Chapter 3
Clinical Symptoms and Course of COVID-19

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SARS-CoV-2 Transmission

The key for the SARS-CoV-2 infection are human-to-human transmissions, however, the virus may also infect and replicate and array of animal hosts, including companion animals, household pets, and farm animals (e.g., minks). Animal replication may play a role as potential reservoir hosts for the virus and associated with possibility of the new variant emergence [1]. First reports on the COVID-19 incubation period defined a medium of 5.5 days with the range between 3 and 14 days. This timeline has been shortened with the emergence of the novel, highly transmissible, and infectious variants. For example, median asymptomatic period for the Omicron variant is three days [2]. Transmission is possible from both asymptomatic and symptomatic hosts. Early stages of the infection are associated with the highest virus transmissibility (the highest viral expression in the upper respiratory tract). Usually the peak of infectivity is 2 days before and 1 day after the symptom onset. However, for the Omicron variant the peak of virus shedding might be delayed to 3–6 days following the initial symptoms. Infectivity of the virus wanes after 7–10 days, except in patients with immunodeficiency where infectivity exceeding 4-week period have been reported [3]. It should be emphasized that viral RNA may be detectable by molecular methods even weeks after infection and **is not a marker of patient infectivity.**

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Virus Replication

In general infection symptoms are dependent on both viral replication and cellular tropism as well as host responses. It is widely known that the S protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), which is well established as a key entry receptor for most host cells [4]. ACE2 is highly expressed on alveolar epithelial cells, intestinal enterocytes or vascular endothelium but also in the array of other tissues including kidneys (tubular and glomerular cells), adipose tissue, heart (myocytes, pericytes and epicardium), nervous system (neurons and glial cells) as well as male and female reproductive system (mostly Leydig and Sertoli cells), skin (epidermis), thyroid gland, thrombocytes, macrophages or even the pancreatic Langerhans islets. This ACE-expression based cellular tropism determines clinical course of the disease [4].

In general two pathways are used by the virus to enter the host cells. The first, early pathway, is the cell surface pathway dependent on the host serine protease (TMPRSS) activation allowing for the S protein to interact with the receptor. Alternative (late) pathway for SARS-CoV-2 entry into host cells is the endosomal-lysosomal endocytic pathway with internalization into endosomes and cathepsin-mediated cleavage triggered by low pH. Pathway use is dependent on the TMPRSS expression: in tissues with the high expression the early pathway is preferentially used, while if the protease is absent, late pathway is utilized. Efficacy of the viral entry is further facilitated by the human Furin, with its cleavage site within the spike protein strengthening the tropism for the airway epithelial cells. After cleavage, viral membranes fuse with the endosomal membrane which facilitates nucleocapsid entry into the cytoplasm [5]. In the cytoplasm the virus releases RNA which is transcribed by the viral RdRP polymerase followed by translation into viral proteins, including structural membrane (M), spike (S), and E. Viral particles are then assembled, packaged, and released by exocytosis. Viral replication results in a negative regulation of ACE2, which in turn leads to the degradation of angiotensin II, production of angiotensins 1–7 and activates the mas oncogene receptor, associated with the negative regulation of angiotensin II, mediated by the type 1 angiotensin II receptor (AT1R) [6, 7]. Activation of AT1R is one of the mechanisms ultimately leading to the acute lung damage. The mechanism of action of the SARS-CoV-2 virus in this context is highly similar to that seen in SARS-CoV [5] (Fig. 3.1).

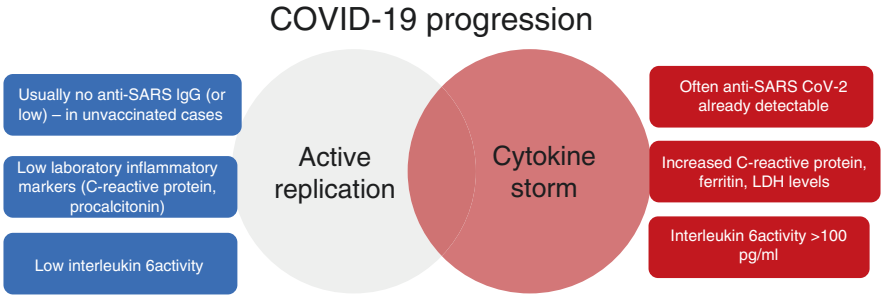

Fig. 3.1 Association between active replication and cytokine storm phase of the SARS CoV-2

Immunological Responses and Cytokine Storm (CS)

Infection with SARS-CoV-2 results in the secretion of large amounts of inflammatory cytokines and chemokines. High levels of IL-2 (interleukin), IL-7, IL-10, G-CSF (granulocyte colony-stimulating factor), TNF (tumor necrosis factor), CXCL10 (CXC-chemokine ligand 10), MCP1 (monocyte chemoattractant protein-1), and MIP1α (macrophage inflammatory protein 1 alpha) in serum were observed in patients with severe COVID-19 resulting in the hyperactivity of the host immune system [5]. Interstitial mononuclear lymphocyte-dominated inflammatory infiltrates in the lungs and severe lymphopenia with hyperactive T cells in the peripheral blood were all found in patients with COVID-19. At the cellular level, in patients with severe COVID-19, release of pro-inflammatory cytokines leads to lymphopenia, lymphocyte dysfunction, and granulocyte and monocyte anomalies [8].

COVID-19-associated cytokine storm (CS) is a unique form of a hyperinflammatory response which has been characterized in association with the SARS CoV-2 infection [5]. Cytokine storm, caused by the excessive secretion of cytokines, leads to a severe systemic inflammatory response [9]. In general, the onset of a cytokine storm resembles systemic inflammatory response syndrome (SIRS) with imbalance between pro-inflammatory and anti-inflammatory responses. By definition, the inflammatory response is designed to protect the host from damaging stimuli and is a mechanism necessary for recovery. However, an overactive inflammatory response, as in a cytokine storm syndrome, may cause widespread tissue damage and is directly linked to mortality [10]. Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12 are produced *inter alia* by an array of immune cells such as B lymphocytes, T lymphocytes, macrophages, dendritic cells or monocytes [11] as a result of the increased expression and activation of TLR7 and TLR8 in lung tissue [12]. IL-6 is an activator of the JAK/STAT3 pathway during inflammation. Studies from 2020 showed that the IL-6-JAK-STAT3 pathway is strongly associated with the severity of COVID-19 symptoms. Cytokine storm is a characteristic of macrophage activation syndrome (MAS), but in SARS-CoV-2 infection, macrophage parameters differ between those found in classical MAS [2]. In COVID-19 patients, an increased activity of the monocyte activation markers sCD14 and sCD163 were observed [13] while monocytes strongly expressed the ACE2 receptor [14] and induced IL-6 expression, thus contributing to an increase in the severity of the cytokine storm.

Cytokine storm in COVID-19 patients is also associated with massive mononuclear cell infiltration in organs, thrombosis, and tissue hypoxia and leads to alveolar structural damage and lung ventilation dysfunction by damaging the lung capillary mucosa and by promoting alveolar edema [15, 16]. CS is largely responsible for multiple organ dysfunction syndrome (MODS) of which ARDS and/or SIRS are major components. Usually CS evolves in the later stages of infection, more than 5–7 days from the initial symptoms. As IL-6 and IL-1 are significant activators of CS and the inflammatory cascade, of these IL-6 levels have become a laboratory marker of CS [17].

The presence of comorbidities have significant impact on the disease course with the following comorbidities significantly increasing the severity of symptoms: hypertension, diabetes, cerebrovascular disease, cardiovascular diseases, respiratory disease, malignancy, chronic kidney disease, and chronic liver diseases. This is further elaborated in the Chapter 4.

Virus Variants and Associated Evolution in the Clinical Course

Evolution of the SARS-CoV-2 variants especially within the spike region is leading to increase of transmissibility and more effective evading the immune system. Evolution of SARS-CoV-2 has been monitored and assessed by WHO and other worldwide institutions since January 2020. Due to the increasing threat to global public health, new variants have been classified into groups, among which the most important from the current global public health perspective are Variants of Concern (VOCs) [18]. Variants of concern associate with the distinct phenotypic characteristics related to the disease severity, transmissibility, risk of reinfection, diagnostics, and vaccine performance. Well established VOCs, associated with pandemic waves include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) with BA subvariants. For example, Delta variant associated with the increased risk of severe infection requiring in-hospital treatment was less commonly associated with the loss of taste and smell if compared to the original Wuhan strains and augmented the probability of the fungal superinfections including mucormycosis. Number of critical care admissions was also significantly higher for the Alpha and Delta VoC compared to the infections in the early pandemics [19]. On the other hand, Omicron variant, despite increased transmissibility, associated with higher rate of asymptomatic infections [20].

In general, infection with the Omicron variant is expected to be milder than infection with earlier circulating variants, especially Delta, but some patients still develop severe disease requiring hospitalization and causing death [18]. Reports from South Africa show a reduction in the need for hospitalization by 29% among people infected with the Omicron variant, while the British reports show a reduction in the risk of any hospitalization and multi-day hospitalization by 20–25% and 40–45%, respectively, among unvaccinated people who did not have an infection before. SARS-CoV-2. People infected with the Omicron variant show symptoms similar to those caused by the previous variants, but their presence and severity are influenced not only by age, comorbidities, but also by a previous SARS-CoV-2 infection and vaccination [18].

Clinical Stages of COVID-19 [21]

Mild and Asymptomatic Stage

The clinical manifestations range from asymptomatic to life-threatening infection. Depending on the cohort, frequency of asymptomatic, mildly symptomatic or cases with short-term transient symptoms is between 25% and 50%. This data are supported by various metanalyses concluding that at least one-third of observed infections were asymptomatic. Serological cohort studies indicated that even >50% of cases might have been unaware of previous contact with the virus. The first data from China shown that most of the patients present with mild to moderate symptoms of the disease, and therefore, may be treated in an ambulatory setting. In asymptomatic or mildly symptomatic patients dyspnea is not usually present and blood oxygen saturation remains normal (SpO2) ≥95% in ambient air.

Symptomatic Stage

In this stage, patients have clinical and radiological signs of mild to moderate interstitial pneumonia with $SpO_2 < 94\%$ in ambient air. Some patients still develop fever, fatigue, and other extrapulmonary symptoms, as well as a dry cough and shortness of breath. In the UK, infections with the Omicron variant were associated with fewer lower respiratory symptoms compared to earlier variants. The most common reported symptoms in this group of hospitalized patients were: fever, cough, fatigue, sputum production, and shortness of breath.

Severe Disease

Severe disease with respiratory failure (dyspnea, respiratory rate greater than 30/min, $SpO_2 < 90\%$ in ambient air, and/or inflammatory lesions in the lungs covering more than 50% of lung fields within 24–48 h of symptom onset) and cytokine storm syndrome may develop in more than 15% of patients. Neurological symptoms affecting both the central and peripheral nervous systems are common among patients with severe infection. There have been reports of acute cerebrovascular disease (ischemic stroke, intracerebral hemorrhage, deep vein thrombosis), encephalitis, Guillain-Barre syndrome, visual disturbances, dizziness, disturbance of consciousness, ataxia, and convulsions. In addition, patients are at risk of psychiatric complications such as mood or psychotic disorders, anxiety, and insomnia. Currently, it is believed that cardiac involvement is more frequent than initially thought, and it also affects asymptomatic patients with mild and moderate COVID-19.

Acute Respiratory Distress Syndrome/Critical Stage

This stage is associated with critical condition that develops in approximately 5% of patients with respiratory failure, septic shock, and/or multiple organ dysfunction. In addition to acute kidney damage, the liver may experience cholecystitis, pancreatitis, intestinal obstruction, or mesenteric ischemia [22]. Cardiac arrhythmias, acute coronary syndrome, heart failure, myocarditis, and hemodynamic instability occur in more than 20% of patients admitted to the intensive care unit [23]. The risk of venous thromboembolism (VTE), including pulmonary embolism, in critically ill patients with COVID-19 was assessed as high at the start of the pandemic. The incidence of this complication among ICU patients was 31%. More recent studies have shown that the overall risk of VTE in patients with COVID-19, regardless of the severity of the disease, is lower (<1%), although it remains higher than in the general population [23]. Coexisting bacterial or fungal infections concern about 8% of patients and constitute one of the main causes of death, in addition to progression to acute respiratory distress syndrome (ARDS) and multiorgan failure. The most frequently isolated microorganisms are: Streptococcus pneumoniae, Klebsiella pneumoniae, Hemophilus influenzae, and Aspergillus fumigatus. Mucormycosis, first described in India, more often affects diabetic patients treated with glucocorticosteroids, tocilizumab, and undergoing mechanical ventilation [23].

Clinical Symptoms of COVID-19

General Symptoms in the Early, Asymptomatic and Mild Infection

Clinical symptoms evolved in time, which, as stated above, associated with the predominating COVID-19 variant in each pandemic wave. In the early studies the most common symptoms were cough, dyspnea, hyposmia, sputum production, and fever. With novel variants of concern symptoms evolved to predominant headaches, sinusitis or sore throat. For example, the most commonly reported symptoms of infection with the Omicron variant are cough, runny nose, sneezing, headache, fatigue, sore throat, and fever [2]. It should be also emphasized that other mild symptoms, namely shortness of breath, disseminated muscular aches, conjunctivitis, nausea, vomiting, abdominal pain, diarrhea well described in the previous pandemic waves remain to be commonly observed. However, the smell and taste abnormalities (anosmia and ageusia) are currently less common. There are also age-related differences in the symptom characteristics. For example, in pediatric cohorts the most common symptoms were fever, cough, nasal symptoms, diarrhea, and nausea/vomiting. On the other hand, elderly may present with confusion or delirium-like conditions, hypothermia, and body temperature decrease prior to respiratory symptoms [24].

Respiratory Manifestations

As the SARS-CoV-2 virus enters lungs cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which are abundantly expressed on the pneumocytes. This mechanism is well-studied with airway epithelial cells, including human alveolar type II cells being the major target for SARS-CoV-2 [4]. Other involved cellular compartments include vascular endothelium, as well as macrophages and monocytes. Viral tropism to the respiratory tract has evolved with the evolution of VoC, as described above. However, following fever, respiratory manifestations are the most prominent in patients affected by the symptomatic disease. Respiratory symptoms range from cough, dyspnea, increased sputum production, to interstitial pneumonia with acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure [25]. Severity of symptoms is resulting from the imbalance between epithelial cell involvement leading to their apoptosis, immune activation associated thrombosis, and neovascularization.

Early stage damage was associated with the microthrombi at the level of the microcirculation, alveolar type II cell hyperplasia, enlargement of interstitial capillaries, thickening of pulmonary venules, and no hyaline changes. On the other hand, in the late stages pneumonia associated with ARDS microangiopathy is present with angiogenesis, endothelial injury, and hyaline membrane formation and fibrin deposits associated with diffuse alveolar damage. Progression to ARDS is associated with altered pulmonary perfusion, hyperinflammation consistent with the cytokine storm features, and hypercoagulability. Furthermore, microcoagulopathy may progress to involvement of the larger vasculature, capillary congestion, and development of pulmonary thrombosis. Over time parenchymal consolidations evolve. Monocular cell and macrophage infiltrations are present in the interstitial space. As the pneumonia progresses, both bacterial and fungal superinfections may exacerbate the patient condition.

Pneumonia evolves in approx. 20% of COVID-19 cases with the most commonly observed bilateral interstitial lung infiltrates, often diffuse associated and associates with dyspnea, cough, and fatigue on presentation. COVID-19 pneumonia is combination of the three factors: inflammation, endothelial damage, and excessive clotting. Typically, pneumonia is observed after 5–7 days of the symptom onset, however, earlier and rapid evolution of this complication was also noted. Early pneumonia is affecting peripheral parts of the lung tissue and is most likely associated with direct cytotoxic effect of virus replication in the alveolar cells, while in the later disease stages it is related to the imbalance in the immunological responses and cytokine release. Cytokine storm syndrome is one of the factors related with late COVID-19 pneumonia and ARDS [15, 17]. The severity of hypoxemia, especially in the early pneumonia is often more severe if compared to the amount of the pulmonary tissue with inflammatory changes, which may associate with the alteration of pulmonary perfusion and imbalance in the ventilation/perfusion ratio [26].

ARDS is a severe complication, and it can also occur in the course of infections with other pathogens (bacteria, virus, fungus) with tropism for the respiratory tract,

or during sepsis, trauma, or aspiration. In ARDS caused by SARS-Cov-2, renin-angiotensin system imbalance plays a crucial role. It is difficult to estimate how many patients will develop serious complications like ARDS or respiratory failure since available data is inconsistent and should account for the variant variability. Early studies shown that ~33–50% of hospitalized cases develop ARDS, however, this percentage is largely dependent on the age and comorbidities. ARDS is undoubtedly a leading cause of COVID-19 associated mortality. Typically, oxygenation defect with PaO_2/FiO_2 ratio < 300 mmHg and increased dead space ventilation is observed. It is commonly concluded that the outcome of ARDS in the course of COVID-19 is commonly less favorable compared to other etiologies [26].

Radiologic imagining either chest X-ray or computed tomography are now widely implemented for the diagnosis of the COVID-19 pneumonia. Typically, bilateral, multifocal ground glass opacities are observed, most commonly located in the peripheral, posterior or basal parts of the lung [27]. Other described radiologic features include thin reticulation, peribronchovascular thickening, and dilatation. Unilateral changes were observed, especially in the early pneumonia before dissemination of lesions. Usually nodules, excavations or lymph tissue enlargement are not observed. Infrequently (<10%) consolidations or "inverse hello sign" as in organizing pneumonia is present. Obviously, if COVID-19 is overlapping the previous pulmonary disease with abnormalities in the lung tissue, radiological picture is less specific. Over time ground glass opacity may be evolving either to areas with crazy paving, where ground glass areas and intralobular reticulations superimpose, or consolidation areas (usually linear). In majority of cases maximum lung involvement is observed approximately 10 days from the onset of the disease symptoms with subsequent resolution. In mild disease complete resolution of lesions is expected, while more severe cases are associated with the prolonged radiological abnormalities, usually beyond 1–2 months. Fibrotic complications may evolve, however, exact proportion and risk are not entirely understood. Based on the percentage of the lung tissue involvement, the French Society of Thoracic Imaging (SIT) recommends grading lung involvement as absent or minimal (< 10%), moderate (10–25%), extensive (25–50%), severe (50–75%) or critical (>75%) [28].

Extra-Respiratory Manifestations

The presence of ACE2 receptors in extrapulmonary tissues and a tropism of SARS-CoV-2 to these receptors may lead to direct tissue and endothelial damage, dysregulation of local immune responses which commonly lead to a wide array of extra-respiratory disease manifestations. Main extra-respiratory manifestations among patients with COVID-19, included, but are not limited to cardiac, gastrointestinal, hepatic, renal, neurological, olfactory, gustatory, ocular, cutaneous, and hematological symptoms [29].

Hematologic Abnormalities

Lymphopenia may be associated with a severe disease course. The development of severe form of lymphopenia, a progressive decrease in lymphocytes, has been correlated with poor disease prognosis [30]. Lymphopenia may be induced by direct infection of SARS-CoV-2 T cells via the ACE2 receptor expressed on their surface and causing their lysis and/or by increased numbers of regulatory T cells (Treg). In COVID-19 patients, damage to lymphocytes, CD4+T cells and especially CD8+T cells has been observed, involving a reduction in the number of lymphocytes in the peripheral blood and subsequent apoptosis [31]. Lymphocyte apoptosis may be associated with hypercytokinemia that may cause disruption of lymphocyte-producing organs and with a depletion phenotype [32]. Differences in lymphocyte subsets are observed in COVID-19 both in mild to moderate and severe cases, with decrease in the lymphocyte CD4 and CD8 levels.

Lymphopenia and increased neutrophil counts correlated with an increased risk of developing ARDS in COVID-19 patients and an overall more severe disease course. Differences in neutrophil-lymphocyte ratio (NLR) in severe and non-severe patients are significant, with increased NLR in patients with severe COVID-19. A steady increase in neutrophil count, like a steady decrease in lymphocyte count, correlated with a poor prognosis among cases with COVID-19 [33].

Additionally, commonly observed hematologic abnormality include thrombocytopenia, either directly induced by the cytotoxic megakaryocyte effect of the virus or resulting from consumption during microthrombi formation. In majority of cases thrombocytopenia is sell limiting, however it has also been associated with decreased survival.

Prothrombotic Events

Another serious manifestations associated with COVID-19 are thromboembolic episodes, which may include both venous and arterial thromboembolic complications. Thromboembolic disorders remain one of the key and serious complications in COVID-19, due to interactions between inflammation, immunity, and coagulation system, especially during the cytokine storm, resulting in alveolitis, endotheliitis, complement activation, recruitment of immune cells, as well as immunothrombosis. SARS-CoV-2 is also associated with hypercoagulation resulting from the array of disfunctions, including inhibition of the plasminogen and complement activation, platelet disfunction, hyperimmune response or production of antiphospholipid, and antiplatelet antibodies [34]. Thrombosis may be initiated in the pulmonary vasculature, commonly resulting in the microangiopathy. Endothelial damage and subsequent coagulopathy are causative factors of the progression to severe manifestation including disseminated intravascular coagulation and multiple organ failures.

Initial studies found that thrombotic events occurred in 7.7% of patients, despite thromboprophylaxis [35]. Further data reported the incidence of the thromboembolic events to exceed 30%, especially among patients requiring mechanical ventilation. The most common presentation is the venous thrombosis, with key manifestation being pulmonary embolism (PE). Meta-analyses indicate a two-fold increased risk of death in COVID-19 patients who developed a venous thrombotic event. A plethora of studies and analyses have already confirmed a correlation between COVID-19 and the risk of thrombosis disclosing prothrombotic activity of this viral infection. For example, a large meta-analysis reported that pulmonary embolism (PE) and deep vein thrombosis (DVT) were observed in 16.5% and 14.8% of COVID-19 patients, respectively, while in more than half of the patients with PE no DVT was observed [36]. Extremely important complication is disseminated intravascular coagulation (DIC), observed in 4.3%–6.2% of COVID-19 patients, characterized by 26.2 times higher incidence of death. Thrombotic complications associated with increased D-dimer levels reported in significant proportion of patients. Increase in D-dimer levels correlated with the risk of death. Activation of an array of coagulation factors is also commonly observed, and includes increase in plasminogen activator inhibitor 1, factor VIII or von Willebrand factor levels. Fibrinogen levels may also increase and associate with disease progression. Hemostatic abnormalities related to COVID-19 may range from mild to moderate (usually with only 2–3 fold D-dimer increase), medium (D-dimer levels up to six-fold upper normal range, thrombocytopenia, mild prolongation of prothrombin time), and severe with venous thromboembolism, multiorgan failure, and features of organ ischemia. Further details on the thromboembolic events and pulmonary embolism are covered in dedicated book Chap. 12.

Cardiovascular Involvement

Cardiovascular complications of both acute SARS CoV-2 infection and post-COVID-19 may include myocardial injury, acute coronary syndrome, acute vascular injuries, myocarditis, heart failure, cardiomyopathy, arrythmias, as well as cardiovascular complications. All these are covered in details in the dedicated book Chaps. 6 and 7.

Neurological and Neuropsychiatric Manifestations

Neurological and psychiatric symptoms have been described as one of the key clinical features impacting COVID-19 [37, 38]. These are not only associated with the neurological complications following intensive care unit care but may also be linked to the viral and immunologic effects of the infection per se. Involvement of the central nervous system related to the possible expression of viral proteins and its

inflammatory and proapoptotic properties resulting in local inflammation and delayed synaptic signaling has been observed. Furthermore, the involvement of both astrocytes and neurons is associated to the ACE-2 expression on these cells which may relate to the neuropsychiatric symptoms, however, cytokine release and coagulation abnormalities may also significantly contribute.

COVID-19 neurological and neuropsychiatric manifestations are diverse [39], which may range from mild-to-moderate symptoms such as headache and dizziness (more commonly observed with Omicron variant), psychomotor deceleration, memory impairment (including "brain fog," associated with mild to moderate disease), anosmia, ataxia, speech disorders, neuralgia and to medium and severe complications such as neuropathic pain, muscular paresis and paralysis, epileptic seizures, and coma. Cognitive impairments, including personality changes, aggressive behavior, confusion have been observed, exacerbate with age and associate with hypoxia, and kidney disfunction. Features of encephalopathy associated with increased mortality. Inflammatory disorders include mainly encephalitis (demyelinating and limbic), encephalomyelitis, but not meningitis (no inflammatory changes in the cerebrospinal fluid). Peripheral nervous system disorders, though not common may include acute polyneuropathies Guillain–Barré syndrome and Miller–Fisher syndrome) and neuralgias, myalgias, polyneuritis, as well as myopathies [40]. Generalized weakness and fatigue are often observed for prolonged periods of time regardless the severity of the COVID-19. As mentioned before depending on the viral variant and cellular tropism divergent frequencies and severity of the smell and taste disorders have been reported, ranging from the partial to complete loss of smell and taste (infrequently long-term). The exact pathomechanism and reason for the variant related frequency differences remains unclear.

Moreover, from a clinical perspective, vascular disorders (cerebral ischemia, thromboembolic events of the cerebral vasculature, and cerebral bleeding) are one of the most common neurological manifestation of the disease – see relevant Chap. 8.

Psychiatric complications of the disease also remain common and are usually secondary to the disease itself. Wide array of psychiatric disfunctions and disturbances were observed, from depressive and mood disorders, insomnia, and anxiety. Features of post-traumatic stress disorders were also common, resulting both from infection itself, but also from the in-hospital experiences of closure, experience of dyspnea, or personal observations of the exacerbating condition of the fellow intreated patients. Psychotic disorders including suicidal tendencies were also reported [41].

Kidney Involvement

Effectively, ACE2 is expressed in the kidney stronger than in the lungs, however, acute kidney injury with the eGFR decrease (increase in serum creatinine levels), hematuria, and proteinuria has been reported with variable frequencies. Kidney

injury was more frequent in elderly, associated with previous kidney disease, hypertension or diabetes. Exacerbation of the chronic kidney injury is moderate to severe COVID-19 cases is common [42].

The virus may enter the kidney by invading podocytes subsequently involving the ACE2 in the proximal tubule [43]. Interestingly, SARS-CoV-2 infection both prevents ACE2 from attaching to the receptor and alternates ACE2 expression within the proximal tubular cells, especially in the areas of acute tubular injury. Accumulation of the AGII protein, not converted to AG1–7, promotes inflammation by increasing cytokine release and allows macrophage and monocyte infiltration. Kidney injury associated with COVID-19 is either indirect and associates with the multiorgan failure or directly induced by the cytotoxic effect of SARS-CoV-2 in the kidneys. The primary findings in renal biopsies were acute tubular injury and epithelial necrosis, but SARS-CoV-2 infection may exacerbate preexisting kidney conditions, such as lupus nephritis or membranous glomerulopathy. Pathophysiology of COVID-19-related acute kidney injury is related to hemodynamic and immunologic effects of the infection, with elevated CRP and Il-6, D-dimer, and fibrinogen being key laboratory markers associated with such injury. The pathological changes in kidney during COVID-19-associated AKI include tubulointerstitial, glomerular, and vascular damage. The kidney picture presents with diffuse proximal tubule injury with loss of the brush border and necrosis accompanied by vacuolar degeneration and tubulointerstitial fibrosis. In the interstitial compartment, inflammatory cell forms infiltrate, and edema can be seen. In the case of severe kidney injury, the basement membrane is the only barrier between the filtrate and the peritubular interstitium. Because of the increased endothelial permeability, glomerular filtrate leaks from the tubular lumen into the interstitium. In the glomeruli the diffuse and focal segmental fibrin thrombus in the glomerular capillary loops and endothelial injury were observed. In the case of collapsing glomerulopathy, glomerular epithelial damage occurs together with loss of podocytes integrity. Glomerular capillaries are segmental or globally collapsed and sclerotic, with hyperplasia and hypertrophy of the glomerular epithelium. Some cases present with diffuse erythrocyte stagnation in the glomerular capillary or glomerular loop occlusion by erythrocytes over peritubular capillaries [44]. On the vascular level, the picture of COVID-19 associated kidney injury demonstrates vasoconstriction of intrarenal vessels, increased vascular permeability, and microthrombi formation. Vascular endothelium damage occurs, which can be observed as swelling of endothelial cells. The leukocyte–endothelium interactions are enhanced, leading to leukocyte migration into the interstitium.

Gastrointestinal and Hepatic Involvement

COVID-19 gastrointestinal symptoms are commonly underreported and range from mild and transient nausea, abdominal discomfort and pain, loss of appetite but also diarrhea. ACE-2 expression in the gut, including enterocytes and the array of

epithelial cells, including gastric duodenal and rectal ones is extensive and associated with wide array of gastrointestinal functions, namely regulating intestinal amino acid homeostasis, modulating the intestinal microbiome, and influencing the expression of antimicrobial peptides [45]. This results in the high prevalence of intestinal abnormalities during SARS CoV-2 infection resulting both from immunologic imbalance and direct viral cytotoxic effect. In total approx. 20% of patients may report gastrointestinal symptoms of the disease. Patients with COVID-19 may present with decreased levels of probiotic bacteria, such as Lactobacillus and Bifidobacterium, in the gut. Fecal genomes SARS-CoV-2 patients are characterized by the abundance of opportunistic pathogens (*Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii*), which may affect the immune system both locally and systemically [46].

Further to gastrointestinal symptoms, abnormality of the liver function tests reflective of the liver injury, was commonly observed among patients with COVID-19. The most common is laboratory abnormality observed in this context is alanine aminotransferase activity increase, followed by elevations in a aspartate aminotransferase, gamma-glutamyl transpeptidase, and alkaline phosphatase and hypoalbuminemia. ACE-2 receptors in the liver are mainly expressed on cholangiocytes (bile duct cells), minimally expressed on hepatocytes and absent on Kupffer cells [47]. The mechanism of liver damage may be directly associated with the viral infection of liver cells or is secondary to coexisting conditions such as the use of potentially hepatotoxic drugs, systemic inflammatory response, disseminated intravascular coagulation (DIC), respiratory distress syndrome-induced hypoxia, and multiple organ dysfunction [48]. Preexisting liver disease including non-alcoholic fatty liver, strongly associate with liver injury during COVID-19.

Skin Associated COVID-19 Symptoms

An increasing number of reports describe the cutaneous manifestations of COVID-19 that often precede common respiratory symptoms. Skin lesions may vary from benign maculopapular rash to tissue necrosis [49, 50]. Skin lesions in the course of COVID-19 infection vary based on the virus variant and geographic location, ranging from 0.2% in China to 7.25% in India and 20.4% in Italy. Morphology of symptoms also varied geographically—symptoms of pseudo-frostbite (pseudo-chilblains) were most common in Europe and North America, while very rare in Asian countries [51, 52].

Skin lesions may be divided into five categories, based on the frequency and severity [53]:

1. Pseudo-chilblains lesions most often present as erythematous or purple papules on acral surfaces. Some reports also include vesicles or papules on the erythematous basis. The picture of these changes corresponds to frostbite, but is not accompanied by previous exposure to cold or other damaging factors. The

occurrence of these skin lesions was more often observed in young people, and was associated with late COVID-19 with high survival rate of >98%.
2. Urticarial lesions, most often with transient papules, most common among middle-aged women. In majority of cases lesions disappeared within 24 h.
3. Erythematous and maculopapular rash, mainly involving the trunk, accompanied by itching. These changes affect women slightly more than men.
4. Vesicular lesions, most often affecting the trunk but with variable morphology. Most often, these are vesicular lesions resembling chickenpox and other manifestations of VZV (Varicella-Zoster Virus) infection. These changes most often appear in patients at the onset of the infection.
5. Vascular occlusive lesions, lesions often resembling livedo reticularis (irregular purple reticular lesions, most often in concentric, circular forms), reticular purpura, and acral ischemia (ischemic lesions on distant parts of the body—mainly fingers and toes). Vascular occlusive lesions are the rarest but have the lowest survival rates >78%.

Some patients may have other skin lesions such as: non-necrotic or necrotic purpura, petechiae, cutaneous mottling, eruptive cherry angioma, violaceous macules, aphthous ulcers, purpuric exanthema or telogen effluvium. Those changes may occur in less than 5% of patients [54].

In children there were noted some cases of Kawasaki-like changes connected to COVID-19 infections.

COVID-19 in Children

SARS-CoV-2 infection in children is usually asymptomatic or has mild symptoms. Life-threatening disease and death from COVID-19 are rare. Only 0.1–1.5% of all COVID-19 cases in children require in-hospital treatment and 0.00–0.02% of all child COVID-19 cases resulted in death [55]. The severe course of the disease is associated with comorbidities. The main risk factors include the coexisting chronic respiratory diseases, neurological diseases, congenital genetic defects, cardiovascular diseases (especially heart defects), metabolic disorders (especially diabetes and obesity with a body mass index [BMI] above the 95th percentile for age) and conditions associated with immunosuppression [56].

The symptoms of infection in children and adults are similar, but differ in terms of frequency. Asymptomatic infections in children with documented SARS-CoV-2 infection fluctuate between 15% and 42%. The most common symptoms of COVID-19 are fever, cough, often productive, and sore throat [56]. Dyspnea in the course of pneumonia is closely related to the development of severe or critical symptoms of the disease, in particular, acute respiratory distress syndrome. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea may occur in up to 25% of cases, and lead to reduction in fluid and solid intake [57]. Less common and atypical symptoms among children include chest pain, loss of taste or smell,

changes in the skin (such as discolored areas on the feet and hands), abdominal pain, chills, muscle aches and pain, fatigue, headache, and nasal congestion. In infants and newborns, feeding difficulties are a frequent additional symptom. Symptoms and signs are almost never isolated in children with COVID-19.

Multisystem inflammatory syndrome is a rare but serious complication of COVID-19 in children. This disease is known in Europe as pediatric inflammatory multisystem syndrome (PIMS) and in America as multisystem inflammatory syndrome in children (MIS-C). Patients diagnosed with MIS-C had persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous changes, and in severe cases, hypotension and shock [58]. Some patients may develop symptoms related to myocarditis, cardiac dysfunction, and acute kidney damage.

Long COVID-19

Following COVID-19 infection and array of symptoms may be observed, ranging from psychiatric, neurological, general, cardiac to vascular. Issue is extensively discussed in the relevant Chaps. 22–24 of the book.

Conclusions

As described above, SARS CoV-2 and resulting COVID-19 is associated with the wide array of clinical symptoms, including virtually all vital tissues—basically any tissue where the ACE-2 is expressed. Symptoms result from the direct cytotoxic effect of the virus and immune response associated cytokine storm, as well as vascular involvement and drug induced complications. Furthermore, frequency and pattern of the observed symptoms vary and evolve over time begin largely dependent on the virus variant and its molecular variability but also on the vaccination history. It is expected, that over time pattern, severity and sequence of symptoms may change, as virus will evolve further.

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