from observing the condi-

tion that afflicts anyone who has been diagnosed with SARS-CoV2, developed COVID-19 and did not come back to the previous level of health and function. After six months, they may be included under the “umbrella” of symptoms pertaining to “post-COVID syndrome” or PASC.

Fundamentally, we can characterize two cohorts of patients who have been affected by the post-COVID syndrome: a) a first group who has experienced some form of damage to lungs, heart, liver, kidneys or brain, which we do not know if permanent or if it will resolve over time. These organs may have affected their ability to work at their best, b) people who continue to experience debilitating symptoms such as exhaustion, fatigue, even after small or moderate exertion, “brain fog”, muscle and joint pain, chronic flu-like symptoms, even if there is no direct evidence of organ damage, especially for lungs. The evidence that SARS-CoV2 targets epithelia expressing the highly ubiquitous ACE2 receptors, may explain the organic-systemic involvement of post-COVID syndrome. Upon some types of infectious diseases, there is lingering illness, and they altogether probably have the same common shared pathophysiology, as observed by Anthony Komaroff<sup>9</sup>, at the Harvard Medical School, Boston, MA (USA). Interestingly, this issue regarded coronavirus infections as a whole.

When SARS was discovered by the Italian physician Carlo Urbani, who at the time was living in Vietnam and died for SARS, viral spread was initially confined into China, Taiwan, Vietnam, Hong Kong and Canada (Toronto)<sup>10,11</sup>. About 5% of people infected still had visible changes in the lungs even after 15 years and 38% showed a reduced oxygen diffusion capacity<sup>12</sup>. Chronic fatigue was observed in SARS infected people<sup>13</sup> and a study, carried out in China, reported that SARS causes long-term symptoms, which could be classified as CFS/ME<sup>14</sup>.

***Post-COVID Syndrome: Sharing Patterns  
with Chronic Fatigue Syndrome/Myalgic  
Encephalomyelitis (CFS/ME)?***

Dr Antony Fauci<sup>15</sup>, Head Director of the National Institute of Allergy and Infectious Diseases at NIH in Bethesda (US), was the first scientist who reported that most people of the second group (b) had developed a clinical condition very similar to what is called as CFS/ME. This condition can also emerge following other infectious diseases, as for instance mononucleosis<sup>16</sup>, Lyme disease, influenza and SARS. One of us (UT) has been seeing personally those patients for more than 30 years, after at-

tending various meetings at the CDC in Atlanta in 1993-1994, to formulate a new classification of the Chronic Fatigue Syndrome (CFS), then published on the journal *Annals of Internal Medicine*<sup>17</sup>.

Global estimations account for about 2,000,000 people affected from CFS/ME in USA, according to the National Academy of Medicine, and roughly the same amount can be estimated in the European Union, with about 500,000 individuals in the sole Italy. CFS/ME can be severely disabling and those subjects suffering from it report significant functional disabilities. Based on current evidence, the underlying pathology of CFS/ME involves energy metabolism, nervous function and the immune response, with alterations such as impaired NK cell function, increased number of CD8+ T cells, presence of various autoantibodies, particularly targeting CNS and ANS and abnormal production of cytokines<sup>17</sup>. We know that most patients with CFS/ME stay ill for many years. A policy statement published very recently in a WHO document (WHO ISSN 1997-8003) underscored how previous experience with CFS has also raised a great concern about the financial burden of job absence caused by long-term sickness, both for human society and economics.

### ***Future Remarks: Are There Therapy Options for Post-COVID Syndrome?***

The clinical sequelae of post-COVID-19 syndrome are still emerging and are therefore to be studied in depth. It is certainly a medical issue of potential serious impact on the population that is treated for COVID-19. A treatment, developed within the Italian Society of Oxygen Ozone Therapy (SIOOT), which uses oxygen-ozone therapy for COVID-19, provided encouraging evidence also in our clinical experience with numerous patients suffering from CFS/ME<sup>18-20</sup>. Ozone may act as a master tuner of the immune response and therefore it can be useful also in treating post-COVID-19 syndrome patients<sup>19</sup>.

Despite these promising suggestions, post-COVID syndrome yet remains a pathology to be further investigated alongside its treatment, as well, and new encouraging research evidence will fuel our knowledge about COVID-19.

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