A proactive approach to fighting SARS-CoV-2 in Germany and Europe (part 7)

Toolbox #10: Post-COVID Syndrome (PCS)

(as of July 15, 2021)

Abstract

Post-Covid Syndrome (PCS) is the term used to describe long-term sequelae of COVID-19 disease. This includes a variety of symptoms that may develop after the acute phase of SARS-CoV-2 infection. They occur both in patients who had no or only mild symptoms in the first phase and were accordingly not hospitalized, as well as in those who have survived a (severe) COVID-19 illness. These after-effects may persist for months, affect different organs and even lead to incapacity to work. There is no treatment for the causes of PCS, so currently only the symptoms are treated. The proportion of COVID-19 patients who develop PCS is in the double-digit percentage range in adults and adolescents and is also relevant in children. Thus, a large proportion of those who are listed as recovered in the statistics suffer from the consequential damage of the disease for a longer period of time. Since there are only a few PCS centers so far, it is difficult for many patients to find competent contact points that can carry out adequate diagnostics, treatment and assessment of partial or complete occupational disability. For the group of children and adolescents, who have hardly been vaccinated so far, there is now - due to the gradual lifting of infection protection measures - an increased risk of becoming infected and contracting PCS.

After a detailed presentation of the clinical picture, we propose in this toolbox the following measures for dealing with PCS in the German healthcare system:

- **Prevention:** Even in a situation of low incidence, it is advisable to further reduce and keep case numbers low through appropriate protective measures and to promote vaccination readiness. A general vaccination recommendation for children and adolescents should be considered in light of what is known about PCS and the expected dynamics of spread if protective measures are discontinued.
- Improving data on PCS: Representative retrospective studies and routine, possibly app-based, symptom screening after surviving infections would help to better assess the prevalence. Additionally, they would provide the data basis for early detection of PCS, the improvement of diagnostics and therapy, and the development and expansion of PCS patient care.
- **Research funding:** Interdisciplinary research collaborations are needed to gain a complete picture of the disease (and its psychosocial side effects), to investigate the as yet not understood causes of PCS, and to develop effective therapeutic options.
- **Care capacities:** In order to treat the many PCS patients in the best possible way, interdisciplinary PCS competence centers should be established at university hospitals, nationwide PCS outpatient clinics (also for children and adolescents) and specialized rehabilitation clinics.
- Education: Particularly in view of the persistent impairments that PCS sufferers can experience in their daily work, school life and social life, it is essential to provide good information for patients, medical professionals and the general public.

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We would like to thank Pauline Helms for her support in completing the manuscript.

The following papers have been published to date on the No-COVID strategy:

A New Proactive Objective for Germany to Combat SARS-CoV-2.

Part 1: Framework document. January 18, 2021.

Part 2: Options for action (toolbox 1-4). February 10, 2021.

Part 3: Testing strategies (toolbox 5). March 04, 2021.

Part 4: Education, schools and daycare centers (Toolbox 6). March 04, 2021.

Part 5: Risk incidence: Just start (Toolbox 7 and 8). March 25, 2021.

Part 6: Immunizations (Toolbox 9). March 25, 2021.

Available at https://nocovid-europe.eu/.

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1. Definition and importance

While many patients recover without apparent sequelae after surviving infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a significant proportion of patients experience long-term sequelae that may persist for months or longer (Augustin et al. 2021; Huang et al. 2021; Sudre et al. 2021; Nalbandian et al. 2021). Acute, symptomatic infection is referred to as coronavirus disease 19 (COVID-19) (Figure 1). When symptoms persist or begin after acute infection has been overcome while SARS-CoV-2 is no longer detectable by PCR, this is referred to as Post-COVID syndrome (PCS) (also commonly known as Long COVID) (Figure 1).



Figure 1: The phases of acute and post-acute COVID-19 (Nalbandian et al., 2021).

The definition of Post-COVID syndrome includes the following elements:

- Evidence of prior SARS-CoV-2 infection.
- Persistent or new onset of symptoms after the acute phase is over and SARS-CoV-2 detection by PCR is again negative.
- Persistent symptoms such as fatigue, shortness of breath, changes in smell and taste, impaired concentration and memory that cannot be explained by another diagnosis.

2. Symptoms and organ manifestations

Because SARS-CoV-2 infection manifests in many organs, PCS can also have different manifestations. The following organs may be affected:

Pulmonary: Common symptoms include dyspnea, decreased exercise capacity, and hypoxia.

Hematology and hemostaseology: Thromboembolic events were found to be <5% in retrospective studies. The risk for thrombotic complications in the post-acute COVID-19 phase is likely related to the duration and severity of a hyperinflammatory state.

Cardiovascular System: Persistent palpitations (autonomic dysfunction), dyspnea, and chest pain are observed.

Neuropsychiatric symptoms: Fatigue, muscle pain, headache, dysautonomia, and cognitive impairment ("brain fog") are reported. Among psychiatric disorders, anxiety, depression, and sleep disturbances are most common.

Endocrine disorders: Endocrine sequelae include new-onset diabetes mellitus, subacute thyroiditis, and osteomalacia (disorders of parathyroid hormone metabolism).

Gastrointestinal disorders: COVID-19 may alter the intestinal microbiome in a way that reduces protection against colonization by other pathogenic agents.

Dermatological disorders: Hair loss and autoimmune skin disorders may occur.

Similar, long-lasting symptoms that extend beyond the respiratory tract are also known from the first SARS-CoV epidemic of 2002/2003. These include persistent disorders such as chronic fatigue syndrome, which was still reported after four years in a relevant proportion of SARS-CoV survivors (Lam et al. 2009), and laboratory changes in blood, which were still detected after 12 years (Wu et al. 2017).

3. Causes

Various organ systems in the body can be affected by PCS. Underlying these diverse disorders is the unique pathophysiology of SARS-CoV-2, which begins with cell entry via the angiotensinconverting-enzyme-2 (ACE2) receptor (Hoffmann et al. 2020) at mucosal sites of the mouth, nose, as well as the lungs, and can subsequently manifest throughout the body. The expression of the ACE2 receptor is particularly high in humans in the epithelia of the lungs, kidneys and small intestine (Hamming et al. 2004; Ziegler et al. 2020; Qi et al. 2021). ACE2 has also been identified in the olfactory neuroepithelium, which explains the association of COVID-19 with loss of the sense of smell (Chen & Shen et al. 2020). In addition, the olfactory nerve can be a way for the virus to get into the central nervous system and cause inflammation there. Alternatively, the virus can enter the brain via ACE2 through endothelial cells of capillaries (Baig et al. 2020). ACE2 has also been detected in the endothelial cells of the heart, testis, substantia nigra in the brain, and in muscle cells (Salamanna et al. 2020; Qi et al. 2021). This epithelial expression, together with the presence of ACE2 in the vascular endothelium of a variety of tissues, explains the high diversity of clinical manifestations associated with COVID-19 (Salamanna et al. 2020).

In addition to the expression of the ACE2 receptor in many organs, virus-specific damage in organs and subsequent immunological and inflammatory disorders likely contribute to the pathogenesis of PCS. Furthermore, evidence of structural (Ackermann et al. 2020) and immunological (Nauen et al. 2021) vascular alterations is accumulating. Interestingly, PCS

appears to be associated with lower serum immunoglobulin G (IgG) titers at disease onset (Augustin et al. 2021).

4. Frequency

Two main groups of PCS patients can be distinguished: a) patients with sequelae after severe COVID-19 disease, which may require intensive care, and b) patients who develop PCS after oligo- or asymptomatic infection and without prior hospitalization. Overall, PCS seems to occur more frequently in female patients (Nielsen et al. 2021).

PCS in hospitalized patients

Patients hospitalized or receiving intensive care for SARS-CoV-2 infection show long-term symptoms that are common to other severe diseases due to mechanical ventilation and prolonged immobilization and are not specific to COVID-19. Huang et al. reported that 6 months after hospitalization for COVID-19, 63% of a total of 1655 patients suffered from fatigue or muscle weakness and 26% had sleep problems (Huang et al. 2021).

The list of organs with long-term dysfunction in the course of PCS following infections with SARS-CoV-2 largely follows the organs whose barrier layers express ACE2 receptors (Luo & Dun 2020; Nalbandian et al. 2021). Specific abnormalities detectable with magnetic resonance imaging in hospitalized patients could be detected in lung, heart, liver, and kidney after 2-3 months (Raman et al. 2021; Huang et al. 2020). In 24% of hospitalized patients in Wuhan, radiologically detectable changes in the lungs were still detected after 12 months (Wu et al. 2021). In a systematic literature review of 18,251 studies, more than 80% of patients were found to have at least one of the symptoms associated with PCS: 58% complained of fatigue, 44% of headache, 27% of difficulty concentrating, 25% of hair loss, 24% of shortness of breath (Lopez-Leon et al. 2021). In a large study in England (Ayoubkahni et al. 2021), over 47,000 hospitalized COVID-19 patients were followed for 4 months after discharge and compared to a precisely matched (age, sex, health status, etc.) control group from a pool of 50 million patients over the past 10 years. While only 9% in the control group reported readmission, 30% of COVID-19 patients were readmitted clinically in the same time window, 21% of them for respiratory illness (versus 1% in the control group).

PCS in patients with initially mild or asymptomatic courses

In a recently published study, approximately 30% of patients who had a mild course during acute COVID-19 illness and were not hospitalized (WHO progression scale 1-3; WHO Working group 2020) experienced persistent or late symptoms consistent with PCS 7 months after infection (Augustin et al. 2021). 11% of patients were still unable to fully participate in daily life and work 7 months after onset (Augustin et al. 2021).

In a study conducted by the Office of National Statistics of the Government of England, more than 360,000 people infected with SARS-CoV2 were followed for several months, whether or not they were symptomatic (Office for National Statistics, UK, 2021). The aim of the study was to examine long-term effects compared with a control group without proven SARS-CoV-2 infection. Among the approximately 22,000 who tested positive, about 14% were still reporting symptoms after 12 weeks (Figure 2). In the control group, this was only 2%, i.e. 7 times less. Furthermore, among

those who tested positive, 9% reported clear activity limitations and 2.5% reported severe limitations in everyday life. The proportion of patients reporting PCS symptoms hardly decreased after 4-5 months (Figure 2). The significant proportion of patients who develop PCS (over 10%) suggests that a larger number of people are affected by PCS than initially assumed. With an accumulated 3.5 million people suffering from COVID-19 (as of May 2021), several hundred thousand people with PCS can be assumed in Germany.



Figure 2: Time course of PCS symptoms. The proportion of patients who report persistent symptoms after surviving an acute SARS-CoV-2 infection. The share decreases over time and stabilizes in the double-digit percentage range after 4-5 months (source: Office for National Statistics, UK, 2021).

5. PCS also affects children and adolescents

PCS can also occur in children and adolescents. According to the Office for National Statistics UK study, the incidence is in the double-digit percentage range and increases with age (Figure 3). The exact proportion is the subject of research. However, if children and adolescents undergo an unrestrained contagion, the number of patients with PCS will be very large. As a result, both the U.S. NIH and the U.K. NHS have allocated resources to research or care for PCS in this age group.¹ Interventions that prevent the contagion of children and adolescents should be reconsidered, including the relation of vaccine injury and PCS.

¹ NIH News Release: NIH effort seeks to understand MIS-C, range of SARS-CoV-2 effects on children (March 02, 2021), https://www.nih.gov/news-events/news-releases/nih-effort-seeks-understand-mis-c-range-sars-cov-2-effects-children; NHS News:HS to set up specialized youth services as part of a £ 100m expansion of COVID coverage, https://www.england.nhs.uk/2021/06/nhs-sets-up-specialist-young-peoples-services-in-100-million-long-covid-care-expansion/, accessed June 23, 2021.



Figure 3: Gender and age distribution of people with symptoms at least 5 weeks after a positive test result. A significant proportion of 2-16 year olds also develop PCS (source: Office for National Statistics, UK, 2021).

6. How can the diagnosis be made?

Since no specific markers in the blood or characteristic radiological abnormalities are known to date, the diagnosis of PCS must be made clinically. A correct diagnosis requires that the relevant symptoms did not already exist before the SARS-CoV-2 infection and that patients experience relevant limitations in daily life as well as a certain level of suffering. Therefore, a differentiated and critical anamnesis to assess the symptoms is an essential step for the diagnosis, which is very time-consuming. The recording of the different symptoms is also important in order to offer the individual patient tailored therapy and rehabilitation suggestions with the aim of shortening the convalescence phase.

7. Treatment options

The pathophysiological relationships of PCS are partly unknown, which complicates the development of causal therapies. Currently, therapy concepts are based on an interdisciplinary approach, measures of physical rehabilitation as well as symptomatic therapy of the different organ disorders. Future identification of targeted therapeutic approaches is therefore of great importance. Further studies are needed on the efficacy of vaccination or administration of antibodies to SARS-CoV-2 in PCS (Arnold et al. 2021). There is preliminary evidence that SARS-CoV2 vaccines may lead to improvement in a proportion of patients (Washington Post 2021; Medscape Pediatrics 2021).

8. Structures for clinical care of PCS patients

Establishment of post-COVID-19 competence centers (PCS competence centers)

Since PCS is a multisystem disease, interdisciplinary collaboration (neurology, psychiatry, pneumology, cardiology, rehabilitation medicine) in cooperation with primary care physicians is required for comprehensive care of these patients in the outpatient setting. Against this background, it is important to establish special PCS competence centers at university hospitals, where specialists from several disciplines can offer integrated care (Figure 4). Such structures have already been established, for example, at the University Hospital of Cologne² and at the Ludwig Maximilian University of Munich.³

Integrated collaboration with primary care physicians is essential to provide optimal care for patients with PCS (Figure 5). The aim is to achieve a rapid recovery and a better quality of life for those affected. This can enable a quick return to work and reduce treatment costs.

² https://www.uk-koeln.de/de/patienten-besucher/coronavirus/post-covid-sprechstunde/, accessed 23.6.2021.

³ https://www.lmu-klinikum.de/aktuelles/pressemitteilungen/ein-jahr-corona-pandemie-in-deutschland/ 3dad60a0892ab5a5, accessed 23.6.2021.



Figure 4: Possible structure of an interdisciplinary PCS competence center. The complexity of the clinical picture of PCS requires the interlocking collaboration of different disciplines.



Figure 5: Integrated collaboration for optimal care of patients with PCS. The treatment of PCS patients requires a good interaction between general practitioners, outpatient clinics, hospitals and rehabilitation facilities.

A major obstacle is that the care of PCS patients has not yet been established in Germany and is therefore not included in the reimbursement system. It is therefore a first step in the right direction that, from July 1, 2021, physicians will be able to prescribe physiotherapy and occupational therapy for the long-term consequences of a coronavirus infection, without their therapeutic products budget being burdened.

9. Research on PCS

It is also important to develop a better understanding of the causes of PCS and the frequency of PCS symptoms. This includes, among other things, the establishment of diagnostic criteria, a severity classification (also with regard to possible occupational disability), and new targeted therapy approaches.

Among other things, the cellular and humoral immune response against SARS-CoV-2 must be investigated, including the gut-associated lymphoid tissue (GALT). In the GALT of the small intestine, SARS-CoV-2 might persist due to high ACE2 expression in the epithelium (Hamming et al. 2004; Gaebler et al., Nature 2021) and contribute to protracted PCS courses via regulation of the cellular immune response and a chronic inflammatory state.

Many patients seem to benefit from holistic outpatient rehabilitation concepts with ergo-, logoand physiotherapeutic measures. However, these subjective improvements should urgently be objectified within the framework of prospective studies in PCS competence centers in order to create a better evidence base.

10. Economic and social impact

PCS can trigger significant psychosocial consequences. Respective studies report a significantly increased incidence of mental disorders (post-traumatic stress disorder, depression, anxiety disorder) immediately following SARS-CoV-2 infections compared to unaffected populations (Vindegaard & Benros 2020). Social consequences are also likely. For example, experiences of stigmatization are reported in connection with surviving COVID-19 disease (Muhidin et al. 2020). In addition, there are individual and societal costs due to inability to work, loss of earnings, job loss, or occupational disability. The expected psychosocial consequences of developing a PCS hit those with a small social network and few opportunities for compensation the hardest and contribute to a widening of the social gap.

11. Required framework

- 1. **Research:** Research on this new condition needs to be coordinated and address questions about both causes and clinical problems. These are:
 - a) Prospective analyses of the long-term course of PCS.
 - b) Development of diagnostic criteria.
 - c) Formulation of targeted therapy and rehabilitation measures.
 - d) Research into the causes of PCS.
- 2. **Structures for medical care:** Since PCS is a multi-organ disease, the treatment of PCS requires an interdisciplinary framework. The establishment of specialized interdisciplinary PCS competence centers (consisting of physicians for internal medicine, ENT, neurology, psychiatry, and cardiology, among others) in cooperation with primary care physicians is necessary in order to ensure individual care, to conduct further research and to develop

improved therapy options and support measures for PCS patients (Figure 4 and 5). Figure 6 illustrates the necessary structures and their interaction.

3. A framework for medical education, training and continuing education: findings from research and the PCS competence centers must be continuously incorporated into the curricula in medical studies as well as in continuing medical education and training.



Figure 6: Structures required for the care of PCS patients (Nalbandian et al., 2021).

12. Policy Recommendations

PCS represents a new, common, serious, and protracted health disorder in individuals after surviving SARS-CoV-2 infection, whether or not they were initially symptomatic. Unlike deaths, hospitalizations, and intensive care treatment for acute SARS-CoV2 infection, PCS is not captured in reporting data and is not part of media coverage of the corona pandemic. This results in lower awareness of this issue to the point of lower vaccination preparedness (COSMO 2021). Increased health education about PCS therefore seems necessary. In addition, increased efforts are needed to research the clinical picture, to improve diagnosability and to provide appropriate care services.

The frequency and the resulting, sometimes severe, health disorders of PCS are a further argument for consistently pursuing a **low-incidence strategy**. The prevention of infection through general protective measures, as well as the implementation of an effective and comprehensive

vaccination campaign, should remain the focus of political efforts in Germany. This also applies to the previously largely unvaccinated age groups, including children and adolescents.

Despite mild or asymptomatic courses, PCS can also affect them - accepting an epidemic in this age group risks many PCS cases. This unnecessarily puts them at risk and could impose currently unestimable long-term costs on healthcare and society. Childhood and adolescent vaccination strategies and infection control measures in care and education settings should take this into account.

More comprehensive **data** (e.g., through routine, possibly digitally assisted, screening of Sars-CoV-2 infected individuals) and targeted **research funding** on PCS as a distinct condition are needed to understand the causes of PCS and improve diagnosis and treatment.

In view of the high numbers of PCS patients, appropriate **care capacities** should be established. This includes, in addition to interdisciplinary competence centers at university hospitals, nationwide outpatient (initial) contact points - also in rural areas - as well as specialized rehabilitation clinics. For children and adolescents, there are currently too few contact points (the Long Covid Outpatient Clinic at the University Hospital of Jena is a good example). In addition, offers for the rehabilitation of PCS patients must be created.

There is a need for a **PCS education and information campaign** aimed at medical professionals, patients, employers and the general public. Part of the campaign can be a website and/or an app that provides information (in different languages spoken in Germany) on symptoms, treatment options and (local) contact points, as well as promoting the networking of experts. The education should be carried out with the aim of improving the recognition and acknowledgement of the disease and creating a social awareness of its existence and the health consequences.

As an individual response to the inadequate care and recognition of PCS symptoms, patients are currently organizing and networking in self-help and information groups worldwide to support each other and advocate for education and better treatment options. These **patient organizations** should be included in the **PCS infrastructures** which need to be created, and in the communication processes.

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