SPECIAL REPORT

Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists as of February 23, 2022

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ABSTRACT

The first Polish recommendations regarding the management of patients with COVID-19 were published by the Polish Society of Epidemiologists and Infectiologists (PTEiLChZ) on March 31, 2020, and the last annex was dated November 12, 2021. The ongoing state of pandemic, the emergence of new variants of the virus, and the availability of new drugs necessitate their updating. Changes introduced in the current version of recommendations for the management of COVID-19 comprised the possibility of using remedesivir in an outpatient setting, previously reserved for inpatient treatment, as well as other antiviral drugs—molnupiravir and nirmatrelvir/ritonavir. We revised the possibility of using monoclonal antibodies due to the resistance of the currently dominant Omicron variant. Anakinra, an antagonist of interleukin 1 receptors, has been added as a treatment option in advanced stages of the disease, and the recommended daily dose of glucocorticosteroids used in the most severe forms of COVID-19 has been increased. Information on vaccination and pre-exposure prophylaxis in specific populations has also been updated.

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Introduction The first Polish recommendations regarding the diagnosis and therapy of patients with COVID-19 were published by the Polish Society of Epidemiologists and Infectiologists (PTEiLChZ) on March 31, 2020.[1] The last annex to the recommendations, dated November 12, 2021, introduced new antiviral and anti-inflammatory drugs.[2] The persistent state of pandemic, the emergence of new viral variants, and the availability of new drugs raised the need to develop an updated version of the recommendations.

The present recommendations for the management of COVID-19 have been supplemented

with the possibility of using remdesivir in an outpatient setting, previously reserved for inpatient treatment, as well as other antiviral drugs— molnupiravir and nirmatrelvir / ritonavir. The possibility of using monoclonal antibodies was revised due to the resistance of the currently dominant Omicron variant. Anakinra, an antagonist of interleukin 1 (IL-1) receptors, has been added to the armamentarium of drugs used in the later stages of the disease, and the recommended daily dose of glucocorticosteroids used in the most severe COVID-19 has been increased. In addition to updating the therapeutic knowledge, the recommendations contain key information on the diagnosis and prevention of COVID-19, both in the course of the underlying disease and post-COVID syndrome.

Molecular variability of SARS-CoV-2 with the evolution of variants and the selection of mutations, mainly in the spike (S) protein coding region, affects the epidemiology of the pandemic, clinical course, effectiveness of vaccination and therapy, risk of reinfection, and sensitivity of diagnostic tools.[3,4] Currently, 5 strains are qualified as variants of concern: Alfa (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.616.2), and Omicron (B1.1.529), and there are 2 variants of interest: Lambda (C.37), and Mu (B.1.621).[5-7]

The clinical picture of the disease The clinical picture of COVID-19 changed with successive waves of the disease and it depended not only on the variable pathogenicity of subsequent variants, but also on the possibilities of and burdens faced by the health care system.[8] The median disease incubation period, ranging from 4 to 5 days for the earlier SARS-CoV-2 variants, was reduced to 3 days for the new Omicron variant.[9,10] Transmission 7 to 10 days after the onset of symptoms is unlikely even in the case of positive genetic tests.[11] Infection with the Omicron variant is milder, and the rate of asymptomatic infections is higher compared with previous SARS-CoV-2 variants, especially Delta, but some patients still develop a severe disease requiring hospitalization and causing death.[12,13] Moreover, infections with the Omicron variant are associated with fewer lower respiratory symptoms than the earlier variants.[14]

Stage 1 of the disease refers to asymptomatic or mildly symptomatic patients without dyspnea and with oxygen saturation (SpO_2) of 94% or greater in ambient air, not requiring hospitalization. In stage 2, patients have clinical and radiological signs of mild-to-moderate interstitial pneumonia, with SpO_2 below 94% in ambient air. Stage 3 is a severe form of disease with respiratory failure, SpO_2 below 90% in ambient air, lung inflammation, and a cytokine storm syndrome. Stage 4 is acute respiratory distress syndrome (ARDS), which develops in approximately 5% of patients and is associated with septic shock and / or multiple organ dysfunction requiring intensive care unit (ICU) stay.

Laboratory diagnosis The standard confirming SARS-CoV-2 infection remains the detection of the the viral genetic material or antigen in samples collected from a patient. Reverse transcription molecular assays with real-time subsequent polymerase chain reaction remain the gold standard of diagnosis. Genetic diagnostics is extended to analysis based on isothermal amplification (reverse-transcriptase loop-mediated isothermal amplification). The molecular test should detect at least 2 regions of the viral genome and should not be used to assess infectivity.[15] Due to the constant evolution of variants, molecular surveillance was introduced using sequencing technologies with virus line identification, mutation characteristics, and phylogenetic analyses determining the dynamics of transmission. The diagnostic specificity of antigen tests should be at least 97%, while the sensitivity at least 90%, although it can be lower for the Omicron variant. Their advantage is the speed of obtaining the result. They allow for the detection of symptomatic infections up to approximately 7 days from the onset of the disease symptoms, and the persistence of a positive result may indicate infectivity, although a negative result does not exclude it.[16,17]

The humoral immune response in SARS-CoV-2 infection can be tested by qualitative and quantitative antibody tests, neutralization tests and neutralizing antibody tests, and the cellular response by quantitative interferon-gamma release assay as well as by counting T-lymphocyte antigens activated by SARS-CoV-2 (enzyme-linked immunospot assay). In order to distinguish a previous infection from a postvaccination response, tests for differentiating antibodies against the S protein and the N protein can be used (the presence of anti-N antibodies indicates a past infection).

Treatment The choice of drugs used in COVID-19 must be determined by the phase of the disease, the patient's clinical condition, and the assessment of risk factors for severe disease. The recommended therapeutic procedures depending on the stage of the disease are described below and summarized in **TABLE 1**.

Stage 1 Patients in stage 1 of the disease, usually treated by a primary care physician, mainly require the assessment of the general condition and SpO_2 monitoring as well as the assessment of risk factors for severe COVID-19, which include: age over 60 years, obesity, diabetes, cancer, chronic heart failure, chronic respiratory failure, chronic renal failure, immunodeficiency, and immunosuppression.

Routine use of antiviral drugs is not necessary in all stage 1 patients. Currently, there are available drugs that inhibit SARS-CoV-2 replication and monoclonal antibodies that neutralize the virus. Drugs that inhibit viral replication, such as molnupiravir, nirmatrelvir (PF-07321332) / ritonavir, or remdesivir, should be administered up

TABLE 1 Recommended pharmacological management in adults at different clinical stages of SARS-CoV-2 infection, including basic and supportive treatment[a] (continued on the next page)

Disease stage	Primary treatment	Supportive treatment
Stage 1: mildly symptomatic • SpO_2 ≥94% • No hospitalization is necessary	The commencement of antiviral therapy is recommended up to 5 days after the onset of symptoms (up to 10 days in immunosuppressed patients), with particular emphasis on patients at risk of a severe course[b] and under direct medical supervision during the qualification and monitoring of treatment. These drugs should not be used in pregnant and lactating women. • Molnupiravir used orally twice daily 800 mg for 5 days[30] or • Nirmatrelvir/ritonavir used orally twice daily 300/100 mg for 5 days.[31] Contraindicated in patients with severe hepatic failure; eGFR <30 ml/min, in patients with eGFR 30–60 ml/min the dose should be reduced to 150/100 mg or • Remdesivir administered intravenously once daily for 3 days, a loading dose of 200 mg on day 1, then a maintenance dose of 100 mg for 2 days. Contraindicated in patients with eGFR <30 ml/min; ALT activity ≥ 5 times the upper limit of normal[32] or • Sotrovimab used as a single intravenous infusion of 500 mg or • Casirivimab/imdevimab used intravenously or subcutaneously as a single dose of 1200 mg (600/600 mg) provided the locally dominant viral variant is not a resistant variant (eg, Omicron)[44]	• Inhaled budesonide at a dose of 2 × 800 µg daily[23] • Antipyretic drugs (paracetamol, ibuprofen, etc) • Rest • Oral hydration • LMWH in chronically bedridden patients and in those with indications for thromboprophylaxis unrelated to COVID-19 • Antitussive drugs for persistent cough • Systemic corticosteroids are contraindicated. • Antibiotics and anti-influenza medications are contraindicated, unless there is a bacterial coinfection or concomitant influenza. • Oxygen saturation control using the Pulsocare remote alarm system (using pulse oximeters)
Stage 2: fully symptomatic • SpO_2 <94% • Usually week 1 after disease onset • Hospitalization is required	The initiation of antiviral therapy is recommended up to 5 days after the onset of symptoms (up to 10 days in immunosuppressed patients). These drugs should not be used in pregnant and lactating women. • Molnupiravir administered orally twice daily 800 mg for 5 days[30] or • Nirmatrelvir/ritonavir used orally twice daily 300/100 mg for 5 days.[31] Contraindicated in patients with severe hepatic failure; eGFR <30 ml/min, in patients with eGFR 30–60 ml/min the dose should be reduced to 150/100 mg or • Remdesivir administered intravenously once daily for 5 days, a loading dose of 200 mg on day 1, then a maintenance dose of 100 mg for 4 days. Contraindicated in patients with eGFR <30 ml/min; ALT activity ≥5 times the upper limit of normal[32] or • Sotrovimab used as a single intravenous infusion of 500 mg or • Casirivimab/imdevimab used intravenously or subcutaneously as a single dose of 1200 mg (600/600 mg) provided the locally dominant viral variant is not a resistant variant (eg, Omicron)[44]	• LMWH in a prophylactic dose, which can be increased in justified cases • Dexamethasone can be considered but only in patients receiving antiviral drugs and oxygen therapy, orally or intravenously 4–8 mg/d; should not be used in the first week of the disease if antiviral drugs are not used. • Antibiotic therapy in the case of secondary bacterial infections • Symptomatic treatment • Oxygen therapy • Oral or intravenous hydration
Stage 3: respiratory failure (cytokine storm) • SpO_2 <90% • Usually week 2 after disease onset • Hospitalization is required	• Tocilizumab in patients with IL-6 concentration >100 pg/ml, in a single intravenous infusion of 800 mg if BW >90 kg; 600 mg if BW 65–90 kg; 400 mg if BW 40–65 kg, and 8 mg/kg if BW ≤40 kg. In the case of no improvement, the second dose may be repeated after 8–24 h. Contraindicated in patients with absolute neutrophil count <2000/µl; active tuberculosis.[35] or • Anakinra in adults with a suPAR plasma concentration ≥6 ng/ml, at a dose of 100 mg subcutaneously once daily for 10 days. Caution should be exercised in people with recurrent infections. Treatment should not be initiated in patients with neutrophil count <1.5 × 10^9/l.[38] or • Baricitinib orally 4 mg a day until the end of hospitalization but not longer than 14 days; recommended especially in patients requiring high-flow oxygen therapy. There is no evidence of benefit with tocilizumab. Contraindicated in patients with eGFR <30 ml/min, dose reduced to 2 mg daily in patients with eGFR 30–60 ml/min and >75 years of age; active tuberculosis.[40] and/or • Dexamethasone phosphate administered intravenously at a daily dose of 6–8 mg[c] for 7–10 days	• LMWH in a prophylactic dose, which can be increased in justified cases • Antibiotic therapy in the case of secondary bacterial infections • Symptomatic treatment • Low- or high-flow oxygen therapy • Intravenous hydration

TABLE 1 Recommended pharmacological management in adults at different clinical stages of SARS-CoV-2 infection, including basic and supportive treatment[a] (continued from the previous page)

Disease stage	Primary treatment	Supportive treatment
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[c] for 7–10 days. If dexamethasone is not available, other glucocorticosteroids may be given at equivalent doses and/or • Tocilizumab in combination with dexamethasone can be administered to patients who require mechanical lung ventilation. It should be administered as soon as possible, in the first 24 h of ventilation. Contraindicated in patients with absolute neutrophil count <2000/µl; active tuberculosis.[35] When used before administration of baricitinib, this therapy may be continued until scheduled completion if it is possible to administer the drug via the intragastric route. Once a patient has received a full course of baricitinib treatment, there is no need to administer tocilizumab.	• High-flow oxygen therapy • Noninvasive ventilation • Invasive ventilation • Extracorporeal veno-venous transmembrane oxygenation in selected patients • LMWH in prophylactic or therapeutic doses, depending on the clinical situation • Empiric antibiotic therapy is not recommended unless there is evidence of a bacterial infection.

a Detailed information on the posology and restrictions on use is provided in the Summary of Product Characteristics (SmPC) for the European Union/Poland.

b Age >60 years, obesity, diabetes mellitus, malignant disease, chronic heart failure, chronic respiratory failure, chronic renal failure, immunodeficiency, immunosuppression

c According to the manufacturer's information, a dose of 6 or 8 mg/ml of dexamethasone phosphate in the available injection solutions corresponds to 4.95 or 6.6 mg/ml of dexamethasone.

Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; BW, body weight; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IL, interleukin; LMWH, low-molecular-weight heparin; SpO_2, oxygen saturation; suPAR, soluble urokinase plasminogen activator receptor

to 5 days after the onset of symptoms in patients with increased risk for developing severe disease (as per the criteria specified above).[18-20] In patients with documented immunosuppression as a result of disease or therapy, the time required to initiate antiviral therapy may be extended to 10 days. An alternative to antiviral drugs are monoclonal antibodies. However, due to the dominance of the Omicron variant, which is not neutralized by them, they are currently not recommended.[21,22]

Patients with mild symptoms of respiratory tract infection without lung involvement and no risk factors for severe COVID-19 usually do not require pharmacotherapy but only clinical monitoring, for example using the Home Medical Care system (DOM, Pulsocare), which should capture patients with SpO_2 below 94%. With regard to symptomatic treatment, patients may require the use of antipyretics (nonsteroidal anti-inflammatory drugs or acetaminophen) and antitussives. In adult patients with mild-to-moderate symptomatic COVID-19, inhaled budesonide should be administered at a dose 800 µg twice daily.[23] Systemic corticosteroids should not be administered at this stage due to their immunosuppressive effects, which may worsen the prognosis.[24] Low-molecular-weight heparin (LMWH) in a prophylactic dose should only be used in chronically immobilized patients and individuals with other indications for thromboprophylaxis unrelated to COVID-19, especially in patients with risk factors for deep vein thrombosis and/or pulmonary embolism.[25,26] Antibiotics should only be used when there is a reasonable suspicion of a bacterial coinfection, as their effectiveness in the treatment of COVID-19 has not been proven.

Stage2 Increasing dyspnea, accompanied by SpO_2 below 94%, requires oxygen therapy, which results in the necessity of hospitalization. Usually, in this phase of the disease, low-flow oxygen therapy, not exceeding 15 l/min, is sufficient. Prophylactic doses of LMWH are part of the standard management of hospitalized patients, and their doses may be increased in justified cases. Antiviral therapy should be started no later than 5 days after the onset of symptoms, primarily in patients at risk of severe COVID-19 (listed in the previous paragraph).[27-29] In immunosuppressed individuals, this period may be extended up to 10 days. Antiviral therapy is recommended but the utility of monoclonal antibodies is limited due to the dominance of the Omicron variant.[22,30-32] It has been proven that adding glucocorticoids to remdesivir has no effect; therefore, such a therapy should not be used routinely at this stage of the disease due to the risk of exacerbation or prolongation of the viral replication. However, in the case of no clinical improvement despite antiviral therapy, the addition of dexamethasone at a daily dose of 4 to 8 mg at the end of the first week of the disease may be considered.[24]

Stage 3 Clinical deterioration at the beginning of the second week of the disease, with increasing dyspnea and a reduction in SpO_2 significantly below 90%, necessitates the use of high-flow oxygen therapy up to 60 l/min in some patients. This may indicate the onset of a cytokine storm. The increase in the IL-6 concentration above 100 pg/ml found at that time justifies the administration of tocilizumab, a monoclonal antibody directed against the IL-6 receptor, which significantly

reduces the risk for mechanical ventilation and death.[33,34] Tocilizumab should be administered as an intravenous infusion over 1 hour as a single dose of up to 800 mg, based on the body weight (dosing details are presented in TABLE 1). If there is no effect, another infusion may be given after 8 to 24 hours, but the second dose has not been proven to be effective. Tocilizumab should not be administered in patients with neutrophil counts below 2×10^9/l, platelet counts below 50×10^3/μl, or alanine aminotransferase levels greater than 5 times the upper limit of normal.[35] The use of glucocorticosteroids may worsen the effect of tocilizumab; therefore, it is recommended to use intravenous dexamethasone at a dose of 6 to 8 mg for 7 to 10 days only when no beneficial effect was achieved after administration of tocilizumab or when it was not used at all.[36,37]

An alternative to tocilizumab in patients at risk of a cytokine storm may be the IL-1 receptor antagonist, anakinra, administered subcutaneously at a dose of 100 mg once daily for 10 days. The use of this drug is recommended when the plasma concentration of soluble urokinase plasminogen activator receptor has increased to at least 6 ng/ml. Caution should be exercised in individuals with recurrent infections, and treatment should not be initiated in patients with neutrophil counts below 1.5×10^9/l.[38] An alternative to IL receptor antagonists may be baricitinib administered orally at a dose of 4 mg per day until the end of hospitalization, but not longer than 14 days, which has been shown to be effective especially in patients requiring high-flow oxygen therapy.[39] Baricitinib is contraindicated in patients with active tuberculosis and estimated glomerular filtration rate (eGFR) below 30 ml/min. In patients with eGFR between 30 and 60 ml/min and over 75 years of age, the dose should be reduced to 2 mg daily.[40]

Stage 4 Due to the deterioration of the patient's condition associated with ARDS, high-flow oxygen therapy becomes inadequate, and the patient requires tracheal intubation and mechanical ventilation of the lungs. In this group of patients, the highest benefits of using glucocorticosteroids have been proven.[24] Currently, it is recommended to use dexamethasone at a dose of 12 mg, which is higher than previously proposed.[41] It is advisable to consider early use of tocilizumab (dosing in TABLE 1), especially in patients with high levels of IL-6 or C-reactive protein. There is no justification for initiating or continuing antiviral therapy in mechanically ventilated patients. Lung protective ventilation should be used, namely, administration of small tidal volumes, choosing appropriate positive end-expiratory pressure values, and adjustment of the administered oxygen content to the arterial oxygen pressure and the oxygen saturation of arterial hemoglobin. Some patients who do not respond to conventional treatments benefit from prone position ventilation.[42] Mortality among patients with COVID-19 requiring mechanical ventilation reaches 67%.[43]

The use of veno-venous extracorporeal membrane oxygenation (VV ECMO) is indicated only in selected patients and should be limited to expert centers with appropriate experience and technical capabilities. This therapy may be beneficial in patients with ARDS (moderate or severe) diagnosed before commencement of mechanical ventilation, with mechanical ventilation used no longer than 7 days, and in those with acute disturbances in gas exchange despite optimal conventional ventilation and the lack of effectiveness of additional methods improving oxygenation (eg, ventilation in an inverted position, neuromuscular block). It is also used as a bridging therapy for lung transplantation. However, there are numerous contraindications to VV ECMO therapy.[45] TABLE 2 shows the benefits of and contraindications to the use of VV ECMO approved by the National Consultant in Anesthesiology and Intensive Care for the development of guidelines and recommendations for critically ill patients with COVID-19.

Drugs with unconfirmed efficacy Based on the research results to date, the following drugs can be found ineffective: chloroquine, hydroxychloroquine, azithromycin, doxycycline, lopinavir / ritonavir, favipiravir, umifenovir, oseltamivir, amantadine, rimantadine, zanamivir, acyclovir, ivermectin, nonsteroidal anti-inflammatory drugs, sarilumab, siltuximab, and niclosamide.

Late sequelae of COVID-19 Post–COVID-19 (long COVID) refers to persistent symptoms or organ dysfunction occurring at least 4 weeks after the acute phase of COVID-19.[46] In October 2021, the World Health Organization published a post–COVID-19 case definition, which states that this syndrome can be diagnosed in patients with probable or confirmed SARS-CoV-2 infection, its symptoms usually appear 3 months after the onset of COVID-19, continue for at least 2 months, and are not related to a different diagnosis.[47]

The incidence of post–COVID-19 ranges from 30% to 80%, depending on methodology of the study.[48] The most common symptoms are pulmonary (dyspnea, hypoxemia, impaired gas diffusion ability, persistent inflammatory changes and / or fibrosis on computed tomography), hematologic (thromboembolic events, anemia), cardiovascular (palpitations, dyspnea, chest pain, arrhythmias, myocardial fibrosis / scarring), and neuropsychiatric (chronic fatigue, muscle aches, headaches, olfactory / taste disturbances, anxiety, depression, sleep disturbances and post-traumatic stress disorder). Numerous laboratory abnormalities are also observed 3 to 6 months after the acute phase of COVID-19, including changes in peripheral blood counts, impaired eGFR, elevated liver function tests, and hyperglycemia, although their clinical relevance

TABLE 2 Criteria for the application and contraindications for the use of veno-venous extracorporeal transmembrane oxygenation approved by the Working Group of the National Consultant in Anesthesiology and Intensive Care for the development of guidelines and recommendations for critically ill patients with COVID-19

VV ECMO therapy has the potential to bring benefits to the following patients in the acute phase of COVID-19:
1) Meeting the criteria for the diagnosis of ARDS before the implementation of invasive ventilation:
a. oxygenation index (PaO_2/FiO_2) ≤200 mm Hg
b. presence of bilateral parenchymal changes in the lungs corresponding to noncardiogenic pulmonary edema
c. no symptoms suggesting severe left ventricular failure (pulmonary wedge pressure <18 mm Hg, no severe impairment of left ventricular contractility on echocardiography, etc)
2) Invasively ventilated for <7 days
3) With severe disturbances in gas exchange during invasive ventilation with optimal ventilator settings (FiO_2 ≥0.8, TV 6 ml/kg due body weight, PEEP ≥10 cm H_2O), in whom attempts were made to improve oxygenation with methods available in the center (eg, an inverted position [prone position] for at least 12–16 h/day, continuous neuromuscular block, etc):
a. oxygenation index (PaO_2/FiO_2) <50 mm Hg for >3 hours, or
b. oxygenation index (PaO_2/FiO_2) <80 mm Hg for >6 hours, or
c. arterial blood pH <7.25 with $PaCO_2$ ≥60 mm Hg with respiratory rate not exceeding 35/min and plateau pressure ≤32 cm H_2O
VV ECMO therapy has no benefit or is not recommended in the following patients:
1) Admitted to the Department of Anesthesiology and Intensive Therapy and assigned with 3rd and 4th priority, in accordance with the Guidelines of the Polish Society of Anesthesiology and Intensive Therapy, which define the rules of qualification and criteria for admitting patients to the Departments of Anesthesiology and Intensive Therapy
2) Ventilated invasively or noninvasively ≥7 days with FiO_2 >0.6
3) Treated with high-flow nasal oxygen therapy ≥7 days with FiO_2 >0.6
4) With body weight over 1 kg/cm of height or BMI >40 kg/m^2
5) With respiratory failure requiring oxygen therapy or noninvasive ventilation in the course of chronic lung disease
6) Requiring support of the functions of other systems and organs apart from respiratory failure, including:
a. need for treatment of acute exacerbations of severe right or left ventricular heart failure (in such patients another type of extracorporeal support should be considered)
b. the use of high doses of one or more inotropic or vasoconstrictive drugs:
• noradrenaline >0.2 μg/kg/min,
• adrenaline >0.1 μg/kg/min,
• dopamine >15 μg/kg/min,
c. chronic renal replacement therapy,
d. hepatic replacement therapy
7) With a history of heparin-induced thrombocytopenia
8) With active neoplastic disease
9) With a low probability of survival assessed using prognostic scales (eg, SAPS-II, SOFA, APACHE)
10) After cardiac arrest, in whom coma persists despite discontinuation of medication disturbing consciousness
11) With irreversible neurological defects
12) With potentially irreversible immunodeficiency and/or bone marrow suppression
13) Who made an earlier decision not to undertake/withdraw from life support therapy
14) In whom it is difficult to obtain adequate vascular access to the femoral or jugular veins
15) With severe frailty syndrome

Abbreviations: ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation score; BMI, body mass index; FiO_2, fraction of inspired oxygen; H_2O, dihydrogen monoxide; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SAPS-II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment score; TV, tidal volume; VV ECMO, veno-venous extracorporeal transmembrane oxygenation

remains uncertain.[48] Pediatric inflammatory multisystem syndrome or multisystem inflammatory syndrome in children is a separate condition that manifests itself after COVID-19 in children and young adults meeting specific diagnostic criteria.[49]

The results of a Polish prospective study SILCOV-19 (the Silesian Complications of COVID-19 Database) showed that the most common symptoms of post–COVID-19 are fatigue, shortness of breath, palpitations, as well as smell and taste disorders.[50] In the same study, more than 100 days after the acute phase, numerous abnormalities were found, including:

- persistence of inflammatory changes on high-resolution computed tomography (9% of nonhospitalized patients and 40% of those hospitalized in the acute phase);
- SpO_2 below 95% (10% of nonhospitalized, 18% of hospitalized patients);
- pulmonary transfer for carbon monoxide below 80% (28% of nonhospitalized, 49% of hospitalized patients);
- episodes of bradycardia (heart rate <40 bpm) in Holter recordings (17% of nonhospitalized, 6% of hospitalized patients);
- anxiety: a score of more than 10 points in the Hospital Anxiety and Depression Scale (9%–11% of patients);
- insomnia: a score of more than 10 points in the Athens Insomnia Scale (17%–27% of patients);
- elevated alanine aminotransferase activity (11%–18% of patients);
- elevated lactate dehydrogenase activity (44%–54% of patients);
- elevated D-dimer concentration (10% and 17% of patients).[50]

This and other studies clearly show that individuals hospitalized in the acute phase of the disease (especially in the ICU), those with multiple comorbidities, the elderly, and women are at a higher risk of post–COVID-19.

Rest, relaxation, and pulmonary rehabilitation play an important role in recovery from COVID-19. There is no evidence that routine thromboprophylaxis is advisable, although high-risk patients may require anticoagulation up to 30 days after discharge (**TABLE 3**).[51,52] Direct-acting oral anticoagulants (DOACs) and LMWH are preferred over vitamin K antagonists. The importance of antiplatelet drugs, glucocorticosteroids, or antifibrotic drugs in post–COVID-19 syndrome has not been established.

Vaccination Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered as the first-line prevention of COVID-19.[53,54] Currently available vaccines have been constructed using mRNA, vector, and recombinant technology. Regardless of the technology used, all COVID-19 vaccines approved by the European Medicines Agency meet strict efficacy and safety criteria when used in accordance with the summary of product characteristics

TABLE 3 The IMPROVE VTE thromboembolic risk assessment model indicating the need for prophylactic anticoagulation after discharge from hospital following COVID-19[52]

Risk factors	Score[a]
Prior venous thromboembolism	3
Diagnosed thrombophilia	2
Current lower limb paralysis	2
Current cancer	2
Bedridden for at least 7 days	1
Stay in the intensive or coronary care unit	1
Age >60 years	1

a A score of 2 or more indicates the need for prophylaxis.

Abbreviations: IMPROVE, the International Medical Prevention Registry on Venous Thromboembolism; VTE, venous thromboembolism

(SPC).[54-58] Vaccination does not eliminate the risk of infection, but significantly reduces the likelihood of severe or fatal disease.[59] The vaccination schedule includes a primary vaccination course (number of doses and dosing interval in accordance with the SPC) and a booster dose. Individuals with impaired immunity should receive an additional dose of the vaccine at least 28 days after the second dose, that is, they should be vaccinated with 3 doses in the basic schedule and a booster dose (a total of 4 doses of the vaccine, preferably with mRNA vaccines).[60] A booster dose of the COVID-19 vaccine is recommended for all individuals at least 5 months after completion of the primary immunization schedule with mRNA (Pfizer-BioNTech or Moderna) or vector Vaxzevria (AstraZeneca) vaccines, and at least 2 months after receiving the primary dose of the Janssen COVID-19 vaccine. Selected issues related to vaccination are presented below.

- Serological testing to assess response to vaccination before an additional dose or a booster dose is not recommended.
- If a dose is delayed, it should be administered as soon as possible. It is not recommended to start the vaccination schedule from the beginning.
- People with a history of COVID-19 (convalescents) can be vaccinated 30 days after a positive genetic or antigen test result. This also applies to patients who fell ill or tested positive after receiving the first dose of the vaccine.
- The optimal timing of vaccination in patients scheduled for or undergoing immunosuppressive or biologic therapy should be established based on current specialist guidelines.
- Revaccination with an mRNA vaccine should be considered 2 to 6 months after autologous and allogeneic hematopoietic stem cell transplantation and 3 to 6 months after CAR-T therapy.
- Due to the risk of extravasation and bleeding, particular caution should be exercised when administering the vaccine to patients with severe coagulation disorders.
- As COVID-19 increases the risk of preterm labor in pregnancy and the benefits of vaccination outweigh the risks, vaccination is recommended for women who are pregnant, breastfeeding, or are planning to become pregnant.[54,61,62]
- Lactation is not a contraindication to vaccination against SARS-CoV-2.
- There is no need to make any interval between COVID-19 vaccination and vaccinations against other diseases; however, it is recommended to vaccinate against COVID-19 with a 4-week interval from vaccines containing live microorganisms.
- A contraindication to COVID-19 vaccination is hypersensitivity to the active substance or any of the excipients contained in the vaccine, or a history of any anaphylactic reaction. It is permissible to vaccinate such a person with full protection against shock in hospital conditions, after prior notification of the possible risk and obtaining written informed consent to vaccination.

Pre-exposure prophylaxis The use of monoclonal antibodies, tixagevimab or cylgavimab (Evusheld), should be considered in pre-exposure prophylaxis (PrEP) of SARS-CoV-2 in adults and adolescents (aged ≥12 years and weighing ≥40 kg), who are not infected with SARS-CoV-2 and have not been recently exposed to an infected person, and who are moderately or severely immunocompromised and may have an inadequate immune response to vaccination against COVID-19, cannot accept any available vaccine, or are at a particularly high risk of severe COVID-19.[22,63] The use of bamlanivimab / etesevimab or casirivimab / imdevimab as part of PrEP is not justified due to the dominance of the Omicron variant of the virus, which is not neutralized by these antibodies.[22]

ARTICLE INFORMATION

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