

# Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists as of April 26, 2021

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**Introduction** In early 2020, the world found out about the novel *Betacoronavirus*, which in December 2019, caused an epidemic of pneumonia in Wuhan, China. The virus was officially named SARS-CoV-2 and the disease received the name COVID-19.<sup>1</sup> The outbreak has spread rapidly in many countries all over the world and on March 11, 2020 the World Health Organization (WHO) declared COVID-19 a pandemic. In the light of the increasing number of affected patients globally, there was an urgent need to establish the management of this emerging disease. In Poland, the first recommendations on the diagnosis and treatment of COVID-19 were issued by the Polish Association of Epidemiologists and Infectiologists on March 31, 2020.<sup>2</sup> Those practical guidelines were created based on the previous experience with 2 known human pathogenic coronaviruses, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), due to similarities and newly available data on SARS-CoV-2. The pathogenesis, transmission routes, methods of protecting against the infection, diagnostic procedures including molecular and serological methods, the definitions of a suspected,

probable, and confirmed case of COVID-19 along with clinical symptoms of the disease were described. However, most attention was given to specific management in various clinical presentations of COVID-19, including asymptomatic or mild, the stable stage with respiratory and/or systemic symptoms, the unstable stage of respiratory failure, and the critical condition with acute respiratory distress syndrome (ARDS). The recommendations have been updated twice due to new data becoming available, especially with regard to pharmacological treatment. The most important change in the first Annex from June 2020 was the recommendation to use remdesivir at an earlier stage of COVID-19, as a consequence of the Emergency Use Authorization issued by the United States Food and Drug Administration and European Medicines Agency (EMA).<sup>3,4</sup> The second amendment from October 2020 solidified the recommendation to apply remdesivir at the stage of viral replication and tocilizumab and/or glucocorticoids at the unstable stage of cytokine storm based on the results from clinical trials and real-world experience studies.<sup>5-8</sup> Moreover, several drugs were delisted due to evidence of therapeutic

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ineffectiveness.<sup>9</sup> After a year of the pandemic, despite global efforts of medical staff, we still do not have control of the disease. New hopes were raised with the development of vaccines; however, to date, vaccination coverage added to the number of people who have experienced SARS-CoV-2 infection is insufficient to achieve herd immunity. In the face of emerging data and growing clinical experience, new recommendations on the management of COVID-19 are needed.

**Etiology** Coronaviruses include a wide variety of viruses that cause disease in humans and animals. So far, 7 species of coronaviruses that are pathogenic for humans, mainly for children, are known. In 2002 and 2012, 2 new species that are highly pathogenic to humans were identified—currently known as SARS-CoV-1 and MERS-CoV. In December 2019 in Wuhan, China, several cases of pneumonia were described, and in January 2020 a new type of *Betacoronavirus* was confirmed as the agent. The genome of the new coronavirus named SARS-CoV-2 showed 79% similarity with SARS-CoV-1 and 50% with MERS-CoV. Like all coronaviruses, it has a positive RNA strand. The full genome sequencing and phylogenetic analysis were done at the beginning of 2020.

**Emerging variants** Novel emerging variants of SARS-CoV-2 are of significant concern due to changes in the binding affinity between the viral spike (S) protein and the angiotensin converting enzyme 2 (ACE2) receptor on the host cells, which may change the infectivity and disease course.<sup>10</sup> It should be noted that viral replicase-introduced errors allow for the emergence of random mutations in the viral genome. Emergence of strains with higher replicative capacity and infectivity is a natural phenomenon which provides an advantage for the novel strains with increased transmissibility.<sup>11</sup> Variants with increased infectivity and most likely pathogenicity are becoming the dominant circulating strains and are characterized by numerous point mutations within the spike region. So far, several such lineages have been identified, the key ones being the B.1.1.7 lineage first detected in the United Kingdom, the B.1.351 lineage originating from South Africa, and the P.1 lineage from Brazil.<sup>12,13</sup> These variants of concern are likely the cause of the epidemic waves observed in multiple countries, and the likelihood of further spread is assessed as high, which may lead to an increase in the hospitalization rates and pressure on the health systems.<sup>14</sup> Also, vaccine responses, infectivity periods, and mortality differ depending on the variant.<sup>15</sup> Molecular surveillance on the emergence and transmission of the novel variants may be achieved by scaling up the sequencing capacity and systematic population sampling. Knowledge on the genomic variation may provide the basis for understanding of the spatiotemporal transmission patterns, vaccine efficacy, and differences in the clinical course of the disease.

**Pathogenesis** SARS-CoV-2 spreads through respiratory droplet transmission as well as contaminated objects or surfaces and enters host cells via the functional cell receptor ACE2, with the support of transmembrane serine protease 2 and integrins. The S proteins of SARS-CoV-2 bind to the ACE2 receptor, localized inter alia on alveolar epithelial type 2 cells. Moreover, ACE2 receptors are highly expressed on the tubular epithelium of the upper esophagus, absorptive enterocytes of the ileum and colon, in the kidney, heart, pancreas, and, which is pathogenically important, in arterial and venous endothelial cells and arterial smooth muscle cells.<sup>16</sup> Immune responses induced by SARS-CoV-2 are biphasic.<sup>16,17</sup> During the incubation period and early stages of the infection, a specific adaptive immune response can eliminate the infection and block progression to more severe stages of this disease. It has been confirmed that susceptibility to various infectious diseases is associated with specific HLA haplotypes. In patients with impaired immune responses (eg, older people with underlying diseases, young persons with impaired or deregulated B-cell and T-cell immune responses), the virus will rapidly replicate with massive destruction of all cells with a high ACE2 expression, for example, alveolar epithelial type 2 in the lungs. This induces innate inflammation in the lungs, mediated by proinflammatory granulocytes and macrophages. Activated macrophages release over 100 cytokines (eg, interleukin [IL] 1, IL-6, and tumor necrosis factor  $\alpha$ ) and chemokines (CXCL10 and CCL2) into the bloodstream (cytokine release storm).<sup>18</sup> These events, endothelial dysfunction (endotheliitis), and procoagulant state lead to life-threatening ARDS and impaired function of other organs.<sup>19</sup>

**Clinical presentation of the disease** The median incubation period for COVID-19 is 5.1 days, and 97.5% of all infections develop within 11.5 days.<sup>20</sup> Infection with SARS-CoV-2 has a broad clinical spectrum from asymptomatic, oligosymptomatic, to moderate or severe disease with multiorgan failure. The rate of asymptomatic infections ranges from 27% to 40%. Overall, approximately 90% of infections are uncomplicated, oligosymptomatic, or with moderate symptoms not leading to hospitalization.<sup>21,22</sup> Older age and comorbidities, such as hypertension, chronic cardiac, pulmonary, or kidney disease, diabetes, obesity as well as immunosuppression and cancer are risk factors for severe disease and death.<sup>23</sup>

Stage 1 of the disease includes asymptomatic and mildly symptomatic patients with oxygen saturation as measured by pulse oximetry ( $\text{SpO}_2$ ) of 94% or greater on room air not requiring hospitalization. Symptoms of COVID-19 at onset vary and most of them are nonspecific, but mainly include: fever, chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, sore throat, runny nose, and conjunctivitis. Some patients also experience

gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhea, and abdominal pain. New loss of smell (anosmia) or taste (ageusia) may be the sole presenting symptom, especially among women and younger or middle-aged patients.<sup>24</sup> Atypical symptoms can precede the respiratory symptoms of COVID-19 in elderly adults, and the most common are diarrhea with dehydration, fluctuating temperature with hypothermia, delirium, and falls. Since SARS-CoV-2 infection induces severe fatigue, falls can be common in older adults at little or no risk of falls.<sup>25</sup>

In stage 2, patients present clinical and radiological signs of mild to moderate interstitial pneumonia with SpO<sub>2</sub> less than 94% on room air. In some patients, fever, dry cough, shortness of breath, fatigue, and other extrapulmonary symptoms are still present.

Stage 3 is a severe form of the disease with respiratory failure (dyspnea, respiratory frequency over 30 breaths/min, SpO<sub>2</sub> of less than 90% on room air, and/or lung infiltrates more than 50% of the lung field within 24 to 48 hours) and cytokine storm syndrome.<sup>26</sup> Respiratory failure without subjective perception of dyspnea ("silent hypoxemia") is a dangerous phenomenon. In such cases, hypocapnia caused by compensatory hyperventilation is an accompanying finding.<sup>27</sup> Skeletal muscle damage associated with increased creatine kinase levels and neurological manifestations involving both the central and the peripheral nervous systems are common among patients with severe infection.<sup>28</sup> Acute cerebrovascular disease (ischemic stroke, intracerebral hemorrhage, deep cerebral venous thrombosis), encephalitis, Guillain-Barre syndrome, vision impairment, dizziness, impaired consciousness, ataxia, and seizure are reported.<sup>29</sup> Cardiovascular manifestations of COVID-19 (myocardial ischemia, myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic instability) are observed but at a lower frequency than in critically ill patients.<sup>30</sup> The typical course of severe disease includes overt dyspnea 6 days after the onset of the first symptoms, hospitalization after further 8 days, and the need for tracheal intubation 10 days after hospitalization.<sup>31</sup>

Stage 4 is a critical condition which develops in around 5% of patients, with hypoxemic respiratory failure, septic shock, and/or multiple organ dysfunction (inter alia acute kidney injury, liver dysfunction, bleeding, and coagulation dysfunction). In the ICU, venous and arterial thromboembolic events occur in 31% to 59% of patients.<sup>25</sup> Death is caused by progression to ARDS and multorgan failure.

**Laboratory diagnostics** Principles of molecular diagnostics Currently, laboratory confirmation of SARS-CoV-2 infection is based on molecular diagnostics: either detection of the viral nucleic acid or antigens from clinical samples. Typically, the highest sensitivity of molecular assays is observed

with the initial symptoms of the disease, with genetic material often also detectable at the end of the presymptomatic phase of the infection.<sup>32</sup>

**Nucleic acid amplification testing** Since the beginning of the SARS-CoV-2 epidemic, nucleic acid amplification techniques allowing for the detection of genetic material of this virus have been rapidly introduced.<sup>33</sup> Techniques based on polymerase chain amplification have been supplemented with loop-mediated isothermal amplification and transcription mediated amplification assays. Nucleic acid amplification tests, currently a gold standard of diagnostics, are designed to detect different genes of SARS-CoV-2 including ORF, E, N, S, RdRp, and other regions. Molecular testing should be performed by a quality-controlled laboratory provider with the test targeting at least 2 (preferably 3) regions of the viral genome. Detected genetic material is not a proof of infectivity, as it may be detectable after several weeks from the onset of infection. Pooling of specimens may be useful for population diagnostics but should not be performed in the hospital setting for clinical purposes.

**Sequencing of the SARS-CoV-2 genome** To investigate molecular evolution of the virus, genomic sequencing techniques may be implemented. This allows for the molecular surveillance of the emergence of mutations affecting transmissibility and pathogenicity of the virus, principally within the spike gene coding region and identification of newly emerging variants with pandemic potential.

**Antigen tests** Detection of viral antigens allows for rapid (15–30 minutes) SARS-CoV-2 diagnosis, improving efficacy of testing and detection of infectious cases and reducing the cost of molecular diagnostics. Sensitivity of antigenic tests is lower compared with nucleic acid amplification testing, and antigen-based testing remains limited to the initial period of infection. The recommended (European Centre for Disease Prevention and Control) diagnostic sensitivity of antigen assays is 90% or greater with specificity of 97% or greater.<sup>34</sup> This testing is intended for symptomatic cases within the first 5 to 7 days after the onset of the disease. In asymptomatic cases, a negative result of the antigen test following the exposure does not rule out the possibility of infection, but a positive antigen test should be regarded as confirmation of active infection. A positive antigenic test in immunocompromised individuals may be indicative of prolonged viral shedding and infectivity.<sup>35</sup>

**Serological testing** Serological tests reflect antibody responses following exposure and may reflect long-term immunity against reinfection. However, protective antibody titers have not yet been established.<sup>33</sup> Data indicate that following an infection, neutralizing antibodies are present

for 3 to 6 months in protective titers, but it is unknown whether neutralizing function will vary for the emerging viral variants. Due to the serological window of 10 to 14 days, tests detecting antibodies are not useful for the diagnosis of active SARS-CoV-2 infection. Their clinical utility lies in confirming infection in cases with clinically suspected COVID-19 and negative molecular test results. Serology may also be used for population surveillance studies, vaccine response analyses, to identify candidates for plasma donation, and in the diagnostic workup of postinflammatory syndromes. To detect antibody responses following vaccination, serological assays detecting IgG antibodies against the S1 subunit of the S protein should be used. Rapid immunochromatographic tests are of low sensitivity and specificity and should not be used in practice.

**Therapy** In mildly symptomatic patients, only antipyretic, antitussive drugs and inhaled budesonide are recommended. Vitamin D3 supplementation and low-molecular-weight heparin in prophylactic doses should be determined individually. The primary treatment in moderate or severe disease is remdesivir, tocilizumab, dexamethasone, or methylprednisolone. Low-molecular-weight heparin, rehydration, antibiotics (if necessary), and symptomatic medications are recommended as a supportive therapy. The vast majority of hospitalized patients require oxygen supplementation, and the flow depends on the demand. In patients with critically severe disease with respiratory failure, it is recommended to use high-flow oxygen therapy, mechanical ventilation, or extracorporeal membrane oxygenation. So the treatment regimen depends on the stage of the disease and is detailed below.

**Stage 1** In the vast majority of patients (80%–90%), SARS-CoV-2 infection develops with no or mild symptoms and such individuals do not require hospitalization.<sup>9</sup> However, in some cases, this clinical form may represent stage 1 of the disease, preceding the fully symptomatic stage 2 (TABLE 1). Stage 1 patients followed by a primary care physician usually require no treatment, and monitoring of their clinical status is a sufficient management option.<sup>9</sup> All adult patients staying at home should be registered in the Home Medical Care (Pulsocare) system with monitoring of SpO<sub>2</sub>, which should be at least 94%. All patients followed by the Pulsocare system who report measurements are looked after by consultants and physicians who will assess indications for hospitalization in the event of alarm values of measurements and may call the emergency medical services. However, baseline oxygen saturation in patients with chronic respiratory diseases can be decreased, which does not necessarily mean that SARS-CoV-2-induced respiratory failure is progressing. If symptoms arise, patients may require antipyretic agents (nonsteroidal

anti-inflammatory drugs or paracetamol are most effective). It is recommended to supplement vitamin D3 in each patient, in accordance with the recommendations for the Polish population.<sup>9</sup> There is evidence indicating a risk of a more severe course of the disease in patients with vitamin D3 deficiency, with a low risk associated with the use of this agent.<sup>36</sup> It is recommended to use antitussive drugs in patients with severe cough (making it difficult to talk and sleep). In severe cases, the use of agents containing codeine can be considered, although its abuse and misuse may cause respiratory depression. In adult patients with symptomatic COVID-19, it is recommended to administer budesonide in a dose of 800 µg twice daily by inhalation.<sup>37</sup> In patients who are chronically bedridden and those with risk factors for deep vein thrombosis and/or pulmonary embolism, a prophylactic dose of a low-molecular-weight heparin is recommended.<sup>38–40</sup> However, there is insufficient evidence to support or not recommend the routine use of antiplatelet drugs in COVID-19.<sup>41</sup> Of note, patients with stage 1 disease should not be treated with glucocorticoids. These drugs have been shown to be ineffective in patients who do not require oxygen therapy. Furthermore, using glucocorticoids too early may increase the viral replication and, hence, worsen patient prognosis.<sup>8</sup>

Treatment with antibiotics or anti-influenza drugs is not recommended in SARS-CoV-2 infection, unless it is required because of another medical condition. Home oxygen therapy is not recommended in the acute phase of the disease due to the risk of a sudden life-threatening deterioration. The need to use oxygen therapy in the treatment of COVID-19 is a definite indication for hospitalization.

**Stage 2** Patients with increasing dyspnea and SpO<sub>2</sub> of less than 94% need oxygen therapy, which requires hospitalization. As part of the thromboembolic prevention, all hospitalized patients should receive a low-molecular-weight heparin, usually at prophylactic doses, which can be increased in justified cases. If symptoms have appeared within 7 days, the patient requires oxygen therapy, and if SpO<sub>2</sub> is below 94%, antiviral therapy is indicated. After 7 days of illness, antiviral therapy becomes useless as viral replication disappears in most patients. The only currently approved antiviral drug with proven efficacy against SARS-CoV-2 in adults and children over 12 years of age is remdesivir, which should be administered by intravenous infusion at a dose of 200 mg on the first day, and 100 mg on the following 4 days.<sup>5,6</sup> Extending the treatment period beyond 5 days does not improve the effectiveness of the therapy.<sup>42</sup> The main contraindication to the use of remdesivir is renal failure with glomerular filtration rate of less than 30 ml/min. Remdesivir should be discontinued if alanine aminotransferase levels exceed 5-fold the upper limit of normal.<sup>43</sup> If remdesivir is unavailable or



there are contraindications to its use, the use of convalescent plasma may be considered. However, its effectiveness has not yet been clearly confirmed.<sup>44</sup> It is assumed that the therapeutic effect can be expected only when plasma with a high antibody titer (at least 1:500) is used. In the event of no clinical improvement despite the use of antiviral therapy, dexamethasone in a daily dose of 4 to 8 mg may be considered.<sup>8</sup> However, it should not be used in the first week of illness due to the risk of an increase in viral replication. Antibiotics can be considered in case of bacterial superinfection.

**Stage 3** Clinical deterioration usually occurring at the beginning of the second week of the disease may be a sign of a commencing cytokine storm. Due to the increasing shortness of breath and the reduction of SpO<sub>2</sub> below 90%, low-flow oxygen therapy ensuring the supply of oxygen up to a maximum of 15 l/min is no longer sufficient. Patients require high-flow oxygen therapy, reaching 60 l/min. In this phase of the disease, it is crucial to detect the onset of the cytokine storm. An increase in the IL-6 concentration above 100 pg/ml justifies the administration of tocilizumab, an inhibitor of IL-6 receptors, which significantly reduces the risk of mechanical ventilation and death.<sup>7,45</sup> Tocilizumab should be administered as an intravenous infusion over 1 hour as a single dose based on body weight up to 800 mg (see TABLE 1 for dosing details). If no effect is observed, another infusion may be given after 8 to 12 hours. Tocilizumab should not be administered in patients with a neutrophil count below  $2 \times 10^9/l$ , a platelet count below  $50 \times 10^3/\mu l$  or alanine aminotransferase levels exceeding 5-fold the upper limit of normal.<sup>46</sup> At this stage of the disease, patients should still receive a low-molecular-weight heparin and glucocorticoids, and antibiotics if necessary due to bacterial infections.

**Stage 4** Further clinical deterioration indicates the stage in which ARDS occurs, requiring the use of high-flow oxygen therapy, and in most such cases, also tracheal intubation and mechanical ventilation, requiring the patient to be transferred to the intensive care unit. At this stage of the disease, 6 to 8 mg of dexamethasone is recommended, although higher doses of glucocorticoids are under investigation. There are no indications for introduction or continuation of remdesivir in patients in the intensive care unit. A lung-protective ventilation strategy should be applied—that means the use of low tidal volumes, appropriate values of positive end-expiratory pressure, adjustment of inspired oxygen fraction to partial pressure of oxygen in the blood (PaO<sub>2</sub>), and arterial oxygen saturation (SaO<sub>2</sub>) values. The use of ventilation in the prone position provides good results in some patients unresponsive to conventional methods of respiratory therapy.<sup>47</sup> Unfortunately, the mortality rate among patients with COVID-19 requiring mechanical ventilation is as

high as 67%.<sup>48</sup> The use of venovenous extracorporeal membrane oxygenation is indicated only in selected individuals, and its use is limited to expert centers with appropriate experience and technical capabilities. It may be beneficial in patients with ARDS (moderate or severe) diagnosed prior to the introduction of mechanical ventilation, ventilated no longer than 7 days, with severe disturbances in lung gas exchange despite optimal conventional ventilation and failed attempts of oxygenation improving methods (eg, prone position, neuromuscular blockade). It is also used as a bridging therapy to lung transplantation. There are also numerous contraindications to this therapy.<sup>49</sup>

**Treatment of unproven efficacy** A number of medications have been considered for use in COVID-19 and a few as a prophylaxis, but only a small proportion have been proved in clinical randomized controlled trials and/or in observational studies. The following medications failed to have their efficacy and safety confirmed or trials are ongoing.

#### Antiviral medications

- Favipiravir is a potent inhibitor of many RNA viruses. Preliminary study results may suggest that the drug can shorten the time to recovery for patients with COVID-19, help achieve viral clearance early so as to positively impact disease transmission in the community, and reduce the health burden by shortening the length of stay at the hospital.<sup>50</sup> Disadvantages include severe side effects, such as anaphylactic shock and pneumonia.
- Anti-influenza medications and nonspecific antiviral drugs: a limited number of trials have evaluated oseltamivir, amantadine, rimantadine, zanamivir, and acyclovir. No significant benefit for repurposed antiviral drugs was observed and oseltamivir may increase mortality.<sup>51</sup>
- Ivermectin: some clinicians concluded that this antiparasitic drug could significantly reduce viral load and accelerate recovery in patients with mild and moderate cases.<sup>52</sup> The WHO and Food and Drug Administration advise against this drug to treat COVID-19.
- Anti-HIV medications have been found ineffective in SARS-CoV-2 infection, but a number of trials are ongoing.
- Interferons: subcutaneous injection of interferon  $\beta$ -1a showed no significant improvement in time to clinical response, but the overall mortality at 28 days was reduced.
- Intravenous immunoglobulin has been used as an adjuvant therapy or in a concentrated (hyperimmune) form. The potential utility of intravenous immunoglobulin for the treatment of SARS-CoV-2 is unknown at this time.
- Monoclonal anti-SARS-CoV-2 antibodies: bamlanivimab with etesevimab and the combination of casirivimab plus imdevimab are anti-SARS-CoV-2 monoclonal antibodies.<sup>53,54</sup> There are currently insufficient data to recommend either for or against their use.

**TABLE 1** Recommended pharmacological management at different clinical stages of SARS-CoV-2 infection including primary and supportive treatment (modified from Flisiak et al<sup>8</sup>)

Disease stage	Primary treatment	Supportive therapy
Stage 1: asymptomatic or mildly symptomatic • SpO <sub>2</sub> ≥94% • No hospitalization is necessary	• Antipyretic drugs (paracetamol, ibuprofen, etc) • Rest • Oral hydration • Low-molecular-weight heparin in chronically bedridden patients • Antitussive drugs for severe cough • Budesonide, 2 × 800 µg daily by inhalation • Systemic glucocorticoids are contraindicated. • Antibiotics and anti-influenza drugs are contraindicated, unless there is a bacterial coinfection or concomitant influenza. • Oxygen saturation control, implementation of the Pulsocare remote alarm system (using pulse oximeters)	–
Stage 2: fully symptomatic (viral multiplication) • SpO <sub>2</sub> <94% • Usually week 1 after disease onset • Hospitalization is required	Remdesivir administered intravenously once daily for 5 days, with a loading dose of 200 mg on day 1, followed by a maintenance dose of 100 mg. If remdesivir is not available, high antibody titer convalescent plasma can be considered.	• Low-molecular-weight heparin at prophylactic or therapeutic doses • Dexamethasone in patients receiving remdesivir and oxygen therapy, intravenously or orally 4–8 mg daily; it should not be used in the first week of the disease if remdesivir is not administered. • Antibiotic therapy in case of secondary bacterial infection • Symptomatic treatment • Oxygen therapy • Oral or intravenous hydration
Stage 3: respiratory failure (cytokine storm) • SpO <sub>2</sub> <90% • Usually week 2 after disease onset • Hospitalization is required	Tocilizumab (in patients with IL-6 >100 pg/ml) is used intravenously in a single dose of 800 mg if PBW >90 kg; 600 mg if PBW >65 kg and ≤90 kg; 400 mg if PBW >40 kg and ≤65 kg; and 8 mg/kg if PBW ≤40 kg. The second dose can be administered 8–24 h after the first one, if the patient's general condition has not improved; and/or Dexamethasone phosphate administered intravenously at a daily dose of 6–8 mg <sup>a</sup> for 7–10 days	• Low-molecular-weight heparin at prophylactic or therapeutic doses • Antibiotic therapy in case of secondary bacterial infection • Symptomatic treatment • Low-/high-flow oxygen therapy • Intravenous hydration
Stage 4: ARDS • Unsuccessful pharmacotherapy to date • Need for mechanical ventilation • ICU treatment is required	Dexamethasone phosphate administered intravenously at a daily dose of 6–8 mg <sup>a</sup> for 7–10 days. If dexamethasone is not available, other glucocorticoids can be used at corresponding doses, ie, hydrocortisone: 50 mg intravenously 3 times daily, methylprednisolone: 10 mg intravenously 4 times daily, prednisone: 40 mg orally once daily; and/or Tocilizumab combined with dexamethasone may be considered in mechanically ventilated individuals (should be started early, within the first day of treatment).	• High-flow oxygen therapy • Noninvasive ventilation • Mechanical ventilation • ECMO in selected cases • Low-molecular-weight heparin in prophylactic or therapeutic doses depending on the clinical scenario • Empiric antibiotic therapy is strongly advised against unless there are evident signs of secondary bacterial infection

<sup>a</sup> According to manufacturers, 6 or 8 mg/ml dexamethasone phosphate contained in the available injection solutions correspond to, respectively, 4.95 and 6.6 mg/ml dexamethasone

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IL-6, interleukin 6; PBW, patient's body weight; SpO<sub>2</sub>, oxygen saturation as measured by pulse oximetry

#### Anti-inflammatory medications

• Data about use of nonsteroidal anti-inflammatory drugs are controversial. There are reports that ibuprofen blocks the diffuse inflammation produced by SARS-CoV-2 and thus might prevent COVID-19 complications.<sup>55</sup> However, nonsteroidal anti-inflammatory drugs do have fairly well-established side effects, so it is reasonable to use these medicines to treat the symptoms of mild COVID-19 but to minimize the dose and duration of treatment where possible.

• Anticytokine medications: apart from tocilizumab, a number of immune antagonists have been studied in clinical trials. So far, there is no confirmation of their efficacy in COVID-19, including anakinra, which failed to improve clinical outcomes in patients with mild-to-moderate COVID-19.<sup>56</sup>

**Unproven prevention: mouthwash and nasal spray**  
 Some recommend gargling with certain mouthwashes to kill viruses in the throat and temporarily reduce the risk of shedding viruses. Antiviral nasal

**TABLE 2** The IMPROVE VTE risk-assessment model to guide prophylactic anticoagulation after hospital discharge after the acute phase of COVID-19<sup>63</sup>

Risk factor	Points <sup>a</sup>
Prior venous thromboembolism	3
Diagnosed thrombophilia	2
Current lower limb paralysis	2
Current cancer	2
Immobilized for at least 7 days	1
Stay in the ICU or coronary care unit	1
Older than 60 years	1

**a** A score of 2 or more suggests the need of prophylaxis

Abbreviations: see [TABLE 1](#)

sprays work by coating viral particles within the nose to block their entrance into cells within the body. There are no clinical studies proving that it is effective in preventing human-to-human transmission.

**Late sequelae of COVID-19** Post-acute COVID-19 syndrome (PC19, long COVID) refers to persistence of symptoms or organ dysfunctions following the acute phase of COVID-19. Although the incidence, clinical presentation, and therapeutic recommendation are yet to be established, PC19 refers to abnormalities beyond 4 weeks after the onset of COVID-19.<sup>57,58</sup> It can be divided into subacute phase within 4 to 12 weeks and chronic phase beyond 12 weeks. The prevalence of PC19 varies between 30% and 80% and depends on the methodology of the study.<sup>59</sup> The most prevalent complications are pulmonary (dyspnea, hypoxia, reduced diffusion capacity, persistent inflammatory lesions and/or fibrosis on computed tomography [CT]), hematologic (thromboembolic events, anemia), cardiovascular (palpitations, dyspnea, chest pain, arrhythmias, myocardial fibrosis/scarring), and neuropsychiatric (chronic fatigue, myalgia, headache, olfactory/gustatory dysfunctions, anxiety, depression, sleep disturbances, and post-traumatic stress disorder). Multiple laboratory abnormalities including reduced estimated glomerular filtration rate, increased liver function test results, and hyperglycemia were reported 3 to 6 months following the acute phase of COVID-19.<sup>59</sup> Pediatric inflammatory multisystem syndrome is a separate post-COVID-19 condition in children and young adults with specific diagnostic criteria.<sup>60</sup>

Preliminary results of the Polish prospective study SILCOV-19 (the Silesian Complications of COVID-19 Database) show that after a median of 90 days of COVID-19 onset, the most prevalent symptoms are: fatigue (approx. 50%), reduced lung diffusion capacity (approx. 30%), ongoing inflammatory lesions on high-resolution CT (35% of hospitalized and 10% of nonhospitalized patients), anxiety (18%–24%), sleep disturbances (19%–34%), depression (5%–15%), and bradyarrhythmias (13%–16%). The most prevalent

laboratory abnormalities are anemia (48%) and neutropenia (28%), N-terminal pro-B-type natriuretic peptide levels above 125 pg/ml (26% of hospitalized and 9% of nonhospitalized patients), increased levels of D-dimer (20% of hospitalized, and 9% of nonhospitalized patients), and hyperbilirubinemia (approx. 10%).<sup>61</sup>

Clinical guidelines for PC19 lack strong evidence and over 40 prospective trials are underway. There is no evidence for routine screening in asymptomatic individuals. Symptom assessment should be performed 4 to 6 weeks and 12 weeks after discharge in patients with moderate to severe COVID-19. Diagnostics should be symptom oriented. The objective methods for pulmonary evaluations are the Borg Dyspnoea Scale, home pulse oximetry, 6-minute walk test, chest X-ray, pulmonary function tests, and, if recommended by a specialist, chest CT/high-resolution CT (usually not earlier than 3 months after COVID-19). For cardiac symptoms: 24-hour Holter monitoring and echocardiogram; in selected cases, cardiac magnetic resonance imaging or CT coronary angiogram. Some authors recommend routine screening for anxiety, depression, and sleep disorders. The need for laboratory testing depends on abnormalities during hospitalization. It is important to follow patients with acute kidney or liver injury, a thromboembolic event, chronic cardiovascular, pulmonary, liver, or metabolic disorders. Currently, there is no recommendation for routine screening for coagulation following COVID-19.

In the post-COVID-19 convalescence, rest, relaxation, and pulmonary rehabilitation with breathing techniques play an important role. There is no evidence for routine thromboprophylaxis, although high-risk patients may require prophylactic anticoagulation for up to 30 days after discharge ([TABLE 2](#)).<sup>62</sup> Direct oral anticoagulants and low-molecular-weight heparins are preferred over vitamin K antagonists. The role of antiplatelet agents has not been established. The therapy of sequelae should be based on general recommendations. It is underlined that a prompt initiation of anxiolytics and antidepressants improves prognosis. The benefits of corticosteroids or antifibrotic agents in post-COVID-19 inflammatory lung disease is not confirmed. It is advisable to include subjects after moderate-severe COVID-19 in prospective studies evaluating PC19.

**Vaccination** The Emergency Use Authorizations of the first COVID-19 vaccine was issued by the EMA in December 2020.<sup>54,65</sup> Currently available vaccines have been constructed using messenger RNA, vector, and recombination technologies. Regardless of the technology used, all EMA-approved COVID-19 vaccines meet stringent efficacy and safety criteria when used in accordance with the summary of product characteristics.<sup>66,67</sup> Recommendations on how to deal with the most common concerns regarding vaccination against SARS-CoV-2 are presented below.

- The priority in vaccination against SARS-CoV-2 infections after vaccination of medical workers should be given to people over the age of 60, in order from the age of over 80. Introducing any groups before the end of vaccination of seniors is unacceptable; such action would be unjustified from the point of view of public health, inhumane, and would increase the number of deaths, extending the duration of the epidemic and consequently prolonging paralysis of the health care system. People with cancer and diabetes under the age of 60, as well as parents of premature babies, should be considered as another group. After completion of vaccinations in the above groups, patients with other chronic diseases should be included. Only after vaccinating people over 60 years of age and chronically ill is it justified to take into account the social factors that determine the priority of vaccination.
- People who develop COVID-19 after the first dose of the vaccine may receive the second dose according to the schedule and time frame permitted by the vaccine summary of product characteristics. If this is not possible due to persistent disease symptoms, consideration should be given to restarting vaccination at least 6 months after the onset of disease symptoms, or after specific antispikes antibodies have disappeared.
- There are no contraindications for vaccination after COVID-19. However, the persistence of the specific immune response following SARS-CoV-2 infection is unknown. Based on the current state of knowledge, it is possible to postpone the vaccination of people who have had COVID-19 up to 6 months. However, it should be emphasized that due to the emerging new research results, the recommended time interval between disease and vaccination will probably be extended.
- Contraindications to vaccination against SARS-CoV-2 are: hypersensitivity to the active substance or to any of the excipients contained in the vaccine, or a history of any anaphylactic reaction in the past. It is permissible to vaccinate such a person with full protection against shock in hospital conditions, after prior notification of possible risks and obtaining written informed consent for vaccination.
- Chronic diseases, including cancer, or treatments, including immunosuppressive, are not contraindications to vaccination against SARS-CoV-2. However, vaccination is not recommended in the course of febrile diseases and during an exacerbation of a chronic disease. In people who have undergone organ or bone marrow transplantation, it is recommended not to vaccinate for 6 months after the procedure. The optimal timing for vaccination in patients scheduled for or undergoing immunosuppressive/biological therapy should be checked with appropriate specialist guidelines. Due to the risk of extravasation and bleeding, particular care should be taken when administering the vaccine to patients with severe coagulation disorders; it is advisable to compensate for any deficiencies before vaccination and apply pressure at the injection site after injection.

- According to the Centers for Disease Control and Prevention, pregnant females with COVID-19 might be at an increased risk of adverse pregnancy outcomes, such as preterm birth, compared with pregnant women without COVID-19.<sup>68</sup> Before deciding whether to vaccinate, pregnant women must be informed about lack of studies on the effects of vaccination against SARS-CoV-2 on fetal development. After considering the risk of infection, which can be dangerous in pregnancy, they should provide written informed consent to be vaccinated when deciding to immunize.
- Lactation is not a contraindication to vaccination against SARS-CoV-2. Due to lack of research in this group, the decision to vaccinate should be made individually by the breastfeeding woman and confirmed by written informed consent to undergo vaccination.
- Vaccination against SARS-CoV-2 can be carried out with a 4-week interval from vaccines containing live microorganisms. In other cases, the interval should be at least 2 weeks in order to differentiate possible postvaccination reactions and avoid the risk of a reduced specific immune response to one of the vaccines.

## ARTICLE INFORMATION

**CONFLICT OF INTEREST** None declared.

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