Long-COVID

Post-Acute Sequelae of COVID (PASC)

EXECUTIVE SUMMARY

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EXECUTIVE SUMMARY

1. Definition of a New Disease:

At the start of the COVID-19 pandemic, medical concern was focused on prevention and treatment of the acute effects of this novel pneumonia. It was soon apparent that this was a multi-organ infection, not just respiratory. Persons complaining of ongoing symptoms, like tiredness, months after infection were a low priority for most medical practices. Now, several years into the ongoing pandemic, there is acceptance of Long-COVID as a separate, but related, entity with its own ICD-10 code, but the incidence, prevalence, symptomatology, and medical management remain uncertain. Concern about the long-term effects of COVID-19 led the US government to establish a new office, the Office of Long COVID Research and Practice, under Admiral Rachel Levine (1). Long-COVID was defined as direct and indirect long-term effects of the SARS-CoV-2 infection (2). Long-COVID consists of some 200 signs and symptoms and 50 conditions (2), so the definition is flexible and defined loosely by time after the initial infection. While the timeframe of onset to be called Long-COVID varies, the UK guidance defined acute COVID-19 as lasting up to 4 weeks, ongoing COVID-19 as lasting 4 to 12 weeks and Long-COVID as signs and symptoms beyond 12 weeks (3).

2. Risk Factors:

Risk factors for Long-COVID include female gender, high age, previous morbidity, prior hospitalization for COVID-19, and a requirement for ventilation. While subjects with mild symptoms can get Long-COVID, those with severe infections are at higher risk.

3. Pathophysiology:

Multiorgan viral invasion and immune system overreactions may play a role in Long-COVID. As in COVID-19, cytokines such as IL-6 are increased in many patients (4), although the extent of the cytokine storm in the pathology of infections remains unclear. Only in severe disease would one expect circulating cytokine levels to be elevated while local levels could be high and influencing local cellular damage. Cellular injury may lead to vascular damage and thrombi formation in the microcirculation in affected organs. Circulating microthrombi from e.g., the heart may contribute to heterogenous symptoms of Long-COVID. Our knowledge is limited, as deaths and autopsy studies are rare in the post-acute phase. Involvement of the olfactory tract may lead to loss of taste and smell and may also be a pathway for viral entry into the CNS. It is also possible that inflammatory changes of the Blood Brain Barrier may open up tight junctions and facilitate viral entry into the CNS and lead to inflammatory changes affecting central functions.

4. Natural Course and Clinical Signs and Symptoms:

Signs and symptoms may be general or reflect the extent of organ involvement. Severity and incidence or prevalence may reflect type of study population ((hospitalization needed or not), length of follow up, type of dominant viral variant, and the design of study (pro- or retro-spective), and data collection (self- or investigator reported). To evaluate symptoms and signs during natural course, the summary below focuses on studies with 1-2 years follow-up.

PRE-OMICRON SURGE - HOSPITALIZED DISCHARGED PATIENTS:

The largest prospective longitudinal study is from UK (2320 subjects, (5)). At 12 months follow-up after discharge 50-60% of subjects had fatigue, muscle ache, physical slowing down, poor

sleep, breathlessness, and 40-50% had joint pain / swelling, slowing down, and short term memory loss. Full recovery was noted in only 25-30% at 5 and 12 months.

Of note, patients with moderate or severe symptoms had increased level of IL-6 and other immune mediators compared to patients with mild symptoms. This supports the hypothesis that hyper-inflammation in the acute phase may lead to dysregulated immunity and multi organ dysfunction.

PRE-OMICRON SURGE - SYMPTOM PROFILES BASED SELF/REPORTED SYMPTOMS:

A large general population study in UK (n= 336,752, (6)) used a National Registry to identify COVID positive patients and smart phones to identify subjects with new symptoms lasting longer than 28 days and analyzed those with symptoms lasting >12 weeks, thus meeting the criteria for Long-COVID. They reported clusters of symptoms for different variants and vaccination status. Four symptom clusters were described (Cardio-respiratory; Neurological; Systemic-inflammatory; Abdominal).

There appeared to be a heterogenous profile for post COVID syndrome based on the type of variant (Delta or Omicron), with the most severe and debilitating cluster of symptoms reported for patients considered to have systemic / multi-organ inflammatory disease.

OMICRON SURGE:

A prospective longitudinal study in more than 97,000 COVID cases in the general population from the first 6 months of 2022 showed that the rate of Long COVID was only 5% among subjects with prior Omicron infection compared to 11% in Delta cases (7).

NEUROLOGICAL & PSYCHIATRIC SYMPTOMS – NATURAL COURSE DURING 2 - YEAR FOLLOW UP:

In the Prospective study in UK (5) with 1 year follow up of 2320 previously hospitalized patients, the rate of slowing down of thinking and short term memory loss was about 45%.

A similar prospective study from Wuhan, China (n= 3233; (8)) found at 1 year follow up using questionnaires, the incidence of cognitive impairment was higher with no difference for early or late onset or progressive disease. Severe COVID-19 resulted in a higher incidence of cognitive impairment.

The largest study so far reported was a retrospective review of healthcare record from an international network (TriNetx including about 89 million patients from hospitals, outpatient or private clinics in US, UK, Australia, Spain Bulgaria, India, Malaysia and Taiwan. Close to 1.3 million patients (including children, adults and elderly) with a previous diagnosis of COVID-19 during a two year period January 20, 2020 to April 13, 2022 were selected and matched 1:1 with patients with another respiratory disease. For the overall population, common psychiatric symptoms such as mood and anxiety disorders. after an initial increase, returned to base line after 1-2 months. By contrast, cognitive deficit (known as “brain fog”), dementia, psychotic disorders, and epilepsy/ seizures kept increasing during the 2-year follow up (9).

A prospective study (Becker JH et al, JAMA 2021) using cognitive testing in 740 patients reported cognitive impairment at average 7.6 months follow up where most prominent findings were reduced memory encoding and memory recall in 23-24% in the overall population and 37-39% in previously hospitalized patients. There was also evidence of reduced executive functioning in 13% and 27% in the two groups, respectively (10).

PEDIATRIC PATIENTS – SIGNS AND SYMPTOMS

In children (n = 185,748) there was no apparent risk for mood or anxiety disorder, whereas they had an increased risk for cognitive deficit, insomnia, intracranial hemorrhage, ischemic stroke, nerve, nerve root /plexus disorders and psychotic disorders. As well as epilepsy/seizure disorders. However, by contrast to adults, cognitive symptoms had a finite risk horizon (75 days) and time to equal incidence compared to control group (491 days).

CDC used medical reports to assess 9 potential post-COVID signs and symptoms (symptoms) and 15 potential post-COVID conditions among 781,419 U.S. children and adolescents aged 0–17 years with COVID-19 compared with 2,344,257 U.S. children and adolescents without recognized COVID-19 during March 1, 2020–January 31, 2022 (11).

- The highest hazard ratios were recorded for acute pulmonary embolism (aHR = 2.01), myocarditis and cardiomyopathy (1.99), venous thromboembolic event (1.87), acute and unspecified renal failure (1.32), and type 1 diabetes (1.23), all of which were rare or uncommon in this study population.
- Compared to subjects without COVID-19, patients with COVID-19 were less likely to experience respiratory signs and symptoms, symptoms of mental conditions, muscle disorders, neurological conditions, anxiety and fear-related disorders, mood disorders, and sleeping disorders, possibly related to how subjects without COVID were selected (visit to healthcare provider for treatment). Differences were noted among age groups of children for COVID subjects vs. COVID-negative:
    - Children aged 2–4 years had higher rates of asthma diagnosis (1.12) and respiratory signs and symptoms (1.07) after COVID-19.
    - Among children aged 5–11 years, the highest aHRs for patients with COVID-19 were for myocarditis and cardiomyopathy (2.84), venous thromboembolic event (2.69), and acute and unspecified renal failure (1.38).
    - Among patients aged 12–17 years, the highest aHRs for those with COVID-19 were for acute pulmonary embolism (2.03), myocarditis and cardiomyopathy (1.66), and venous thromboembolic event (1.52).

5. Incidence and Prevalence:

Although Omicron variants are less likely to cause Long-COVID, the incidence and prevalence may still be high or increased as these variants spread more rapidly and thus increase the number of infected persons in the general population.

6. Socioeconomic Impact:

In May 2022 CDC estimated a cumulative number of 81 million COVID cases and 995,000 deaths. The tentative Guidelines are being drafted by Health authorities and preliminary Guidelines have been issued in UK number of Long COVID is roughly 9.6 million or 10 times higher than the number of deaths, as only about 25% of the patients recovered at 12 months follow up. Thus, there may be long term impact on health, which may increase cost of health care and reduce hours worked and income earned.

7. Management of Long-COVID:

Preliminary Guidelines have been issued in UK and are being considered by other Health Authorities. To date no antiviral or immunomodulatory drug has proven effective for the treatment of Long-COVID in clinical trials. The presence of long-lasting systemic inflammation in some patients with long COVID would suggest that anti-inflammatory agents might have potential not only during the acute phase of infection, but also during the post-acute phase.

A clinical trial of the efficacy of vaccination in the treatment of Long-COVID symptoms was proposed and designed by clinicians. A case-control study of 1.2 million users of a COVID symptom tracker app in the UK showed that there were lower odds of symptoms lasting ≥28 days in individuals who had received 2 vaccine doses (OR 0.51 [0.32–0.82]; p=0.0060)—i.e., the risk of developing Long-COVID was reduced by around 50% in those who were double vaccinated.

The US government allocated $1.2 B for Long COVID research and support in the form of a 40,000 patient RECOVER study conducted at 30 centers in the US to define the long term effects of COVID. The Recover study aims to complete enrollment of more than 17,000 adults by September and 20,000 children by the end of the year 2022; as of 8 September 2022, 8225 adults were enrolled. The NIH has issued a Research Opportunity Announcement (ROA) for Clinical Trials for the Prevention and/or Treatment of Post-Acute Sequelae of SARS-CoV-2 infection (PASC) as part of the NIH RECOVER initiative in the form of an emergency competitive revision to existing NIH awards. Considering the magnitude and emergency of the problem, it seems important to make additional funding available for trials evaluating new treatment paradigms to prevent long-term potentially debilitating effects of Long COVID.

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