Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists. Annex no. 2 as of October 13, 2020

To the editor **Introduction** In light of new emerging data and accumulated experience, it became necessary to amend the recommendations of the Polish Association of Epidemiologists and Infectiologists (Polskie Towarzystwo Epidemiologów i Lekarzy Chorób Zakaźnych [PTEiLChZ]) for the management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection published on March 31, 2020 and the subsequent amendments regarding pharmacotherapy, introduced in Annex no. 1 as of June 8, 2020.[1,2]

The objective of the PTEiLChZ recommendations is to provide practical guidelines for the diagnostic workup and pharmacotherapy of SARS-CoV-2 infection, which would be useful both in primary healthcare and hospital settings. The recommendations are based on published research findings and the authors' own experience, but they do not include detailed guidelines for patient management in intensive care units (ICUs) with regard to mechanical ventilation and extracorporeal membrane oxygenation.

The changes introduced to the recommendations relate both to primary and supportive treatment at successive stages of the disease (TABLE 1) and the diagnostic workup of SARS-CoV-2 infection. They emerged as a consequence of the rapid accumulation of knowledge on the efficacy (or inefficacy) of therapeutic options under consideration.[3] The results of subsequent studies have confirmed the benefit of using remdesivir at the stage of viral multiplication as well as immunomodulatory drugs and/or glucocorticosteroids at the cytokine storm stage (Flisiak et al 2020, unpublished data).[4-8] Moreover, the rationale behind convalescent plasma and low-molecular-weight heparin use has been validated.[9,10] Based on evidence showing that lopinavir/ritonavir, chloroquine, and hydroxychloroquine are not therapeutically effective, they were finally excluded from coronavirus disease 2019 (COVID-19) treatment.[11-13] Also, studies have failed to demonstrate any therapeutic benefit of azithromycin, favipiravir, ruxolitinib, oseltamivir, opaganib, and verdinexor use.

Diagnostic recommendations Preliminary remarks Testing of potentially infectious material (swabs from the upper or lower airways including pharyngeal, nasopharyngeal, and nasal swabs, samples of sputum, saliva, and bronchopulmonary washing) regardless of the test used (molecular, antigen, or serological) should be performed in strict compliance with the epidemiological safety procedures to minimize the risk of transmitting infection to the staff. The results of molecular and antigen tests do not determine the replication activity or infectivity of SARS-CoV-2, so the periods of infectivity should be defined on the basis of in vitro tests and not the results of diagnostic tests. There are no firm data available regarding the period of infectivity in immunodeficient individuals and it may be prolonged.[14]

Molecular diagnostic workup Techniques detecting the SARS-CoV-2 genetic material (nucleic acid amplification testing), including polymerase chain reaction (PCR) techniques with real-time signal detection (real-time PCR, nested PCR) or isothermal amplification methods, are the basis for the diagnosis of active SARS-CoV-2 infection. Tests detecting viral genetic material should be performed in individuals meeting the criteria for suspected COVID-19. Rapid molecular tests (yielding results within 45 to 60 minutes) meet all the requirements applicable to genetic testing methods and are particularly useful in admission rooms of infectious disease wards and in hospital emergency departments where they facilitate patient triage. The optimal time for performing a molecular test is the period of viral replication in the upper respiratory tract epithelium, which usually lasts up to day 10 after the onset of clinical symptoms.[15] After this time interval, the sensitivity of molecular tests

gradually decreases, falling below 50% 14 days after disease onset.[16]

Serological tests Serological tests evaluate the humoral response to SARS-CoV-2 during and after acute infection. Although neutralizing antibodies have been detected in the majority of patients after laboratory-confirmed SARS-CoV-2 infection, there are incomplete data as to how long the antibodies remain present after past infection and whether they maintain the protective function.[17] Serological tests can cross-detect antibodies against other pathogenic coronaviruses, and the risk of cross-reactions depends on the type of antibodies detected. When using serological tests, including rapid cassette tests, a high degree of caution should be exercised with regard to the manufacturer's notes on test sensitivity and specificity. It is advisable to validate test sensitivity and specificity in the local population. Serological tests (based on enzyme immunoassay techniques and their variants) detecting antibodies are not useful for the diagnosis of early COVID-19 because of their insufficient sensitivity. However, they can be performed to improve diagnostic reliability in patients with negative molecular test results who present typical clinical and radiological manifestations, especially at disease stages 2 to 4; in the diagnostic workup of postinflammatory syndromes developing as a complication of SARS-CoV-2 infection; in epidemiological studies evaluating the immune status of the population (incidence rates and epidemiological modeling), and to identify convalescents for the purpose of obtaining therapeutic plasma (specific antibodies).

Rapid immunoserological tests Because of extremely low sensitivity and specificity, the currently available rapid cassette tests detecting antibodies should not be used for either the diagnosis of active disease or the assessment of patients' immune status. Rapid antibody cassette tests should be validated and evaluated based on reliable studies conducted independently of the test manufacturer, the epidemiology of infections with SARS--CoV-2 and other coronaviruses in a particular area, and own experience verified by the results of genetic tests.

Antigen tests The use of antigen tests in clinical practice is limited to the initial period of infection, when the viral load in the test material reaches the highest level (typically 5 to 7 days after the onset of clinical symptoms depending on the test manufacturer). The majority of antigen tests detecting SARS-CoV-2 proteins are characterized by medium sensitivity and high specificity, so both negative and positive results should be confirmed by a molecular test. First-generation antigen tests (developed at the outset of the pandemic) were of limited use in the diagnostic workup of COVID-19, as their sensitivity reached approximately 40%. Second-generation antigen tests (for example those detecting the SARS-CoV-2 nucleocapsid protein), which became available in September 2020, require further evaluation in clinical practice. The interpretation of negative results should be correlated with clinical data and the disease stage (late stages—including the cytokine storm and acute respiratory distress syndrome—are associated with an increased likelihood of obtaining false negative results). There are no data on the use of antigen tests in asymptomatic populations and for the assessment of infectivity. The characteristics of the antigen test used should include not only its sensitivity and specificity ranges but also a clear definition of the antigen type to be detected (eg, SARS-CoV-2 nucleocapsid); tests not labeled with such information should not be used owing to diagnostic unreliability.

Therapeutic recommendations 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. 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 up by a primary care physician usually require no treatment, and monitoring of their clinical status is a sufficient management option. Here, the currently tested electronic monitoring systems for oxygen saturation (SpO_2), which should not be lower than 95%, may be useful. 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. Of note, patients with stage 1 disease should not be treated with glucocorticosteroids. These drugs have been shown to be ineffective in patients who do not require oxygen therapy. Furthermore, using glucocorticosteroids too early may increase the viral replication rate and, hence, worsen patient prognosis.[6] Treatment with antibiotics, anti-influenza drugs, vitamin D, or low-molecular-weight heparin is not recommended in SARS-CoV-2 infection, unless it is required because of another medical condition.

If the patient's condition worsens, referral to the hospital should be considered. A potentially helpful tool for the evaluation of indications for hospitalization is the CRB-65 score designed for grading the severity of pneumonia. The score includes the following risk factors: confusion (1 point), respiratory rate ≥30 breaths per minute (1 point), blood pressure ≤90/60 mm Hg (1 point), and age >65 years (1 point). If a patient scores 2 points, hospital referral should be considered, whereas patients scoring 3 or 4 points should be referred to the hospital. If the patient's condition is good, remote forms of contact (phone and video calls) and patient self--diagnosis (measurement of pulse and respiratory rates) should be considered and the patient needs to be counseled about alarm symptoms.

TABLE 1 Recommended pharmacological management at different clinical stages of SARS-CoV-2 infection including primary and supportive treatment

Disease stage	Primary treatment	Supportive treatment
Stage 1: • Asymptomatic or mildly symptomatic • SpO_2 ≥95% • No hospitalization is necessary.	• Antipyretic drugs (paracetamol, ibuprofen, etc) • Rest • Oral hydration • Glucocorticosteroids are contraindicated. • Antibiotics and anti-influenza drugs are contraindicated, unless there is bacterial coinfection or concomitant influenza. • There are no indications for vitamin D and low-molecular-weight heparin treatment, unless justified due to comorbidities. • Oxygen saturation monitoring and, possibly, implementing a remote alert system for general practitioners and/or emergency medical services (based on pulse oximeter use).	
Stage 2: • Fully symptomatic (viral multiplication) • SpO_2 <95% • Usually at week 1 after disease onset • Hospitalization required	• Remdesivir administered intravenously once daily, at a loading dose of 200 mg on day 1, followed by a maintenance dose of 100 mg for 4 days, and/or • Convalescent plasma (ABO-compatible), 200–400 ml in volume. The transfusion of convalescent plasma involves the same procedures as treatment with other blood products.	• Low-molecular-weight heparin at prophylactic or therapeutic doses • Dexamethasone in patients receiving remdesivir and oxygen therapy, orally or intravenously at 4 mg daily, starting from day 2–5 of remdesivir treatment and continuing until the end of week 2 after disease onset • Antibiotic therapy, if necessary • Symptomatic treatment • Oxygen therapy • Oral or intravenous hydration
Stage 3: • Respiratory failure (cytokine storm) • SpO_2 <90% • Usually week 2 after disease onset • Hospitalization required	• Tocilizumab[a] (in patients with elevated IL-6 levels) administered intravenously at 8 mg/kg (maximum dose: 800 mg) in a single dose (1-hour infusion). If no improvement is observed, the second dose may be administered after 8 to 12 hours; and/or • Dexamethasone administered intravenously at a daily dose of 8 mg for 5 days, followed by a daily dose of 4 mg for at least 3 days	• Low-molecular-weight heparin at prophylactic or therapeutic doses • Antibiotic therapy, if necessary • Symptomatic treatment • Low- or high-flow oxygen therapy • Intravenous hydration
Stage 4: • ARDS • Unsuccessful pharmacotherapy to date • Need for mechanical ventilation • ICU treatment required	• Dexamethasone administered intravenously at a daily dose of 24 mg for 5 days, followed by a daily dose of 12 mg for 3 days, and a daily dose of 4 mg for 2 days or • Methylprednisolone administered intravenously at a daily dose of 1 mg/kg for 5 days, followed by a daily dose of 40 mg for 3 days, and a daily dose of 10 mg for 2 days	• High-flow oxygen therapy • Mechanical ventilation • ECMO • Low-molecular-weight heparin at prophylactic or therapeutic doses • Antibiotic therapy • Intravenous hydration

a Tocilizumab can be used after bioethics committee approval.

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IL-6, interleukin 6; SpO_2, oxygen saturation as measured by pulse oximetry

Stage 2 The increased severity of COVID-19 symptoms indicates the development of stage 2 disease, in which patients require hospitalization owing to the potential need for oxygen therapy, thromboembolic prevention, and antiviral treatment (TABLE 1). Remdesivir is the only currently approved antiviral drug, which should be used for 5 days. Longer therapy (10-day treatment was initially recommended) does not bring any additional benefits (Flisiak et al 2020, unpublished data).[5,18] Low doses of dexamethasone should be considered in patients treated with remdesivir and concurrent oxygen therapy in order to prevent the cytokine storm.[6] Also, convalescent plasma may be administered as part of antiviral therapy at this stage of the disease.

Stage 3 Clinical deterioration despite antiviral therapy—which can be manifested by increased dyspnea and a drop in SpO_2 below 90% in spite of oxygen therapy—may indicate the development of stage 3 disease, in which the cytokine storm plays a key role. In some patients, the risk of life-threatening effects can be reduced by using tocilizumab, an interleukin-6 receptor antagonist.[8,19] Low-dose glucocorticosteroid treatment can also be implemented for the same purpose (TABLE 1).[6]

Stage 4 Further deterioration of the patient's condition despite following appropriate management strategies indicates the development of stage 4 disease, ie, acute respiratory distress syndrome. The patient should be transferred to the ICU, as it is highly possible that they would require mechanical ventilation. At this stage of the disease, it is frequently advisable to administer relatively high doses of glucocorticosteroids and, typically, empiric broad-spectrum antibiotic therapy against microbiological factors, which are probably responsible for infections in a particular ICU (TABLE 1).

Important notes

• Treatment with remdesivir in patients who do not require oxygen therapy and those after the stage of viral multiplication (typically one week after the onset of symptoms) is of no benefit and has no clinical justification.

• Furthermore, there is no rationale for using antibiotics (eg, azithromycin), chloroquine, hydroxychloroquine, lopinavir / ritonavir, anti-influenza drugs (oseltamivir, favipiravir), and vitamin D for the treatment of SARS-CoV-2 infection.

• Glucocorticosteroids used at stage 1 of the disease may increase the risk of an adverse course of COVID-19 owing to their potential effect on viral replication. Low doses of glucocorticosteroids at disease stage 2 are acceptable, provided that antiviral drugs (remdesivir) are concurrently administered.

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